SYNTHETIC AND REACTIVITY STUDIES ON THE
CYCLISATION REACTIONS OF α,β:γ,δ-UNSATURATED
NITRILE YLIDES

by

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FOR

Mum, Dad,
Carol and Lorna

A man ought to read just as inclination leads him; for what he reads as a task will do him little good.

Samuel Johnson 1709-1784
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Finally, I would like to thank my colleagues in Room 200, Messrs Harding and Reece, for making life interesting throughout the three short years.
DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record was carried out by myself, and that it has not been submitted in any previous application for a Higher Degree.

Kevin E. Cullen

POST-GRADUATE COURSES

The following is a statement of post-graduate courses attended during the period of this work.

Organic Research Seminars - various lecturers (3 years attendance).

Medicinal Chemistry - Dr. R. Baker, Dr. P. Leeson, Prof. Sammes (15 lectures).

Current Topics in Organic Chemistry - various lecturers (3 years attendance).

Chemistry in Industry - Dr. S. Korn (5 lectures).

Business Management - Prof. A. Coke (5 lectures).

EUCHEM Conference - "1,3-Dipoles and 6π-Reactions in Heterocyclic Synthesis" - various lecturers.
This work is concerned with the 1,7-electrocyclisation reactions of \( \alpha,\beta;\gamma,\delta \)-unsaturated nitrile ylides and, in particular, with an investigation of the factors affecting the rates of cyclisation of these systems.

A series of dibenz[c,e]azepines were prepared using this reaction to assess its synthetic scope for the case where both the \( \alpha,\beta- \) and \( \gamma,\delta- \) double bonds were aromatic. Several attempts were then made to devise a technique capable of quantitatively measuring the effects of various substituents on the reaction rate.

An approach using intramolecular competition reactions was developed, which showed that the 1,7-electrocyclisation reaction is accelerated by both electron-donor and electron-acceptor substituents. Stabilisation of the transition-state by substituents was proposed to explain these results. Although all electronic effects were shown to accelerate the reaction, it was shown that ortho-substituents can prevent 1,7-electrocyclisation from taking place due to steric effects.
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>123</td>
</tr>
<tr>
<td>EXPERIMENTAL</td>
<td>266</td>
</tr>
<tr>
<td>APPENDICES</td>
<td>379</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>400</td>
</tr>
</tbody>
</table>
1

INTRODUCTION

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>1,3-DIPOLES</td>
<td>3</td>
</tr>
<tr>
<td>1.1</td>
<td>STRUCTURE</td>
<td>3</td>
</tr>
<tr>
<td>1.2</td>
<td>REACTIONS</td>
<td>6</td>
</tr>
<tr>
<td>1.2.1</td>
<td>Intermolecular 1,3-Dipolar Cyclo-additions</td>
<td>7</td>
</tr>
<tr>
<td>1.2.2</td>
<td>Intramolecular 1,3-Dipolar Cyclo-additions</td>
<td>18</td>
</tr>
<tr>
<td>1.2.3</td>
<td>Electrocyclic Reactions</td>
<td>19</td>
</tr>
<tr>
<td>2)</td>
<td>NITRILE YLIDES</td>
<td>31</td>
</tr>
<tr>
<td>2.1</td>
<td>STRUCTURE</td>
<td>31</td>
</tr>
<tr>
<td>2.2</td>
<td>GENERATION</td>
<td>35</td>
</tr>
<tr>
<td>2.3</td>
<td>REACTIONS</td>
<td>41</td>
</tr>
<tr>
<td>2.3.1</td>
<td>Intermolecular Reactions of Nitrile Ylides</td>
<td>41</td>
</tr>
<tr>
<td>2.3.2</td>
<td>Intramolecular Reactions of Nitrile Ylides</td>
<td>48</td>
</tr>
<tr>
<td>2.3.3</td>
<td>Electrocyclisation Reactions of Nitrile Ylides</td>
<td>58</td>
</tr>
<tr>
<td>2.3.3.1</td>
<td>1,5-Electrocyclisation Reactions of Nitrile Ylides</td>
<td>58</td>
</tr>
<tr>
<td>2.3.3.2</td>
<td>1,7-Electrocyclisation Reactions of Nitrile Ylides</td>
<td>63</td>
</tr>
</tbody>
</table>
3) REACTIVITY STUDIES IN PERICYCLIC SYSTEMS 71
3.1 PERICYCLIC CYCLOADDITION REACTIONS 72
3.2 ELECTROCYCLIC REACTIONS 90
1. 1,3-DIPOLES

1.1 STRUCTURE

The term 1,3-dipole applies to a class of reactive intermediates which may be defined\(^1,2\) as systems \(a-b-c\) in which \(a\) has an electron sextet, i.e. an incomplete valence shell, and carries a formal positive charge and \(c\) is a negatively charged centre with an unshared electron pair.

Although some classes of 1,3-dipole have been known for over a century\(^3\), it was not until the classification of 1,3-dipoles by Huisgen\(^4\) in the 1960's that these systems became the subject of intense study.

1,3-Dipoles are isoelectronic with either the allyl or propargyl anion, possessing four \(\pi\)-electrons spread over the \(a-b-c\) system.

Dipoles in which the positive centre \(a\) is an electron deficient carbon, nitrogen or oxygen atom are, in general, too unstable for long-lived existence. The system may, however, be stabilised if atom \(b\) is capable of donating an electron pair as shown below.

\[
\begin{array}{ccc}
  + & \cdot & - \\
  a & b & c \\
\end{array}
\quad \longrightarrow \quad
\begin{array}{ccc}
  + & \cdot & - \\
  a & b & c \\
\end{array}
\]

This donation leads to the formation of a more stable "all octet" configuration in which the site of formal
positive charge is shifted to atom b. By varying the atoms a, b and c it is possible to construct a series of octet stabilised 1,3-dipoles as shown in Table 1.

Table 1. 1,3-Dipoles with octet stabilisation
(Only two of the contributing resonance structures are shown for each dipole).

(a) 1,3-Dipoles of the allenyl-propargyl type

\[
\begin{align*}
\text{Nitrile Ylides} & : & \quad \begin{array}{c}
\text{CN} \\
\begin{array}{c}
\text{C} \\
\text{N}
\end{array}
\end{array} \\
\text{Nitrile Imines} & : & \quad \begin{array}{c}
\text{CN} \\
\begin{array}{c}
\text{C} \\
\text{N}
\end{array}
\end{array} \\
\text{Nitrile Oxides} & : & \quad \begin{array}{c}
\text{CN} \\
\begin{array}{c}
\text{C} \\
\text{N}
\end{array}
\end{array} \\
\text{Diazalkanes} & : & \quad \begin{array}{c}
\text{NN} \\
\begin{array}{c}
\text{C} \\
\text{N}
\end{array}
\end{array} \\
\text{Azides} & : & \quad \begin{array}{c}
\text{NN} \\
\begin{array}{c}
\text{C} \\
\text{N}
\end{array}
\end{array} \\
\text{Nitrous Oxide} & : & \quad \begin{array}{c}
\text{NN} \\
\begin{array}{c}
\text{C} \\
\text{N}
\end{array}
\end{array}
\end{align*}
\]
Octet stabilised 1,3-dipoles may be divided into two classes, those with an orthogonal double bond, i.e. the allenyl-propargyl type, and those without an orthogonal double bond, i.e. the allyl type.

Allenyl-propargyl type 1,3-dipoles have nitrogen as the central atom since nitrogen is the only element capable of contributing an unshared electron pair whilst in a neutral trivalent state. Allyl type 1,3-dipoles can have nitrogen or oxygen as the central atom.

The presence of the orthogonal double bond generally
leads to 1,3-dipoles of the allenyl-propargyl type being linear, whereas 1,3-dipoles of the allyl type are bent.

The structure of 1,3-dipoles is best represented through a series of resonance structures, e.g. the canonical forms (i)-(v) for a nitrile ylide shown in Scheme 1.

\[
\begin{align*}
& \text{(i)} \quad \text{R-C=\dot{\text{N}}-\text{CR}_2} \quad \text{R-C=\dot{\text{N}}-\text{CR}_2} \\
& \text{(ii)} \quad \text{R-C=\dot{\text{N}}-\text{CR}_2} \quad \text{R-C=\dot{\text{N}}-\text{CR}_2} \\
& \text{(iii)} \quad \text{R-C=\dot{\text{N}}-\text{CR}_2} \quad \text{R-C=\dot{\text{N}}-\text{CR}_2} \\
& \text{(iv)} \quad \text{R-C=\dot{\text{N}}-\text{CR}_2} \quad \text{R-C=\dot{\text{N}}-\text{CR}_2} \\
\end{align*}
\]

The all-octet configurations (ii) and (iii) are the main contributors to the stability of the nitrile ylide although the term 1,3-dipole applies strictly only to structures (i) and (iv). It is, however, accepted that the term 1,3-dipole is applicable to the molecule as a whole as it best describes the observed reactivity.

1.2 REACTIONS

1,3-Dipoles react readily with most multiple bond systems\(^1,^5\) \((d\equiv e; \text{the dipolarophile})\) via a \([3+2\to 5]\) cycloaddition reaction to give a five membered cyclic product.
The reaction leads to the formation of two new \( \sigma \)-bonds at the \( a \) and \( c \) termini, to give a product with no net charge. 1,3-Dipolar cycloadditions can occur both inter- and intramolecularly.

If the 1,3-dipole is attached to a system through which its conjugation can be extended then there is also the possibility of electrocyclic reaction.

These three reaction types will now be discussed under separate headings.

1.2.1 **Intermolecular 1,3-Dipolar Cycloadditions**

The general features of mechanism and patterns of reactivities and selectivities in 1,3-dipolar cycloaddition reactions were established by Huisgen et al.\(^2\),\(^6\) in the early sixties.

These reactions are thermally allowed \( 4\pi + 2\pi \) processes which possess certain characteristic features. (i) Neither rate nor stereochemistry of the reaction is markedly affected by solvent polarity. (ii) The products are 5-membered rings with the stereochemistry of the dipolarophile retained. (iii) The reactions exhibit low enthalpies of and large negative entropies of activation and (iv) the reaction rates are increased by conjugation in the dipolarophile, but reduced by steric effects in dipole and dipolarophile.

The mechanism of 1,3-dipolar cycloadditions has been, for many years, the topic of lively debate.
Huisgen\(^2\) originally proposed a concerted \([3+2]\) mechanism involving a cyclic transition state with no discrete intermediate. This was later reinforced by the Woodward and Hoffmann rules\(^7\), which showed that this mechanism is allowed on the basis of conservation of orbital symmetry. A later proposal by Firestone\(^8,9\) involves a two step mechanism in which the formation of a discrete spin-paired diradical is the rate determining step. In this case the stereochemistry of the reaction was explained in terms of ring-closure being energetically more favourable than bond rotation in the diradical. Firestone also suggested that the effects of conjugation and solvent effects could be better explained by the diradical mechanism.

In the debate over concerted versus stepwise mechanism the major problem was the regioselectivity of the reaction\(^6,9,10\). Both sides claimed this as a flaw in the others theory while conceding their own inability to fully explain it.

In 1973 Houk and co-workers\(^11,12\) developed a powerful method which rationalised substituent effects on rates, regioselectivity and periselectivity of concerted 1,3-dipolar cycloadditions. The method was based on perturbation theory and utilised relative energies and coefficients of the frontier orbitals in the interacting 1,3-dipoles and dipolarophiles. These were calculated by CNDO/2. The calculated orbital energies were then
adjusted using known ionisation potentials, electron affinities and $\pi-\pi^*$ transitions in alkenes.

For formonitrile methylide the values of the frontier molecular orbital coefficients were calculated to be as follows:

$$\begin{array}{c}
\text{C} & \text{N} & \text{C} \\
\text{LU} & 0.38 & 0.75 & 0.76 \\
\text{HO} & 0.83 & 0.21 & 0.53 \\
\end{array}$$

It can be seen from the calculations that the two termini have different orbital coefficients. As this is also the case with unsymmetrical dipolarophiles then this will result in differences in orbital overlap between the two possible orientations in the transition state (2) and (3).
Fukui had earlier postulated that reactions take place in the direction of maximum frontier molecular orbital overlap. This results from the union of the two centres of highest frontier orbital density and the union of the two centres of lowest frontier orbital density, i.e. 2 above.

Since the relative energies and orbital coefficients of the HO and LU are strongly affected by the substituents, and are the main factors affecting the regioselectivity and rates of reaction, Houk was able to achieve an almost complete rationalisation of the observed results in terms of substituent effects. The exception to the above was in the case of nitrile ylides for which CNDO/2 with no geometry optimisation gave inaccurate orbital coefficients for the 1,3-dipoles. This was later corrected using more refined calculations. The structure of nitrile ylides will be discussed in detail later in this thesis.

These results also lend credence to Huisgen's assertion that the effects of conjugation and solvent polarity could be best explained by concerted, but not necessarily synchronous, bond formation at the dipole termini. That is, the bond a-d in 2 above will be more fully developed in the early part of the reaction than that between c and e. Huisgen maintained, however, that, although not completely synchronous, the reaction involved only one step.
In recent years there has been increasing activity in the search for two step 1,3-dipolar cycloadditions. In Figure 1 the frontier \( \pi \)-molecular orbitals of a 1,3-dipole and an ethylenic dipolarophile are depicted. The diagram reflects the two-directional flow of electrons during a concerted cycloaddition; from HO (1,3-dipole) to LU (dipolarophile) and back from HO (dipolarophile) to LU (1,3-dipole).

**Figure 1**

\[
\begin{align*}
\Delta E &= - \frac{[\text{Ca}C'd\text{Bad} + \text{Ce}C'e\text{Bce}]}{\text{E}_I} + \frac{[\text{Ca}'C'd\text{Bad} + \text{Ce}'C'e\text{Bce}]}{\text{E}_{II}} \\
\text{E}_I &= E\psi_2 - E\psi_B = \text{HO (1,3-Dipole)} - \text{LU (Dipolarophile)} \\
\text{E}_{II} &= E\psi_A - E\psi_3 = \text{HO (Dipolarophile)} - \text{LU (1,3-Dipole)}
\end{align*}
\]
Sustmann’s PMO model of concerted cycloadditions\textsuperscript{15,16} envisions two cases in which the stepwise mechanism might compete with the concerted one. Firstly, if the energy differences between the two interacting HO-LU pairs are large and of the same magnitude then the sum of the two energy gains $\Delta E_1 + \Delta E_2$ is small. This corresponds to a minimum of rate and a diradical mechanism may be expected to compete if radical stabilising substituents are present.

The first example of this pathway was recently reported by Baran and Mayr\textsuperscript{17}. The sterically hindered 1,3-diene (5) combined with diphenyl nitrone to give 32\% of the diastereomeric (3+2) adducts and 18\% of a (3+4) adduct (9). Orbital symmetry forbids the formation of (9) by a concerted [$\pi 4 + \pi 4$] process, therefore the diradical intermediate (6) must be formed. This intermediate, stabilised as a nitroxyl radical and an allyl radical, looks attractive and would give the observed products via 1,5- and 1,7-recombination (Scheme 2).

\begin{center}
\begin{tabular}{ccc}
\textbf{Scheme 2} & & \\
(5) & [ & (6) \\
\end{tabular}
\end{center}
A second limiting case for two-step reaction might be expected when the interaction HO (1,3-Dipole) - LU (Dipolarophile) is strongly dominant in the transition state. This situation would arise when the \(\pi\)-molecular orbital energies of HO (1,3-dipole) and LU (dipolarophile) are similar and those of HO (dipolarophile) and LU (1,3-dipole) are widely different (Figure 2).

\[
\begin{align*}
1,3\text{-Dipole} & \quad \text{TS} & \quad \text{Dipolarophile} \\
\begin{array}{c}
a \quad b \quad c \\
\end{array} & \quad \begin{array}{c}
a \quad b \quad c \\
\end{array} & \quad \begin{array}{c}
d \quad e \\
\end{array}
\end{align*}
\]

\[
\begin{align*}
\Psi_3 \text{ LU} & \quad \Psi_2 \text{ HO} & \quad \Psi_1 \\
\end{align*}
\]

\[\Delta E \gg \Delta E_{\text{II}}\]

\[
\begin{align*}
E_1 &= E_{\Psi_2} - E_{\Psi_3} = \text{HO (1,3-Dipole)} - \text{LU (Dipolarophile)} \\
E &= E_{\Psi_3} - E_{\Psi_3} = \text{HO (Dipolarophile)} - \text{LU (1,3-Dipole)}
\end{align*}
\]

Figure 2
Scheme 3
Further lifting of the $\pi$-molecular orbitals of the 1,3-dipole and/or lowering of those of the dipolarophile will, in extremis, lead to the second interaction energy gain ($\Delta E_{II}$) being negligibly small. $\Delta E_{II}$ will no longer be able to pay the "entropy price" required for the highly ordered transition state for concerted reaction and a unidirectional electron flow will occur leading to a zwitterionic intermediate (11).

\[
\begin{array}{c}
\text{concerted transition state} \\
(10)
\end{array}
\qquad
\begin{array}{c}
\text{zwitterionic transition state} \\
(11)
\end{array}
\]

Huisgen found that aliphatic thiocarbonyl ylides and ethylene derivatives bearing four electron withdrawing substituents provided a reactant pair with widely different molecular orbital energies.

The reaction of 2,4,4,4-tetramethylcyclobutan-1-one-3-thione-S-methylide (12) with dimethyl-2,3-dicyanofumarate gave the cis,trans-isomeric cycloadducts (16) and (17) in 94\% yield and 48:52 ratio. Rotation of the zwitterionic intermediates (14) and (15) were considered responsible for the non-stereospecific course (Scheme 3).
In a further piece of work, Huisgen succeeded in intercepting the zwitterionic intermediate from reaction of the thiocarbonyl ylide (12) and tertracyanoethylene in moist THF as the spiro structure (21) (Scheme 4). Two intermediates (19) and (20) explain formation of the product.

![Scheme 4](image)

A further piece of evidence for this mechanism was provided when an X-ray structure of the intermediate (23) was obtained. In this system the 5-membered ring is more rigid and the trifluoromethyl groups help stabilise the ketene imine structure.
These cases where a stepwise reaction is almost certainly taking place prompted Huisgen to pose the question: "Is it conceivable that all 1,3-dipolar cycloadditions take the two step course and that \( k_{\text{rot}}/k_{\text{cycl}} \) is too small as a rule to allow the detection of the non-stereospecific portion?" In answer to his own question he cites the work of Bihlmaier where the addition of diazomethane to methyl tiglate gave retention of \( > 99.997\% \). This would require \( \Delta G_{\text{rot}} \) to be more than 6.2 kcal mol\(^{-1}\) greater than \( \Delta G_{\text{cycl}} \), a figure which would be difficult to rationalise. Houk, Firestone and co-workers tested the addition of 4-nitrobenzonitrile oxide to cis and trans-dideuteroethylene and observed \( > 98\% \) retention, concluding that the concerted mechanism was the more likely.

It appears then that, despite these highly specialised limiting cases where the reaction undoubtedly follows a stepwise path, the 'normal', stereospecific 1,3-dipolar cycloadditions follow a fundamentally different mechanism involving no intermediates.

Despite the controversy over mechanism the usefulness
of the 1,3-dipolar cycloaddition reaction as a route to five-membered heterocycles has never been questioned. Numerous papers and reviews\textsuperscript{23} have dealt with 1,3-dipolar cycloadditions to alkenes\textsuperscript{2}, alkynes\textsuperscript{24} and other double bonded functional groups\textsuperscript{5}.

1.2.2 \textbf{Intramolecular 1,3-Dipolar Cycloadditions}

In contrast to the extensive literature pertaining to the bimolecular 1,3-dipolar cycloaddition it is only recently that intramolecular examples have started to receive more widespread attention.

Intramolecular 1,3-dipolar cycloadditions require a molecule which contains both 1,3-dipole and dipolarophilic groups. The cyclisation occurs via a [3+2→5] mechanism, as described for the intermolecular case, to form a fused five-membered ring heterocycle.

Lebel and Whang\textsuperscript{25} reported the first example of an intramolecular 1,3-dipolar cycloaddition in 1959. The nitrone (26), prepared either by oxidation of an
N-alkenylhydroxylamine (24) by mercuric oxide or by condensation of an unsaturated aldehyde (25) with N-methylhydroxylamine, gave a fused bicyclic isoxazolidine (27).

Several reviews\textsuperscript{26, 27, 28} of intramolecular cycloadditions have been published and numerous papers have reported the use of this reaction in the synthesis of natural products\textsuperscript{29, 30}. Nitrile ylides, nitrile imines, azomethine imines, azides, diazoalkanes, nitrones, nitrile oxides and carbonyl oxides have all been shown to undergo intramolecular cycloaddition\textsuperscript{27}.

1.2.3 Electrocyclic Reactions

In cases where the 1,3-dipole is in direct conjugation with the dipolarophile there is the possibility of electrocyclic reaction\textsuperscript{31}. An electrocyclic reaction is defined\textsuperscript{32} as one in which an unsaturated system undergoes a ring closure in a process that can be regarded
as a cyclic electron shift, the net result being the conversion of a $\pi$-bond into a $\sigma$-bond. In principle electrocyclisation is a reversible process and cyclic systems can open, via the same energy profile as the ring-closure, to give polyenes.

\[
\begin{array}{c}
\text{C} \\
\Rightarrow \\
\text{C} = \text{C}
\end{array}
\]

Electrocyclisation can occur in both neutral and charged species of various ring sizes$^{32,33}$. Electroyclic processes belong to the class of one-step pericyclic reactions which conform to the principle of conservation of orbital symmetry. The stereochemical course of these reactions may be predicted by inspection of the symmetry of the highest occupied molecular orbital.

1,3-Dipolar electrocyclic reactions fall into three main classes; (i) $4\pi$-1,3-retroelectrocyclisation, (ii) $6\pi$-1,5-electrocyclisation and (iii) $8\pi$-1,7-electrocyclisation.

1,3-Retroelectrocyclisations have been widely used for the generation of 1,3-dipoles, especially nitrile ylides (see later), azomethine ylides (29), via the thermolysis of aziridines (28)$^{34}$, azomethine imines (31) via the thermolysis of diaziridines (30)$^{35}$ and carbonyl ylides
(33) via the thermolysis or photolysis of oxiranes (32)\textsuperscript{36,37} (Figure 3).

![Chemical Structures]

\[ \text{Ph-C=0-C-R} \]

(R2)

\[ \text{R'\textsuperscript{31}C=0-C-R} \]

(R3)

\[ \text{R'\textsuperscript{30}C-O-C\textsuperscript{32}R} \]

(29)

(30)

(31)

(32)

(33)

1,3-Dipoles of both the allenyl-propargyl and the allyl type are capable of 6π-1,5-electrocyclisation when conjugated with a double bond, to form charge free five-membered rings. For example the thermal elimination of nitrogen from N-aroyl or N-acyltetrazoles (34) gives the carbonylnitrile imine (35) which undergoes 1,5-electrocyclisation to 1,3,4-oxadiazoles (36) in excellent yields\textsuperscript{38}. (Scheme 5).
1,5-Electrocyclisation of 1,3-dipoles has been used in the synthesis of many monocyclic and fused unsaturated, aromatic and heteroaromatic systems and has been the subject of major reviews. Of more direct importance to this thesis is the process of 1,7-electrocyclisation of 1,3-dipoles. This type of reaction may compete with 1,5-electrocyclisation when the 1,3-dipole is in conjugation with an $\alpha,\beta:\gamma\delta-$
unsaturated system (37).

These electrocyclisations involve an 8π-electron system and are isoelectronic with the ring closure of the heptatrienyl anion. On the basis of conservation of orbital symmetry these reactions are predicted to proceed, thermally, via a conrotatory ring closure to form seven membered heterocycles (39) → (40).

\[ X = \text{CR}_2; \text{NR}; \text{O} \]
A variety of $\alpha,\beta-\gamma,\delta$-unsaturated 1,3-dipoles have been shown to undergo reactions of this type\textsuperscript{39}.

The first and most thoroughly studied 1,3-dipolar systems found to undergo 1,7-electrocyclisation were diazocompounds. For example, diazoalkanes of the type (42) undergo 1,7-electrocyclisation to give the benzo-diazepines (43)\textsuperscript{40}. The initially formed diazepine undergoes a 1,5-hydrogen migration to give the isolated product (Scheme 6).

\begin{equation*}
\begin{align*}
(41) & \quad \xrightarrow{\Delta} \quad (42) \\
(43) & \quad \xrightarrow{} \\
\end{align*}
\end{equation*}

Scheme 6

Systems of these types have been shown to be sensitive to steric effects in the conjugated system\textsuperscript{41} and also to substituents on the terminus of the double bond. For example\textsuperscript{42}, the diazocompound (44) with $\alpha,\beta; \gamma,\delta$-olefinic
unsaturation, undergoes 1,7-electrocyclisation followed by a [1,5] sigmatropic hydrogen shift when \( R' = H \). When \( R' \neq H \), however, the reaction proceeds via 1,5-electrocyclisation followed by successive [1,5]-vinyl and hydrogen migrations to give the pyrazoles (46) and (47) (Scheme 7).

![Diagram showing the reaction process](image)

**Scheme 7**

When the \( \alpha, \beta \)-unsaturation is aromatic in character, 1,7-electrocyclisation followed by a [1,5]-hydrogen shift again occurs when a *cis* hydrogen is present on the terminal double bond. When no *cis*-hydrogen is present the diazocompound loses nitrogen and reacts to give carbene derived compounds (Scheme 8).
The mechanism of these 1,7-electrocyclisation reactions was postulated by Robertson and Sharp\textsuperscript{42} to proceed via a helical transition state (48). This transition state leads to the minimum distortion of the diazo group from its preferred linear geometry. Recent ab-initio calculations by Houk\textsuperscript{43} have supported this hypothesis.
Most recently this reaction has been used for the preparation of chiral 1H-2,3-benzodiazepines. Harding found that trans-chiral groups at the olefinic terminus of the α,β; γ,δ-unsaturated system (49) induced asymmetry in the transition state, leading to attack 'above' or 'below' the molecular plane (Scheme 9). This asymmetry is maintained in the intermediates (50) and (52) and transferred during the subsequent sigmatropic hydrogen shift to give the chiral products (51) and (53).

Scheme 9
Another 1,3-dipole of the allenyl-propargyl type known to undergo 1,7-electrocyclisation reactions is the nitrile imine system. \( \alpha,\beta; \gamma,\delta \)-Unsaturated nitrile imines, like diazocompounds, give diazepine-type products. For example, treatment of the hydrazoneyl chloride (54) with triethylamine generates the nitrile imine (55). This species undergoes 1,7-electrocyclisation followed by a 1,5-sigmatropic hydrogen shift to give the benzodiazepine (57)\(^{45} \) (Scheme 10).

![Scheme 10](image)

In contrast to diazocompounds, however, these reactions proceed if either of the terminal substituents on the olefinic double bond is hydrogen. That is, \( cis \) and
trans olefinic double bonds will undergo reaction of this type as long as one of the substituents is hydrogen.

The third major class of allenyl-propargyl 1,3-dipoles known to undergo 1,7-electrocyclisation, nitrile ylides, will be discussed in a later section of this thesis.

Of the allyl type 1,3-dipoles only carbonyl ylides have been shown to undergo 1,7-electrocyclisation. The 8π-electrocyclisation reactions of carbonyl ylides have been thoroughly investigated by Eberbach and co-workers46, 47, 48. Thermolysis of butadienyloxiranes (58) gives rise to the carbonyl ylides (59), which may undergo 1,5- or 1,7-electrocyclisation47, 48. 1,7-Electrocyclisation has been observed to occur partially, predominantly or exclusively.
1,7-Electrocyclisation can occur with the participation of one or two aromatic double bonds. For example, the oxirane (62) ring opens to give the carbonyl ylide (63) which then undergoes 1,7-electrocyclisation to the dibenzohydrooxepine (64).

Examination of the HOMO of these systems leads to the prediction of a thermal conrotatory ring closure. In two cases Eberbach has shown that the 8π-ring closure of carbonyl ylides does indeed proceed in this manner.

In some recent work on systems which are basically azomethine oxides in which the γ,δ-unsaturation is an alkyne, Eberbach and Maier have proposed a 1,7-electrocyclisation mechanism as the initial step in the rearrangement of α-butenylnyl substituted pyridine N-oxides (65) to 4-oxo-4H-quinolizines (68) and 2-acylindolizines (69) (Scheme 11).
2. NITRILE YLIDES

2.1 STRUCTURE OF NITRILE YLIDES

Nitrile ylides belong to the class of 1,3-dipoles generally called nitrilium betaines; they are based upon a C-N-C system and have an orthogonal double bond.
Nitrile ylides are the least stable of the classes of nitrilium betaines and are only isolable in a matrix at very low temperature. Under normal reaction conditions their presence can sometimes be observed due to a transient red colour.

The heat of formation of the nitrile ylide (73) was recently determined by La Villa and Goodman. Using photoacoustic calorimetry the heat of formation of the nitrile ylide from the photolysis of diazirine (72) in acetonitrile was determined to be 70.8 ± 10.2 kcalmol⁻¹.

\[
\begin{align*}
\triangleleft \text{N} - \text{N} & \quad \text{hv} \\
\text{CH}_2 & \quad \text{CH}_3\text{CN} \\
(72) & \quad \text{CH}_3\text{C}≡\text{N-CH}_2 (73)
\end{align*}
\]

As mentioned previously the existence of a \( \pi \)-bond in the plane perpendicular to the allyl system generally leads to allenyl-propargyl nitrile ylides adopting a linear conformation. In 1963 Huisgen suggested that, in order to maximise allyl resonance and give maximum overlap for the orthogonal double bond, nitrile ylides would have a preferred linear and planar conformation (76), the bent form (75) being less important.

MO calculations based upon the linear geometry showed the HOMO of nitrile ylides to be heavily localised.
on the methylene terminus (74). Predictions based upon this model, however, always led to the opposite regioisomer to that obtained experimentally.

HOMO of formonitrile methylide from CNDO/2 calculations

Houk concluded that these calculations must, therefore, be wrong and carried out further MO calculations with geometry optimisation. These ab initio calculations indicated that the geometry of the nitrile ylide is appreciably different from the linear-planar conformation suggested by Huisgen. He concluded that the bent nitrile ylide (75) is more stable than the linear structure (76) by 11.1 kcal mol⁻¹ and thus resembles a bent allenyl anion rather than a planar propargyl anion.
Houk's calculations show that the bent nitrile ylide HOMO is now heavily localised at the nitrile terminus (C-1), but still resembles the normal three-orbital, four \( \pi \)-electron system of other 1,3-dipoles, so that concerted cycloadditions can still occur.

The preference for H-C-N bending has been attributed to the mixing of the very high lying HOMO in nitrile ylides with the vacant orbital which is mainly \( \sigma_{C\text{CH}} \) in character.

Figure 4 shows the FMO's and gross heavy atomic charges for the optimised geometry of formonitrile methylide.
The large HOMO coefficient at C-1 makes this the more nucleophilic terminus. Thus the regioselectivity of the cycloadditions to electron deficient alkenes where C-1 adds to the more electrophilic terminus can be accounted for.

The destabilisation of the linear relative to the bent conformation can be compensated for by placing electron withdrawing groups on the methylene (C-3) terminus. This results in the HOMO decreasing in energy and becoming more localised at the C-3 terminus. Thus bending results in less mixing of the HOMO with the $\sigma_{CH}^*$ orbital. This loss of stabilisation is compensated for by the increase in allyl resonance in the planar form. For example bis(trifluoromethyl)benzonitrile ylide adds to electron deficient alkenes to give the opposite regioisomers to those of simple nitrile ylides\textsuperscript{53}. Thus electron acceptors at C-3 stabilise the linear relative to the bent species and electron donors at C-3 favour the bent form.

$\pi$-Acceptor and $\sigma$-donor substituents at C-1 lessen the energy difference between the bent and linear forms as do conjugating groups at this terminus.

2.2 GENERATION

The first reported nitrile ylides\textsuperscript{54} was generated by Huisgen as part of a programme of research into nitrilium betaines. By analogy to the generation of nitrile oxides by treatment of hydroxamic acid chlorides with bases, the
corresponding imidoyl chlorides were expected to form nitrile ylides under similar conditions. Thus \( N-(p\text{-nitro-benzyl})benzimidoyl \) chloride (77) was treated with triethylamine in benzene at 0-20°C to give benzonitrile-\( p\)-nitrophenylmethanide (78) (Scheme 12).

The reaction was accompanied by the precipitation of triethylamine hydrochloride and a transient deep violet colouration, indicating the presence of the intermediate (78). The 1,3-dipolar nature of the intermediate was demonstrated by the formation of cycloadducts when the reaction was carried out in the presence of trapping agents.

The base catalysed dehydrochlorination of imidoyl chlorides represents a general route to nitrile ylides as the synthesis of the starting materials (80) involves a straightforward chlorination of the readily made amides (79) (Scheme 13). The chlorination of the amide may generally be achieved by treatment with thionyl chloride, phosphorus pentachloride or phosgene \(^{55}\).
Other thermal routes to nitrile ylides (81) include (i) the elimination of a phosphoric acid ester from 2,3-dihydro-1,4,2\(\lambda^5\)-oxazaphospholes (83)\(^{56,57}\), (ii) elimination of alkyl thiophosphates from 2,3-dihydro-1,4,2\(\lambda^5\)-thiazaphospholes (84)\(^{58,59}\) and (iii) thermal extrusion of carbon dioxide from 3-oxazolin-5-ones (86)\(^{60}\) (Scheme 14).
Nitrile ylides may also be generated by photochemical means. Two of the thermolytic precursors to nitrile ylides, i.e. 2,3-dihydro-1,4,2\(\lambda^5\)-oxazaphospholes (83) and 3-oxazolin-5-ones (86) also give the nitrile ylide on photolysis. 3-Imino-1-azetidines (85) lose isocyanides to give nitrile ylides photochemically\(^5\). The most thoroughly studied method of nitrile ylide generation is the photolytic ring-opening of 2\(H\)-azirines (82)\(^6\) (Scheme 14).

The reaction was first studied by the group of Schmid\(^6\) while investigating the behaviour of 3,5-diaryl-2-isoxazolines (87) under photolytic conditions. Upon irradiation these compounds undergo ring contraction to form the 2\(H\)-azirine (88) and benzaldehyde. The 2\(H\)-azirine then ring-opens, by a 1,3-dipolar cycloreversion, to the nitrile ylide (89) which reacts with the extruded benzaldehyde to form the 4,5-diaryl-3-oxazolines (90) (Scheme 15).

\[\text{(87)} \xrightarrow{h\nu} \text{(88)} + \text{PhCHO} \]

\[\text{(89)} \xrightarrow{h\nu} \text{(90)} \]

Scheme 15
The generation of nitrile ylides by the photolysis of 2H-azirines has since been thoroughly investigated and is the subject of a comprehensive review\textsuperscript{61}. The usefulness of this approach stems from the fact that a wide range of substituted 2H-azirines (91) are available by photolysis of vinyl azides\textsuperscript{63} or by the modified Neber reaction\textsuperscript{64} (Scheme 16).
The presence of benzonitrile benzylide (92) from the photolysis of 2,3-diphenyl-2H-azirine (91) in a glassy matrix at \(-196^\circ\text{C}\) was demonstrated by the U.V. absorption at 344 nm\(^{50}\). This absorption decreased on warming to \(-160^\circ\text{C}\) in the presence of methyl trifluoroacetate due to the formation of a cycloadduct (93) (Scheme 17).

\[
\begin{align*}
\text{(91)} && 
\text{(92)} & \xrightarrow{\text{h}^+} \text{CF}_3\text{CO}_2\text{Me} & \rightarrow \text{(93)} \\
\text{(94)} && 
\text{(95)} \xrightarrow{\text{CF}_3\text{CO}_2\text{Me}} \\
\text{(96)} && 
\text{(97)} \\
\end{align*}
\]

Scheme 17
The above scheme also shows some of the other possible reactions of nitrile ylides. The formation of the bicyclic product (94) results from the \([3+2\rightarrow 5]\) cycloaddition of the nitrile ylide with the \(2\text{H}-\text{azirine}\) precursor (91). This product then ring-opens to the zwitterion (95) which ring-opens to the dimer (96). The dimer (96) may also be formed directly from the nitrile ylide via a head-to-head dimerisation reaction. The dimer can then undergo electrocyclic ring closure with subsequent oxidation to the pyrazine (97).

Reactions of nitrile ylides will be discussed more fully in the following section.

2.3 REACTIONS OF NITRILE YLIDES

2.3.1 Intermolecular Reactions of Nitrile Ylides

Nitrile ylides undergo typical 1,3-dipolar reactions such as dimerisation\(^5\),\(^6\) and \([2+3]\) cycloadditions to multiple bonds to form five-membered heterocycles\(^6\),\(^4\) (Scheme 17). Since the discovery of nitrile ylides by Huisgen\(^4\) a large number of their cycloadditions have been reported. The regioselectivities exhibited in these reactions can be explained by frontier molecular orbital theory.

The 1,3-dipolar cycloaddition reactions of nitrile ylides with all dipolarophiles, except the very electron rich, are HOMO controlled according to Sustmann’s classification\(^1\). That is, the dominant frontier orbital
interaction is that between the 1,3-dipole HOMO and the dipolarophile LUMO. This explains the reactivity of nitrile ylides towards electron-deficient multiple bonds. Dipolarophiles of this type have LUMOs which are lower in energy and which can, therefore, mix better with the nitrile ylide HOMO.

Substituents on the nitrile (C-1) terminus have been shown to have little effect on the HO-LU separation of nitrile ylides and therefore have no substantial reactivity or regioselectivity effect on the reaction with electron deficient double bonds. Substitution at the methylene (C-3) terminus, however, does affect both regioselectivity and reaction rate. Substituents which lower the dipole HO i.e. electron-withdrawing or conjugating groups, lead to slower reaction of the nitrile ylide. Electron-withdrawing groups at the C-3 terminus affect the regioselectivity of the nitrile ylide cyclo-addition by making the energy difference between the bent and linear configurations much smaller, as explained earlier. For example, Burger found that two trifluoromethyl groups on the methylene carbon of the nitrile ylide (98) gave a mixture of regioisomers in the reaction with phenyl vinyl ether (Scheme 18).
Increasing the LU energy of the dipolarophile through electron donating substituents suppresses the rate of 1,3-dipolar cycloaddition whereas electron-withdrawing or conjugating groups on the dipolarophile lower the LU energy and accelerate cycloaddition\textsuperscript{67, 68}.

Substituted dipolarophiles also affect the regioselectivity of cycloaddition. In unsymmetrically substituted dipolarophiles with electron-withdrawing or conjugated substituents at only one end, the larger coefficient in the LUMO is at the dipolarophile terminus remote from the substituents. As described earlier, the preferred mode of reaction involves attachment of the dipole and dipolarophile termini with the larger coefficients. Thus, in the reaction of nitrile ylide (99) with acrylonitrile the C-1 terminus of the 1,3-dipole becomes attached to the unsubstituted end of the dipolarophile\textsuperscript{2}. 
Nitrile ylides have also been reported to undergo 1,3-dipolar cycloaddition with C=S, C=N, C=O and cumulated double bonds as well as with carbon-carbon triple bonds to give pyrroles.

Reactions of nitrile ylides with E and Z alkenes have shown that the reaction is stereospecific, with the stereochemistry of the alkene being retained in the product. This provides strong evidence for the proposed concerted mechanism. For example, photolysis of 2,3-diphenylazirine (91) gave the nitrile ylide (92) which, on reaction with dimethyl fumarate gave only two of the four possible pyrroles (101) and (102) (Scheme 19).
Kinetic studies of the stereoselective addition of 1,3-dipoles to $E$ and $Z$ alkenes indicate a higher reactivity for the trans-isomers. This fact has been attributed to two factors. Firstly a steric hindrance of resonance in the cis-form caused by the two cis-substituents. This hindrance of resonance weakens the activating effect of electron-withdrawing and conjugating substituents towards cycloaddition.

The second and more important factor involves steric effects during the reaction itself. During the concerted addition of the 1,3-dipole, hybridization of the central carbon atoms of the olefinic dipolarophile changes gradually from $sp^2$ to $sp^3$. Even though this results in a
lengthening of the olefin C-C bond, the resulting shrinkage of the bond angles from 120° to 109° causes considerable compression of the Van der Waals radii of the eclipsed cis-substituents (Figure 5). This increase in Van der Waals repulsion during the activation process leads to an increase in activation energy from which the trans-isomer does not suffer.

![Figure 5](image)

The mechanism of the 1,3-dipolar cycloaddition of nitrile ylides has been proposed to proceed via a "parallel-planes" transition state. That is, the 1,3-dipole and dipolarophile approach each other to form a two-plane orientation complex² (Figure 6).
During the activation process the "linear" bond system of the nitrile ylide must bend in order to place the termini in contact with the termini of the $\pi$-bond system in the dipolarophile. This involves disruption of the orthogonal double bond, but leaves the allylic $\pi$-system intact. The loss of $\pi$-bond energy is partly compensated for by a gain in stabilisation resulting from rehybridisation and accommodation of a lone-pair of electrons in an orbital of high $s$-character.

During the reaction the nitrile ylide nitrogen moves upwards, as shown in Figure 6, to become coplanar with the four carbon atoms in the product. This explains why the rate of addition to triple bonds does not profit from the aromatic resonance of the product. The new $p$-orbitals which later become part of the aromatic $\pi$-system are...
insufficiently developed in the transition state to affect the activation energy.

Huisgen demonstrated experimentally that the "parallel-planes" transition state rather than the alternative planar transition state was general to all 1,3-dipolar cycloadditions. \( \psi \)-Oxazolone (103) reacts with dipolarophiles, showing all the characteristics of normal 1,3-dipolar cycloaddition. As a planar aromatic structure only the "parallel-planes" orientation is possible in the transition state.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
R^1 & \quad + \quad R \\
\text{R}^2 & \\
(103)
\end{align*}
\]

2.3.2 Intramolecular Reactions of Nitrile Ylides

As discussed previously 1,3-dipolar cycloadditions proceed via a "parallel-planes" transition state. In molecules which contain both a nitrile ylide and a dipolarophilic moiety, normal 1,3-dipolar cycloaddition may take place if the two groups can attain this geometry. For example photolysis of the azirine (104) gives the expected cycloadduct (105) in good yield.\(^2\)
If this approach geometry cannot be attained then a different mode of reaction becomes dominant.

Houk's calculations\sup{52} have shown that, for the bent nitrile ylide geometry, the HOMO and LUMO bear a strong resemblance to the HOMO and LUMO of a singlet carbene (Figure 7).

\begin{align*}
\text{Nitrile Ylide} & \quad \text{Carbene} \\
\text{Diagram 1} & \quad \text{Diagram 2} \\
\text{Diagram 3} & \quad \text{Diagram 4}
\end{align*}

\textbf{Figure 7}
Since singlet carbenes readily react with double bonds then an analogous 1,1-cycloaddition of nitrile ylides with double bonds might be expected. This type of reaction was first observed by Padwa and Carlsen in 1975. When a deaerated solution of 2-allyl-2-methyl-3-phenyl-2H-azirine (106) was irradiated in cyclohexane with light of wavelength > 280 nm, an extremely rapid and clean conversion to 3-methyl-1-phenyl-2-azabicyclo[3.1.0]-hex-2-ene (109) was observed (Scheme 20).

\[
\begin{align*}
\text{Ph-C} & \equiv \text{N} \rightarrow \text{C} & \equiv \text{Me} \\
& \text{(a) (107)} \\
\text{Ph-C} & \equiv \text{N} \rightarrow \text{C} & \equiv \text{Me} \\
& \text{(b) (109)} \\
\text{MeO}_2\text{CC} & \equiv \text{CCO}_2\text{Me} \\
& \text{(108) (109) (110)} \\
\end{align*}
\]

Scheme 20
The intermediacy of the nitrile ylide (107) in this process was demonstrated by trapping with a reactive dipolarophile. For example when carried out in the presence of acetylenedicarboxylate the 1,1-cycloaddition was entirely suppressed and only the cycloadduct (108) derived from 1,3-dipolar cycloaddition was isolated.

Reactions of this type can be empirically understood by invoking the carbene-like resonance hybrid (107b) of the nitrile ylide as the reacting species in 1,1-cycloadditions.

Numerous examples of isolable 1,1-cycloadducts have been reported. For example photolysis of o-allyloxyphenyl substituted 2H-azirines results in two different modes of reaction taking place\(^3\) (Scheme 21).

The dimethyl nitrile ylide (112, \(R=R'=\text{CH}_3\)) reacts exclusively by 1,1-cycloaddition to give the cycloadduct (115, \(R=R'=\text{CH}_3\)) in very high yield. The dihydro analogue (112, \(R=R'=\text{H}\)), on the other hand, undergoes 1,3-dipolar cycloaddition to give (114, \(R=R'=\text{H}\)) as the major product. The monomethyl analogue (112, \(R=\text{H}, R'=\text{CH}_3\)) gives a mixture of 1,1- and 1,3-cycloadducts.

In all three cases the intermediacy of the nitrile ylide was demonstrated by trapping with methyl acrylate to give the intermolecular [3+2] cycloadduct (113) (Scheme 21).
These results can be rationalised in terms of the electron-donating effect of the methyl groups destabilising the linear form of the nitrile ylide. The
resultant bending of the nitrile ylide causes C-1 to become carbene-like and promotes 1,1-cycloaddition. The carbene-like reactivity of nitrile ylides arises when the parallel-planes complex required for 1,3-dipolar cycloaddition cannot be attained. The two-plane transition state requires a high degree of order, and geometric constraints may prevent the four centres required for reaction from coming together with the required geometry. The transition-state for 1,1-cycloaddition has lower geometric requirements as only three centres are involved. Thus geometric constraints make the 1,1-cycloaddition competitive by disfavouring the 1,3-dipolar cycloaddition.

In 1977 Padwa and Carlsen proposed a stepwise carbenic reaction of allyl-substituted nitrile ylides to explain the fact that the reaction gave a mixture of products (Scheme 22).

It was suggested that photolysis of the azirine led to formation of the nitrile ylide. Prevented by geometric constraints from reacting via 1,3-dipolar cycloaddition the nitrile ylide reacts by the 1,1-cycloaddition route. Padwa proposed that attack of the carbene carbon of the dipole at the terminal position of the allyl double bond generated a six-membered intermediate. Subsequent collapse of this intermediate was proposed to give the mixture of 2-azabicyclohexene products and (120).
The "non-concertedness" of this reaction was surprising given that singlet carbenes undergo concerted cycloaddition with olefins\textsuperscript{75}. That the reaction is, in
fact, concerted was demonstrated by Fischer and Steglich\textsuperscript{76}, who generated analogous nitrile ylides by thermal methods. Thus, thermolysis of the 3-oxazolin-5-one (121) gave the nitrile ylide (122). This reacted via 1,1-cycloaddition to give the 2-azabicyclo[3.1.0]hexene (123) with total retention of stereochemistry, confirming that the reaction is, in fact, concerted. Subsequent irradiation of the product caused an equilibrium of the endo- and exo-isomers to be set-up, thus accounting for the product mixture observed by Padwa (Scheme 23).

\[ \text{Scheme 23} \]
Sharp\textsuperscript{27} also found that the nitrile ylides (125) generated by dehydrochlorination of the imidoyl chloride (124) underwent reaction which gave the products expected from a concerted 1,1-cycloaddition. In all cases there was complete retention of stereochemistry, consistent with a concerted reaction. The nitrile ylide (125), however, possesses an $\alpha,\beta:\gamma,\delta$-conjugated system and it is possible that the reaction proceeds via 1,7-electrocyclisation to give the benzazepine (126), which rapidly ring-collapses to the cycloprop[c]isoquinoline (127) (Scheme 24).

\begin{align*}
\begin{array}{c}
\text{Scheme 24}
\end{array}
\end{align*}
The mode of intramolecular cycloaddition also depends on substituents\textsuperscript{61,78}. For example nitrile ylide (128, \( R=\text{Me} \)) reacts cleanly via 1,1-cycloaddition to give (129), but the presence of electron withdrawing groups on the double bond (128, \( R=\text{CO}_2\text{Me} \)) leads to a switch in mechanism with (130, \( R=\text{CO}_2\text{Me} \)) being the only isolated product\textsuperscript{61} (Scheme 25).

![Scheme 25](image-url)
This effect is explicable in terms of the electron-withdrawing group \((R=\text{CO}_2\text{Me})\) causing a lowering of the dipolarophile LUMO energy and making 1,3-dipolar cycloaddition the more favourable route.

The dual reactivity of nitrile ylides in intramolecular cycloadditions, as demonstrated by the above reactions, can be explained by the flexibility of the 1,3-dipole.

The linear form is understood to be the species which reacts in 1,3-dipolar cycloadditions via a transition state which involves bending of the 1,3-dipole, whereas the bent form is responsible for the carbene-like 1,1-cycloadditions. The ability to bend and rehybridise with only a small energy demand is crucial for the attainment of the transition-state geometries required for both 1,1- and 1,3-cycloaddition.

2.3.3 Electrocyclisation Reactions of Nitrile Ylides

2.3.3.1 1,5-Electrocyclisation Reactions of Nitrile Ylides

Conjugated nitrile ylides of the type \((131)\) are isoelectronic with the pentadienyl anion. This system is known to undergo disrotatory electrocyclisation to the cyclopentenyl anion, therefore the analogous reaction of the nitrile ylide might be expected to give products of the type \((132)\).
1,5-Electrocyclisation reactions of nitrile ylides have been covered in two major reviews on 1,3-dipolar electrocyclisations.

The first 1,5-electrocyclisation of a nitrile ylide was reported by Singh and Ullman in 1967. They observed the photochemically induced ring contraction of 3,5-diphenylisoxazole (133) to 3-phenyl-2-benzoyl-2H-azirine. On irradiation with light of wavelength 3130Å or less the azirine ring opens to the carbonyl nitrile ylide which undergoes 1,5-electrocyclisation to give the oxazole (134) (Scheme 26).

Scheme 26
Numerous other examples of photochemical transformations of isoxazoles into oxazoles via nitrile ylides are known and have been reviewed.\textsuperscript{39}

Photolysis of 3-vinyl-1-azirines (135) gives vinyl substituted nitrile ylides which undergo 1,5-electrocyclisation to give pyrrole products (138).\textsuperscript{80} These reactions are the most thoroughly studied 1,5-electrocyclisations of nitrile ylides. The initial product of electrocyclisation gives the pyrrole (138) by a 1,3-hydrogen migration (Scheme 27).

It should be noted that, although azirines also give pyrrole products (139) on thermolysis, these products are formed via a vinylnitrene intermediate (137) and not a nitrile ylide (Scheme 27).
Iminonitrile ylides are also accessible from substituted azirine systems and these also undergo 1,5-electrocyclisation\textsuperscript{39, 81}. For example imines (141), available from the condensation of amines with 2-phenyl-3-formyl-1-azirine (140), on photolysis give imidazoles (144) via 1,5-electrocyclisation. Once again thermal treatment of the azirine (141) gives the pyrazole (143) via a nitrene intermediate (Scheme 28).

\begin{align*}
\text{Ph} & \text{CHO} \quad \text{RNH}_2 \\
(140) & \\
\text{Ph} & \text{CH=NR} \\
(141) & \\
\Delta & \\
\text{Ph-CN-CH} & \\
(142) & \\
\text{Ph} & \text{NR} \\
(143) & \\
\text{Ph} & \text{NR} \\
(144) & \\
\text{Scheme 28}
\end{align*}
An interesting competition between 1,5-electrocyclisation to carbon or oxygen was observed in nitrile ylides of the type (146). Generated from the corresponding azirine (145) it was found that cyclisation occurred exclusively to oxygen. The alternative pyrrole product (148) was not observed (Scheme 29).

Scheme 29
Finally, vinylnitrile ylides can be trapped with external dipolarophiles, indicating a relatively large activation energy for 1,5-electrocyclisation relative to 1,3-dipolar cycloaddition. On the other hand carbonyl-nitrile ylides can only be intercepted in exceptional circumstances. Thus the activation energy for 1,5-electrocyclisation onto a carbonyl function is much lower, in agreement with the result of the competition experiment above.

