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Cycloaddition reactions of imidazolium and phthalazinium
dicyanomethanide 1,3-dipoles: synthesis, mechanism
and the effect of water

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Thesis presented for the Ph.D. Degree
of the
National University of Ireland

Department of Chemistry, National University of Ireland, Galway
May 2017

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Supervisors: Professor R.N. Butler, D.Sc.
Dr. Niall Geraghty
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Abstract

The cycloaddition reactions of imidazolium-3-dicyanomethanide 1,3-dipoles with electron poor alkene and alkyne dipolarophiles were explored. The reactions of these azolium 1,3-dipoles with alkyne dipolarophiles generated unstable initial cycloadducts that rearranged \textit{in situ} to yield ring expanded products. The imidazo[2,3-\textit{a}]pyridine products were formed as loss of aromaticity in the initial fused cycloadduct drove the subsequent ring expansion rearrangement. Single regioisomers were produced when unsymmetrical dipolarophiles were used in the reactions.

An imidazo[2,3-\textit{a}]pyridine product was also generated when the 1-methyl-imidazolium-3-dicyanomethanide 1,3-dipole was reacted with the electron poor alkene \textit{N}-phenylmaleimide. However, imidazolium-3-dicyanomethanide 1,3-dipoles reacted with maleic anhydride to form novel ylide products. These Michael Addition reactions generated unstable intermediates that underwent \textit{in situ} 1,2-rearrangement to form the new spirally twisted imidazolium ylide compounds.

The reaction of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 1,3-dipole with DMAD produced a stable initial cycloadduct that could be isolated under cold conditions. The initial cycloadduct easily underwent ring expansion rearrangement in solution at room temperature to form a 1,2,4-triazolo[4,5-\textit{a}]pyridine product. Tracking the rearrangement by NMR spectroscopy revealed the presence of an intermediate that could be seen to develop and decline as the initial cycloadduct converted into the ring expanded product.

The cycloaddition reaction of the phthalazinium dicyanomethanide 1,3-dipole with benzylidene acetone dipolarophiles was also examined in both acetonitrile and water. New 1,2-substituted tetrahydropyrrolo[2,1-\textit{a}]phthalazine derivatives were synthesized. The reactions produced two products, both with the aryl substituent on the C-2 position. The major product in each case had the aryl substituent in the \textit{endo} position.
The kinetics of the cycloaddition reactions of phthalazinium dicyanomethanide 1,3-dipole with benzylidene acetone dipolarophiles was also explored. Large rate accelerations were observed when the reactions were completed in aqueous acetonitrile rather than pure acetonitrile. Experimentally and theoretically derived Hammett plots ruled out increased polarity of the cycloaddition transition state as the cause of rate accelerations observed in the presence of water. The accelerations are most likely due to special hydrogen bonding effects.

Cycloaddition reactions involving solid phthalazinium dicyanomethanide 1,3-dipole and the solid dipolarophiles $p$-chlorobenzylidene acetone and $N$-phenylmaleimide were completed using pure water as the reaction solvent. The $p$-chlorobenzylidene acetone dipolarophile required liquefaction to allow the “on water” cycloaddition to proceed. Liquefaction of $N$-phenylmaleimide was not required as the dipolarophile had sufficient solubility in water to generate an oil layer. Solid-solid reactions have therefore been shown to be possible using the “on water” methodology.
Acknowledgments

Thanks to my parents, Francis and Marie, who supported me every step of the way.

My sincerest thanks to Prof. R.N. Butler whose guidance, patience and wisdom is both greatly appreciated and greatly missed. Ar dheis Dé go raibh a anam.

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I gratefully acknowledge the receipt of an IRCSET postgraduate research scholarship.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DEAD</td>
<td>Diethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless enhancement by polarization transfer</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional theory</td>
</tr>
<tr>
<td>DMAD</td>
<td>Dimethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>EP</td>
<td>Ethyl propiolate</td>
</tr>
<tr>
<td>EVK</td>
<td>Ethyl vinyl ketone</td>
</tr>
<tr>
<td>FMO</td>
<td>Frontier molecular orbital</td>
</tr>
<tr>
<td>GnCl</td>
<td>Guanidinium chloride</td>
</tr>
<tr>
<td>HFP</td>
<td>Hexafluoro-2-propanol</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest occupied molecular orbital</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>MP</td>
<td>Methyl propiolate</td>
</tr>
<tr>
<td>MVK</td>
<td>Methyl vinyl ketone</td>
</tr>
<tr>
<td>NOEDS</td>
<td>Nuclear Overhauser enhanced differential spectroscopy</td>
</tr>
<tr>
<td>RORC</td>
<td>Ring opening, ring closing</td>
</tr>
<tr>
<td>TCNEO</td>
<td>Tetracyanoethylene oxide</td>
</tr>
<tr>
<td>TCNE</td>
<td>Tetracyanoethylene</td>
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Dedicated to my parents, Francis and Marie
Chapter 1

Introduction: azolium and azinium
dicyanomethanide 1,3-dipoles
1.1 Introduction

The 1,3-dipolar cycloaddition is an important reaction in organic synthesis, used to generate a wide variety of heterocyclic rings. The generality of the reaction was discovered by Huisgen in the 1960s. A 1,3-dipole is a three atom π electron system with four π electrons delocalized over the three atoms. This three atom system can be made up of a variety of combinations of C, O, N and S. Cycloaddition to a 2π dipolarophile, a double or triple bond, generates a five membered heterocyclic ring (Figure 1).

![Figure 1](image_url)

The 1,3-dipolar cycloaddition is useful in synthesis due to its high regio- and stereoselectivity. Concerted 1,3-dipolar cycloadditions are stereospecific. A large number of dienes and dipolarophiles are potential substrates for the reaction, leading to a considerable range of products. The reaction is characterized by high yields under relatively mild conditions. It also displays insensitivity to solvent polarity, as the rate of concerted reactions does not vary greatly on changing the polarity of the solvent.

The term 1,3-dipole is derived from the fact that it is not possible to write electron-paired resonance structures for 4π electrons delocalized over three atoms without using charges in the structure. These charges are delocalized and interchangeable. The molecules themselves are not particularly polar. Many 1,3-dipoles contain a heteroatom as the central atom. This can be formally sp or sp³ hybridised depending upon whether or not there is a π bond orthogonal to the delocalized π system. This allows two categories of 1,3-dipoles to be defined. Those with an orthogonal π bond are linear in the ground state (Figure 2). This system can easily bend in the transition state, facilitating cycloaddition reactions with dipolarophiles. Examples of
Chapter 1

this class of dipole include benzonitrile oxide 1, as well as azides, nitrile ylides and diazo compounds.

\[
\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \quad \text{benzonitrile oxide 1}
\]

\[
\text{R}_1, \text{R}_2, \text{R}_3 \text{ can be lone pairs or substituents}
\]

**Figure 2**

Those without orthogonal π bonds are bent in the ground state (**Figure 3**). C,N-diphenyl nitrone 2 is shown as an example. Other dipoles of this kind include azomethine ylides, carbonyl ylides and ozone.

\[
\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \quad \text{R}_4 \quad \text{R}_5 \quad \text{C, N-diphenyl nitrone 2 (E-isomer)}
\]

\[
\text{R}_1-\text{R}_5 \text{ can be substituents or lone pairs}
\]

**Figure 3**

The stability of 1,3-dipoles varies with their ability to obtain octet stabilization. Dipoles containing an electron sextet at a carbon, nitrogen or oxygen atom are unstable. Stabilization is possible if a non-bonding pair of electrons can form an additional bond, thus relieving electron deficiency (**Table 1**).
Table 1: 1,3-Dipoles with octet stabilization

<table>
<thead>
<tr>
<th>Sextet Structure</th>
<th>Octet Structure</th>
<th>Remarks</th>
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<tr>
<td>$\hat{\text{C}}=\text{N}^+\text{C}^-$</td>
<td>$\text{C}≡\text{N}^+\text{C}^-$</td>
<td>nitrile ylides (nitrilium methanides)</td>
</tr>
<tr>
<td>$\hat{\text{C}}=\text{N}^-\text{O}^-$</td>
<td>$\text{C}≡\text{N}^-\text{O}^-$</td>
<td>nitrile oxides</td>
</tr>
<tr>
<td>$\text{N}^+\hat{\text{C}}=\text{O}^-$</td>
<td>$\text{C}≡\text{N}^+\text{O}^-$</td>
<td>azomethine ylides (iminium methanides)</td>
</tr>
</tbody>
</table>

If the central atom of the 1,3-dipole is a carbon, then internal octet stabilization is prevented by the lack of an available free electron pair. These 1,3-dipoles exist as short lived intermediates which can be trapped by reaction with in situ dipolarophiles.

Table 2: 1,3-Dipoles without octet stabilization

<table>
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<th>Sextet Structure</th>
<th>Octet Structure</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>$\text{N}^+\hat{\text{C}}=\text{N}^-$</td>
<td>$\text{C}≡\text{N}^+\text{N}^-$</td>
<td>imino carbenes</td>
</tr>
<tr>
<td>$\text{N}^+\hat{\text{C}}=\text{O}^-$</td>
<td>$\text{C}≡\text{N}^+\text{O}^-$</td>
<td>keto carbenes</td>
</tr>
<tr>
<td>$\text{N}^+\hat{\text{C}}=\text{N}^-$</td>
<td>$\text{N}^+\text{N}^-$</td>
<td>imino nitrenes</td>
</tr>
<tr>
<td>$\text{N}^+\hat{\text{C}}=\text{C}^-$</td>
<td>$\text{N}^+\text{C}^-$</td>
<td>vinyl nitrenes</td>
</tr>
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1.2 Synthesis of azinium and azolium dicyanomethane 1,3-dipoles

Dicyanomethane 1,3-dipoles were first reported by Linn and Webster in the 1960s. The first examples of this class of 1,3-dipole were based on six-membered heterocycles. Stable azinium dicyanomethane 1,3-dipoles were generated from pyridine 3, pyrazine 4, and isoquinoline 5. Boekelheide used a similar procedure to generate dicyanomethane 1,3-dipoles from five-membered rings such as 1-methylimidazole 6 and thiazole 7 (Figure 4).

![Figure 4](image)

Synthesis of these dicyanomethane 1,3-dipoles involves treatment of a tertiary aromatic base with tetracyanoethylene oxide 8 (TCNO). TCNO 8 can be produced by treating a cooled solution of tetracyanoethylene 9 with aqueous H₂O₂ 10 (Scheme 1).

![Scheme 1](image)
In contrast with normal epoxides, TCNEO 8 is not attacked by electrophilic reagents due to the presence of the strongly electron withdrawing cyano groups. It does however react readily with nucleophilic reagents. Formation of the ylides involves nucleophilic attack by a pyridine-type nitrogen of the aromatic base on the oxirane ring (Scheme 2). The reactivity of a heterocycle towards TCNEO 8 is governed by two key factors - the nucleophilicity of the nitrogen atom and the steric hindrance around the nitrogen atom. The nucleophilicity of a heterocycle depends on its structure and on the electrophile it is attacking. However, its variation generally parallels the basicity, and basic pKa values have been used as a guide to nucleophilicity. It has been shown that the nucleophilic reactivity of aromatic heterocycles with five- or six-membered rings increases monotonically with basic pKa.8

The reactivity of heterocycles towards TCNEO 8 is therefore found to increase with basicity and decrease with steric hindrance. Only one dicyanomethanide group can be transferred to diazine and diazole rings as its presence lowers the nucleophilic electron density at the second ring nitrogen. Several alternative methods of dicyanomethanide 1,3-dipole synthesis have been proposed. Leonte and Zugravescu9 generated the pyridinium dicyanomethanide 1,3-dipole 11 by treating the pyridinium alkoxy carbonylcyanomethanides 12 with methyl bromocyanooacetate 13 (Scheme 3). Phenyliodonium dicyanomethanide10 14a or its conjugate acid 14 has also been used to transfer a dicyanomethanide group to pyridine 3, as well as various substituted pyridine and isoquinoline heterocycles (Scheme 3).
1.3 Structure of azinium and azolium 1,3-dipoles

The first structural study on an azinium 1,3-dipole was reported by Bugg et al.$^{11,12}$ The X-ray crystal structure of pyridinium dicyanomethanide 1,3-dipole 11 proved to be non-planar. The observed dimensions of the molecule are shown below (Figure 5). The C-C and C-N bond lengths displayed by the pyridine ring were shown to be similar$^{13}$ to bond lengths associated with pyridine 3.
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The two cyano groups were found to be inclined, with the carbon and nitrogen atoms being 0.08 Å and 0.13 Å from the pyridinium ring plane respectively. The C(5)-C(6)-N(7) unit therefore makes an angle of 3˚ with respect to this plane. Computational studies by Karzazi et al.\textsuperscript{14} have shown that planarity in cycloimmonium ylides is determined by the size of the electron withdrawing groups bound to the ylidic carbon. Dicyanomethanide 1,3-dipoles, bearing two small cyano groups, display a small angle between the pyridinium plane (P1) and the anion plane (P2). Replacement of one of the cyano groups with a more bulky CONH\textsubscript{2} group to form amidocyano-pyridinium methanide \textbf{15 (Figure 6)}, causes the angle between P1 and P2 to increase to 15.45˚. When two bulky groups are bound to the ylidic carbon, as in di-trifluoroacetyl-pyridinium methanide \textbf{16 (Figure 6)}, P1 is almost perpendicular to P2 (97˚).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Bond distances (Å) and angles in pyridinium dicyanomethanide 11. (bond distances quoted to two decimal places only)}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Figure 6}
\end{figure}
The value of 1.13 Å for the pyridinium dicyanomethanide 1,3-dipole 11 C(6)-N(7) bond is shorter than for a normal C-N triple bond (Figure 5). The bond length is similar to those measured for the dicyanomethanide groups of related zwitterions such as the tributylphosphine adduct of 4-chlorobenzylidenemalonitrile 17 and carbanions such as the lithium/hexamethylphosphoric triamide complex of malononitrile 18 (Figure 7). This indicates that the dicyanomethanide group of 11 possesses substantial anionic character. IR data also supports this conclusion, as the cyano stretching bands of 11 (2182, 2145 cm⁻¹)¹⁵ are considerably lower than those of molecules containing typical nitrile groups (2280-2220 cm⁻¹).¹⁶ Azolium dicyanomethanide 1,3-dipoles show similar cyano stretching bands.

Independent computational studies¹⁵,¹⁷ have shown that the ylidic carbon of 11 is insignificantly charged, while the ylidic nitrogen bears a small positive charge. It has also been concluded from these calculations that the cyano groups are negatively charged. Azinium 1,3-dipoles are highly stable species, with characteristically high melting points. The strong delocalization of positive charge on the aromatic ring and negative charge on the carbanion is the primary reason for the stability of dicyanomethanide 1,3-dipoles. Other factors which determine cycloimmonium ylide stability,¹⁸ such as the Coulomb attraction and the resonance interaction between the heterocycle and the negative carbanion system may also contribute to the dipole stability. It is of interest that the corresponding unsubstituted–azinium and azolium
methanide (CH$_2$) 1,3-dipoles, obtained by treating trimethylsilylmethyl trifluoromethane sulfonate salts with CsF$^{19-21}$ e.g. 19 and 20, have only fleeting existence and must be generated in the presence of excess dipolarophile in order to achieve useful synthesis (Figure 8).

![Figure 8](image)

Also of interest in the structure of compound 11 is the length of the N(4)-C(5) bond (Figure 5). The experimental value obtained, 1.42 Å, is shorter than that expected for a single C(sp$^2$)-N(sp$^2$) bond. Matsumoto$^{22, 23}$ has investigated the factors affecting this bond length in some detail. Electron withdrawing groups increase the double bond character of the ylidylic C-N bond. This is borne out by X-ray crystallographic studies$^{22}$ on 4-methylpyridinium dicyanomethanide 1,3-dipole 21 and 4-acetylpyridinium dicyanomethanide 1,3-dipole 22, which display slightly longer (1.427 Å) and slightly shorter ylidylic C-N bond lengths (1.415 Å), respectively, than the parent pyridinium dicyanomethanide 1,3-dipole 11. The diazinium dicyanomethanides display even shorter ylidylic C-N bonds, pyridazinium dicyanomethanide 1,3-dipole 23 having a bond length of 1.403 Å while pyrazinium dicyanomethanide 1,3-dipole 24 has a bond length of 1.404 Å (Figure 9).
1.4 Some cycloaddition reactions of azinium and azolium dicyanomethanide 1,3-dipoles

1.4.1 Reactions with symmetrical acetylenic dipolarophiles
Linn and Webster’s\textsuperscript{5} first cycloadditions with dicyanomethanide 1,3-dipoles involved the use of dimethyl acetylenedicarboxylate 25 (DMAD) as dipolarophile. The reaction of pyridinium dicyanomethanide 11 with DMAD 25 yielded a single product 27 in 48\% yield. The expected initial cycloadduct 26 was not observed as 1,4-elimination occurred to generate 27 with \textit{in situ} loss of HCN (Scheme 4).
The first cycloaddition reactions of azolium dicyanomethanide 1,3-dipoles were reported by Boekelheide and Fedoruk. The 1-methylimidazolium dicyanomethanide 1,3-dipole 28 and thiazolium dicyanomethanide 1,3-dipole 29 were reacted with DMAD 25. In both cases, a single ring-expanded product was obtained (Scheme 5). The structures of products 30 and 31 were assigned on the basis of their $^1$H NMR and UV spectra. The mechanism of this intriguing ring-expansion rearrangement will be the subject of more detailed discussion in Chapter 2.
Linn and Webster\textsuperscript{5} also studied the reaction of isoquinolinium dicyanomethanide 32 with DMAD 25. Two products were isolated, both 1:1 adducts. Product 33 was formed in a similar manner to 27, by \textit{in situ} elimination of HCN from the direct cycloadduct (Scheme 6). However, the second product was originally assigned the wrong structure. On the basis of the ring-expanded products obtained by Boekelheide\textsuperscript{6} it was assumed that a similar rearrangement had occurred. Re-examination of this reaction by Basketter and Plunkett\textsuperscript{24} led to the conclusion that the second product of the reaction is in fact compound 34 (Scheme 6). Kobayashi\textsuperscript{25} subsequently confirmed the structure of 34. This product is formed as the initial cycloadduct undergoes a 1,3-H shift, thereby restoring conjugation. This 1,3-H shift is not allowed suprafacially by Woodward and Hoffman HOMO orbital symmetry and may be solvent assisted. A 1,2-elimination of HCN from product 34 does not occur under the conditions studied and the product is stable.
Mättner and Neunhoeffer\textsuperscript{26} succeeded in isolating the initial cycloadducts formed in the reactions between various substituted 1,2,3-triazinium-2-dicyanomethanide 1,3-dipoles 35 and DMAD 25. The reactions, which were carried out under solvent free conditions, yielded bicyclic compounds 36 that were stable under inert gas at 0\(^\circ\)C (Scheme 7). The compounds proved to be unstable in solution, as rearrangement followed by oxidation led to destruction of the triazine ring.
The pyridinium dicyanomethanide 11 has also been reacted with electron rich dipolarophiles. Matsumoto has treated the 1,3-dipole 11 with benzyne$^{27, 37}$ and cyclooctyne$^{28}$ 38 (Scheme 8). The products 39 and 40 arose from in situ elimination of HCN after the cycloaddition step. These reactions have been described as HOMO$_{dipole}$-LUMO$_{dipolarophile}$ controlled without any mechanistic study.$^{27, 28}$

\[
\begin{align*}
\text{Scheme 8}
\end{align*}
\]

1.4.2 Reactions with unsymmetrical acetylenic dipolarophiles

The reaction of pyridazinium dicyanomethanide 23 with cyanoacetylene 41 was investigated by Sasaki et al.$^{29}$ (Scheme 9). The initial cycloadduct proved unstable, and in situ elimination of HCN yielded the final product 42 in 30% yield. Only one regioisomer was obtained.
Chapter 1

Scheme 9

The reaction of isoquinolinium dicyanomethanide 1,3-dipole 32 with methyl propiolate (MP) 43 was investigated separately by Basketter and Plunkett\(^ {24} \) and Matsumoto.\(^ {30} \) Both isolated a single regioisomer 44 (Scheme 10). The unsubstituted terminus of the dipolarophile was attached to the dicyanomethanide terminus of the 1,3-dipole. The initial cycloadduct was unstable, and so in situ elimination of HCN occurred. The regiochemistry is consistent with HOMO\(_{\text{dipole}}\)-LUMO\(_{\text{dipolarophile}}\) control.