2.3.3.2 1,7-Electrocyclisation Reactions of Nitrile Ylides

Nitrile ylides of the type (149) which possess $\alpha,\beta:\gamma,\delta$-conjugation are isoelectronic with the heptatrienyl anion. This system is known to undergo thermal conrotatory electrocyclisation to the cycloheptadienyl anion, therefore the analogous reaction of the nitrile ylide would be expected to give products of the type (150).

\[
\begin{array}{c}
\begin{array}{c}
R^1 \\
R \\
C=\text{N} \equiv C-R^3 \\
\vdots \\
X \\
\end{array}
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
\begin{array}{c}
R^1 \\
R^2 \\
N \equiv X \\
\vdots \\
R^3 \\
\end{array}
\end{array}
\]

\((149) \quad (150)\)

$X = \text{CR}_2; \text{NR}; \text{O}$
Padwa and co-workers\textsuperscript{80} found that irradiation of (Z)-3-phenyl-2-styryl-2\textsubscript{H}-azirine (151) in benzene gave rise to one major product (80\%) which was identified as 1-phenyl-3\textsubscript{H}-2-benzazepine (154). The formation of this product was explained in terms of a 1,7-electrocyclisation of the nitrile ylide (152) followed by a [1,5] sigmatropic hydrogen shift (Scheme 30).
Photolysis of the corresponding (E)-azirine (156), on the other hand, proceeded via a 1,5-electrocyclisation to give 2,3-diphenylpyrrole (157) as the major product. This product was also identified as a minor component of the reaction mixture derived from the (Z)-azirine.

These results were explained in terms of the transition-state for 1,7-electrocyclisation being more easily attained than that for 1,5-electrocyclisation when both are possible. For the nitrile ylide derived from the (E)-isomer the 1,7-electrocyclisation transition-state is geometrically impossible and the reaction proceeds by 1,5-electrocyclisation.

Photolysis of the (Z)-azirine in the presence of methanol substantially retarded the formation of the benzazepine (154). Under these conditions the major product isolated (90%) was \(N-(1\text{-methoxy-3-phenyl-2-propylidene})\)benzalimine (155). The formation of the methanol adduct strongly supports the intermediacy of the nitrile ylide (152) (Scheme 30).
Photolysis of the bicyclic isoxazoline (158) is believed to involve the intermediacy of the (Z)-azirine (159). This species could not be isolated but ring-opens to the nitrile ylide (160). The 1,7-electrocyclisation of this nitrile ylide gives 2-phenyl-1,3-oxazepine (161)$^{83}$ (Scheme 31).

In recent years the scope of the 1,7-electrocyclisations of nitrile ylides has been broadened by the work of Sharp and co-workers.

Nitrile ylides of the type (163), thermally generated
via the 1,3-dehydrochlorination of imidoyl chlorides (162) were shown to undergo 1,7-electrocyclisation to give dibenz[c,e]azepines (165)\(^8\) (Scheme 32).

Further work studying the directive effects of substituents on the 1,7-electrocyclisation used nitrile ylides of the type (167)\(^8\). Two isomeric benzazepines (168 a,b) were formed and their ratio calculated (Scheme...
The versatility of 1,7-electrocyclisation reactions of nitrile ylides of this type was extended by incorporation of the thiophene nucleus into the $\alpha,\beta;\gamma,\delta$-unsaturated system. Nitrile ylides of the types (169), (170) and (171) were all shown to give the products expected from 1,7-electrocyclisation (172), (173) and (174) respectively (Scheme 34).
Scheme 34

It is not absolutely clear, however, whether these products derive directly from the 1,7-electrocyclisation reaction followed by 1,5-hydrogen migration or from the 1,1-cycloaddition of the nitrile ylide across the olefinic
The same question applies to the reaction of nitrile ylides of the type (175). Here the isolated products (177) are those formally derived from 1,1-cycloaddition (Scheme 35).

Most recently Sharp and Reece have generated the nitrile ylides (178) and (179), which have been observed to undergo 1,7-electrocyclisation to give the products (180) and (181) (Scheme 36). This represents the first
electrocyclisation of a nitrile ylide onto a heterocyclic moiety.

![Scheme 36](image)

3. **REACTIVITY IN PERICYCLIC SYSTEMS**

In order to maximise the utility of any reaction, it is essential to develop an understanding of the factors
which affect rate and reactivity. An understanding of these factors enables the scope of the reaction to be broadened and also provides insight into the reaction mechanism.

Over the years much work has been done in trying to understand the factors governing reactivity in pericyclic systems. This will now be discussed under two general headings.

3.1 **PERICYCLIC CYCLOADDITION REACTIONS**

This section shall deal with two of the most useful and versatile reactions known to the organic chemist, the Diels-Alder reaction and the 1,3-dipolar cycloaddition reaction.

Many parallels exist between these two reactions. Firstly, individual cases of each have been known for almost a century, however, it was many years before their generality was recognised. In the case of the Diels-Alder reaction this generality was discovered through the work of Diels and Alder in the 1920's. The vast scope of 1,3-dipolar cycloaddition chemistry was demonstrated by Huisgen in the 1960's.

At a more fundamental level, however, the reactions are both 6π-electron pericyclic reactions, the Diels-Alder being a [4+2]6π- and 1,3-dipolar cycloaddition a [3+2]6π-reaction.
Both reactions involve the formal conversion of \(2\pi\)-bonds into \(2\sigma\)-bonds during a ring closure mechanism. The reactions are generally high yielding and show certain peculiarities in their activation parameters. Low activation energies accompanied by high negative values of activation entropy indicate the requirement of highly organised transition states.

The rates of both reaction types are not much affected by solvent polarity, indicating that the transition states are not much different from the reactants in terms of polarity. Both reactions are stereospecific, with stereochemistry of the reactants being maintained in the product.

All of these observations are consistent with the concerted mechanism generally accepted for both reactions. The mechanism of 1,3-dipolar cycloaddition was discussed in an earlier section of this thesis (Section 1.2.1). As it is generally accepted that the Diels-Alder reaction
follows an exactly analogous mechanism, this will not be discussed in any great detail here.

Suffice to say that both reactions involve a parallel-planes transition state with concerted bond formation at both termini (182) and (183).

The reactivity of pericyclic cycloadditions of these types defied understanding for many years. It was not until the work of Sustmann\textsuperscript{15} in 1971 that a rationale for the observed reactivity of these systems became available.

Sustmann proposed a simple HMO-perturbational model which elegantly explained the effects of substituents on these pericyclic cycloadditions. Using perturbation theory to assess the effects of substituents on the energies of the frontier molecular orbitals of both reactants a simple model for predicting the effect of substituents on reaction rate was developed.

Molecular orbital theory states that the overall
energy change, $\Delta E$, for the reaction of molecules $r$ and $s$ may be defined:

$$\Delta E = \left\langle \begin{array}{c} r_s \\ \text{occ} \\ \text{unocc} \\ \text{occ} \\ \text{unocc} \end{array} \right\rangle - \left\langle \begin{array}{c} r_s \\ \text{occ} \\ \text{unocc} \\ \text{unocc} \end{array} \right\rangle \frac{2(\Sigma_{ab}C_{ra}C_{sb}\beta_{ab})^2}{E_r - E_s}$$

where $r, s = \text{reactant molecules}$
- $a = \text{bond forming centres of } r$
- $b = \text{bond forming centres of } s$
- $c = \text{atomic orbital coefficients at } a \text{ and } b$
- $\beta = \text{resonance integral, reflecting the}$
  \text{efficiency of m.o. overlap}$

$E_r, E_s = \text{energies of the interacting pairs of m.o.s.}$

This rather complex equation simply defines the change in energy of the two reactant systems resulting from all of the possible interactions between occupied and unoccupied orbitals.

Fukui$^{13}$ recognised that the frontier M.O.s would contribute most to the energy change and that a good approximation could be made by considering only the HOMOs and LUMOs of the reactant pair.

The restriction to F.M.O.s simplifies the previous equation, thus, for 1,3-dipolar cycloaddition the equation becomes:

$$\Delta E = \frac{[C_aC'd\beta_{ad} + C_C'C_e\beta_{ce}]^2}{E_I} + \frac{[C'aC'd\beta_{ad} + C'C_Ce\beta_{ce}]^2}{E_{II}}$$
where
\[ E_I = E_{HO}(\text{dipole}) - E_{LU}(\text{dipolarophile}) \]
\[ E_{II} = E_{HO}(\text{dipolarophile}) - E_{LU}(\text{dipole}) \]
\[ C_x = \text{orbital coefficient of HO at atom } x \]
\[ C'_x = \text{orbital coefficient of LU at atom } x \]
\[ \beta = \text{resonance integral at new } \sigma\text{-bond} \]

An exactly analogous equation applies to the Diels-Alder reaction. From this equation we can see that \( \Delta E \) is inversely proportional to the difference in energy between each interacting HO-LU pair. That is, if the HO and LU are close in energy the denominator will be small and the overall term large. Conversely, if the HO and LU are widely separated in energy the denominator becomes large and the overall term tends to zero. This leads to the important conclusion that the interacting pair closer in energy provides the dominant interaction.

The relationship between stabilisation (\( \Delta E \)) and the energy difference between the interacting HOMOs and LUMOs (\( E_I \) and \( E_{II} \)) can best be demonstrated in a molecular orbital diagram. For example the Diels-Alder reaction can be represented as shown (Figure 8).
Thus, when $E_I$ is small, the resulting stabilisation, $\Delta E_I$, is large. $E_{II}$, however, is much larger and the stabilisation due to the $LU$(diene)$-HO$(dienophile) interaction, $\Delta E_{II}$, is much smaller.

Sustmann rationalised observed reaction rates in terms of interactions of these types. By observing that three types of dienophile/diene (or dipolarophile/dipole) interaction are possible (Figure 9), three different types of reactivity were uncovered.

The three types of interaction are shown in Figure 9:
In each case the major interaction(s) is shown by an arrow. By considering the effect of substituents upon these interactions we can assess their effect upon reactivity. We shall now consider the three types in turn.

**Type I.** A system of this type involves a diene or 1,3-dipole (henceforth generically called $4\pi$-systems) of higher energy than the dienophile or dipolarophile ($2\pi$-systems). The major stabilising interaction in this case is that between the HO($4\pi$) and LU($2\pi$). The other interaction, LU($4\pi$)/HO($2\pi$) is also stabilising, but to a much lesser extent.

The introduction of substituents into either or both of the reagents will affect these interactions. First consider substituents in the $4\pi$-system.
Electron withdrawing substituents lead to a lowering of both the HO and LU energies. This results in the major interaction HO(4\pi)-LU(2\pi) becoming smaller. A concomitant increase in the LU(4\pi)-HO(2\pi) interaction also results, but due to inverse proportionality does not compensate fully for the loss of stabilisation from the major interaction. This leads to the prediction that electron-withdrawing groups on the 4\pi-system in a type I reaction will retard the reaction.

Electron donating substituents in the 4\pi-system act to raise both the HO and LU. Thus, the major interaction becomes more stabilising, this time by more than the minor interaction is destabilised. Electron donors in the 4\pi-system are therefore predicted to accelerate the reaction.

Conjugating substituents act to raise the HO and lower the LU. This leads to both major and minor interactions become more stabilising and an increased rate is predicted.

The type of behaviour described above is that shown by dienes in the normal Diels-Alder reaction\textsuperscript{1}. 1,3-Dipoles exhibiting behaviour of this type are those with high lying HO/LU energies, such as diazoalkanes\textsuperscript{89} and nitrile ylides\textsuperscript{70}. We may therefore conclude that the Diels-Alder reaction and the 1,3-dipolar cycloaddition reactions of these 1,3-dipoles involve type I interactions.

The same treatment may be applied to the effect of substituents on the 2\pi-system. Thus, electron donors
diminish $\text{HO}(4\pi)/\text{LU}(2\pi)$ by more than they increase the $\text{LU}(4\pi)/\text{HO}(2\pi)$ interaction and will therefore slow the reaction. Electron-acceptors will increase the major by more than it diminishes the minor interaction and will enhance reaction rate. Conjugating substituents again enhance both interactions and are predicted to increase reactivity.

These effects are again observed experimentally in reactions with the $4\pi$-systems mentioned above.

We would therefore predict that in type I reactions the greatest rate will be observed when an electron-rich $4\pi$-system reacts with an electron-poor $2\pi$-system.

It is known that the Diels-Alder reaction proceeds most smoothly when the components are electron-rich or conjugated dienes and electron-poor or conjugated dienophiles' in line with this prediction. Nitrile ylides react very quickly with electron-poor or conjugated alkenes, but react sluggishly or not at all with electron rich double bonds.

**TYPE II.** In type II systems both of the $\text{HO}/\text{LU}$ interactions are of similar magnitude.
As shown in Figure 10, \( E_1E_1 \) results in \( \Delta E_1=\Delta E_{II} \). The introduction of substituents, however, causes this to change. Again we will first consider substitution in the 4\( \pi \)-system.

Electron-withdrawing substituents lower both HO and LU. Thus \( E_1 \) decreases and \( E_{II} \) increases. Again, due to inverse proportionality, this leads to \( \Delta E_1 \), the stabilisation derived from the LU(4\( \pi \))/HO(2\( \pi \)) interaction, increasing by more than \( \Delta E_{II} \) decreases. A rate increase is therefore predicted.

Electron donors raise both HO(4\( \pi \)) and LU(4\( \pi \)). In this case \( \Delta E_{II} \) increases to more than compensate for the decrease in \( \Delta E_1 \). An increased rate is again predicted.

Conjugating substituents decrease \( E_1 \) and \( E_{II} \), leading to an increase in both \( \Delta E_1 \) and \( \Delta E_{II} \). Once again an increase in rate is predicted.

It seems, therefore, that any type of substitution in the 4\( \pi \)-system will lead to an increase in the rate of cycloaddition and a U-shaped reactivity curve is
predicted, with a rate minimum for the unsubstituted system.

A similar treatment of the effect of substituents in the 2π-system leads to the same prediction. That is, all substituent types will accelerate the reaction.

This type of behaviour is exhibited in the cycloaddition reactions of several 1,3-dipoles. For example, phenyl azide shows a U-shaped reactivity curve in its reactions with monosubstituted ethylenes\(^9\) (Figure 11).

\[ \text{Ph-N=N=N} \quad + \quad \text{R} \equiv \text{R}' \quad \rightarrow \quad \text{Ph} \quad \text{N} \quad \text{N} \quad \text{R} \quad \text{R}' \quad \text{N} \quad \text{Ph} \]

**Figure 11**
This behaviour has also been exhibited by, for example, diphenylnitrile imine (184)\textsuperscript{91}, benzonitrile oxide (185)\textsuperscript{92}, azomethine imine (186)\textsuperscript{93} and 1,3-dicyano-1,3-diphenylcarbonyl ylide (187)\textsuperscript{37}.

\begin{align*}
\begin{array}{c}
\text{C} & \text{N} & \text{N} \\
\text{C} & \text{N} & \text{N} \\
\end{array} & \quad \begin{array}{c}
\text{C} & \text{N} & \text{N} \\
\text{C} & \text{N} & \text{N} \\
\end{array} \\
(184) & \quad (185)
\end{align*}

A Hammett plot of the Diels-Alder reactions of phenacyclones (188) with substituted styrenes (189) reveals an example of a Diels-Alder reaction showing this type II reactivity (Figure 12).
TYPE III. Cycloaddition reactions involving type III systems show behaviour opposite to that exhibited by type I systems. This is readily rationalised by inspection of the M.O. diagrams of the two systems (Figure 13).
As can be seen from this figure, the M.O. diagrams for types I and III are virtually mirror images of each other. In type III the $2\pi$-system is of higher energy than the $4\pi$-system and the major interaction is LU($4\pi$)/HO($2\pi$). That is, $E_{II}$ is small ($\Delta E_{II}$ large) and $E_I$ is large ($\Delta E_I$ small), the opposite of the interactions for type I.

Thus, substitution of a type III system will be expected to show reverse effects to those shown by type I.

Substitution of the $4\pi$-system with electron donors
will reduce the major interaction by more than it stabilises the minor \((HO(4\pi)/LU(2\pi))\) and will slow the reaction. Electron withdrawing substituents will increase the major interaction and enhance the rate. Once again, conjugating substituents, which raise the HOMO and lower the LUMO, will stabilise both interactions and are predicted to make the reaction faster.

A similar treatment of the \(2\pi\)-system predicts that electron-rich and conjugated double bonds should enhance rate while electron-poor double bond will react more slowly.

Two 1,3-dipolar systems displaying the behaviour described above are known. Ozone reacts with olefins by 1,3-dipolar cycloaddition to give 1,2,3-trioxolanes (190) as the first step of the ozonolysis reaction. Although substitution of ozone is not feasible, this system shows a very high affinity for electron-rich double bonds\(^9\). Tetraethylethylene reacts with ozone 200,000 times faster than does tetrachloroethylene.

\[
\begin{align*}
&\text{O} \\
&\text{O} \\
&\text{+} \\
&R_2C\equiv\text{CR}_2
\end{align*}
\]

\[
\begin{align*}
&\text{O} \\
&\text{O} \\
&\text{R}_2\text{C}=\text{CR}_2
\end{align*}
\]

\[
\begin{align*}
&\text{O} \\
&\text{O} \\
&R_2\text{C}=\text{CR}_2
\end{align*}
\]

\[
\begin{align*}
&\text{R}=\text{Cl}; k_{rel}=1 \\
&\text{R}=\text{Me}; k_{rel}=200,000
\end{align*}
\]
The other 1,3-dipole showing this type of behaviour is nitrous oxide \((\text{N}^+\text{N}^-\text{O}^-)\). Again this system is incapable of substitution, but shows a marked preference for electron-rich or conjugated double bonds.

Examples of Diels-Alder reactions showing the substituent effects described above have been known for many years. Generically named "Diels-Alder reactions with inverse electron demand", the behaviour of these systems was not clearly understood until the advent of Sustmann's P.M.O. treatment.

This behaviour occurs in systems where the diene component of the reaction is very electron-poor. For example, hexachloropentadiene reacts over 50 times faster with \(p\)-methoxystyrene than with maleic anhydride'. This affinity for electron-rich double bonds is in contrast to the normal preference for electron-poor dienophiles.

Sustmann's treatment elegantly explains this apparently anomalous reactivity. As described previously "normal" Diels-Alder reactions are type I, i.e. the major interaction is \(\text{HO}(4\pi)/\text{LU}(2\pi)\). Successive substitution of the diene with electron withdrawing groups, however, lowers the \(\text{HO}\) and \(\text{LU}\) of the diene to such an extent that the \(\text{LU}(4\pi)/\text{HO}(2\pi)\) interaction becomes dominant. This results in the reaction switching from type I to type III and thus assuming the properties described above (Figure 14).
It is clear, therefore, that this very simple perturbational model, as devised by Sustmann, elegantly rationalises the effects of substituents upon pericyclic cycloaddition reactions.

The treatment is based upon a qualitative assessment of the effect of substituents upon ground state energies and the stabilisation achieved in the transition state through the interaction of different ground state energy
levels.

In recent years Sustmann has used the same approach in a more quantitative manner. For example perturbation theory was used, in concert with ab-initio calculations, to provide information on the energy components which determine cycloaddition transition state structures.

Nevertheless, P.M.O. theory in its most simple form still provides a readily accessible means of predicting relative reactivities (Figure 15).

Figure 15
The three diagrams above show the predicted effect of substituted $2\pi$-systems on reaction rate. As information on double-bond electron density is readily available, rate predictions can be made very easily. This provides the chemist with a powerful tool for predicting the relative rates of new reactions.

3.2 ELECTROCYCLIC REACTIONS

Despite the fact that the concept of 'conservation of orbital symmetry' derived directly from the studies by Woodward & Hoffmann on electrocyclic reactions, this class of pericyclic reaction has been the least well studied.

Observations that in electrocyclic reactions thermal and photochemical activation gave different stereochemical results led to the development of this theory.

The theory itself is remarkably simple. Basically, the phase-relations among $p$-orbital electrons in a fully conjugated system reacting via a cyclic transition state will permit an energetically favourable transition to bonding orbitals of the product only under certain rotational operations. The consequences of this can be observed in the product stereochemistry. The orbital conversions can be mapped via symmetry operations and correlation diagrams (Figure 16).
Construction of the correlation diagram for the butadiene-cyclobutene electrocyclic reaction. (Shaded and nonshaded lobes represent opposite phases.)

Figure 16

Many electrocyclisation reaction types are known, from the two electron cyclopropyl cation-allyl cation interconversion to twelve and more electron systems98 (Figure 17).
Despite the vast range of known electrocyclic reactions, relatively little is known about factors affecting the reactivity of the systems.

Predictions of the orbital symmetry theory are derived from unsubstituted systems. Perturbations resulting from substitution of the system could perhaps alter this prediction. This is particularly true if the energy barrier to the 'symmetry forbidden' transition state is relatively small. It is of interest, therefore, to consider the potential influence of substituents on the stereochemistry of the reaction.

Epiotis used both a perturbation treatment and a configuration interaction approach to this question. Essentially, the two approaches lead to the same
qualitative conclusions. An inspection of the correlation diagram of the butadiene-cyclobutene interconversion (Figure 16) shows that the symmetry-forbidden disrotatory ring closure would become symmetry allowed if one or both HOMO electrons were promoted to the LUMO of butadiene. It follows, therefore that the energy required to promote these electrons represents the energy barrier of the symmetry-forbidden, relative to the symmetry-allowed reaction. If, in some way, the HOMO and LUMO levels are brought closer together in energy then the energy barrier to disrotatory, relative to conrotatory, ring-closure will decrease.

Epitotics suggested that butadiene could be considered as two ethylene units. If these units are substituted then the HOMO-LUMO energy gap can be altered significantly. For example the union of an electron-rich and an electron-poor olefin will reduce the HOMO-LUMO gap (Figure 18).

![Figure 18](attachment:image.png)
Both electron-withdrawing and electron-donating substituents are predicted to reduce the energy gap between the HOMO and the LUMO for butadiene. Similarly, heteroatom substitution in the polyene skeleton will bring the HOMO and LUMO closer together, leading in extremis to the symmetry forbidden reaction becoming competitive. These approaches led to predictions of the relative rates of allowed versus forbidden electrocyclic reactions, but do not give any information about the effect, due to substituents, on absolute rates of electrocyclisation.

In 1977 Carpenter developed a simple model for predicting the effect of substituents upon the rates of pericyclic reactions.

By assuming that the degree of delocalisation during the reaction is affected by substituents and that this change is the sole determinant of the substituent influence on rate, Carpenter predicted the effects of various substituent types upon rates of electrocyclisation. The π-electron energies of the reactants were calculated by the Hückel molecular orbital method. As a model for the transition state of each reaction, the corresponding completely conjugated cyclic hydrocarbon (e.g. benzene for the Cope rearrangement), was used, the energies of these also being calculated using the Hückel method. It was anticipated that particular types of substituents, e.g. π-donors, would follow the usual trend, i.e. NMe₂>OMe>Me etc. Therefore, the π-donor system was
represented by a doubly occupied carbon 2pₓ orbital. Similarly, electron-acceptor substituents were represented by a vacant carbon 2pₓ orbital while conjugating but non-polar substituents were represented by a vinyl group.

Using these model systems the effect of a type of substituent could be determined and the relative magnitude of the effect could be predicted. An example of the predictions obtained by this method is shown below for the cyclopropyl anion to allyl anion conrotatory ring opening (Figure 19).

![Figure 19](image)

<table>
<thead>
<tr>
<th>Substituent Position</th>
<th>Substituent Type</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ACC</td>
<td>1.038</td>
</tr>
<tr>
<td></td>
<td>DON</td>
<td>-0.340</td>
</tr>
<tr>
<td></td>
<td>CON</td>
<td>0.399</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>0.000</td>
</tr>
<tr>
<td>2</td>
<td>ACC</td>
<td>-0.962</td>
</tr>
<tr>
<td></td>
<td>DON</td>
<td>-0.340</td>
</tr>
<tr>
<td></td>
<td>CON</td>
<td>-0.429</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Estimated Substituent Effects on the Activation Energy of Cyclopropyl Anion to Allyl Anion Ring Opening
The column $\Delta$ gives the relative 'activation energies' in absolute $\beta$ units relative to an arbitrary zero for the unsubstituted case. Reactions with a negative $\Delta$ value are predicted to have a higher rate than the unsubstituted reference.

It is interesting to note that, while acceptor and conjugating substituents in the 1-position are predicted to slow the reaction, all substituent types in the 2-position are predicted to enhance the rate. In accordance with these predictions the rather sluggish ring opening of the cyclopropyl anion is accelerated by acceptor substituents (anion stabilising) in the 2-position.

When the ring contains an even number of carbon atoms the addition of a single atom substituent gives an odd numbered system. This system must have a non-bonding molecular orbital. Acceptor substituents leave this orbital empty whilst donor substituents leave it occupied. In either case this non-bonding M.O. makes no contribution to the total $\pi$-electron energy of the system. The calculations consequently predict identical behaviour for both donor and acceptor substituents and these can all be classified as polar. For example the predicted effect of substituents on both symmetry allowed (CON) and forbidden (DIS) ring opening and closure of the cyclobutene $\rightarrow$ butadiene system are summarised below (Figure 20).
In general, substituents at position B are expected to have effects as large or larger than those at position A.

It is of interest that substituent effects are predicted to be much larger for the forbidden (DIS) reaction than for the symmetry-allowed (CON) reaction, i.e. in all cases substituents are predicted to promote disrotatory relative to conrotatory reaction. This is in direct agreement with the calculations of Epiotis\textsuperscript{99} discussed previously.

In an extension of this work Wilcox, Carpenter and Dolbier\textsuperscript{102} looked at the effects of benzannelation and
bis-methylenation on four-membered ring opening rates. Conventional argument would expect that transformation of (194) to (195) would have higher activation energy than (192) to (193) (Figure 21). This would be anticipated due to the aromatic stabilisation lost in (194) upon ring opening. Experimentally, however, the opposite is found to be true.

Figure 21

As in the model described above, the difference in \( \tau \)-electron energy (calculated by the Hückel M.O. method) and the model transition state were recorded as \( \Delta E \) (in \( \beta \) units). Where the cyclobutene is monocyclic, the reaction was presumed to go con, whereas bicyclic systems were presumed to go dis, due to steric constraints.

The most striking feature of these calculations is the fact that benzannelation is predicted to decrease the activation energy for disrotatory ring opening (negative
\( \Delta \Delta E_x \), but to increase it for conrotatory reaction (positive \( \Delta \Delta E_x \)). These predictions find some support experimentally (Figure 22).

<table>
<thead>
<tr>
<th>Reaction Stereochemistry</th>
<th>( \Delta E_x^a )</th>
<th>( \Delta H^f b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON</td>
<td>0.362</td>
<td>ca. 6.5</td>
</tr>
<tr>
<td>DIS</td>
<td>-0.381</td>
<td>-7.8</td>
</tr>
</tbody>
</table>

Figure 22

a. \( \Delta E_x \) is the difference in Hückel \( \pi \)-electron energy (in \( \beta \) units) for the reactant and the model transition state. \( \Delta \Delta E_x \) is the difference in \( \Delta E_x \) for the two molecules shown in each line.

b. \( \Delta \Delta H^f \) is the difference in observed activation enthalpy for the ring opening reactions in kcal mol\(^{-1} \).

An alternative explanation for the observed results was not considered by Carpenter. It is conceivable that the systems which are sterically constrained from reacting by a conrotatory mechanism (192) and (194), proceed via a non-concerted route. The most obvious alternative mechanism involves C-C bond cleavage to give the diradical species (196) and (197).
This non-concerted mechanism does not involve disruption of the aromatic ring of (194) during formation of the diradical intermediate (197). Also the intermediate (197) would be expected to be more stable than (196) due to the possible stabilisation of two benzyl radicals. This alternative mechanism would therefore predict that the benzannelated system would be more reactive than its non-fused equivalent (192).

It appears, however, that Carpenter's very simple model is capable, at least qualitatively, of providing a useful framework from which to predict the effects of various types of substituents upon electrocyclisation rates. Carpenter warns, however, against estimating the effects of several substituents from the individual effects of each group. Hückel calculations for each individual case are therefore required, a fairly daunting task in the case of large polysubstituted systems.

A further degree of complexity would be introduced by the incorporation of heteroatoms into the polyene skeleton. These would affect not only the overall Hückel \( \pi \)-energy, but also have the effect of moving nodal centres away from individual atoms. Whether very small (almost nodal) contributions in these cases would have much effect on the overall calculations is not clear.

In recent years Houk and co-workers\(^{103} \) have investigated the effect of substituents on the "torquoselectivity" of electrocyclic reactions. That is,
the preference of groups to rotate 'outwards' or 'inwards' during stereospecific con or disrotatory reaction (Figure 23).

![Chemical structure](image)

**Figure 23**

It would be anticipated that the preference for outward or inward rotation would be governed by steric factors. The preferred product being that with least steric interactions. This was shown not to be the case, however, when Dolbier et al.\(^{104}\) demonstrated that 3,4-bis-trifluoromethylcyclobutene (198) ring-opens to form the more crowded product (199) arising from inward rotation of the two bulky trifluoromethyl groups.
Houk rationalised the effect of substituents on torquoselectivity in terms of molecular orbital interactions in the transition state. Take, for example, the outward rotation of a $\pi$-donor substituent. Upon rotation this orbital can mix with the distorted cyclobutene LUMO to give a stabilising interaction. This is only partly counteracted by the destabilising interaction of the donor orbital with $C_4$ of the cyclobutene (Figure 24). The overall effect of the outward rotation is therefore stabilising, leading to a lowering of the activation energy.
Inward rotation, on the other hand, leads to a significant interaction of the donor orbital with both C₃ and C₄ (Figure 25). The interaction of an inwardly rotating donor orbital with the distorted cyclobutene LUMO is less than that of the outwardly rotating case because the signs of the neighbouring lobes are opposite (upper lobe at C₃, lower at C₄ in Figure 25). At the same time, the donor orbital overlaps more with the cyclobutene HOMO due to overlap at C₃ and C₄. This destabilising interaction is larger for inward than for outward rotation. Thus σ-donor substituents are predicted to have an outward torquoselectivity.
In the case of \( \pi \)-acceptor substituents, the interaction with the distorted cyclobutene HOMO becomes a 2-electron, stabilising interaction. This is maximised when the substituent rotates inwards and may cause the torquoselectivity described above to be reversed. Experimentally, acceptor substituents show little torquoselectivity.

Further \textit{ab-initio} calculations concluded that the pentadienyl cation system would have the torquoselectivities described above\textsuperscript{103}. 
In 1989 Houk et al. carried out experimental and theoretical studies of substituent effects on an orbital symmetry forbidden electrocyclisation. These studies were carried out with the intention of giving a broader understanding of the more general subject of substituent effects on allowed and forbidden pericyclic reactions. The system studied was the symmetry forbidden disrotatory cyclobutene-butadiene interconversion. Systems of this type have been observed to undergo disrotatory reaction when geometric constraints exist (Scheme 37).

As was shown earlier for the conrotatory reaction, the HOMO and LUMO of the disrotatory transition structure are primarily $\sigma$ and $\sigma^*$ orbitals, distorted and moved closer in energy by the decrease in overlap between the orbitals at $C_3$ and $C_4$. The degree of overlap is maintained longer into the process for disrotation than for conrotation as can be seen in Figure 26.
This greater overlap leads to the transition-state HOMO being of high energy due to mixing of the breaking $\sigma_{\text{CC}}$ with the cyclobutene $\pi$-orbitals upon disrotatory motion. The LUMO is the $\sigma_{\text{CC}}^*$ orbital mixed slightly, in a bonding fashion with the cyclobutene $\pi^*$ (Figure 27).
The relatively high energies of the HOMO and LUMO are important in explaining substituent effects. The fact that the HOMO of the disrotatory transition state is raised, through more efficient overlap, by more than the LUMO is lowered results in the efficiency of mixing with substituent orbitals being altered. The very high energy HOMO will mix efficiently with high-lying vacant substituent orbitals in a stabilising interaction. The high lying LUMO will not, however, mix so effectively with the relatively low-lying substituent donor orbital (Figure 28).

Figure 28
This leads to the prediction that τ-acceptor substituents, which stabilise the HOMO, will have a larger effect upon the transition state energy than will τ-donors, which stabilise the LUMO. These predictions find experimental support in the effects displayed by substituents on the disrotatory electrocyclisations of bridged o-xylylenes¹⁰⁵ (Scheme 37).

These two models show that the effort to understand reactivity in electrocyclic systems is gathering momentum. Neither model, however, is as yet applicable to more complex systems such as multiply substituted 1,3- dipolar electrocyclisations.

1,3-Dipolar electrocyclisations are now well established as useful synthetic routes and have been the subject of major reviews³³,³⁹,⁹⁸.

Despite the extensive use of 1,3-dipolar electrocyclisations, remarkably little is known about the factors affecting the reaction rates of these systems.
What information does exist is sparse and provides little scope for interpretation of general effects upon reactivity. For example, Heimgartner\textsuperscript{82} carried out a reaction which provided a nitrile ylide (146) with two possible modes of 1,5-electrocyclisation (Scheme 29).

Scheme 29
The nitrile ylide thus prefers 1,5-electrocyclisation onto the carbonyl double bond relative to the olefinic bond.

Vinylidene nitrile ylides (200) can be intercepted by dipolarophiles, whereas carbonylnitrile ylides (201) generally undergo 1,5-electrocyclisation preferentially.

\[
\begin{align*}
R-CN-C & \\
(200) & \\
\end{align*}
\]

\[
\begin{align*}
R-CN-CN & \\
\rightarrow & \\
R-C & \\
(201) & \\
\end{align*}
\]

Factors such as preferential electrocyclisation onto certain double bond types and relative rates of electrocyclisation have been noted, but have not been subject to any kind of quantitative study.

Another type of relative reactivity can exist in systems which possess \(\alpha, \beta: \gamma, \delta\) unsaturation.
For example, Sharp\textsuperscript{40,106} has found that the periselectivity of electrocyclisations is dependent upon the nature and positions of the conjugated double bonds (Scheme 38). It was found, however, that steric constraints in the system could be used to promote either 1,5- or 1,7-periselectivity\textsuperscript{106} (Scheme 38).

\begin{center}
\includegraphics[width=\textwidth]{scheme38.png}
\end{center}

Scheme 38
These results lead to the conclusion that the activation energies for these two cyclisation types are not very different and can be readily manipulated.

Lippmann and co-workers\textsuperscript{107} carried out a series of experiments designed to determine the relative reactivities of different modes of electrocyclisation. Nitrile imines possessing a C-(2-nitrophenyl) substituent, as in (210), can undergo an intramolecular cyclisation to give anthranil-1-oxide (211) (Scheme 39).

![Scheme 39](image-url)
In the Lippmann investigation, two such nitrile imines were generated, each having both 1,5-electrocyclisation and cyclisation at the nitro group open to them. In each case 1,5-electrocyclisation was the preferred route (Scheme 39). A further experiment designed to test the relative reactivities of 1,5- and 1,7-electrocyclisation using the nitrile imine (215) gave a complex mixture.

Padwa and co-workers\textsuperscript{80} found that irradiation of the azirine (151) gave the benzazepine (154) as the major product (80%). Only 4% of the product derived from 1,5-electrocyclisation was observed (Scheme 40).

\begin{center}
\includegraphics[width=\textwidth]{Scheme_40.png}
\end{center}
It was found that this process is a general phenomenon when the substituent attached to the double bond is a \textit{cis}-aryl group. The preference for cyclisation to the seven, rather than the five-membered ring was attributed to stereoelectronic factors. The near-linear nitrile ylide achieving the transition-state for 1,7-electrocyclisation more readily than that for the 1,5-mode.

Calculations carried out by the same group\textsuperscript{80} indicate that for the nitrile ylide (152) cyclisation to pyrrole is ca. 40\% less efficient, in terms of quantum yield, than cyclisation to the azepine (154).

In one of the few examples of quantitative studies on electrocyclisation reactions, Padwa carried out trapping experiments on the nitrile ylides (217) and (152).
The two 1,3-dipoles, derived from the corresponding azirines, were generated in the presence of methyl acrylate. By assuming that the rate of cycloaddition of each nitrile ylide with methyl acrylate was the same the relative rate difference for seven-membered versus five-membered ring formation was calculated to be ca. 16:1. The assumption that the rates of cycloaddition of both nitrile ylides were the same was tested. The relative rates of the cycloadditions with a series of dipolarophiles were obtained (Table 2).

**Table 2**

Relative reactivity of a series of olefins towards nitrile ylides (217) and (152).

<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>Rel. Rate with (217)</th>
<th>Rel. Rate with (152)</th>
<th>Rel. Rate with Diphenylazirine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethylacetylene-dicarboxylate</td>
<td>6.2</td>
<td>4.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>1.97</td>
<td>1.72</td>
<td>1.13</td>
</tr>
<tr>
<td>Dimethyl maleate</td>
<td>1.15</td>
<td>1.10</td>
<td>1.04</td>
</tr>
<tr>
<td>Methyl acrylate</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>
These results suggest that the assumption made previously was a reasonable one. The conclusion that the azepine formation is ca. 16 times faster than formation of the pyrrole via 1,5-electrocyclisation is in excellent agreement with the ratio of observed yields of the products from the irradiation of azirine (151) i.e. \(80\%:4\%\).

The most recent work on reactivity in 1,3-dipolar 1,7-electrocyclisations has been carried out in the group of Sharp. These studies again concerned the reactions of nitrile ylides.

In contrast to the preceding results it was found that nitrile ylide, thermally generated, in which the \(\gamma,\delta\)-double bond was olefinic did not give the azepine product (218) directly (Scheme 41).

\[\text{Scheme 41}\]
The product of the reaction is a cycloprop[c]isoquinoline (177). This can be formally derived from a 1,1-cycloaddition of a 'carbenic' nitrile ylide across the olefinic double bond. An alternative explanation is the initial 1,7-electrocyclisation of the nitrile ylide to give (176) followed by rapid ring collapse to the isoquinoline derivative (177). Heating of the cycloprop[c]isoquinoline at 80°C in an aproptic solvent gives the benzodiazepine (218) formally derived from 1,7-electrocyclisation followed by 1,5-hydrogen shift.

Of interest is the fact that diazocompounds of this type do not show this type of behaviour\(^{108}\). In the system (48) when \(R^1=H\) the product is the \(1H\)-2,3-benzodiazepine (219). If \(R^1\neq H\), however, the products are derived from carbene intermediates (220) (Scheme 42).
These results are rationalised in terms of postulated helical transition state (48), described earlier, being blocked by cis-substituents on the alkene terminus. Investigation of these reactions at low temperature showed no evidence for an imino-nitrene 1,1-cycloaddition. In contrast to this, the reaction of nitrile imines (221) to give 1,2-benzodiazepines (226), like that of nitrile ylides to give azepines, can proceed whether the hydrogen on the alkene terminus is cis or trans. In this reaction, in analogy to that of nitrile ylides, the initially isolated product is the cyclopropa[c]cinnoline (223), which is formed with retention of configuration. Heating of the product gives the benzodiazepine (226). The mechanism proposed by Padwa and Nahm is shown below (Scheme 43).
An important question in reactions of this type is whether or not the initial cyclisation step is reversible. Sharp and co-workers found, using kinetic isotope effects, that the first step is reversible for diazocompounds (227), (228) and (229).

Since formation of the benzodiazepine products (232) and (233) is irreversible, either the initial cyclisation ($k_1$), the sigmatropic shift ($k_2$) or both must be irreversible (Scheme 44). The fact that neither intermediate, (230) or (231), was detected and the nature of the second step led to the assumption that $k_2$ was irreversible. If the first step ($k_1$) is irreversible then the kinetic isotope effect will tend to unity. If, however, the first step is a rapid preequilibrium followed by a rate determining $k_2$ then the ratio $k_H/k_D$ should tend to 7, i.e. the breaking of the C-H/C-D bond is rate determining.
For the cyclisation of the diazo-compound (227) above, the product ratio (232)/(233) was obtained from $^2$D n.m.r. and was found to be 4.4$^{110}$. This result clearly indicates that $k_2$ is the rate determining step and since no build-up of the intermediate is observed then $k_{-1}$ is 0, i.e. the initial attack is reversible.

A similar experiment carried out by Groundwater$^{111}$ on the nitrile ylide (234) gave a value very close to unity, indicating that for nitrile ylides the initial attack is essentially irreversible, i.e. slower than $k_2$. 

Scheme 44
The difference between these results is, perhaps, not surprising. The initially formed C-N bond in the diazo case has a much lower bond energy (~ 290 kJ mol\(^{-1}\)) than the stronger C-C bond (~ 345 kJ mol\(^{-1}\)) formed upon cyclisation of the nitrile ylide.

Further work by Groundwater and Sharp\(^{85}\) investigated the effect of substituents on the relative reactivities of the positions ortho and para to the substituent \(R\) in (236) (Scheme 45).

**Scheme 45**
These results indicate that nitrile ylides prefer to attack ortho to the substituent, irrespective of the polar electronic influence. Given that the initial attack is irreversible the directive influence must be exerted at this stage.

In contrast, the strongly electron withdrawing trifluoromethyl substituent leads to para attack being favoured over ortho attack in the case of the diazo-compound. These results were not readily rationalised, but appear to discount a carbenic first stage. Work by Schechter\textsuperscript{112} has shown that methoxy and chloro groups exert different and opposite directive effects (Scheme 46).
DISCUSSION

PROGRAMME OF RESEARCH 126

SECTION 1 129

Synthetic Studies on the 1,7-Electro cyclisation Reactions of Benzonitrile-2-Arylbenzyl Ylides 129

PREAMBLE 129

1.1 SYNTHESIS OF N-SUBSTITUTED-2-ARYLBENZYL-AMINES 133

1.2 GENERATION AND REACTION OF THE NITRILE YLIDES DERIVED FROM SUBSTITUTED N-(2-ARYLBENZIMIDOYL CHLORIDES 138

SECTION 2 149

Measurement of Relative Reactivities in 1,7-Electrocyclisation Reactions of Nitrile Ylides 149

PREAMBLE 149

PART 1. "EXTERNAL COMPETITION" APPROACH TO RELATIVE RATE MEASUREMENT 155

2.1.1 Thermally Generated Nitrile Ylides 155

2.1.2 Photochemically Generated Nitrile Ylides 166
### PART 2. "INTERNAL COMPETITION" APPROACH TO RELATIVE RATE MEASUREMENT

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2.1</td>
<td>via Grignard Reactions of N-2,6-dimethoxybenzylidene Isopropylamine</td>
</tr>
<tr>
<td>2.2.2</td>
<td>via Palladium-catalysed cross-coupling reactions</td>
</tr>
<tr>
<td>2.2.2.1</td>
<td>Attempted sequential palladium-catalysed cross-coupling of 4-(N-benzoylamino)methyl)-3,5-dibromobenzoic acid methyl ester</td>
</tr>
<tr>
<td>2.2.2.2</td>
<td>Attempted preparation of aryl bromides via ortho-metalation reactions</td>
</tr>
</tbody>
</table>

### PART 3. MEASUREMENT OF RELATIVE RATES OF ELECTROCYCLISATION VIA INTRAMOLECULAR COMPETITION REACTIONS

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3.1</td>
<td>Synthetic Strategy</td>
</tr>
<tr>
<td>2.3.2</td>
<td>The Competition Reaction Methods</td>
</tr>
<tr>
<td>2.3.3</td>
<td>The Competition Reactions</td>
</tr>
<tr>
<td>2.3.3.1</td>
<td>Alkenyl and thienyl</td>
</tr>
<tr>
<td>2.3.3.2</td>
<td>meta-Substituted aryl rings</td>
</tr>
<tr>
<td>2.3.3.3</td>
<td>para-Substituted aryl rings</td>
</tr>
</tbody>
</table>
2.3.3.4 "Competition cycles" (para versus para) 233
2.3.3.5 ortho-Substituted aryl rings 238
2.3.4 Rationalisation of Results 246
This thesis is concerned with $\alpha, \beta; \gamma, \delta$-unsaturated nitrile ylides (239) and, in particular, with the factors which control the rates of the 1,7-electrocyclisation reactions of these systems.

It has recently been shown that nitrile ylides (234), in which the $\gamma, \delta$-unsaturation forms part of an aromatic ring, undergo 1,7-electrocyclisation followed by a 1,5-hydrogen shift to give benzazepines$^{85}$ (237) (Scheme 47).

On the other hand, when the $\gamma, \delta$-unsaturation is olefinic the nitrile ylide (175) cyclises to give a cycloprop[c]isoquinoline (177) as the primary product. This is formally derived via 1,1-cycloaddition of the nitrile ylide to the olefinic double bond$^{77}$. These cycloprop[c]isoquinolines are isomerised to benzazepines (218) upon heating (Scheme 47).
Before the start of this project some preliminary work had also been carried out on analogous systems (239) in which both the $\alpha,\beta$- and $\gamma,\delta$-double-bonds are aromatic. These compounds cyclised to give the dibenzazepines (240) in good yield$^{84}$ (Scheme 47).
The work described in this thesis was carried out with two objectives. Firstly to investigate the synthetic scope of this reaction. Secondly, it was hoped to use systems of this type to probe the effect of substituents and the nature of the \( \gamma,\delta \)-double-bond on the rate of 1,7-electrocyclisation and on the mechanism of the reaction.
SECTION ONE

Synthetic Studies on the 1,7-Electrocyclisation Reactions of Benzonitrile-2-Arylbenzyl Ylides

Preamble

This section is concerned with the reactions of systems of the type (239), i.e. diene conjugated nitrile ylides in which the α,β;γ,δ-unsaturation is incorporated in two benzene rings.

\[ \text{R} \]
\[ \text{H} \]
\[ \text{C} \cdot \text{N} \equiv \text{C} - \text{Ar} \]

(239)

The reactions of these systems were of interest for two reasons. Firstly to establish the synthetic viability of the reaction as a route to azepine products. Azepines have been an area of intense interest in the pharmaceutical industry in recent years and it was felt that this reaction would present a convenient synthetic route to systems of this type.

Overall the conversion of the amide (243) into the dibenzazepine (244) is equivalent to a Bischler-Napieralski-type reaction\(^{1,3}\), but is achieved under very mild conditions (Scheme 48). It is known that the Bischler-Napieralski reaction works well only when bond
formation is to an electron-rich ring. It was therefore of interest to investigate the electronic requirements and synthetic utility of the electrocyclisation reaction.

\[
\begin{align*}
\text{(241)} \quad \text{POCl}_3 \quad \text{(242)}
\end{align*}
\]

\[
\begin{align*}
\text{(243)} \quad \text{1,7-Electrocyclisation} \quad \text{(244)}
\end{align*}
\]

Scheme 48

The second reason for investigation of this reaction was as a logical extension to and for comparison with work previously carried out in this group on systems in which the \(\alpha,\beta\) or \(\gamma,\delta\) unsaturation was olefinic (234) and (175). As described previously (Introduction pp. 56 and 67) these two systems appear to display different reaction mechanisms.
It was proposed to carry out several preparative reactions using substrates substituted in both the ring under attack during electrocyclisation and in the ring attached to C-1 of the nitrile ylide. This was in order to determine whether the reaction was subject to electronic or steric limitations.

A further reason for interest in systems of this type was because of their potential as easily modifiable prototypes for carrying out reactivity studies. The system would provide scope for carrying out modifications in order to ascertain the factors affecting the 1,7-electrocyclisation reactions of nitrile ylides. This aspect of the work will be discussed in detail in Section two of this thesis.

Given the complications that can arise with photochemically generated intermediates and in order to be consistent with previous work of this group, it was decided initially to generate the nitrile ylides by a
non-photochemical route.

The method of choice was the 1,3-dehydrochlorination of imidoyl chlorides (246) with base. Imidoyl chlorides can be prepared by the chlorination of amides $^{55}$ (245).

Thus the first objective was the synthesis of a series of $N$-substituted-2-arylbenzylamines (245).

In earlier work the investigators had used a specific route to the amide (245, Ar=Ph, R=H) via the ring opening of fluorenone. This route, however, was not easily adaptable to a range of analogues with various substituents as the R group. The objective was therefore to find a viable and versatile synthetic route to compounds of this type. The first method tried was an adaptation of Meyers oxazoline based biaryl synthesis as described in the next section.
1.1 SYNTHESIS OF N-SUBSTITUTED-2-ARYLBENZYLAMINES

The synthesis of the title compounds (245, a-d) was achieved by the route shown in Scheme 49.

The key step in this synthetic pathway involved the connection of an aryl group to the position on the benzene ring ortho to that to which the nitrile ylide would be attached. A high yielding route, insensitive to a wide range of substituents was required.
Previous work by Meyers\textsuperscript{114} has shown that oxazoline groups can be used to activate o-methoxy or o-fluoro groups in aromatic systems to substitution by organometallic reagents.

The suggested mechanism of the methoxy group displacement involves initial complexation of the methoxy and oxazoline groups to the metal, followed by nucleophillic 1,4-addition of the R group. The oxazoline moiety provides an excellent activating group due to the ready chelation leading to an enamine-like intermediate (256)\textsuperscript{115} (Scheme 50).

The product oxazoline is readily hydrolysed to a carboxylic acid, but in the envisaged synthesis the aldehyde (251) would be required. Reduction/hydrolysis of the methiodide salt of the oxazoline (257) to give the
aldehyde is effective in many cases, but a preliminary investigation in this research group has shown that it is severely inhibited by the presence of electron donating groups in the aryl ring\textsuperscript{116} (Scheme 51).

\begin{center}
\begin{align*}
\text{(257)} & \xrightarrow{\text{Mel}} \quad \text{(258)} \\
\text{Cl} & \quad \text{Ar} & \quad \text{Me} & \quad \text{Ar} & \quad \text{N}^+Me & \quad \text{I} \\
\text{OMe} & \quad \text{Ar} & \quad \text{Cl} & \quad \text{Ar} & \quad \text{Ar} & \quad \text{CHO} & \quad \text{Ar}
\end{align*}
\end{center}

Scheme 51

However, in the literature there was one report of the use of the \textit{N}-isopropylimine group (259) as an activating group adjacent to the methoxy substituent\textsuperscript{117}. This is
obviously much more attractive than oxazoline as a carbonyl precursor.

Extension of this to provide a synthesis of o-aryl-benzaldehydes would require an analogous reaction of the aldimine (249). Although it has been reported that simple imines of the type (261) react exclusively by 1,2-addition\(^{118}\) (Scheme 52), it was decided to attempt the reaction using the imine (249). It was hoped that the bulky isopropyl group would hinder 1,2-addition and hence favour o-substitution (Scheme 52).

\[
\begin{align*}
\text{(261)} & \quad \xrightarrow{\text{PhCH}_2\text{MgCl}} \quad \text{(262)} \\
\text{(249)} & \quad \xrightarrow{\text{ArMgBr}} \quad \text{(250)} & \text{H}^+ & \quad \xrightarrow{\Delta} \quad \text{(251)} \\
\text{Ar} & \quad \\
\text{Ph} (77\%) & \quad \\
4-\text{OMe-}C_6H_4 (76\%) & \quad \\
4-\text{Cl-}C_6H_4 (64\%) & \quad \\
2-\text{Me-}C_6H_4 (85\%) & \quad \\
\end{align*}
\]

Scheme 52
In the event, these reactions proceeded cleanly at reflux in T.H.F. overnight. The reactions were conveniently monitored by g.l.c. and gave the ortho-arylated imines in good yield. The imines were readily hydrolysed to the corresponding aldehydes by heating at reflux in 4N sulphuric acid for 1½ hours (Scheme 52).

That no product was derived from 1,2-addition by the Grignard reagent seems remarkable, indicating that the ortho-substitution reaction is a relatively low energy pathway.

The mechanism of the coupling reaction is thought to be analogous to that involving oxazolines. The imine nitrogen here taking the place of the oxazoline nitrogen (Scheme 50).