Scheme 10

The phthalazinium-2-dicyanomethanide 1,3-dipole 45 has been extensively studied in these laboratories.\(^ {31-34} \) It has been determined that dipole 45 is a Sustmann type II dipole. It can react via normal or inverse electron demand. The change in mechanism\(^ {33} \) is accompanied by a change in regiochemistry (Scheme 11). The reaction between 1,3-dipole 45 and the electron rich dipolarophile phenyl acetylene 46 is LUMO\(_{\text{dipole}}\) controlled and generates a single product (Scheme 11). However, the reaction of 45 with the electron poor dipolarophile methyl propiolate 43 is HOMO\(_{\text{dipole}}\) controlled and produces a single compound 48.\(^ {33} \)
Elguero et al.\textsuperscript{35} have investigated the reactions of $N$-substituted benzimidazolium dicyanomethanide 1,3-dipoles 49 and 50 with unsymmetrical dipolarophiles. 1-Methylbenzimidazolium dicyanomethanide 1,3-dipole 49 was reacted with the electron rich dipolarophile phenyl acetylene 46 to yield the single regioisomer 51 in 8\% yield (Scheme 12). The reaction of 1-ethylbenzimidazolium dicyanomethanide 1,3-dipole 50 with the electron poor dipolarophile methyl propiolate also yielded a single regioisomer 52, in 25\% yield (Scheme 12). Both structures arose from a complex ring-expansion rearrangement in the initial cycloadduct.
Matsumoto\textsuperscript{36} has reacted pyridinium dicyanomethanide 1,3-dipole 11 with the unsymmetrical electron rich dipolarophile 3,4-pyridyne 53 (Scheme 13). Only one regioisomer 54, generated from \textit{in situ} loss of HCN from the cycloadduct, was isolated. The product was obtained in 27\% yield.
1.4.3 Reactions with alkenes

The stereochemistry of the cycloaddition reactions of phthalazinium-2-dicyanomethanide 1,3-dipole 45 has been investigated using various alkene dipolarophiles. Treatment of 45 with electron poor N-substituted maleimides\textsuperscript{33} led to the isolation of single products 55 displaying *endo* stereochemistry (Scheme 14). The stereochemistry was assigned by nuclear Overhauser enhancement difference spectra (NOEDS). An X-ray crystal structure of the product obtained from the reaction of 45 with N-(*t*-butyl) maleimide confirmed the assigned structure (Figure 10). The presence of the *t*-butyl group did not influence the stereochemical outcome nor did a variety of other R groups.

![Scheme 14](image)

**Figure 10:** X-Ray crystal structure of compound 55 (R=\textsuperscript{t}Bu)
Chapter 1

Phthalazinium-2-dicyanomethanide 1,3-dipole 45 has also been treated with a number of unsymmetrical olefinic dipolarophiles.\textsuperscript{33} The reaction of 45 with the electron rich dipolarophile \textit{n}-butyl vinyl ether 56 led to the isolation of a single regioisomer 57 in 86\% yield (Scheme 15). This product displays the same regiochemistry as the products obtained from unsymmetrical electron rich alkynes. The stereochemistry on the C-2 position was found to be \textit{exo} on the basis of NOEDS. This was later confirmed with an X-ray crystal structure (Figure 11).

![Scheme 15](image)

**Figure 11:** X-ray crystal structure of compound 57
Tsuge et al.\textsuperscript{37} have explored the reactions of the thiazolium dicyanomethanide 1,3-dipole \textsuperscript{29} with dimethyl fumarate \textsuperscript{58}, dimethyl maleate \textsuperscript{59} and \textit{trans}-1,2-dibenzoylethylene \textsuperscript{60}. The reactions yielded only the \textit{endo} stereoisomers \textsuperscript{61, 62, 63} (Scheme 16).

![Scheme 16]

Reactions between thiazolium dicyanomethanide 1,3-dipole \textsuperscript{29} and \textit{N}-substituted maleimides were found to yield mixtures of the \textit{endo} and \textit{exo} isomers. It was concluded that the \textit{endo} product was isomerising into the \textit{exo} product.\textsuperscript{38}
1.4.4 Double cycloadditions

The reactions of dicyanomethanide 1,3-dipoles with methylene cyclopropanes bearing unsaturated substituents at the 4-position are of interest as they provide the first examples of double cycloadditions that include at least one 1,3-dipolar cycloaddition.\(^ {37}\) The reaction of 1-methylimidazolium dicyanomethanide 28 with 2-benzoyl-2-(1',2'-diphenyl-3'-cyclopropenylidene) acetonitrile 64 yields a single pentacyclic caged structure\(^ {39}\) 66 in 76% yield (Scheme 17).

The first step is the stereo- and regiospecific 1,3-dipolar cycloaddition of 28 across the endocyclic double bond of 64. The cycloadduct 65 formed is unstable due to the loss of aromaticity in the imidazolium ring. An intramolecular Diels-Alder reaction subsequently occurs across the newly formed olefinic double bond, yielding the cage

![Scheme 17](image-url)
compound 66. The thiazolium dicyanomethanide 1,3-dipole\textsuperscript{40} 29 and pyridinium dicyanomethanide 1,3-dipole\textsuperscript{41} 11 have been reported to react with 64 to form similar products.

### 1.5 Kinetic studies

Kinetic studies on dicyanomethanide 1,3-dipoles are quite rare. Sauer et al.\textsuperscript{42} have reported on kinetic investigations of various monocyclic and bicyclic dicyanomethanide 1,3-dipoles. The reactions of the substituted dihydropyridazinium dicyanomethanide 1,3-dipole 67 with cyclooctyne 38, ynamine 68 and DMAD 25 were studied (Figure 12).

![Chemical Structures](image)

**Figure 12**

<table>
<thead>
<tr>
<th>1,3-Dipole 67</th>
<th>Cyclooctyne 38</th>
<th>Ynamine 68</th>
<th>DMAD 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. R= -C\textsubscript{6}H\textsubscript{4}-OMe</td>
<td>122</td>
<td>574</td>
<td>2.94</td>
</tr>
<tr>
<td>b. R= -C\textsubscript{6}H\textsubscript{4}-Me</td>
<td>240</td>
<td>1210</td>
<td>3.96</td>
</tr>
<tr>
<td>c. R= -C\textsubscript{6}H\textsubscript{5}</td>
<td>436</td>
<td>2140</td>
<td>4.02</td>
</tr>
<tr>
<td>d. R= -C\textsubscript{6}H\textsubscript{4}-Cl</td>
<td>799</td>
<td>5180</td>
<td>5.11</td>
</tr>
<tr>
<td>e. R= -C\textsubscript{6}H\textsubscript{4}-CF\textsubscript{3}</td>
<td>2080</td>
<td>15300</td>
<td>7.72</td>
</tr>
</tbody>
</table>

*Table 3: Kinetic rate data for 1,3-dipoles 67a-e with dipolarophiles 25, 38 and 68 in dioxane; values for k\textsubscript{2} (dm\textsuperscript{3} mol\textsuperscript{-1}s\textsuperscript{-1})/10\textsuperscript{4}.*
The 1,3-dipoles 67a-e (Table 3) react preferentially with electron rich dipolarophiles such as 38 and 68. There is a marked decline in the rate constants for the reactions with the electron poor DMAD 25. Variation of the dipole substituents has a profound effect on the reaction rates. The dipoles 67a-b bearing electron donating substituents display slower rates than those with electron withdrawing substituents 67d-e. It can therefore be concluded that these cycloadditions are under LUMO\textsubscript{dipole}-HOMO\textsubscript{dipolarophile} control. The small positive Hammet \( \rho \)-values obtained for these reactions suggest that the reactions are inverse electron demand cycloadditions (Table 4) involving the LUMO\textsubscript{dipole}-HOMO\textsubscript{dipolarophile} interaction. Electron withdrawing substituents enhance the reactions by lowering the LUMO\textsubscript{dipole} energy level. The 1,3-dipoles 67a-e are therefore Sustmann type III.

Table 4: The Hammet \( \rho \)-values for the cycloadditions of 67a-e with cyclooctyne 38, ynamine 68 and DMAD 25

<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>Hammet ( \rho )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclooctyne 38</td>
<td>1.44</td>
</tr>
<tr>
<td>Ynamine 68</td>
<td>1.69</td>
</tr>
<tr>
<td>DMAD 25</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Extensive kinetic studies\textsuperscript{34, 43, 44} have been undertaken in this Department on the phthalazinium-2-dicyanomethanide 1,3-dipole 45 and the pyridazinium dicyanomethanide 1,3-dipole 23. The former was found to be a Sustmann type II case while the later was a Sustmann type I species, reacting only with electron poor dipolarophiles. In particular, the effect of water on cycloaddition rates was examined. The introduction of water as cosolvent into cycloaddition reactions of pyridazinium dicyanomethanide 23 and phthalazinium-2-dicyanomethanide 45 in acetonitrile gave small initial rate enhancements followed by larger rate increases as the mole fraction of the solvent mixture approached pure water. The influence of water on the rates was about 10 times larger for some dipolarophiles, and these dipolarophiles, which were mainly vinyl ketones, were classified as water-super because of this. Other dipolarophiles, such as vinyl esters and vinyl nitriles showed
smaller water effects and were classed as water-normal. One of the aims of this thesis (Chapter 3) was to explore whether water-induced changes in the polarity of the cycloaddition transition state might contribute to the distinction between water-super and water normal reactions for a fixed 1,3-dipole.

Azinium and azolium 1,3-dipoles are synthetically important molecules as the loss of aromaticity in their fused cycloadducts often leads to interesting rearrangements. Typically, the initial cycloadducts of azinium dicyanomethanide 1,3-dipoles re-establish aromaticity by the in situ elimination of HCN (Scheme 4). The loss of aromaticity in the fused cycloadducts of azolium 1,3-dipoles drives an interesting ring-expansion rearrangement (Scheme 5). The mechanism of this intriguing rearrangement has received very little attention in the literature. Another aim of this thesis was to explore the synthetic and mechanistic features of the cycloadditions and subsequent ring expansions of 1,3-dipole 28 and some related molecules (Figure 13).
Chapter 2

Synthetic and mechanistic studies on the
cycloaddition reactions of imidazolium
dicyanomethanide 1,3-dipoles and the 1-phenyl-
1,2,4-triazolium-4-dicyanomethanide 1,3-dipole
2.1 Introduction

Cycloaddition reactions are among the most important reactions in all of organic chemistry. The generation of new ring systems is of particular importance to the pharmaceutical industry, which strives to create novel biologically active molecules. The hetero Diels-Alder and the Huisgen 1,3-dipolar cycloaddition are fundamental chemical reactions which may be used in the construction of heterocyclic rings.

The Diels-Alder reaction\(^{45}\) involves the cycloaddition of a conjugated \(4\pi\) 1,3-diene and a \(2\pi\) dienophile to form a six membered ring (Figure 14). The discoverers of the reaction, Otto Diels and Kurt Alder, received the Nobel Prize for their work in 1950. The 1,3-dipolar cycloaddition was pioneered by Huisgen in the 1960s\(^{1,2}\) and is a remarkably efficient and versatile reaction used in the construction of five-membered heterocycles. Such heterocycles are subunits found in numerous natural products and in many pharmaceuticals. The reaction is capable of generating complex structures with new chiral centres, making it an invaluable tool for asymmetric synthesis.

The majority of 1,3-dipolar cycloadditions are considered to be concerted reactions that proceed in accordance with the Evans principle.\(^{46}\) This states that thermal pericyclic reactions take place preferentially via an aromatic transition state. The mechanism can be viewed in terms of the Frontier Molecular Orbital (FMO) Theory approach\(^{47}\) similar to the Diels-Alder reaction. The reactions are characterized by high negative entropies\(^{48}\) and moderate enthalpies,\(^{49}\) indicating a highly ordered
transition state. The reaction rate is typically unaffected by changes in solvent polarity.\(^{50}\) The cycloaddition reaction is generally thought to proceed through an asynchronous transition state in which one of the new \(\sigma\)-bonds is more developed than the other (Figure 15).

![Diagram of the cycloaddition reaction](image)

6\(\pi\) transition state

Figure 15

An alternative to the one step concerted cycloaddition was proposed by Firestone\(^{51}\) who suggested that a diradical intermediate was formed which rapidly closed stereospecifically if generated in the correct conformation. This theory is generally not accepted\(^{52}\) as FMO provides a better explanation for the reactivity and regioselectivity of these reactions on the basis of the concerted \((\pi 4s + \pi 2s)\) mechanism. However stepwise cycloadditions involving both biradical intermediates\(^{53}\) and zwitterionic intermediates\(^{54}\) have been discovered. Huisgen\(^{55}\) has demonstrated that a spectrum of 1,3-dipolar mechanisms exist, ranging from fully concerted to two-step processes. However the majority are asynchronous concerted reactions and it is only in cases with specially selected substituents that the two-step reactions are encountered.

### 2.1.1 Frontier molecular orbital theory and Sustmann classification

Frontier molecular orbital theory is a powerful tool for understanding the different reactivities of 1,3-dipoles with different dipolarophiles. In FMO theory,\(^{47}\) only the highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbitals (LUMO) of both reactants are considered during bond formation. The theory can only be applied to a reaction with a concerted mechanism which proceeds through a single transition state. No intermediates are formed and the symmetry of
the frontier orbitals is conserved in the change to products. Any other orbital interactions between the occupied and unoccupied orbitals of the reactants are ignored. Generally, the HOMO of one reactant reacts with the LUMO of the other. The favoured interaction occurs between those orbitals with the lowest HOMO-LUMO energy gap.

The actual energy of the frontier orbitals is determined by both the skeletal atoms and the substituents of the molecule in question. Electron withdrawing groups such as ketones and esters lower the energies of molecular orbitals. Electron donating groups, on the other hand, raise the energies of the molecule’s orbitals. Different substituents can therefore play a significant role in the outcome of a reaction.

Sustmann\textsuperscript{56, 57} has classified 1,3-dipolar cycloadditions into three categories based on the relative FMO energies of the dipole and the dipolarophile (Figure 16).

**Type I:** HOMO\textsubscript{dipole}-LUMO\textsubscript{dipolarophile} interaction is dominant.  
(normal electron demand)

**Type II:** Both HOMO-LUMO gaps are approximately equal.  
(neutral electron demand)

**Type III:** LUMO\textsubscript{dipole}-HOMO\textsubscript{dipolarophile} interaction is dominant.  
(inverse electron demand)
2.1.2 Regiochemistry of 1,3-dipolar cycloadditions

A 1,3-dipolar cycloaddition can potentially produce a mixture of products. Regiochemistry is concerned with the way in which the dipolarophile adds onto the 1,3-dipole. In the case of an unsymmetrical dipolarophile, there may be two regioisomers (Figure 17).

However, most 1,3-dipolar cycloadditions are highly selective and give only one of the two possible regioisomers. Two key pieces of information are required in order to determine the preferred product of a 1,3-dipolar cycloaddition.

- The dominant HOMO-LUMO interaction between the two reactants
- The orbital coefficients of the reactants
In the addition of diazomethane 69 to methyl methacrylate 70 the dominant interaction is $\text{HOMO}_{\text{dipole}}-\text{LUMO}_{\text{dipolarophile}}$. The reaction can potentially produce two regioisomers, compounds 71 and 72 (Scheme 18). However, only compound 71 is isolated as the dominant frontier orbitals both have larger atomic orbital coefficients on the CH$_2$ carbons rather than at the other termini. In cycloaddition reactions the bonding of atoms with the largest atomic orbital coefficients leads to a more stable transition state, and so is favoured energetically.

![Scheme 18](image)

**2.1.3 Azolium 1,3-dipoles**

The scope of 1,3-dipoles has been further extended by the development of 1,3-dipoles where two of the four $\pi$-electrons are part of an azole ring. Azolium 1,3-dipoles are of interest because the loss of azole aromaticity in the fused cycloadducts derived from them often leads to unexpected rearrangements (Scheme 19).

![Scheme 19](image)
In many cases, the initial 1,3-dipolar cycloaddition is followed by multi-step rearrangements. The complexity of these rearrangements was not always appreciated in the early reports, and so many products were erroneously described as the simple primary adducts. The 1,3-dipolar cycloadditions of various azolium 1,3-dipoles have been studied extensively in these labs. The reactions of the 1,2,3-triazolium-1-aminide 1,3-dipole 73 with a range of dipolarophiles involve interesting rearrangements (Scheme 20).

The initial cycloadduct 74 (Scheme 20) is particularly unstable due to the presence of the extremely labile exocyclic N-N bond. The adduct undergoes 1,4-sigmatropic rearrangement to give the fused structure 75, referred to as the first generation product. This may in turn be converted into the second generation product 76 if structural changes occur in situ or are induced. The 1,4-sigmatropic rearrangement is a nitrogen analogue of the ubiquitous 1,5-rearrangements of 1,3-diene systems allowed by Woodward-Hoffmann HOMO symmetry. In the C-analogue, four $\pi$-electrons are delocalised over four C-atoms, leading to a 1,5-migration over two $\pi$-
bonds. In the heteroanalogue, the four π-electrons are delocalised over three atoms, thus causing the 1,4-shift instead of the 1,5-migration.

The 1,2,3-triazolium-1-aminide 73 is a type I 1,3-dipole\textsuperscript{64} and reacts with a wide range of 2π systems, examples of which are shown below (Scheme 21).\textsuperscript{59, 61, 62} The reactions show a high degree of stereo- and regioselectivity in all cases.

![Scheme 21](image)

In some cases, further rearrangements can be induced in the first generation products.\textsuperscript{59} Compound 85, produced using DMAD 25 as dipolarophile, can be converted into the second generation product 90 on heating in decalin at 175 °C (Scheme 22).\textsuperscript{65}
However, when the unsymmetrical alkyne dipolarophiles methyl propiolate and ethyl propiolate were reacted with the 1,3-dipole 73 a mixture of first and second generation products was obtained (Scheme 22). The second generation products 93 and 94 were found to be the major products. In each case the reaction proved to be regiospecific. The first generation products 91 and 92 possess a H atom at C-5 and a double bond at C-5 and C-6 and are highly labile, rearranging *in situ* with ring expansion. The proposed mechanism involves a dipolar intermediate 95 which arises from heterolytic cleavage of the C(3a)-N(4) bond in the first generation product (Scheme 23). Compound 85 is stable due to the presence of a carboxymethyl group instead of a H atom at C-5, and so further heating is required to induce rearrangement.
2.1.4 Imidazolium ylides

Boekelheide and Fedoruk pioneered the use of imidazolium 1,3-dipoles in cycloaddition reactions. The first reported\textsuperscript{6} imidazolium ylide was synthesized by the treatment of 1-methylimidazole \textbf{6} with phenacyl bromide \textbf{96} which yielded 1-methyl-3-phenacylimidazolium bromide \textbf{97} (Scheme 24).