It is of interest that shortly after the completion of this stage of the project a formally analogous synthesis was reported for Grignard cross-coupling to o-halo arylimines (263)\(^{19}\).

\[\text{(263)} \rightarrow \text{(264)}\]
With the 2-arylbenzaldehydes in hand, the remaining stages of the synthesis of the \( N \)-substituted-2-arylbenzylamines followed conventional methods. The aldehydes were converted to their oximes under mild conditions using hydroxylamine hydrochloride and base. This resulted in precipitation of the solid oxime \((252)\) in excellent yield. Conversion of the oximes to the appropriate amines \((253)\) was achieved by reduction with zinc dust and ammonium acetate by refluxing in ethanol and ammonia overnight. After concentrating in vacuo the amines were extracted into ether and precipitated as their hydrochloride salts by passing hydrogen chloride gas through the solution.

The amines were then converted to the desired \( N \)-substituted-2-arylbenzylamines \((245)\) by reaction with the appropriate aroyl chloride. These reactions went in good to excellent yield at room temperature overnight.

1.2 GENERATION AND REACTION OF THE NITRILE YLIDES DERIVED FROM SUBSTITUTED \( N \)-(2-ARYLBENZYL)BENZIMIDOYL CHLORIDES

The preparation of imidoyl chlorides from amides is generally carried out using reagents of the type \("XCl_2\)\), where \(X = PCl_3; POC_1; CO\) or \(SO\). The by-products of the reaction are \("X=O\) and \(HCl\).

The method of choice involved the use of thionyl chloride as both by-products, being gaseous, could be readily removed. The amide \((245)\) was chlorinated using a large excess of thionyl chloride in ether at reflux.
overnight. The by-products, HCl and SO$_2$, were removed under high vacuum at ambient temperature.

The nitrile ylide (239) was generated at 0°C by dissolving the imidoyl chloride (246) in dry T.H.F. and adding 2 equivalents of solid potassium tert-butoxide (Scheme 53). Earlier work by Robertson$^7$ and Motion$^8$ had shown that nitrile ylides of this type could not be generated from the corresponding imidoyl chloride with triethylamine. The excess of potassium tert-butoxide was added to ensure that sufficient base was present to dehydrochlorinate the imidoyl chloride as well as react with any residual by-products from the chlorination and any adventitious moisture.

\[
\begin{align*}
\text{CH}_2\text{NHCOAr} \quad \xrightarrow{\text{SOCl}_2} \quad \text{CH}_2\text{N}=\text{C}-\text{Ar} \\
\text{(245)} \quad \text{(246)} \\
\end{align*}
\]

(a) $R=\text{H}; Ar=\text{Ph}$
(b) $R=\text{p-Cl}; Ar=p\text{-Me-C}_6\text{H}_4$
(c) $R=\text{p-OMe}; Ar=p\text{-Me-C}_6\text{H}_4$
(d) $R=\text{o-Me}; Ar=\text{Ph}$

**Scheme 53**
The addition of the base at 0°C was generally followed by the immediate appearance of a yellow colour. On one occasion, when the T.H.F. solution of imidoyl chloride (246a) was cooled in an ice/salt bath to ca. -10°C, addition of base resulted in a purple colour which faded to yellow over 2-3 minutes.

In reactions of this type, the appearance of a purple colour has generally been attributed to the presence of a nitrile ylide intermediate (239). In this experiment, the fact that the colour was only seen at a low temperature indicated that, if this were the case, the nitrile ylide was very short lived. This lies in contrast to the observations of Motion\textsuperscript{86} and Groundwater\textsuperscript{111} in work on systems of these types (175) and (234) respectively.

\[
\begin{align*}
\text{C—N\equiv C—Ph} \\
\text{R} \\
\text{H'} \\
\text{R'} \\
\end{align*}
\]  

In the case of (175), Motion\textsuperscript{86} noted that addition of the same base to a T.H.F. solution of the corresponding imidoyl chloride at room temperature gave a red colour lasting a few minutes. Groundwater\textsuperscript{111} noted that generation of the nitrile ylide (234) at 0°C gave a purple colour which persisted for ca. 15 minutes.
If, in all three cases, the deep colouration is indicative of the nitrile ylide then the conclusion must be that the nitrile ylide (239) is the most reactive. This is surprising, given that formation of the intermediate (265) from (239) involves disruption of the aromaticity of two rings, whereas the intermediate (235) from (234), for example, only requires disruption of the aromaticity of one.

\[ \text{(265)} \]
\[ \text{(235)} \]

This again raised the question of how well the mechanisms of reactions of this type are understood and provided further impetus for the quantitative work described later in this thesis.

After addition of the base the reaction mixture of the nitrile ylides (239) were stirred at 0°C for 10 minutes and for a further 30 minutes at room temperature. Quenching with aqueous ammonium chloride, extraction, dry flash chromatography on t.l.c. silica and crystallisation
of the products from the reactions of nitrile ylides (239 a-c) gave the expected products (244), (267) and (268).

These 5-aryl-7H-dibenz[c,e]azepines were characterised by elemental analysis and spectral data. All three gave $^1$H n.m.r. spectra showing the signals characteristic of compounds of this type. That is, all showed two doublets in the region $\delta 3.0-5.0$. For example, 5-phenyl-7H-dibenz[c,e]azepine (244) showed doublets at $\delta 4.92$ (J 10.5 Hz) and $\delta 3.96$ (J 10.5 Hz). The doublet at $\delta 4.92$ can be assigned to the equatorial H in the dibenzazepine (269) whereas that at $\delta 3.96$ can be assigned to the axial H. The equatorial hydrogen is deshielded because it lies in the anisotropic deshielding zones of both the imine and the aromatic double bonds. The geminal coupling constant of 10.5 Hz is consistent with those in related azepine
systems\textsuperscript{120}.

In addition to this work on unsubstituted and para-substituted rings, one example has been studied of the reaction of a nitrile ylide of type (270) with an ortho-substituted terminal ring. This work was carried out in conjunction with Mr. D.J. Sloan as part of his honours research project.
It had been thought that an ortho-methyl group on the ring under attack during electrocyclisation would simply direct attack towards the other ortho-position. However, it was found that (270) did not cyclise to give any of the dibenz[c,e]azepine product (271).

The amide precursor (245d) gave a $^1$H n.m.r. spectrum which indicated that the methylene protons were non-equivalent. Thus it appeared that the o-methyl group was restricting free rotation of the phenyl ring to which it was attached (Figure 29).

Figure 29

![Chemical structure image]
A Dreiding model of the system showed that there was considerable steric interaction between the methyl group and both the amide group and the hydrogen ortho to the biphenyl linkage.

Work-up and chromatography of the reaction of the nitrile ylide derived from this amide gave two products. Both were shown by mass spectrometry to be dimeric, but further spectroscopic techniques indicated complex structures. Attempts to crystallise samples for X-ray analysis were unsuccessful. The major of the two products has been tentatively assigned the structure (273).
This assignment was based on both spectroscopic data and the known behaviour of nitrile ylides. The $^{13}$C spectrum showed signals at $\delta$20.04 (CH$_3$), six quaternary carbons ($\delta$134.3-144.1), carbon atoms in aromatic systems ($\delta$125.1-130.8) and a signal at $\delta$158.5, possibly corresponding to H-C=N.

The $^1$H n.m.r. showed a methyl signal ($\delta$2.11), a large aromatic multiplet and a sharp singlet ($\delta$9.76) assigned as the signal from the H-C=N proton. These data are consistent with the proposed structure.

It is known that nitrile ylides undergo dimerisation in a 'head-to-head' fashion$^{50}$. This is generally followed by electrocyclisation and oxidation to pyrazines (276) (Scheme 54).

\[ R-C=\equiv-N-C-R \]
\[ \xrightarrow{\text{dimerisation}} \]
\[
\begin{align*}
R & \equiv N \equiv R \\
& \equiv N \equiv R
\end{align*}
\]
\[ (274) \]
\[ \xrightarrow{\text{oxidation}} \]
\[
\begin{align*}
R & \equiv N \equiv R \\
& \equiv N \equiv R
\end{align*}
\]
\[ (275) \]
\[ \xrightarrow{\text{}} \]
\[
\begin{align*}
R & \equiv N \equiv R \\
& \equiv N \equiv R
\end{align*}
\]
\[ (276) \]

Scheme 54
That the proposed dimer (273) does not undergo this electrocyclic reaction can be rationalised in terms of the large groups on the termini of the triene system which will disfavour the disrotatory transition state required for thermal cyclisation.

At first sight it seems very surprising that the nitrile ylide (270) completely fails to undergo electrocyclisation when this mode of reaction is so readily accessible for the para-substituted analogues (239 a-c). However, on closer consideration of the steric effect of the ortho-methyl group in the transition-state for cyclisation it appears less so. The methyl group obviously does not provide any hindrance at the site of potential attack, but may destabilise the helical transition-state\textsuperscript{42} for cyclisation by its interaction with the ortho-hydrogen on the adjacent ring (277). A Dreiding model shows that this interaction is considerable. This will act to raise the activation energy for electrocyclisation and divert the nitrile ylide into the lower energy pathway to dimerisation.

\[
\text{H} \quad \text{C-N-C-Ph} \quad \text{H} \quad \text{CH}_3
\]

\hspace{1cm} (277)
This small exploratory study on substituent effects indicates that the 1,7-cyclisation is not inhibited by the presence of either electron-withdrawing or electron-donating groups in the para-position of the ring under attack. However, it does appear to be sensitive to the steric effects of ortho-substituents. This is an area where further investigation using smaller ortho-groups would be of value.
SECTION TWO

Measurement of Relative Reactivities in 1,7-Electrocyclisation Reactions of Nitrile Ylides

2.1 PREAMBLE

As explained in the introduction to this thesis (Section 3.2), the factors affecting reactivity in electrocyclic reactions are poorly understood. Although models now exist\textsuperscript{100-105} for predicting the effect of substituents upon rates, their nature makes application to polysubstituted dipolar systems impossible without detailed calculations.

A simple predictive model of the type devised by Sustmann\textsuperscript{5} and Houk\textsuperscript{52} for 1,3-dipolar cycloaddition is not available. The development of such a model is inhibited by the fact that there is little experimental data on the factors controlling the rates of electrocyclisation of unsaturated 1,3-dipoles.

It was our intention, in this work, to carry out a quantitative study on the 1,7-electrocyclisation reactions of nitrile ylides in order to evaluate the factors which control reactivity and thus hopefully gain an insight into the mechanism.

The major problem involved in this research is that these reactions are very fast, involving transient intermediates which are generated \textit{in situ}. This makes the direct measurement of absolute reaction rates very
difficult. Given that conventional monitoring techniques are not applicable to systems of this type, it was decided to adopt a 'competition reaction' approach.

Two general approaches to competition studies of this type can be envisaged.

a) "External Competition"

In this case a series of substituted nitrile ylides would be generated, in turn, in the presence of some appropriate trapping species (Scheme 55).
The assumption would have to be made that the rate of 1,3-dipolar cycloaddition was approximately constant for all of the nitrile ylides, i.e. little affected by the nature of R in (239). From the relative yields of (240) and (278) for a range of substituents, R, it would be possible to obtain a measure of the effects of substituents on the rate of the 1,7-electrocyclisation reaction. Substituents promoting electrocyclisation would increase the proportion of the dibenzazepine (240) relative to the cycloadduct (278) and vice versa.

It was envisaged that this approach might involve two problems. Firstly, the assumption that rates of cycloaddition are independent of substituents in the nitrile ylides is intuitively suspect. For example, one might expect the two nitrile ylides (279) and (280) to add to a given dipolarophile at different rates.

\[
\begin{align*}
\text{(279)} & \quad \text{(280)} \\
\text{(281)} & \quad \text{(282)} \\
\text{(283)}
\end{align*}
\]
Work by Padwa has shown that the rates of cycloaddition of the nitrile ylides (281), (282) and (283) to a series of dipolarophiles differ by less than a factor of two. This indicates that the systems under study, in which substituents are remote from the site of cycloaddition, would be expected to have very similar rates of reaction with dipolarophiles.

The second problem would involve identification of a suitable dipolarophile. A multiple bond system, insensitive to potassium tert-butoxide, giving readily indentifiable or separable products at a rate similar to that of 1,7-electrocyclisation would be required. Given that the object of the study was the measurement of different rates of electrocyclisation, a dipolarophile which gave measurable amounts of cycloadduct with a range of nitrile ylides undergoing electrocyclisation at various rates was essential. The alternative of using different dipolarophiles with different nitrile ylides and attempting to correlate the rates was not attractive.

b) "Internal Competition"

In this type of competition reaction the electrocyclisation would compete against another intramolecular reaction of the nitrile ylide. This could be a cycloaddition - using a non-conjugated alkene, or another electrocyclic reaction. Given the nature of the reactant, it seemed appropriate in this case to use another 1,7-
electrocyclisation as the comparator reaction, in a nitrile ylide of the type (284). The nitrile ylide would be generated in the normal way and would have the option of two rings onto which to electrocyclise (Scheme 56).

The ratio of the two isomeric dibenz[c,e]azepines (285) and (286) would directly reflect the relative effects of $R$ and $R'$ on rates of electrocyclisation. In effect a 'league table' could be constructed with $R=H$ taken as the comparator, i.e. all of the substituted rings would be competed against a phenyl ring. A study of this type would require the development of a synthetic route to precursors of the type (287).
In addition, this approach should easily be capable of extension to the measurement of relative reactivities of various alkenes (288) and heterocycles (289).

![Chemical structures](image)

In systems of this type the assumption has to be made that varying the substituted ring does not greatly affect the ground state energy of the molecule as a whole. That is, substituents do not have much effect on the activation energy of electrocyclisation onto the comparator ring.

Since there are underlying assumptions in both "external" and "internal" competition reactions, it was decided that both should be attempted in the hope that the results from each would corroborate those from the other.

The "external" and "internal" competition approaches will be discussed in parts 1 and 2 respectively.
PART 1. "EXTERNAL COMPETITION" APPROACH TO RELATIVE RATE MEASUREMENT

2.1.1 Thermally Generated Nitrile Ylides

As described in Section 1 a convenient route to variously substituted N-benzoyl-2-arylbenzylamines was developed. As a logical extension to this work it was decided to carry out competition reactions on the nitrile ylides generated from these precursors.

The first objective was to identify a dipolarophile which would give a measurable ratio of (240):(278) (Scheme 57). It was also necessary that the cycloadduct (278) should itself be stable to the reaction conditions.
It was decided to carry out the initial studies using relatively low activity dipolarophiles. In each case the nitrile ylide was generated in the usual way in a solution of dipolarophile in T.H.F.

Trans-stilbene (2 equivalents) gave only one product, identified as 5-phenyl-7H-dibenz[c,e]azepine. No product derived from cycloaddition was observed. Norbornene (5 and 50 equivalents) and styrene (50 equivalents) also gave the azepine as the only product.

These results seemed to indicate that a dipolarophile of high reactivity in cycloaddition reactions was required to compete effectively with the electrocyclic process. Nitrile ylides are 1,3-dipoles of Type 1 as defined by Sustmann. That is, nitrile ylides undergo cycloaddition most efficiently with dipolarophiles possessing low-lying HOMO and, more especially, LUMO energies. Conjugated, electron-poor double-bonds have suitable F.M.O. energies and generally undergo [3+2] cycloaddition with nitrile ylides smoothly and in high yield.

Generation of the nitrile ylide (290) at 0°C in a T.H.F. solution containing two equivalents of dimethyl fumarate gave a brown, oily solid. This material was shown by $^1$H n.m.r. to contain a complex mixture of products including amide starting material (239, R=H) and unreacted dimethyl fumarate.

This result was rationalised in terms of excess base leading to further reaction of the product (291) (Scheme
Since no 5-phenyl-7H-dibenz[c,e]azepine was observed it appeared that cycloaddition to dimethyl fumarate was a much faster reaction. The 1-pyrroline product (291) contains two acidic protons which could be abstracted by excess tert-butoxide and thus lead to chemical degradation.

The experiment was repeated using only one equivalent of base in the hope that this would minimise secondary reaction. This led to a very similar product mixture containing a higher proportion of recovered amide starting material. These observations appeared to indicate that the base was in some way being scavenged at a rate
comparable to that of its reaction with the imidoyl chloride.

As explained above, it appeared that electrocyclisation was too slow to compete with the alternative reaction. It was therefore decided to use a less active dipolarophile. Dimethyl maleate is the cis-isomer of dimethyl fumarate. As explained in the introduction (pp. 45), cis-substituted olefins react more slowly in 1,3-dipolar cycloaddition reactions than the corresponding trans-isomers. In this case dimethyl maleate is 502 times slower than the fumarate\(^{121}\).

Generation of the nitrile ylide (290), using two equivalents of base, in the presence of five equivalents of dimethyl maleate again gave a complex mixture. Chromatography of the mixture gave a fraction identified as dimethyl fumarate, indicating that the olefin was active to attack by the base (Scheme 59). A control experiment confirmed that this was the case. Once again no dibenzazepine was observed.

![Scheme 59](image)
As in the previous case a significant amount of the amide starting material (239, R=H) was recovered. This indicates that a large proportion of the base was being consumed elsewhere. It is clear that a proportion of the base was reacting with the dipolarophile, however some of the imidoyl chloride is being consumed, presumably through conversion to nitrile ylide by reaction with base. It seems, therefore, that a proportion of the butoxide reacts with the trap, a proportion with the imidoyl chloride and presumably the remainder is consumed on reaction with the cycloadduct to give degradation products.

These conclusions agree with the observed results. A further conclusion must therefore be that the cycloadduct, once formed, is much more reactive to attack by base than is the imidoyl chloride precursor. This is understandable in terms of the highly activated hydrogens present on the pyrroline ring (292).

It was clear, therefore, that disubstituted olefins of
this type gave products unstable to the reaction conditions. The objective was therefore to find a dipolarophile with low lying HO/LU energies, but which did not possess hydrogens on the sp\(^2\) atoms which would be 'activated' to base attack in the cycloadduct. It was also required that the dipolarophile itself would be unreactive to direct attack by potassium tert-butoxide.

Aldehydes and ketones react readily with nitrile ylides to give oxazolines\(^{122}\) (295). The nitrile ylide (293), generated from the corresponding 2H-azirine has been shown to undergo 1,3-dipolar cycloaddition with \(\alpha,\alpha,\alpha\)-trifluoroacetophenone (294) in 90\% yield\(^{123}\).

\[
\begin{align*}
\text{Ph-CH-N} & \equiv \text{C-Ph} \\
(293)
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \equiv \text{C-Ph} \\
(294)
\end{align*}
\]

\[
\begin{align*}
\text{Ph-CH-N} & \equiv \text{C-Ph} \\
+ & \text{cycloaddition} \\
\text{PhACF}_3 & \equiv \text{PhNPh} \\
(295)
\end{align*}
\]

This dipolarophile, containing an oxygen heteroatom in
the double bond and electron-withdrawing and conjugating substituents would be expected to possess suitably low HO/LU energies. Also the expected cycloadduct (296) would not possess acidic protons susceptible to attack by base (Scheme 60). However, there still remained the possibility that the dipolarophile itself might be subject to attack by potassium tert-butoxide.

\[
\begin{align*}
\text{H} & \quad \begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{C} & \quad \text{N} = \text{C} \cdot \text{Ph}
\end{align*}
\end{align*}
\]

(290) +

\[
\begin{align*}
\text{Ph} & \quad \text{CF}_3 \\
\text{O}
\end{align*}
\]

(294)

\[
\text{KOBu}^+ \quad \?
\]

Scheme 60

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{O} & \quad \begin{align*}
\text{Ph} & \quad \text{CF}_3 \\
\text{Ph}
\end{align*}
\end{align*}
\]

(296)

The reaction was carried out using 5 equivalents of \(\alpha,\alpha,\alpha\)-trifluoroacetophenone and two equivalents of base. The usual work-up gave one major product (52%) as a white crystalline solid. This was identified as \(N,N\)-dibenzoyl-2-phenylbenzylamine (297) and its structure was confirmed
by X-ray analysis.

A large number of experiments were carried out with this system using different base:dipolarophile:imidoyl chloride ratios and it became clear that the 5-phenyl-7H-dibenz[c,e]azepine (244) was formed only when base was present in greater concentration than the ketone.

The rationalisation of these results is based on some known chemistry of imidoyl chlorides\(^{124}\) and imidate esters\(^{125}\). The first step appears to be the rapid scavenging of the added KOBut by the ketone to give the alkoxide salt (298). Imidoyl chlorides, e.g. (299), are known to exist in equilibrium with nitrilium salts (300) via the loss of chloride ion\(^{124}\). It seems possible that (298) and (300) could combine to give the imidate ester (301) with the formation of potassium chloride (observed as a precipitate) (Scheme 61).
Imidate esters (302) are known to add alkyl halides (R^4X) across the C=N double bond\textsuperscript{125}. Loss of a different alkyl halide (R^3X) gives the amide (304) (Scheme 62). The trifluoromethyl group is known to behave as a pseudo-halogen. Reaction of a second mole of trifluoroaceto-phenone as a pseudo acyl halide with (300) in a manner analogous to that described for alkyl halides with imidate...
esters would give the observed \(N,N\)-dibenzoyl-2-phenylbenzylamine (297) (Scheme 62).

\[
\begin{align*}
R^1 - N = C - R^2 & \quad \xrightarrow{R^4 X} \quad R^1 - N = C - R^2 \\
\text{(302)} & \quad \text{(303)} & \quad \text{(304)}
\end{align*}
\]

\[
\begin{align*}
\text{Ar-CH}_2 - N = C - \text{Ph} & \quad \xrightarrow{\text{PhCOCF}_3} \quad \text{PhCOCF}_3 \\
\text{(300)} & \quad \text{(305)}
\end{align*}
\]

\[
\begin{align*}
\text{Ar} = & \\
\text{Ph} & \quad \text{CF}_3 \\
\text{Ph} & \quad \text{CF}_3 \\
\text{OBu'} & \quad \text{Ph} \\
\text{OBu'} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar} = & \\
\text{CH}_2 & \quad \text{N} \quad \text{Ph} \\
\text{Ph} & \quad \text{O} \\
\end{align*}
\]

\[
\text{Ph}_2 = \text{N} \quad \text{Ph}
\]

Scheme 62

Thus, it appeared that potassium tert-butoxide was too
active as a nucleophile towards this dipolarophile. It was therefore decided to attempt to generate the nitrile ylides using alternative, less nucleophillic bases.

Although previous work in this group\(^7\),\(^8\) had shown that triethylamine was unsatisfactory for the generation of related nitrile ylides, it was decided that this base should, at least, be tested. Treatment of the imidoyl chloride (299) with triethylamine at room temperature gave no reaction. Heating the mixture to reflux resulted in a black tar being formed, confirming the conclusions of Motion\(^8\) and Robertson\(^7\).

Lithium diisopropylamide proved successful in generating the nitrile ylide (290) which cyclised to give azepine (244) in the absence of traps. It was also successful in that it did not promote formation of the \(N,N\)-dibenzoyl compound (297) with \(\alpha,\alpha,\alpha\)-trifluoroacetophenone. However, the trap proved ineffective in competition with the electrocyclic reaction and only 5-phenyl-7\(H\)-dibenz[c,e]azepine was isolated. Other dipolarophiles were tried using L.D.A. as base, but as expected, they showed the same behaviour as with potassium tert-butoxide, e.g. styrene gave azepine product exclusively and dimethyl maleate gave a complex mixture and recovered starting material.

Thus the attempts to find a dipolarophile reactive enough to compete with electrocyclisation and stable to the reaction conditions had failed. It was therefore
decided to seek a route to the nitrile ylide which did not involve the use of a strong base.

2.1.2 Photochemically Generated Nitrile Ylides

The generation of nitrile ylides by photolysis of 2H-azirines has been extensively used and developed by the group of Padwa. The most widely used route to 2H-azirines is via a modified Neber reaction. This method was used in the attempted synthesis of 2H-azirine (311) (Scheme 63).

\[
\begin{align*}
\text{CH}_2\text{CO}_2\text{H} & \xrightarrow{(i) \text{PCl}_3} \text{CH}_2\text{COPh} \\
\text{Br} & \quad \text{Br} \\
(306) & \quad (307) \\
\xrightarrow{(ii) \text{AlCl}_3/\text{Benzene}} & \\
\text{N-NMe}_2 & \xrightarrow{\text{MeNNH}_2} \\
\text{CH}_2\text{C-Ph} & \quad \text{CH}_2\text{COPh} \\
\text{Ph} & \quad \text{Ph} \\
(309) & \quad (308) \\
\text{Mel} & \xrightarrow{+ \text{N-NMe}_3 \text{I}^-} \\
\text{CH}_2\text{C-Ph} & \xrightarrow{\text{NaH}} \\
\text{Ph} & \quad \text{Ph} \\
(310) & \quad (311)
\end{align*}
\]

Scheme 63
The first stage was carried out using a literature method\textsuperscript{127}, the Friedel-Crafts reaction giving 2-bromo-phenyl acetophenone (307) in good yield. The second step involved a palladium catalysed cross-coupling reaction\textsuperscript{128} with phenylboronic acid. This method will be discussed in a later part of this thesis. Condensation of 2-phenyl-phenyl acetophenone (308) with unsym-$N,N$-dimethylhydrazine gave the $N,N$-dimethylhydrazone (309) in good yield as a yellow crystalline solid.

The next stage involved the formation of the methiodide salt (310) of the hydrazone. This step proved to be very difficult to achieve cleanly and the product was also difficult to purify. The optimum conditions were found to involve heating the hydrazone (309) with methyl iodide in D.M.F. at ca. 60°C for several hours. Removal of the solvent under high vacuum gave a brown oil. Trituration with ether gave a cream coloured paste which was shown by $^1$H n.m.r. to be the methiodide salt (310) in an impure form.

It was hoped that conversion of this impure product to the 2$H$-azirine would give a material capable of purification. Treatment of the hydrazonium iodide (310) in D.M.S.O. with one equivalent of sodium hydride gave, after work-up, a brown oil which was shown by $^1$H n.m.r. to contain a significant proportion of the desired 2$H$-azirine (311).

The method normally employed for purification of 2$H$-
azirines involves distillation at low pressure. Attempts to distil the impure azirine (311), however, resulted only in the formation of a black tar. Apparently, the high molecular weight of this system makes distillation impossible. All attempts to purify the azirine by chromatography were unsuccessful.

To confirm its structure a sample of the impure azirine (311) was irradiated in cyclohexane. Work-up gave a yellow foam shown by t.l.c. and $^1$H n.m.r. to contain 5-phenyl-7H-dibenz[c,e]azepine (244) (Scheme 64).

![Scheme 64](image-url)
Since it was impossible to purify the azirine, quantitative studies on reactions of the system were impossible. An accurate knowledge of at least the proportion of azirine present would be essential, but even so, the possibility of side reactions involving the impurities precluded quantitative studies.

Thus, this route was shown to give 2-(2-phenylphenyl)-3-phenyl-2H-azirine (311), but in a form insufficiently pure for the projected quantitative research.

PART 2. "INTERNAL COMPETITION" APPROACH TO RELATIVE RATE MEASUREMENT

As explained in the preamble to Section 2 a study of this type requires the development of a synthetic route to systems of the type (287).
Terphenyls of this type are not common in the literature, although there is some recent work by Hart\textsuperscript{129, 130} which involves sequential formation and reaction of arynes with Grignard reagents (Scheme 65).

This route, however, is only suitable for the construction of symmetrical systems. It was therefore required to develop a new synthetic approach to \emph{N}-benzoyl-2,6-diarylbenzylamines.
Approaches to the Preparation of
N-Benzoyl-2,6-diarylbenzylamines

2.2.1 via Grignard Reactions of N-2,6-Dimethoxybenzylidene isopropylamine

This approach was based on the method used for the preparation of N-benzoyl-2-arylbenzylamines as described in Section 1 (pp. 129). It was envisaged that this could be extended to allow the preparation of triaryl systems (287) as shown (Scheme 66).

\[ \text{(312)} \]

\[ \text{(313)} \]

\[ \text{(314)} \]

\[ \text{(315)} \]

\[ \text{(287)} \]

\[ \text{(316)} \]

Scheme 66
2,6-Dimethoxybenzaldehyde (313) was prepared from m-dimethoxybenzene (312) using the method of Wittig\textsuperscript{131}. Condensation of the aldehyde (313) with isopropylamine gave the desired imine (314) in good yield. This was added to a solution of phenylmagnesium bromide in T.H.F. and as in the method used in Section 1, the mixture was heated to reflux. G.l.c. analysis showed that the reaction had gone to completion in under 30 minutes, compared to ca. 16 hours for the monomethoxy analogue. The chromatograph indicated the presence of two products as well as unreacted starting material. These were identified by \textsuperscript{1}H n.m.r. as 2-methoxy-6-phenylbenzaldehyde (317) and 2,6-diphenylbenzaldehyde (318) in the ratio 1:2.

\begin{align*}
\text{CHO} & \quad \text{CHO} \\
\text{MeO} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}

(317) 
(318)

Thus it appeared that the substitution of the second methoxy group was more energetically favourable than displacement of the first. The energy difference could not, however, be very large as a substantial amount of
(317) was present. If the energy difference were large only the doubly substituted product (318) and the dimethoxy starting material would be isolated.

It was found that the selectivity of the reaction could be improved by carrying out the reaction at low temperature. Adding the imine (314) to a cold solution of phenylmagnesium bromide (1 equivalent) over 15 minutes followed by stirring at 0°C for 1.5 hours gave, after hydrolysis, 2-methoxy-6-phenylbenzaldehyde (317) in 53% yield. 2,6-Diphenylbenzaldehyde (318) was isolated in 12% yield and unreacted starting material 24%. The overall recovery was thus 89% after chromatography.

Scheme 67
Two factors require explanation. Firstly, why this dimethoxy system (314) reacts so much more readily than the monomethoxy analogue (249) (Scheme 67). It is conceivable that the second methoxy group, acting as a strong electron donor, could promote chelation of the imine with the Grignard reagent (Scheme 68). An effect of this type would assist formation of the chelated complex (320) postulated as an intermediate in the substitution reaction. If the initial chelation were the rate determining step this effect would accelerate the reaction.

This does not, however, explain why the phenyl group, attached in the first substitution, appears to promote substitution more effectively than a methoxy group. One
can envisage the phenyl group exerting a buttressing effect on the imino-group, pushing it around into the correct orientation for chelation with a second molecule of Grignard reagent. It is difficult to imagine, however, that this effect would be comparable with the electron donor effect of the methoxy group noted above. It appears, therefore, that several aspects of this reaction are not yet fully understood.

2-Methoxy-6-phenylbenzaldehyde (317) was condensed with isopropylamine and reacted with 4-chlorophenylmagnesium bromide. Hydrolysis gave the 2,6-diarylbenzaldehyde (316b). The two aldehydes (316 a,b) were converted to the amides (287 a,b) using the methods described in Section 1 (Scheme 69).

\[
\begin{align*}
\text{(316)} & \quad \text{CHO} \quad \text{NH}_2\text{OH} \quad \text{Ph} \\
\text{(317)} & \quad \text{NOH} \quad \text{Ph} \\
\text{(321)} & \quad \text{NH}_2\text{OAc},\text{NH}_3 \\
\text{(322)} & \quad \text{PhCOCl} \\
\text{(287)} & \quad \text{COPh} \quad \text{NH} \quad \text{CH}_2
\end{align*}
\]

Scheme 69
Thus this sequence of reactions achieved the first synthesis of the required 2,6-diaryl-amide (287). It was thought important at this stage to assess whether the steric effects of the two aryl groups would have any deleterious effect on the conversion of the amide group in (287) to the imidoyl chloride or on the subsequent nitrile ylide generation and cyclisation.

It was found that $N$-benzoyl-2,6-diphenylbenzylamine (287a) could be easily converted to the imidoyl chloride (323) using thionyl chloride in the usual way. Treatment of this with potassium tert-butoxide in T.H.F. at 0°C followed by the usual work-up and chromatography gave 5,8-diphenyl-7H-dibenz[c,e]azepine (324) as a white crystalline solid (Scheme 70).
Thus it was shown that nitrile ylides of this type could be generated and would react in the manner expected. The results of the reaction of the nitrile ylide derived from the imidoyl chloride prepared from amide (287b) will be discussed in a later section.

At this stage it was felt that, although this route was capable of furnishing systems of the type required, the process was somewhat cumbersome for the synthesis of a large number of variants. The low yields at an early stage together with the necessity to couple on the substituted aromatic rings three stages from the target compounds were not attractive. An alternative approach was therefore sought.

2.2.2 via Palladium Catalysed Cross-Coupling Reactions

During the early stages of this work research was being carried out in the same group by Mr Donald Reece. Following the work of Suzuki\textsuperscript{28}, Reece developed a route to \textit{N}-benzoyl-2-arylbenzylamines (326) using a palladium catalysed cross-coupling protocol (Scheme 71).

It was envisaged that a system of this type could be developed to provide an elegant route to the desired amides (287) (Scheme 71).
It was hoped that by coupling the aromatic rings at this late stage substantial savings in time and material could be made. That is, a large batch of the $N$-benzoyl-2-bromo-6-phenylbenzylamine (328) could be prepared and the appropriate substituted phenylboronic acids coupled on as required.

Two further advantages were envisaged. Firstly, this
route would allow the preparation of systems of the types (288) and (289) as heteroarylboronic acids and alkenylboronic acids are known to couple with aryl bromides.

The second major advantage would be the possibility of preparing an authentic sample of one of the predicted isomers resulting from the competition reaction (Scheme 72). Thus, 8-bromo-5-phenyl-7H-dibenzo[c,e]azepine (329) could be formed by converting the amide (328) to its nitrile ylide. If the bromoazepine (329) could be induced to undergo cross-coupling with substituted phenylboronic acids, the azepine (331) would be accessible. This would enable the identification of one product from the competition reaction (Scheme 72).
Given the advantages of this approach it was decided to pursue methods giving access to systems of the type (327).

2.2.2.1 Attempted Sequential Palladium Catalysed Cross-Coupling of 4-(N-Benzoylaminomethyl)-3,5-dibromo-benzoic Acid Methyl Ester

As described above it was hoped that an elegant route to the amides (287) could be developed using a palladium catalysed cross-coupling protocol. The most obvious route would involve sequential coupling of the 2,6-dibromo-compound (327). The logical precursor to this system was 2,6-dibromotoluene (333) which could be converted to the amide (327) using conventional chemistry before coupling (Scheme 73).

![Scheme 73]

Scheme 73
Unfortunately, 2,6-dibromotoluene (333) is not readily available, the literature method\textsuperscript{132} being a complex, low-yielding route. In contrast, the benzoic acid derivative (336) was readily available\textsuperscript{133}. It was hoped that the ester group could be removed at an early stage using flash vacuum pyrolysis (F.V.P.) methods, but even if it could not, the system would allow testing of the cross-coupling protocol. Also, it was not thought that the presence of the ester group would interfere to any important degree with the intended nitrile ylide competition reactions. The para-ester group would be expected to exert equivalent effects on both modes of electrocyclisation, therefore relative reactivities would be unchanged.

The title compound was prepared by the route shown in Scheme 74.

\begin{center}
\begin{tikzpicture}
\begin{scope}
\node at (0,0) {\(\text{CH}_3\)};
\node at (1,0) {\(\text{COCl}\)};
\node at (1.5,0) {\((335)\)};
\node at (2.5,0) {\(\text{Br}\)};
\node at (3,0) {\(\text{Br}\)};
\node at (3.5,0) {\(\text{Br}\)};
\node at (4,0) {\(\text{Br}\)};
\node at (4.5,0) {\(\text{Br}\)};
\node at (5,0) {\(\text{Br}\)};
\node at (5.5,0) {\(\text{Br}\)};
\node at (6,0) {\(\text{CO}_2\text{R}\)};
\node at (6.5,0) {\((336)\)};
\node at (7,0) {\(\text{R}=\text{Me}\)};
\node at (7.5,0) {\(\text{R}=\text{Et}\)};
\node at (8,0) {\(\text{CO}_2\text{Me}\)};
\node at (8.5,0) {\((337)\)};
\node at (9,0) {\(\text{K.Pthal}\)};
\node at (0,-1) {\(\text{H}_2\text{NNNH}_2\)};
\node at (1,-1) {\(\text{Br},\text{Br}\)};
\node at (1.5,-1) {\(\text{CO}_2\text{Me}\)};
\node at (2,-1) {\((338)\)};
\node at (3,-1) {\(\text{NH}_2\)};
\node at (3.5,-1) {\(\text{NH}_2\)};
\node at (4,-1) {\(\text{CH}_2\)};
\node at (4.5,-1) {\(\text{CH}_2\)};
\node at (5,-1) {\(\text{Br},\text{Br}\)};
\node at (5.5,-1) {\(\text{PhCOC}\)};
\node at (6,-1) {\(\text{CO}_2\text{Me}\)};
\node at (6.5,-1) {\((339)\)};
\node at (7,-1) {\(\text{CO}_2\text{Me}\)};
\node at (7.5,-1) {\((340)\)};
\end{scope}
\end{tikzpicture}
\end{center}
3,5-Dibromo-4-methylbenzoic acid methyl ester (336) was prepared using the method of Pearson, Stamper and Suthers. This method uses a 'swamping catalyst effect' as developed by the same group. It is thought that this effect involves halogenation of an aluminium chloride complex of (335) by the reactive halogenation species $\text{Br}^+\text{AlCl}_3\text{Br}$ which cannot be formed unless more than one equivalent of aluminium chloride is present. Quenching of the brominated complex with methanol or ethanol gave the esters (336) or (341) with the liberation of HBr.

Attempted removal of the methyl ester group by F.V.P. with furnace temperatures from 750°C to 950°C failed. Attempted removal of the ethyl ester in (341) failed likewise (Scheme 75).

\[
\begin{align*}
\text{CH}_3 & \quad \text{Br} \quad \text{Br} \quad \text{CO}_2\text{Me} \\
\text{(336)} & \quad \text{F.V.P.} \quad \text{750-950°C} \\
\text{CH}_3 & \quad \text{Br} \quad \text{Br} \\
\text{(333)} & \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{Br} \quad \text{Br} \quad \text{CO}_2\text{Et} \\
\text{(341)} & \quad \text{F.V.P.} \quad \text{750-950°C} \\
\text{CH}_3 & \quad \text{Br} \quad \text{Br} \\
\text{(333)} & \\
\end{align*}
\]

Scheme 75
As explained previously, however, it was felt that studies on the benzoic acid ester would be useful and the synthesis was continued. The remainder of the synthesis involved conventional methods.

Bromination of the methyl group in (336) using N-bromosuccinimide gave (337). Reaction of this with potassium pthalimide in D.M.F.\textsuperscript{134} gave (338) in the first stage of the Gabriel reaction\textsuperscript{135}. This pthalimido derivative (338) was cleaved with hydrazine hydrate\textsuperscript{136} to give the amine (339) and pthaloyl hydrazide (343).

![Chemical structures]

\[ \text{O} \quad \text{9-} \quad \text{0} \quad \text{NH}_2 \quad \text{0} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{Br} \quad \text{Br} \quad \text{Br} \quad \text{H}_2 \text{NNH}_2 \quad \text{Br} \quad \text{NH} \quad \text{NH} \quad \text{CO}_2 \text{Me} \quad \text{CO}_2 \text{Me} \]

\[ \text{O} \quad \text{(338)} \quad \text{NH}_2 \quad \text{CH}_2 \quad \text{Br} \quad \text{(339)} \quad \text{+} \quad \text{NH} \quad \text{NH} \quad \text{(343)} \]

It was found that the two products (339) and (343) had very similar physical properties. The most convenient method of separation involved soxhlet extraction with chloroform as solvent. This extracted the amine (339) into the solvent in 94\% yield. The amine was converted to
4-(N-benzoylaminoethyl)-3,5-dibromobenzoic acid (340) with benzoyl chloride.

The next objective involved the monophenylation of the amide (340). This was attempted using the method of Suzuki\textsuperscript{128}. The procedure involves treatment of an aryl halide with an arylboronic acid in the presence of base and tetrakis (triphenylphosphine) palladium catalyst (Scheme 76).

\[
\begin{array}{c}
\text{Z} & \text{Br} \\
\end{array}
+ \quad \begin{array}{c}
\text{B(OH)}_2 \\
\end{array}
\xrightarrow{\text{Pd(PPh}_3\text{)}_4, \text{Na}_2\text{CO}_3}
\begin{array}{c}
\text{Z} & \text{Y} \\
\end{array}
\]

Scheme 76

In the present case it was hoped that treatment of the 2,6-dibromoamide (340) with one equivalent of phenylboronic acid would show some selectivity and give the monophenylated product (344) as the major product. It was expected that even if a mixture was obtained that it would be separable by chromatography. It was found by h.p.l.c. (ODS - 5 \( \mu \)m, reverse phase) that two products
were formed. These were completely inseparable by preparative chromatographic techniques, but were shown, by $^1$H n.m.r. and mass spectrometry, to be the mono- and diphenylated amides (344) and (345) in the ratio 1.1:1.0 (Scheme 77).

![Chemical structure](image)

**Scheme 77**

These two products, as well as being inseparable from each other, were also inseparable from the starting material (340). This process was therefore unsuitable for the preparation of unsymmetrically arylated amides of the type (287).

The catalytic cross-coupling process is summarised in
Scheme 78. The reason for the second coupling occurring almost as readily as the first is not altogether clear. Earlier work\textsuperscript{8,7} had indicated that the presence of electron withdrawing groups in the aryl halide accelerate the reaction, but here the substitution of Br by Ph appears to make little difference. Further work showed that even with a deficiency of phenylboronic acid (0.5 equivalents) there was virtually no selectivity between mono- and di-substitution.

![Scheme 78](attachment:Scheme78.png)
Attempted monophenylation of 3,5-dibromo-4-methylbenzoic acid methyl ester (336) under the same conditions showed that this system too displays little selectivity between mono- and diphenylation and the products were again inseparable.

As it appeared that no selectivity could be induced in the palladium catalysed cross-coupling of meta-dibromo systems, other methods of preparing materials of the type (287) were sought. It was thought that recently developed ortho-metalation procedures might provide a convenient route to systems of this type.

2.2.2.2 Attempted Preparation of Aryl Bromides via Ortho-Metalation Reactions

In recent years there has been considerable interest in the area of ortho-metalation reactions. A variety of ortho-directing groups have been utilised on aromatic rings to direct regiospecific metalation. For example, Sniekus' has used a variety of groups in the synthesis of triaryl systems (Scheme 79).

\[
\begin{align*}
\text{DMG} & \xrightarrow{(i)RL\text{I/TMSCl}} \text{DMG} \\
& \xrightarrow{(ii)BBr_3} \xrightarrow{(iii)H^+} \xrightarrow{\text{ArBr}/\text{Pd}^0/\text{Na}_2\text{CO}_3} \text{Ar}
\end{align*}
\]

\[
\text{DMG=CON(Pr)_2OCONEt_2OMOM;NHCO_2Bu'}
\]

Scheme 79
A study of the literature showed that the amide group required in the present work does not direct ortho-lithiation, but is doubly lithiated as shown in Scheme 80138. This exclusive lithiation at the benzyl carbon was the first reported example of a metalation α to N of a monosubstituted amide.

The lithiated intermediate (347) reacts readily with electrophiles to give (348) (Scheme 80).

As direct ortho-lithiation of the amide was impossible, suitable directing groups, capable of conversion to the amide, were sought.

The first such group studied was CH₂OH, known to promote o-metalation in benzyl alcohol. 2-Biphenyl-
methanol (350) was treated with n-butyllithium in the presence of tetramethylethylene diamine (TMEDA) in the hope that this would lead to lithiation ortho to the methanol group. Quenching with bromine would then give the ortho-bromo compound (353) (Scheme 81) which could be converted to the required amide using standard methods.

Scheme 81
It was found, however, that treatment of the commercially available 2-biphenylmethanol with 2 equivalents of n-butyllithium at room temperature, followed by addition of bromine gave one product which was identified as 2-phenylbenzaldehyde (251a) by comparison with an authentic sample. The formation of this product can be rationalised as shown in Scheme 82.

Thus it appears that the methylene proton in (350) is more susceptible to metalation than the ortho-aryl proton. Double lithiation therefore occurs as shown. Addition of bromine leads to the loss of two equivalents of lithium bromide with formation of the aldehyde (251a). Attempted quenching with 1,2-dibromoethane at -78°C gave the same result.

An alternative approach involved recent work by Comins and Brown. These workers have shown that $N,N,N-$
trimethylethylenediamine can be used as an aldehyde protecting group which is capable of directing ortho-lithiation (Scheme 83).

Scheme 83

It was hoped that treatment of 2-phenylbenzaldehyde in this way followed by quenching with an electrophile would give access to systems of the type (354, R=6-Ph).

2-Phenylbenzaldehyde was treated with the lithium salt of N,N,N-trimethylethylenediamine at -20°C in T.H.F. A further equivalent of n-butyllithium followed by addition of trimethylsilyl chloride and acidic work-up gave the silylated product (355) in moderate yield.
This indicated that the ortho-lithiation reaction was occurring as expected. However, attempts to extend the reaction using different electrophiles were unsuccessful. For example, iodine gave a black, multi-component mixture while triisopropylborate gave unreacted starting material.

Given that an appropriate electrophile could not be found it was decided to attempt to modify the trimethylsilyl group. Work by Pray\textsuperscript{40} and Eaborn\textsuperscript{141,142} has shown that the silyl group can be cleaved by bromine in an ipso-bromodesilylation process (Scheme 84).

This reaction was attempted using various conditions in an attempt to convert 6-phenyl-2-trimethylsilylbenzaldehyde (355) to 2-bromo-6-phenylbenzaldehyde (356). All of the conditions used, however, gave unreacted starting material. Further attempts to replace the trimethylsilyl group by a boronic acid (357) using the method of Snieckus\textsuperscript{137} also failed, giving black intractible mixtures.

![Scheme 84](image-url)
As modification of the trimethylsilyl group appeared to be impossible and reaction of the lithiated species with common electrophiles was unsuccessful a slightly different approach was attempted.

There has been a considerable amount of work done recently on the palladium catalysed cross-coupling reactions of organotin compounds\textsuperscript{143,144}. Organostannanes may be coupled with aryl halides in a reaction analogous to the cross-coupling of boronic acids with aryl halides. With this in mind, it was thought that, if trimethyltin chloride were to behave like trimethylsilyl chloride as an electrophile, a convenient route to the required triaryl systems would be possible (Scheme 85). The ortho-trimethyltin substituent in (359) could be conveniently coupled with aryl halides to give the target amides (287).

Scheme 85
When the reaction was carried out only one product was isolated which was characterised as 2-ethenyl-6-phenylbenzaldehyde (360). The formation of this unexpected and interesting product was rationalised as shown in Scheme 86. An intramolecular cyclisation eliminates trimethyltin dimethylamine to give the fused six-membered ring system (361). Ring opening, followed by a second elimination gives the observed product (360).

Scheme 86
Thus, this route too was shown to be inapplicable to the synthesis of the target amides (287).

The previous sections contain descriptions of the early attempts to devise a versatile synthetic route to the 2,6-disubstituted amides required as nitrile ylide precursors for the internal competition reactions. These routes were all unsatisfactory in some way. The next section and the remainder of the discussion describe the successful route to these amides and the relative reactivity studies which followed.
PART 3. MEASUREMENT OF RELATIVE RATES OF ELECTROCYCLISATION via INTRAMOLECULAR COMPETITION REACTIONS

The details and results of the competition reactions undertaken are described in the following sections together with a brief rationale of why these particular experiments were carried out. The overall set of results is then rationalised in a mechanistic sense in Section 2.3.4 (pp. 246).

Following a description of the synthetic strategy used in the preparation of the nitrile ylide precursors an outline is given of the methods used for determining relative rates and for product identification. The competition reactions themselves are discussed under five headings: 1) alkenyl and thienyl, 2) meta-substituted aryl rings, 3) para-substituted aryl rings, 4) "competition cycles" - (para versus para) and 5) ortho-substituted aryl rings. An overview of the accumulated results is then presented together with our rationalisation and conclusions.

2.3.1 Synthetic Strategy

It was shown in the previous sections that sequential coupling reactions of meta-dibromocompounds with arylboronic acids show virtually no selectivity. That is, the second coupling takes place at a similar rate to the first (Scheme 77). It became necessary, therefore, to
Scheme 87
devise a synthetic route which would enable the coupling reactions to be carried out at different stages.

The route devised is shown in Scheme 87. The starting material chosen was 6-bromo-2-nitrotoluene (363). This starting material allowed the first coupling reaction to be carried out regiospecifically at the only bromo group present. It was envisaged that the nitro group could be subsequently converted to a bromo group for participation in the second coupling reaction. The methyl group could, in principle, be converted to the required amide using chemistry described earlier in this thesis (pp. 183).

6-Bromo-2-nitrotoluene was prepared from commercially available 2-methyl-3-nitroaniline (362) using the method of Harrington and Hegedus$^{145}$, steam distillation gave the pure product (363) in good yield. This was then coupled with phenylboronic acid, under the normal conditions, to give 2-nitro-6-phenyltoluene (364) in excellent yield. The nitro compound was reduced to the amine (365) using hydrogen and palladium on carbon catalyst. This reduction required ca. 2 days at S.T.P., but was achieved in several hours using a Parr hydrogenator and 35 p.s.i. of hydrogen, which gave the amine in quantitative yield.

Conversion of the amine (365) to the bromo compound (366) was achieved using a Sandmeyer reaction analogous to that used in the preparation of (363) from (362). A second product formed during this reaction was identified
as the phenol (370).

![Chemical structures](image)

Varying the temperature of decomposition of the diazonium salt was found to have little effect on the ratio of these two products. Formation of the by-product (370) was minimised by using a large excess of copper(I) bromide in the decomposition step. This by-product was inseparable by steam distillation, therefore large scale dry flash chromatography was used to isolate 2-bromo-6-phenyltoluene (366) in 65% yield. This was the lowest yielding step in the entire synthesis.

With the bromo group, required for the second cross-coupling reaction, in place, modification of the methyl group, which would eventually form part of the nitrile ylide, was begun.

Using chemistry described in Section 2.2.2.1 of this thesis the methyl group was converted to the target amide
Bromination of (366) with N-bromosuccinimide gave (367) in almost quantitative yield. This was converted to the amine (369) via the pthalimido derivative (368) using the Gabriel synthesis. The final stage in the preparation of the amide involved treatment of this benzylamine with benzoyl chloride. The amide was isolated in two stages. Firstly a bulk recrystallisation from ethanol gave the first crop in 65% yield. The crystallisation mother liquor was then subjected to dry flash chromatography to give a second crop of white crystals (overall yield 82%).

With a large batch of N-benzoyl-2-bromo-6-phenylbenzylamine (328) in hand, the study of relative reactivity in the 1,7-electrocyclisation reactions of nitrile ylides was begun.

The methods of preparing the various nitrile ylide precursors, relative rate measurement and product identification were general to all of the competitions and these are outlined in the next section.

2.3.2 The Competition Reaction Methods

This section describes the methods used to prepare the nitrile ylide precursors (287), the nitrile ylides (330) and the authentic sample (331) used to identify one of the product isomers. The overall reaction scheme used in the competitions is shown in Scheme 88.
Scheme 88

In all cases the amides (287), required as nitrile ylide precursors, were prepared from the bromocompound (328) by a Pd$^\circ$ catalysed cross coupling reaction with the appropriate boronic acid. After purification the amides were converted to imidoyl chlorides in the usual way, that is by heating at reflux in thionyl chloride and ether.
overnight.

Each nitrile ylide (330) was generated from the corresponding imidoyl chloride in T.H.F. at 0°C with potassium tert-butoxide, the mixture was stirred at 0°C for two hours then at room temperature for 1 hour. After quenching with ammonium chloride solution the crude reaction product mixture was obtained by extraction with methylene chloride and evaporation.

Analysis of the mixture for the (331):(332) ratio was carried out by 'H n.m.r. (360 MHz), generally using the peaks due to the methylene protons of the azepine ring. In cases where alternative signals could be used for measurement, e.g. CH₃, OCH₃, these were used as a check. All of the competition reactions were carried out in duplicate and in most cases were done in both T.H.F. and D.M.F. to discover the effect of changing solvent polarity.

As mentioned previously an advantage of this method was the possibility of preparing an authentic sample of one of the isomeric products. This was achieved by converting the bromo compound (328) to the imidoyl chloride then nitrile ylide by the usual methods. This gave 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (329) in 90% yield. By simply coupling this compound with the appropriate boronic acid an authentic sample of (331) was prepared.

It was found that the simplest method of product
Repeat of above with "authentic" (331) added
identification involved adding a sample of (331) to the crude reaction mixture and repeating the 'H n.m.r. spectrum. This showed enhancement of signals corresponding to the isomer (331), having no effect on the signals due to (332) and allowed the isomers to be identified as shown in Figure 30.

In several cases a control experiment was carried out on the reaction mixture to which the authentic azepine (331) had been added. The sample was reduced to dryness, dissolved in T.H.F. at 0°C and treated with two equivalents of potassium tert-butoxide. After work-up the sample was again studied by 'H n.m.r. and in each case the relative amounts of (331) and (332) were unchanged. This confirmed two things, firstly that the two products are not interconvertible under the reaction conditions, i.e. the products are formed under kinetic control and are not in equilibrium. Secondly this shows that both products are stable to the reaction conditions (Scheme 89).

![Scheme 89](image)
In general each competition reaction was carried out twice, firstly on an n.m.r. scale (50 mg of amide (287)) and secondly on 0.5 mmolar scale. The reactions were duplicated firstly to ensure that the observed results were reproducible and secondly so that the larger scale product mixture could be purified (by chromatography) and characterised. In most cases the products (331) and (332) were inseparable by preparative chromatography, and purification was shown not to alter the isomer ratio.

In one instance an attempt was made to quantify the minimum detectability limit of the minor isomer. A sample of the authentic dibenzazepine (331) which was 1% by weight of a pure sample of (332) was added to an n.m.r. solution. This led to the appearance of the expected signals giving measurable integrals. Thus it appears that this technique will show the presence of minor isomers whose concentration is less than 0.01 that of the major isomer.

It has been shown, therefore, that this technique provides a convenient, sensitive method of carrying out the "internal competition reactions" leading to stable isomeric mixtures, one isomer being readily identified. Using the general methods described above the competition reactions were carried out on a range of nitrile ylides, the details of these experiments will now be discussed.
2.3.3 **The Competition Reactions**

The competition reactions which were carried out may be conveniently divided into five groups. The reasons for carrying out each set and the results observed are discussed under five headings.

2.3.3.1 *Alkenyl and Thiienyl*

One of the major factors which led to this study of relative reactivity was the observation that the nitrile ylide (239) appeared to undergo 1,7-electrocyclisation much faster than the analogues (175) and (234). This inference was based on the duration of the deep purple colour, taken to be the nitrile ylide, which appears immediately upon addition of potassium tert-butoxide to the imidoyl chloride precursors. The details of the observed colour changes were described earlier in this thesis (pp. 140-141), but it is worth reiterating that while the nitrile ylides (175) and (234) gave purple colours lasting several minutes at 0°C, nitrile ylides of the type (239) gave an observable purple colour only when cooled to -10°C. The apparently much faster cyclisation of (239) is not in accord with what would be predicted by theory as this involves disruption of two aromatic systems compared with disruption of only one in (176) and (235). (Scheme 90).
The situation is complicated by the fact that (175) gives (177) as a primary product, via a formal 1,1-cycloaddition, which rearranges to the azepine (218) on heating. It is not at present certain that formation
of (177) occurs by a single step 1,1-cycloaddition process. It is possible that (175) undergoes 1,7-electrocyclisation to give the intermediate (176) followed by a rapid 6π electrocyclic ring collapse to give (177) which occurs faster at 0°C than the sigmatropic hydrogen shift to give (218) (Scheme 91).

However, whatever the mechanism, the apparently much faster cyclisation rate of (239) relative to (175) and (234) was an anomaly not easy to explain.

Accordingly the first competition experiment was carried out between a phenyl group and an ethenyl group in
the nitrile ylide (288).

The nitrile ylide precursor (371) was prepared by the cross-coupling of the bromo-compound (328) with 2-phenylethenylboronic acid. The boronic acid was made by the method of Brown and Gupta¹⁴⁶ and I would like to thank Mr F. McAllister for his assistance in the preparation of this material. The coupling reaction, in common with all of the subsequent couplings, was monitored by h.p.l.c. and continued until the bromocompound was completely consumed (ca. 30 minutes). Crystallisation from ethanol/toluene gave the amide (371) in 81% yield.

The nitrile ylide (288) was generated in the usual way from the imidoyl chloride and the mixture allowed to stir
for 2 hours at 0°C and 1 hour at room temperature. After the usual work-up the 'H n.m.r. of the crude product indicated that no azepine was present. The spectrum did, however, show signals characteristic of the cycloprop[c]isoquinoline (372) (Scheme 92) (see Appendix 2).

An authentic sample of (373) was prepared by coupling the vinylboronic acid with the bromodibenzazepine as shown
in the general scheme (Scheme 88). From the n.m.r. spectrum of this compound it was clear that it was completely absent from the product mixture of the competition reaction. To check that the signals had not been shifted by solvent or solute interactions a sample of this product was added to the competition reaction n.m.r. sample. This led to the appearance of the characteristic pair of doublets at $\delta$3.75 and $\delta$5.41, confirming that no azepine was present in the original mixture. A control experiment, as described previously, showed that the products were both stable to the reaction conditions and non-interconvertible.

Thermolysis of the cycloprop[c]isoquinoline (372) at 80°C for 4 hours gave the benzazepine (375) in high yield (Scheme 93). Thus the initially formed product exhibits behaviour analogous to systems reported previously??.

![Scheme 93](image)
It appears from this competition reaction that cyclisation of the nitrile ylide onto the terminal olefinic bond is very much faster (> 100x) than attack on the aromatic double bond. This observation is sensible on the basis of the mechanisms discussed earlier, but is directly opposite to the inference drawn about rates of cyclisation from the duration of the violet colour. Two conclusions may be drawn from this: (i) even rough estimates of rates of cyclisation based on the duration of the red/violet colour, thought to be due to the nitrile ylide, are unreliable and (ii) the colour may not be due to the nitrile ylide, but may perhaps be due to the quinonoid intermediate, e.g. (374) postulated as the primary product of electrocyclisation.

The next competition reaction studied involved competition between phenyl and thienyl rings. Recent work in this laboratory has shown that nitrile ylides of the type (376) undergo 1,7-electrocyclisation at the 2,3-position in thiophene to give azepines of the type (377) in high yield.

![Diagram](image)
The 2,3-double bond in thiophene may be considered intermediate in double bond character between the fully localised double bond of an alkene and the fully delocalised double bond in benzene. The exclusive preference of the nitrile ylide for olefinic relative to aromatic double bonds, demonstrated in the previous experiment, made this system interesting.

The nitrile ylide precursor (378) was prepared in the usual way by coupling (328) with 2-thiopheneboronic acid in 98% yield. Generation and reaction of the nitrile ylide under the normal conditions gave a product, identified by 'H n.m.r. as the thienobenzazepine (379) (Scheme 94). This product showed the normal pair of methylene doublets, somewhat broadened due to the lower-energy barrier to ring inversion, a feature characteristic of systems of this type.
Addition of a sample of the authentic dibenzazepine (380) caused the appearance of a pair of sharp doublets not originally present. Thus, as far as could be detected by n.m.r. analysis, the nitrile ylide (378) undergoes 1,7-electrocyclisation exclusively at the thiophene ring.

It appears therefore that the reactivity of the alkenyl group and of the thiophene ring are at least 100 times greater than that of the unsubstituted phenyl ring.

Attention was next turned to competitions between substituted and unsubstituted phenyl rings. By varying the nature of substituents on the phenyl ring it was hoped that the 'electronic demand' of the reaction could be determined. The first systems to be studied were those containing meta-substituents on the phenyl ring (N.B. meta refers to the position of the substituent relative to the biphenyl linkage).

2.3.3.2 meta-Substituted Aryl Rings

In the synthetic study, described in Section 1 of this thesis, it had been found that the presence of a fairly strong electron withdrawing group (Cl) or a strong electron donating group (OMe) in the para-position of the ring did not reduce the yield of azepine. It was of interest, therefore, to find out in a more quantitative sense, how the rate of this electrocyclic aromatic substitution process was affected by the electronic properties of ring substituents.
It was decided, first of all, to carry out competitions on meta-disubstituted systems of the type (381, X=H; F).

Systems of this type were chosen for the following reasons: (i) the two substituent types, i.e. CH₃ and CF₃, are known to exert opposite effects (electron-donor and electron-withdrawing respectively), (ii) neglecting the possibility of hyperconjugation, both groups exert their effects in an inductive manner, thus complications arising from conjugative effects are minimised, (iii) the symmetrically substituted ring offers two positions of attack, both of which lead to identical products, thus removing the complication of identifying more than two isomers and (iv) it was hoped that the combined effect of two substituents would maximise the chance of observing a clear distinction between the two modes of 1,7-electrocyclisation.

The starting materials were prepared in the usual way by the coupling of (328) with the appropriate boronic acid. The nitrile ylides were then generated and reacted
in the normal way each giving product mixtures containing two isomeric products (382) and (383). The signals corresponding to (383) were identified by addition of an authentic sample prepared from the bromo-dibenzazepine (329) in the usual way.

The results of the competition reactions are presented in Table 3 below. In both cases the products were inseparable by chromatography.

Table 3

<table>
<thead>
<tr>
<th>Solvent</th>
<th>a) X = H</th>
<th>8.3</th>
<th>1.0*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T.H.F.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D.M.F.</td>
<td>7.6</td>
<td>1.0*</td>
</tr>
<tr>
<td>b) X = F</td>
<td>T.H.F.</td>
<td>32.0</td>
<td>1.0*</td>
</tr>
<tr>
<td></td>
<td>D.M.F.</td>
<td>*</td>
<td>major</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>minor</td>
</tr>
</tbody>
</table>

# Signals identified by addition of an authentic sample.
* Baseline noise in spectrum made accurate integration impossible.
These competition reactions show that the presence of two electron-withdrawing CF₃ groups activate the ring to electrocyclisation by a factor of 32. Quite remarkably the two electron-donating CH₃ groups also activate the ring, but by only ca. 8 times.

It is also interesting to note that in the case of (381, X=H), an increase in solvent polarity (T.H.F.→ D.M.F.) appears to lead to a slight diminution of selectivity. If this were the case it would indicate that the preference for attack at the substituted ring, in whatever form it takes, is partially neutralised by highly polar solvents.

The next two nitrile ylide systems studied introduced a further level of complexity. The two nitrile ylides (384 a,b), each containing only one meta-substituent were investigated.
The reasons for the choice of these two are as follows: (i) the substituents once again possess opposite characteristics, this time being mainly of a mesomeric nature. The NO$_2$ group is a powerful conjugative electron withdrawing group whereas OMe is a moderately strong conjugative electron-donor and (ii) a study of this type would provide a direct extension to that carried out by Groundwater and Sharp$^{85}$ on nitrile ylides of the type (236b). These workers observed that nitrile ylides of this type show a marked preference for attack at the ring position ortho to the substituent irrespective of substituent type (Table 4).

![Chemical structures](image)

<table>
<thead>
<tr>
<th>X</th>
<th>236b</th>
<th>237b</th>
<th>238b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>2.5</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>1.5</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>2.1</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>CF$_3$</td>
<td>1.5</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Table 4
In the present study it can be seen that the nitrile ylides (384) have three potential sites of attack: (i) attack on the unsubstituted ring, (ii) attack ortho to the substituent in the substituted ring, or (iii) attack para to the substituent in the substituted ring. It was hoped, therefore, to determine the effect of substituents on both regioselectivity and upon overall reactivity.

The nitrile ylides (384) were generated and reacted under the normal conditions. Integration of the relevant signals in the 360 MHz n.m.r. spectra gave the isomer ratios shown below (Table 5).
In the nitro case (384a) only two isomeric products were formed showing characteristic azepine methylene doublets at $\delta 3.63$, 3.81, 5.16 and 5.22. Addition of an authentic sample of (385a) resulted in the appearance of new doublets at $\delta 3.71$ and 4.90. The two products were successfully separated by dry-flash chromatography and identified by their $^1$H n.m.r. spectra.

The isomer (387a) showed a highly deshielded singlet at $\delta 8.68$ which was attributed to the bay-ring proton ortho to NO$_2$. The other isomer (386a) showed a deshielded doublet of doublets at $\delta 8.08$ attributed to the bay-ring proton coupled with two aromatic hydrogen atoms ortho and meta to it (Figure 31) (see Appendix 2).
This result therefore shows that the single meta-nitro group activates the ring so that it is at least 100 times more reactive than the unsubstituted ring. It also shows that a single nitro-group activates the ring more strongly than do two CF\(_3\) groups and much more so than two CH\(_3\) groups. A further point of interest is that, as in the work of Groundwater\(^8\), the position ortho to the substituent is much more reactive to attack than the para-position.

In the case of the methoxy-substituted nitrile ylide (384b), three isomeric products were obtained. The methylene signals derived from these were not resolvable at 360 MHz, therefore the methoxy signals, which were fairly well separated, were used for identification and integration. The signal due to the isomer resulting from electrocyclisation onto the unsubstituted ring (385b) was identified by addition of an authentic sample while the other two isomers gave methoxy signals at \(\delta3.54\) and 3.96. The signal at \(\delta3.54\) was attributed to (386b) as a Dreiding model showed that this methoxy group lies above the face of the pendant phenyl ring and will experience a shielding effect.
All three isomers were inseparable by chromatography, their ratios, determined by integration of the methoxy signals in the $^1$H n.m.r. spectrum are shown in Table 5.

This result again showed several interesting features. Firstly, in analogy to the work of Groundwater$^{85}$, attack at the ring position ortho to the substituent is favoured over para-attack. Secondly, the product ratios are influenced by solvent polarity, indicating that charge separation in the transition state is an important factor. Thirdly, and most remarkable is the observation that the methoxy group, like the nitro group, activates the substituted ring to electrocyclisation.

The results obtained from the competitions involving meta-substituted aryl rings were remarkable and not readily explicable. It was found that, in all cases, the substituted ring was the more reactive, regardless of the nature of the substituent. It should be noted here that although methoxy is a conjugative electron donor it also possesses an inductive electron-withdrawing effect which might be important.

Nevertheless, the results so far have shown that both inductive and resonance properties in the substituents...
appear to activate the electrocyclic reaction in some way. Solvent polarity also appears to have some influence on the selectivity of the system, but this appears to be a less important factor.

It was felt that, in this type of electrocyclic reaction, the ring position of the substituent might be an important factor, as will be explained in the following section, therefore a range of para-substituted systems were studied.

2.3.3.3 *para*-Substituted Aryl Rings

Work on the *meta*-substituted systems had shown that the presence of both electron-withdrawing and electron donating groups close to the site of cyclisation had a strong influence on cyclisation rate. It was of interest to determine whether the effect of these groups was enhanced, diminished or reversed in the *para*-position.

A very interesting factor involved the possibility of extended conjugation of the substituent. In the *meta*-substituted cases it was thought that the major effect of the substituent would be limited to the ring under attack. This follows from the fact that 'out-of-ring' conjugation is impossible for *meta*-substituents. *Para*-substituents, on the other hand, are capable of extended conjugation right through to the nitrile ylide itself (Figure 32).
As shown, the possibility of delocalisation leads to further canonical forms of the nitrile ylide systems and this could lead to different effects on reactivity to those seen for the same substituents in the meta-position.

a) Inductive Substituents

The first substituents studied were the para-CX₃ (X=H; F) groups. These were again chosen for their structural similarity and their opposite electronic properties.
These substituents are both inductive in character, thus providing a starting point free of the possible resonance effects.

The nitrile ylide precursors were again prepared by coupling of the bromo compound (328) with the appropriate boronic acid. The nitrile ylides (388) were prepared and reacted in the usual way and one product isomer identified by addition of an authentic sample prepared from the bromodibenzazepine (329).

The results of the competition reactions involving para-CH₃ and para-CF₃ are shown in Table 6.

![Chemical Structures](attachment:image.png)

Table 6

<table>
<thead>
<tr>
<th>Solvent</th>
<th>a) X = H</th>
<th>b) X = F</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.H.F.</td>
<td>1.5</td>
<td>2.8</td>
</tr>
<tr>
<td>D.M.F.</td>
<td>2.1</td>
<td></td>
</tr>
</tbody>
</table>

(388) \rightarrow (389) \rightarrow (390)
Once again the results showed the remarkable effect that both substituents, irrespective of their electronic properties, activated the ring to electrocyclisation. Both of these substituents exert an influence which is purely inductive, a short range effect which is therefore expected to be evident only within the ring under attack. That these results are consistent with, though smaller than, those observed for the meta-substituted systems (384 a,b) is therefore not surprising.

Another observation worthy of comment is that, as in the meta-substituted cases, increasing solvent polarity (T.H.F.→D.M.F.) leads to a lessening of the selectivity between attack at the substituted and unsubstituted rings. It appears then that in the para-substituted cases too, charge separation in the transition state may be a significant factor.

b) Conjugating Substituents

Having shown that para-substituents of both +I and -I character enhance 1,7-electrocyclisation an investigation of the effect of conjugating substituents was undertaken.

The first system to be investigated was that containing a para-dimethylamino substituent (394). This was chosen as the substituent is known to be a powerful electron donor, having a Hammett $\sigma$-value of $\sigma_p = -0.83$.

Although the amide starting material (392) was prepared in the usual way it was found that attempts to
prepare the imidoyl chloride (393) by the normal method gave only intractable mixtures. This observation was attributed to salt formation, between the basic amino group and HCl, leading to side reactions. The imidoyl chloride was therefore prepared by an alternative method using a more powerful chlorinating agent.

The chlorinating agent (391) is formed by the reaction of thionyl chloride with D.M.F. This species gave the imidoyl chloride (393) with (392) at room temperature overnight (Scheme 95).

Scheme 95
The imidoyl chloride (393) prepared in this way was dissolved in T.H.F. at 0°C and the nitrile ylide (394) generated in the usual way by treatment with potassium tert-butoxide. The normal work-up and analysis of the crude product mixture indicated the presence of two azepines (395) and (396) in the ratio 1.3:1.0 (Figure 33). Once again (396) was identified by addition of an authentic sample.

![Chemical Structure](image)

Figure 33

The small activating effect shown by the dimethylamino group was somewhat surprising compared with the larger effects exhibited by the \( \text{CX}_3 \) groups which possess much lower \( \sigma_p \) values. It is conceivable that this lower activating effect results from resonance contributions due
to the introduction of the powerful $\pi$-donor substituent. Alternatively, resonance effects may have little bearing on the observed effect and only inductive effects are important.

It should be noted that the reactions of the para-dimethylamino system gave messy product mixtures when carried out in T.H.F. The n.m.r. spectrum of the crude product mixture indicated the presence of by-products although $^1$H n.m.r. showed that the imidoyl chloride had been formed cleanly. Dry flash chromatography of the crude mixture gave only ca. 50% yield of the isomeric azepines (395) and (396) which were inseparable. When the reaction was attempted using D.M.F. as solvent no azepine formation was observed. The worked-up reaction mixture gave mainly recovered amide (392) and several unidentified by-products.

From the competition reaction product ratios, however, it appeared that this powerful resonance electron-donor substituent had only a small activating effect on the substituted ring.

Methoxy is also known to be a $\sigma$-electron donating substituent, although less powerful than NMe$_2$, having $\sigma_p$ = -0.27. This substituent was studied for several reasons. Firstly, as a $\tau$-donor which also possesses significant -I character, its effect relative to that of NMe$_2$, which has only a small inductive effective was of interest. Secondly, the preliminary synthetic studies described in
Section 1 of this thesis showed that a para-methoxy substituent led to clean azepine formation in good yield with none of the by-products observed in the para-NMe₂ case. It was of interest, therefore, to discover whether the reaction also proceeded cleanly in this more complex system. Finally, the effect of para-methoxy was required for direct comparison with that observed for the meta-methoxy case described previously.

The imidoyl chloride and the nitrile ylide (397) were generated and reacted using the usual methods. The result of this competition reaction is shown in Figure 34.

The para-methoxy group thus has a greater activating effect than para-dimethylamino, but much less than meta-methoxy where the overall preference for attack at the substituted ring was 6.4:1.0. It is conceivable that the
larger effect of p-OMe relative to p-NMe₂ comes about due to lower +R character or through higher -I character.

These reactions were shown to proceed cleanly, giving excellent yields of the isomeric azepines (398) and (399) which were inseparable by chromatography. No by-products of the type observed in the reactions of the p-NMe₂ system (394) were observed in these reactions.

Having studied conjugative electron donors in the para-position, the most obvious next step would be to investigate the effect of conjugative electron-withdrawing groups. The most extreme substituent to study would be the para-nitro group. Synthesis of the required precursor would involve the coupling of the bromo compound (328) with 4-nitrophenylboronic acid (400). This compound is not commercially available and several attempts to prepare it at low temperature using the methods of Parham and Bradsher¹⁴⁷ were unsuccessful, yielding only black oils.
c) **Halogen Substituents**

Halogens are commonly used substituents which are inductively electron withdrawing in character, but also weakly electron donating through resonance.

Two halogen substituents (Cl and F) were studied to assess the effect of this class of para-substituent on the 1,7-electrocyclisation reaction.

The nitrile ylides (401 a,b) were generated in the usual way and the isomers (403 a,b) were identified by addition of an authentic sample. The results of the competition reactions are shown in Table 7.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>a) $X = \text{Cl}$</th>
<th>b) $X = \text{F}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.H.F.</td>
<td>2.2</td>
<td>1.2</td>
</tr>
<tr>
<td>D.M.F.</td>
<td>1.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Table 7*
These results show that in T.H.F. both substituents again led to enhanced reactivity of the substituted ring, chloro to a large and fluoro to a small extent. When carried out in D.M.F., the generally observed effect of diminished selectivity was once again apparent. In the case of the para-fluoro group, the substituent activating effect was completely suppressed.

In common with the meta-substituted systems, all of the para-substituted nitrile ylides studied show similar characteristics. Firstly, all substituents, irrespective of electronic properties, activate the substituted ring to electrocyclisation. Secondly, it was generally observed that higher solvent polarity acted to diminish the selectivity to some extent, leading to a complete loss of selectivity between the substituted and unsubstituted rings in the para-fluoro case.

The general preference for cyclisation at the substituted ring raised the question of whether the substituents exerted their effect by in some way disfavouring cyclisation at the unsubstituted ring. The work described in the following section was designed to test this possibility.

2.3.3.4 "Competition Cycles" (para versus para)

The previously described experiments indicate that all types of substituent in the meta and para-positions favour electrocyclisation at the substituted ring.
It will be recalled that one assumption made at the beginning of this study was that, in each case, the rate of cyclisation at the unsubstituted ring would be constant. That is, the rate of cyclisation at the comparator ring (A) would be unaffected by the presence of different groups in the other ring (B) (284). It is conceivable, however, that the presence of various groups in B could alter the ground-state of the system as a whole and lead to the activation energy of cyclisation at A being altered.

The following experiments were carried out in order to test whether the rate of cyclisation at A is independent of the nature of a substituent in B. In the general case the question is whether the rate of cyclisation onto one ring is independent of the nature of the other ring. If it is, then if both rings are substituted, the substituent effects should be additive, e.g. if Ar' is 6 times faster
than Ph and Ar is 3 times faster than Ph then Ar' should be 2 times faster than Ar'.

In this pilot study two systems (404 X=H; F) were chosen for investigation. In each case a para-substituent was competed against a para-chloro group. This group was chosen as a moderately strong electron-withdrawing substituent which shows a relatively large activating effect in these competition reactions.

![Chemical structure]

The required bromoamide (405) was prepared in a manner exactly analogous to that shown in Scheme 87 (p. 197), replacing phenylboronic acid by 4-chlorophenylboronic acid in the first coupling step. Conditions and yields were very similar to those described previously. 4-Methylphenylboronic acid and 4-trifluoromethylphenylboronic acid were coupled with N-benzoyl-2-bromo-6-(4-chlorophenyl)-
benzylamine (405) in the usual way as the final steps to (406a and b) (Scheme 96). 8-Bromo-3-chloro-5-phenyl-7H-dibenz[c,e]azepine (407) was prepared from (405) by the usual method and the authentic azepines (408a,b) made by coupling this with the appropriate boronic acid (Scheme 96).

Solvent

<table>
<thead>
<tr>
<th>Solvent</th>
<th>a) X = H</th>
<th>b) X = F</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.H.F.</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>D.M.F.</td>
<td>1.3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Scheme 96
The results observed for these competition reactions are shown in Scheme 96. In the case of (404a) the nitrile ylide was shown to cyclise at the para-chloro substituted ring in preference to the para-methyl substituted ring. In the other case (404b), where \( X = F \), the selectivity is reversed and the isomer (409b) is formed in preference to (408b).

These results are compared with those observed in competitions versus an unsubstituted ring (Table 8).

![Diagram of chemical structures]

<table>
<thead>
<tr>
<th>( X )</th>
<th>( Y )</th>
<th>Ratio in T.H.F.</th>
<th>Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>( H )</td>
<td>( CF_3 )</td>
<td>1.0</td>
<td>2.8</td>
</tr>
<tr>
<td>( H )</td>
<td>( Cl )</td>
<td>1.0</td>
<td>2.2</td>
</tr>
<tr>
<td>( H )</td>
<td>( CH_3 )</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>( Cl )</td>
<td>( CH_3 )</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>( Cl )</td>
<td>( CF_3 )</td>
<td>1.0</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Table 8

This set of figures demonstrates that the relative magnitudes of the substituted effects are maintained in this more complex system. That is, in order of decreasing
effect versus an unsubstituted phenyl ring the substituents were \( \text{CF}_3 > \text{Cl} > \text{CH}_3 \). The "competition cycle" results confirm that chloro is less activating than trifluoromethyl, but more activating than methyl.

A simple numerical test of whether the substituent effects are purely additive (or subtractive) may be applied by simply dividing ratios. That is, para-chloro gave a ratio of 2.2:1.0 versus phenyl whereas para-methyl gave a ratio of 1.5:1.0. Simple additivity would therefore predict chloro to be favoured over methyl in the ratio 2.2:1.5 = 1.47. This is in close agreement with the observed ratio of 1.4:1. A similar treatment of the effects of chloro and trifluoromethyl predicts that trifluoromethyl will be more activating than chloro in the ratio 2.8:2.2 = 1.27. This compares with the observed ratio of 1.1:1.

It would be hazardous to draw firm conclusion from this limited data. However, it does appear from these results that the values obtained from the original competition reactions may be used, at least qualitatively, to predict relative rates in systems where substituents are competing against each other, but further work is required in this area.

2.3.3.5 ortho-Substituted Aryl Rings

Having established that all meta and para-substituents activate the substituted ring to electrocyclisation, it
was of interest to investigate the effect of ortho-substituents on the 1,7-electrocyclisation reaction.

It will be recalled that in Section 1 of this thesis the reaction of the nitrile ylide (270) was studied. The reaction did not proceed via 1,7-electrocyclisation, but gave two products identified as dimers. It was thought that steric inhibition of the transition-state for 1,7-electrocyclisation increased the activation energy to such an extent that the reaction was diverted to another route. A priori, the possibility also exists that the effect of the methyl group is exerted on the dimerisation reaction rather than on the electrocyclic process. It is possible that the methyl group increases the rate of dimerisation or, given the uncertainty about the precise structures of the dimers, induces a new type of reaction, e.g. dimerisation of a cyclisation intermediate (410). The methods developed in this section provide the opportunity of further investigation using the nitrile ylide (411).
The nitrile ylide (411) was prepared and generated in the usual way. The reaction was carried out in both T.H.F. and D.M.F. at 0°C and the crude product was studied by 360 MHz $^1$H n.m.r.

At first glance the n.m.r. spectrum appeared to show two azepines in the ratio 2:1 (Figure 35b). Addition of an authentic sample of (412), however, led to all of these signals being enhanced to the same extent and the n.m.r. of the authentic sample showed an identical spectrum. Purification of the reaction mixture gave a white crystalline solid which was shown to be identical to (412) by a mixed melting point experiment. Thus it appears that the only product formed is that derived from electrocyclisation at the unsubstituted ring (Scheme 97).
This result supports the conclusion reached earlier that the ortho-methyl substituted nitrile ylide (270) undergoes dimerisation due to destabilisation of the electrocyclisation transition state. The alternative explanation involving a new, low-energy route is not compatible with the observation that reaction takes place preferentially and exclusively via electrocyclisation at the unsubstituted phenyl ring.

That the ortho-substituent blocks electrocyclisation is understandable. Two alternative positions of the attack are possible, either at the position to which the methyl group is attached or at the other position ortho to the biphenyl linkage. In the first case it is clear that the methyl group will inhibit approach of the two termini through steric interaction. Why the alternative mode of attack is disfavoured is not so obvious. Dreiding models, however, show that a significant steric interaction exists between the methyl group and the ortho-proton in the other ring. This can be seen to inhibit the system from achieving the geometry required in the transition state (277).

![Diagram](image-url)
Figure 35

COPh
NH
CH₂

(413)

Figure 35
The steric effects of the methyl group in both the amide (413) and the azepine (412) were studied in more detail by variable temperature n.m.r. experiments. Figure 35 shows the n.m.r. spectra obtained from the two compounds at ambient temperature.

The 200 MHz $^1$H n.m.r. of the amide (413) shows a singlet corresponding to the methyl group. The methylene signals, however, indicate that the two protons are non-equivalent, coupling with each other as well as with the adjacent proton on the nitrogen atom. It appears therefore that the presence of the ortho-methyl group inhibits free rotation of the phenyl ring to which it is attached so that the lifetime of the structure (414) is long on the n.m.r. timescale. The methylene protons are non-equivalent as one is shielded due to its closer proximity to the methyl group. It should be noted that rotation of the methyl-substituted ring through 180° leads to a structure which is the mirror image of (414), i.e. the protons $H_a$ and $H_b$ interconvert. If the ring is allowed to rotate freely these two protons therefore become equivalent.

![Chemical Structure](image)
The sample was dissolved in diphenyl ether and its $^1$H n.m.r. spectrum recorded at elevated temperatures. This study showed that the methylene signals collapsed to the normal doublet at ca. 125°C, indicating that at this temperature the methyl substituted ring is rotating rapidly on the n.m.r. timescale. From this coalescence temperature the free energy of ring rotation ($\Delta G_{\text{rot}}$) was calculated to be ca. 83 kJ mol$^{-1}$. This large value indicates that steric hindrance to rotation exists even in the starting material, supporting the assertion that electrocyclisation is disfavoured due to steric effects.

The $^1$H n.m.r. spectrum of the azepine (412) at room temperature (Figure 35b) shows two distinct methyl signals and four methylene doublets. Variable temperature n.m.r. in diphenyl ether showed that the methyl signals coalesce at ca. 130°C, at the same time the methylene signals collapse to the usual pair of doublets. This once again indicates that the ortho-methyl group inhibits rotation of the ring to which it is attached. The spectrum appears to show that two distinct azepine structures are present, these are presumably (412a) where the methyl group points above the "bow" of the azepine boat structure and (412b) where it lies below.
From the coalescence temperature of the methyl signals the free energy of ring rotation was calculated to be ca. 87 kJ mol$^{-1}$. This value is in excellent agreement with that found for the amide (413). The slightly higher value in this case is attributed to the presence of the 'rigid' azepine ring. Attempts to find the coalescence temperature of the azepine methylene signals were inhibited by the temperature range of the n.m.r. instrument. The signals showed signs of broadening at 143°C, but higher temperatures could not be achieved. It is obvious, however, that the value of $\Delta G_{\text{inv}}$ would be higher than that of 86.1 kJ mol$^{-1}$ obtained for the related dibenzazepine$^{87}$ (415).
Thus, it appears that, although a wide range of meta- and para-substituents can be accommodated in the 1,7-electrocyclisation reactions of nitrile ylides, the mechanism is somewhat sensitive to the steric effects of ortho-substituents.

2.3.4 Rationalisation of Results

It can be seen from the results obtained from the competition reactions (Appendix 1) that the rate of 1,7-electrocyclisation is enhanced by both electron-donating and electron-withdrawing substituents. The Hammett substituent constants$^{148}$, $\sigma_m$ and $\sigma_p$, provide a quantitative measure of the electron-donating or
withdrawing properties of each group. In attempting to rationalise the results a correlation between the \( \sigma \)-value and the activating effect of each substituent was sought.

The effects of para-substituents were inspected first. From Table 9 it can be seen that, with one exception, there is a rough correlation between the activating effect on electrocyclisation and the absolute value of \( \sigma_p \) for each substituent. That is, the larger the numerical value of \( \sigma_p \), be it positive or negative, the greater the reactivity of the substituted ring towards 1,7-electrocyclisation. Another, possibly important, observation is that, in general, electron withdrawing substituents show a larger effect.

<table>
<thead>
<tr>
<th>para-substituent</th>
<th>( \sigma_p )</th>
<th>Reactivity relative to Ph in T.H.F.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CF}_3 )</td>
<td>0.54</td>
<td>2.8</td>
</tr>
<tr>
<td>Cl</td>
<td>0.23</td>
<td>2.2</td>
</tr>
<tr>
<td>F</td>
<td>0.06</td>
<td>1.2</td>
</tr>
<tr>
<td>( \text{CH}_3 )</td>
<td>-0.17</td>
<td>1.5</td>
</tr>
<tr>
<td>OMe</td>
<td>-0.27</td>
<td>1.6</td>
</tr>
<tr>
<td>( \text{NMe}_2 )</td>
<td>-0.83</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**Table 9**

The one striking exception in the table is the dimethylamino group. This has the largest numerical value
of $\sigma_p$, but shows one of the smallest activating effects. It may be significant that, although NMe$_2$ has a large $\sigma_p$ value, this derives mainly from its $+R$ effect and in terms of inductive effects alone NMe$_2$ is not a powerful substituent. This one result aside, however, it appears that these results follow a U-shaped reactivity curve with a minimum of rate for the unsubstituted phenyl ring.

A similar treatment of the meta-substituted aryl systems gives the results shown in Table 10.

<table>
<thead>
<tr>
<th>meta-substituent</th>
<th>$\sigma_m$</th>
<th>Reactivity relative to one ring position on Ph in T.H.F.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO$_2$</td>
<td>0.71</td>
<td>$&gt;100$</td>
</tr>
<tr>
<td>2xCF$_3$</td>
<td>0.43</td>
<td>32.0</td>
</tr>
<tr>
<td>OMe</td>
<td>0.12</td>
<td>12.8</td>
</tr>
<tr>
<td>2xCH$_3$</td>
<td>-0.07</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Table 10

Once again there appears to be some kind of correlation between the absolute value of $\sigma_m$ and the activating effect of the substituent. These results indicate that reactivity towards the 1,7-electrocyclisation reaction is closely related to the electronic properties of substituents, with both donor and acceptor character leading to rate enhancement.
In providing a more detailed rationalisation for the observed results two assumptions are made: (i) the reaction takes place via a 1,7-electrocyclisation process involving a helical transition state as postulated for the related reactions of diazo-compounds. (ii) That the carbon-carbon bond forming cyclisation step is irreversible, as demonstrated by Groundwater for a closely related nitrile ylide 1,7-electrocyclisation reaction.

A priori, any substituent must exert its influence on the rate of cyclisation by its effect on the energies of the reactant (416) and/or the two alternative transition states for electrocyclisation (417) and (419) (Scheme 98).
It seems likely that the effect of the substituents on the energy of the reactant (416) will be relatively small since any enhanced electron delocalisation by resonance will be severely restricted by steric limitation of coplanarity between the substituted ring and the system to which it is attached. That is, the substituted ring will spend very little time in any conformation which could permit "out of ring" resonance.

In contrast to this, the transition states for electrocyclisation (417) and (419) have, by definition, the geometry for maximum conjugation between the ring under attack and the rest of the conjugated nitrile ylide system. The energy of the transition state will therefore be much affected by substituents which enhance or extend electron delocalisation.

In discussing the effect of substituents on the transition-state energy it will be assumed that the transition-state (419) is closely related in structure to the intermediate (420), i.e. a considerable degree of bond formation exists in the transition state, a similar assumption to that made in rationalising substituent effects in electrophilic aromatic substitution reactions. The intermediate (420) is therefore taken as a model for the transition state and it is assumed that any factor affecting its stability will similarly affect the transition-state (419) (Scheme 99).
Consider firstly the meta-substituted systems, substituents at the ring position $m$ in the intermediate (420) are capable of direct conjugation through to the atoms derived from the original nitrile ylide. They can therefore exert a strong stabilising effect via the contribution of dipolar canonical forms such as (421) and (422) shown below.
In these structures, charge developed in the ring under attack can be delocalised at the positions shown. It follows that substituents at these positions, if capable of stabilising this charge, will lower the energy of the intermediate (420) and therefore the transition state (419).

The results observed in the meta-substituted aryl cases may therefore be explained as follows. The meta-nitro substituted nitrile ylide (384a) will lead to preferential attack at the substituted ring due to stabilisation of the transition state by canonical forms of the type (421). Similarly, in the meta-methoxy system (384b), attack at the substituted ring will be favoured due
to canonical forms of the types (422).

In both of these systems it was shown that attack ortho was preferred over attack para to the substituent. If both inductive and resonance effects contribute to stabilisation of the transition state it would seem likely that, although resonance would have an equal effect on both "ortho" and "para" transition state, inductive effects would favour ortho attack. This follows from the fact that inductive effects are of short range and closer proximity to the site of attack would be expected to enhance stabilisation. It seems likely therefore, that the preference for transition state (423) over (424) derives mainly from the inductive properties of the substituent.

![Diagram](image)

(423) Substituent ortho to position of attack

(424) Substituent para to position of attack
A second factor which may be significant is the difference in position of the stabilising substituent within the delocalised system. It is conceivable that the substituent in structure (425), being at the terminus of the delocalised system, will have a greater stabilising effect than that in structure (426) which is attached to the middle of the system.

Turning now to the meta-disubstituted systems (427), it can be seen that both substituents are in ring positions capable of stabilising these additional canonical forms. The combined stabilising effects of the substituents would be expected to combine additively by increasing the scope for charge delocalisation. In the two systems of this type studied (381 a,b), the stabilising effect of the two substituents was indeed relatively large.

It appears, therefore, that substituents in the meta-
position(s) of the ring under attack are capable of lowering the energy of the transition state (activation energy) by charge stabilisation, via either inductive or resonance effects.

The situation involving para-substituted aryl rings is slightly different. As mentioned previously, substituents in this position are capable of conjugation in the nitrile ylide starting material as shown below.

(428) \[ \text{Ph} \overset{\text{C}}{\text{C}} \underset{\text{N}}{\text{CH} \cdot \text{S}} \text{Ph} \]

(429) \[ \text{Ph} \overset{\text{C}}{\text{C}} \underset{\text{N}}{\text{CH} \cdot \text{S}} \]

It might be expected that delocalisation of this type would lead to a lowering of the ground-state energy, effectively increasing the activation energy of the reaction. As explained, however, it seems unlikely that the system will have an appropriate geometry for this factor to be important.

It will be recalled that a para-dimethylamino substituent gave a low selectivity in the competition reaction. Bearing in mind that dimethylamino was by far
the most powerful conjugating para-substituent studied, it is possible that the factor mentioned above is important. Further work on strong conjugative para-substituents will be required to determine whether this is the case.

Electrocyclisation of para-substituted systems (428) leads to the formation of intermediates of the type (431). In this case the substituent is not directly conjugated to the nitrile ylide atoms and is not capable of enhancing the electron delocalisation via dipolar canonical structure such as in the previous case.

\[
\begin{align*}
\text{(428)} & \quad \text{(430)} & \quad \text{(431)}
\end{align*}
\]

It would be expected that substituents in the para-position would help stabilise delocalised charge as described before, but to a much lesser extent. That is, partial charges cannot be delocalised directly onto the substituents through resonance, but the proximate electron donor/acceptor groups will help stabilise these charges to a lesser degree through inductive effects in (432) and (433).
Another factor which may be explicable by this rationale was the observation that, in general, electron withdrawing substituents show larger effects. Due to the presence of nitrogen in the azepine ring, resonance forms of the type (434) may be further stabilised by delocalisation of charge onto nitrogen. This further delocalisation would be expected to enhance the stability of this system relative to that possessing electron donor substituents.
A final factor requiring explanation is the generally observed lowering of selectivity in D.M.F. In general it would be expected that polar solvents would enhance charge separation of the kind described and increase selectivity. It is conceivable, however, that the partially dipolar D.M.F. acts to solvate both the 1,3-dipole and charges developing in the ring under attack. The presence of these solvating molecules would act as a steric barrier, preventing the termini from coming together and also to dissipate the attractive charges developing between the two termini (436).

\[
\text{Ph}^+ \quad \text{Me} = \text{Me}^+ \quad \text{N} = \text{CH}^- \quad \text{O}^-
\]

The rationale presented above accords well with the experimental observations made on meta and para-substituted aryl systems. Extension of these arguments to the competition between phenyl and thienyl rings may help to explain the high reactivity of the thiophene ring in reactions of this type (289)\rightarrow(379).
A major factor leading to enhanced reactivity in this system is likely to be the nature of the $\gamma,\delta$-double bond. The thiophene bond is intermediate in character between those of alkenes and benzene. Olefinic double-bonds, as shown earlier, are much more reactive towards the nitrile ylide than aromatic double bonds. Enhanced reactivity of thiophene relative to benzene is therefore not surprising. However, the exclusive preference for cyclisation onto thiophene was more unexpected.

Using the arguments developed above we can see that thiophene provides the possibility of electron delocalisation in the intermediate (437). Once again assuming that factors which stabilise this intermediate will assist formation of the transition state we can see that the thiophene ring may promote the reaction as follows. Firstly, sulphur is known to be capable of
stabilising α-carbanion centres. Thus this effect will result in stabilisation of the canonical form (438). Further delocalisation may also help stabilise formation of the transition state, e.g. (439) (Scheme 100).

Thus a rationalisation has been provided for the observed reactivity of aryl rings towards 1,7-electrocyclisation reactions of nitrile ylides. As discussed previously the effect of ortho-substituents has been attributed to steric factors inhibiting the reaction. The
results obtained from the "competition cycles" are explicable by the rationale presented. The substituent which leads to greater stabilisation of delocalised charge in the transition state will have the greater activating effect.
CONCLUSIONS

The major conclusions which have been drawn from the work described in this thesis are summarised here.

The first objective of the project, as described in Section 1, was to gain an insight into the scope of 1,7-electrocyclisation reactions of $\alpha,\beta; \gamma,\delta$-unsaturated nitrile ylides in which both $\alpha,\beta$ and $\gamma,\delta$-double bonds were aromatic. The work described in Section 1 and the subsequent studies in Section 2, part 3, have shown that a very wide range of substituents are compatible with this reaction. Thus a very wide range of polysubstituted dibenz[c,e]azepines are available by a straightforward synthetic route. Systems of this type have been the subject of intense study in the pharmaceutical industry in recent years and it is hoped that the present work will prove to be of synthetic value.

The major conclusions, however, are those drawn from the reactivity study of the 1,7-electrocyclisation reaction. The competition reaction approach to reactivity studies has furnished interesting and unexpected results. The first was the observation that $\gamma,\delta$-olefinic double bonds are much more reactive toward attack by the nitrile ylide than are phenyl double bonds. This agrees with predictions based on the loss of aromatic stabilisation energy, but is in complete contradiction to inferences drawn from colour changes observed in these reactions.

It was also observed that the nitrile ylide reacts by
electrocyclisation exclusively at the 2,3-bond in thiophene in preference to attack at a phenyl ring. This has been attributed in part to the high double bond character in the thiophene ring and in part to stabilisation of the transition-state by the presence of sulphur. Given that the nitrile ylide reacts exclusively at both alkenyl and thienyl in preference to phenyl double bonds, it would be of interest to carry out a direct competition between these two groups using the system (440).

\[
\begin{align*}
\text{Ph} & \\
\text{C} & \\
I & \\
\text{CH} & \\
\text{Ph} & \\
\end{align*}
\]

(440)

The studies on relative reactivities of substituted phenyl rings have furnished some unexpected results. It was thought likely that the reaction would be accelerated by some substituents and retarded by others. The present study has demonstrated, however, that all meta and para-substituents, irrespective of their electronic properties, accelerate the electrocyclisation. This, the preference for attack ortho relative to para to the substituent and the effect of polar solvents were rationalised in terms of stabilisation of the transition state via the contribution
of dipolar canonical structures, involving electron-withdrawal or donation by the substituent (441).  

The additivity/subtractivity of substituent effects was demonstrated in a pilot study in which differently substituted rings competed against each other using systems of the type (442). This preliminary study indicated that the preferred direction of electrocyclisation may be predicted qualitatively and that semi-quantitative predictions may be possible although further work is required in this area.
Finally, it was shown that, although all meta- and para-substituents activate the ring to reaction, the cyclisation can be cleanly diverted to electrocyclisation at the unsubstituted ring by the presence of an ortho-methyl substituent. This effect was attributed to steric inhibition of transition-state formation. It is felt that further work in this particular area, using smaller ortho-substituents, will yield information on the steric requirements of the 1,7-electrocyclisation reaction.

It is hoped that the present study has provided a framework for the deeper understanding of reactions of this type and that the methods developed will prove useful for application to other reaction types.
SYMBOLS AND ABBREVIATIONS 282
INSTRUMENTATION AND TECHNIQUES 283

SECTION 1
SYNTHETIC STUDIES ON THE 1,7-ELECTRO-
CYCLISATION REACTIONS OF BENZONITRILE-2-
ARYLBENZYL YLIDES 287

I. Preparation of Starting Materials 287
   (i) N-2-Methoxybenzylidene Isopropylamine 287
   (ii) N-2-Arylbenzylidene Isopropylamines 287
       1) N-2-Phenylbenzylidene isopropylamine 288
       2) N-2-(4-Chlorophenyl)benzylidene isopropylamine 288
       3) N-2-(4-Methoxyphenyl)benzylidene isopropylamine 289
       4) N-2-(2-Methylphenyl)benzylidene isopropylamine 289
   (iii) 2-Arylbenzaldehydes 290
       1) 2-Phenylbenzaldehyde 290
       2) 2-(4-Chlorophenyl)benzaldehyde 291
       3) 2-(4-Methoxyphenyl)benzaldehyde 291
       4) 2-(2-Methylphenyl)benzaldehyde 292
(iv) 2-Arylbenzaldehyde Oximes
1) 2-Phenylbenzaldehyde oxime
2) 2-(4-Chlorophenyl)benzaldehyde oxime
3) 2-(4-Methoxyphenyl)benzaldehyde oxime
4) 2-(2-Methylphenyl)benzaldehyde oxime

(v) 2-Arylbenzylamine Hydrochlorides
1) 2-Phenylbenzylamine hydrochloride
2) 2-(4-Chlorophenyl)benzylamine hydrochloride
3) 2-(4-Methoxyphenyl)benzylamine hydrochloride
4) 2-(2-Methyiphenyl)benzylamine hydrochloride

(vi) N-Substituted-2-Arylbenzylamines
1) N-Benzoyl-2-phenylbenzylamine
2) N-(4-Methylbenzoyl)-2-(4-chlorophenyl)benzylamine
3) N-(4-Methylbenzoyl)-2-(4-methoxyphenyl)benzylamine
4) N-Benzoyl-2-(2-methylphenyl)benzylamine
# II. Generation and Reaction of the Nitrile Ylides Derived from Substituted \( N-(2-\text{Arylbenzyl})\text{Benzimidoyl Chlorides} \)

1. Generation and Reaction of the Nitrile Ylide Derived from \( N-(2\text{-phenylbenzyl})\text{-benzimidoyl Chloride} \)
2. Generation and Reaction of the Nitrile Ylide Derived from \( N-(2\text{-}(4\text{-Chlorophenyl})\text{benzyl})\text{-4-methylbenzimidoyl Chloride} \)
3. Generation and Reaction of the Nitrile Ylide Derived from \( N-(2\text{-}(4\text{-Methoxyphenyl})\text{benzyl})\text{-4-methylbenzimidoyl Chloride} \)
4. Generation and Reaction of the Nitrile Ylide Derived from \( N-(2\text{-}(2\text{-Methylphenyl})\text{benzyl})\text{benzimidoyl Chloride} \)
SECTION 2
MEASUREMENT OF RELATIVE REACTIVITIES IN 1,7-
ELECTROCYCLISATION REACTIONS OF NITRILE
YLIDES 304

Part 1. "External Competition" Approach to
Relative Rate Measurement 304

(i) Attempted Generation and Reaction
of the Nitrile Ylide Derived from
N-(2-Phenyl benzyl) benzimidoyl
Chloride in the Presence of
External Dipolarophiles 304
1) With dimethyl fumarate as
   external dipolarophile 304
2) With dimethyl maleate as
   external dipolarophile 305
3) With trans-stilbene as
   external dipolarophile 306
4) With norbornene as
   external dipolarophile 306
5) With styrene as external
dipolarophile 307
6) With $\alpha,\alpha,\alpha$-trifluoroaceto-
  phenone as external dipolar-
  ophile 307
(ii) Attempted Generation and Reaction of the Nitrile Ylide Derived from \(N-(2\text{-Phenylbenzyl})\text{benzimidoyl} \) Chloride in the Presence of External Dipolarophiles

1) Using triethylamine as base 308
2) Using lithium diisopropylamine as base 308

(iii) Attempted Synthesis of 2-(2-Phenylphenyl)-3-phenyl-2H-azirine

1) 2-Bromophenyl acetophenone 309
2) 2-Phenylphenyl acetophenone 310
3) 2-Phenylphenyl acetophenone-\(N,N\)-dimethylhydrazone 311
4) Attempted preparation of 2-(2-phenylphenyl)-3-phenyl-2H-azirine 311
5) Photolysis of impure 2-(2-phenylphenyl)-3-phenyl-2H-azirine 312
Part 2. "Internal Competition" Approach to

Relative Rate Measurement 312

Approaches to Preparation of $N$-Benzoyl-2,6-diarylbenzylamines 312

APPROACH 1: via Grignard Reactions of $N$-2,6-dimethoxybenzylidene Isopropylamines 312

Preparation of Starting Materials 312

(i) 2,6-Dimethoxybenzaldehyde 313

(ii) $N$-2,6-Dimethoxybenzylidene Isopropylamine 313

(iii) 2-Methoxy-6-phenylbenzaldehyde 313

(iv) $N$-2-Methoxy-6-phenylbenzylidene Isopropylamine 315

(v) 2-Aryl-6-phenylbenzaldehydes 315
   1) 2,6-Diphenylbenzaldehyde 315
   2) 2-(4-Chlorophenyl)-6-phenylbenzaldehyde 316

(vi) 2-Aryl-6-phenylbenzaldehyde Oximes 317
   1) 2,6-Diphenylbenzaldehyde oxime 317
   2) 2-(4-Chlorophenyl)-6-phenylbenzaldehyde oxime 318

(vii) 2-Aryl-6-phenylbenzylamines 318
   1) 2,6-Diphenylbenzylamine 318
   2) 2-(4-Chlorophenyl)-6-phenylbenzylamine 319
Part 2. Cont’d.