The ylide \textbf{98} was then generated by treating a solution of the imidazolium bromide \textbf{97} in dimethylformamide with anhydrous potassium carbonate. The ylide \textbf{98} proved to be unstable, and could not be isolated. Instead, it was trapped \textit{in situ} by reaction with ethyl propiolate (Scheme 25). The initial cycloadduct \textbf{99} formed from this cycloaddition also proved to be unstable, as dehydrogenation gave rise to the aromatised 1,3a-diazapentalene \textbf{100}. A single regioisomer was isolated.
The reactions of substituted benzimidazolium methanides\textsuperscript{68} demonstrate the range of products that can arise due to rearrangement of the initial cycloadduct. Treatment of 1-methyl-3-phenacylbenzimidazolium bromide \textbf{101} with base generates the corresponding benzimidazolium methanide 1,3-dipole \textbf{102}. This can be trapped \textit{in situ} with DMAD \textbf{25} to yield a mixture of \textbf{103} and \textbf{104} (Scheme 26). These products are formed following rearrangement of the initial cycloadduct. This rearrangement may occur due to oxidation arising from the presence of excess dipolarophile or ring opening to form an intermediate.
Treating the corresponding 1-methyl-3-ethoxycarbonylmethyl benzimidazolium bromide 105 with DMAD 25 under the same conditions generates an initial cycloadduct which undergoes loss of a molecule of ethanol to produce the stable final product. This compound has been the subject of some confusion. Initially, Ogura and Kikuchi\(^{68}\) proposed that compound 108 was the final product of the reaction (Scheme 27). The proposed mechanism involves ring opening of the initial cycloadduct 106 to generate 107, which subsequently loses ethanol in a nucleophilic ring closure (Scheme 27). The authors reported that the mechanism was similar to that proposed by Boekelheide and Fedoruk\(^6\) for the reaction of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 with DMAD 25 (Scheme 5).
This was disputed by Zugravescu, who alternatively proposed the novel structure 109 on the basis of UV, IR and $^1$H NMR data (Figure 18).
Both of these structures were subsequently disproved by Meth-Cohn,\textsuperscript{70} on the basis of a \textsuperscript{13}C NMR spectrum of the product. The \textsuperscript{13}C NMR data immediately ruled out the benzimidazole-type structure \textit{109} as no low field signal characteristic of the C-2 of benzimidazole was observed. The 1,3-dipole \textit{105} was also prepared with a \textsuperscript{13}C label at the 2-position. The product obtained from the reaction this dipole contained a labelled CH group with long range coupling to two ester groups and one quaternary carbon (\textbf{Scheme 28}). Meth-Cohn\textsuperscript{70} proposed that the initial cycloadduct \textit{106} is converted into the pyrrole \textit{110}, following the tautomeric shift of an acidic proton. This intermediate \textit{110} can then cyclise to the pyrroloquinoxaline \textit{111} with loss of ethanol (\textbf{Scheme 28}).
2.1.5 Project outline

Our long standing interest in the rearrangements of azolium 1,3-dipoles led us to explore the imidazolium dicyanomethanide 1,3-dipole system in more detail. Having previously confirmed the structure of the ring expanded products by X-Ray crystallography, we explored the generality of this rearrangement by synthesizing a series of similar compounds. The regiochemistry of these reactions was investigated by the use of unsymmetrical dipolarophiles. Further interesting results were observed by using alkenes as dipolarophiles. The reactions of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 and 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112 with maleic anhydride yielded interesting structures that provided new insights into this intriguing rearrangement. In order to probe the reaction mechanism it was necessary to isolate the initial cycloadduct, and then monitor the rearrangement by spectroscopic methods. Elguero\textsuperscript{35} has previously isolated the initial cycloadduct from the reaction of an azolium dicyanomethanide 1,3-dipole and DMAD 25. Studying this reaction allowed us to both confirm Elguero’s original assignment and to follow the rearrangement of the initial cycloadduct by \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopy. Tracking the conversion of initial cycloadduct to ring-expanded product shed new light on this intriguing rearrangement.
2.2 Synthesis of imidazolium dicyanomethanide 1,3-dipoles

As discussed previously (Section 1.2), tetracyanoethylene oxide (TCNEO) 8 has been used to generate a wide variety of azinium and azolium dicyanomethanide 1,3-dipoles.4-7, 26 TCNEO 8 can be efficiently synthesized4, 5 by the action of hydrogen peroxide 10 on tetracyanoethylene (TCNE) 9 (Scheme 1). A solution of TCNE 9 in acetonitrile was cooled to -5 °C and treated dropwise with an equimolar amount of H2O2 10 (30%), such that the temperature of the reaction remained below 12 °C. Following completion of the addition, the reaction mixture was stirred for a further 5 min before being diluted with ice-cold water. This caused the precipitation of TCNEO 8 as a white solid which was collected by filtration. TCNEO 8 slowly evolves hydrogen cyanide when exposed to moist air at room temperature, and so must be used quickly.

2.2.1 Synthesis of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28

The procedure described by Boekelheide6 was used to prepare 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28. A cooled solution of TCNEO 8 in ethyl acetate was treated dropwise with an equimolar amount of 1-methylimidazole 6, neat or in ethyl acetate, such that the reaction temperature remained below 10 °C (Scheme 29). Following addition of the heterocyclic base, the dipole separated from solution as a pale brown solid in 65% yield, and was collected by filtration. The structure was supported by IR, 1H and 13C NMR spectroscopy.
The IR spectrum contained two strong cyano bands at 2180 and 2134 cm\(^{-1}\). In the \(^1\)H NMR spectrum, the proton of C-2 showed the greatest deshielding and appeared at \(\delta\) 9.08. Only one signal at 123.2 ppm was observed for the two cyano groups in the \(^{13}\)C NMR spectrum. Theoretical calculations carried out in collaboration with Professor Luke Burke of Rutgers University have indicated\(^{71}\) that barrier of rotation in the exocyclic N-C bond is less that 1 kcal/mol. This suggests that resonance form \(28A\) is the appropriate suitable representation of the ylide, as only one \(^{13}\)C NMR signal would be expected for the equivalent cyano groups. If the resonance form \(28B\) represented the structure of the 1,3-dipole, then the \(^{13}\)C NMR spectrum would be expected to show separate signals for the cyano groups, which would be non-equivalent (Figure 19).

![Figure 19](image)

In the \(^{13}\)C NMR spectrum a very weak signal at 60.3 ppm was observed for the methanide carbon. These signals are typically quite weak and have not been widely reported.\(^{72}\) A pulse delay of 3 seconds and a large number of scans (17,000) were required to detect the signal.
Chapter 2

1H NMR (DMSO-d$_6$)  

![1H NMR spectrum](image)

13C NMR (DMSO-d$_6$)  

![13C NMR spectrum](image)

**Figure 20:** 1H NMR and 13C NMR assignments for compound 28

2.2.2 Synthesis of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole

The 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112 has not been reported in the literature to date. It was prepared by treating a cooled solution of 1-benzylimidazole 113 in ethyl acetate with TCNE 8 also in cooled ethyl acetate. (Scheme 30).

![Scheme 30](image)

The product precipitated from solution as a brown solid in 73% yield. The structure was supported by IR, 1H and 13C NMR spectroscopy. Two strong cyano bands at 2160 and 2180 cm$^{-1}$ were observed in the IR spectrum. In the 1H NMR spectrum, the proton on C-2 showed the greatest deshielding and appeared at δ 9.33. The two cyano groups are equivalent, and so only one cyano signal at 123.0 ppm appeared in the 13C NMR spectrum. Despite extensive efforts, the methanide carbon signal was not detected. It is possible that the carbon is relaxing at a very slow rate, and because
of this the signal may be too weak to be seen due to saturation. The NMR assignments are shown below (Figure 21).

**1H NMR (DMSO-d$_6$)**

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Multiplicity</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.73 (dd, 1H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.64 (dd, 1H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.32-7.39 (m, 5H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.33 (s, 1H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.30 (s, 2H)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**13C NMR (DMSO-d$_6$)**

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>123.0</td>
<td></td>
</tr>
<tr>
<td>124.7</td>
<td></td>
</tr>
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<td>122.6</td>
<td></td>
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<td>136.4</td>
<td></td>
</tr>
<tr>
<td>52.1</td>
<td></td>
</tr>
<tr>
<td>128.3</td>
<td></td>
</tr>
<tr>
<td>128.7</td>
<td></td>
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<tr>
<td>129.0</td>
<td></td>
</tr>
<tr>
<td>134.9</td>
<td></td>
</tr>
<tr>
<td>132.6</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 21:** 1H NMR and 13C NMR assignments for compound 112

### 2.2.3 Synthesis of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole 114

The 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole 114 was first synthesized by Elguero et al. The 1,3-dipole 114 was generated by treating a solution of 1-phenylimidazole 115 in cooled ethyl acetate with a solution of TCNEO 8, also in cooled ethyl acetate (Scheme 31).

![Scheme 31](image)

Compound 114 precipitated from solution as an off-white solid in 81% yield. The structure was supported by IR, 1H and 13C NMR spectroscopy. Two strong cyano bands were observed at 2175 and 2114 cm$^{-1}$ in the IR spectrum. In the 1H NMR
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spectrum, the hydrogen at C-2 appeared the most deshielded at δ 9.75. The two cyano groups gave one signal at 123.3 ppm in the $^{13}$C NMR spectrum. The methanide carbon signal was not observed despite numerous attempts to locate it. The NMR assignments are shown below (Figure 22).

$^1$H NMR (DMSO-$d_6$) $^{13}$C NMR (DMSO-$d_6$)

Figure 22: $^1$H NMR and $^{13}$C NMR assignments for compound 114
2.3 Cycloaddition reactions of imidazolium dicyanomethanide 1,3-dipoles with alkyne dipolarophiles

2.3.1 Cycloaddition reactions of 1,3-dipole 28 with symmetrical electron poor alkyne dipolarophiles (DMAD/DEAD)

The first reported cycloaddition reaction\textsuperscript{6} of 1-methylimidazolium-3-dicyanomethanide 28 involved treatment of a solution of the ylide in dimethylformamide with neat DMAD 25 (Section 1.4.1, Scheme 5). The product was isolated as a yellow crystalline solid in 70\% yield following column chromatography. Spectroscopic analysis of the product indicated that a substituted imidazo[2,3-a]pyridine ring system had been generated. We repeated this reaction using acetonitrile as solvent. After stirring for 1 h at room temperature, the product precipitated from solution and was collected by filtration. Recrystallisation from ethanol afforded compound 30 in 81\% yield.

The melting point obtained agreed with the data presented in the original study.\textsuperscript{6} The \textsuperscript{1}H NMR spectrum previously reported\textsuperscript{6} was also in agreement with that recorded by us (Figure 25). In both studies the N-H signal was not observed. However no \textsuperscript{13}C NMR data (Figure 25) have previously been published for this compound. The structure of compound 30 features a characteristic structural signature, an embedded enediamine unit involving atoms C-8, C-8a, N-1 and N-4 (Figure 23). Vinylic resonance has a profound effect on the \textsuperscript{13}C NMR spectrum of compound 30. The enamine \textalpha-carbon, C-8a, is exceptionally deshielded, and appeared at 146.3 ppm in the \textsuperscript{13}C NMR spectrum. Conversely, C-8, the \textbeta-carbon is extremely shielded, and appeared at 88.7 ppm.
The IR spectrum contained bands at 1610 (C=N), and 3293 cm$^{-1}$ (NH), confirming the presence of the imine group and consequently ring-expansion. The IR spectrum also showed bands at 1736 and 1709 cm$^{-1}$, corresponding to the two carbonyl groups. In related compounds, the higher absorbance has been assigned to the ester group attached to C-7, which is conjugated with the electron withdrawing cyano group. Determination of the X-Ray crystal structure of 1-methyl-5-imino-6-cyano-7,8-dimethoxycarbonyl imidazo[2,3-a]pyridine 30 provided conclusive proof for the structural assignment (Figure 24).
The original structural assignment is therefore proven to be correct. Boekeleide’s\textsuperscript{6} proposed structure, based on rather limited data, was a remarkable and intuitive assignment.

\textbf{Figure 24:} X-Ray crystal structure of compound 30

\textbf{Figure 25:} \textsuperscript{1}H NMR and \textsuperscript{13}C NMR assignments for compound 30
The reaction between 1-methylimidazolium-3-dicyanomethanide 28 and DEAD 116 yielded a similar ring expanded product, compound 117 (Scheme 32). A solution of 28 in acetonitrile was treated with DEAD 116 and the solution stirred at room temperature for 2 h. The solvent was then removed under reduced pressure and the residue crystallized from methanol to give compound 117 in 51% yield.

![Scheme 32]

The structure of 117 was confirmed by $^1$H NMR, $^{13}$C NMR and IR spectroscopy. The IR spectrum was similar to that of compound 30, containing a characteristic NH band at 3291 cm$^{-1}$ and a cyano band at 2207 cm$^{-1}$. The $^1$H NMR spectrum (Figure 27) was also similar to that of compound 30, with the imidazole protons H-2 and H-3 both appearing as doublets at δ 7.04 and 7.99 respectively (Figure 27). The assignments of H-2 and H-3 were supported by NOEDS (Figure 26).

![Figure 26: NOEDS enhancements of compound 117 in CDCl$_3$]

In the $^{13}$C NMR spectrum (Figure 27), the characteristic enediamine signals appeared at 88.7 ppm for C-8 and 146.3 ppm for C-8a (Figure 27).
2.3.2 Cycloaddition reactions of 1,3-dipole 28 with unsymmetrical electron poor alkyne dipolarophiles (MP/EP)

The 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 was treated with methyl propiolate 43 in acetonitrile at 0-5 °C (Scheme 33). A single product, compound 119, was isolated in 52% yield by fractional crystallization from diethyl ether. The structural assignment of compound 119 was supported by IR, $^1$H NMR and $^{13}$C NMR spectroscopy.

The IR spectrum featured bands corresponding to an NH bond at 3107 and cyano group at 2204 cm$^{-1}$. The $^1$H NMR spectrum (Figure 28) contained two doublets at $\delta$ 7.01 and 8.01, corresponding to H-2 and H-3, respectively. The signal for H-7 appeared at $\delta$ 8.05. The $^{13}$C NMR spectrum contained a single carbonyl signal at 163.2 ppm and a signal at 142.3 ppm corresponding to C-7. The embedded
enediamine unit was also identifiable in the spectrum, with C-8 appearing at 90.0 ppm and C-8a at 141.9 ppm (Figure 28).

\[
\begin{align*}
&\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3})} \\
&\begin{array}{c}
8.01 (d, 1H) \\
7.01 (d, 1H) \\
4.03 (s, 3H) \\
3.83 (s, 3H) \\
8.05 (s, 1H) \\
4.01 (s, 3H) \\
6.99 (d, 1H)
\end{array} \\
&\begin{array}{c}
\text{7.99 (d, 1H)} \\
\text{6.99 (d, 1H)} \\
\text{4.01 (s, 3H)} \\
\text{4.26 (q, 2H)} \\
\text{1.36 (t, 3H)} \\
\text{3.83 (s, 3H)} \\
\text{4.01 (s, 3H)}
\end{array}
\end{align*}
\]

\[
\begin{align*}
&\text{\textsuperscript{13}C NMR (CDCl\textsubscript{3})} \\
&\begin{array}{c}
111.7 \\
123.4 \\
90.6 \\
123.5 \\
142.8 \\
142.3 \\
152.2 \\
83.2 \\
\end{array} \\
&\begin{array}{c}
39.2 \\
39.5 \\
141.9 \\
142.3 \\
142.8 \\
142.3 \\
152.5 \\
60.8 \\
\end{array}
\end{align*}
\]

**Figure 28:** \textsuperscript{1}H NMR and \textsuperscript{13}C NMR assignments for compound 119

Treatment of the 1,3-dipole 28 with ethyl propiolate (EP) 118 also led to the isolation of a single regioisomer 120 in 33% yield (Scheme 33). The structural assignment of compound 120 (Figure 29) was supported by IR, \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopy. The \textsuperscript{1}H NMR spectrum was similar to that of 119, possessing a singlet at δ 8.05 corresponding to H-7. In the \textsuperscript{13}C NMR spectrum, the carbonyl carbon and C-7 appeared at 163.2 and 142.8 ppm, respectively. The signals for C-8 and C-8a appeared at 90.6 and 142.3 ppm, respectively (Figure 29).

\[
\begin{align*}
&\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3})} \\
&\begin{array}{c}
7.99 (d, 1H) \\
6.99 (d, 1H) \\
4.01 (s, 3H) \\
1.36 (t, 3H) \\
8.05 (s, 1H) \\
4.26 (q, 2H) \\
1.36 (t, 3H)
\end{array} \\
&\begin{array}{c}
\text{7.99 (d, 1H)} \\
\text{6.99 (d, 1H)} \\
\text{4.01 (s, 3H)} \\
\text{4.26 (q, 2H)} \\
\text{1.36 (t, 3H)} \\
\text{3.83 (s, 3H)} \\
\text{4.01 (s, 3H)}
\end{array}
\end{align*}
\]

\[
\begin{align*}
&\text{\textsuperscript{13}C NMR (CDCl\textsubscript{3})} \\
&\begin{array}{c}
112.1 \\
123.5 \\
90.6 \\
118.0 \\
142.8 \\
142.3 \\
152.5 \\
83.3 \\
\end{array} \\
&\begin{array}{c}
39.5 \\
39.2 \\
141.9 \\
142.3 \\
142.8 \\
142.3 \\
152.5 \\
60.8 \\
\end{array}
\end{align*}
\]

**Figure 29:** \textsuperscript{1}H NMR and \textsuperscript{13}C NMR assignments for compound 120
IR data were used to help determine the structures of 119 and 120 (Table 5): both compounds contained a single carbonyl stretching frequency at 1689 and 1696 cm\(^{-1}\), respectively. These absorbances correspond to the lower frequency carbonyl absorbances observed for the related compounds with two ester groups, 30 and 117. The higher of the two carbonyl stretching frequencies in 30 and 119 is assigned to the carbonyl on C-7, as this is conjugated with the electron withdrawing cyano group. Therefore in all the cases the lower stretching frequency arises from the ester group on C-8, allowing the structure of 119 and 120 to be determined.

The \(^{13}\)C NMR spectra of 119 and 120 also supported the assignment of regiochemistry. The C-7 signal was significantly stronger than the C-8 signal in both \(^{13}\)C NMR spectra which indicated a hydrogen atom was attached to C-7. This was confirmed by distortionless enhancement by polarization transfer (DEPT) spectra. Therefore the regiochemistry observed in these reactions is that whereby the unsubstituted terminus of the dipolarophile is attached to the dicyanomethanide terminus of the 1,3-dipolarophile. This is consistent with investigations conducted by Elguero et al.\(^{35}\)

**Table 5:** Carbonyl stretching frequencies for the products arising from the reactions of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 with alkyne dipolarophiles

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dipolarophile</th>
<th>Dipole</th>
<th>IR/cm(^{-1}) (νCO)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C7 CO(_2)R</td>
</tr>
<tr>
<td>30</td>
<td>DMAD 25</td>
<td>28</td>
<td>1736</td>
</tr>
<tr>
<td>119</td>
<td>MP 43</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>117</td>
<td>DEAD 116</td>
<td>28</td>
<td>1739</td>
</tr>
<tr>
<td>120</td>
<td>EP 118</td>
<td>28</td>
<td>-</td>
</tr>
</tbody>
</table>

The assignments of H-2 and H-3 in the \(^1\)H NMR spectra were supported by NOEDS (Figure 30).
2.3.3 Cycloaddition reactions of 1,3-dipole 112 with symmetrical electron poor alkyne dipolarophiles (DMAD/DEAD)

An ice-cold solution of the 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112 in DMF was treated with DMAD 25, and then left to stand at 0 °C for 4 h. The mixture was subsequently added to cooled water, causing precipitation of compound 121 in 53% yield as a yellow solid (Scheme 34). The structural assignment of compound 121 was supported by IR, ¹H NMR and ¹³C NMR spectroscopy.

The IR spectrum of compound 121 displayed stretching frequencies of 3305 (NH), 2208 (C≡N) and 1615 cm⁻¹ (C=N). These are characteristic of a ring-expanded product. In the ¹H NMR spectrum (Figure 31), the methoxy protons appeared as singlets at δ 3.63 and 3.91. The imidazole protons, H-2 and H-3, appeared at δ 7.02 and 8.00, respectively. Each of the signals was a doublet with a J value of 1.8 Hz. The ¹³C spectrum (Figure 31) included two signals at 163.3 and 166.1 ppm.
corresponding to the two carbonyl groups present. The embedded enediamine unit was also evident, with C-8 appearing at 89.1 ppm and C-8a at 146.1 ppm.

\[ ^1H \text{ NMR (CDCl}_3\text{)} \quad ^{13}C \text{ NMR (CDCl}_3\text{)} \]

![Chemical structure with NMR data](image)

**Figure 31:** \(^1H\) NMR and \(^{13}C\) NMR assignments for compound 121

Compound 122 was prepared by treating solution of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112 in ice-cold acetonitrile with an equimolar amount of DEAD 116. The mixture was allowed to stir at 0 °C for 4 h. Compound 122 separated from solution as a yellow precipitate in 42% yield (Scheme 34). The assignment of compound 122 was supported by IR, \(^1H\) NMR and \(^{13}C\) NMR spectroscopy.

The IR spectrum of compound 122 displayed the characteristic ring-expanded product bands at 3303 (NH), 2204 (C≡N) and 1620 cm\(^{-1}\) (C=N). The \(^1H\) NMR spectrum featured two doublets at δ 7.07 and 8.07, corresponding to H-2 and H-3, respectively (Figure 32). The assignments of these signals were supported by NOEDS (Figure 33). In the \(^{13}C\) NMR spectrum, the enediamine carbons appeared at 146.0 (C8a) and 89.3 ppm (C-8) (Figure 32). The spectrum also contained signals at 151.3 ppm due to the imine carbon and at 116.0 ppm attributable to the carbon of the cyano group.
$^1$H NMR (CDCl$_3$) \hspace{3cm} ^{13}$C NMR (CDCl$_3$)

![NMR Spectra](image)

**Figure 32:** $^1$H NMR and $^{13}$C NMR assignments for compound 122

![NOEDS Spectra](image)

**Figure 33:** NOEDS enhancements of compound 122 in CDCl$_3$

2.3.4 Cycloaddition reactions of 1,3-dipole 112 with unsymmetrical electron poor alkyne dipolarophiles (MP/EP)

A solution of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112 in acetonitrile was treated with an equimolar amount of MP 43 (Scheme 35). The mixture was allowed to stir at ambient temperature for 48 h, during which time compound 123 separated from solution as a buff precipitate in 48% yield. The structural assignment of compound 123 was supported by IR, $^1$H NMR and $^{13}$C NMR spectroscopy.
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Scheme 35

The IR spectrum featured bands corresponding to a NH bond at 3292 cm\(^{-1}\) and a cyano group at 2203 cm\(^{-1}\). The spectrum also contained a band at 1694 cm\(^{-1}\) corresponding to the methoxy group at the C-7 position. The \(^1\)H NMR spectrum (Figure 34) contained doublets at \(\delta 7.00\) and 8.03, corresponding to H-2 and H-3, respectively. The signal for H-7 appeared slightly further downfield at \(\delta 8.04\) (Figure 34). The assignments of the \(^1\)H NMR signals of 123 were supported by NOEDS (Figure 35). The \(^{13}\)C NMR spectrum contained a single carbonyl signal at 163.1 ppm and a signal at 142.7 ppm corresponding to C-7. The embedded enediamine unit was also identifiable in the spectrum, with C-8 appearing at 90.4 ppm and C-8a at 141.7 ppm (Figure 34).

\(\text{H NMR (CDCl}_3\) \quad \text{\^{13}C NMR (CDCl}_3\)

Figure 34: \(^1\)H NMR and \(^{13}\)C NMR assignments for compound 123
Figure 35: NOEDS enhancements of compound 123 in CDCl₃

Treatment of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112 with an equimolar amount of EP 118 in acetonitrile led to the isolation of compound 124. The mixture was stirred at ambient temperature for 51 h. The solvent was then removed under reduced pressure, yielding a sticky brown solid. Fractional crystallization from diethyl ether gave 124 as a pale yellow solid in 27% yield, together with an orange gum. The orange gum was subjected to a Soxhlet extraction with ether which afforded further 124 in 36% yield.

Figure 36: ¹H NMR and ¹³C NMR assignments for compound 124

The structural assignment of compound 124 was supported by IR, ¹H NMR and ¹³C NMR spectroscopy. The ¹H NMR spectrum was similar to that of 123, possessing a singlet at δ 8.02 corresponding to H-7 and doublets at δ 6.98 (H-2) and 8.00 (H-3). The ¹³C NMR spectrum contained signals at 163.5 (carbonyl group) and 143.0 ppm
(C-7). The signals for C-8 and C-8a appeared at 91.1 and 141.9 ppm respectively, (Figure 36).

IR data, specifically carbonyl stretching frequencies, were used, as before, to help determine the regiochemistry of these reactions (Table 6). The assignment was also supported by $^{13}$C NMR spectra which showed the presence of a hydrogen at C-7 in compounds 123 and 124, and its absence in products 121 and 122. The assignment of C-7 was confirmed by DEPT spectra.

**Table 6:** Carbonyl stretching frequencies for the products arising from the reactions of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112 with alkyne dipolarophiles

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dipolarophile</th>
<th>Dipole</th>
<th>IR/cm$^{-1}$ (νCO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>121</td>
<td>DMAD 25</td>
<td>112</td>
<td>1720 1704</td>
</tr>
<tr>
<td>123</td>
<td>MP 43</td>
<td>112</td>
<td>- 1694 1698</td>
</tr>
<tr>
<td>122</td>
<td>DEAD 116</td>
<td>112</td>
<td>1727 1698</td>
</tr>
<tr>
<td>124</td>
<td>EP 118</td>
<td>112</td>
<td>- 1682</td>
</tr>
</tbody>
</table>

2.3.5 Cycloaddition reactions of 1,3-dipole 114 with symmetrical electron poor alkyne dipolarophiles (DMAD/DEAD)

A solution of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole 114 in acetonitrile was treated with an equimolar amount of DMAD 25. The mixture was stirred at ambient temperature for 3.5 h. The solvent then was removed under reduced pressure at room temperature to yield a brown gum which solidified overnight. Crystallisation from hot ethanol yielded compound 125 in 67% yield (Scheme 36). The structural assignment of compound 125 was supported by IR, $^1$H NMR and $^{13}$C NMR spectroscopy.
Scheme 36

The IR spectrum contained the three characteristic bands of a ring expanded product- 3320 (NH), 2206 (C≡N) and 1617 cm$^{-1}$ (C=N). The two carbonyl groups afforded signals at 1724 and 1696 cm$^{-1}$. The $^1$H NMR spectrum (Figure 37) featured two doublets at $\delta$ 7.22 and 8.12, corresponding to H-2 and H-3, respectively (Figure 37). NOEDS was used to confirm these assignments, however no enhancement was found from the phenyl ring to the imidazole ring protons (Figure 38). In the $^{13}$C NMR spectrum, the enediamine carbons appeared at 140.5 (C-8a) and 88.4 ppm (C-8) (Figure 37). The spectrum also contained a signal at 151.3 ppm due to the imine carbon and at 116.0 ppm attributable to the carbon of the cyano group.

$^1$H NMR (CDCl$_3$)

$^{13}$C NMR (CDCl$_3$)

Figure 37: $^1$H NMR and $^{13}$C NMR assignments for compound 125
Compound 126 was produced by treating a solution of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole 114 in acetonitrile with an equimolar amount of DEAD 116 (Scheme 36). The mixture was stirred at ambient temperature for 3.5 h. The solvent was then removed under reduced pressure at room temperature, yielding a brown gum which solidified overnight. Crystallisation from hot ethanol yielded compound 126 in 55% yield.

The structural assignment of compound 126 was supported by IR, $^1$H NMR and $^{13}$C NMR spectroscopy. The IR spectrum of compound 126 displayed the characteristic ring-expanded product bands at 3296 (NH), 2206 (C≡N) and 1615 cm$^{-1}$ (C=N). The $^1$H NMR spectrum featured two doublets at $\delta$ 7.23 and 8.16, corresponding to H-2 and H-3, respectively (Figure 39). In the $^{13}$C NMR spectrum, the enediamine carbons appeared at 140.2 (C-8a) and 89.0 ppm (C-8) (Figure 39). The spectrum
also contained a signal at 151.3 ppm due to the imine carbon and at 115.9 ppm due to the carbon of the cyano group.

2.3.6 Cycloaddition reactions of 1,3-dipole 114 with unsymmetrical electron poor alkyne dipolarophiles (MP/EP)

A solution of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole 114 in acetonitrile was treated with an equimolar amount of MP 43 (Scheme 37). The mixture was stirred at ambient temperature for 48 h. Compound 127 separated from solution as a buff precipitate in 25% yield. The assignment of compound 127 was supported by IR, $^1$H NMR and $^{13}$C NMR spectroscopy.

![Scheme 37]

The IR spectrum featured bands corresponding to the NH bond at 3341 cm\(^{-1}\) and cyano group at 2198 cm\(^{-1}\). The spectrum also contained a band at 1688 cm\(^{-1}\) corresponding to the carbomethoxy group at the C-8 position. The $^1$H NMR spectrum (Figure 40) contained doublets at $\delta$ 7.17 and 8.16, corresponding to H-2 and H-3, respectively. The signal for H-7 appeared as a singlet at $\delta$ 8.01 ppm (Figure 40). The $^{13}$C NMR spectrum contained a carbonyl signal at 163.0 ppm and a signal at 143.3 ppm corresponding to C-7. The embedded enediamine unit was also identifiable in the spectrum, with C-8 appearing at 90.3 ppm and C-8a at 141.4 ppm (Figure 40).
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\[ ^1H\text{NMR (CDCl}_3\text{)} \quad ^{13}C\text{NMR (CDCl}_3\text{)} \]

![Figure 40: \(^1H\) NMR and \(^{13}C\) NMR assignments for compound 127](image)

A solution of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole 114 in acetonitrile was treated with ethyl propiolate 118. The mixture was stirred at ambient temperature for 51 h. Solvent was removed under reduced pressure to yield a dark brown solid, which was recrystallized from ethanol to yield pure 128 in 44% yield.

\[ ^1H\text{NMR (CDCl}_3\text{)} \quad ^{13}C\text{NMR (CDCl}_3\text{)} \]

![Figure 41: \(^1H\) NMR and \(^{13}C\) NMR assignments for compound 128](image)

The structural assignment of compound 128 was supported by IR, \(^1H\) NMR and \(^{13}C\) NMR spectroscopy. The IR spectrum contained the characteristic ring-expanded product bands at 3314 (NH), 2205 (C≡N) and 1622 cm\(^{-1}\) (C=N). The spectrum also displayed a single carbonyl band at 1683 cm\(^{-1}\). The \(^1H\) NMR spectrum (Figure 41) possessed a singlet at δ 7.99 corresponding to H-7. Doublets at δ 7.18 and 8.11 corresponded to H-2 and H-3, respectively. NOEDS was used to help determine
these assignments, however again no enhancement was found from the phenyl ring to the imidazole ring protons (Figure 42). In the $^{13}$C NMR spectrum (Figure 41), the carbonyl group appeared at 162.6 ppm, while C-7 was present at 143.0 ppm. The signals for C-8 and C-8a appeared at 90.7 and 141.3 ppm, respectively (Figure 41).

![Figure 42: NOEDS enhancements of compound 128 in CDCl$_3$](image)

IR data, specifically carbonyl stretching frequencies, were again used to help determine the regiochemistry of these reactions (Table 7). The $^{13}$C NMR spectra of 127 and 128 also contained signals for C-7 that were significantly stronger than the C-8 signals, indicating that a hydrogen atom was attached to C-7. This was confirmed by a DEPT spectrum.

**Table 7:** Carbonyl stretching frequencies for the products arising from the reactions of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole 114 with alkyne dipolarophiles

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dipolarophile</th>
<th>Dipole</th>
<th>IR/cm$^{-1}$ (νCO)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C7</td>
</tr>
<tr>
<td>125</td>
<td>DMAD 25</td>
<td>114</td>
<td>1724</td>
</tr>
<tr>
<td>127</td>
<td>MP 43</td>
<td>114</td>
<td>-</td>
</tr>
<tr>
<td>126</td>
<td>DEAD 116</td>
<td>114</td>
<td>1730</td>
</tr>
<tr>
<td>128</td>
<td>EP 118</td>
<td>114</td>
<td>-</td>
</tr>
</tbody>
</table>

The structural assignments of the products arising from unsymmetrical dipolarophiles are also supported by $^1$H NMR data (Table 8, Table 9). The products
derived from the symmetrical dipolarophile DMAD (30, 121, 125) contain two carbomethoxy groups. The chemical shift of the methoxy group of the ester attached to C-7 would not be expected to vary widely in the $^1$H spectra of these compounds. These groups are too far away to be influenced by changes in the imidazole portion of the molecule. Conversely the methoxy group of the ester attached to C-8 would be expected to vary as it is adjacent to the imidazole portion of the cycloadduct. The carboxymethoxy group attached to C-8 is influenced by the nearby methyl, benzyl or phenyl group. As a result the methoxy attached to the ester group on C-8 in 125 is more shielded than the corresponding methoxy in 30 due to shielding from the imidazole substituent. The variation in the methoxy $^1$H NMR shifts for the unsymmetrical products 117, 123 and 127 indicates that this methoxy is part of an ester group attached to C-8 and so is subject to influence from the adjacent imidazole portion of the compound. Similar trends are observed in the $^1$H NMR for the CH$_2$ signals of the ethoxy groups in the products derived from DEAD and EP (Table 9).

**Table 8: Comparison of methoxy $^1$H NMR shifts of cycloadducts derived from the reactions of imidazolium 1,3-dipoles with DMAD and MP**

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Compound</th>
<th>Dipolarophile</th>
<th>Dipole</th>
<th>$^1$H NMR/ppm (CH$_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C7</td>
</tr>
<tr>
<td>Methyl</td>
<td>30</td>
<td>DMAD 25</td>
<td>28</td>
<td>3.96</td>
</tr>
<tr>
<td>Methyl</td>
<td>117</td>
<td>MP 43</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>Benzyl</td>
<td>121</td>
<td>DMAD 25</td>
<td>112</td>
<td>3.91</td>
</tr>
<tr>
<td>Benzyl</td>
<td>123</td>
<td>MP 43</td>
<td>112</td>
<td>-</td>
</tr>
<tr>
<td>Phenyl</td>
<td>125</td>
<td>DMAD 25</td>
<td>114</td>
<td>3.92</td>
</tr>
<tr>
<td>Phenyl</td>
<td>127</td>
<td>MP 43</td>
<td>114</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 9: Comparison of ethoxy CH$_2^1$H NMR shifts of cycloadducts derived from the reactions of imidazolium 1,3-dipoles with DEAD and EP

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Compound</th>
<th>Dipolarophile</th>
<th>Dipole</th>
<th>$^1$H NMR /ppm (CH$_2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C7</td>
<td>C8</td>
</tr>
<tr>
<td>Methyl</td>
<td>119</td>
<td>DEAD 116</td>
<td>28</td>
<td>4.42 4.24</td>
</tr>
<tr>
<td>Methyl</td>
<td>120</td>
<td>EP 118</td>
<td>28</td>
<td>- 4.26</td>
</tr>
<tr>
<td>Benzyl</td>
<td>122</td>
<td>DEAD 116</td>
<td>112</td>
<td>4.45 4.17</td>
</tr>
<tr>
<td>Benzyl</td>
<td>124</td>
<td>EP 118</td>
<td>112</td>
<td>- 4.21</td>
</tr>
<tr>
<td>Phenyl</td>
<td>126</td>
<td>DEAD 116</td>
<td>114</td>
<td>4.41 3.51</td>
</tr>
<tr>
<td>Phenyl</td>
<td>128</td>
<td>EP 118</td>
<td>114</td>
<td>- 3.72</td>
</tr>
</tbody>
</table>

2.3.7 The rearrangement mechanism as proposed by Boekelheide and Fedoruk

The products derived from the reactions of imidazolium 1,3-dipoles 28, 112 and 114 with acetylenic dipolarophiles confirm the generality of the Boekelheide-Fedoruk rearrangement. In their 1968 paper, Boekelheide and Fedoruk$^6$ proposed a mechanism for the formation of the ring expanded product 30 from the reaction of 1,3-dipole 28 and DMAD 25 (Scheme 38). The mechanism involves the conversion of the initial cycloadduct 129 into an anion intermediate 130 which subsequently rearranges into the ring expanded product 30. The anion is formed through loss of the bridgehead H-7a proton and cleavage of the N-4/C-5 bond. Attack by the delocalised N-4 anion on a nitrile carbon leads to the ring expanded final product 30. The proposed rearrangement is therefore an E1cb type process followed by a 6-exo-dig ring closure. This mechanism provides a credible explanation for the formation of 30, but the results of subsequent reactions prompted us to reassess the mechanism.
2.4 Cycloaddition reactions of imidazolium dicyanomethanide 1,3-dipoles with alkene dipolarophiles

2.4.1 Cycloaddition reaction of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 with N-phenylmaleimide 131

In an effort to further probe this interesting ring expansion mechanism, it was decided to investigate the reactions of the imidazolium 1,3-dipoles with alkene dipolarophiles. The reaction of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 with N-phenylmaleimide 131 in acetonitrile at ambient temperature yielded compound 132 in 77% yield (Scheme 39). The product precipitated from solution after 2 h as a dark orange solid. The structural assignment of compound 132 was supported by IR and $^1$H and $^{13}$C NMR spectra.
The IR spectrum contained bands characteristic of a ring expanded product. The bands at 3307 (NH), 2209 (C≡N), and 1614 cm\(^{-1}\) (C=N) were similar to those observed in the ring-expanded products derived from the imidazolium 1,3-dipoles and alkyne dipoles. Two amido carbonyl stretching frequencies at 1759 and 1708 cm\(^{-1}\) were also observed. The product proved to be very insoluble in organic solvents, and so DMSO-d\(_6\) was used to obtain NMR spectra. The \(^1\)H NMR spectrum (Figure 43) featured the N-Me group at δ 4.28, while H-2 and H-3 were present at δ 8.16 and 8.44, respectively. The remaining signals in the spectrum correspond to the aromatic protons of the phenyl ring. The protons due to the maleimide ring were not observed, which is proof that ring expansion has occurred. The highly insoluble nature of the product made obtaining a complete \(^{13}\)C NMR spectrum difficult. Despite extensive efforts one weak signal proved elusive and was not observed. The missing signal is tentatively assigned to C-6, and is expected to be found between 80 ppm and 90 ppm. A signal for the C-6 carbon was observed in the \(^{13}\)C NMR spectra of all other imidazo[2,3-a]pyridine products, though these compounds display superior solubilities in deuterated solvents. The main signals obtained for 132 are shown below (Figure 43).
Chapter 2

$^1$H NMR (DMSO-$d_6$)

$^{13}$C NMR (DMSO-$d_6$)

Figure 43: $^1$H NMR and $^{13}$C NMR assignments for compound 132

Conclusive proof of the structure of 132 has been obtained from previous work in NUI Galway.\textsuperscript{73} Exhaustive repetitive recrystallizations of compound 132 from acetonitrile eventually yielded crystals suitable for X-ray analysis. The X-ray structure of the orange plate-like crystals revealed 132 to be a flat molecule with the 5-imino proton syn coplanar with the 6-cyano group at a distance of 2.809 Å from the triple bond (Figure 44).
The reaction of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 with \( N \)-phenylmaleimide 131 therefore parallels the reaction of 28 with alkyne dipolarophiles. The initial cycloadduct formed in both sets of reactions is unstable, and so rearranges to form the ring-expanded product. In this case, the initial cycloadduct 133 is oxidised \textit{in situ}, and so rearrangement occurs, yielding compound 132 (Scheme 40). The oxidation may be promoted by air, or by the maleimide present in the reaction mixture. Attempts to exclude air from the reaction by nitrogen purging the system and carrying out the reaction under a steady flow of nitrogen failed to prevent the oxidation, leading to isolation of compound 132 in all cases.\(^{73}\)
2.4.2 Reactions of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 and 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112 with maleic anhydride 134

The reactions of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 and 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112 with maleic anhydride 134 yielded altogether different compounds. The products of these reactions, ylides 135 and 136 (Scheme 41), were formed via apparent Michael reactions followed by 1,2-rearrangements. Despite the switch from a cycloaddition to Michael type reaction, the Boekelheide-Fedoruk rearrangement still occurred. These reactions therefore provide an interesting new perspective on the rearrangement.
Compound 135 was formed when a solution of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 in acetonitrile was treated with a slight excess of maleic anhydride 134, also in acetonitrile (Scheme 41). The mixture was stirred at ambient temperature for 3 h. The solvent was then removed under reduced pressure at a temperature below 35 °C. Addition of ether to the residue caused precipitation of the product 135 as a green solid in 70% yield. Evaporation of the ethereal solution led only to isolation of an oily residue from which no product was isolated. The structural assignment of compound 135 was supported by IR, $^1$H NMR and $^{13}$C NMR spectroscopy. Compound 135 was initially stable at ambient temperature, but decomposed on standing to an imidazole containing gum.