(viii) \( N\)-Benzoyl-2-aryl-6-phenylbenzylamines 319
   1) \( N\)-Benzoyl-2,6-diphenylbenzylamine 319
   2) \( N\)-Benzoyl-2-(4-chlorophenyl)-6-phenylbenzylamine 320

Generation and Reaction of the Nitrile Ylides Derived from \( N\)-(2-Aryl-6-phenylbenzyl)benzimidoyl Chlorides 321
   (i) Generation and Reaction of the Nitrile Ylide Derived from \( N\)-(2,6-Diphenylbenzyl)benzimidoyl Chloride 321
   (ii) Generation and Reaction of the Nitrile Ylide Derived from \( N\)-(2-(4-Chlorophenyl)-6-phenylbenzyl)benzimidoyl Chloride 322

APPROACH 2: via Palladium Catalysed Cross-coupling Reactions 322

I. Attempted Sequential Palladium Catalysed Cross-coupling of 4-(\( N\)Benzoylaminomethyl)-3,5-Dibromobenoic Acid Methyl Ester 322
   Preparation of Starting Material 322
   (i) 3,5-Dibromo-4-methylbenzoic Acid Methyl Ester 322
I. Cont’d

(ii) 4-(Bromomethyl)-3,5-dibromobenzoic Acid Methyl Ester 323

(iii) 3,5-Dibromo-4-(pthalimidomethyl)-benzoic Acid Methyl Ester 323

(iv) 4-(Aminomethyl)-3,5-dibromobenzoic Acid Methyl Ester 324

(v) 4-(N-Benzoylaminomethyl)-3,5-dibromo- benzoic Acid Methyl Ester 325

Attempted Sequential Cross-coupling of 4-(N-Benzoylaminomethyl)-3,5-Dibromo- benzoic Acid Methyl Ester 326

II. Attempted Preparation of Aryl Bromides via Ortho-metalation Reactions 327

(i) Attempted o-lithiation of 2- biphenyl methanol 327

(ii) o-Lithiation of 2-phenylbenzaldehyde 328

1) 6-Phenyl-2-trimethylsilyl- benzaldehyde 328

2) Attempted ipso-bromo- desilylation of 6-phenyl-2- trimethylsilylbenzaldehyde 329

(iii) Attempted o-stannylation of 2- phenylbenzaldehyde 330
Part 3. **Measurement of Relative Rates of Electrocyclisation via Intramolecular Competition Reactions**

A. **Boronic Acids**

(i) 2-Phenylethenylboronic Acid

(ii) 2-Thiopheneboronic Acid

(iii) Phenylboronic Acids

1) Phenylboronic acid

2) 3-Nitrophenylboronic acid

3) 3-Methoxyphenylboronic acid

4) 3,5-Dimethylphenylboronic acid

5) 3,5-Bis-trifluoromethylphenylboronic acid

6) 4-Methylphenylboronic acid

7) 4-Trifluoromethylphenylboronic acid

8) 4-Dimethylaminophenylboronic acid

9) 4-Methoxyphenylboronic acid

10) 4-Fluorophenylboronic acid

11) 4-Chlorophenylboronic acid

12) 2-Methylphenylboronic acid
B. Preparation of $N$-Benzoyl-2-Aryl-
Benzylamines

(i) 6-Bromo-2-nitrotoluene 335

(ii) 6-Aryl-2-nitrotoluenes 336
   1) 2-Nitro-6-phenyltoluene 336
   2) 6-(4-Chlorophenyl)-2-nitrotoluene 337

(iii) 3-Aryl-2-methylanilines 337
   1) 2-Methyl-3-phenylaniline 337
   2) 6-(4-Chlorophenyl)-2-methylaniline 338

(iv) 6-Aryl-2-bromotoluenes 338
   1) 2-Bromo-6-phenyltoluene 338
   2) 2-Bromo-6-(4-chlorophenyl)-toluene 339

(v) 6-Aryl-2-bromobenzyl bromides 340
   1) 2-Bromo-6-phenylbenzyl bromide 340
   2) 2-Bromo-6-(4-chlorophenyl)benzyl bromide 340

(vi) 3-Aryl-2-(pthalimidomethyl)bromo-
benzenes 341
   1) 3-Phenyl-2-(pthalimidomethyl)-bromobenzene 341
   2) 3-(4-Chlorophenyl)-2-(pthalimidomethyl)bromobenzene 342
### B. Cont’d.

<table>
<thead>
<tr>
<th>Page No</th>
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<tbody>
<tr>
<td>342</td>
<td>(vii) 6-Aryl-2-Bromobenzylamines</td>
</tr>
<tr>
<td></td>
<td>1) 2-Bromo-6-phenylbenzylamine 342</td>
</tr>
<tr>
<td></td>
<td>2) 2-Bromo-6-(4-chlorophenyl)benzylamine 343</td>
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<tr>
<td>343</td>
<td>(viii) N-Benzoyl-6-aryl-2-bromobenzylamines</td>
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<td></td>
<td>1) N-Benzoyl-2-bromo-6-phenylbenzylamine 343</td>
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<td>2) N-Benzoyl-2-bromo-6-(4-chlorophenyl)benzylamine 344</td>
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<td>345</td>
<td>(ix) N-Benzoyl-6-phenyl-2-(2-phenylethenyl)benzylamine</td>
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<td>(x) N-Benzoyl-6-phenyl-2-(2-thienyl)benzylamine</td>
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<td>346</td>
<td>(xi) N-Benzoyl-2-aryl-6-phenylbenzylamines</td>
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<tr>
<td></td>
<td>1) N-Benzoyl-2-(3-nitrophenyl)-6-phenylbenzylamine 346</td>
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<td></td>
<td>2) N-Benzoyl-2-(3-methoxyphenyl)-6-phenylbenzylamine 347</td>
</tr>
<tr>
<td></td>
<td>3) N-Benzoyl-2-(3,5-dimethylphenyl)-6-phenylbenzylamine 348</td>
</tr>
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<td></td>
<td>4) N-Benzoyl-2-(3,5-bis-trifluoromethylphenyl)-6-phenylbenzylamine 348</td>
</tr>
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<td>5) N-Benzoyl-2-(4-methylphenyl)-6-phenylbenzylamine 349</td>
</tr>
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(xi) Cont’d.  

6) N-Benzoyl-2-(4-trifluoromethylphenyl)-6-phenylbenzylamine 349
7) N-Benzoyl-2-(4-dimethylaminophenyl)-6-phenylbenzylamine 350
8) N-Benzoyl-2-(4-methoxyphenyl)-6-phenylbenzylamine 351
9) N-Benzoyl-2-(4-fluorophenyl)-6-phenylbenzylamine 351
10) N-Benzoyl-2-(4-chlorophenyl)-6-phenylbenzylamine 352
11) N-Benzoyl-2-(2-methylphenyl)-6-phenylbenzylamine 352

(xii) N-Benzoyl-6-aryl-2-(4-chlorophenyl)-benzylamines 353
1) N-Benzoyl-2-(4-chlorophenyl)-6-(4-methylphenyl)benzylamine 353
2) N-Benzoyl-2-(4-chlorophenyl)-6-(4-trifluoromethylphenyl)benzylamine 354

C. Preparation of Authentic Azepines 355
(i) 8-Bromo-5-phenyl-7H-dibenz[c,e]-azepine 355
(ii) 8-Bromo-3-chloro-5-phenyl-7H-dibenz-[c,e]azepine 356
C. Cont'd.  

<table>
<thead>
<tr>
<th>Page No.</th>
<th>Compound Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>356</td>
<td>5-Phenyl-8-(2-phenylethenyl)-7H-dibenz[c,e]azepine</td>
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<tr>
<td>357</td>
<td>5-Phenyl-8-(2-thienyl)-7H-dibenz[c,e]azepine</td>
</tr>
<tr>
<td>358</td>
<td>8-Aryl-5-phenyl-7H-dibenz[c,e]azepines</td>
</tr>
<tr>
<td>358</td>
<td>1) 8-(3-Nitrophenyl)-5-phenyl-7H-dibenz[c,e]azepine</td>
</tr>
<tr>
<td>358</td>
<td>2) 8-(3-Methoxyphenyl)-5-phenyl-7H-dibenz[c,e]azepine</td>
</tr>
<tr>
<td>359</td>
<td>3) 8-(3,5-Dimethylphenyl)-5-phenyl-7H-dibenz[c,e]azepine</td>
</tr>
<tr>
<td>360</td>
<td>4) 8-(3,5-Bis-trifluoromethylphenyl)-5-phenyl-7H-dibenz[c,e]azepine</td>
</tr>
<tr>
<td>360</td>
<td>5) 8-(4-Methylphenyl)-5-phenyl-7H-dibenz[c,e]azepine</td>
</tr>
<tr>
<td>361</td>
<td>6) 8-(4-Trifluoromethylphenyl)-5-phenyl-7H-dibenz[c,e]azepine</td>
</tr>
<tr>
<td>361</td>
<td>7) 8-(4-Dimethylaminophenyl)-5-phenyl-7H-dibenz[c,e]azepine</td>
</tr>
<tr>
<td>362</td>
<td>8) 8-(4-Methoxyphenyl)-5-phenyl-7H-dibenz[c,e]azepine</td>
</tr>
<tr>
<td>362</td>
<td>9) 8-(4-Fluorophenyl)-5-phenyl-7H-dibenz[c,e]azepine</td>
</tr>
<tr>
<td>363</td>
<td>10) 8-(4-Chlorophenyl)-5-phenyl-7H-dibenz[c,e]azepine</td>
</tr>
</tbody>
</table>
C. (Cont'd)

11) 8-(2-Methylphenyl)-5-phenyl-7H-dibenz[c,e]azepine 364

(vi) 8-Aryl-3-chloro-5-phenyl-7H-dibenz[c,e]azepines 364

1) 3-Chloro-8-(4-methylphenyl)-5-phenyl-7H-dibenz[c,e]azepine 364

2) 3-Chloro-5-phenyl-8-(4-trifluoromethylphenyl)-7H-dibenz[c,e]-azepine 365

D. Intramolecular Competition Reactions 365

(i) Generation and Reaction of the Nitrile Ylide Derived from N-(6-phenyl-2-(2-phenylethenyl)benzyl)benzimidoyl chloride 366

(ii) Generation and Reaction of the Nitrile Ylide Derived from N-(6-phenyl-2-(2-thienyl)benzyl)benzimidoyl chloride 367

(iii) Generation and Reaction of the Nitrile Ylides Derived from N-(2-aryl-6-phenylbenzyl)benzimidoyl Chlorides 368

1) N-(2-(3-Nitrophenyl)-6-phenylbenzyl)benzimidoyl chloride 368

2) N-(2-(3-Methoxyphenyl)-6-phenylbenzyl)benzimidoyl chloride 369
(iii) Cont'd.

3) $N-(2-(3,5$-Dimethylphenyl$)-6$-phenyl-phenylbenzyl)benzimidoyl chloride 370

4) $N-(2-(3,5$-Bis-Trifluoromethylphenyl$)-6$-phenylbenzyl)benzimidoyl chloride 370

5) $N-(2-(4$-Methylphenyl$)-6$-phenylbenzyl)benzimidoyl chloride 371

6) $N-(2-(4$-Trifluoromethylphenyl$)-6$-phenylbenzyl)benzimidoyl chloride 372

7) $N-(2-(4$-Dimethylaminophenyl$)-6$-phenylbenzyl)benzimidoyl chloride 373

8) $N-(2-(4$-Methoxyphenyl$)-6$-phenylbenzyl)benzimidoyl chloride 374

9) $N-(2-(4$-Fluorophenyl$)-6$-phenylbenzyl)benzimidoyl chloride 374

10) $N-(2-(4$-Chlorophenyl$)-6$-phenylbenzyl)benzimidoyl chloride 375

11) $N-(2-(2$-Methylphenyl$)-6$-phenylbenzyl)benzimidoyl chloride 376

(iv) Generation and Reaction of the Nitrile Ylides Derived from $N-(6$-aryl$-2$-(4-chlorophenyl)benzyl)benzimidoyl Chlorides

1) $N-(2-(4$-Chlorophenyl$)-6$-(4-methylphenyl)benzyl)benzimidoyl chloride 377
(iv) Cont'd.

2) \( N-(2-(4\text{-Chlorophenyl})-6-(4-\text{trifluoromethylphenyl})\text{benzyl})- \text{benzimidoylchloride} \)
SYMBOLS AND ABBREVIATIONS

m.p. melting point
b.p. boiling point
t.l.c. thin layer chromatography
g.l.c. gas-liquid chromatography
h.p.l.c. high pressure liquid chromatography
n.m.r. nuclear magnetic resonance
Hz hertz
MHz megahertz
br. broad
s;d;t singlet; doublet; triplet
q;sept;m quartet; septuplet; multiplet
quat. quaternary
J coupling constant
δ chemical shift
i.r. infra-red
κ wave numbers
m/z mass to charge ratio
p.p.m. parts per million
mol:mmol moles; millimoles
M molar
l;ml litres; millilitres
T.H.F. tetrahydrofuran
D.M.F. N,N-dimethylformamide
D.M.S.O. dimethyl sulphoxide
p.s.i. pounds per square inch
NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

\(^1\)H n.m.r. spectra were obtained using; (1) Jeol PMX60 (60 MHz) and Bruker WP80 (80 MHz) spectrometers for routine samples; (ii) Bruker WP80 (80 MHz), WP200 (200 MHz) and WH360 (360 MHz) for spectra of new compounds and variable temperature studies. Isomeric ratios from intramolecular competition reactions were obtained using the Bruker WH360 (360 MHz) spectrometer. \(^1\)\(^3\)C n.m.r. spectra were obtained using the Bruker WP200 (50.3 MHz) spectrometer. Carbon multiplicity was established by distortionless enhancement by polarisation transfer (D.E.P.T.). Spectra are recorded as \(\delta\) values for solutions in deuteriochloroform unless otherwise stated. The spectrometers were operated by Miss H. Grant, Mr. J.R.A. Millar, Dr. D. Reed and Dr. I.H. Sadler.

MASS SPECTROMETRY

Mass spectra were obtained using an Associated Electrical Industries MS902 spectrometer operated by Miss E. Stevenson, or a Kratos MS50 spectrometer operated by Mr. A. Taylor.
INFRA-RED SPECTROSCOPY

Liquid samples were examined as thin films and solid samples as nujol mulls, on sodium chloride plates on a Perkin Elmer 781 or 298 spectrometer. Spectra were calibrated with the polystyrene peak at 1603 cm\(^{-1}\).

ELEMENTAL ANALYSIS

Microanalysis for carbon, hydrogen and nitrogen were carried out on a Carlo-Erba model 1106 instrument operated by Mrs. E. McDougall.

X-RAY CRYSTALLOGRAPHY

X-ray structures were obtained using a Stoè STADI-4 four circle diffractometer operated by Dr. A. Blake.

MELTING POINTS

Melting points were determined using a Gallenkamp melting-point apparatus.

GAS-LIQUID CHROMATOGRAPHY (g.l.c.)

A Pye Unicam series 204 chromatograph using a flame ionisation detector and nitrogen carrier gas gave analytical chromatograms. The column used had internal diameter of 4 mm and length 1m and was packed with a silicone oil stationary phase (ovi - 2.5%) supported on 80-100 mesh celite.
HIGH-PRESSURE LIQUID CHROMATOGRAPHY (h.p.l.c.)

Analytical chromatograms were obtained using a Cecil Instruments CE212 variable wavelength ultraviolet monitor. The column used was packed with a reverse phase stationary phase (ODS) of 5 μm diameter and was 10 cm in length. Altex model 110A pumps were used and all solvent systems were isocratic.

THIN LAYER CHROMATOGRAPHY (t.l.c.)

This was carried out using pre-coated 0.2 mm sheets of silica (Kodak 13181 silica-gel with fluorescent indicator). Components in the developed chromatograms were detected by their quenching of fluorescence under ultra-violet light, and their staining by iodine.

DRY FLASH CHROMATOGRAPHY

This was carried out using silica gel (Fluka, Kieselgel GF_{254}; for thin layer chromatography) in porosity 3 cylindrical sinters (40 x 50 mm or 100 x 120 mm). The samples were preadsorbed on silica gel and packed onto the column. The products were eluted by adding successive portions of increasing polarity eluent (petroleum ether 40/60 containing either ethyl acetate or ether) and allowing the column to be sucked dry after each addition. The fractions were examined by thin layer chromatography.
DRIYING

Anhydrous magnesium sulphate was used to dry all organic solutions, unless otherwise stated.

PURIFICATION OF SOLVENTS

Tetrahydrofuran was distilled from sodium and benzophenone as required. Cyclohexane, n-hexane and \( N, N \)-dimethylformamide were distilled from calcium hydride as required. 1,2-Dimethoxyethane was passed through a column of activated alumina and stored over molecular sieve 4Å. Toluene, benzene and diethyl ether were distilled over and stored over sodium wire. Carbon tetrachloride, chloroform, dichloromethane and acetone were distilled from phosphorus pentoxide and stored over molecular sieve 4Å.

PALLADIUM CATALYSED CROSS-COUPLING REACTIONS

These were carried out using the method of Suzuki\(^2\). 1,2-Dimethoxyethane was prepared as described above. Tetrakis-triphenylphosphine palladium was purchased from Aldrich. All reactions were monitored by h.p.l.c. and continued until the arylbromide starting material had been completely consumed.
SECTION 1: SYNTHETIC STUDIES ON THE 1,7-ELECTRO-
CYCLISATION REACTIONS OF BENZONITRILE-2-
ARYLBENZYL YLIDES

I. PREPARATION OF STARTING MATERIALS

(i) N-2-METHOXYBENZYLIDENE ISOPROPYLAMINE

o-Anisaldehyde (40.80 g, 0.30 mol) and isopropylamine (35.40 g, 0.60 mol) were stirred under dry nitrogen and concentrated hydrochloric acid (5 drops) was added. The mixture was stirred until the solution cooled to room temperature and for a further hour at room temperature. The mixture was left to stand over sodium hydroxide pellets overnight, filtered and dried. Removal of excess isopropylamine in vacuo followed by distillation gave N-2-methoxybenzylidene isopropylamine as a pale green oil (45.55 g, 86%), b.p. 96°C at 0.3 mm Hg (Found: C, 74.5; H, 8.5; N, 7.9. C_{11}H_{15}NO requires C, 74.6; H, 8.7; N, 7.9%); (Found: m/z 177.1159. C_{11}H_{15}NO requires 177.1154); \( \delta_H \) (200 MHz) 1.26(d, J 6.3 Hz, 2xCH₃), 3.55(sept, J 6.3 Hz, pri-H), 3.82(s, OCH₃), 6.84-6.99(m, 2H), 7.29-7.38(m, 1H), 7.96(dd, J 5.9 and 1.8 Hz, 1H), 8.73(s, 1H); m/z 176(20%), 162(77), 134(100), 119(69); \( \nu_{\text{max(film)}} \) 1630 cm⁻¹ (C=N).

(ii) N-2-ARYLBENZYLIDENE ISOPROPYLAMINES

General method with N-2-phenylbenzylidene isopropylamine as example.
1) **N-2-Phenylbenzylidene Isopropylamine**

Bromobenzene (16.50 g, 0.104 mol) in T.H.F. (50 ml) was added to dry magnesium turnings (2.51 g, 0.104 mol) with stirring under dry nitrogen at such a rate as to maintain the mixture at gentle reflux. After the addition was complete the mixture was stirred for 30 minutes at room temperature. A solution of N-2-methoxybenzylidene isopropylamine (14.18 g, 0.08 mol) in T.H.F. (30 ml) was added dropwise with stirring over 10 minutes, the mixture stirred for a further 10 minutes then heated to reflux under dry nitrogen overnight, after which g.l.c. (OVI - 2.5%, \( N_2 = 60 \text{ cm}^3 \text{ min}^{-1} \), \( T = 148^\circ\text{C} \)) indicated >90% conversion. The mixture was poured, with vigorous stirring into 25% w/v ammonium chloride solution (100 ml) and stirred at room temperature for 1 hour. The mixture was extracted with methylene chloride (1 x 100 ml, 1 x 25 ml), dried and the solvent removed in vacuo to yield N-2-phenylbenzylidene isopropylamine as a yellow oil (17.76 g, 99%). (Found: m/z 223.1347. \( C_{16}H_{12}N \) requires 223.1360); \( \delta_H(200 \text{ MHz}) \) 1.25(d, \( J 6.3 \text{ Hz} \), 2xCH\(_3\)), 3.41(sept, \( J 6.3 \text{ Hz}, \text{ pri-}H\)), 7.32-7.48(m, 8H), 8.09(dd, \( J 4.4 \text{ and } 2.3 \text{ Hz} \)), 8.27(s, 1H); m/z 223(20%), 222(100), 180(65), 165(74); \( \nu_{\text{max}}(\text{film}) 1630 \text{ cm}^{-1} \) (C=N).

2) **N-2-(4-Chlorophenyl)benzylidene Isopropylamine**

Using the method of (ii).1.

4-Bromochlorobenzene (19.91 g, 0.104 mol) in T.H.F.
(50 ml) and N-2-methoxybenzylidene isopropylamine (14.18 g, 0.08 mol) in T.H.F. (30 ml). Conditions and work-up as in (ii).1. gave N-2-(4-chlorophenyl)benzylidene isopropylamine as a pale green amorphous solid (16.10 g, 98%) which resisted crystallisation from any solvent system. (Found: m/z 257.0970. C_{16}H_{16}ClN requires 257.0971); δH(200 MHz) 1.22(d, J 6.3 Hz, 2xCH₃), 3.40(sept, J 6.3 Hz, Prᵢ-H), 7.24-7.45(m, 7H), 8.06(dd, J 5.0 and 2.7 Hz, 1H), 8.21(s, 1H); m/z 259(9%), 257(29), 256(100), 214(30); νmax(film) 1630 cm⁻¹ (C=N).

3) N-2-(4-Methoxyphenyl)benzylidene Isopropylamine

Using the method of (ii).1.

4-Bromoanisole (19.45 g, 0.104 mol) in T.H.F. (50 ml) and N-2-methoxybenzylidene isopropylamine (14.18 g, 0.08 mol) in T.H.F. (30 ml). Conditions and work-up as in (ii).1. gave N-2-(4-methoxyphenyl)benzylidene isopropylamine as a yellow oil (21.46 g, 81%). (Found: m/z 253.1455. C_{12}H_{19}NO requires 253.1467); δH(200 MHz) 1.24(d, J 6.3 Hz, 2xCH₃), 3.43(sept, J 6.3 Hz, Prᵢ-H), 3.86(s, OCH₃), 6.96-7.44(m, 7H), 8.06(dd, J 5.6 and 2.0 Hz, 1H), 8.28(s, 1H); m/z 253(30%), 252(100), 195(77), 152(19); νmax(film) 1630 cm⁻¹ (C=N).

4) N-2-(2-Methylphenyl)benzylidene Isopropylamine

Using the method of (ii).1.

2-Bromotoluene (17.79 g, 0.104 mol) in T.H.F. (50 ml)
and N-2-methoxybenzylidene isopropylamine (14.18 g, 0.08 mol) in T.H.F. (30 ml). Conditions and work-up as in (ii).1. gave N-2-(2-methylphenyl)benzylidene isopropylamine as a yellow amorphous solid (18.47 g, 97%) which resisted crystallisation from any solvent system. (Found: m/z 237.1513. \( C_{12}H_{19}N \) requires 237.1517); \( \delta_H(80 \text{ MHz}) \)
1.19(d, \( J \) 6.3 Hz, 2\( xCH_3 \)), 2.09(s, \( CH_3 \)), 3.32(sept, \( J \) 6.3 Hz, \( pr\)-H), 7.13-7.53(m, 7H), 7.99(s, 1H), 8.09-8.20(m, 1H); m/z 236(2%), 222(100), 180(57), 69(92); \( \nu_{\max}(\text{film}) \)
1640 cm\(^{-1}\) (C=N).

(iii) 2-ARYLBENZALDEHYDES

General method with 2-phenylbenzaldehyde as example.

1) 2-Phenylbenzaldehyde

\( N-2\)-Phenylbenzylidene isopropylamine (17.76 g, 0.08 mol) and 4N sulphuric acid (100 ml) was heated at reflux under dry nitrogen for 1.5 hours. The mixture was cooled, extracted with methylene chloride (2 x 50 ml), dried and the solvent removed in vacuo. Distillation of the product gave 2-phenylbenzaldehyde as a pale green oil (11.20 g, 77%). b.p. 138-140°C at 5 mm Hg (lit. 149-150°C at 7 mm Hg); (Found: m/z 182.0727. \( C_{13}H_{10}O \) requires 182.0732); \( \delta_H(200 \text{ MHz}) \) 7.35-7.68(m, 8H), 8.04(dd, \( J \) 6.3 and 0.8 Hz, 1H), 9.96(d, \( J \) 0.8 Hz, \( CHO \)); \( \nu_{\max}(\text{film}) \)
1690 cm\(^{-1}\) (C=O).
2) 2-(4-Chlorophenyl)benzaldehyde

*N*-2-(4-Chlorophenyl)benzylidene isopropylamine (18.96 g, 0.06 mol) and 4N sulphuric acid were heated at reflux for 1.5 hours. Work-up as in (iii).1. followed by Kügelrohr distillation gave 2-(4-chlorophenyl)benzaldehyde as a white crystalline solid (10.66 g, 69%) m.p. 63-65°C (from n-hexane). (Found: C, 72.0; H, 4.2; N, 0. \text{C}_{13}\text{H}_9\text{ClO} requires C, 72.1; H, 4.2; N, 0%); (Found: m/z 216.0340. \text{C}_{13}\text{H}_9^{35}\text{ClO} requires 216.0342); \delta_H(200 \text{ MHz}) 7.25-7.68(m, 7H), 8.02(dd, J 6.2 and 1.4 Hz, CHO), 9.96(d, J 0.8 Hz, 1H); m/z 218(33%), 216(100), 181(83), 152(70); \nu_{\text{max}}(\text{nujol}) 1685 \text{ cm}^{-1} (\text{C=O}).

3) 2-(4-Methoxyphenyl)benzaldehyde

*N*-2-(4-Methoxyphenyl)benzylidene isopropylamine (20.07 g, 0.08 mol) and 4N sulphuric acid (100 ml) were heated at reflux for 1.5 hours. Work-up as in (iii).1. followed by Kügelrohr distillation gave 2-(4-methoxyphenyl)benzaldehyde as a white crystalline solid (12.40 g, 73%) m.p. 52-53°C (from 60-80 petrol). (Found: C, 79.3; H, 5.7. \text{C}_{14}\text{H}_{12}\text{O}_2 requires C, 79.2; H, 5.7%); (Found: m/z 212.0836. \text{C}_{14}\text{H}_{12}\text{O}_2 requires 212.0837); \delta_H(200 \text{ MHz}) 3.87(s, \text{OCH}_3), 6.98-7.66(m, 7H), 8.00(dd, J 6.1 and 0.8 Hz, 1H), 9.99(d, J 0.8 Hz, CHO); m/z 212(100%), 211(27), 169(31), 141(30); \nu_{\text{max}}(\text{nujol}) 1695 \text{ cm}^{-1} (\text{C=O}).
4) **2-(2-Methylphenyl)benzaldehyde**

N-2-(2-Methylphenyl)benzylidene isopropylamine (10.57 g, 0.044 mol) and 4N sulphuric acid (100 ml) were heated at reflux for 1.5 hours. Work-up as in (iii).1. followed by Kugelrohr distillation gave 2-(2-methylphenyl)benzaldehyde as a white amorphous solid which resisted crystallisation from any solvent system (7.34 g, 85%) b.p. 94-98°C at 0.25 mm Hg. (Found: m/z 196.0889. C_{14}H_{12}O requires 196.0881); δH(200 MHz) 2.10(s, CH₃), 7.16-7.67(m, 6H), 8.00-8.05(m, 1H), 9.75(d, J 0.8 Hz, CHO); m/z 196(100%), 181(48), 165(45), 152(33); νmax (nujol) 1695 cm⁻¹ (C=O).

(iv) **2-ARYLBENZALDEHYDE OXIMES**

General method with 2-phenylbenzaldehyde oxime as example.

1) **2-Phenylbenzaldehyde Oxime**

2-Phenylbenzaldehyde (11.00 g, 0.06 mol) was dissolved in ethanol (120 ml) and warmed to 35°C. A solution of sodium acetate (5.60 g, 0.066 mol) in water (25 ml) was added to a solution of hydroxylamine hydrochloride (4.60 g, 0.066 mol) in water (25 ml) and the mixture added rapidly with stirring to the warm aldehyde solution, resulting in the precipitation of a light coloured solid. Water (60 ml) was added and the mixture stored in the cold overnight. Filtration of the mixture gave 2-phenyl-
benzaldehyde oxime as a white powder (9.92 g, 83%) m.p. 114-116°C (from ethanol) (lit. 115°C). (Found: m/z 197.0823. \( \text{C}_{13}\text{H}_{11}\text{NO} \) requires 197.0840); \( \delta_H \) (360 MHz) 7.32-7.47 (m, 8H), 7.89-7.92 (m, 1H), 8.14 (s, H-C=N), 8.66 (br.s, OH); \( \nu_{\text{max}} \) (nujol) 3170 cm\(^{-1}\) (OH).

2) 2-(4-Chlorophenyl)benzaldehyde Oxime

2-(4-Chlorophenyl)benzaldehyde (6.50 g, 0.03 mol) in ethanol (60 ml); sodium acetate (2.80 g, 0.033 mol) in water (12 ml) and hydroxylamine hydrochloride (2.30 g, 0.033 mol) in water (12 ml). Method and work-up as in (iv).1. gave 2-(4-chlorophenyl)benzaldehyde oxime as a white powder (6.54 g, 94%) m.p. 161-162°C (from ethanol). (Found: C, 67.3; H, 4.3; N, 6.0. \( \text{C}_{13}\text{H}_{10}\text{ClNO} \) requires C, 67.4; H, 4.4; N, 6.0%); (Found: m/z 233.0413 \( \text{C}_{13}\text{H}_{10}\text{ClNO} \) requires 233.0421); \( \delta_H \) (200 MHz) 7.22-7.48 (m, 7H), 7.87-7.91 (m, 2H), 8.06 (s, 1H); m/z 233 (31%), 231 (100), 214 (99), 152 (21); \( \nu_{\text{max}} \) (nujol) 3170 cm\(^{-1}\) (OH).

3) 2-(4-Methoxyphenyl)benzaldehyde Oxime

2-(4-Methoxyphenyl)benzaldehyde (10.63 g, 0.05 mol) in ethanol (100 ml); sodium acetate (4.67 g, 0.055 mol) in water (20 ml) and hydroxylamine hydrochloride (3.83 g, 0.055 mol) in water (20 ml). Method and work-up as in (iv).1. gave 2-(4-methoxyphenyl)benzaldehyde oxime as a white powder (10.83 g, 95%) m.p. 110-111°C (from cyclohexane/ethanol). (Found: C, 73.8; H, 5.8; N, 6.1.
C_{14}H_{13}NO_{2} requires C, 74.0; H, 5.8; N, 6.2%; (Found: m/z 227.0940. C_{14}H_{13}NO_{2} requires 227.0946; \delta_H(200 \text{ MHz}) 3.86(s, OCH_{3}), 6.95-7.01(m, 2H), 7.21-7.41(m, 5H), 7.87(d, J 7.4 Hz, 1H), 8.14(s, 1H), 8.48(s, 1H); m/z 227(79%), 226(91), 209(100), 195(25), 167(44); \nu_{\text{max}}(\text{nujol}) 3200 \text{ cm}^{-1} (OH).

4) 2-(2-Methylphenyl)benzaldehyde Oxime

2-(2-Methylphenyl)benzaldehyde (4.91 g, 0.025 mol) in ethanol (50 ml); sodium acetate (2.33 g, 0.028 mol) in water (10 ml) and hydroxylamine hydrochloride (1.92 g, 0.028 mol) in water (10 ml). Method and work-up as in (iv).1. gave 2-(2-methylphenyl)benzaldehyde oxime as a white powder (4.85 g, 92%) m.p. 98-100°C (from n-hexane/ethanol). (Found: C, 79.8; H, 6.4; N, 6.7. C_{14}H_{13}NO requires C, 79.6; H, 6.2; N, 6.6%); (Found: m/z 211.0996. C_{14}H_{13}NO requires 211.0997); \delta_H(200 \text{ MHz}) 2.08(s, CH_{3}), 7.11-7.47(m, 7H), 7.85-7.93(m, 2H); m/z 196(100%), 179(59), 165(24); \nu_{\text{max}}(\text{nujol}) 3320 \text{ cm}^{-1} (OH).

(v) 2-ARYLBENZYLAMINE HYDROCHLORIDES

General method with 2-phenylbenzylamine hydrochloride as example.

1) 2-Phenylbenzylamine Hydrochloride

2-Phenylbenzaldehyde oxime (1.58 g, 0.008 mol), zinc dust (4.0 g), ammonium acetate (0.51 g), ethanol (25 ml)
and concentrated aqueous ammonia (s.g. 0.88, 55 ml) were heated at reflux under dry nitrogen overnight. The solvent was removed in vacuo and the residue stirred with 33% w/v aqueous potassium hydroxide solution for 1 hour. Ether (50 ml) was added, the mixture filtered through a pad of celite and the ether layer separated and dried. Passage of hydrogen chloride gas through the solution gave 2-phenylbenzylamine hydrochloride as a white powder (1.20 g, 68%). (Found: m/z 183.1050. 2-phenylbenzylamine C_{13}H_{13}N requires 183.1048); δ_H(360 MHz, D_2O) 3.97(s, CH_2), 7.23-7.67(m, 9H, Ar-H); m/z 183(24%), 182(52), 166(100), 165(82), 69(68).

2) 2-(4-Chlorophenyl)benzylamine Hydrochloride

2-(4-Chlorophenyl)benzaldehyde oxime (4.17 g, 0.018 mol), zinc dust (9.0 g), ammonium acetate (1.15 g), ethanol (60 ml) and concentrated aqueous ammonia (s.g. 0.88, 125 ml) were heated at reflux under dry nitrogen overnight. Work-up as in (v).1. gave 2-(4-chlorophenyl)benzylamine hydrochloride as a white powder (3.38 g, 74%). (Found: m/z 217.0658. 2-(4-chlorophenyl)benzylamine C_{13}H_{12}ClN requires 217.0658); δ_H(200 MHz, D_2O) 4.11(s, CH_2), 6.80-7.01(m, 2H), 7.11-7.19(m, 3H), 7.31-7.52(m, 3H); m/z 219(13%), 217(42), 216(83), 165(100).

3) 2-(4-Methoxyphenyl)benzylamine Hydrochloride

2-(4-Methoxyphenyl)benzaldehyde oxime (4.55 g,
0.02 mol), zinc dust (10.0 g), ammonium acetate (1.28 g), ethanol (65 ml) and concentrated aqueous ammonia (s.g. 0.88, 140 ml) were heated at reflux under dry nitrogen overnight. Work-up as in (v).1. gave 2-(4-methoxyphenyl) benzylamine hydrochloride as a white powder (2.84 g, 57%). (Found: m/z 213.1157. 2-(4-methoxyphenyl)benzylamine \( \text{C}_{14}\text{H}_{15}\text{NO} \) requires 213.1154); \( \delta_{\text{H}}(200 \text{ MHz, CDCl}_3) \) 3.82(s, OCH\(_3\)), 4.03(s, CH\(_2\)), 6.91-6.95(m, 2H), 7.21-7.38(m, 5H), 7.65-7.69(m, 1H), 8.63(br.s, NH\(_2\)); \( \text{m/z} \) 213(77%), 196(100), 181(36), 152(22).

4) 2-(2-Methylphenyl)benzylamine Hydrochloride

2-(2-Methylphenyl)benzaldehyde oxime (4.23 g, 0.02 mol), zinc dust (10 g), ammonium acetate (1.28 g), ethanol (65 ml) and concentrated aqueous ammonia (s.g. 0.88, 140 ml) were heated at reflux under dry nitrogen overnight. Work-up as in (v).1. gave 2-(2-methylphenyl) benzylamine hydrochloride as a white powder (2.66 g, 57%). (Found: m/z 197.1213. 2-(2-methylphenyl)benzylamine \( \text{C}_{14}\text{H}_{15}\text{N} \) requires 197.1204); \( \delta_{\text{H}}(200 \text{ MHz, CDCl}_3) \) 2.01(s, CH\(_3\)), 3.81(dd, J 14.2 and 5.9 Hz, CH\(_2\)), 7.13-7.49(m, 7H, Ar-H), 7.68-7.72(m, 1H, Ar-H), 8.51(br.s, NH\(_3\)); \( \text{m/z} \) 197(47%), 180(100), 179(87), 165(77).

(vi) \text{N-SUBSTITUTED-2-ARYLBENZYLAMINES}

1) \text{N-Benzoyl-2-phenylbenzylamine}

2-Phenylbenzylamine hydrochloride (1.10 g, 5 mmol) was
dissolved in methylene chloride (15 ml). Sodium carbonate (1.20 g, 12 mmol) was added and the mixture stirred for 10 minutes. Benzoyl chloride (0.78 g, 5.5 mmol) was added dropwise with stirring and the mixture stirred at room temperature under dry nitrogen overnight. Water (8 ml) was added and the mixture stirred for 1 hour. 5M aqueous sodium hydroxide (20 ml) was added and the mixture stirred for 0.5 hours. The organic layer was separated, washed with water (2 x 10 ml) and the solvent removed in vacuo to leave an oily residue. Crystallisation from n-hexane/ethanol gave N-benzoyl-2-phenylbenzylamine as a white crystalline solid (1.28 g, 89%). m.p. 94.5-95.5°C. (Found: C, 83.6; H, 5.9; N, 5.0. C$_{20}$H$_{17}$NO requires C, 83.6; H, 6.0; N, 4.9%); (Found: m/z 287.1316. C$_{20}$H$_{17}$NO requires 287.1310); $\delta_H$(200 MHz) 4.62(d, J 5.6 Hz, CH$_2$), 6.23(br.s, NH), 7.25-7.50(m, 12H), 7.60-7.64(m, 2H); m/z 287(37%), 286(40), 166(77), 165(100), 77(49); $r_{\text{max}}$(nujol) 1625 cm$^{-1}$ (C=O), 3320 cm$^{-1}$ (NH).

2) N-(4-Methylbenzoyl)-2-(4-chlorophenyl)benzylamine

2-(4-Chlorophenyl)benzylamine hydrochloride (1.27 g, 5 mmol) was dissolved in methylene chloride (15 ml). Sodium carbonate was added and the mixture stirred for 10 minutes. 4-Toluoyl chloride (0.85 g, 5.5 mmol) was added dropwise and the mixture stirred under dry nitrogen overnight. Work-up as in (vi)1. followed by crystallisation from n-hexane/ethanol gave N-(4-methyl-
benzoyl)-2-(4-chlorophenyl)benzylamine as a white crystalline solid (1.08 g, 64%) m.p. 149.5-151°C (Found: C, 75.3; H, 5.7; N, 4.3. C\(_{21}\)H\(_{18}\)ClNO requires C, 75.1; H, 5.4; N, 4.2%); (Found: m/z 337.1047 C\(_{21}\)H\(_{18}\)ClNO requires 337.1047); δ\(_{H}\)(200 MHz) 2.37(s, CH\(_3\)), 4.56(d, J 5.6 Hz, CH\(_2\)), 6.33(br.s, NH), 7.16-7.49(m, 10H), 7.54-7.58(m, 2H); m/z 337(22%), 335(61), 200(27), 165(90), 119(100); ν\(_{max}\)(nujol) 1630 cm\(^{-1}\) (C=O); 3270 cm\(^{-1}\) (NH).

N-(4-Methylbenzoyl)-2-(4-methoxyphenyl)benzylamine

2-(4-Methoxyphenyl)benzylamine hydrochloride (1.25 g, 5 mmol) was dissolved in methylene chloride (15 ml). Sodium carbonate (1.20 g, 12 mmol) was added and the mixture stirred for 10 minutes. 4-Toluoyl chloride (0.85 g, 5.5 mmol) was added dropwise and the mixture stirred under dry nitrogen overnight. Work-up as in (vi).1. followed by crystallisation from n-hexane/ethanol gave N-(4-methylbenzoyl)-2-(4-methoxyphenyl)benzylamine as a white crystalline solid (1.44 g, 87%) m.p. 131-133°C. (Found: C, 79.7; H, 6.4; N, 4.2. C\(_{22}\)H\(_{21}\)NO\(_2\) requires C, 79.7; H, 6.4; N, 4.2%); (Found: m/z 331.1575. C\(_{22}\)H\(_{21}\)NO\(_2\) requires 331.1572); δ\(_{H}\)(200 MHz) 2.37(s, CH\(_3\)), 3.83(s, OCH\(_3\)), 4.61(d, J 5.6 Hz, CH\(_2\)), 6.32(br.s, NH), 6.92-6.99(m, 2H), 7.14-7.57(m, 10H); m/z 331(55%), 196(100), 136(31), 119(46), 91(35); ν\(_{max}\)(nujol) 1625 cm\(^{-1}\) (C=O), 3320 cm\(^{-1}\) (NH).
4) **N-Benzoyl-2-(2-methylphenyl)benzylamine**

2-(2-Methylphenyl)benzylamine hydrochloride (1.17 g, 5 mmol) was dissolved in methylene chloride (15 ml). Sodium carbonate (1.20 g, 12 mmol) was added and the mixture stirred for 10 minutes. Benzoyl chloride (0.78 g, 5.5 mmol) was added dropwise and the mixture stirred under dry nitrogen overnight. Work-up as in (vi.l) with crystallisation from n-hexane/ethanol gave N-benzoyl-2-(2-methylphenyl)benzylamine as a white crystalline solid (1.04 g, 69%) m.p. 109-110°C (Found: C, 83.4; H, 6.4; N, 4.7. C_{21}H_{19}NO requires C, 83.7; H, 6.4; N, 4.7%); (Found: m/z 301.1468. C_{21}H_{19}NO requires 301.1467). δ_H(200 MHz) 2.07(s, CH₃), 4.29(dd, J 14.9 and 5.5 Hz, CH), 4.51(dd, J 14.9 and 6.2 Hz, CH), 6.19(br.s, NH), 7.14-7.67(m, 13H); m/z 301(82%), 281(6), 180(100), 179(37), 165(53), 105(48).

II. GENERATION AND REACTION OF THE NITRILE YLIDES DERIVED FROM SUBSTITUTED N-(2-ARYLBENZYL)-BENZIMIDOYL CHLORIDES

(i) GENERATION AND REACTION OF THE NITRILE YLIDE DERIVED FROM N-(2-PHENYLBENZYL)BENZIMIDOYL CHLORIDE

N-Benzoyl-2-phenylbenzylamine (0.68 g, 2.4 mmol), dry ether (40 ml) and thionyl chloride (10 ml) were heated at reflux under dry nitrogen overnight. The solvent was removed in vacuo and the residue dried under high vacuum for 3 hours. Dry T.H.F. (30 ml) was added and the
solution cooled to 0°C. Solid potassium tert-butoxide (0.54 g, 4.8 mmol) was added in one portion with rapid stirring under dry nitrogen. The mixture was stirred at 0°C for 10 minutes, allowed to warm to room temperature and stirred for 30 minutes. 25% w/v aqueous ammonium chloride (25 ml) was added and the mixture stirred vigorously for 5 minutes. Methylene chloride (25 ml) was added, the organic layer separated and the aqueous layer extracted with methylene chloride (2 x 10 ml). The combined organic layers were dried and the solvent removed in vacuo. Dry flash chromatography of the residue (silica, ethyl acetate:petrol 1:10 to 2:10) afforded 5-phenyl-7H-dibenz[c,e]azepine as a white crystalline solid (0.42 g, 65%) m.p. 95-96°C (from cyclohexane). (Found: C, 89.4; H, 5.6; N, 5.3. \( \text{C}_{20}\text{H}_{15}\text{N} \) requires C, 89.2; H, 5.6; N, 5.2%); (Found: m/z 269.1208. \( \text{C}_{20}\text{H}_{15}\text{N} \) requires 269.1204); \( \delta_H(200 \text{ MHz}) \) 3.96(d, J 10.4 Hz, 7-H), 4.92(d, J 10.4 Hz, 7'-H), 7.19-7.81(m, 13H, Ar-H); m/z 269(70%), 268(100), 165(30), 134(12); \( v_{\text{max}}(\text{nujol}) \) 1600 cm\(^{-1} \) (C=N).

(ii) GENERATION AND REACTION OF THE NITRILE YLIDE DERIVED FROM N-2-(4-CHLOROPHENYL)BENZYL)-4- METHYL BENZIMIDOYL CHLORIDE

\( N-\text{(4-Methylbenzoyl)}-2-(4-\text{chlorophenyl})\text{benzylamine} \) (0.167 g, 0.5 mmol), dry ether (10 ml) and thionyl chloride (3 ml) were heated at reflux under dry nitrogen overnight. The solvent removed in vacuo and the residue
dried under high vacuum for 3 hours. Dry T.H.F. (7 ml)
was added and the solution cooled to 0°C. Solid potassium
tert butoxide (0.11 g, 1 mmol) was added in one portion
with rapid stirring under dry nitrogen. The mixture was
stirred at 0°C for 10 minutes, allowed to warm to room
temperature and stirred for 30 minutes. The reaction was
worked up as in (i). then subjected to dry flash
chromatography (silica, ethyl acetate:petrol, 1:19 to 1:9)
which afforded 3-chloro-5-(4-methylphenyl)-7H-dibenz[c,e]-
azepine as a white crystalline solid (0.12 g, 77%) m.p.
98-100°C (from cyclohexane). (Found: C, 79.2; H, 5.4; N,
4.4. C_{21}H_{16}ClN requires C, 79.3; H, 5.1; N, 4.4); (Found:
m/z 319.0940. C_{21}H_{16}^{37}ClN requires 319.0942); δ_H(200 MHz)
2.35(s, CH₃), 3.91(d, J 10.5 Hz, 7-H); 4.91(d, J 10.5 Hz,
7'-H), 7.12-7.16(m, 2H), 7.25-7.70(m, 9H); m/z 319(27%)
317(100), 282(64), 165(87); ν_max(nujol) 1605 cm⁻¹ (C=N).

(iii) GENERATION AND REACTION OF THE NITRILE YLIDE
DERIVED FROM N-(2-(4-METHOXYPHENYL)BENZYL)-4-
METHYLBENZIMIDOYL CHLORIDE

N-(4-Methylbenzoyl)-2-(4-methoxyphenyl)benzylamine
(0.73 g, 2.2 mmol), dry ether (50 ml) and thionyl chloride
(10 ml) were heated at reflux under dry nitrogen
overnight. The solvent was removed in vacuo and the
residue dried under high vacuum for 3 hours. Dry T.H.F.
(30 ml) was added and the solution cooled to 0°C. Solid
potassium tert-butoxide (0.50 g, 4.4 mmol) was added in
one portion with rapid stirring under dry nitrogen. The mixture was stirred at 0°C for 10 minutes, allowed to warm to room temperature and stirred for 30 minutes. The reaction was worked up as in (i). then subjected to dry flash chromatography (silica, ethyl acetate:petrol, 1:19 to 1:9) which afforded 3-methoxy-5-(4-methylphenyl)-7H-dibenzo[c,e]azepine as a colourless oil which, on trituration with n-hexane gave a white crystalline solid (0.62 g, 90%) m.p. 96-97°C (from cyclohexane). (Found: C, 84.2; H, 6.1; N, 4.5. C_{22}H_{19}NO requires C, 84.3; H, 6.1; N, 4.5%); (Found: m/z 313.1464. C_{22}H_{19}NO requires 313.1467); \delta_H(200 \text{ MHz}) 2.33(s, CH_3), 3.77(s, OCH_3), 3.92(d, J 10.4 Hz, 7-H), 4.86(d, J 10.4 Hz, 7'-H), 7.08-7.73(m, 11H); m/z 313(20%), 312(16), 69(100); \nu_{max}(nujol) 1600 \text{ cm}^{-1} (C=N).

(iv) GENERATION AND REACTION OF THE NITRILE YLIDE DERIVED FROM N-(2-(2-METHYLPHENYL)BENZYL)BENZIMIDOYL CHLORIDE

N-Benzoyl-2-(2-Methylphenyl)benzylamine (0.30 g, 1 mmol), dry ether (20 ml) and thionyl chloride (6 ml) were heated at reflux under dry nitrogen overnight. The solvent was removed in vacuo and the residue dried under high vacuum for 3 hours. Dry T.H.F. (20 ml) was added and the solution cooled to 0°C. Solid potassium tert-butoxide (0.224 g, 2 mmol) was added in one portion with rapid stirring under dry nitrogen. The mixture was stirred at
0°C for 10 minutes, allowed to warm to room temperature and stirred for 30 minutes. The reaction was worked-up as in (i). then subjected to dry flash chromatography (silica, ethyl acetate:petrol 1:19 to 1:9) which afforded two products.

(a) Yellow solid (0.12 g) which resisted recrystallisation from any solvent system.

Mass spectrum: m/z 567(13%, indicates dimeric structure); 565(78); 550(20); 387(60); 385(60); 178(100); 165(94).

n.m.r.: $\delta_H$(200 MHz) 2.11(s, CH$_3$); 7.60-7.11(m); 7.62(t, J 7.5 Hz); 8.04(d, J 7.5 Hz); 9.75(s, possibly H-C=N).

$\delta_C$(50 MHz) 20.04(CH$_3$); 125.12-129.95(at least 11 xquat.); 134.34-144.09(6 x CH); 158.50 (possibly H-C=N).

(b) Yellow oil (0.20 g).

Mass spectrum: m/z 567(33%, indicates dimeric structure); 566(82); 551(41); 385(100); 283(36); 178(40); 165(95).

$^1$H n.m.r. showed a complex series of signals which could not be interpreted.
PART 1. "EXTERNAL COMPETITION" APPROACH TO RELATIVE RATE MEASUREMENT

(i) ATTEMPTED GENERATION AND REACTION OF THE NITRILE YLIDE DERIVED FROM N-(2-PHENYL BENZYL) BENZIMIDOYL CHLORIDE IN THE PRESENCE OF EXTERNAL DIPOLAROPHILES

1) With Dimethyl Fumarate as External Dipolarophile

N-Benzoyl-2-phenylbenzylamine (0.57 g, 2 mmol), dry ether (30 ml) and thionyl chloride (10 ml) were heated at reflux under dry nitrogen overnight. The solvent was removed in vacuo and the residue dried under high vacuum for 3 hours. Dry T.H.F. (20 ml) and dimethyl fumarate (0.58 g, 4 mmol) were added and the solution cooled to 0°C. Solid potassium tert-butoxide (0.44 g, 4 mmol) was added in one portion under dry nitrogen. The mixture was stirred at 0°C for 30 minutes. 25% w/v ammonium chloride solution (20 ml) was added with vigorous stirring. The mixture was extracted with methylene chloride (3 x 20 ml), the organic fractions dried and the solvent removed in vacuo to give a brown oil (1.16 g). Dry flash chromatography (silica, ethyl acetate:petrol 1:19 to 1:4) gave 4 products.

(a) White solid (0.58 g) : Identified by 'H n.m.r. as
unreacted dimethyl fumarate.

(b) White foam (0.08 g) : Identified by 'H n.m.r. as 5-phenyl-7H-dibenz[c,e]azepine (15%). See experiment (i) Section 1.II.

(c) White solid (0.29 g) : Identified by 'H n.m.r. as unreacted N-benzoyl-2-phenylbenzylamine (51%).

(d) Brown oil (0.16 g) : shown by 'H n.m.r. to be a complex mixture which was not investigated further.

2) With Dimethyl Maleate as External Dipolarophile

Using the method of 1 above, dry T.H.F. (20 ml) and dimethyl maleate (1.44 g, 10 mmol) were added to the imidoyl chloride prepared from N-benzoyl-2-phenylbenzylamine (0.57 g, 2 mmol). Reaction with potassium tert-butoxide (0.44 g, 4 mmol) at 0°C for 30 minutes followed by the usual work-up gave a dark brown oil (2.08 g). Dry flash chromatography (silica, ethyl acetate:petrol, 1:19 to 1:3) gave four products.

(a) White solid (0.52 g) : Identified by 'H n.m.r. as dimethyl fumarate.

(b) Colourless oil (0.41 g) : Identified by 'H n.m.r. as unreacted dimethyl maleate.

(c) White solid (0.19 g) : Identified by 'H n.m.r. as unreacted N-benzoyl-2-phenylbenzylamine (33%).

(d) Brown oil (0.37 g) : Shown by 'H n.m.r. to be a complex mixture which was not investigated further.
3) **With trans-stilbene as External Dipolarophile**

Using the method of 1 above, dry T.H.F. (20 ml) and trans-stilbene (0.72 g, 4 mmol) were added to the imidoyl chloride prepared from N-benzoyl-2-phenylbenzylamine (0.57 g, 2 mmol). Reaction with potassium tert-butoxide (0.44 g, 4 mmol) at 0°C for 30 minutes followed by the usual work-up gave a yellow solid. Dry flash chromatography (silica, ethyl acetate:petrol, 1:49 to 1:9) gave:

(a) Trans-stilbene (0.70 g); Identified by comparison with an authentic sample.