The IR spectrum contained characteristic bands at 3330 (N-H) and 2175 cm$^{-1}$ (C≡N). The two carbonyl groups afforded signals at 1792 and 1734 cm$^{-1}$. The NMR spectra of the product clearly indicated the presence in the product of the simple intact imidazolium unit, an imine unit bonded to the imidazole N-3 and an altered maleic anhydride unit (Figure 45). The $^1$H NMR spectrum featured singlets at δ 7.53, 7.58 and 8.84. These signals correspond to the imidazolium ring protons H-2, H-3 and H-5, respectively. A singlet further up field at δ 5.12 has been assigned to the proton attached to the C$^-$ carbon of the maleic anhydride moiety. The intact imidazolium ring was also evident in the $^{13}$C NMR spectrum (Figure 45), the ring carbons appearing at 120.7, 123.4 and 136.3 ppm. The spectrum also contained a signal at 149.6 ppm due to the imine carbon and at 118.3 ppm attributable to the carbon of the cyano group. The C$^-$ of the maleic anhydride unit was observed at 92.1 ppm. The signal for the C-7 carbon appeared at 59.7 ppm, though it was quite weak and proved to be elusive at first. It was eventually observed by increasing the pulse delay to 5 seconds and scanning the sample in excess of 9000 times.
Compound 136 was generated by treating a solution of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112 with maleic anhydride 134 (Scheme 41). The mixture was stirred at 50 °C for 27 h under nitrogen. Evaporation of the solvent under reduced pressure at ambient temperature yielded compound 136 as a sticky brown solid in 86% yield. The structural assignment of compound 136 was supported by 1H NMR and 13C NMR spectra. The product decomposed on standing to an imidazole containing gum, and so had to be analysed rapidly upon isolation.
The $^1$H NMR spectrum contained a singlet at $\delta$ 8.52 corresponding to imidazolium H-5 (Figure 46). The signals for the remaining imidazolium ring protons, H-2 and H-3, were part of a series of multiplets at $\delta$ 7.27-7.39 which also included signals for the protons associated with the benzyl group’s phenyl ring. The signal at $\delta$ 5.24 corresponded to the proton attached to C’ carbon of the maleic anhydride moiety. The $^{13}$C NMR spectrum demonstrated the presence of the intact imidazolium ring linked to the altered maleic anhydride unit. The imidazolium ring carbons were present at 121.5 (C-2), 121.8 (C-3) and 135.4 ppm (C-5) (Figure 46). The imine carbon appeared at 150.0 ppm and the cyano carbon at 118.8 ppm. The C’ of the maleic anhydride was observed at 92.2 ppm. In keeping with compound 135, the signal for C-7 was very weak and difficult to detect. However, increasing the pulse delay to 4 seconds and scanning the sample in excess of 12,800 times allowed the signal to be observed at 62.2 ppm.

Structures of this type$^{74}$ have previously been reported in the literature. The ylides 137 and 138 were reacted with DMAD 25 in acetonitrile to yield adducts 139 and 140 respectively (Scheme 42). The $^{13}$C NMR spectra reported for these ylide products indicate that the C’ carbon appears at 84.5 ppm for 139 and 79.0 ppm for 140.

![Scheme 42](image)
2.4.3 Reactions of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 with maleic anhydride 134: theoretical analysis

The unusual nature of the products arising from these reactions prompted us to carry out a theoretical study in collaboration with Professor Luke Burke of Rutgers University at Camden. Calculated transition states for the reactions of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 with maleic anhydride 134, maleimide and N-phenylmaleimide 131 are presented below (Table 10).

Table 10: Calculated reaction energies ($\Delta E_R$), activation energies ($E_a$) and distances

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>Cycloaddition Reactions</th>
<th>Cycloadducts</th>
<th>Transition States</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\Delta E_R$ (kJ mol$^{-1}$)</td>
<td>$a$ (Å)</td>
<td>$b$ (Å)</td>
</tr>
<tr>
<td>1</td>
<td>O</td>
<td>endo</td>
<td>1.600</td>
<td>1.633</td>
</tr>
<tr>
<td>2</td>
<td>O</td>
<td>exo</td>
<td>1.603</td>
<td>1.604</td>
</tr>
<tr>
<td>3</td>
<td>O</td>
<td>$E_{diff}$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>O</td>
<td>exo/endo</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>NH</td>
<td>endo</td>
<td>1.596</td>
<td>1.618</td>
</tr>
<tr>
<td>6</td>
<td>NH</td>
<td>exo</td>
<td>1.597</td>
<td>1.592</td>
</tr>
<tr>
<td>7</td>
<td>NH</td>
<td>$E_{diff}$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>NH</td>
<td>exo/endo</td>
<td>12.02</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>NPh</td>
<td>endo</td>
<td>1.598</td>
<td>1.620</td>
</tr>
<tr>
<td>10</td>
<td>NPh</td>
<td>exo</td>
<td>1.595</td>
<td>1.592</td>
</tr>
<tr>
<td>11</td>
<td>NPh</td>
<td>$E_{diff}$</td>
<td>5.19</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>NPh</td>
<td>exo/endo</td>
<td>7.48</td>
<td>-</td>
</tr>
</tbody>
</table>

Compound 132 is the product from the cycloaddition reaction of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 and N-phenylmaleimide 131 (Scheme 40). Theoretical calculations of the transition state for this reaction indicate
that a normal Huisgen cycloaddition takes place. Both new bonds in the transition state are almost equally developed \((a: 2.122 \, \text{Å}, \, b: 2.100 \, \text{Å})\) and the activation energy \((E_a)\) is lower by 7.46 \text{kJmol}^{-1} for endo approach of the dipolarophile rather than exo (Table 10, entries 9, 11).

This contrasts with the transition state calculations for the reaction of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 and maleic anhydride 134. The activation energy is also lower for the endo transition state, but only one new bond is formed in this case \((a: 1.794 \, \text{Å}, \, b: 2.719 \, \text{Å})\) (Table 10, entry 1). The theoretical calculations indicate that the transition state structure is twisted such that the maleic anhydride unit spirals under the imidazole ring. A normal cycloaddition where both new bonds are well formed would have an activation energy of 12.79 \text{kJ/mol}^{-1} higher and involve an unfavoured exo transition state (Table 10, entry 3).

Therefore the theoretical results agree well with experimental observations. Dipole 28 reacts with \(N\)-phenylmaleimide 131 via a Huisgen cycloaddition addition to yield the unstable cycloadduct 133 which ultimately rearranges to yield the ring expanded product 132 (Scheme 40). With maleic anhydride 134 the reaction changes to a potentially two step cycloaddition, but the second step fails to complete. Instead a Michael reaction takes place, though once again the initial adduct 141 proves to be unstable. The adduct undergoes a Boekelheide-Fedoruk type rearrangement to give the ylide product 135. This more stable conjugated product may potentially be formed by a 1,2-shift of the N-C bond and an intermolecular H-shift (Scheme 43). The rearrangement could also parallel the Steven’s Rearrangement\(^{75}\) which involves short lived caged diradicals.
The mechanism proposed by Boekelheide and Fedoruk, however (Scheme 38), does not adequately explain the formation of products 135 and 136. The reaction of maleic anhydride 134 with 28 and 112 indicate that ring expansion is not necessarily part of the Boekelheide-Fedoruk rearrangement. The originally proposed mechanism also involves loss of the imidazole H-5 proton, though this does not occur in the formation of these products. Therefore the unusual ylide product arising from these reactions prompted us to reassess the rearrangement mechanism as originally proposed by Boekelheide and Fedoruk.

2.5 Isolation and study of an initial cycloaddition adduct

It was felt that NMR spectroscopy could be used to help increase our understanding of the rearrangement process. Central to this approach was the isolation and investigation of an initial cycloadduct. The only initial cycloadduct isolated for this class of reactions to date was discovered by Elguero.35 The reaction of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 1,3-dipole 142 with DMAD 25 yields a cycloadduct intermediate 143 that can be easily transformed into the ring expanded product 144 with gentle heating (Scheme 44). Revisiting this cycloadduct intermediate proved to be crucial to our understanding of the ring expansion reaction.
2.5.1 Synthesis of 1-phenyl-1,2,4-triazole 145

The compound 1-phenyl-1,2,4-triazole 145 was produced by heating phenylhydrazine 146 in an excess of formamide 147 (Scheme 45). The resulting reaction mixture was then diluted with water and the product extracted with diethyl ether. Column chromatography afforded the product as a white solid in 43% yield, along with recovered starting materials 146 and 147.

The structure of 145 was confirmed by IR, $^1$H NMR and $^{13}$C NMR spectra which were found to be in agreement with those in the literature.
2.5.2 Synthesis of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 142

The procedure described by Elguero\textsuperscript{7} was used to generate the 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 1,3-dipole 142. A mixture of 1-phenyl-1,2,4-triazole 145 and TCNEO 8 in ether was stirred at room temperature for 3 days, yielding the ylide in 23\% (Scheme 46), along with recovered 145.

The lower reactivity of 145 towards TCNEO 8, relative to the imidazole heterocycles, can be explained by its low basic pKa value of 1.9.\textsuperscript{7} The reactivity of heterocycles towards TCNEO 8 increases with basicity and decreases with steric hindrance. The structure of compound 142 was confirmed by IR, \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopy. Two strong cyano bands at 2128 and 2184 cm\textsuperscript{-1} were observed in the IR spectrum. In the \textsuperscript{1}H NMR spectrum, the proton of C-5 showed the greatest deshielding and appeared at δ 10.86. The two cyano groups are NMR chemical shift
equivalent, and so only one cyano signal at 122.6 ppm appeared in the $^{13}$C NMR spectrum. Despite extensive efforts, the methanide carbon signal was not observed in $^{13}$C NMR spectrum (Figure 48).

$^{1}$H NMR (DMSO-$d_6$)

$^{13}$C NMR (DMSO-$d_6$)

![Figure 48: $^1$H NMR and $^{13}$C NMR assignments for compound 142](image)

2.5.3 Cycloaddition reaction of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 142 with DMAD 25: isolation of the initial cycloadduct 143

The procedure outlined by Elguero$^{35}$ was used to isolate the initial cycloadduct 143 formed in the reaction between of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 1,3-dipole 142 and DMAD 25. A solution of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 1,3-dipole 142 in DMF (cooled to 0 °C) was treated with DMAD 25 and allowed to stand at 0 °C for 4.5 h. The resulting mixture was filtered through a cooled funnel, and the filtrate added to ice-cold water. The resulting brown precipitate was collected on a jacketed sintered glass funnel at -5 °C and washed with cooled ethanol and diethyl ether. The crude cycloadduct product 143 was isolated as a brown solid in 71% yield. The assignment of compound 143 was supported by $^1$H and $^{13}$C NMR spectra.
The $^1$H and $^{13}$C NMR spectra of the initial cycloadduct were measured at 0 °C due to the ease with which the ring expansion rearrangement occurs in solution. The compound could not be purified further following isolation due to its propensity for rearrangement. CD$_3$CN was used in NMR experiments rather than CDCl$_3$ as in the original Elguero study. However, the $^1$H NMR spectrum closely matched that previously reported. The $^1$H contained four singlet signals corresponding to the two methyl groups (δ 3.85 and 3.66), the H-3 proton (δ 7.30) and the H-7a proton (δ 6.77) (Figure 49).

Our $^{13}$C NMR spectrum benefited from the availability of a higher field NMR spectrophotometer than that used by Elguero in the early 1980s and so weaker signals not previously found were observed. Thus all carbons were accounted for in our $^{13}$C NMR spectrum. Separate signals were observed for both cyano groups (111.6 ppm and 109.6 ppm) and the C-5 carbon was detected at 58.6 ppm (Figure 49). We also observed the bridgehead carbon C-7a at 86.1 ppm which had not previously been reported. Slightly different shifts were observed for the phenyl ring carbons, but the $^{13}$C NMR spectra were in agreement with one another, and the structure originally proposed by Elguero is confirmed to be correct, namely the only reported un-rearranged cycloadduct from an azolium dicyanomethanide 1,3-dipole.
Further support of the structure was provided by theoretical calculations carried out in collaboration with Professor Luke Burke of Rutgers University. A set of predicted NMR shifts for the $^1$H and $^{13}$C NMR spectra of the initial cycloadduct was found to be in good agreement with both our own (Figure 49) and Elguero’s experimentally observed values (Figure 50).

\[
\begin{align*}
\text{\textbf{1}H NMR (Predicted)} \\
\text{\textbf{1}3 C NMR (Predicted)}
\end{align*}
\]

![Figure 50: Predicted $^1$H NMR and $^{13}$C NMR assignments for 143 (See Figure 49)](image)

Therefore, in contrast with the reactions of the imidazolium 1,3-dipoles, the reaction of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 1,3-dipole 142 with DMAD 25 leads to the isolation of the initial cycloadduct 143. Studying the rearrangement of this compound was critical to our understanding of the rearrangement mechanism.

2.5.4 Cycloaddition reaction of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 142 with DMAD 25: generation of the ring expanded product 144

The initial cycloadduct 143 is unstable, and rearranges in solution to the ring expanded product 144 (Scheme 44). This rearrangement occurs readily at room temperature. In order to ensure full conversion to the desired ring expanded product, a solution of 143 in acetonitrile was stirred at 50 °C for 2 h and then ambient temperature for a further 50 h to ensure full conversion. Removal of the solvent
under reduced pressure yielded the ring expanded product 144 as a yellow crystalline solid in 80% yield.

\[\text{1H NMR (CD}_{3}\text{CN)} \]

\[\text{13C NMR(CD}_{3}\text{CN)} \]

**Figure 51:** 1H NMR and 13C NMR assignments for compound 144

The assignment of compound 144 was supported by IR, 1H NMR and 13C NMR spectroscopy. The IR spectrum displayed the characteristic ring-expanded product bands at 3316 (NH), 2204 (C≡N) and 1624 cm\(^{-1}\) (C=N). The 1H NMR spectrum contained three singlets corresponding to H-3 and the two carboxymethyl groups (Figure 51). The carboxymethyl group attached to C-8 is considerably more shielded (δ 2.96 ppm) than that associated with C-7 (δ 3.85). This is potentially due to shielding effects of the phenyl ring, similar to those observed in the products from the reactions of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole 114 and alkyne dipolarophiles. Another point to note is that H-3 and the phenyl ring protons are all deshielded relative to the initial cycloadduct 143, probably due to aromatisation of the core fused ring system.

The 13C NMR spectrum features the embedded enediamine unit indicative of ring expansion (Figure 51). The enamine α-carbon C-8a is highly deshielded and appears at 144.1 ppm. Conversely C-8 the β-carbon is extremely shielded and appears at 86.4 ppm. This is in contrast with the initial cycloadduct 143 where C-7 (143.2 ppm) was far more deshielded than the bridgehead carbon C-7a (86.1 ppm). As was observed
in the $^1$H NMR spectrum, the phenyl ring carbons were found to have shifted downfield relative to the initial cycloadduct 143.

Both the IR and $^1$H NMR spectra agreed well with those previously reported by Elguero for compound 144. However $^{13}$C NMR data for 144 was not reported in the original study, preventing us from making a direct comparison. The $^1$H and $^{13}$C NMR spectra acquired for 144 do agree well with the predicted spectra developed in conjunction with Professor Luke Burke (Figure 52).

![Figure 52: Predicted $^1$H NMR and $^{13}$C NMR assignments for compound 144](image)

Hence the reaction of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 1,3-dipole 142 with DMAD 25 initially generates the direct cycloadduct 143 which is converted quite easily to the ring expanded product 144. This system is therefore ideally suited to investigating the mechanism of this intriguing rearrangement.

### 2.5.5 Cycloaddition reaction of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 142 with DMAD 25: investigation of the ring expansion rearrangement by NMR spectroscopy

Having isolated and confirmed the structures of both the initial cycloadduct 143 and ring expanded product 144, our efforts turned to investigating the rearrangement mechanism. A sample of cycloadduct 143 was dissolved in CD$_3$CN at 0 °C and the $^1$H NMR spectrum recorded. The sample was kept cold in the NMR spectrometer
chamber using liquid nitrogen. The sample temperature was then raised to typical probe temperature (19 +/- 1 °C) and $^1$H NMR spectra measured at 30 min intervals over 16 h. Unsurprisingly, over this period the signals of the initial cycloadduct 143 were seen to decline, while those of the ring expanded product 144 grew. At the end of the experiment all traces of compound 143 were gone, and only compound 144 was present in the sample.

The $^1$H NMR spectra also revealed the presence of an intermediate 148 which was seen to develop once the solution had been raised to probe temperature (Figure 54, 55). The intermediate displayed four simple singlet signals. Two carboxymethyl groups were identified at $\delta$ 3.39 and 3.72. Signals corresponding to the two triazole ring protons were initially observed at $\delta$ 7.53 and 8.55. The signal at $\delta$ 8.55 was found to drift upfield during the course of the experiment. The signal at $\delta$ 7.53 became impossible to track over the course of the rearrangement due to its overlap with developing aromatic protons.

Shortly after this intermediate appeared signals characteristic of the ring expanded product 144 were observed. After about 6 h the intermediate reached its maximum concentration. At this point the initial cycloadduct, the intermediate and the ring expanded product were all present in similar concentrations. As the experiment progressed the ring expanded product began to dominate, and finally full conversion to 144 was observed.

In the 30 min intervals between $^1$H NMR scans, $^{13}$C NMR spectra were collected. Due to the large number of close and overlapping signals, assignments based on these spectra are tenuous. However, a number of signals we believe to be associated with the intermediate 148 were observed (Figure 53). The two methyl groups appeared at 52.1 ppm and 52.3 ppm while the triazole ring carbons appeared at 137.5 ppm and 138.0 ppm.
We believe that the structure of this intermediate is an azolium ylide type structure that may be similar to that of compounds 135 and 136, formed in the separate reactions between 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 and 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112 and maleic anhydride 134 (Scheme 41). The ylide 148 contains resonance-stabilised termini, an intact triazole ring and two carboxymethyl groups (Scheme 47, Figures 54, 55).

Figure 53: $^1$H NMR and $^{13}$C NMR assignments for possible intermediate 148
Note 1: Key signals for initial cycloadduct 143 highlighted in green
Note 2: Key signals for intermediate 148 highlighted in red
Note 3: Key signals for ring-expanded product 144 highlighted in pink

Figure 54: $^1$H NMR spectra of conversion of 143 to 144 via 148- 0, 4 and 6 h
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Note 1: Key signals for initial cycloadduct 143 highlighted in green
Note 2: Key signals for intermediate 148 highlighted in red
Note 3: Key signals for ring-expanded product 144 highlighted in pink

Figure 55: $^1$H NMR spectra for conversion of 143 to 144 via 148 - 12, 24 and 67 h
2.5.6 Mechanism of the rearrangement

Our study of the reactions of the Boekelheide-Fedoruk rearrangement leads us to believe that the originally proposed mechanism does not capture the full complexity of the rearrangement. This is apparent from the ylide products 135 and 136 which are formed via Boekelheide-Fedoruk rearrangement of an initial Michael adduct (Scheme 41). This rearrangement occurs without ring expansion or loss of the imidazole H-4 proton. The mechanism as proposed by Boekelheide and Fedoruk requires that both these events take place. The transformation of 143 into 144 may proceed via an intermediate 148 that possesses a similar structure to the ylides 135 and 136.

The presence of the two triazole ring protons suggests that the intermediate may have been formed by ring opening of the C(7)-C(7a) bond. In parallel with the formation of 135 and 136 this may undergo 1,2-rearrangement to the ylide diradical 149 which then ring closes (RORC) to form 150 which aromatises to form the ring expanded product 144 (Scheme 47).
Scheme 47
2.6 Conclusion

We have investigated the reactions of imidazolium dicyanomethanide 1,3-dipoles with a variety of electron poor alkyne and alkene dipolarophiles. These reactions generate unstable initial cycloadducts that rearrange in situ to form the isolated ring-expanded products. We refer to this conversion of the initial cycloadduct to the ring-expanded product as the Boekelheide-Fedoruk rearrangement.

A series of ring-expanded compounds was synthesized by reacting the imidazolium dicyanomethanide 1,3-dipoles with both symmetrical and unsymmetrical dipolarophiles. The regiochemistry observed in these reactions is that whereby the unsubstituted terminus of the dipolarophile is attached to the dicyanomethanide terminus of the 1,3-dipole.

The reactions of the imidazolium dicyanomethanide 1,3-dipoles with alkene dipolarophiles also produced unstable intermediates that rearranged to generate the final product. The reaction of the 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28 with N-phenylmaleimide 131 provided a ring-expanded compound similar to the products formed by the reactions of the imidazolium dicyanomethanide 1,3-dipoles with alkyne dipolarophiles. However the reactions of imidazolium dicyanomethanide 1,3-dipoles with maleic anhydride 134 gave a new ylide product. The reaction proceeded via Michael Addition to form an unstable intermediate that underwent 1,2-rearrangement to form the novel ylide product.

The rearrangement mechanism was further probed using low temperature NMR spectroscopy to follow the conversion of an unstable, but isolatable, initial cycloadduct from a 1,2,4-triazole-4-dicyanomethanide to the final ring-expanded product. Combined with theoretical calculations, these experiments provide an interesting new perspective on the Boekelheide-Fedoruk rearrangement and reopen the question of its mechanism.
2.7 Postscript

Following completion of the work herein, a paper on it was published. During the intervening years, an in-depth computational study of remaining questions concerning the rearrangement was carried out by Professors L.A. Burke and R.N. Butler. This study further highlighted the overall complexity of the reaction. The mechanism of the rearrangement of the cycloadduct is now considered to involve (i) opening of the N4-C5 bond in the cycloadduct; (ii) H-migration from imidazole C7a to N4 giving an azolium ylide intermediate; (iii) a 1,7-H-shift to give a ketenimine intermediate; (iv) ring closure to give the aromatic fused 5,6 ring structure (Scheme 48).

Computed NMR shifts as well as energies of intermediates and transitions states suggest that the transient intermediate detected herein for the 1,2,4-triazole case was the azolium ylide species 153 rather than the azolium ylide 148. Ring opening of the C7-C7a bond did not prove to be thermodynamically viable once it was formed.
Scheme 48
2.8 Experimental

Melting points were measured on an Electrothermal apparatus. IR spectra were measured on a Perkin-Elmer Spectrum 1000 spectrophotometer. Microanalyses were measured on a Perkin-Elmer Model 240 CHN analyser. NMR spectra were measured on a JEOL GXFT 400 instrument with tetramethylsilane as an internal reference. Deuteriochloroform, hexadeuteriomethyl sulphoxide and acetonitrile-d$_3$ were used as solvents. $^1$H NMR assignments were supported by selective proton decoupling and COSY spectra. $J$ values are given in Hz. $^{13}$C NMR assignments were supported by DEPT spectra. Assignments of stereochemistry were determined by NOEDS. Solvents were purified according to literature procedures$^{80}$. Acetonitrile was HPLC grade and was used without purification.

Chemicals were purchased as follows:

**Sigma-Aldrich:** DMSO-d$_6$, acetonitrile-d$_3$, tetracyanoethylene, hydrogen peroxide (30%), formamide, phenylhydrazine, N-methylimidazole, N-benzylimidazole, N-phenylimidazole, DMAD, DEAD, methyl propiolate, ethyl propiolate, N-phenylmaleimide.

**Lancaster:** maleic anhydride.

**Fluorochem:** chloroform-d$_1$
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The numbering and naming system below is used in this chapter and has been accepted for publication.

**1.3-Dipoles**

![1-methylimidazolium-3-dicyanomethanide 1,3-dipole](image)

1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28

**Cycloadducts**

![1-phenyl-5,5-dicyano-6,7-dimethoxycarbonyl-5,8-dihydropyrrolo[1,2-d]1,2,4-triazole](image)

1-phenyl-5,5-dicyano-6,7-dimethoxycarbonyl-5,8-dihydropyrrolo[1,2-d]1,2,4-triazole 143

![1-phenyl-5-imino-6-cyano-7,8-dimethoxycarbonyl-1,2,4-triazolo[4,5-a]pyridine](image)

1-phenyl-5-imino-6-cyano-7,8-dimethoxycarbonyl-1,2,4-triazolo[4,5-a]pyridine 144
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1-methyl-5-imino-6-cyano-7,8-dimethoxycarbonyl imidazo[2,3-α]pyridine 30

imidazolium ylide 135

1-methyl-5-imino-6-cyano-7,9-(dicarboxy-N-phenylimido) imidazo[2,3-α]pyridine 132
Synthesis of tetracyanoethylene oxide 8

A solution of tetracyanoethylene (3.00 g, 23 mmol) in acetonitrile (22 cm$^3$) was cooled to –5 °C in an acetone-ice bath. Hydrogen peroxide (30%) (2.66 cm$^3$, 23 mmol) was added drop-wise at such a rate that the temperature of the reaction remained between 10-12 °C. When addition was complete, the reaction mixture was stirred for a further 5 min and then diluted with ice cold water (150 cm$^3$). The precipitated solid was collected by filtration and washed with water. The solid was left to dry on a suction pump for 1 h and then used immediately. The product was obtained as a white solid (2.53 g, 75%), mp 177-179 °C (sealed tube) (Lit.$^4$, mp 177-178 °C); (Found C, 50.0; N, 38.7. C$_6$N$_4$O requires C, 50.0; N, 38.9%).

CAUTION: Both TCNE and TCNEO evolve hydrogen cyanide when exposed to water. All operations must be carried out in a fume hood.

Synthesis of 1-phenyl-1,2,4-triazole 145

Phenylhydrazine (10.80 g, 9.83 cm$^3$, 0.10 mol) in formamide (45 g, 40 cm$^3$, 1.00 mol) was heated for 8 h at 160-170 °C. The resulting reaction mixture was added to 100 cm$^3$ of water, and extracted using 5 x 100 cm$^3$ portions of diethyl ether. The mixture was concentrated to an oil under vacuum, then placed neat on a flash column of silica (230-400 mesh ASTM), made up in dichloromethane. The column was eluted with dichloromethane and diethyl ether in the gradient 1:0 to 95:5 to give the product 145 as an oil which solidified to an off-white solid on cooling in ice. Compound 145: (6.25 g, 43%), mp 41-43 °C (ethanol) (Lit.,$^{77, 81}$ mp 46-47 °C); (Found C, 66.3; N, 5.0; H, 28.6. C$_8$H$_7$N$_3$ requires C, 66.2; H, 4.85; H, 28.95%); $\nu_{\text{max}}$/cm$^{-1}$ 638, 790 (Ph); $\delta_H$ (CDCl$_3$) 7.36-7.40 (m, 1H, H-4'), 7.47-7.51 (m, 2H, H-3'), 7.65-7.67 (m, 2H, H-2'), 8.09 (s, 1H, H-3), 8.54 (s, 1H, H-5); $\delta_C$ (CDCl$_3$) 120.2 (C-2'), 128.3 (C-4'), 129.9 (C-3'), 130.3 (C-3), 137.1 (C-1'), 141.0 (C-5), 152.7 (C-3).

$\delta_H$ (DMSO-d$_6$) 7.37-7.40 (m, 1H, H-4'), 7.51-7.55 (m, 2H, H-3'), 7.82-7.84 (m, 2H, H-2'), 8.21 (s, 1H, H-3), 9.27 (s, 1H, H-5); $\delta_C$ (DMSO-d$_6$) 119.9 (C-2'), 128.3 (C-4'), 130.3 (C-3'), 137.3 (C-1'), 142.8 (C-5), 153.0 (C-3).
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Preparation of dicyanomethanide 1,3-dipoles

Synthesis of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole 28

To a solution of tetracyanoethylene oxide (1.74 g, 12.1 mmol) in ethyl acetate (15 cm$^3$) at 0 °C, 1-methylimidazole (0.96 cm$^3$, 12.1 mmol), also in ethyl acetate (3 cm$^3$), was added drop-wise with stirring such that the reaction temperature remained below 10 °C. When the addition was complete a pale brown solid separated from the solution. The product 28 (1.15 g, 65%), mp 143-144 °C (from ethanol using Norit) (Lit., mp 143-144 °C); was filtered off and washed with cold ethyl acetate. The filtrate rapidly turned dark brown. Attempts to isolate more product or starting material from the filtrate by removing the solvent under reduced pressure led to a brown sticky residue due to decomposition of TCNEO. Compound 28: (Found: C, 57.45; H, 3.95; N, 38.2. C$_7$H$_6$N$_4$ requires C, 57.55; H, 4.1; N, 38.35%); $\nu_{\text{max}}$/cm$^{-1}$ 2180 cm$^{-1}$ and 2134 cm$^{-1}$ (C≡N); $\delta_{\text{H}}$ NMR (DMSO-d$_6$): 3.75 (s, 3H, CH$_3$), 7.60 (dd, 2H, J 1.6, 1.9, H-4), 7.62 (dd, 2H, J 1.6, 1.9, H-5), 9.08 (s, 1H, H-2); $\delta_{\text{C}}$ NMR (DMSO-d$_6$): 35.8 (CH$_3$), 60.3 (C ) 123.2 (CN), 123.5 (C-5), 124.4 (C-4), 137.5 (C-2); (for C' pulse delay, 3 seconds, 17,000 scans).

Synthesis of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole 112

A solution of TCNEO (0.31 g, 2.15 mmol) in ethyl acetate (3 cm$^3$) was cooled to 0 °C in an ice-bath and treated with a cooled solution of 1-benzylimidazole (0.34 g, 2.15 mmol) in ethyl acetate (3 cm$^3$) dropwise with stirring. The mixture was stirred for a further 10 min in the ice-bath and then filtered to give the product 112 (0.35 g, 73%), mp 177-179 °C (ethanol). The filtrate rapidly turned dark brown. Attempts to isolate more product or starting material from the filtrate by removing the solvent under reduced pressure led to a brown sticky residue due to decomposition of TCNEO. Compound 112: (Found: C, 70.1; H, 4.7; N, 25.3. C$_{13}$H$_{10}$N$_4$ requires C, 70.25; H, 4.55; N, 25.2%); $\nu_{\text{max}}$/cm$^{-1}$ 2160, 2180 (C≡N); $\delta_{\text{H}}$ NMR (DMSO-d$_6$): 5.30 (s, 2H, benzyl CH$_2$), 7.32-7.39 (m, 5H, Ph), 7.64 (dd, J 1.6, 1.6, 1H, H-5), 7.73 (dd, 1H, J 1.6, 1.6, H-4), 9.33 (s, 1H, H-2); $\delta_{\text{C}}$ NMR (DMSO-d$_6$) 52.1 (benzyl CH$_2$),
122.6 (C-5), 123.0 (CN), 124.7 (C-4), 128.3 (C-3'), 128.7 (C-4'), 129.0 (C-2'), 134.9 (C-1'), 136.4 (C-2).

**Synthesis of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole 114**

A solution of 1-phenylimidazole (0.95 cm$^3$, 7.51 mmol) in ethyl acetate (12 cm$^3$) was cooled to 0 °C in an ice-bath and treated with a cooled solution of TCNEO (1.08 g, 7.51 mmol) in ethyl acetate (8 cm$^3$) dropwise with stirring. The mixture was stirred for a further 5 min in the ice-bath and then filtered to give the product 114 (1.27 g, 81%), mp 202-203 °C (ethanol) (Lit.$^7$ 210-212 °C). The filtrate rapidly turned dark brown. Attempts to isolate more product or starting material from the filtrate by removing the solvent under reduced pressure led to a brown sticky residue due to decomposition of TCNEO. Compound 114: (Found: C, 69.5; H, 3.8; N, 27.25. C$_{12}$H$_8$N$_4$ requires C, 69.2; H, 3.9; N, 26.9%); ν$_{\text{max}}$/cm$^{-1}$ 2175, 2114 (C≡N); δ$_H$ (DMSO-d$_6$) 7.48-7.51 (m, 1H, H-4'), 7.55-7.59 (m, 2H, H-3'), 7.75-7.77 (m, 2H, H-2'), 7.89 (dd, 2H, J 1.8, 1.9, H-5), 8.25 (dd, 1H, J 1.6, 1.9, H-4), 9.73 (dd, 1H, J 1.6, 1.6, H-2); δ$_C$ (DMSO-d$_6$) 121.9 (C-5), 122.4 (C-2'), 123.3 (C≡N), 125.7 (C-4), 130.0 (C-4'), 130.5 (C-3'), 135.3 (C-1'), 135.5 (C-2).

**Synthesis of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 1,3-dipole 142**

A solution of 1-phenyl-1,2,4-triazole (1.50 g, 16.40 mmol) in diethyl ether (50 cm$^3$) was treated with TCNEO (1.48 g, 16.40 mmol), also in diethyl ether (50 cm$^3$). The reaction mixture was stirred at room temperature for 72 h in a nitrogen rich atmosphere. During this time the product precipitated from solution and was collected by filtration to give a light brown solid, compound 142 (0.50 g, 23%), mp >300 °C (ethanol) (Lit.$^7$ mp >260 °C); (Found: C, 62.9; H, 3.7; N, 33.45. C$_{11}$H$_7$N$_5$ requires C, 63.15; H, 3.4; N, 33.5%); ν$_{\text{max}}$/cm$^{-1}$ 2184, 2128 (C≡N); δ$_H$ NMR (DMSO-d$_6$) 7.53-7.56 (m, 1H, Ph H-4'), 7.59-7.63 (m, 2H, H-3'), 7.87-7.89 (m, 2H, H-2'), 9.43 (s, 1H, H-3), 10.86 (s, 1H, H-5); δ$_C$ (DMSO-d$_6$) 121.2 (C-2'), 122.6 (C≡N), 130.5 (C-3'), 130.7 (C-4'), 135.8 (C-1'), 142.3 (C-3), 146.6 (C-5).
$^1$H and $^{13}$C NMR spectra for product 28 in DMSO-d$_6$
$^1$H and $^{13}$C NMR spectra for product 112 in DMSO-$d_6$
1,3-Dipolar cycloaddition reactions

Synthesis of 1-methyl-5-imino-6-cyano-7,8-dimethoxycarbonyl imidazo[2,3-a]pyridine 30

A solution of 1-methylimidazolium-3-dicyanomethanide (0.20 g, 1.37 mmol) in acetonitrile (5 cm$^3$) was treated with DMAD (0.17 cm$^3$, 1.38 mmol) and the solution stirred at room temperature for 1 h. During this time the product, compound 30 separated, (0.32 g, 81%), mp 190-192 °C (ethanol), (lit. $^6$, mp 190-191 °C); (Found C, 54.3; H, 4.0; N, 19.55. C$_{13}$H$_{12}$N$_4$O$_4$ requires C, 54.2; H, 4.2; N, 19.4%); $\nu_{\max}$/cm$^{-1}$ 3293 (NH), 2204 (C≡N), 1736, 1709 (C=O), 1610 (C=N); $\delta$H (CDCl$_3$) 3.79 (s, 3H, OCH$_3$), 3.84 (s, 3H, NCH$_3$), 3.96 (s, 3H, OCH$_3$), 7.04 (d, 1H, J 2.3, H-2), 8.01 (d, 1H, J 2.3, H-3); $\delta$C (CD$_3$Cl$_3$) 38.9 (NCH$_3$), 52.4 (OCH$_3$), 53.5 (OCH$_3$), 82.3 (C-6), 88.2 (C-8), 112.2 (C-2), 116.1 (C=N), 124.0 (C-3), 141.3 (C-7), 146.4 (C-8a), 151.2 (C-5), 163.0 (C=O), 166.2 (C=O).

Synthesis of 1-methyl-5-imino-6-cyano-7,8-diethoxycarbonyl imidazo [2,3-a]pyridine 117

A solution of 1-methylimidazolium-3-dicyanomethanide (0.18 g, 1.23 mmol) in acetonitrile (5 cm$^3$) was treated with DEAD (0.20 cm$^3$, 1.23 mmol) and the solution stirred at room temperature for 2 h. The solvent was then removed under reduced pressure and the residue crystallized from methanol to give the product, compound 117, (0.20 g, 51%), mp 129-130 °C (methanol). Evaporation of the methanolic filtrate led only to an oily brown residue and no further product was isolated. (Found C, 56.5; H, 4.9; N, 18.2. C$_{15}$H$_{16}$N$_4$O$_4$ requires C, 56.95; H, 5.1; N, 17.7%); $\nu_{\max}$/cm$^{-1}$ 3291 (NH), 2207 (C=O), 1739, 1697 (C=O), 1619 (C=O); $\delta$H (CDCl$_3$) 1.31 (t, 3H, J 7.1, CH$_3$), 1.42 (t, 3H, J 7.1, CH$_3$), 3.83 (s, 3H, N-CH$_3$), 4.24 (q, 2H, J 7.1, CH$_2$), 4.42 (q, 2H, J 7.1, CH$_2$), 7.04 (d, 1H, J 2.3, H-2), 7.99 (d, 1H, J 2.3, H-3); $\delta$C (CDCl$_3$) 14.1 (2 x CH$_3$), 38.9 (N-CH$_3$) 61.7 (CH$_2$), 62.8 (CH$_2$), 82.1 (C-6), 88.7 (C-8), 112.1 (C-2), 116.1 (C=O), 124.1 (C-3), 141.3 (C-7), 146.3 (C-8a), 151.3 (C-5), 162.7 (C=O), 165.6 (C=O).
$^1$H and $^{13}$C NMR spectra for product 117 in CDCl$_3$
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Synthesis of 1-methyl-5-imino-6-cyano-8-methoxycarbonyl imidazo[2,3-a]pyridine 119

A solution of 1-methylimidazolium-3-dicyanomethanide (0.28 g, 1.92 mmol) in acetonitrile (5 cm$^3$) was treated with MP (0.17 cm$^3$, 1.92 mmol) and the solution stirred at 0-5 °C (ice-bath) for 72 h. The solvent was removed under reduced pressure to give a crude dark brown solid (0.42 g, 95%). Fractional crystallisation from diethyl ether gave 119 as a pale yellow solid (0.23 g, 52%) mp 155-157 °C (ethanol) and a dark red gum. (Found: C, 57.4; H, 4.4; N, 24.3 %); $\nu$ max/cm$^{-1}$ 3107 (NH), 2204 (C≡N), 1723 (C=O), 1613 (C=N); $\delta$H (CDCl$_3$) 3.83 (s, 3H, OCH$_3$), 4.03 (s, 3H, N-CH$_3$), 7.01 (d, 1H, J 2.4, H-2), 8.01 (d, 1H, J 2.4, H-3), 8.05 (s, 1H, H-7); $\delta$C (CDCl$_3$) 39.2 (N-CH$_3$), 51.6 (OCH$_3$), 83.2 (C-6), 90.0 (C-8), 111.7 (C-3), 117.7 (C=N), 123.4 (C-2), 141.9 (C-8a), 142.3 (C-7), 152.2 (C-5), 163.2 (C=O).