(b) 5-Phenyl-7H-dibenz[c,e]azepine (0.52 g, 97%) : Identified by comparison with an authentic sample (See Section 1.11, experiment (i)).

4) **With Norbornene as External Dipolarophile**

Using the method of 1 above, dry T.H.F. (20 ml) and norbornene (0.94 g, 10 mmol) were added to the imidoyl chloride prepared from N-benzoyl-2-phenylbenzylamine (0.57 g, 2 mmol). Reaction with potassium tert-butoxide (0.44 g, 4 mmol) at 0°C for 30 minutes followed by the usual work-up gave a yellow oil. Dry-flash chromatography (silica, ethyl acetate:petrol, 1:49 to1:9) gave;

(a) Norbornene (0.90 g) : Identified by comparison with an authentic sample.

(b) 5-Phenyl-7H-dibenz[c,e]azepine (0.49 g, 91%) : Identified by comparison with an authentic sample.
(See Section 1.II, experiment (i)).

5) **With Styrene as External Dipolarophile**

Using the method of 1 above, dry T.H.F. (10 ml) and styrene (10.42 g, 0.10 mol) were added to the imidoyl chloride prepared from N-benzoyl-2-phenylbenzylamine (0.57 g, 2 mmol). Reaction with potassium tert-butoxide (0.44 g, 4 mmol) at 0°C for 30 minutes followed by the usual work-up gave a yellow oil. Dry flash chromatography (silica, ethyl acetate:petrol, 1:49 to 1:9) gave;

(a) Styrene (9.39 g) : Identified by comparison with an authentic sample.

(b) 4-Phenyl-7H-dibenz[c,e]azepine (0.45 g, 84%) : Identified by comparison with an authentic sample. (See Section 1.II, experiment (i)).

6) **With α,α,α-Trifluoroacetophenone as External Dipolarophile**

Using the method of 1 above, dry T.H.F. (10 ml) and α,α,α-trifluoroacetophenone (1.74 g, 10 mmol) were added to the imidoyl chloride prepared from N-benzoyl-2-phenylbenzylamine (0.57 g, 2 mmol). Reaction with potassium tert-butoxide (0.44 g, 4 mmol) at 0°C for 30 minutes, followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:49 to 1:9) gave a white crystalline solid which was identified as N,N-dibenzoyl-2-phenylbenzylamine (0.41 g, 52%) m.p. 148-149°C (from
cyclohexane/toluene). (Found: C, 83.1; H, 5.4; N, 3.7.
C₂₂H₂₁NO₂ requires C, 82.8; H, 5.4; N, 3.5%); (Found: m/z 391.1577. C₂₂H₂₁NO₂ requires 391.1572); δH(200 MHz) 5.21(s, 2H), 7.10-7.48(m, 18H, Ar-H); 7.65-7.70(m, 1H, Ar-H); m/z 391(10%), 286(29), 165(30), 105(49), 69(100); νmax(nejol) 1690 cm⁻¹ (C=O).

Structure confirmed by X-ray crystallography.

(ii) ATTEMPTED GENERATION AND REACTION OF THE NITRILE YLIDE DERIVED FROM N-(2-PHENYL BENZYL) BENZIMIDOYL CHLORIDE USING ALTERNATIVE BASES

1) Using Triethylamine as Base

Triethylamine was completely unsuccessful in the 1,3-dehydrochlorination of N-(2-phenylbenzyl)benzimidoyl chloride. When added at room temperature and stirred overnight only N-benzyol-2-phenylbenzylamine was recovered. When the mixture was heated to reflux for several hours the product was an intractable tar.

2) Using Lithium Diisopropylamide as Base

(a) Lithium diisopropylamide (2.2 mmol from diisopropylamine (0.22 g) and n-butyllithium (2.0M, 1.1 ml)) was added to a solution of N-(2-phenylbenzyl)benzimidoyl chloride (from N-benzyol-2-phenylbenzylamine (0.57 g, 2 mmol)) in T.H.F. (5 ml). After reaction at 0°C for 30 minutes the usual work-up followed by dry flash chromatography (silica, ethyl acetate:petrol, 1:19 to
1:9) gave the expected 5-phenyl-7H-dibenz[c,e]azepine (0.38 g, 71%).

(b) The above experiment carried out in the presence of dipolarophiles gave results identical to those carried out using potassium tert-butoxide as base, e.g.

(i) Dimethyl maleate gave recovered starting material and a complex mixture.

(ii) Styrene gave 5-phenyl-7H-dibenz[c,e]azepine (0.41 g, 76%).

(c) The above experiment carried out in the presence of α,α,α-trifluoroacetophenone gave dibenzazepine only.

(iii) ATTEMPTED SYNTHESIS OF 2-(2-PHENYLPHENYL)-3-PHENYL-2H-AZIRINE

1) 2-Bromophenyl Acetophenone

This was made using the method of Mulvaney and Carr\textsuperscript{27}. A stirred solution of phosphorus trichloride (6 ml) and 2-bromophenylacetic acid (10.75 g, 0.05 mol) was heated at 90°C for 2 hours. Benzene (15 ml) was added and the solution decanted from the yellow precipitate. The solution was added slowly to anhydrous aluminium chloride (8.78 g, 0.06 mol) in benzene (25 ml) and the mixture heated to reflux for 2.5 hours. The solution was poured onto a mixture of ice (250 g) and 10M hydrochloric acid (40 ml). The benzene layer was separated and washed with 10% sodium hydroxide solution (20 ml) then dried and the solvent removed \textit{in vacuo}. The product was crystallised
from ethanol to give 2-bromophenyl acetophenone as a white crystalline solid (10.97 g, 80%) m.p. 68-70°C (lit.78 69.5-70°C); $\nu_{\text{max}}$(nujol) 1690 cm$^{-1}$ (C=O).

2) 2-Phenylphenyl Acetophenone

2-Bromophenyl acetophenone (5.50 g, 0.02 mol) and tetrakis-triphenylphosphine palladium (0.46 g, 4 x 10$^{-4}$ mol, 2% catalyst) were stirred in 1,2-dimethoxyethane (50 ml) under dry nitrogen for 20 minutes. Phenylboronic acid (2.85 g, 0.024 mol) and sodium carbonate (2.21 g, 0.02 mol) in water (20 ml) was added and the mixture heated to reflux under dry nitrogen for 1 hour. The dimethoxyethane was removed in vacuo and the mixture extracted with methylene chloride (50 ml). The solvent was removed in vacuo to leave a black oil which was subjected to dry-flash chromatography (silica, ethyl acetate:petrol, 1:9 to 1:4) to give 2-phenylphenyl acetophenone as a colourless oil (5.20 g, 100%). (Found: m/z 272.1200. C$_2$H$_{16}$O requires 272.1201) $\delta_{\text{H}}$(200 MHz) 4.29(s, CH$_2$), 7.31-7.56(m, 12H, Ar-H), 7.80-7.81(2H o to c=o); m/z 272(22%), 165(12), 105(100), 77(20); $\nu_{\text{max}}$(film) 1690 cm$^{-1}$ (C=O).
3) 2-Phenylphenyl Acetophenone-N,N-dimethyl-
hydrazone

2-Phenylphenylacetophenone (2.75 g, 10 mmol), unsym-
dimethylhydrazine (10 ml), sodium acetate (1.25 g) and
glacial acetic acid (3 drops) were heated at reflux under
dry nitrogen for 67 hours. Ether (25 ml) was added and
the mixture dried. The solvent and excess dimethyl-
hydrazine were removed in vacuo and the product
crystallised from ethanol to give 2-phenylphenyl aceto-
phenone-N,N-dimethylhydrazone as a yellow crystalline
solid (2.39 g, 76%) m.p. 116-117°C. (Found: C, 83.9; H,
7.0; N, 9.0. C₂₂H₂₂N₂ requires C, 83.9; H, 7.1; N, 8.9%);
δH(200 MHz) 2.58(s, NMe₂), 4.26(s, CH₂), 7.07-7.51(m, 14H,
Ar-H); m/z 314(52%), 270(9), 166(100), 147(30), 44(63);
γmax(nujol) 1610 cm⁻¹ (C=N).

4) Attempted Preparation of 2-(2-Phenylphenyl)-3-
phenyl-2H-azirine

2-Phenylphenylacetophenone-N,N-dimethylhydrazone
(1.10 g, 3.5 mmol), methyl iodide (4.97 g, 0.035 mol) and
dry D.M.F. were heated at 60°C for 3 hours. The mixture
was reduced in vacuo and ether (10 ml) was added. After
stirring for 30 minutes the ether was removed by
decantation and the residue washed with further ether (2 x
10 ml). The product was dried under high vacuum to leave
a cream coloured paste which resisted further purification
(1.68 g, 105%). The product was dissolved in D.M.S.O.
Sodium hydride (0.22 g of a 60% suspension in oil, 5.5 mmol) was added in two equal portions 10 minutes apart and the resulting green mixture stirred for 15 minutes. Water (20 ml) was added, the mixture extracted with n-pentane (3 x 15 ml), dried and the solvent removed in vacuo to give a brown oil (0.58 g). Although \(^1\)H n.m.r. indicated the presence of the desired azirine (\(\delta 3.21\) (s)) it was impossible to purify this product by either distillation or chromatography.

5) **Photolysis of Impure 2-(2-Phenylphenyl)-3-phenyl-2H-azirine**

The impure azirine (0.27 g) was dissolved in dry cyclohexane (150 ml) and the solution was irradiated for 2 hours. Removal of the solvent in vacuo gave a yellow foam (0.22 g) shown by \(^1\)H n.m.r. and t.l.c. to contain 5-phenyl-7H-dibenz[c,e]azepine (ca. 60%). This product could not be purified by chromatographic methods.

**PART 2. "INTERNAL COMPETITION" APPROACH TO RELATIVE RATE MEASUREMENT**

**Approaches to Preparation of N-benzoyl-2,6-diarylbenzylamines**

**APPROACH 1:** *Via Grignard Reactions of N-2,6-Dimethoxybenzylidene Isopropylamines*

**Preparation of Starting Materials**
(i) **2,6-DIMETHOXYBENZALDEHYDE**

This was prepared after the method of Wittig\(^{131}\) from m-dimethoxybenzene (6.91 g, 0.05 mol), n-butyllithium (37 ml of a 1.5M solution in hexanes) and \(N,N\)-dimethyl formamide (4.39 g, 0.06 mol). Crystallisation of the product from ethyl acetate gave 2,6-dimethoxybenzaldehyde as a white crystalline solid (3.24 g, 39%) m.p. 96-98°C (lit.\(^{131}\) 97-98°C); \(\delta_H(80 \text{ MHz})\) 3.86(s, 2xOCH\(_3\)), 6.53(d, J 7.4 Hz, 2H), 7.32(t, J 7.4 Hz, 1H), 10.50(s, CHO).

(ii) **N-2,6-DIMETHOXYBENZYLIDENE ISOPROPYLAMINE**

2,6-Dimethoxybenzaldehyde (2.32 g, 0.014 mol) and isopropylamine (3.30 g, 0.056 mol) were stirred under dry nitrogen. Concentrated hydrochloric acid (2 drops) was added and the mixture stirred until the solution cooled to room temperature and for a further hour at room temperature. The mixture was left to stand over sodium hydroxide pellets overnight, filtered and dried. Removal of excess isopropylamine in vacuo gave \(N-2,6\)-dimethoxybenzylidene isopropylamine as a yellow powder (2.83 g, 98%). This product was used without further purification. \(\delta_H(80 \text{ MHz})\) 1.24(d, J 6.3 Hz, 2xCH\(_3\)), 3.24(sept, J 6.3 Hz, pri-H), 3.73(s, 2xOCH\(_3\)), 6.46(d, J 8.3 Hz, 1H), 6.98-7.28(m, 2H), 8.40(s, H-C=N).

(iii) **2-METHOXY-6-PHENYLBENZALDEHYDE**

Bromobenzene (6.91 g, 0.044 mol) in T.H.F. (25 ml) was
added to dry magnesium turnings (1.07 g, 0.044 mol) with stirring under dry nitrogen at such a rate as to maintain the mixture at gentle reflux. After the addition was complete the mixture was stirred for 30 minutes at room temperature. The Grignard reagent was transferred to a dropping funnel and added dropwise to a chilled (0°C) solution of N-2,6-dimethoxybenzylidene isopropylamine (5.89 g, 0.028 mol) in T.H.F. (10 ml). After 15 minutes at 0°C glc. \((\text{OVI}-2.5\% , \; \text{N}_2 = 60 \; \text{cm}^3 \; \text{min}^{-1}, \; T = 189^\circ \text{C})\) indicated a 3-component mixture. 25% w/v aqueous ammonium chloride (40 ml) was added and the mixture stirred for 30 minutes. The mixture was extracted with methylene chloride (1 x 75 ml, 2 x 30 ml), dried and the solvent removed in vacuo. The residue was heated to reflux with 4N sulphuric acid (50 ml) for 1 hour. The mixture was extracted with methylene chloride (1 x 50 ml, 2 x 20 ml), dried and the solvent removed in vacuo. The product was subjected to dry flash chromatography (silica, ethyl acetate:petrol, 1:19 to 1:4) to give 2-methoxy-6-phenylbenzaldehyde as a white crystalline solid (3.07 g, 52%) m.p. 77-78°C (from cyclohexane) \((\text{Found C, 79.4; H, 5.7. } \text{C}_{14}\text{H}_{12}\text{O}_2 \text{ requires C, 79.2; H, 5.6%}; \text{ Found m/z 212.0835. } \text{C}_{14}\text{H}_{12}\text{O}_2 \text{ requires 212.0837); } \delta_H(200 \text{ MHz}) 3.95(s, \text{ OCH}_3), 6.94-7.02(m, 2\text{H}), 7.25-7.56(m, 6\text{H}), 10.07(s, \text{ CHO}); m/z 212(100%), 211(80), 180(28), 152(34), 69(56); \gamma_{\text{max}}(\text{nujol}) 1690 \text{ cm}^{-1} (\text{C}=\text{O}). \)

A second product was identified as 2,6-diphenylbenz-
aldehyde (22.46, 34%) by comparison with an authentic sample (see experiment (v) later).

(iv) **N-2-METHOXY-4-PHENYLBENZYLIDENE ISOPROPYLANINE**

A mixture of 2-methoxy-6-phenylbenzaldehyde (1.06 g, 5 mmol) and isopropylamine (1.18 g, 0.02 mol) was stirred under dry nitrogen. Concentrated hydrochloric acid (1 drop) was added and the mixture stirred until the solution cooled to room temperature and for a further hour at room temperature. Methylene chloride (10 ml) and anhydrous sodium carbonate were added. The mixture was dried consecutively with magnesium sulphate and calcium sulphate. The solvent and excess isopropylamine were removed *in vacuo* to yield *N*-2-methoxy-6-phenylbenzylidene isopropylamine as a yellow oil (1.27 g, 100%). This product was used without further purification. (Found: m/z 253.1465. C_{17}H_{19}N0 requires 253.1467); δH(80 MHz) 1.07(d, J 5.3 Hz, 2xCH₃), 3.51(sept, J 5.3 Hz, pri-H), 3.83(s, OCH₃), 6.83–6.99(m, 2H), 7.23–7.43(m, 6H), 8.28(s, H-C=N); m/z 253(22%), 252(100), 210(34), 195(42); v max(film) 1625 cm⁻¹ (C=N).

(v) **2-ARYL-6-PHENYLBENZALDEHYDES**

1) **2,6-Diphenylbenzaldehyde**

A mixture of bromobenzene (0.90 g, 5.75 mmol) in T.H.F. (3 ml) was added to dry magnesium turnings (0.14 g, 5.75 mmol) with stirring under nitrogen at such a rate as
to maintain the mixture at gentle reflux. After the addition was complete the mixture was stirred for 30 minutes at room temperature. A solution of N-2-methoxy-6-phenyl benzylidene isopropylamine (1.27 g, 5 mmol) in T.H.F. (2 ml) was added dropwise with stirring over 5 minutes. The mixture was heated to reflux for 30 minutes after which g.l.c. (OVI-2.5%, \( N_2 = 60 \text{ cm}^3 \text{ min}^{-1} \), \( T = 152^\circ \text{C} \)) indicated complete digestion of the starting material. 25% w/v aqueous ammonium chloride was added and the mixture stirred at room temperature for 30 minutes. The mixture was extracted with methylene chloride, dried, and the solvent removed in vacuo. The residue was heated to reflux with 4N sulphuric acid (25 ml) for 1.5 hr. The mixture was extracted with methylene chloride (3 x 15 ml), dried and the solvent removed in vacuo. The product was subjected to dry flash chromatography (silica, ethyl acetate:petrol, 1:19 to 1:9) to give 2,5-diphenylbenzaldehyde as a white crystalline solid (0.75 g, 58%) m.p. 77-78\(^\circ\)C (from cyclohexane) (Found: C, 88.3; H, 5.4; N, 0. C\(_{19}\)H\(_{14}\)O requires C, 88.3; H, 5.5; N, 0%); (Found: m/z 258.1037 C\(_{19}\)H\(_{14}\)O requires 258.1045); \( \delta_H(200 \text{ MHz}) \) 7.34-7.64(m, 13H, Ar-H), 9.98(s, CHO); m/z 258(100%), 257(67), 228(25), 181(21); \( \nu_{\text{max}}(\text{nujol}) \) 1695 cm\(^{-1}\) (C=O).

2) 2-(4-Chlorophenyl)-6-phenylbenzaldehyde

Using the method of 1. above the Grignard reagent was prepared from 4-bromochlorobenzene (2.87 g, 15 mmol) in
T.H.F. (8 ml) and magnesium turnings (0.36 g, 15 mmol). Reaction with N-2-methoxy-6-phenylbenzylidene isopropylamine (1.90 g, 7.5 mmol) in T.H.F. (3 ml) at reflux for 1.5 hours followed by the usual work-up and dry flash chromatography (silica, ether:petrol, 1:100 to 1:20) gave 2-(4-chlorophenyl)-6-phenylbenzaldehyde as a white crystalline solid (1.44 g, 66%) m.p. 95-96°C (from n-hexane/ethanol). (Found: C, 77.6; H, 4.4; N, 0. C_{19}H_{13}ClO requires C, 77.9; H, 4.5; N, 0%); (Found: m/z 294.0635 C_{19}H_{13}^{37}ClO requires 294.0625); δH(200 MHz) 7.23-7.64(m, 12H, Ar-H), 9.93(s, CHO); m/z 294(33%), 292(100), 257(73), 228(30); v(nujol) 1705 cm⁻¹ (C=O).

(vi) 2-ARYL-6-PHENYL BENZALDEHYDE OXIMES

1) 2-6-Diphenylbenzaldehyde Oxime

2,6-Diphenylbenzaldehyde (0.26 g, 1 mmol) was dissolved in ethanol (3 ml) and warmed to 35°C. A solution of sodium acetate (0.09 g, 1.1 mmol) in water (0.5 ml) was added to a solution of hydroxylamine hydrochloride (0.08 g, 1.1 mmol) in water (0.5 ml) and the mixture added rapidly with stirring to the warm aldehyde solution. Water (4 ml) was added and the mixture stored in the cold overnight. Filtration gave 2,6-diphenylbenzaldehyde oxime as a white powder (0.27 g, 98%) m.p. 145-147°C (from cyclohexane/ethanol). (Found: C, 83.5; H, 5.5; N, 5.1. C_{19}H_{15}NO requires C, 83.4; H, 5.5; N, 5.1%); Found: m/z 273.1148. C_{19}H_{15}NO requires 273.1154); δH(360
MHz) 7.17(br.s, OH), 7.25-7.48(m, 13H, Ar-H), 7.93(s, H-C=N); m/z 273(40%), 272(100), 256(51), 69(39); υ\text{max}(nujol) 3300 cm\(^{-1}\) (br., OH).

2) 2-(4-Chlorophenyl)-6-phenylbenzaldehyde oxime

Using the method of 1. above the oxime was prepared from 2-(4-chlorophenyl)-6-phenylbenzaldehyde (0.66 g, 2.25 mmol) in ethanol (3 ml), sodium acetate (0.20 g, 2.48 mmol) and hydroxylamine hydrochloride (0.17 g, 2.48 mmol). Filtration of the mixture gave 2-(4-chlorophenyl)-6-phenylbenzaldehyde oxime as a white powder (0.64 g, 92%) m.p. 162-163°C (from ethanol/n-hexane) (Found: C, 73.6; H, 4.5; N, 4.5. \(\text{C}_{19}\text{H}_{14}\text{ClNO}\) requires C, 74.0; H, 4.6; N, 4.6%); (Found: m/z 309.0727. \(\text{C}_{19}\text{H}_{14}\text{ClNO}\) requires 309.0734); δ\text{H}(200 MHz) 7.21-7.61(m, 13H), 7.87(s, 1H); m/z 309(5%), 307(15), 306(38), 290(18), 69(100); υ\text{max}(nujol) 3230 cm\(^{-1}\) (br., OH).

(vii) 2-ARYL-6-PHENYLBENZYLAMINES

1) 2,6-Diphenylbenzylamine

2,6-Diphenylbenzaldehyde oxime (0.41 g, 1.6 mmol), zinc dust (0.8 g), ammonium acetate (0.10 g), ethanol (5.5 ml) and concentrated aqueous ammonia (s.g. 0.88, 12 ml) were heated at reflux under dry nitrogen overnight. The solvent was removed in vacuo and the residue stirred with 33% w/v aqueous potassium hydroxide solution (20 ml) for 1 hour. Ether (10 ml) was added and the mixture
filtered through a pad of celite. The ether layer was separated and dried. The solvent was removed in vacuo to yield 2,6-diphenylbenzylamine as a colourless oil (0.32 g, 77%). This product was used without further purification. (Found: m/z 259.1356. C_{19}H_{17}N requires 259.1361); δ_H(360 MHz) 3.71(s, CH₂), 6.86-7.48(m, 15H, Ar-H and NH₂); m/z 259(6%), 242(46), 84(100), 69(66); ν_max(film) 3350 cm⁻¹ (NH).

2) 2-(4-Chlorophenyl)-6-phenylbenzylamine

Using the method of 1. above the benzylamine was prepared from 2-(4-chlorophenyl)-6-phenylbenzaldehyde oxime (0.52 g, 1.7 mmol). After heating at reflux overnight the usual work-up gave 2-(4-chlorophenyl)-6-phenylbenzylamine as a colourless oil (0.44 g, 88%). This product was used without further purification. (Found: m/z 295.0954. C_{19}H_{16}ClN requires 295.0942); δ_H(360 MHz) 3.69(s, CH₂), 6.85-7.63(m, 14H, Ar-H and NH₂); m/z 295(11%), 293(30), 292(42), 276(100), 241(68); ν_max(film) 3370 cm⁻¹ (N-H).

(viii) N-BENZOYL-2-ARYL-6-PHENYLBENZYLAMINES

1) N-Benzoyl-2,6-diphenylbenzylamine

2,6-Diphenylbenzylamine (0.26 g, 1 mmol) was dissolved in methylene chloride (5 ml). Sodium carbonate (0.16 g, 1.5 mmol) was added and the mixture stirred for 10 minutes. Benzoyl chloride (0.15 g, 1.1 mmol) was added
dropwise with stirring. The mixture was heated to reflux for 30 minutes and allowed to cool. Water (2 ml) was added and the mixture stirred for 1 hour. 5M aqueous sodium hydroxide (4 ml) was added and the mixture stirred for 30 minutes. The organic layer was separated, washed with water (2 x 2 ml), dried, and the solvent removed in vacuo to leave an oily residue. Crystallisation from isopropanol gave N-benzoyl-2,6-diphenylbenzylamine as a white crystalline solid (0.16 g, 44%) m.p. 172-174°C (ethanol/n-hexane) (Found: C, 85.7; H, 6.1; N, 3.8. C_{26}H_{21}NO requires C, 85.9; H, 5.8; N, 3.9%); (Found: m/z 363.1624. C_{26}H_{21}NO requires 363.1623); δH(200 MHz) 4.60(d, J 5.1 Hz, CH₂), 5.75(br.s, NH), 7.25-7.44(m, 18H, Ar-H); m/z 363(52%), 242(100), 122(43), 105(27); νmax(nujol) 3360 cm⁻¹ (N-H), 1660 cm⁻¹ (C=O).

2) N-Benzoyl-2-(4-chlorophenyl)-6-phenylbenzylamine

Using the method of 1. above the amide was prepared from 2-(4-chlorophenyl)-6-phenylbenzylamine (0.35 g, 1.2 mmol) in methylene chloride (5 ml), sodium carbonate (0.19 g, 1.8 mmol) and benzoyl chloride (0.19 g, 1.3 mmol). Reaction at room temperature followed by the usual work-up gave an oily residue. Crystallisation from toluene/ethanol gave N-benzoyl-2-(4-chlorophenyl)-6-phenylbenzylamine as a white crystalline solid (0.32 g, 67%). m.p. 163-165°C (from n-hexane/ethanol). (Found: C, 78.1; H, 5.0; N, 3.5. C_{26}H_{20}ClNO requires C, 78.5; H,
5.1: N, 3.5%; (Found: m/z 399.1204. $C_{26}H_{20}^{37}ClNO$ requires 399.1204); $\delta_H(200\ \text{MHz})$ 4.57 (d, $J \ 5.2\ Hz$, CH$_2$), 5.92 (br.s, NH), 7.24-7.45 (m, 17H); m/z 399 (32%), 397 (93), 276 (96), 241 (88), 122 (100); $\nu_{max}(\text{nujol})$ 1635 cm$^{-1}$ (C=O), 3310 cm$^{-1}$ (N-H).

**GENERATION AND REACTION OF THE NITRILE YLIDES DERIVED FROM N-(2-ARYL-6-PHENYL BENZYL)BENZIMIDOYL CHLORIDES**

(i) **GENERATION AND REACTION OF THE NITRILE YLIDE DERIVED FROM N-(2,6-DIPHENYL BENZYL)BENZIMIDOYL CHLORIDE**

N-benzoyl-2,6-diphenylbenzylamine (75 mg, 0.2 mmol), ether (4 ml) and thionyl chloride (1 ml) were heated at reflux under dry nitrogen overnight. The solvent was removed in vacuo and the residue dried under high vacuum for 3 hours. Dry T.H.F. (3 ml) was added and the solution cooled to 0°C. Solid potassium tert-butoxide (0.046 g, 0.4 mmol) was added in one portion with rapid stirring under dry nitrogen. The mixture was stirred at 0°C for 10 minutes then at room temperature for 30 minutes. 25% w/v aqueous ammonium chloride (3 ml) was added and the mixture stirred vigorously for 5 minutes. Methylene chloride (3 ml) was added, the organic layer separated and the aqueous layer extracted with methylene chloride (2 x 2 ml). The combined organic fractions were dried and the solvent removed in vacuo. Dry flash chromatography of the residue (silica, ethyl acetate: petrol 1:19 to 1:9) gave
5,8-diphenyl-7H-dibenz[c,e]azepine as a white foam (52 mg, 68%) m.p. 125-126°C (from cyclohexane) (Found: C, 90.4; H, 5.6; N, 4.2. \( \text{C}_26\text{H}_{19}\text{N} \) requires C, 90.4; H, 5.5; N, 4.1%); (Found: m/z 345.1518. \( \text{C}_26\text{H}_{19}\text{N} \) requires 345.1517); \( \delta_H(360 \text{ MHz}) \) 3.66(d, J 10.3 Hz, 7-H), 5.05(d, J 10.3 Hz 7'-H), 7.25-7.79(m, 17H, Ar-H); m/z 345(93%), 344(100), 319(12), 239(13), 51(54); \( \nu_{\max}(\text{nujol}) \) 1610 cm\(^{-1} \) (C=N).

(ii) GENERATION AND REACTION OF THE NITRILE YLIDE DERIVED FROM \( \text{N}-(2-(4-\text{CHLOROPHENYL})-6-\text{PHENYL}-\text{BENZYL})\text{BENZIMIDOYL CHLORIDE} \)

See Section 2, part 3.

APPROACH 2: \textit{via Palladium Catalysed Cross-Coupling Reactions}

I. ATTEMPTED SEQUENTIAL PALLADIUM CATALYSED CROSS-COUPLING OF 4-(\( \text{N}-\text{BENZOYLAMINOMETHYL} \))-3,5-DIBROMO-BENZOIC ACID METHYL ESTER

PREPARATION OF STARTING MATERIAL

(i) 3,5-DIBROMO-4-METHYLBENZOIC ACID METHYL ESTER

This was prepared by the method of Pearson, Stamper and Suthers\textsuperscript{133} from 4-toluoyl chloride (20.72 g, 0.13 mol), anhydrous aluminium chloride (44.01 g, 0.33 mol) and methanol (200 ml). The crude product was crystallised from methanol to afford 3,5-dibromo-4-methylbenzoic acid methyl ester as a white crystalline solid (17.46 g, 44%)
m.p. 86-88°C (lit. 87.5-88.5°C); δH(60 MHz) 2.81(s, CH₃), 4.12(s, CO₂CH₃), 8.27(s, 2H, Ar-H).

(ii) 4-(BROMOMETHYL)-3,5-DIBROMOBENZOIC ACID METHYL ESTER

3,5-Dibromo-4-methylbenzoic acid methyl ester (4.62 g, 15 mmol) and N-bromosuccinimide (2.67 g, 15 mmol) were dissolved in carbon tetrachloride (10 ml). Benzoyl peroxide (10 mg) was added and the mixture heated to reflux for 7 hours. Methylene chloride (50 ml) was added, the organic layer separated and washed with 2% w/v sodium carbonate solution (2 x 50 ml). The organic portion was dried and the solvent removed in vacuo. The crude product was crystallised from carbon tetrachloride to afford 4-(bromomethyl)-3,5-dibromobenzoic acid methyl ester as a white crystalline solid (3.76 g, 65%) m.p. 110-111°C (from toluene/methanol) (Found: C, 27.8; H, 1.8; N, 0%. C₁₀H₁₁Br₂O₂ requires C, 27.9; H, 1.8; N, 0%); (Found: m/z 387.7941. C₁₀H₁₁Br₂O₂ requires 387.7958); δH(200 MHz) 3.92(s, CO₂CH₃), 4.81(s, CH₂), 8.18(s, 2H, Ar-H); m/z 387(8%), 385(8), 307(100), 51(75); v_max(nujol) 1725 cm⁻¹ (C=O).

(iii) 3,5-DIBROMO-4-(PTHALIMIDOMETHYL)BENZOIC ACID METHYL ESTER

This was made using the Gabriel synthesis following the method of Sheehan and Bolhofer. 4-(Bromomethyl)-
3,5-dibromobenzoic acid methyl ester (1.38 g, 3.5 mmol) was dissolved in D.M.F. (15 ml). Dry potassium pthalimide (0.71 g, 3.85 mmol) was added and the mixture stirred at room temperature overnight. The D.M.F. was removed under high vacuum and methylene chloride (25 ml) was added. The mixture was washed with 2M aqueous sodium hydroxide (15 ml), water (15 ml) then dried and the solvent removed in vacuo. The product was crystallised from toluene to give 3,5-dibromo-4-(pthalimidomethyl)benzoic acid methyl ester as a white crystalline solid (1.22 g, 77%) m.p. 164-165°C (Found: C, 45.1; H, 2.5; N, 3.1. C_{12}H_{11}Br_{2}NO_{4} requires C, 45.1; H, 2.4; N, 3.1%); δH(360 MHz) 3.91(s, OCH₃), 5.19(s, CH₂), 7.25-7.81(m, 4H, Ar-H), 8.19(s, 2H o to CO₂Me); m/z(FAB, glycerol) 456(m+1, 18%), 455(43); 454(28), 453(70), 452(16), 451(39), 307(100); vₜₐₓ(nujol) 1730 cm⁻¹ (C=O), 1705 cm⁻¹ (C=O).

(iv) 4-(AMINOMETHYL)-3,5-DIBROMOBENZOIC ACID METHYL ESTER

This was made after the method of Bolhofer and Sheehan. 3,5-Dibromo-4-(pthalimidomethyl)benzoic acid methyl ester (1.82 g, 4 mmol), methanol (20 ml) and hydrazine hydrate solution (85% v/v, 0.34 ml) were heated at reflux under dry nitrogen for 2 hours. The solvent was removed in vacuo and the residual solid was subjected to Soxhlet extraction with chloroform (100 ml) for 2 hours. The chloroform was removed in vacuo to give 4-(amino-
methyl)-3,5-dibromobenzoic acid methyl ester as a
colourless oil (1.22 g, 94%). This product was used
without further purification. $\delta_H(200 \text{ MHz})$ 3.91(s, OCH$_3$),
5.19(s, CH$_2$), 8.20(s, 2H, Ar-H); m/z(FAB, glycerol)
326(m+1, 28%), 324(62), 322(43), 307(84), 135(64),
32(100); $\nu_{\max}(\text{film})$ 3360, 3300 cm$^{-1}$ (N-H), 1725 cm$^{-1}$
(C=O).

(v) 4-((N-BENZOYLAMINOMETHYL)3,5-DIBROMOBENZOIC ACID
METHYL ESTER

4-(Aminomethyl)-3,5-dibromobenzoic acid methyl ester
(0.48 g, 1.5 mmol) was dissolved in methylene chloride
(5 ml). Sodium carbonate (0.24 g, 2.25 mmol) was added
and the mixture stirred for 10 minutes. Benzoyl chloride
(0.24 g, 1.7 mmol) was added dropwise and the mixture
heated to reflux for 30 minutes. After cooling, water
(3 ml) was added and the mixture was extracted with
methylene chloride (2 x 5 ml). The organic fractions were
dried and the solvent removed in vacuo. Crystallisation
of the product from ethanol/toluene gave 4-((N-benzoyl-
aminomethyl)-3,5-dibromobenzoic acid methyl ester as a
white crystalline solid (0.45 g, 70%) m.p. 167-168°C (from
ethanol/toluene) (Found: C, 44.8; H, 2.9; N, 3.2.
C$_{16}$H$_{13}$Br$_2$NO$_3$ requires C, 45.0; H, 3.0; N, 3.3%); $\delta_H(360$
MHz) 3.92(s, OMe), 5.01(d, J 5.5 Hz, CH$_2$), 6.50(br.s, NH),
8.20(s, 2H o to CO$_2$Me); m/z(FAB, glycerol) 430(m+1, 63%),
428(100), 350(25), 348(32), 105(78).
ATTEMPTED SEQUENTIAL CROSS-COUPLING OF 4-(N-BENZOYLAMINO-
METHYL)-3,5-DIBROMOBENZOIC ACID METHYL ESTER

4-(N-Benzoylaminomethyl)-3,5-dibromobenzoic acid methyl ester (0.31 g, 0.73 mmol) and tetrakis-triphenyl-
phosphine palladium catalyst (0.035 g, 3.0 x 10^-5 mol) were stirred in 1,2-dimethoxyethane (5 ml) under dry
nitrogen for 20 minutes. Phenylboronic acid (0.089 g, 0.73 mmol) and sodium carbonate (0.08 g, 0.77 mmol) were
added and the mixture stirred at room temperature. The reaction was monitored by h.p.l.c. (ODS, 5 μm, reverse
phase, methanol:water, 60:40). After 3 hours h.p.l.c. indicated no reaction. The mixture was heated to reflux
for 1 hour after which h.p.l.c. indicated complete disappearance of starting material with the appearance of
two products. The dimethoxyethane was removed in vacuo and the mixture extracted with methylene chloride. After
drying the solvent was removed in vacuo to give a white powder (0.27 g). 1H n.m.r. indicated the presence of two
products identified as 4-(N-benzyolaminomethyl)-3,5-
diphenylbenzoic acid methyl ester and 4-(N-benzyolamino-
methyl)-3-bromo-5-phenylbenzoic acid in the ratio 60:40.
These products were inseparable by preparative chromatography. δH(80 MHz) 3.89(s, OCH₃), 5.64(d, J 5.8
Hz), 5.72(d, J 5.8 Hz), 7.29-7.47(m, Ar-H), 7.95(s).
II. ATTEMPTED PREPARATION OF ARYL BROMIDES VIA ORTHO METALATION REACTIONS

(i) ATTEMPTED o-LITHIATION OF 2-BIPHENYL METHANOL

(a) This was attempted using the method of Meyer and Seebach. n-Butyllithium (1.43 ml of a 2.1M solution in hexanes) was added in two portions, one half over a period of 10 minutes and the second all at once, to a vigorously stirred mixture of 2-biphenyl methanol (0.18 g, 1 mmol), n-pentane (2 ml) and tetramethyl-ethylenediamine (0.23 g, 2 mmol) at room temperature under dry nitrogen. The mixture was heated to reflux for 11 hours then cooled to -78°C. Bromine (0.11 g, 0.7 mmol) in n-pentane (2 ml) was added and the temperature allowed to rise to room temperature. The mixture was poured into dilute sulphuric acid, extracted with ether, dried and the solvent removed in vacuo. Kugelrohr distillation (175-180°C/0.1 mm Hg) gave a green oil which was identified as 2-phenylbenzaldehyde by comparison with an authentic sample (0.12 g, 67%).

(b) Repeating the above method using 1,2-dibromo ethane (1.32 g, 7 mmol) as the electrophile also gave 2-phenylbenzaldehyde as the only isolated product (0.11 g, 61%).
(ii) o-LITHIATION OF 2-PHENYL BENZALDEHYDE

1) 6-Phenyl-2-trimethylsilylbenzaldehyde

This was made using the method of Comins and Brown\textsuperscript{139}. n-Butyllithium (1.28 ml of a 2.5M solution in hexanes) was added dropwise at -20°C to a solution of \(N,N,N\)-trimethyl-ethylenediamine (0.33 g, 3.2 mmol) in T.H.F. (8 ml) under dry nitrogen and the mixture stirred at -20°C for 15 minutes. 2-Phenylbenzaldehyde (0.55 g, 3 mmol) was added and the mixture stirred at -20°C for 15 minutes. n-Butyllithium (12 ml of a 2.5M solution in hexanes) was added dropwise and the mixture stored at -20°C overnight. The mixture was cooled to -78°C and trimethylsilylchloride (1.63 g, 0.015 mol) was added dropwise. The mixture was stirred at -78°C for 15 minutes then allowed to warm to room temperature. 10% v/v Hydrochloric acid (20 ml) was added slowly with stirring, the mixture extracted with ether (3 x 20 ml), the combined organic portions were dried and the solvent removed in vacuo. The residue was subjected to dry flash chromatography (silica, petrol: ether, 100:0 to 98:2) to afford 6-phenyl-2-trimethylsilylbenzaldehyde as a white crystalline solid (0.61 g, 80%) m.p. 87-88°C (from n-hexane). (Found: C, 75.8; H, 7.2; N, 0. C\(_{16}\)H\(_{18}\)O\(_3\)Si requires C, 75.5; H, 7.1; N, 0%); (Found: m/z 254.1127. C\(_{16}\)H\(_{18}\)O\(_3\)Si requires 254.1127); \(\delta\)\(\text{H}(200\text{ MHz})\) 0.36(s, 3xCH\(_3\)), 7.35-7.48(m, 6H), 7.59(t, J 7.5 Hz, 1H), 7.75-7.79(m, 1H), 9.96(s, CHO); m/z 254(4%), 239(100), 165(28), 69(59); \(\nu_{\text{max}}\) (nujol) 1680 cm\(^{-1}\) (C=O).
2) Attempted ipso-bromodesilylation of 6-phenyl-2-trimethylsilylbenzaldehyde

This was attempted using the methods of Eaborn\textsuperscript{141,142}. The various conditions tried were:

(a) 6-Phenyl-2-trimethylsilylbenzaldehyde (0.13 g, 0.5 mmol) and bromine (0.08 g, 0.5 mmol) were heated on a steam bath for 3 hours. Removal of the bromine in vacuo gave unchanged starting material.

(b) 6-Phenyl-2-trimethylsilylbenzaldehyde (0.13 g, 0.5 mmol) and bromine (0.08 g, 0.5 mmol) in carbon tetrachloride (1 ml) were heated at reflux for 3 hours. Removal of the solvent and bromine in vacuo gave unchanged starting material.

(c) 6-Phenyl-2-trimethylsilylbenzaldehyde (0.13 g, 0.5 mmol) and bromine (0.08 g, 0.5 mmol) in a 1.5% water/acetic acid mixture (2 ml) were heated at 50°C for 3 hours. Extraction into ether and removal of the ether in vacuo gave unchanged starting material.

(d) 6-Phenyl-2-trimethylsilylbenzaldehyde (0.13 g, 0.5 mmol) and bromine (0.08 g, 0.5 mmol) in carbon tetrachloride (2 ml) were heated at reflux over iron filings (0.1 g) for 2 hours. Filtration and removal of the solvent in vacuo gave unchanged starting material.

(e) 6-Phenyl-2-trimethylsilylbenzaldehyde (0.13 g, 0.5 mmol) in methylene chloride (2 ml) was cooled to
-78°C. Boron tribromide (0.19 g, 0.75 mmol) in methylene chloride (1 ml) was added and the mixture allowed to warm slowly to room temperature. 5% aqueous hydrochloric acid was added, the organic layer separated and dried. Removal of the solvent in vacuo gave a black oil (0.09 g) from which no product could be isolated.

(iii) ATTEMPTED o-STANNYLA TION OF 2-PHENYLBENZALDEHYDE

(a) This was attempted using the methods of Comins and Brown. n-Butyllithium (1.33 ml of a 2.4M solution in hexanes) was added dropwise at -20°C to a solution of N,N,N-trimethylethylenediamine (0.33 g, 3.2 mmol) in T.H.F. (8 ml) under dry nitrogen and the mixture stirred at -20°C for 15 minutes. 2-Phenylbenzaldehyde (0.55 g, 3 mmol) was added and the mixture stirred at -20°C for 15 minutes. n-Butyllithium (3.75 ml of a 2.4 molar solution in hexanes) was added dropwise and the mixture stored at -20°C overnight. The mixture was cooled to -78°C and trimethyltin chloride (3.97 g, 12.2 mmol) was added dropwise. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature. 10% v/v Hydrochloric acid (20 ml) was added slowly with stirring and the mixture extracted with ether (3 x 20 ml). The combined organic portions were dried and the solvent removed in vacuo. The residue was subjected to dry flash
chromatography (silica, petrol:ether, 100:0 to 95:5) to afford a colourless oil identified as 6-ethenyl-2-phenylbenzaldehyde (0.37 g, 59%) (Found: m/z 208.0891. C_{15}H_{12}O requires 208.0888); \( \delta_H (200 \text{ MHz}) \): 9.98 (s, 1H, CHO), 7.65-7.32 (m, 9H), 5.73 (dd, \( J_{HH} = 17.4 \text{ Hz} \), 1.3 Hz, 1H, =C-H), 5.44 (dd, \( J_{HH} = 10.9 \text{ Hz} \), 1.3 Hz, 1H, =C-H); m/z 208 (17%), 207 (10), 178 (5), 69 (100); \( \nu_{\text{max}} \) (film), 1690 cm\(^{-1}\) (C=O).

(b) Using the above method with tri-n-butyl tin chloride gave identical results.

PART 3. MEASUREMENT OF RELATIVE RATES OF ELECTROCYCLISATION VIA INTRAMOLECULAR COMPETITION REACTIONS

A. BORONIC ACIDS

(i) 2-PHENYLETHENYLBORONIC ACID

This was prepared by the method of Brown and Gupta\(^{1,46}\). A mixture of phenylacetylene (10.2 g, 0.1 mol) and catecholborane (12.0 g, 0.1 mol) was stirred at 70°C under dry nitrogen for 4 hours. The product was stirred with water (100 ml) at 80°C for 1 hour. Cooling gave a white crystalline solid. Recrystallisation from hexane/T.H.F.

\( \uparrow \) Boronic acids exist normally as mixed anhydrides which means that characterisation by combustion analysis is impossible. Boronic acids do not, in general, give parent ions in mass spectrometry. Each of the boronic acids prepared was characterised by melting point and infra-red spectrometry. All products of cross-coupling reactions were consistent with those expected from the respective boronic acid.
gave 2-phenylethenylboronic acid as a white crystalline solid (8.5 g, 58%) m.p. 162-164°C (lit.\(^{146}\) 163-164°C); \(\nu_{\text{max}}\) (nujol) 3350 cm\(^{-1}\) (br. OH).

The following boronic acids were made by a general method with 2-thiopheneboronic acid as example.

(ii) **2-THIOPHENEBORONIC ACID**

n-Butyllithium (26.25 ml of a 2.0M solution in hexanes) was added dropwise with stirring to a solution of 2-bromothiophene (8.15 g, 0.05 mol) in T.H.F. (30 ml) at \(-78^\circ\)C under dry nitrogen. The mixture was stirred at \(-78^\circ\)C for 30 minutes then triisopropylborate (9.41 g, 0.05 mol) was added dropwise. The mixture was stirred at \(-78^\circ\)C for 1 hour then allowed to warm to room temperature. The mixture was neutralised with 2M hydrochloric acid and extracted with ether (50 ml). The ether layer was washed with chilled water (30 ml), dried and the solvent removed in vacuo. The product was crystallised from water to give 2-thiopheneboronic acid as a white crystalline solid (3.90 g, 61%) m.p. 128-130°C (lit.\(^{152}\) 132-133°C); \(\nu_{\text{max}}\) (nujol) 3270 cm\(^{-1}\) (br., OH).

(iii) **PHENYLBORONIC ACIDS**

1) **Phenylboronic Acid**

Available commercially from Lancaster Synthesis.
2) 3-Nitrophenylboronic Acid
Available commercially from Lancaster Synthesis.

3) 3-Methoxyphenylboronic Acid
Using the method of (ii), the boronic acid was prepared from 3-bromoanisole (9.35 g, 0.05 mol), n-butyllithium (26.25 ml of a 2.0M solution) and triisopropylborate (9.41 g, 0.05 mol). Crystallisation of the crude product from cyclohexane gave 3-methoxyphenylboronic acid as a white crystalline solid (3.62 g, 48%) m.p. 145-147°C (lit. 147°C); $\nu_{\text{max}}$ (nujol) 3320 cm$^{-1}$ (br., OH).

4) 3,5-Dimethylphenylboronic Acid
Using the method of (ii), the boronic acid was prepared from 5-bromo-m-xylene (9.25 g, 0.05 mol), n-butyllithium (25 ml of a 2.1M solution) and triisopropylborate (9.41 g, 0.05 mol). Crystallisation of the crude product from benzene gave 3,5-dimethylphenylboronic acid as a white crystalline solid (2.34 g, 31%) m.p. 235-238°C; $\nu_{\text{max}}$ (nujol) 3220 cm$^{-1}$ (br., OH).

5) 3,5-Bis-trifluoromethylphenylboronic Acid
Available commercially from Lancaster Synthesis.

6) 4-Methylphenylboronic Acid
Available commercially from Lancaster Synthesis.
7) **4-Trifluoromethylphenylboronic Acid**

Using the method of (ii). above, the boronic acid was prepared at -100°C from 4-trifluoromethylbromobenzene (8.55 g, 0.038 mol) and n-butyllithium (20 ml of a 2.0M solution). Quenching with triisopropylborate (7.15, 0.038 mol) at -78°C followed by the usual work-up and crystallisation from benzene gave 4-trifluoromethylphenylboronic acid as a white crystalline solid (3.68 g, 51%) m.p. 233-235°C; $\nu_{\text{max}}$(nujol) 3290 cm$^{-1}$ (br., OH); (Found: m/z 190.0412. C$_7$H$_6$BF$_3$0$_2$ requires 190.0413); m/z 190(82%), 189(14), 126(79), 45(100).

8) **4-Dimethylaminophenylboronic acid**

Using the method of (ii) above, the boronic acid was prepared from 4-bromo-$N$-$N$-dimethylaniline (10.00 g, 0.05 mol), n-butyllithium (25 ml of a 2.1M solution) and triisopropylborate (9.41 g, 0.05 mol). Crystallisation of the crude product from benzene gave 4-dimethylaminophenylboronic acid as a white powder (3.86 g, 47%) m.p. 268-272°C (lit.$^{154}$ 270-275°C); $\nu_{\text{max}}$(nujol) 3400 cm$^{-1}$ (br., OH).

9) **4-Methoxyphenylboronic Acid**

Available commercially from Lancaster Synthesis.

10) **4-Fluorophenylboronic Acid**

Available commercially from Lancaster Synthesis.
11) **4-Chlorophenylboronic Acid**

Available commercially from Lancaster Synthesis.

12) **2-Methylphenylboronic Acid**

Using the method of (ii) above the boronic acid was prepared from 2-bromotoluene (8.55 g, 0.05 mol), n-butyl-lithium (26.3 ml of a 2.0M solution) and triisopropylborate (9.41 g, 0.05 mol). Crystallisation of the crude product from n-hexane gave 2-methylphenylboronic acid as a white crystalline solid (1.43 g, 21%) m.p. 166-168°C (lit. 153-168°C); $\nu_{\max}$(nujol) 3210 cm$^{-1}$ (br., OH).

**B. PREPARATION OF N-BENZOYL-2-ARYLBENZYLAMINES**

(i) **6-BROMO-2-NITROTOLUENE**

This was made by the method of Harrington and Hegedus. 2-Methyl-3-nitroaniline (18.26 g, 0.12 mol) in water (150 ml) was heated to reflux. 48% Hydrobromic acid (62 ml) was added, the mixture maintained at reflux for 20 minutes then cooled to 0°C. Sodium nitrite (8.26 g, 0.12 mol) in water (45 ml) was added with rapid stirring and the resultant diazonium salt solution stirred at 0°C for 15 minutes. This was added slowly, while cold, to a rapidly stirring mixture of copper(I) bromide (20.20 g, 0.14 mol) in 48% hydrobromic acid (40 ml) and water (100 ml). The thick suspension was stirred at room temperature for 20 minutes then heated on a steam bath for
20 minutes and allowed to stand overnight. Steam distillation of the mixture gave 6-bromo-2-nitrotoluene as a pale yellow solid (22.86 g, 88%) m.p. 38-40°C (lit.\textsuperscript{155} 42°C); $\delta_H(200 \text{ MHz})$ 2.55 (s, CH$_3$), 6.93-7.35 (m, 1H), 7.52-7.88 (m, 2H).

(ii) 6-ARYL-2-NITROTOLUENES

1) 2-Nitro-6-phenyltoluene

This was made using the Pd\textsuperscript{0}-catalysed cross-coupling methodology of Suzuki\textsuperscript{128}. 2-Bromo-6-nitrotoluene (10.80 g, 0.05 mol) and tetrakis-triphenylphosphine palladium (0.56 g, 0.5 x 10\textsuperscript{-3} mol, 1% catalyst) were stirred in 1,2-dimethoxyethane (75 ml) under dry nitrogen for 20 minutes. Phenylboronic acid (6.70 g, 0.055 mol) and sodium carbonate (5.53 g, 0.05 mol) in water (30 ml) were added and the mixture heated to reflux under dry nitrogen overnight. The dimethoxyethane was removed in vacuo and methylene chloride (50 ml) was added. The organic layer was separated and filtered through a thick pad of activated alumina. The solvent was removed in vacuo to leave a brown solid. Crystallisation from n-hexane gave 2-nitro-6-phenyltoluene as a pale brown crystalline solid (9.32 g, 87%) m.p. 69-71°C (Found: C, 73.0; H, 5.1; N, 6.4. C$_{13}$H$_{11}$NO$_2$ requires C, 73.2; H, 5.2; N, 6.6%); $\delta_H(200 \text{ MHz})$ 2.36 (s, CH$_3$), 7.25-7.51 (m, 7H, Ar-H), 7.77-7.82 (m, 1H o to NO$_2$); m/z 213 (78%), 196 (70), 165 (100), 152 (57); $\nu_{\text{max}}$(nujol) 1530 cm$^{-1}$, 1360 cm$^{-1}$ (NO$_2$).
2) 6-(4-Chlorophenyl)-2-nitrotoluene

Using the method of 1. above this was prepared from 2-bromo-6-nitrotoluene, tetrakis-triphenylphosphine palladium (0.56 g, 0.5 x 10^-3 mol, 1% catalyst) and 4-chlorophenylboronic acid (8.60 g, 0.055 mol) in 1,2-dimethoxyethane and water. Reaction at reflux overnight followed by the usual work-up and crystallisation from n-hexane gave 6-(4-chlorophenyl)-2-nitrotoluene as a pale brown crystalline solid (11.76 g, 95%) m.p. 55-56°C (Found: C, 63.3; H, 4.0; N, 5.7. C_{13}H_{10}ClNO_{2} requires C, 63.0; H, 4.1; N, 5.7%); δ_H(200 MHz) 2.33(s, CH₃), 7.20-7.44(m, 6H), 7.79(dd, J 7.6 and 2.0 Hz, 1H o to NO₂); m/z 249(24%), 247(70), 230(38), 212(50), 165(100); ν_max(nujol) 1530 cm⁻¹, 1360 cm⁻¹ (NO₂).

(iii) 3-ARYL-2-METHYLANILINES

1) 2-Methyl-3-phenylaniline

A solution of 2-nitro-6-phenyltoluene (21.32 g, 0.10 mol) in ethanol (250 ml) was hydrogenated using palladium on charcoal catalyst (10% Pd/C, 1.07 g) under 35 p.s.i. of hydrogen overnight. The mixture was filtered through a pad of celite and the solvent was removed in vacuo to give 2-methyl-3-phenylaniline as a white crystalline solid (18.33 g, 100%) m.p. 64-65.5°C (from cyclohexane) (Found: C, 85.2; H, 6.9; N, 7.6 C_{13}H_{13}N requires C, 85.2; H, 7.1; N, 7.6%); δ_H(200 MHz) 2.10(s,
CH₃), 3.64(br.s, NH₂), 6.72-6.78(m, 2H), 7.08-7.16(m, 1H), 7.32-7.49(m, 5H); m/z 183(100%), 182(40), 165(22), 32(55); δmax(nujol) 3410 cm⁻¹, 3340 cm⁻¹ (NH₂).

2) 6-(4-Chlorophenyl)-2-methylaniline

A solution of 6-(4-chlorophenyl)-2-nitrotoluene (11.15 g, 0.045 mol) in ethanol (100 ml) was hydrogenated using palladium on charcoal catalyst (10% Pd/c, 0.56 g) under 35 p.s.i. of hydrogen overnight. The mixture was filtered through a pad of celite and the solvent was removed in vacuo to give 6-(4-chlorophenyl)-2-methylaniline as a colourless oil (9.47 g, 97%) (Found: m/z 219.0626. C₁₃H₁₂ClN requires 219.0629; m/z 219(33%), 218(20), 217(100), 216(20), 180(18), 69(87); δH(200 MHz) 2.05(s, CH₃), 3.70(br.s, NH₂), 6.65-6.73(m, 2H), 7.07(t, J 7.5 Hz, 1H), 7.21-7.39(m, 4H); δmax(film) 3470 cm⁻¹, 3380 cm⁻¹ (NH₂).

(iv) 6-ARYL-2-BROMOTOLUENES

1) 2-Bromo-6-phenyltoluene

This was made using the method of Harrington and Hegedus. 2-Methyl-3-phenylaniline (5.13 g, 0.028 mol) in water (50 ml) was heated to reflux. 48% Hydrobromic acid (15 ml) was added, the mixture maintained at reflux for 20 minutes then cooled to 0°C. Sodium nitrite (1.93 g, 0.028 mol) in water (15 ml) was added with rapid stirring and the resultant diazonium salt solution stirred...
at 0°C for 30 minutes. This was added slowly, while cold, to a rapidly stirring mixture of copper(I) bromide (20.08 g, 0.14 mol) in 48% hydrobromic acid (12 ml) and water (30 ml). The thick suspension was stirred at room temperature overnight then heated on a steam bath for 1 hour. The mixture was extracted with ether (3 x 50 ml) the organic portion dried and the solvent removed in vacuo. The residue was subjected to dry flash chromatography (silica, petrol:ether, 100:0 to 24:1) to give 2-bromo-6-phenyltoluene as a colourless oil (4.17 g, 60%) (Found: m/z 248.0029. C_{13}H_{11}Br requires 248.0025); δH(200 MHz) 2.36 (s, CH₃), 7.07-7.62 (m, 8H); m/z 248(13%); 246(13), 167(11), 131(21), 69(100).

2) 2-Bromo-6-(4-chlorophenyl)toluene

Using the method of 1. above this was prepared from 6-(4-chlorophenyl)-2-methylaniline (9.14 g, 0.042 mol) in water (50 ml), 48% hydrobromic acid (27 ml) and sodium nitrite (2.90 g, 0.042 mol) in water (20 ml). Decomposition of the diazonium salt with copper(I) bromide (30.14 g, 0.021 mol) in 48% hydrobromic acid (16 ml) and water (40 ml) followed by the usual work-up and dry-flash chromatography (silica, petrol) gave 2-bromo-6-(4-chlorophenyl)toluene as a colourless oil (6.59 g, 56%) (Found: m/z 279.9654. C_{13}H_{10}^{79}Br^{35}Cl requires 279.9655); δH(360 MHz) 2.30 (s, CH₃), 7.06-7.58 (m, 7H, Ar-H); m/z 284(19%), 283(14), 282(84), 281(49), 280(64), 279(4),
v) 6-ARYL-2-BROMOBENZYL BROMIDES

1) 2-Bromo-6-phenylbenzyl Bromide

To 2-bromo-6-phenyltoluene (11.86 g, 0.048 mol) in carbon tetrachloride (60 ml) was added N-bromosuccinimide (13.01 g, 0.072 mol) and benzoyl peroxide (0.4 g). The mixture was heated at reflux for 2 hours then allowed to cool to room temperature. Methylene chloride (50 ml) was added and the mixture was washed with 2% w/v sodium carbonate solution (2 x 50 ml) then water (50 ml). The solvent was removed in vacuo and the residue subjected to dry flash chromatography (silica, petrol:ether, 19:1) to give 2-bromo-6-phenylbenzyl bromide as a yellow oil (15.54 g, 99%); (Found: m/z (FAB, glycerol) 325.91308. C_{13}H_{10}Br_{2} requires 325.91306); δ_{H}(200 MHz) 4.53(s, CH<sub>2</sub>), 7.19-7.22(m, 2H), 7.64-7.46(m, 6H); m/z (FAB, glycerol) 329(m+1, 9%), 327(9), 325(4), 245(48); 166(100).

2) 2-Bromo-6-(4-chlorophenyl)benzyl Bromide

To 2-bromo-6-(4-chlorophenyl)toluene (6.19 g, 0.022 mol) in carbon tetrachloride (30 ml) was added N-bromosuccinimide (4.77 g, 0.026 mol) and benzoyl peroxide (0.2 g). The mixture was heated at reflux for 1 hour then allowed to cool to room temperature. Methylene chloride (30 ml) was added and the mixture was washed with 2% w/v sodium carbonate solution (2 x 50 ml) then water (50 ml).
The solvent was removed in vacuo and the residue crystallised from n-hexane to give 2-bromo-6-(4-chlorophenyl)benzyl bromide as a white crystalline solid (6.89 g, 87%) m.p. 75-76°C (Found: C, 43.0; H, 2.4. \( \text{C}_{13}\text{H}_9\text{Br}_2\text{Cl} \) requires C, 43.3; H, 2.5%); \( \delta \)\textsubscript{H}(360 MHz) 4.47(s, CH\(_2\)), 7.14-7.25(m, 2H, Ar-H), 7.37-7.44(m, 2H, Ar-H), 7.62(dd, J 7.6 and 1.7 Hz, 1H); m/z (FAB, glycerol) 365(m+1, 3%), 363(8), 361(2), 359(12), 355(43), 299(39), 32(100).

(vi) 3-ARYL-2-(PHTHALIMIDOMETHYL)BROMOBENZENES

1) 3-Phenyl-2-(phtalimidomethyl)bromobenzene

This was made by the Gabriel synthesis\(^{134} \) using the method of Sheehan and Bolhofer\(^{135} \). 2-Bromo-6-phenylbenzylbromide (14.67 g, 0.045 mol) was dissolved in \( N,N \)-dimethyl- formamide (60 ml). Dry potassium pthalimide (9.25 g, 0.05 mol) was added and the mixture stirred at room temperature overnight. The solvent was removed under high vacuum and methylene chloride (50 ml) was added. The mixture was washed with 2M aqueous sodium hydroxide (50 ml), water (50 ml) then dried and the solvent removed in vacuo. The product was crystallised from toluene/ethanol to give 3-phenyl-2-(phtalimidomethyl)bromobenzene as a white crystalline solid (14.09 g, 80%) m.p. 104-105°C (Found: C, 64.2; H, 3.5; N, 3.6. \( \text{C}_{21}\text{H}_{14}\text{BrNO}_2 \) requires C, 64.3; H, 3.6; N, 3.6%); \( \delta \)\textsubscript{H}(200 MHz) 4.93(s, CH\(_2\)), 7.16-7.34(m, 8H), 7.54-7.72(m, 4H); m/z (FAB, glycerol) 394(m+1, 30%), 392(30), 312(36), 160(100); \( r_{\text{max}} \) (nujol)
Using the method of 1. above, this was prepared from 2-bromo-6-(4-chlorophenyl)benzyl bromide (6.49 g, 0.018 mol) in D.M.F. (30 ml) and potassium pthalimide (3.70 g, 0.02 mol). Reaction at room temperature overnight followed by the usual work-up and crystallisation from toluene/ethanol gave 3-(4-chlorophenyl)-2-(pthalimidomethyl)bromobenzene as a white crystalline solid (5.95 g, 77%) (Found: C, 58.9; H, 2.9; N, 2.9. \( \text{C}_2\text{H}_1\text{BrClNO}_2 \) requires C, 59.1; H, 3.1; N, 3.3); \( \delta_H(360 \text{ MHz}) \) 4.90(s, \( \text{CH}_2 \)), 7.14-7.25(m, 6H, Ar-H), 7.64-7.72(m, 5H, Ar-H); m/z (FAB, glycerol) 430(m+1, 25%), 428(40), 426(31), 274(50), 257(100); \( \nu_{\text{max}} \) (nujol) 1720 cm\(^{-1}\) (C=O).

(vii) 6-ARYL-2-BROMOBENZYLAMINES

1) 2-Bromo-6-phenylbenzylamine

This was made using the Ing-Manske\(^{136} \) procedure. 3-Phenyl-2-(pthalimidomethyl)bromobenzene (13.73 g, 0.035 mol) and hydrazine hydrate (100% solution, 2.63 g, 0.053 mol) were dissolved in methanol (150 ml). The mixture was heated at reflux for 1 hour. The solvent was removed in vacuo to give 2-bromo-6-phenylbenzylamine as a yellow oil (8.44 g, 92%). This product was used without
further purification. (Found: m/z 263.0112. C_{13}H_{12}BrN requires 263.0133); \delta_H(200 MHz) 1.88(br,s, NH_2), 3.82(s, CH_2), 7.08-7.60(m, 8H); m/z 262(7%), 244(18), 182(39), 165(100), 152(26); vmax (film) 3370 cm^{-1} (NH).

2) 2-Bromo-6-(4-chlorophenyl)benzylamine

This was made using the Ing-Manske \cite{136} procedure. 3-(4- Chlorophenyl)-2-(phthalimidomethyl)bromobenzene (5.55 g, 0.013 mol) and hydrazine hydrate (100% solution, 0.98 g, 0.02 mol) were dissolved in methanol (50 ml). The mixture was heated at reflux for 1 hour. The solvent was removed in vacuo and ether (30 ml) was added. The insoluble pthaloyl hydrazide was removed by filtration then the ether was removed in vacuo to give 2-bromo-6-(4-chlorophenyl)benzylamine as a yellow oil (3.86 g, 100%). This product was used without further purification. (Found: m/z 294.9773. C_{13}H_{11}Br^{35}ClN requires 294.9764); \delta_H(360 MHz) 1.79(br,s, NH_2), 3.80(s, CH_2), 7.09-7.56(m, 7H, Ar-H); m/z 299(7%), 298(10), 297(9), 296(21), 295(22), 294(16), 216(100), 152(49); vmax (nujol) 3360 cm^{-1}, 3280 cm^{-1} (NH).

(viii) \textit{N-BENZOYL-6-ARYL-2-BROMOBENZYLAMINES}

1) \textit{N-Benzoyl-2-bromo-6-phenylbenzylamine}

2-Bromo-6-phenylbenzylamine (9.17 g, 0.035 mol) was dissolved in methylene chloride (100 ml). Sodium carbonate (5.60 g, 0.053 mol) was added and the mixture
stirred for 10 minutes. Benzoyl chloride (10.19 g, 0.07 mol) was added and the mixture stirred at room temperature under dry nitrogen overnight. Water (100 ml) was added and the mixture stirred for 1 hour. The organic layer was separated, washed with water (2 x 50 ml), dried and the solvent removed in vacuo. The oily residue was crystallised from ethanol to give N-benzoyl-2-bromo-6-phenylbenzylamine as a white crystalline solid (9.38 g, 73%). m.p. 177-178°C (Found: C, 65.6; H, 4.4; N, 3.8. C_{20}H_{16}BrNO requires C, 65.6; H, 4.4; N, 3.8%); (Found: m/z 365.0392. C_{20}H_{16}^{79}BrNO requires 365.0415); δ_H(200 MHz) 4.66(d, J 5.0 Hz, CH$_2$), 6.23(br.s, NH), 7.17-7.50(m, 10H), 7.59-7.71(m, 3H); m/z 286(100%), 165(38), 105(30), 77(33); $\nu_{\text{max}}$(nujol) 3270 cm$^{-1}$ (NH), 1625 cm$^{-1}$ (C=O).

2) N-Benzoyl-2-bromo-6-(4-chlorophenyl)benzylamine

Using the method of 1. above the amide was prepared from 2-bromo-6-(4-chlorophenyl)benzylamine (1.93 g, 6.5 mmol), sodium carbonate (1.04 g, 9.75 mmol) and benzoyl chloride (1.89 g, 0.013 mol). Reaction at room temperature for 1 hour followed by the usual work-up and crystallisation from ethanol/toluene gave N-benzoyl-2-bromo-6-(4-chlorophenyl)benzylamine as a white crystalline solid (1.95 g, 75%) m.p. 170-172°C (Found: C, 59.8; H, 3.6; N, 3.5. C$_{20}$H$_{15}$BrClNO requires C, 59.9; H, 3.8; N, 3.5%); (Found: m/z 399.0016. C$_{20}$H$_{15}^{79}$Br$_{35}$ClNO requires 399.0026); δ_H(200 MHz) 4.63(d, J 5.1 Hz, CH$_2$), 6.40(br.s,
NH), 7.19-7.72 (m, 12H, Ar-H); m/z 403 (1%), 401 (1), 399 (1), 322 (32), 320 (100); $\nu_{\text{max (nujol)}}$ 2290 cm$^{-1}$ (NH), 1630 cm$^{-1}$ (C=O).

The following reactions (ix) to (xii) were carried out using a general palladium catalysed cross-coupling method. The preparation of $N$-benzoyl-6-phenyl-2-(2-phenylethenyl)-benzylamine is given as an example.

(ix) $N$-BENZOYL-6-PHENYL-2-(2-PHENYLETHENYL)BENZYLAMINE

This was made using the cross-coupling method of Suzuki$^{28}$. $N$-benzoyl-2-bromo-6-phenylbenzylamine (0.76 g, 2.1 mmol) and tetrakis-triphenylphosphine palladium (0.07 g, 6 x $10^{-5}$ mol, 3% catalyst) were stirred in 1,2-dimethoxyethane (10 ml) under dry nitrogen for 20 minutes. 2-Phenylethenyl boronic acid (0.37 g, 2.5 mmol) and sodium carbonate (0.22 g, 2.1 mmol) in water (6 ml) were added and the mixture heated to reflux under dry nitrogen for 20 minutes. The dimethoxyethane was removed in vacuo and methylene chloride (10 ml) was added. The organic layer was separated, dried and the solvent removed in vacuo. The product was crystallised from ethanol/toluene to give $N$-benzoyl-6-phenyl-2-(2-phenylethenyl)benzylamine as a white crystalline solid (0.66 g, 81%) m.p. 200-202°C (Found: C, 86.1; H, 6.0; N, 3.5. $C_{28}H_{23}NO$ requires C, 86.3; H, 6.0; N, 3.6%); (Found: m/z 389.1775. $C_{28}H_{23}NO$ requires 389.1779); $\delta_{\text{H}}$ (200 MHz) 4.73 (d, J 5.0 Hz, CH$_2$),
6.05 (br.s, NH), 7.06 (d, J 16.0 Hz, 1H), 7.20-7.34 (m, 19H); m/z 389 (22%), 268 (100), 105 (31), 77 (22); \( \nu_{\text{max}} \) (nujol) 3240 cm\(^{-1} \) (NH), 1620 cm\(^{-1} \) (C=O).

\( \text{(x)} \quad \text{N-BENZOYL-6-PHENYL-2-THIENYLBENZYLAMINE} \)

Using the method of (ix) above this was prepared from N-benzoyl-2-bromo-6-phenylbenzylamine (0.58 g, 1.6 mmol) and 2-thiopheneboronic acid. Reaction in 1,2-dimethoxyethane/water for 2 hours followed by the usual work-up and dry-flash chromatography (silica, ethyl acetate:petrol, 1:6 to 1:4) gave N-benzoyl-6-phenyl-2-(2-thienyl)benzylamine as a pale brown crystalline solid (0.58 g, 98%) m.p. 153-155°C (from cyclohexane/ethanol) (Found: C, 78.0; H, 5.0; N, 3.6. \( \text{C}_{24}\text{H}_{19}\text{NOS} \) requires C, 78.0; H, 5.2; N, 3.8%); (Found: m/z 369.1204. \( \text{C}_{24}\text{H}_{19}\text{NOS} \) requires 369.1187); \( \delta_{\text{H}} \) (200 MHz) 4.67 (d, J 4.9 Hz, \( \text{CH}_2 \)), 5.92 (br.s, NH), 7.07-7.49 (m, 16H, Ar-H); m/z 369 (48%), 249 (21), 248 (100), 247 (35); \( \nu_{\text{max}} \) (nujol) 3290 cm\(^{-1} \) (NH), 1625 cm\(^{-1} \) (C=O).

\( \text{(xi)} \quad \text{N-BENZOYL-2-ARYL-6-PHENYLBENZYLAMINES} \)

1) \( \text{N-Benzoyl-2-(3-nitrophenyl)-6-phenylbenzylamine} \)

Using the method of (ix) above, this was prepared from N-benzoyl-2-bromo-6-phenylbenzylamine (0.76 g, 2.1 mmol) and 3-nitrophenylboronic acid. Reaction at reflux for 30 minute followed by the usual work-up and crystallisation from toluene/ethanol gave N-benzoyl-2-(3-nitrophenyl)-6-
phenylbenzylamine as a white crystalline solid (0.74 g, 86%) m.p. 181-183°C (Found: C, 76.5; H, 4.8; N, 6.9. C\textsubscript{26}H\textsubscript{20}N\textsubscript{2}O\textsubscript{3} requires C, 76.5; H, 4.9; N, 6.9%); (Found: m/z 408.1467. C\textsubscript{26}H\textsubscript{20}N\textsubscript{2}O\textsubscript{3} requires 408.1474); \(\delta\)\textsubscript{H}(200 MHz) 4.53(d, J 5.2 Hz, CH\textsubscript{2}), 5.79(br.s, NH), 7.25-7.63(m, 14H), 7.75-7.80(m, 1H), 8.17-8.27(m, 2H); m/z 391(10%), 287(34), 270(83), 105(100); \(\nu\)\textsubscript{max}(nujol) 3280 cm\textsuperscript{-1} (NH), 1625 cm\textsuperscript{-1} (C=O).

2) \(N\)-Benzoyl-2-(3-methoxyphenyl)-6-phenylbenzylamine

Using the method of (ix) above, this was prepared from \(N\)-benzoyl-2-bromo-6-phenylbenzylamine (0.44 g, 1.2 mmol) and 3-methoxyphenylboronic acid (0.21 g, 1.4 mmol). Reaction at reflux for 30 minutes followed by the usual work-up and dry-flash chromatography (silica, ethyl acetate:petrol, 1:6 to 1:4) gave \(N\)-benzoyl-2-(3-methoxyphenyl)-6-phenylbenzylamine as a white crystalline solid (0.43 g, 91%) m.p. 162.5-164°C (Found: C, 81.9; H, 5.8; N, 3.7. C\textsubscript{27}H\textsubscript{23}NO\textsubscript{2} requires C, 82.3; H, 5.9; N, 3.6%); (Found: m/z 393.1734. C\textsubscript{27}H\textsubscript{23}NO\textsubscript{2} requires 393.1729); \(\delta\)\textsubscript{H}(200 MHz) 3.78(s, OMe), 4.62(d, J 5.1 Hz, CH\textsubscript{2}), 5.83(br.s, NH), 6.88-7.03(m, 3H), 7.25-7.45(m, 14H); m/z 393(30%), 392(23), 272(100), 143(44); \(\nu\)\textsubscript{max}(nujol) 3365 cm\textsuperscript{-1} (NH), 1620 cm\textsuperscript{-1} (C=O).
3) \(N\)-Benzoyl-2-(3,5-dimethylphenyl)-6-phenylbenzylationine

Using the method of (ix) above, this was prepared from \(N\)-benzoyl-2-bromo-6-phenylbenzylationine (0.76 g, 2.1 mmol) and 3,5-dimethylphenylboronic acid (0.37 g, 2.5 mmol). Reaction at reflux for 15 minutes followed by the usual work-up and dry-flash chromatography (silica, ethyl acetate:petrol, 1:6 to 1:2) gave \(N\)-benzoyl-2-(3,5-dimethylphenyl)-6-phenylbenzylationine as a white crystalline solid (0.81 g, 99%) m.p. 170-172°C (from n-hexane/ethanol) (Found: C, 85.7; H, 6.4; N, 3.6. \(C_{28}H_{25}NO\) requires C, 85.9; H, 6.4; N, 3.6%); (Found: m/z 391.1943. \(C_{28}H_{25}NO\) requires 391.1936); \(\delta_H(200 MHz)\) 2.33(s, 2xCH\(_3\)), 4.59(d, J 5.1 Hz, CH\(_2\)), 5.80(br.s, NH), 7.019(s, 1H), 7.023(s, 2H), 7.25-7.44(m, 13H); m/z 391(41%), 270(100), 255(23), 122(50); \(\nu_{\text{max}}(\text{nujol})\) 3310 cm\(^{-1}\) (NH), 1625 cm\(^{-1}\) (C=O).

4) \(N\)-Benzoyl-2-(3,5-bis-trifluoromethylphenyl)-6-phenylbenzylationine

Using the method of (ix) above, this was prepared from \(N\)-benzoyl-2-bromo-6-phenylbenzylationine (0.76 g, 2.1 mmol) and 3,5-bis-trifluoromethylphenylboronic acid (0.68 g, 2.5 mmol). Reaction at reflux for 15 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:6 to 1:3) gave \(N\)-benzoyl-2-(3,5-bis-trifluoromethylphenyl)-6-phenylbenzylationine as a white crystalline solid (0.89 g, 85%) m.p. 233-234°C (from
N-Benzoyl-2-(4-methylphenyl)-6-phenylbenzylamine

Using the method of (ix) above, this was prepared from N-benzoyl-2-bromo-6-phenylbenzylamine (0.38 g, 1 mmol) and 4-methylphenylboronic acid (0.17 g, 1.25 mmol). Reaction at reflux for 30 minutes followed by the usual work-up and dry-flash chromatography (silica, ethyl acetate:petrol, 1:6 to 1:4) gave N-benzoyl-2-(4-methylphenyl)-6-phenylbenzylamine as a white crystalline solid (0.34 g, 90%) m.p. 137-138.5°C (from n-hexane/ethanol) (Found: C, 86.0; H, 6.1; N, 3.7. C_{27}H_{23}NO requires C, 85.9; H, 6.1; N, 3.7%); (Found: m/z 377.1788. C_{27}H_{23}NO requires 377.1780); δ_H(200 MHz) 1.67(s, CH₃), 4.61(d, J 5.1 Hz, CH₂), 5.78(br.s, NH), 7.21-7.44(m, 17H); m/z 377(49%), 256(100), 122(32), 69(99); ν_max(nujol) 3290 cm⁻¹ (NH), 1620 cm⁻¹ (C=O).

N-Benzoyl-2-(4-trifluoromethylphenyl)-6-phenylbenzylamine

Using the method of (ix) above, this was prepared from...
N-benzoyl-2-bromo-6-phenylbenzylamine (0.76 g, 2.1 mmol) and 4-trifluoromethylphenylboronic acid (0.47 g, 2.5 mmol). Reaction at reflux for 30 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:6 to 1:3) gave N-benzoyl-2-(4-trifluoromethylphenyl)-6-phenylbenzylamine as a white crystalline solid (0.83 g, 93%) m.p. 157-159°C (from n-hexane/ethanol) (Found: C, 75.2; H, 4.7; N, 3.3. C_{27}H_{20}F_{3}NO requires C, 75.2; H, 4.7; N, 3.2%); δ_{H}(200 MHz) 4.58(d, J 5.1 Hz, CH\textsubscript{2}), 5.88(br.s, NH), 7.24-7.47(m, 13H), 7.54(d, J 8.1 Hz, 2H), 7.68(d, J 8.1 Hz, 2H); m/z 431(40%), 310(100), 122(85), 105(72); ν\text{max}(nujol) 3310 cm\textsuperscript{-1} (NH), 1625 cm\textsuperscript{-1} (C=O).

7) N-Benzoyl-2-(4-dimethylaminophenyl)-6-phenylbenzylamine

Using the method of (ix). above, this was prepared from N-benzoyl-2-bromo-6-phenylbenzylamine (0.76 g, 2.1 mmol) and 4-dimethylaminophenylboronic acid (0.41 g, 2.5 mmol). Reaction at reflux for 45 minutes followed by the usual work-up and crystallisation from ethanol/n-hexane gave N-benzoyl-2-(4-dimethylaminophenyl)-6-phenylbenzylamine as a white crystalline solid (0.67 g, 78%) m.p. 161-163°C (Found: C, 82.5; H, 6.2; N, 6.9. C_{28}H_{26}N_{2}O requires C, 82.7; H, 6.4; N, 6.9%); (Found: m/z 406.2039. C_{28}H_{26}N_{2}O requires 406.2045); δ_{H}(200 MHz) 2.97(s, 2xCH\textsubscript{3}), 4.65(d, J 5.1 Hz, CH\textsubscript{2}), 5.85(br. s, NH),
6.81(d, J 8.7 Hz, 2H o to NMe₂), 7.24-7.43(m, 15H); m/z 406(3%), 285(3.5), 269(4), 131(100); νmax(nujol) 3400 cm⁻¹ (NH), 1620 cm⁻¹ (C=O).

8)  
N-Benzoyl-2-(4-methoxyphenyl)-6-phenylbenzylamine

Using the method of (ix) above, this was prepared from N-benzoyl-2-bromo-6-phenylbenzylamine (0.38 g, 1 mmol) and 4-methoxyphenylboronic acid (0.19 g, 1.25 mmol). Reaction at reflux for 15 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:6 to 1:4 gave N-benzoyl-2-(4-methoxyphenyl)-6-phenylbenzylamine as a white crystalline solid (0.36 g, 88%) m.p. 151-152.5°C (from n-hexane/ethanol) (Found: C, 82.2; H, 5.9; N, 3.6. C₂₇H₂₃NO₂ requires C, 82.4; H, 5.9; N, 3.6%); (Found: m/z 393.1721. C₂₇H₂₃NO₂ requires 393.1729); δH(200 MHz) 3.82(s, OCH₃), 4.61(d, J 5.1 Hz, CH₂), 5.80(br. s, NH), 6.96(d, J 8.8 Hz, 2H o to OCH₃), 7.25-7.44(m, 15H); m/z 393(31%), 272(100), 122(24), 77(32); νmax(nujol) 3250 cm⁻¹ (NH), 1635 cm⁻¹ (C=O).

9)  
N-Benzoyl-2-(4-fluorophenyl)-6-phenylbenzylamine

Using the method of (ix) above, this was prepared from N-benzoyl-2-bromo-6-phenylbenzylamine (0.76 g, 2.1 mmol) and 4-fluorophenylboronic acid (0.35 g, 2.5 mmol). Reaction at reflux followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:6 to
1:3) gave $N$-benzoyl-2-(4-fluorophenyl)-6-phenylbenzylamine as a white crystalline solid (0.69 g, 87%) m.p. 178-180°C (from n-hexane/ethanol) (Found: C, 81.8; H, 5.3; N, 3.7. $C_{26}H_{20}FN\text{O}$ requires C, 81.9; H, 5.3; N, 3.7%); (Found: m/z 381.1529. $C_{26}H_{20}FN\text{O}$ requires 381.1529); $\delta_{H}(200 \text{ MHz})$ 4.58(d, J 5.1 Hz, CH$_2$), 5.81(br. s, NH), 7.06-7.15(m, 2H o to F), 7.25-7.45(m, 15H); m/z 381(33%), 260(100), 122(60), 77(77); $\nu_{\text{max}}$(nujol) 3290 cm$^{-1}$ (NH), 1620 cm$^{-1}$ (C=O).

10) $N$-Benzoyl-2-(4-chlorophenyl)-6-phenylbenzylamine

Using the method of (ix) above, this was prepared from $N$-benzoyl-2-bromo-6-phenylbenzylamine (0.76 g, 2.1 mmol) and 4-chlorophenylboronic acid (0.39 g, 2.5 mmol). Reaction at reflux for 20 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:6 to 1:3) gave $N$-benzoyl-2-(4-chlorophenyl)-6-phenylbenzylamine as a white crystalline solid (0.51 g, 61%) m.p. 163-165°C (from n-hexane/ethanol) (Found: C, 78.1; H, 5.0; N, 3.5. $C_{26}H_{20}Cl\text{N}\text{O}$ requires C, 78.5; H, 5.1; N, 3.5%); (Found: m/z 399.1212. $C_{26}H_{20}^{37}Cl\text{N}\text{O}$ requires 399.1204); $\delta_{H}(200 \text{ MHz})$ 4.57(d, J 5.2 Hz, CH$_2$), 7.80(br. s, NH), 7.24-7.45(m, 17H); m/z 399(2%), 397(6), 276(7), 241(6), 122(100); $\nu_{\text{max}}$(nujol) 3310 cm$^{-1}$ (NH), 1635 cm$^{-1}$ (C=O).

11) $N$-Benzoyl-2-(2-methylphenyl)-6-phenylbenzylamine

Using the method of (ix) above, this was prepared from
N-benzoyl-2-bromo-6-phenylbenzylamine (0.76 g, 2.1 mmol) and 2-methylphenylboronic acid (0.34 g, 2.5 mmol). Reaction at reflux for 45 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:19 to 1:4) gave N-benzoyl-2-(2-methylphenyl)-6-phenylbenzylamine as a white crystalline solid (0.79 g, 100%) m.p. 126-128°C (from cyclohexane/ethanol) (Found: C, 85.8; H, 6.2; N, 3.8. C_{27}H_{23}NO requires C, 85.9; H, 6.1; N, 3.7%); (Found: m/z 377.1779. C_{27}H_{23}NO requires 377.1779); δ_{H}(200 MHz) 2.13(s, CH₃), 4.28(dd, J 14.8 and 4.9 Hz, CH), 4.56(dd, J 14.8 and 5.5 Hz, CH), 5.73(br. s, NH), 7.18-7.45(m, 17H, Ar-H); m/z 377(66%), 256(100), 241(31), 122(39); r_{max}(nujol) 3370 cm⁻¹ (NH), 1640 cm⁻¹ (C=O).

(xii) N-BENZOYL-6-ARYL-2-(4-CHLOROPHENYL)BENZYLAMINES
1) N-Benzoyl-2-(4-chlorophenyl)-6-(4-methylphenyl)benzylamine

Using the method of (ix) above this was prepared from N-benzoyl-2-bromo-6-(4-chlorophenyl)benzylamine (0.64 g, 1.6 mmol) and 4-methylphenylboronic acid (0.26 g, 1.9 mmol). Reaction at reflux for 30 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:3) gave N-benzoyl-2-(4-chlorophenyl)-6-(4-methylphenyl)benzylamine as a white crystalline solid (0.56 g, 85%) m.p. 180-181°C (from cyclohexane/ethanol) (Found: C, 78.3; H, 5.3; N, 3.3.
C₂₇H₂₂ClN requires C, 78.7; H, 5.4; N 3.4%; (Found: m/z 411.1393 C₂₇H₂₂ClN 411.1389); δ_H(200 MHz) 2.39(s, CH₃), 4.58(d, J 5.1 Hz, CH₂), 6.80(br. s, NH), 7.22-7.44(m, 16H, Ar-H); m/z 413(17%), 411(46), 290(100), 255(46), 122(82); υ_max(nujol) 3290 cm⁻¹ (NH), 1635 cm⁻¹ (C=O).

2) N-Benzoyl-2-(4-chlorophenyl)-6-(4-trifluoromethylphenyl)benzylamine

Using the method of (ix) above, this was prepared from N-benzoyl-2-bromo-6-(4-chlorophenyl)benzylamine (0.56 g, 1.4 mmol) and 4-trifluoromethylphenylboronic acid (0.32 g, 1.66 mmol). Reaction at reflux for 1 hour followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:5 to 1:3) gave N-benzoyl-2-(4-chlorophenyl)-6-(4-trifluoromethylphenyl)benzylamine as a white crystalline solid (0.48 g, 73%) m.p. 175-177°C (from cyclohexane/ethanol) (Found: C, 69.7; H, 3.9; N, 3.3. C₂₁H₁₉ClF₃NO requires C, 69.6; H, 4.1; N, 3.0%); (Found: m/z 465.1104. C₂₁H₁₉ClF₃NO requires 465.1107); δ_H(200 MHz) 4.58(d, J 5.2 Hz, CH₂), 5.70(br. s, NH), 7.24-7.55(m, 14H, Ar-H), 7.67(d, J 8.2 Hz, 2H o to CF₃); m/z 467(8%), 465(22), 309(39), 122(76), 105(100); υ_max(nujol) 3310 cm⁻¹ (NH), 1625 cm⁻¹ (C=O).
C. PREPARATION OF AUTHENTIC AZEPINES

(i) 8-BROMO-5-PHENYL-7H-DIBENZ[c,e]AZEPINE

N-Benzoyl-2-bromo-6-phenylbenzylamine (1.12 g, 3 mmol), dry ether (50 ml) and thionyl chloride (10 ml) were heated at reflux under dry nitrogen overnight. The solvent was removed in vacuo and the residue dried under high vacuum for 2 hours. Dry T.H.F. (50 ml) was added and the mixture cooled to 0°C. Solid potassium tert-butoxide (0.67 g, 6 mmol) was added in one portion with rapid stirring under dry nitrogen. The mixture was stirred at 0°C for 30 minutes, allowed to warm to room temperature and stirred for 1 hour. 25% w/v Aqueous ammonium chloride (50 ml) was added and the mixture stirred vigorously for 5 minutes. Methylene chloride (50 ml) was added, the organic layer separated and the aqueous layer extracted with methylene chloride (2 x 20 ml). The combined organic layers were dried and the solvent removed in vacuo. Dry flash chromatography of the residue (silica, ethyl acetate:petrol, 1:19 to 1:9) gave 8-bromo-5-phenyl-7H-dibenz[c,e]azepine as a white crystalline solid (0.97 g, 93%) m.p. 142-143°C (from cyclohexane/ethanol) (Found: C, 68.7; H, 4.0; N, 4.0. C₂₀H₁₄BrN requires C, 69.0; H, 4.0; N, 4.0%); (Found: m/z 349.0295. C₂₀H₁₄BrN requires 349.0290); δH(200 MHz) 3.76(d, J 10.7 Hz, 7-H), 5.53(d, J 10.7 Hz, 7'-H), 7.17-7.74(m, 12H); m/z 349(77%), 347(79), 267(18), 239(15), 165(60); vmax(nujol) 1610 cm⁻¹ (C=N).
(ii) 8-BROMO-3-CHLORO-5-PHENYL-7H-DIBENZ[c,e]AZEPINE

The imidoyl chloride was prepared as in (i) using N-benzoyl-2-bromo-6-(4-chlorophenyl)benzylamine (0.53 g, 1.33 mmol), dry ether (20 ml) and thionyl chloride (5 ml). After drying the imidoyl chloride was dissolved in T.H.F. (20 ml) and cooled to 0°C. Solid potassium tert-butoxide (0.30 g, 2.66 mmol) was added in one portion with rapid stirring under dry nitrogen. The mixture was stirred at 0°C for 1 hour, allowed to warm to room temperature and stirred for a further hour. After work-up as in (i) the product was subjected to dry-flash chromatography (silica, ethyl acetate:petrol, 1:19 to 1:9) to give 8-bromo-3-chloro-5-phenyl-7H-dibenz[c,e]azepine as a colourless oil (Found: m/z 380.9903. C_{20}H_{17}Br_{35}ClN requires 380.9920); δH(360 MHz) 3.72(d, J 10.7 Hz, 7-H), 5.54(d, J 10.7 Hz, 7′-H), 7.19-7.66(m, 11H, Ar-H); m/z 385(22%), 384(38), 383(90), 382(98), 381(100), 380(68), 346(51), 163(49); vmax(nujol) 1610 cm⁻¹ (C=N).

The following reactions (iii)-(vi) were carried out using a general palladium catalysed cross-coupling method. The preparation of 5-phenyl-8-(2-phenylethenyl)-7H-dibenz[c,e]azepine is given as an example.

(iii) 5-PHENYL-8-(2-PHENYLETHENYL)-7H-DIBENZ[c,e]AZEPINE

This was made using the cross-coupling methodology of Suzuki. 8-Bromo-5-phenyl-7H-dibenz[c,e]azepine (0.17
g, 0.5 mmol) and tetrakis-triphenylphosphine palladium (0.018 g, 1.5 x 10^{-5} mol; 3% catalyst) were stirred in 1,2-dimethoxyethane (3 ml) under dry nitrogen for 20 minutes. 2-Phenylethynyl boronic acid (0.092 g, 0.63 mmol) and sodium carbonate (0.055 g, 0.53 mmol) in water (2 ml) were added and the mixture heated to reflux under dry nitrogen for 35 minutes. The dimethoxyethane was removed in vacuo. The mixture was extracted with methylene chloride (3 x 3 ml), dried and the solvent removed in vacuo. The residue was subjected to dry-flash chromatography (silica, ethyl acetate:petrol, 1:49 to 1:19) to afford 5-phenyl-8-(2-phenylethynyl)-7H-dibenz-[c,e]azepine as a white crystalline solid (0.18 g, 97%) m.p. 159-161°C (from cyclohexane/toluene) (Found: C, 90.6; H, 5.7; N, 3.9. C_{28}H_{21}N requires C, 90.5; H, 5.7; N, 3.8); (Found: m/z 371.1676. C_{28}H_{21}N requires 371.1674); m/z 371(99%), 370(100), 269(63), 143(30); $\nu_{\text{max}}$(nujol) 1610 cm^{-1} (C=N).

For nmr data see appendix 2.

(iv) 5-PHENYL-8-(2-THIENYL)-7H-DIBENZ[c,e]AZEPINE

Using the method of (iii) above, this was prepared from 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.17 g, 0.5 mmol) and 2-thiopheneboronic acid (0.08 g, 0.63 mmol). Reaction at reflux for 1 hour followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:49 to 1:9) gave 5-phenyl-8-(2-thienyl)-
7H-dibenz[c,e]azepine as a pale brown crystalline solid (0.17 g, 97%) m.p. 144-145°C (from cyclohexane) (Found: C, 81.4; H, 4.7; N, 3.7. C_{24}H_{19}NS requires C, 81.8; H, 4.9; N, 4.0%); (Found: m/z 351.1089. C_{24}H_{19}NS requires 351.1082); m/z 351(100%), 350(37), 318(37), 281(95); ν_max(nujol) 1605 cm⁻¹ (C=N).

For nmr data see appendix 2.

(v) 8-ARYL-5-PHENYL-7H-DIBENZ[c,e]AZEPINES

1) 8-(3-Nitrophenyl)-5-phenyl-7H-dibenz[c,e]azepine

Using the method of (iii) above, this was prepared from 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.14 g, 0.4 mmol) and 3-nitrophenylboronic acid (0.083 g, 0.5 mmol). Reaction at reflux for 15 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:24 to 1:10) gave 8-(3-nitrophenyl)-5-phenyl-7H-dibenz[c,e]azepine as a yellow crystalline solid (0.11 g, 70%) m.p. 157-158.5°C (from cyclohexane) (Found: C, 80.2; H, 4.5; N, 7.4. C_{26}H_{18}N_{2}O_{2} requires C, 80.0; H, 4.6; N, 7.2%); (Found: m/z 390.1377. C_{26}H_{18}N_{2}O_{2} requires 390.1368); m/z 390(100%), 389(83), 281(47), 239(29); ν_max(nujol) 1605 cm⁻¹ (C=N).

For nmr data see appendix 2.

2) 8-(3-Methoxyphenyl)-5-phenyl-7H-dibenz[c,e]-azepine

Using the method of (iii) above, this was prepared
from 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.17 g, 0.5 mmol) and 3-methoxyphenylboronic acid (0.095 g, 0.63 mmol). Reaction at reflux for 20 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:49 to 1:24) gave 8-(3-methoxyphenyl)-5-phenyl-7H-dibenz[c,e]azepine as a white crystalline solid (0.19 g, 100%) m.p. 166-168°C (from cyclohexane) (Found: C, 86.3; H, 5.6; N, 3.8. \( \text{C}_{27}\text{H}_{21}\text{NO} \) requires C, 86.4; H, 5.6; N, 3.7%); (Found: m/z 375.1613. \( \text{C}_{27}\text{H}_{21}\text{NO} \) requires 375.1623); m/z 375(65%), 374(100), 360(15), 188(9); \( \nu_{\max}(\text{nujol}) \) 1660 cm\(^{-1} \) (C=N).

For nmr data see appendix 2.

3) 8-(3,5-Dimethylphenyl)-5-phenyl-7H-dibenz[c,e]azepine

Using the method if (iii) above, this was prepared from 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.17 g, 0.5 mmol) and 3,5-dimethylphenylboronic acid (0.094 g, 0.63 mmol). Reaction at reflux for 10 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:49 to 1:33) gave 8-(3,5-dimethylphenyl)-5-phenyl-7H-dibenz[c,e]azepine as a colourless oil (0.17 g, 91%) (Found: 373.1829. \( \text{C}_{28}\text{H}_{23}\text{N} \) requires 373.1830); m/z 373(17%), 372(16), 210(64), 84(100); \( \nu_{\max}(\text{thin film}) \) 1605 cm\(^{-1} \) (C=N).

For n.m.r. data see appendix 2.
4) 8-(3,5-Bis-trifluoromethylphenyl)-5-phenyl-7H-dibenz[c,e]azepine

Using the method of (iii) above, this was prepared from 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.17 g, 0.5 mmol) and 3,5-bis-trifluoromethylphenylboronic acid (0.17 g, 0.63 mmol). Reaction at reflux for 20 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:49) gave 8-(3,5-bis-trifluoromethylphenyl)-5-phenyl-7H-dibenz[c,e]azepine as a white crystalline solid (0.21 g, 87%) m.p. 160-162°C (from cyclohexane) (Found: C, 69.6; H, 3.5; N, 3.0. C\textsubscript{28}H\textsubscript{17}F\textsubscript{6}N requires C, 69.9; H, 3.6; N, 2.9%); (Found: m/z 481.1264. C\textsubscript{28}H\textsubscript{17}F\textsubscript{6}N require 481.1265); m/z 481(97%), 480(100), 149(37), 143(33); \nu\text{max}(\text{nujol}) 1605 cm\textsuperscript{-1} (C=N).

For nmr data see appendix 2.

5) 8-(4-Methylphenyl)-5-phenyl-7H-dibenz[c,e]azepine

Using the method of (iii) above, this was prepared from 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.17 g, 0.5 mmol) and 4-methylphenylboronic acid (0.085 g, 0.63 mmol). Reaction at reflux for 45 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:24) gave 8-(4-methylphenyl)-5-phenyl-7H-dibenz[c,e]azepine as a white crystalline solid (0.10 g, 56%) m.p. 158-160°C (from cyclohexane) (Found: C, 90.1, H, 5.9; N, 3.9. C\textsubscript{27}H\textsubscript{21}N requires C, 90.2; H, 5.9; N, 3.9%); (Found: m/z 359.1676. C\textsubscript{27}H\textsubscript{21}N requires
359.1674); m/z 359(47%); 358(57), 182(10), 69(100);
\( \nu_{\text{max(nujol)}} \) 1605 cm\(^{-1}\) (C=N).

For nmr data see appendix 2.

6) 8-(4-Trifluoromethylphenyl)-5-phenyl-7H-dibenz-
    \[c,e\]azepine

Using the method of (iii) above, this was prepared
from 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.17 g,
0.5 mmol) and 4-trifluoromethylphenylboronic acid (0.12 g,
0.63 mmol). Reaction at reflux for 30 minutes followed by
the usual work-up and dry flash chromatography (silica,
ethyl acetate:petrol, 1:49 to 1:33) gave 8-(4-trifluoro-
methyiphenyl)-5-phenyl-7H-dibenz[c,e]azepine as a white
crystalline solid (0.16 g, 77%) m.p. 187-189°C (from
cyclohexane) (Found: C, 78.5; H, 4.4; N, 3.4. \( \text{C}_{27}\text{H}_{18}\text{NF}_{3} \)
requires C, 78.4; H, 4.4; N, 3.4%); m/z 413(86%),
412(100), 310(14), 239(17), 32(61); \( \nu_{\text{max(nujol)}} \) 1610 cm\(^{-1}\)
(C=N).

For nmr data see appendix 2.

7) 8-(4-Dimethylaminophenyl)-5-phenyl-7H-dibenz-
    \[c,e\]azepine

Using the method of (iii) above this was prepared from
8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.17 g, 0.5 mmol)
and 4-dimethylaminophenylboronic acid (0.10 g, 0.63 mmol).
Reaction at reflux for 1 hour followed by the usual
work-up and dry flash chromatography (silica, ethyl
acetate:petrol, 1:19 to 1:9) gave 8-(4-dimethylamino-phenyl)-5-phenyl-7H-dibenz[c,e]azepine as a white crystalline solid (0.17 g, 88%) m.p. 197-198°C (from cyclohexane/ethanol) (Found: C, 86.7; H, 6.3; N, 7.1). C_{28}H_{24}N_{2} requires C, 86.6; H, 6.2; N, 7.2%; (Found: m/z 388.1928. C_{28}H_{24}N_{2} requires 388.1939); m/z 388(100%), 387(59), 194(14), 142(13); \nu_{\text{max}}{(\text{nujol})} 1615 \text{ cm}^{-1} (\text{C=N}).

For nmr data see appendix 2.

8) 8-(4-Methoxyphenyl)-5-phenyl-7H-dibenz[c,e]-azepine

Using the method of (iii) above this was prepared from 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.17 g, 0.5 mmol) and 4-methoxyphenylboronic acid (0.095 g, 0.63 mmol). Reaction at reflux for 1 hour followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:24 to 1:19) gave 8-(4-methoxyphenyl)-5-phenyl-7H-dibenz[c,e]azepine as a white crystalline solid (0.16 g, 85%) m.p. 156-157°C (from cyclohexane) (Found: C, 86.3; H, 5.6; N, 3.8. C_{29}H_{21}NO requires C, 86.4; H, 5.6; N, 3.7%); (Found: m/z 375.1631. C_{29}H_{21}NO requires 375.1623); m/z 375(100%), 374(92), 272(14), 188(10), 143(18); \nu_{\text{max}}{(\text{nujol})} 1605 \text{ cm}^{-1} (\text{C=N}).

For nmr data see appendix 2.

9) 8-(4-Fluorophenyl)-5-phenyl-7H-dibenz[c,e]azepine

Using the method of (iii) above, this was prepared
from 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.17 g, 0.5 mmol) and 4-fluorophenylboronic acid (0.087, 0.63 mmol). Reaction at reflux for 30 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:33 to 1:19) gave 8-(4-fluorophenyl)-5-phenyl-7H-dibenz[c,e]azepine as a white crystalline solid (0.18 g, 99%) m.p. 153-154.5°C (from cyclohexane) (Found: C, 85.6; H, 5.0; N, 4.0. \( \text{C}_{26}\text{H}_{18}\text{FN} \) requires C, 85.9; H, 5.0; N, 3.9%); m/z (FAB, glycerol) 364 (100%), 363 (20), 362 (21) 259 (8), 165 (10), \( \nu_{\text{max}} \) (nujol) 1605 cm\(^{-1} \) (C=N).

For nmr data see appendix 2.

10) 8-(4-Chlorophenyl)-5-phenyl-7H-dibenz[c,e]azepine

Using the method of (iii) above, this was prepared from 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.17 g, 0.5 mmol) and 4-chlorophenylboronic acid (0.098 g, 0.63 mmol). Reaction at reflux for 30 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:49 to 1:33) gave 8-(4-chlorophenyl)-5-phenyl-7H-dibenz[c,e]azepine as a white crystalline solid (0.15 g, 79%) m.p. 173.5-175.5°C (from cyclohexane) (Found: C, 81.9; H, 4.7; N, 3.6. \( \text{C}_{26}\text{H}_{18}\text{ClN} \) requires C, 82.2; H, 4.8; N, 3.7%); m/z 381 (34%), 379 (100), 239 (22), 170 (14); \( \nu_{\text{max}} \) (nujol) 1605 cm\(^{-1} \) (C=N).

For nmr data see appendix 2.
11) 8-(2-Methylphenyl)-5-phenyl-7H-dibenz[c,e]azepine

Using the method of (iii) above, this was prepared from 8-bromo-5-phenyl-7H-dibenz[c,e]azepine (0.14 g, 0.4 mmol) and 2-methylphenylboronic acid (0.06 g, 0.5 mmol). Reaction at reflux for 2 hours, followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:49 to 1:24) gave 8-(2-methylphenyl)-5-phenyl-7H-dibenz[c,e]azepine as a white crystalline solid (0.12 g, 83%) m.p. 131-133°C (from n-hexane) (Found: C, 90.1; H, 6.0; N, 3.8. C_{27}H_{21}N requires C, 90.2; H, 5.9; N, 3.9%); (Found: m/z 359.1677. C_{27}H_{21}N requires 359.1674); m/z 359(100%), 358(60), 344(33), 143(23); \nu_{\text{max}}(\text{nujol}) 1610 \text{ cm}^{-1} (C=N).

For nmr data see appendix 2.

(vi) 8-ARYL-3-CHLORO-5-PHENYL-7H-DIBENZ[c,e]AZEPINES

1) 3-Chloro-8-(4-methylphenyl)-5-phenyl-7H-dibenz- [c,e]azepine

Using the method of (iii) above, this was prepared from 8-bromo-3-chloro-5-phenyl-7H-dibenz[c,e]azepine (0.13 g, 0.35 mmol) and 4-methylphenylboronic acid (0.06 g, 0.44 mmol). Reaction at reflux for 30 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:49) gave 3-chloro-8-(4-methylphenyl)-5-phenyl-7H-dibenz[c,e]azepine as a white crystalline solid (0.13 g, 94%) m.p. 155-156.5°C (from
cyclohexane) (Found: m/z 393.1254. C$_{27}$H$_{20}$^{35}ClN requires 393.1284); m/z 395(33%), 394(53), 393(100), 392(98), 381(59), 143(52); $v_{\text{max}}$(nujol) 1610 cm$^{-1}$ (C=N).

For nmr data see appendix 2.