Synthesis of 1-methyl-5-imino-6-cyano-8-ethoxycarbonyl imidazo[2,3-a]pyridine 120

A solution of 1-methylimidazolium-3-dicyanomethanide (0.20 g, 1.36 mmol) in acetonitrile (5 cm$^3$) was treated with EP (0.138 cm$^3$, 1.36 mmol) and the solution stirred at ambient temperature for 26 h. The solvent was removed under reduced pressure to give a crude dark brown solid (0.31 g, 93%). Crystallisation from hot ethanol gave 120 as a pale orange solid (0.11 g, 33%), mp 164-165 °C (ethanol); (Found: C, 58.8; H, 5.25; N, 23.0. C$_{12}$H$_{12}$N$_4$O$_2$ requires C, 59.0; H, 4.95; N, 22.9%); $\nu$ max/cm$^{-1}$ 3314 (NH), 2205 (C=N), 1695 (C=O), 1615 (C=N); $\delta$H (CDCl$_3$) 1.36 (t, 3H, J 7.1, CH$_3$), 4.01 (s, 3H, N-CH$_3$), 4.26 (q, 2H, J 7.1, CH$_2$), 6.99 (d, 1H, J 2.3, H-2), 7.99 (d, 1H, J 2.3, H-3), 8.05 (s, 1H, H-7); $\delta$C (CDCl$_3$) 14.5 (CH$_3$), 39.5 (N-CH$_3$), 60.8 (CH$_2$), 83.3 (C-6), 90.6 (C-8), 112.1 (C-2), 118.0 (C=N), 123.5 (C-3), 142.3 (C-8a), 142.8 (C-7), 152.5 (C-5), 163.2 (C=O).
$^1$H and $^{13}$C NMR spectra for product 119 in CDCl$_3$
Synthesis of 1-benzyl-5-imino-6-cyano-7,8-dimethoxycarbonyl imidazo[2,3-a]pyridine 121

A solution of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole (0.22 g, 1.00 mmol) in dimethyl formamide (5 cm³) was cooled to 0 °C, then treated with DMAD (0.123 cm³, 1.00 mmol). The mixture was allowed to stand at 0 °C for 4 h, and subsequently added to cooled water. Compound 121 precipitated as a yellow solid (0.19 g, 53%), mp 131-133 °C (ethanol); (Found: C, 62.3; H, 4.1; N, 15.8. C₁₉H₁₆N₄O₄ requires C, 62.6; H 4.4; N, 15.4%); νmax/cm⁻¹ 3305 (NH), 2208 (C≡N), 1720, 1704 (C=O), 1615 (C=N); δH (CDCl₃) 3.63 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 5.43 (s, 2H, benzyl CH₂), 7.02 (d, 1H, J 1.8, H-2), 7.06-7.08 (m, 2H, H-2' of Ph), 7.33-7.36 (m, 3H, H-3' and H-4' of Ph), 8.00 (d, 1H, J 1.8, H-3); δC(CDCl₃) 52.5 (OCH₃), 53.4 (OCH₃), 54.3 (benzyl CH₂), 82.3 (C-6), 89.1 (C-8), 112.2 (C-2), 116.2 (C=N), 123.1 (C-3), 127.7 (C-2') 129.1 (C-4'), 129.4 (C-3'), 133.9 (C-1'), 140.6 (C-7), 146.1 (C-8a), 151.4 (C-5), 163.3 (C=O), 166.1 (C=O).

Synthesis of 1-benzyl-5-imino-6-cyano-7,8-diethoxycarbonyl imidazo[2,3-a]pyridine 122

A solution of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole (0.30 g, 1.44 mmol) in acetonitrile (8 cm³) was cooled to 0 °C and treated with DEAD (0.232 cm³, 1.44 mmol). The mixture was allowed to stir at 0 °C for 4 h. Compound 122 separated from solution as a yellow solid (0.22 g, 42%), mp 153-155 °C (ethanol); (Found: C, 63.9; H, 4.65; N, 13.9. C₂₁H₂₀N₄O₄ requires C, 64.3; H, 5.1; N, 14.3%); νmax/cm⁻¹ 3303 (NH), 2204 (C≡N), 1727, 1698 (C=O), 1620 (C=N); δH (CDCl₃) 1.24 (t, 3H, J 7.1, CH₃), 1.47 (t, 3H, J 7.1, CH₃), 4.17 (q, 2H, J 7.1, CH₂), 4.45 (q, 2H, J 7.1, CH₂), 5.53 (benzyl CH₂), 7.07 (d, 1H, J 2.2, H-2), 7.14-7.16 (m, 2H, H-2' of Ph), 7.40-7.45 (m, 3H, Ph H-3'and H-4' of Ph), 8.07 (d, 1H, J 2.2, H-3); δC(CDCl₃) 13.7 (CH₃), 13.9 (CH₃), 54.1 (benzyl CH₂), 61.5 (CH₂), 62.6 (CH₂), 82.1 (C-6), 89.3 (C-8), 112.0 (C-2), 116.0 (C=N), 122.8 (C-3), 127.6 (C-2'), 128.9 (C-4'), 129.2 (C-3') 133.9 (C-1'), 140.5 (C-7), 146.0 (C-8a), 151.3 (C-5), 162.9 (C=O), 165.4 (C=O).
$^1$H and $^{13}$C NMR spectra for product 121 in CDCl$_3$
Chapter 2

Synthesis of 1-benzyl-5-imino-6-cyano-8-methoxycarbonyl imidazo[2,3-a]pyridine 123

A solution of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole (0.39 g, 1.76 mmol) in acetonitrile (16 cm³) was treated with ethyl propiolate (0.178 cm³, 1.76 mmol). The mixture was stirred at ambient temperature for 51 h. The solvent was removed under reduced pressure, yielding a sticky brown solid. Fractional crystallization from diethyl ether gave 124 as a pale yellow solid (0.15 g, 27%), mp 133-134 °C (ethanol) and an orange gum. The orange gum was subjected to a Soxhlet extraction with ether which yielded further 124 (0.20 g, 36%). (Found: C, 67.1; H, 4.8; N, 17.4. C₁₅H₁₆N₄O₂ requires C, 67.5; H, 5.0; N, 17.4%); v max/cm⁻¹ 3289 (NH), 2206 (C≡N), 1682 (C=O), 1613 (C=N); δ H (CDCl₃) 4.21 (q, 2H, J 7.1, CH₂), 5.74 (s, 2H, benzyl CH₂), 6.98 (d, 1H, J 2.3, H-2), 7.09-7.11 (m, 2H, H-2' of Ph), 7.31-7.35 (m, 3H, H-3' and H-4' of Ph), 8.00 (d, 1H, J 2.3, H-3), 8.02 (s, 1H, H-7); δ C (CDCl₃) 14.4 (CH₃), 54.4 (benzyl CH₂), 61.0 (CH₂), 83.6 (C-6), 91.1 (C-8), 112.4 (C-2), 118.0 (C≡N), 122.4 (C-3), 127.8 (C-2'), 128.8 (C-4'), 129.4 (C-2'), 133.9 (C-1'), 141.9 (C-8a), 143.0 (C-7), 152.7 (C-5), 163.5 (C=O).

Synthesis of 1-benzyl-5-imino-6-cyano-8-ethoxycarbonyl imidazo[2,3-a]pyridine 124

A solution of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole (0.30 g, 1.44 mmol) in acetonitrile (8 cm³) was treated with methyl propiolate (0.128 cm³, 1.44 mmol). The mixture was allowed to stir at ambient temperature for 48 h. Compound 123 separated from solution as a buff solid (0.21 g, 48%), mp 190-191 °C (ethanol); (Found: C, 66.8; H, 4.1; N, 18.2. C₁₇H₁₄N₄O₂ requires C, 66.7; H, 4.6; N, 18.3%); v max/cm⁻¹ 3292 (NH), 2203 (C≡N), 1694 (C=O), 1616 (C=N); δ H (CDCl₃) 3.78 (s, 3H, OCH₃), 5.76 (s, 2H, benzyl CH₂), 7.00 (d, 1H, J 2.2, H-2), 7.12-7.14 (m, 2H, H-2' of Ph), 7.31-7.35 (m, 3H, H-3' and H-4' of Ph), 8.03 (d, 1H, J 2.2, H-3), 8.04 (s, 1H, H-7); δ C (CDCl₃) 51.8 (OCH₃), 54.2 (benzyl CH₂), 83.5 (C-6), 90.4 (C-8), 112.2 (C-2), 117.7 (C≡N), 122.2 (C-3), 127.6 (C-2'), 128.6 (C-4'), 129.0 (C-3') 134.7 (C-1'), 141.7 (C-8a), 142.7 (C-7), 152.3 (C-5), 163.1 (C=O).
$^1$H and $^{13}$C NMR spectra for product 123 in CDCl$_3$
Synthesis of 1-phenyl-5-imino-6-cyano-7,8-dimethoxycarbonyl imidazo [2,3-a]pyridine 125

A solution of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole (0.30 g, 1.44 mmol) in acetonitrile (26 cm$^3$) was treated with DMAD (0.177 cm$^3$, 1.44 mmol). The mixture was stirred at ambient temperature for 3.5 h. The solvent was removed under reduced pressure at room temperature yield a brown gum which solidified overnight. Crystallisation from hot ethanol yielded compound 125 (0.34 g, 67%), mp 176-177 °C (Lit. $^{35}$ 177-178 °C); (Found: C, 61.2; H, 4.1; N, 15.9. C$_{18}$H$_{14}$N$_4$O$_4$ requires C, 61.7; H, 4.0; N, 16.0%); $\nu_{\max}$/cm$^{-1}$ 3320 (NH), 2206 (C≡N), 1724, 1696 (C=O), 1617 (C=N); $\delta_H$ (CDCl$_3$) 2.99 (s, 3H, OCH$_3$), 3.92 (s, 3H, OCH$_3$), 7.22 (d, 1H, J 1.9, H-2), 7.31-7.33 (m, 2H, H-2' of N-Ph) 7.48-7.55 (m, 3H, H-3' and H-4' of N-Ph), 8.12 (d, 1H, J 1.9, H-3); $\delta_C$ (CDCl$_3$) 51.5 (OCH$_3$), 53.6 (OCH$_3$), 82.8 (C-6), 88.4 (C-8), 112.8 (C-2), 116.0 (C=N), 123.8 (C-3), 124.2 (C-2'), 129.6 (C-4'), 130.3 (C-3'), 138.2 (C-1'), 140.5 (C-8a), 146.9 (C-7), 151.3 (C-5), 162.4 (C=O), 165.9 (C=O).

Synthesis of 1-phenyl-5-imino-6-cyano-7,8-diethoxycarbonyl imidazo [2,3-a]pyridine 126

A solution of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole (0.20 g, 0.96 mmol) in acetonitrile (12 cm$^3$) was treated with DEAD (0.154 cm$^3$, 0.96 mmol). The mixture was stirred at ambient temperature for 3.5 h. The solvent was removed under reduced pressure at room temperature yield a brown gum which solidified overnight. Crystallisation from hot ethanol yielded compound 126 (0.20 g, 55%), mp 117-119 °C; (Found: C, 62.9; H, 4.5; N, 14.6. C$_{20}$H$_{18}$N$_4$O$_4$ requires C, 63.5; H, 4.8; N, 14.8%); $\nu_{\max}$/cm$^{-1}$ 3296 (NH), 2206 (C≡N), 1730, 1710 (C=O), 1615 (C=N); $\delta_H$ (CDCl$_3$) 0.93 (t, 3H, J 7.2, CH$_3$), 1.40 (t, J 7.1, 3H, CH$_3$), 3.52 (q, J 7.1, 2H, CH$_2$), 4.42 (q, 2H, J 7.2, CH$_2$), 7.23 (d, 1H, J 2.5, H-2), 7.35-7.37 (m, 2H, H-2' of N-Ph), 7.50-7.54 (m, 3H, H-3' and H-4' of N-Ph), 8.16 (d, J 2.5, 1H, H-3); $\delta_C$ (CDCl$_3$) 13.7 (CH$_3$), 13.8 (CH$_3$), 61.0 (CH$_2$), 62.7 (CH$_2$) 82.3 (C-6), 89.0 (C-8), 112.6 (C-2), 115.9 (C=N), 123.5 (C-3), 124.0 (C-2'), 129.4 (C-4'), 130.0 (C-3'), 137.8 (C-1'), 140.2 (C-8a), 146.3 (C-7), 151.3 (C-5), 162.0 (C=O), 165.2 (C=O).
$^1$H and $^{13}$C NMR spectra for product 125 in CDCl$_3$
$^1$H and $^{13}$C NMR spectra for product 126 in CDCl$_3$
Synthesis of 1-phenyl-5-imino-6-cyano-8-methoxycarbonyl imidazo[2,3-a]pyridine 127

A solution of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole (0.20 g, 0.96 mmol) in acetonitrile (15 cm³) was treated with methyl propiolate (0.085 cm³, 0.96 mmol). The mixture was stirred at ambient temperature for 48 h. Compound 127 separated from solution as a buff precipitate (0.07 g, 25%), mp 198-200 °C (Lit.35 205-206 °C); (Found: C, 65.2; H, 4.1; N, 19.3. C₁₆H₁₂N₄O₂ requires C, 65.7; H, 4.1; N, 19.2%); νmax/cm⁻¹ 3314 (NH), 2198 (C≡N), 1688 (C=O), 1621 (C=N); δH (CDCl₃) 3.20 (s, 3H, OCH₃), 7.17 (d, 1H, J 2.4, H-2), 7.30-7.32 (m, 2H, H-2' of N-Ph) 7.48-7.56 (m, 3H, H-3' and H-4' of N-Ph), 8.01 (s, 1H, H-7), 8.16 (d, 1H, J 2.4, H-3); δC (CDCl₃) 51.3 (CH₃), 84.6 (C-6), 90.3 (C-8), 112.7 (C-2), 117.7 (C=N), 123.3 (C-3), 124.3 (C-2'), 129.3 (C-4'), 129.9 (C-3'), 138.9 (C-1'), 141.4 (C-8a), 143.1 (C-7), 152.5 (C-5), 163.0 (C=O).

Synthesis of 1-phenyl-5-imino-6-cyano-8-ethoxycarbonyl imidazo[2,3-a]pyridine 128

A solution of 1-phenylimidazolium-3-dicyanomethanide 1,3-dipole (0.20 g, 0.96 mmol) in acetonitrile (15 cm³) was treated with ethyl propiolate (0.097 cm³, 0.96 mmol). The mixture was stirred at ambient temperature for 51 h. Solvent was removed under reduced pressure to yield a crude dark brown solid (0.29 g, 98%). This was recrystallized from ethanol to yield clean 128 (0.13 g, 44%) mp 191-192 °C (ethanol); (Found: C, 66.4; H, 4.2; N, 18.3. C₁₇H₁₄N₄O₂ requires C, 66.7; H, 4.6; N, 18.3%); νmax/cm⁻¹ 3314 (NH), 2205 (C≡N), 1683 (C=O), 1621 (C=N); δH (CDCl₃) 0.97 (t, 3H, J 7.1, CH₃), 3.72 (q, 2H, J 7.1, CH₂), 7.18 (d, 1H, J 2.5, H-2), 7.30-7.32 (m, 2H, H-2' of N-Ph), 7.46-7.52 (m, 3H, H-3' and H-4' of N-Ph), 7.99 (s, 1H, H-7), 8.11 (d, 1H, J 2.5, H-3); δC (CDCl₃) 14.2 (CH₃), 60.6 (CH₂), 84.3 (C-6), 90.7 (C-8), 112.7 (C-2), 117.9 (C=N), 123.3 (C-3), 124.1 (C-2'), 129.2 (C-4'), 129.9 (C-3'), 138.9 (C-1'), 141.3 (C-8a), 143.0 (C-7), 152.6 (C-5), 162.6 (C=O).
Reaction of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole with maleic anhydride

A solution of 1-methylimidazolium-3-dicyanomethanide (0.48 g, 3.28 mmol) in acetonitrile (10 cm$^3$) was treated with a solution of maleic anhydride (0.32 g, 3.26 mmol) in acetonitrile, and the mixture stirred at room temperature for 3 h. The solution was then evaporated under reduced pressure at a temperature below 35 °C. Addition of ether to the residue caused precipitation of the green product, compound 135 (0.58 g, 70%), mp 180-181 °C (from acetonitrile). Evaporation of the ethereal solution only led to isolation of an oily residue. (Found: C, 54.35; H, 3.60; N, 22.70. C$_{11}$H$_8$NaO$_3$ requires C, 54.10; H, 3.30; N, 22.95%); $\nu_{\text{max}}$/cm$^{-1}$ 3330 cm$^{-1}$(N-H), 2175 (C≡N), 1792, 1734 (C=O); $\delta$H NMR (DMSO-d$_6$) 3.80 (s, 3H, N-CH$_3$), 5.12 (s, 1H, H-9), 7.53 (s, 1H, H-2), 7.58 (s, 1H, H-3), 8.84 (s, 1H, H-5); $\delta$C NMR (DMSO-d$_6$) 35.8 (N-CH$_3$), 59.7 (C-7), 92.1 (C-9), 118.3 (C=N), 119.7 (C-8), 120.7 (C-2), 123.4 (C-3), 136.3 (C-5), 149.6 (C-6), 165.0 (C=O), 165.8 (C=O); for C-7 pulse delay 5 s, >9000 scans).

Reaction of 1-benzylimidazolium-3-dicyanomethanide 1,3-dipole with maleic anhydride

A solution of 1-benzylimidazolium-3-dicyanomethanide (0.27 g, 1.21 mmol) in acetonitrile (10 cm$^3$) was treated with a solution of maleic anhydride (0.12 g, 1.22 mmol) in acetonitrile (5 cm$^3$), and the solution stirred for 27 h at 50 °C under N$_2$. The solution was then evaporated under reduced pressure at ambient temperature to yield compound 136 as a sticky brown solid (0.33 g, 86%); $\delta$H NMR (CD$_3$CN) 5.24 (s, 1H, H-9), 5.31 (s, 2H, CH$_2$), 7.27-7.39 (m, 7H, H-2, H-3 and Ph), 8.52 (s, 1H, H-5), 9.8 - 11.62 (broad s, 1H, NH); $\delta$C NMR (CD$_3$CN) 52.4 (CH$_2$), 62.2 (C-7), 92.2 (C-9), 118.8 (C=N), 119.5 (C-8), 121.5 (C-2), 121.8 (C-3), 128.5 (C-2'), 129.1 (C-4'), 129.3 (C-3'), 134.2 (C-1'), 135.4 (C-5), 150.0 (C-6), 165.4 (C=O), 166.1 (C=O); (for C-7 pulse delay 4 s, 12,800 scans).
$\text{H NMR spectra for product } 135 \text{ (DMSO-d$_6$) and 136 (CD$_3$CN)}$
Reaction of 1-methylimidazolium-3-dicyanomethanide 1,3-dipole with N-phenylmaleimide

A solution of 1-methylimidazolium-3-dicyanomethanide (0.50 g, 3.42 mmol) in acetonitrile (8 cm$^3$) was treated with a solution of N-phenylmaleimide (0.59 g, 3.42 mmol) in acetonitrile (5 cm$^3$). The mixture was stirred at ambient temperature for 2 h during which time the product, compound 132 precipitated as an orange solid (0.84 g, 77%), mp >300 °C. Evaporation of the filtrate led a dark red gum and no further product was isolated. (Found: C, 64.0; H, 3.75; N, 22.4. C$_{17}$H$_{11}$N$_5$O$_2$ requires C, 64.35; H, 3.5; N, 22.1%); $\nu_{\text{max}}$/cm$^{-1}$ 3307 (NH), 2209 (C≡N), 1759, 1708 (C=O), 1614 (C=N); $\delta_H$ (DMSO-d$_6$) 4.28 (s, 3H, CH$_3$), 7.40-7.47 (m, 3H, H$_3$ and H$_4'$ of N-Ph), 7.51-7.55 (m, 2H, H$_2'$ of N-Ph), 8.16 (s, 1H, H-2), 8.44 (s, 1H, H-3); $\delta_C$ (DMSO-d$_6$) 38.2 (N-CH$_3$), 76.4 (C-8), 112.9 (C=N), 113.8 (C-2), 127.9 (C-2'), 128.1 (C-7), 129.1 (C-4'), 129.6 (C-3'), 131.7 (C-3), 137.1 (C-1'), 140.7 (C-8a), 151.5 (C-5), 163.0 (C=O), 163.9 (C=O).