2) 3-Chloro-5-phenyl-8-(4-trifluoromethylphenyl)-7H-dibenz[c,e]azepine

Using the method of (iii) above, this was prepared from 8-bromo-3-chloro-5-phenyl-7H-dibenz[c,e]azepine (0.20 g, 0.52 mmol) and 4-trifluoromethylphenylboronic acid (0.12 g, 0.65 mmol). Reaction at reflux for 30 minutes followed by the usual work-up and dry flash chromatography (silica, ethyl acetate:petrol, 1:49) gave 3-chloro-5-phenyl-8-(4-trifluoromethylphenyl)-7H-dibenz-[c,e]azepine as a colourless oil (0.20 g, 86%) (Found: m/z 447.1001. C$_{27}$H$_{17}$^{35}ClF$_3$N requires 447.1011); m/z 449(35%), 448(56), 447(100), 446(99), 412(35), 309(17); $v_{\text{max}}$(nujol) 1610 cm$^{-1}$ (C=N).

For nmr data see appendix 2.

D. INTRAMOLECULAR COMPETITION REACTIONS

The following reactions (i)-(iv) were carried out using a general method. The reaction of the nitrile ylide derived from N-(6-phenyl-2-(2-phenylethenyl)benzyl)-benzimidoyl chloride is given as an example.
(i) REACTION OF THE NITRILE YLIDE DERIVED FROM N-(6-
PHENYL-2-(2-PHENYLETHENYL) BENZYL) BENZIMIDOYL

CHLORIDE

N-Benzoyl-6-phenyl-2-(2-phenylethenyl) benzylamine
(0.19 g, 0.5 mmol), dry ether (10 ml) and thionyl chloride
(3 ml) were heated at reflux under dry nitrogen overnight.
The solvent was removed in vacuo and the residue dried
under high vacuum for 3 hours. Dry T.H.F. (10 ml) was
added and the solution cooled to 0°C. Solid potassium
tert-butoxide (0.112 g, 1 mmol) was added in one portion
with rapid stirring under dry nitrogen. The mixture was
stirred at 0°C for 2 hours, allowed to warm to room
temperature and stirred for 1 hour. 25% w/v ammonium
chloride solution (10 ml) was added and the mixture
stirred vigorously for 15 minutes. The mixture was
extracted with methylene chloride (3 x 10 ml), the
combined organic fractions were dried and the solvent
removed in vacuo to give a pale brown foam. This was
identified by ¹H n.m.r. as 2aH,3,3a-dihydro-2a,3,7-
triphenylcycloprop[c]isoquinoline (0.18 g, 97%). (See
appendix 1) (Found: m/z 371.1666. C₂₂H₂₁N requires
371.1674); m/z 371(65%), 370(100), 281(12), 268(39),
189(10), 178(10), 165(13).

For nmr data see appendix 2.

A duplicate experiment using 0.05 g, 1.3 x 10⁻⁴ mol of
amide gave the same result.

Two further duplicate experiments on this scale using
DMF as the cyclisation solvent gave the same result.

(i)a. Thermolysis of 2aH,3,3a-dihydro-2a,3,7-triphenyl- 
cycloprop[c]isoquinoline (0.10 g) in refluxing 
cyclohexane for 4 hours gave a brown oil. Dry 
flash chromatography (silica, ether:petrol, 1:19) 
gave 3,4,9-triphenyl-1H-2-benzazepine as a 
yellow oil (0.08 g, 80%) (Found: m/z 371.1666. 
C_{27}H_{21}N requires 371.1674); m/z 371(43%), 
370(71), 268(24), 105(100), 77(54), 51(28). 

For nmr data see appendix 2.

(ii) REACTION OF THE NITRILE YLIDE DERIVED FROM N-(6-
PHENYL-2-(2-THIENYL)BENZYL)BENZIMIDOYL CHLORIDE

The imidoyl chloride made from N-benzoyl-6-phenyl-2-
(2-thienyl)benzylamine (0.18 g, 0.5 mmol) was treated with 
potassium tert-butoxide (0.112 g, 1 mmol) in T.H.F. at 
0°C. The usual work-up gave a brown oil (0.17 g) 
identified by 'H nmr as 4,7-diphenyl-6H-thienobenz[c,e]- 
azepine (see appendix 1). (Found: m/z 351.1075. C_{24}H_{17}NS 
requires 351.1082); m/z 351(100%), 350(71), 318(22), 
281(76). 

For nmr data see appendix 2.

A duplicate experiment using 0.05 g, 1.4 x 10^{-4} mol of 
amide gave the same result.

Two further duplicate experiments on this scale using 
DMF as the cyclisation solvent gave the same result.
REACTIONS OF THE NITRILE YLIDES DERIVED FROM N-(2-ARYL-6-PHENYLBENZYL) BENZIMIDOYL CHLORIDES

1) The Nitrile Ylide Derived from N-(2-(3-nitrophenyl)-6-phenylbenzyl)benzimidoyl Chloride

The imidoyl chloride made from N-benzoyl-2-(3-nitrophenyl)-6-phenylbenzylamine (0.20 g, 0.5 mmol) was treated with potassium tert-butoxide (0.112 g, 1 mmol) in T.H.F. at 0°C. The usual work-up gave a pale brown foam (0.20 g) identified by 'H nmr as a mixture of 4-nitro- and 2-nitro-5,8-diphenyl-7H-dibenz[c,e]azepines in the ratio 2:5:1 (see appendix 1).

For nmr data see appendix 2.

Dry flash chromatography (silica, ethyl acetate: petrol, 1:33 to 1:7) gave;

(a) 2-nitro-5,8-diphenyl-7H-dibenz[c,e]azepine as a pale orange solid (0.06 g, 30%) (Found: m/z 390.1366. C_{26}H_{18}N_{2}O_{2} requires 390.1368); m/z 390(100%), 389(75), 381(83), 143(88).

For nmr data see appendix 2.

(b) 4-nitro-5,8-diphenyl-7H-dibenz[c,e]azepine as a white solid (0.14 g, 70%) (Found: m/z 390.1366. C_{26}H_{18}N_{2}O_{2} requires 390.1368); m/z 390(100%), 389(65), 285(43), 239(42), 105(51).

For nmr data see appendix 2.

A duplicate experiment using 0.05 g, 1.4 x 10^{-4} mol of
amide gave the same result.

Two further duplicate experiments on this scale using D.M.F. as the cyclisation solvent gave the same products in the ratio 4.3:1 (see appendix 1).

2) The Nitrile Ylide Derived From N-(2-(3-methoxy-phenyl)-6-phenylbenzyl)benzimidoyl Chloride

The imidoyl chloride prepared from N-benzoyl-2-(3-methoxyphenyl)-6-phenylbenzylamine (0.16 g, 0.4 mmol) was treated with potassium tert-butoxide (0.09 g, 0.8 mmol) in T.H.F. at 0°C. The usual work-up gave a colourless oil (0.13 g) identified by 'H nmr as a 3-component mixture containing 4-methoxy and 2-methoxy-5,8-diphenyl-7H-dibenz-[c,e]azepines and 8-(3-methoxyphenyl)-5-phenyl-7H-dibenz-[c,e]azepine in the ratio 5.6:0.8:1.0 (see appendix 1). None of these compounds were separable by chromatography. (Found: m/z 375.1637. C_{22}H_{21}NO requires 375.1623); m/z 375(100%), 374(83), 281(38), 272(60).

For isomer nmr data see appendix 2.

A duplicate experiment using 0.05 g, 1.3 x 10^{-4} mol of amide gave the same result.

Two further duplicate experiments on this scale using D.M.F. as the solvent gave the same products in the ratio 1.4:0.3:1.0 (see appendix 1).
The Nitrile Ylide Derived From \( N-(2-(3,5\text{-dimethylphenyl})-6\text{-phenylbenzyl})\text{benzimidoyl} \) Chloride

The imidoyl chloride prepared from \( N\)-benzoyl-2-(3,5-dimethylphenyl)-6-phenylbenzylamine (0.20 g, 0.5 mmol) was treated with potassium tert-butoxide (0.112 g, 1 mmol) in T.H.F. at 0°C. The usual work-up gave a yellow foam (0.20 g) identified by 'H nmr as a mixture of 2,4-dimethyl-5,8-diphenyl-7H-dibenz[c,e]azepine and 8-(3,5-dimethylphenyl)-5-phenyl-7H-dibenz[c,e]azepine in the ratio 8.3:1.0 (see appendix 1). These products were inseparable by chromatography. (Found: m/z 373.1817. \( C_{28}H_{23}N \) requires 373.1830); m/z 373(69%), 271(58), 119(74), 57(100); \( \nu \)max(nujol) 1610 cm\(^{-1}\) (C=N).

For isomer nmr data see appendix 2.

A duplicate experiment using 0.05 g, 1.3 \( \times 10^{-4} \) mol of amide gave the same result.

Two further duplicate experiments on this scale using D.M.F. as the cyclisation solvent gave the same products in the ratio 7.6:1.0 (see appendix 1).

The Nitrile Ylide Derived From \( N-(2-(3,5\text{-bis-trifluoromethylphenyl})-6\text{-phenylbenzyl})\text{benzimidoyl} \) Chloride

The imidoyl chloride prepared from \( N\)-benzoyl-2-(3,5-bis-trifluoromethylphenyl)-6-phenylbenzylamine (0.25 g, 0.5 mmol) was treated with potassium tert-butoxide
(0.112 g, 1 mmol) in T.H.F. at 0°C. The usual work-up gave a white foam (0.24 g) identified by \(^1\)H nmr as a mixture of 2,4-bis-trifluoromethyl-5,8-diphenyl-7H-dibenz-[c,e]azepine and 8-(3,5-bis-trifluoromethylphenyl)-5-phenyl-7H-dibenz[c,e]azepine in the ratio 32:1 (see appendix 1). These products were inseparable by chromatography. (Found: m/z 481.1267. C\(_{28}\)H\(_{17}\)F\(_6\)N requires 481.1265); m/z 481(100%), 480(90), 378(18), 69(33); \(\nu_{\text{max}}\) (nujol) 1605 cm\(^{-1}\) (C=N).

For isomer nmr data see appendix 2.

A duplicate experiment using 0.06 g, 1.2 \(\times\) 10\(^{-4}\) mol of amide gave the same result.

5) **The Nitrile Ylide Derived from N-(2-(4-methyl-phenyl)-6-phenylbenzyl)benzimidoyl Chloride**

The imidoyl chloride prepared from N-benzoyl-2-(4-methylphenyl)-6-phenylbenzylamine (0.19 g, 0.5 mmol) was treated with potassium tert-butoxide (0.112 g, 1 mmol) in T.H.F. at 0°C. The usual work-up gave a colourless oil (0.16 g) identified by \(^1\)H nmr as a mixture of 5,8-diphenyl-3-methyl-7H-dibenz[c,e]azepine and 8-(4-methylphenyl)-5-phenyl-7H-dibenz[c,e]azepine in the ratio 1.5:1.0 (see appendix 1). These products were inseparable by chromatography. (Found: m/z 359.1667. C\(_{27}\)H\(_{21}\)N requires 359.1673); m/z 359(70%), 358(72), 119(74), 57(100); \(\nu_{\text{max}}\) (film) 1610 cm\(^{-1}\) (C=N).

For isomer nmr data see appendix 2.
A duplicate experiment using 0.05 g, 1.3 x 10^{-4} mol of amide gave the same result.

6) The Nitrile Ylide Derived From N-(2-(4-trifluoromethylphenyl)-6-phenylbenzyl)benzimidoyl Chloride

The imidoyl chloride prepared from N-benzoyl-2-(4-trifluoromethylphenyl)-6-phenylbenzylamine (0.22 g, 0.5 mmol) was treated with potassium tert-butoxide in T.H.F. at 0°C. The usual work-up gave a yellow gum (0.22 g) identified by 'H nmr as a mixture of 5,8-diphenyl-3-trifluoromethyl-7H-dibenz[c,e]azepine and 5-phenyl-8-(4-trifluoromethyl-phenyl)-7H-dibenz[c,e]azepine in the ratio 2.8:1.0 (see appendix 1). These products were inseparable by chromatography. (Found: m/z 413.1396. C_{27}H_{18}F_{3}N requires 413.1391); m/z 413(92%), 412(100), 344(11), 69(70); \nu_{\text{max}}(\text{nujol}) 1610 \text{ cm}^{-1} (\text{C=N}).

For isomer nmr data see appendix 2.

A duplicate experiment using 0.05 g, 1.2 x 10^{-4} mol of amide gave the same result.

Two further duplicate experiments on this scale using D.M.F. as the cyclisation solvent gave the same products in the ratio 2.1:1.0 (see appendix 1).
7) *The Nitrile Ylide Derived From N-2-(4-dimethylaminophenyl)-6-phenylbenzyl)benzimidoyl Chloride*

The normal method of imidoyl chloride preparation was unsuccessful in this case, resulting in a complex mixture.

The imidoyl chloride was prepared from *N*-benzoyl-2-(4-dimethylaminophenyl)-6-phenylbenzylamine (0.05 g, 1.3 x 10^-4 mol) dissolved in thionyl chloride (0.5 ml). Dry D.M.F. (0.019 g, 2.6 x 10^-4 mol) was added and the mixture stirred at room temperature under dry nitrogen overnight. The D.M.F. and thionyl chloride were removed under high vacuum and the resulting imidoyl chloride was dried in the usual way. The imidoyl chloride was dissolved in THF (2 ml) and cooled to 0°C. Solid potassium tert-butoxide (0.073 g, 6.5 x 10^-4 mol) was added with rapid stirring under dry nitrogen. The mixture was stirred for 2 hours at 0°C and 1 hour at room temperature. The usual work-up gave a pale brown foam (0.05 g). The product was identified as a mixture of 3-dimethylamino-5,8-diphenyl-7H-dibenz[c,e]azepine and 8-(4-dimethylaminophenyl)-5-phenyl-7H-dibenz[c,e]azepine in the ratio 1.3:1.0 (see appendix 1). These products were inseparable by chromatography. (Found: m/z 388.1942. C_{28}H_{24}N_{2} requires 388.1939); m/z 388(2%), 355(6), 281(22), 207(33), 69(100); ν_{max}(nujol) 1615 cm⁻¹ (C=N).

For nmr isomer data see appendix 2.

A duplicate experiment on the same scale gave the same result.
Two further duplicate experiments on the same scale using D.M.F. as the cyclisation solvent gave unreacted starting material.

8) **The Nitrile Ylide Derived From N-(2-(4-methoxyphenyl)-6-phenylbenzyl)benzimidoyl Chloride**

The imidoyl chloride prepared from N-benzoyl-2-(4-methoxyphenyl)-6-phenylbenzylamine (0.20 g, 0.5 mmol) was treated with potassium tert-butoxide in T.H.F. at 0°C. The usual work-up gave a brown oil (0.20 g) identified by \(^1\)H nmr as a mixture of 5,8-diphenyl-3-methoxy-7H-dibenz-[c,e]azepine and 8-(4-methoxyphenyl)-5-phenyl-7H-dibenz-[c,e]azepine in the ratio 1.6:1.0 (see appendix 1). These products were inseparable by chromatography. (Found: m/z 375.1621. C\(_{22}\)H\(_{21}\)N\(_2\)O requires 375.1623); m/z 375(36%), 374(34), 119(49), 105(85), 57(100); \(\nu\)\(_{\text{max}}\)(nujol) 1605 cm\(^{-1}\) (C=N).

For isomer nmr data see appendix 2.

A duplicate experiment using 0.05 g, 1.3 × 10\(^{-4}\) mol of amide gave the same result.

9) **The Nitrile Ylide Derived From N-(2-(4-fluoro phenyl)-6-phenylbenzyl)benzimidoyl Chloride**

The imidoyl chloride prepared from N-benzoyl-2-(4-fluorophenyl)-6-phenylbenzylamine (0.19 g, 0.5 mmol) was treated with potassium tert-butoxide (0.112 g, 1 mmol) in T.H.F. at 0°C. The usual work-up gave a white foam
(0.19 g) identified by 'H nmr as a mixture of 5,8-diphenyl-3-fluoro-7H-dibenz[c,e]azepine and 8-(4-fluorophenyl)-5-phenyl-7H-dibenz[c,e]azepine in the ratio 1.2:1.0 (see appendix 1). These products were inseparable by chromatography. (Found: m/z 363.1428. C_{26}H_{18}FN requires 363.1423); m/z 363(92%), 362(100), 260(13), 257(13); ν\text{max}(\text{nujol}) 1605 \text{ cm}^{-1} (\text{C=N}).

For isomer nmr data see appendix 2.

A duplicate experiment using 0.05 g, 1.3 \times 10^{-4} \text{ mol} of amide gave the same result.

Two further duplicate experiments on this scale using D.M.F. as the cyclisation solvent gave the same product in the ratio 1.0:1.0 (see appendix 1).

10) The Nitrile Ylide Derived From N-(2-(4-chlorophenyl)-6-phenylbenzyl)benzimidoyl Chloride

The imidoyl chloride prepared from N-benzoyl-2-(4-chlorophenyl)-6-phenylbenzylamine (0.20 g, 0.5 mmol) was treated with potassium tert-butoxide (0.112 g, 1 mmol) in T.H.F. at 0°C. The usual work-up gave a white foam (0.20 g) identified by 'H nmr as a mixture of 3-chloro-5,8-diphenyl-7H-dibenz[c,e]azepine in the ratio 2.2:1.0 (see appendix 1). These products were inseparable by chromatography. (Found: m/z 381.1079. C_{26}H_{18}^{37}ClN requires 381.1098); m/z 381(15%), 380(24), 379(44), 378(43), 69(100); ν\text{max}(\text{nujol}) 1605 \text{ cm}^{-1} (\text{C=N}).

For isomer nmr data see appendix 2.
A duplicate experiment using 0.05 g, 1.3 x 10^{-4} mol of amide gave the same result.

Two further duplicate experiments on this scale using D.M.F. as the cyclisation solvent gave the same products in the ratio 1.6:1.0 (see appendix 1).

11) **The Nitrile Ylide Derived From N-(2-(2-methylphenyl)-6-phenylbenzyl)benzimidoyl Chloride**

The imidoyl chloride prepared from N-benzoyl-2-(2-methylphenyl)-6-phenylbenzylamine (0.05 g, 1.3 x 10^{-4} mol) was treated with potassium tert-butoxide (0.03 g, 2.6 x 10^{-4} mol) in T.H.F. at 0°C. The usual work-up gave a colourless oil (0.05 g) identified by 'H nmr as 8-(2-methylphenyl)-5-phenyl-7H-dibenz[c,e]azepine. Crystallisation from n-hexane gave a white crystalline solid (0.03 g, 60%) which was confirmed to have this structure by comparison with the authentic sample. m.p. 130-132°C (Found: m/z 359.1662. C_{22}H_{21}N requires 359.1673); m/z 359(100%), 358(59), 344(33), 143(21); \nu_{\text{max (film)}} 1610 \text{ cm}^{-1} (C=\text{N}).

For nmr data see appendix 2.

A duplicate experiment on the same scale gave the same result.

Two further duplicate experiments using D.M.F. as the cyclisation solvent gave the same result.
(iv) **GENERATION AND REACTION OF THE NITRILE YLIDES DERIVED FROM N-(6-ARYL-2-(4-CHLOROPHENYL)BENZYL)-BENZIMIDOYL CHLORIDES**

1) **The Nitrile Ylide Derived From N-(2-(4-chlorophenyl)-6-(4-methylphenyl)benzyl)benzimidoyl Chloride**

The imidoyl chloride prepared from N-benzoyl-2-(4-chlorophenyl)-6-(4-methylphenyl)benzylamine (0.16 g, 0.4 mmol) was treated with potassium tert-butoxide (0.09 g, 0.8 mmol) in T.H.F. at 0°C. The usual work-up gave a white foam (0.16 g) identified by $^1$H nmr as a mixture of 3-chloro-8-(4-methylphenyl)-5-phenyl-7H-dibenz[c,e]azepine and 8-(4-chlorophenyl)-3-methyl-5-phenyl-7H-dibenz[c,e]azepine in the ratio 1.4:1.0 (see appendix 1). These products were inseparable by chromatography. (Found: m/z 393.1283. C$_{27}$H$_{20}$^{35}ClN requires 393.1284); m/z 395(33%), 394(55), 393(99), 392(100), 381(24), 143(23); $v_{max}$(nujol) 1605 cm$^{-1}$ (C=N).

For isomer nmr data see appendix 2.

A duplicate experiment using 0.05 g, 1.3 $\times$ 10$^{-4}$ mol of amide gave the same result.

Two further duplicate experiments on this scale using D.M.F. as the cyclisation solvent gave the same products in the ratio 1.3:1.0 (see appendix 1).
2) **The Nitrile Ylide Derived From N-(2-(4-chlorophenyl)-6-(4-trifluoromethylphenyl)benzyl)benzimidoyl Chloride**

The imidoyl chloride prepared from N-benzoyl-2-(4-chlorophenyl)-6-(4-trifluoromethylphenyl)benzylamine (0.14 g, 0.3 mmol) was treated with potassium tert-butoxide (0.07 g, 0.6 mmol) in T.H.F. at 0°C. The usual work-up gave a yellow oil (0.14 g) identified by $^1$H nmr as a mixture of 3-chloro-5-phenyl-8-(4-trifluoromethylphenyl)-7H-dibenz[c,e]azepine and 8-(4-chlorophenyl)-5-phenyl-3-trifluoromethyl-7H-dibenz[c,e]azepine in the ratio 1.0:1.1 (see appendix 1). These products were inseparable by chromatography. (Found: m/z 447.0989, C$_{22}$H$_{12}$Cl$_{35}$N requires 447.1001); m/z 449(33%), 448(54), 447(99), 446(100), 412(17), 309(15); $\nu_{\text{max}}$(film) 1620 cm$^{-1}$, 1610 cm$^{-1}$ (C=N).

For isomer nmr data see appendix 2.

A duplicate experiment using 0.05 g, $1.1 \times 10^{-4}$ mol of amide gave the same result.
APPENDIX 1

Product ratios from the 1,7-electrocyclisation competition reactions of nitrile ylides.

REACTION OF THE NITRILE YLIDE DERIVED FROM
N-(6-PHENYL-2-(2-PHENYLETHENYL)BENZYL)BENZIMIDOYL CHLORIDE

SOLVENT

0 T.H.F. 100%
0 D.M.F. 100%
APPENDIX 1

REACTION OF THE NITRILE YLIDE DERIVED FROM

\[ N-(6\text{-phenyl}-2\text{-}(2\text{-thienyl})\text{benzyl})\text{benzimidoyl chloride} \]

\[
\begin{array}{c}
\text{Ph} \\
\text{C} \\
+ \text{N} \\
\text{Ph} \\
\text{CH}_2 \\
\end{array}
\]

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Thienyl} \\
\text{Thienyl} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Thienyl} \\
\text{Thienyl} \\
\end{array}
\]

SOLVENT

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.H.F.</td>
<td>100%</td>
</tr>
<tr>
<td>D.M.F.</td>
<td>100%</td>
</tr>
</tbody>
</table>
APPENDIX 1

REACTION OF THE NITRILE YLIDE DERIVED FROM
N-(2-(3-NITROPHENYL)-6-PHENYLBENZYL) BENZIMIDOYL CHLORIDE

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{I} \quad \text{NO}_2 \\
\quad \text{Ph} & \quad \text{N} \quad \text{I} \quad \text{NO}_2 \\
\quad \text{Ph} & \quad \text{N} \quad \text{I} \quad \text{NO}_2
\end{align*}
\]

SOLVENT
T.H.F. 0
D.M.F. 0

REACTION OF THE NITRILE YLIDE DERIVED FROM
N-(2-(3-METHOXYPHENYL)-6-PHENYLBENZYL) BENZIMIDOYL CHLORIDE

\[
\begin{align*}
\text{Ph} & \quad \text{O} \quad \text{Me} \\
\quad \text{Ph} & \quad \text{O} \quad \text{Me} \\
\quad \text{Ph} & \quad \text{O} \quad \text{Me}
\end{align*}
\]

SOLVENT
T.H.F. 1.0
D.M.F. 1.0
APPENDIX 1

REACTIONS OF THE NITRILE YLIDES DERIVED FROM

a) \( N-(2-(3,5\text{-dimethylphenyl})-6\text{-phenylbenzyl})\) benzimidoyl chloride

b) \( N-(2-(3,5\text{-bis-trifluoromethylphenyl})-6\text{-phenylbenzyl})\) benzimidoyl chloride

\[
\begin{align*}
\text{Ph} & \quad \text{C} \\
\quad & \quad \text{N} \\
\text{Ph} & \quad \text{N}
\end{align*}
\]

\[\text{(381)}\]

a) \( X=H \)
   - 1.0  T.H.F.  8.3
   - 1.0  D.M.F.  7.6

b) \( X=F \)
   - 1.0  T.H.F.  32.0
APPENDIX 1

REACTIONS OF THE NITRILE YLIDES DERIVED FROM
N-(2-ARYL-6-PHENYL BENZYL) BENZIMIDOYL CHLORIDES

\[
\begin{array}{c}
\text{Nitrile Ylide} \quad \text{Ar} \quad \text{SOLVENT} \quad \text{RATIO} \\
388a \quad \text{Ph} \quad \text{CH}_3 \quad \text{T.H.F.} \quad 1.0 \quad 1.5 \\
388b \quad \text{Ph} \quad \text{CF}_3 \quad \text{T.H.F.} \quad 1.0 \quad 2.8 \\
388b \quad \text{Ph} \quad \text{CF}_3 \quad \text{D.M.F.} \quad 1.0 \quad 2.1 \\
394 \quad \text{Ph} \quad \text{NMe}_2 \quad \text{T.H.F.} \quad 1.0 \quad 1.3 \\
397 \quad \text{Ph} \quad \text{OMe} \quad \text{T.H.F.} \quad 1.0 \quad 1.6 \\
401a \quad \text{Ph} \quad \text{Cl} \quad \text{T.H.F.} \quad 1.0 \quad 2.2 \\
401b \quad \text{Ph} \quad \text{F} \quad \text{T.H.F.} \quad 1.0 \quad 1.2 \\
401b \quad \text{Ph} \quad \text{F} \quad \text{D.M.F.} \quad 1.0 \quad 1.0 \\
411 \quad \text{Ph} \quad \text{CH}_3 \quad \text{T.H.F.} \quad 100\% \quad 0 \\
411 \quad \text{Ph} \quad \text{CH}_3 \quad \text{D.M.F.} \quad 100\% \quad 0 \\
\end{array}
\]
APPENDIX 1

REACTIONS OF THE NITRILE YLIDES DERIVED FROM
N-(2-(4-CHLOROPHENYL)-6-ARYLBENZYL)BENZIMIDOYL CHLORIDES

<table>
<thead>
<tr>
<th>Nitrile Ylide</th>
<th>Ar</th>
<th>SOLVENT</th>
<th>RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>404a</td>
<td>$\text{Ph}_2$</td>
<td>T.H.F.</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D.M.F.</td>
<td>1.3</td>
</tr>
<tr>
<td>404b</td>
<td>$\text{Ph}_{2}\text{CH}_3$</td>
<td>T.H.F.</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.1</td>
</tr>
</tbody>
</table>
APPENDIX 2

Nmr data on the products of the intramolecular electrocyclic competition reactions and the isomers made by a different route.

(i) **THE NITRILE VLYDE DERIVED FROM N-(6-PHENYL-2-(2-PHENYLETHENYL) BENZY) BENZIMIDOVYL CHLORIDE**

\[
\begin{align*}
\text{(288)} & \quad \text{(372)} & \quad \text{(375)} \\
\end{align*}
\]

(372) \( \delta_H(360 \text{ MHz}) \) 1.86(d, J 6.0 Hz, 1H); 3.54(d, J 6.0 Hz, 1H); 6.94-7.61(m, 18H, Ar-H); 8.33(s, H-C=N).

(373) \( \delta_H(360 \text{ MHz}) \) 3.79(d, J 10.0 Hz, 1H); 5.31(d, J 10.0 Hz, 1H); 7.05-7.68(m, 18H; Ar-H), 7.91(s, H-C=N).

**AUTHENTIC: 5-PHENYL-8-(2-PHENYLETHENYL)-7H-DIBENZ[c,e]AZEPINE**

\[
\begin{align*}
\text{(373)} \\
\end{align*}
\]

\( \delta_H(360 \text{ MHz}) \) 3.75(d, J 10.7 Hz, 7-H); 5.41(d, J 10.7 Hz, 7'-H); 7.08(d, J 16.0 Hz, H-C=C); 7.30-7.89(m, 18H, Ar-H and H-C=C).
APPENDIX 2

(ii) **THE NITRILE YLIDE DERIVED FROM N-(6-PHENYL-2-(2-THIENYL) BENZYL BENZIMIDOYL CHLORIDE**

\[
\begin{align*}
\text{Ph} & \quad \text{C} \\
& \quad \text{+N} \\
\text{CH} & \quad \text{Ph}
\end{align*}
\]

\[\text{(379)}\]

\(\delta_{H}(360 \text{ MHz}) 3.83(\text{d}, J 10.6 \text{ Hz}, 7\text{-H}); 5.39(\text{d}, J 10.6 \text{ Hz}, 7'\text{-H}); 7.09-7.87(\text{m}, 15\text{H}, \text{Ar-H}).\)

**AUTHENTIC: 5-PHENYL-8-(2-THIENYL)-7H-DIBENZ[c,e]AZEPINE**

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{Ph} & \quad \text{C} \\
\text{CH} & \quad \text{Ph}
\end{align*}
\]

\[\text{(380)}\]

\(\delta_{H}(360 \text{ MHz}) 3.71(\text{d}, J 10.3 \text{ Hz}, 7\text{-H}); 5.32(\text{d}, J 10.3 \text{ Hz}, 7'\text{-H}); 7.16-7.80(\text{m}, 15\text{H}, \text{Ar-H}).\)
APPENDIX 2

(iii) THE NITRILE YLIDE DERIVED FROM N-(2-(3-NITROPHENYL-6-PHENYLBENZYL) BENZIMIDOYL CHLORIDE

![Diagram](384a) → ![Diagram](386a) + ![Diagram](387a)

(386a) $\delta_H$(360 MHz) 3.81(d, $J$ 10.3 Hz, 7-H); 5.22(d, $J$ 10.3 Hz, 7'-H); 7.23-7.76(m, 14H, Ar-H); 7.99(dd, $J$ 8.0 and 1.3 Hz, 1H); 8.08(dd, $J$ 8.0 and 1.3 Hz, 1H, o to NO$_2$).

(387a) $\delta_H$(360 MHz) 3.63(d, $J$ 10.5 Hz, 7-H); 5.16(d, $J$ 10.5 Hz, 7'-H); 7.12-7.85(m, 14H, Ar-H); 8.21(dd, $J$ 8.6 and 2.3 Hz, 1H); 8.68(d, $J$ 2.3 Hz, 1H, o to NO$_2$).

AUTHENTIC: 8-(3-NITROPHENYL)-5-PHENYL-7H-DIBENZ[c,e]-AZEPINE

![Diagram](385a)

$\delta_H$(360 MHz) 3.71(d, $J$ 10.5 Hz, 7-H); 4.90(d, $J$ 10.5 Hz, 7'-H); 7.31-7.81(m, 13H, Ar-H); 8.08(d, $J$ 6.6 Hz, 1H); 8.27(dd, $J$ 5.9 and 2.3 Hz, 1H, o to NO$_2$); 8.48(s, 1H, o to NO$_2$).
APPENDIX 2

(iv) THE NITRILE YLIDE DERIVED FROM N-(2-(3-METHOXY-PHENYL)-6-PHENYLBENZYL) BENZIMIDOYL CHLORIDE

\[
\begin{align*}
\text{(384b)} & \quad \rightarrow \\
\text{(386b)} & + \text{(387b)}
\end{align*}
\]

REACTION MIXTURE CONTAINING 385b, 386b and 387b: \(\delta_H(360\text{ MHz})\)

<table>
<thead>
<tr>
<th></th>
<th>OCH(_3)</th>
<th>7-H/7'-H</th>
<th>Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.54 (s)</td>
<td>3.69-3.87 (m)</td>
<td>6.98-7.01 (m)</td>
</tr>
<tr>
<td></td>
<td>3.91 (s)</td>
<td>5.10-5.28 (m)</td>
<td>7.25-7.77 (m)</td>
</tr>
<tr>
<td></td>
<td>3.96 (s)</td>
<td></td>
<td>(7.80(d, J 7.6\text{ Hz}))</td>
</tr>
</tbody>
</table>

The boxed signals were enhanced on addition of an authentic sample of (385b). See below.

AUTHENTIC: 8-(4-METHOXYPHENYL)-5-PHENYL-7H-DIBENZ[c,e]AZEPINE

\[
\begin{align*}
\delta_H(360\text{ MHz}) & \quad 3.90 (s, \text{ OCH}_3); 3.69(d, J 10.3 \\
& \quad \text{Hz, 7-H}); 5.11(d, J 10.3 \text{ Hz, 7'-H}); \\
& \quad 6.96-6.99(m, 1H); 7.22-7.68(m, 14H, \text{ Ar-H}); 7.80(d, J 7.6 \text{ Hz, 1H}).
\end{align*}
\]
APPENDIX 2

The nitrile ylide derived from N-(2-(3,5-dimethylphenyl)-6-phenylbenzyl)benzimidoyl chloride

\[
\begin{align*}
\text{Ph} & \quad \text{C} & \quad \text{Me} \\
\text{Ph} & \quad \text{N} & \quad \text{Ph} & \quad \text{Me} & \quad \text{Me} \\
\end{align*}
\]

(381a)

The reaction mixture containing 382a and 383a: \( \delta_H(360 \text{ MHz}) \)

<table>
<thead>
<tr>
<th>CH(_3)</th>
<th>7-H/7'-H</th>
<th>Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.98 (s)</td>
<td>3.69 (d, J 10.2 Hz)</td>
<td>7.06-7.10 (m)</td>
</tr>
<tr>
<td>2.43 (s)</td>
<td>3.71 (d, J 10.0 Hz)</td>
<td>7.25-7.81 (m)</td>
</tr>
<tr>
<td>2.49 (s)</td>
<td>5.04 (d, J 10.0 Hz)</td>
<td>5.14 (d, J 10.2 Hz)</td>
</tr>
</tbody>
</table>

The boxed signals were enhanced on addition of an authentic sample of 383a. See below.

Authentic: 8-(3,5-dimethylphenyl)-5-phenyl-7H-dibenzo[c,e]azepine

\[
\delta_H(360 \text{ MHz}) 2.43 (s, 2xCH\(_3\)); 3.69 (d, J 10.2 \text{ Hz, 7-H}); 5.15 (d, J 10.2 \text{ Hz, 7'-H}); 7.08 (s, 1H of both CH\(_3\)); 7.25-7.69 (m, 13H, Ar-H); 7.79-7.81 (m, 1H).
APPENDIX 2

(vi) THE NITRILE YLIDE DERIVED FROM N-(2-(3,5-bis-
TRIFLUOROMETHYLPHENYL)-6-PHENYL)BENZYL)-
BENZIMIDOYL CHLORIDE

\[
\begin{align*}
\text{Ph} & \quad \text{CF}_3 \\
\text{N} & \quad \text{CF}_3 \\
\text{C} & \quad \text{CH} \\
\text{Ph} & \quad \text{CF}_3 \\
\text{Ph} & \quad \text{CF}_3
\end{align*}
\]

\[(381b) \quad \rightarrow \quad (382b) + (383b) \]

REACTION MIXTURE CONTAINING 382b AND 383b: \( \delta_H(360 \text{ MHz}) \)

<table>
<thead>
<tr>
<th>7-H/7'-H</th>
<th>Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.65(d, J 10.3 Hz)</td>
<td>7.25-7.79 (m)</td>
</tr>
<tr>
<td>3.75(d, J 10.5 Hz)</td>
<td>7.96 (s)</td>
</tr>
<tr>
<td>4.89(d, J 10.5 Hz)</td>
<td>8.00 (s)</td>
</tr>
<tr>
<td>5.15(d, J 10.3 Hz)</td>
<td>8.25 (s)</td>
</tr>
</tbody>
</table>

The boxed signals were enhanced on addition of an authentic sample of 383b. See below.

AUTHENTIC: 8-(3,5-bis-TRIFLUOROMETHYLPHENYL)-5-PHENYL-
7H-DIBENZ[c,e]AZEPINE

\[
\begin{align*}
\delta_H(360 \text{ MHz}) & \quad 3.75(d, J 10.5 \text{ Hz}, 7-H); 4.89(d, J 10.5 \text{ Hz}, 7'-H); 7.33-7.65(m, 12H, Ar-H); 7.77(d, J 7.7 \text{ Hz}, 1H); 7.79(d, J 7.7 \text{ Hz}, 1H); 7.96(s, 1H o to both CF}_3). \n\end{align*}
\]
APPENDIX 2

(vii) THE NITRILE YLIDE DERIVED FROM N-(2-(4-METHYL-PHENYL)-6-PHENYL-BENZYL) BENZIMIDOYL CHLORIDE

\[
\text{(388a)} \quad \xrightarrow{\text{N}} \quad \text{(389a)} + \text{(390a)}
\]

**REACTION MIXTURE CONTAINING 389a AND 390a: \( \delta_H(360 \text{ MHz}) \)**

<table>
<thead>
<tr>
<th></th>
<th>( \text{CH}_3 )</th>
<th>7-H/7'-H</th>
<th>Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.44 (s)</td>
<td>3.74(d, J 10.2 Hz)</td>
<td>7.09-7.86 (m)</td>
</tr>
<tr>
<td></td>
<td>2.51 (s)</td>
<td>3.75(d, J 10.2 Hz)</td>
<td>5.15(d, J 10.2 Hz)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.18(d, J 10.2 Hz)</td>
<td></td>
</tr>
</tbody>
</table>

The boxed signals were enhanced on addition of an authentic sample of 390a. See below.

**AUTHENTIC: 8-(4-METHYLPHENYL)-5-PHENYL-7H-DIBENZ[c,e]-AZEPINE**

\[
\text{\( \delta_H(360 \text{ MHz}) \)} 2.45(s, \text{CH}_3); 3.65(d, J 10.2 Hz, 7-H); 5.07(d, J 10.2 Hz, 7'-H);
7.25-7.77(m, 15H, Ar-H); 7.80-7.83(m, 1H).
\]
APPENDIX 2

(viii) THE NITRILE YLIDE DERIVED FROM N-(2-(4-TRIFLUOROMETHYLPHENYL)-6-PHENYLBENZYL)BENZIMIDOYL CHLORIDE

[Chemical structure]

(388b) → (389b) + (390b)

REACTION MIXTURE CONTAINING 389b AND 389b: $\delta_H(360$ MHz)

<table>
<thead>
<tr>
<th>7-H/7'-H</th>
<th>Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.64(d, J 10.4 Hz)</td>
<td>7.31-7.86 (m)</td>
</tr>
<tr>
<td>3.69(d, J 10.4 Hz)</td>
<td>7.92-7.94 (m)</td>
</tr>
<tr>
<td>4.96(d, J 10.4 Hz)</td>
<td></td>
</tr>
<tr>
<td>5.12(d, J 10.4 Hz)</td>
<td></td>
</tr>
</tbody>
</table>

The boxed signals were enhanced on addition of an authentic sample of 390b. See below.

AUTHENTIC: 8-(4-TRIFLUOROMETHYLPHENYL)-5-PHENYL-7H-DIBENZ[c,e]AZEPINE

$\delta_H(360$ MHz) 3.67(d, J 10.4 Hz, 7-H); 4.93(d, J 10.4 Hz, 7'-H); 7.25-7.80(m, 16H, Ar-H).
APPENDIX 2
(ix) THE NITRILE YLIDE DERIVED FROM N-(2-(4-METHOXY-PHENYL-6-PHENYLBENZYL)BENZIMIDOYL CHLORIDE

\[
\begin{align*}
\text{(397)} & \quad \text{(398)} & \quad \text{(399)} \\
\end{align*}
\]

REACTION MIXTURE CONTAINING 398 AND 399: \( \delta_H(360 \text{ MHz}) \)

<table>
<thead>
<tr>
<th>OMe</th>
<th>7-H/7′-H</th>
<th>Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.79 (s)</td>
<td>3.67(d, J 10.3 Hz)</td>
<td>6.91(d, J 2.7 Hz)</td>
</tr>
<tr>
<td>3.89 (s)</td>
<td>3.69(d, J 10.2 Hz)</td>
<td>7.05(d, J 8.9 Hz)</td>
</tr>
<tr>
<td>5.07(d, J 10.2 Hz)</td>
<td>7.08-7.67 (m)</td>
<td></td>
</tr>
<tr>
<td>5.09(d, J 10.3 Hz)</td>
<td>7.73(d, 7 8.7 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.79-7.81 (m)</td>
<td></td>
</tr>
</tbody>
</table>

The boxed signals were enhanced on addition of an authentic sample of 399. See below.

AUTHENTIC: 8-(4-METHOXYPHENYL)-5-PHENYL-7H-DIBENZ[c,e]-AZEPINE

\( \delta_H(360 \text{ MHz}) \) 3.89(s, OMe); 3.67(d, J 10.3 Hz, 7-H); 5.09(d, J 10.3 Hz, 7′-H); 7.05(d, J 8.9 Hz, 2H o to OMe); 7.29-7.67(m, 13H, Ar-H); 7.79-7.81(m, 1H).
APPENDIX 2

(x) **THE NITRILE YLIDE DERIVED FROM** \(N-(2-(4\text{-DIMETHYLAMINOPHENYL})-6\text{-PHENYLBENZYL})\) **BENIMIDOYL CHLORIDE**

\[
\begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{NMe}_2
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{NMe}_2
\end{array}
\end{array}
\rightarrow
\begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{NMe}_2 + \\
\text{Ph} \\
\text{NMe}_2
\end{array}
\end{array}
\]

REACTION MIXTURE CONTAINING 395 AND 396: \(\delta_H(360\ \text{MHz})\)

<table>
<thead>
<tr>
<th>NMe(_2)</th>
<th>7-H/7'-H</th>
<th>Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.92 (s)</td>
<td>3.65(d, J 10.2 Hz)</td>
<td>6.65(d, J 2.8 Hz)</td>
</tr>
<tr>
<td>2.01 (s)</td>
<td>3.72(d, J 10.2 Hz)</td>
<td>6.87(d, J 9.0 Hz)</td>
</tr>
<tr>
<td>5.03(d, J 10.2 Hz)</td>
<td>6.98(dd, J 8.8 and 2.8 Hz)</td>
<td>7.24-7.67 (m)</td>
</tr>
<tr>
<td>5.15(d, J 10.2 Hz)</td>
<td></td>
<td>7.77-7.80 (m)</td>
</tr>
</tbody>
</table>

The boxed signals were enhanced on addition of an authentic sample of 396. See below.

**AUTHENTIC: 8-(4-DIMETHYLAMINOPHENYL)-5-PHENYL-7H-DIBENZ[c,e]AZEPINE**

\[
\begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{NMe}_2
\end{array}
\end{array}
\rightarrow
\begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{NMe}_2
\end{array}
\end{array}
\]

\(\delta_H(360\ \text{MHz})\) 3.01(s, NMe\(_2\)); 3.65(d, J 10.2 Hz, 7-H); 5.15(d, J 10.2 Hz, 7'-H); 6.87(d, J 9.0 Hz, 2H \(\xi\) to NMe\(_2\)); 7.25-7.63(m, 13H, Ar-H); 7.77-7.80(m, 1H).
APPENDIX 2

(xi) THE NITRILE YLIDE DERIVED FROM N-(2-(4-FLUORO-PHENYL)-6-PHENYLBENZYL)BENZIMIDOYL CHLORIDE

\[
\begin{align*}
\text{Ph} & \quad \text{C} \\
\text{Ph} & \quad \text{N} \\
\text{C6H5} & \quad \text{CH} \\
\text{F} & \quad \text{H}
\end{align*}
\]

(401a) \quad \rightarrow \quad \begin{align*}
\text{Ph} & \quad \text{N} \\
\text{Ph} & \quad \text{N} \\
\text{C6H5} & \quad \text{C6H5} \\
\text{F} & \quad \text{F}
\end{align*}

(402a) \quad + \quad \begin{align*}
\text{Ph} & \quad \text{N} \\
\text{Ph} & \quad \text{N} \\
\text{C6H5} & \quad \text{C6H5} \\
\text{F} & \quad \text{F}
\end{align*}

(403a)

REACTION MIXTURE CONTAINING 402a AND 403a: \( \delta_H(360 \text{ MHz}) \)

\[
\begin{array}{cc}
7\text{-H}/7'\text{-H} & \text{Ar-H} \\
3.67(d, J 10.3\text{Hz}) & 7.12-7.71 (m) \\
3.69(d, J 10.3\text{Hz}) & 7.76-7.81 (m) \\
5.02(d, J 10.3\text{Hz}) & 5.11(d, J 10.3\text{Hz}) \\
\end{array}
\]

The boxed signals were enhanced on addition of an authentic sample of 403a. See below.

AUTHENTIC: 8-(4-FLUOROPHENYL)-5-PHENYL-7H-DIBENZ[c,e]-AZEPINE

\[
\begin{align*}
\delta_H(200 \text{ MHz}) & 3.69(d, J 10.3 \text{ Hz, 7-H}); 5.02(d, J 10.3 \text{ Hz, 7'-H}); 7.16-7.20(m, 2H o to F); 7.25-7.71(m, 13H, \text{ Ar-H}); 7.78-7.81(m, 1H).
\end{align*}
\]
APPENDIX 2

(xii) THE NITRILE YLIDE DERIVED FROM N-(2-(4-CHLORO-PHENYL)-6-PHENYL-BENZYL) BENZIMIDOYL CHLORIDE

\[
\begin{align*}
\text{(401b)} & \quad \text{\begin{center} \hspace{1cm} \text{(402b)} \end{center}} \quad \text{\begin{center} \hspace{1cm} \text{(403b)} \end{center}}
\end{align*}
\]

REACTION MIXTURE CONTAINING 402b AND 403b: \( \delta_H(360 \text{ MHz}) \)

<table>
<thead>
<tr>
<th>7-H/7'-H</th>
<th>Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.64(d, J 10.3 Hz)</td>
<td>7.31-7.73 (m)</td>
</tr>
<tr>
<td>3.66(d, J 10.3 Hz)</td>
<td>7.78-7.82 (m)</td>
</tr>
<tr>
<td>4.98(d, J 10.3 Hz)</td>
<td>5.08(d, J 10.3 Hz)</td>
</tr>
</tbody>
</table>

The boxed signals were enhanced on addition of an authentic sample of 403b. See below.

AUTHENTIC: 8-(4-CHLOROPHENYL)-5-PHENYL-7H-DIBENZ[c,e]-AZEPINE

\[
\begin{align*}
\delta_H(360 \text{ MHz}) & \quad 3.66(d, J 10.3 \text{ Hz}, 7-H); 4.98(d, J 10.3 \text{ Hz}, 7'-H); 7.31-7.70(m, 15H, Ar-H); 7.78-7.82(m, 1H).
\end{align*}
\]
APPENDIX 2

(xiii) THE NITRILE YLIDE DERIVED FROM N-(2-(2-METHYL-PHENYL)-6-PHENYL BENZYL) BENZIMIDOYL CHLORIDE

\[ \text{Ph} \quad \text{C} \quad + \text{N} \quad \text{CH} \]

\[ \text{Ph} \quad \text{C} \quad \text{CH}_3 \]

\[ \xrightarrow{\text{(411)}} \]

\[ \text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{C} \quad \text{CH}_3 \]

\[ \xrightarrow{\text{(412)}} \]

\( ^1H \text{ nmr of reaction mixture was identical to that of an authentic sample of (412) prepared by a different route. (See below).} \)

**AUTHENTIC: 8-(2-METHYLPHENYL)-5-PHENYL-7H-DIBENZ[c,e]-AZEPINE**

\[ \delta_{H}(360 \text{ MHz}) \]

2.12(s, 0.6 CH\(_3\)); 2.23(s, 0.4 CH\(_3\)); 3.63(d, J 10.5 Hz, 0.4x7-H); 3.68(d, J 10.3 Hz, 0.6x7-H); 4.73(d, J 10.3 Hz, 0.6x7'-H); 4.76(d, J 10.5 Hz, 0.4x7'-H); 7.11-7.83(m, 16H, Ar-H).
APPENDIX 2

THE NITRILE YLIDE DERIVED FROM \(N-(2-(4\text{-CHLORO-}
\text{PHENYL})-6-(4\text{-METHYLPHENYL})\text{BENZYL})\text{BENIMIDOYL}\)

CHLORIDE

\[
\begin{align*}
\text{Cl} & \quad \text{Ph} \\
\text{C} & \quad \text{Cl} \\
\text{Ph} & \quad \text{Cl}
\end{align*}
\]

(404a) \quad (409a) \quad (408a)

**REACTION MIXTURE CONTAINING 408a AND 409a: \(\delta_H(360\text{ MHz})\)**

<table>
<thead>
<tr>
<th>CH(_3)</th>
<th>7-H/7'-H</th>
<th>Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.40 (s)</td>
<td>3.64 (d, J 10.3 Hz)</td>
<td>72.5-7.76 (m)</td>
</tr>
<tr>
<td>2.45 (s)</td>
<td>3.68 (d, J 10.4 Hz)</td>
<td>5.03 (d, J 10.4 Hz)</td>
</tr>
<tr>
<td></td>
<td>5.14 (d, J 10.3 Hz)</td>
<td></td>
</tr>
</tbody>
</table>

The boxed signals were enhanced on addition of an authentic sample of 408a. See below.

**AUTHENTIC: 3-CHLORO-8-(4-METHYLPHENYL)-5-PHENYL-7H-DIBENZ[c,e]AZEPINE**

\[
\delta_H(360\text{ MHz}) \quad 2.45(s, \text{ CH}_3) ; \quad 3.64(d, \text{ J} 10.3\text{ Hz}, \text{ 7-H}) ; \quad 5.10(d, \text{ J} 10.3\text{ Hz}, \text{ 7'-H}) ; \quad 7.25-7.75(m, 15\text{H}, \text{ Ar-H}) .
\]

(408a)
APPENDIX 2

THE NITRILE YLIDE DERIVED FROM \( N-(2-(4-CHLOROPHENYL) -6-(4-TRIFLUOROMETHYLPHENYL)BENZYL) -\)BENZIMIDOYL CHLORIDE

\[
\begin{align*}
\text{Ph} & \quad + N \quad \text{Cl} \\
\text{I} & \quad \text{CF}_3 + \\
\text{Cl} & \quad \text{N} \quad \text{Ph} \quad \text{Cl} \\
\text{Ph} & \quad \text{I} \quad \text{CF}_3 \\
\end{align*}
\]

REACTION MIXTURE CONTAINING 408b AND 409b: \( \delta_H (360 \text{ MHz}) \)

<table>
<thead>
<tr>
<th>7-H/7'-'H</th>
<th>Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.63(d, J 10.5 Hz)</td>
<td>7.25-7.93 (m)</td>
</tr>
<tr>
<td>3.65(d, J 10.5 Hz)</td>
<td></td>
</tr>
<tr>
<td>4.96(d, J 10.5 Hz)</td>
<td></td>
</tr>
<tr>
<td>5.02(d, J 10.5 Hz)</td>
<td></td>
</tr>
</tbody>
</table>

The boxed signals were enhanced on addition of an authentic sample of 408b. See below.

AUTHENTIC: 3-CHLORO-8-(4-TRIFLUOROMETHYLPHENYL)-5-PHENYL-7H-DIBENZ[c,e]AZEPINE

\[
\begin{align*}
\delta_H (360 \text{ MHz}) & \quad 3.65(d, J 10.5 \text{ Hz}, 7-\text{H}); \\
4.98(d, J 10.5 \text{ Hz}, 7'-\text{H}); 7.33-7.60(m, 15\text{H}).
\end{align*}
\]
REFERENCES

43. K.N. Houk and J.C. Evanseck, unpublished calculations.

69. Ref. 5, supplement A.


71. A. Padwa, ref. 23, Chapter 12.


122. ref. 121, p. 250.


126. ref. 121, Chapter 2 and references cited therein.