Reaction of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 1,3-dipole with DMAD: isolation of the initial cycloadduct

Synthesis of 1-phenyl-5,5-dicyano-6,7-dimethoxycarbonyl-5,8-dihydropyrrolo[1,2-d]1,2,4-triazole 143

A solution of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 1,3-dipole (0.37 g, 1.77 mmol) in DMF (20 cm$^3$), cooled to 0 °C, was treated with DMAD (0.218 cm$^3$, 1.77 mmol), and allowed to stand at 0 °C for 4.5 h. The resulting mixture was filtered through a cooled funnel, and the filtrate added to ice-cold water. The resulting brown precipitate was collected on a jacketed sintered glass funnel at -5 °C, washed with ethanol (10 x 1 cm$^3$, 0 °C) and diethyl ether (3 x 1 cm$^3$, 0 °C). The crude product 143 cannot be purified further since it affords 144 by simple crystallization. Compound 143: (0.44 g, 71%); $\delta_H$ (CD$_3$CN, 0 °C) 3.67 (s, 3H, OCH$_3$), 3.85 (s, 3H, OCH$_3$), 6.77 (s, 1H, H-7a), 6.92 – 6.96 (m, 2H, H-3 and H-4' of N-Ph) 7.27 – 7.32 (m, 2H, H-2' of N-Ph), 7.30 (s, 1H, H-3); $\delta_C$ (CD$_3$CN, 0 °C ) 53.6 (OCH$_3$), 53.9
(OCH₃), 58.6 (C-5), 86.1 (C-7a), 109.6, 111.6 (C≡N), 113.6 (C-2'), 121.6 (C-4'), 127.5 (C-6), 129.6 (C-3') 138.5 (C-3), 143.2 (C-7), 148.4 (C-1'), 159.0 (C=O), 162.1 (C=O).

δ_H (CDCl₃, -10 °C) 3.70 (s, 3H, OCH₃), 3.96 (s, 3H, OCH₃), 6.59 (s, 1H, H-7a), 6.98 – 7.02 (m, 2H, H-3 and H-4' of N-Ph), 7.11 (s, 1H, H-3), 7.30 – 7.34 (m, 2H, H-2' of N-Ph).

**Reaction of 1-phenyl-1,2,4-triazolium-4-dicyanomethanide 1,3-dipole with DMAD: isolation of the ring expanded product**

**Synthesis of 1-phenyl-5-imino-6-cyano-7,8-dimethoxycarbonyl-1,2,4-triazolo[4,5-a]pyridine 144**

A solution of 143 (0.20 g, 0.50 mmol) in CH₃CN (15 cm³) was stirred at 50 °C for 2 h and then ambient temperature for 50 h. Removal of the solvent under reduced pressure yielded compound 144 (0.16 g, 80%), mp 167 °C (lit.⁵⁵, mp 172-174 °C); (Found: C, 58.1; H, 3.8; N, 20.2. C₁₇H₁₃N₅O₄ requires C, 58.1; H, 3.7; N, 19.9%); ν_max/cm⁻¹ 3316 (NH), 2204 (C≡N), 1742, 1714 (C=O), 1624 (C=N); δ_H (CD₃CN) 2.96 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 7.39-7.41 (m, 2H, H-2' of N-Ph) 7.51-7.57 (m, 3H, H-3' and H-4' of N-Ph), 9.14 (s, 1H, H-3); δ_C (CD₃CN) 51.1 (OCH₃), 53.3 (OCH₃), 83.3 (C-6), 86.4 (C-8), 115.2 (C≡N), 124.5 (C-2'), 129.8 (C-3'), 129.9 (C-4'), 135.1 (C-3), 139.0 (C-7), 144.1 (C-8a), 149.1 (C-1'), 149.5 (C-5), 161.9 (C=O), 165.9 (C=O).

δ_H (CDCl₃) 3.03 (s, 3H, OCH₃), 3.96 (s, 3H, OCH₃), 7.38-7.40 (m, 2H, H-2' of N-Ph) 7.50-7.56 (m, 3H, H-3' and H-4' of N-Ph), 9.09 (s, 1H, H-3); δ_C (CDCl₃) 51.5 (OCH₃), 53.8 (OCH₃), 85.2 (C-6), 86.0 (C-8), 114.8 (C≡N), 124.2 (C-2'), 129.8 (C-3'), 130.0 (C-4'), 134.7 (C-3), 138.8 (C-7), 143.5 (C-8a), 149.4 (C-1'), 149.6 (C-5), 161.6 (C=O), 165.5 (C=O).
$^{1}$H and $^{13}$C NMR spectra for product 143 in CD$_3$CN at 0 °C
$^1$H and $^{13}$C NMR spectra for product 144 in CDCl$_3$
Chapter 3

A study of synthesis, kinetics and water solvent effects in the reactions of phthalazinium-2-dicyanomethanide with $p$-substituted benzyldiene acetones: comparisons with substituted styrenes and alkyl vinyl ketones
Chapter 3

3.1 Introduction

Historically, chemists have avoided using water as a reaction medium for organic chemical reactions. Organic solvents have traditionally been selected based on their ability to dissolve reactants, thereby ensuring that the compounds are fully available for reaction. Water has also been eschewed in order to avoid hydrolysis and other unwanted interactions with reactants, intermediates and products.

However, interest in the use of water as a reaction solvent has greatly increased over the last number of years. In part, this can be associated with an increase in concern for the environment. Water is a green solvent, non-toxic, non-flammable and easily handled. Water is also abundantly available and relatively cheap to process. The replacement of organic solvents with water has the potential to have both positive environmental and financial impacts for the chemical industry.

The increased interest in water is also associated with the remarkable effects water can have on chemical reactions. Breslow was the first to report the increase in reaction rate associated with completing the Diels-Alder reaction in water. It was observed that the reaction of cyclopentadiene $\text{156}$ and methyl vinyl ketone $\text{157}$ to form compound $\text{158}$ was more than 700 times faster in water than in the hydrocarbon solvent isooctane. Completing the reaction in methanol let to a modest 12-fold increase in rate over isooctane (Scheme 49). This suggested that the large rate increase in water was not simply due to a solvent polarity effect.

Scheme 49
The reaction of cyclopentadiene 156 with acrylonitrile 159 to form 160 was also investigated\textsuperscript{82} in various solvents (Scheme 49). A significant rate increase was observed on completing the reaction in water rather than isooctane. Once again, a more modest increase was observed on using methanol as solvent. Overall it was demonstrated that water had much more beneficial effect on the rate of the methyl vinyl ketone 157 reaction rather than the acrylonitrile 159 reaction (Table 11). Breslow\textsuperscript{82} proposed that the large rate acceleration observed was due to the hydrophobic effect.

**Table 11:** Kinetic data for the reactions of cyclopentadiene 156 with methyl vinyl ketone 157 and acrylonitrile 159

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Additional Component</th>
<th>(k_2/10^5) (M(^{-1})s(^{-1})) (^a)</th>
<th>Relative Rate (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclopentadiene 156 and methyl vinyl ketone 157 at 20 °C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isooctane</td>
<td>-</td>
<td>5.94</td>
<td>1.0</td>
</tr>
<tr>
<td>Methanol</td>
<td>-</td>
<td>75.5</td>
<td>12.0</td>
</tr>
<tr>
<td>Water</td>
<td>-</td>
<td>4400.0</td>
<td>740</td>
</tr>
<tr>
<td>Water LiCl (4.86M)</td>
<td>10800.0</td>
<td>1818</td>
<td></td>
</tr>
<tr>
<td>Water GnCl (4.86M)</td>
<td>4300</td>
<td>722</td>
<td></td>
</tr>
<tr>
<td>Cyclopentadiene 156 and acrylonitrile 159 at 30 °C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isooctane</td>
<td>-</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Methanol</td>
<td>-</td>
<td>4.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Water</td>
<td>-</td>
<td>59.3</td>
<td>31.0</td>
</tr>
</tbody>
</table>

\(^a\) M\(^{-1}\)s\(^{-1}\) = dm\(^3\)mol\(^{-1}\)s\(^{-1}\)

\(^b\) Relative to isooctane.

### 3.1.1 The hydrophobic effect

The hydrophobic effect is the tendency of non-polar species to aggregate in water solution so as to decrease the hydrocarbon-water interfacial area.\textsuperscript{83} As such, it is a specific example of solvophobicity. Breslow\textsuperscript{84} has claimed that packing of the non-polar surfaces in the transition states of the reactions is favoured in water, thereby lowering the transition energies and increasing reaction rates.
Chapter 3

Breslow has probed the hydrophobic effect by examining the effect of adding various salts to the reaction mixtures. Structure making salts, such as LiCl, were found to increase the hydrophobic effect by promoting electrostriction (increased structure making) of water. This decreases the solubility of organic molecules and thus promotes their association. The effect parallels the technique of “salting out” used to drive the partition of an organic product into an organic layer during aqueous-organic solvent extractions by adding NaCl to the water. The increase in hydrophobic effect is accompanied by an increase in reaction rate. Completing the reaction of cyclopentadiene 156 with methyl vinyl ketone 157 in 4.86 molar LiCl solution increased the reaction rate 2.5 fold over that in pure water (Table 11).

Structure breaking salts (e.g. guanidinium chloride) had the opposite effect, causing a reduction in the hydrophobic effect. There was a 3 fold decrease in reaction rate when the reaction was completed in 4.86 molar GnCl solution versus the rate in pure water. Breslow has suggested that the “salting in” effect observed with these salts is more complex than a simple structure breaking effect. The anti-hydrophobic effect of the salt is the result of directly solvating hydrocarbons rather than disrupting the water structure.

Breslow has also demonstrated that completing reactions in water has the potential to influence the endo/exo ratio of products in a Diels-Alder reaction. The reaction of cyclopentadiene 156 with methyl vinyl ketone 157 (Scheme 50) displayed a large increase in the endo/exo ratio when completed in water (21.4) as opposed to excess cyclopentadiene 156 (3.85) or ethanol (8.5).

![Scheme 50](image)
Reactions with methyl acrylate 163, dimethyl maleate 59 and methyl methacrylate 70 also display an increased preference for the \textit{endo} cycloadduct in water (Figure 56, Table 12). The enhancements are not as large as experienced by methyl vinyl ketone 157, but a clear trend of \textit{endo}-isomer enhancement in water is apparent. Breslow\textsuperscript{87} has suggested that hydrophobic effects favour the \textit{endo} transition state due to its smaller exposed non-polar surface. The \textit{endo}-transition states for these reactions are more compact than the \textit{exo}-transition states, and so are more favoured when water is used as the reaction solvent.

This conclusion is supported by the impact of salts on the \textit{endo/exo} ratio of reaction of cyclopentadiene 156 with methyl vinyl ketone 157 (Scheme 50). Adding LiCl to the reaction mixture increased the preference for the \textit{endo} isomer by increasing the hydrophobic effect. The presence of guanidinium chloride had the opposite effect, leading to a decrease in the \textit{endo-exo} ratio. Therefore the \textit{endo-exo} ratio of this reaction in water can be manipulated by using salts to adjust the strength of the hydrophobic effect.

![Figure 56]

\textbf{Table 12:} Cycloadduct \textit{endo/exo} ratios\textsuperscript{86} for the reactions of cyclopentadiene 156 with selected dipolarophiles in various solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Methyl vinyl ketone 157</th>
<th>Methyl acrylate 163</th>
<th>Dimethyl maleate 59</th>
<th>Methyl methacrylate 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclopentadiene</td>
<td>3.85</td>
<td>2.9</td>
<td>2.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Ethanol</td>
<td>8.5</td>
<td>5.2</td>
<td>4.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Water</td>
<td>21.4</td>
<td>9.3</td>
<td>13.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>

120
Engberts\textsuperscript{88} has used the term “enforced” hydrophobic interactions to distinguish the bonding of reactants during the activation process from other hydrophobic interactions which may lead to complexes of different geometries. The enforced hydrophobic aggregation of organic molecules results in an increase in the Gibbs free enthalpy of the starting materials. However the activated complexes and transitions states of these reactions remain unaffected by hydrophobic effect and so overall there is a reduction in activation energy.\textsuperscript{89, 90} Engberts\textsuperscript{91} has also demonstrated that in addition to the hydrophobic effect, changes in hydrogen bonding effects during the activation process play a key role in rate enhancements.

3.1.2 Special hydrogen bonding

Water molecules will form H-bonds with reactants that contain hydrogen bond acceptors, both in the initial and reaction transition states. H-bonding lowers the energy of frontier molecular orbitals by reducing electron density and inter-orbital repulsion. Water H-bonding therefore has a similar effect to electron withdrawing substituents on frontier molecular orbitals.

The relative lowering of frontier molecular orbital energies impacts on a cycloaddition reaction’s HOMO-LUMO energy gap. In cases where the gap is lowered the reaction rate will be increased. However, water H-bonding may also cause an increase in the HOMO-LUMO energy gap, and so lead to a decrease in reaction rate. The impact of H-bonding is therefore governed by the dominant HOMO-LUMO gap and the number and strength of hydrogen bond acceptors on the reactants (Figure 57).
The reactions of cyclopentadiene 156 with two structurally related dienophiles, methyl vinyl ketone 157 (Scheme 50) and methyl vinyl sulfone 164 (Scheme 51), show the importance of hydrogen bonding interactions. Methyl vinyl sulfone 164 is a weaker H-bond acceptor than methyl vinyl ketone 157 due to the insulating effect of the sulfur atom. 88, 92 The decreased sensitivity of methyl vinyl sulfone 164 to hydrogen bonds resulted in a smaller water related rate increase than that experienced by methyl vinyl ketone 157. The reaction of cyclopentadiene 156 with methyl vinyl sulfone 164 also underwent much less pronounced accelerations in ethanol and hexafluoropropanol (Table 13).

Scheme 51
Chapter 3

Table 13: Relative rate constants\textsuperscript{92} of cyclopentadiene 156 with methyl vinyl ketone 157 and methyl vinyl sulfone 164 in water and organic solvents of different hydrogen bonding capacities

<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>CH\textsubscript{3}CN</th>
<th>EtOH</th>
<th>HFP</th>
<th>H\textsubscript{2}O</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl vinyl ketone 157</td>
<td>1</td>
<td>4.97</td>
<td>100</td>
<td>290</td>
</tr>
<tr>
<td>methyl vinyl sulfone 164</td>
<td>1</td>
<td>2.49</td>
<td>23</td>
<td>71</td>
</tr>
</tbody>
</table>

Jorgenson\textsuperscript{93, 94} has stated that the hydrophobic effect contributes a relatively constant rate enhancement while special hydrogen bonding effects in the transition state are primarily responsible for large rate increases. Computer simulations\textsuperscript{93} have been used to determine that the free energies of activation for the reactions of cyclopentadiene 156 with acrylonitrile 159, methyl vinyl ketone 157 (Scheme 49) and naphtoquinone 165 (Scheme 52) were reduced by 1.5, 2.8 and 4.4 kcal mol\textsuperscript{-1} respectively on going from gas phase to water solution. These values are in good agreement with experimental results for transfer from hydrocarbon solvents to water (2.1, 3.8 and 5.0 kcal mol\textsuperscript{-1} respectively).

\begin{center}
\begin{tikzpicture}
  \node at (0,0) (cyclopentadiene) {\includegraphics[width=0.5\textwidth]{cyclopentadiene.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 52}

It was concluded that the rate accelerations observed for these reactions is primarily due to enhanced hydrogen bonding between water molecules and the polarized transition states. The hydrophobic association of reactants was acknowledged as also contributing to the rate accelerations.
3.1.3 Polarity effects

Engberts\textsuperscript{88} has also investigated the possibility that the activated complex in a Diels-Alder reaction may have more polar character in water than in other solvents. Water is a highly polar solvent, and so reactions with transition states more polar than the initial states would be expected to be faster in water. The Hammett rho value\textsuperscript{95} ($\rho$) may be used to determine the polarity or development of charge in reaction transition states. The Diels-Alder reaction between 5-substituted-1,4-naphtoquinone 167 and cyclopentadiene 156 (Scheme 53) was chosen for investigation.

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

\textbf{Scheme 53}

Hammet plots were used to assess the substituents effects on the reaction in water compared with a series of six organic solvents. Larger substituents effects in water than in the other solvents would be expected for an activated complex experiencing a larger build-up of charge in the water.

Considering that the substituents are three bonds away from the reacting double bond, the $\rho$-values obtained indicate that the activated complex is rather polar, even in organic solvents. Rho values of 1.6 and 1.3 were obtained for $n$-hexane and acetonitrile, respectively. Hammett plots in protic solvents, particularly water and hexafluoro-2-propanol (HFP), were strongly non-linear. This is in part due to unexpected solvent-dependent behaviour associated with the methoxy substituent. This substituent slowed the reaction in $n$-heptane as expected for a HOMO$_{\text{diene}}$-LUMO$_{\text{dienophile}}$ controlled reaction. However the reaction was accelerated in water and HFP, possibly due to a solvent-mediated interaction between the methoxy group and the nearby carbonyl group. It was concluded that the charge separation in the activated complex in water was not dissimilar from that in the other solvents studied.
3.1.4 “On Water” reactions

Investigations into the use of water as solvent initially involved dilute, homogenous solutions in which both reactants were in the same phase. This allowed reaction kinetics to be measured directly and also satisfied the widely held belief that reactants must be in solution to react successfully. Breslow\textsuperscript{87} and Grieco\textsuperscript{96} provided rare examples of reactions completed in aqueous suspensions, however overall scant attention was paid to the kinetics of reactions under heterogeneous aqueous conditions.\textsuperscript{97}

In 2005, Sharpless\textsuperscript{98} and co-workers demonstrated that a number of reactions involving water insoluble reactants undergo substantial rate accelerations when stirred in aqueous suspension. The reaction of quadricyclane \textbf{169} with dimethyl azodicarboxylate \textbf{170} (Scheme 54) in toluene or benzene at 80 °C requires 24 h or longer to reach completion. The “on water” reaction is completed in 10 minutes at ambient temperature.

![Scheme 54]

The “on water” method involves vigorously stirring water insoluble reactants with water to generate an aqueous suspension. As the reactants are initially floating on the surface of water, the term “on water” is used to describe the method. The reaction product is also typically water insoluble, allowing for easy isolation by phase separation or filtration.

It was demonstrated\textsuperscript{98} that both the presence of water and a heterogeneous reaction mixture was crucial for the large rate increases. Methanol could be added to the quadricyclane \textbf{169} with dimethyl azodicarboxylate \textbf{170} (Scheme 54) reaction mixture with no impact on rate, up until the point the reaction mixture became homogenous. The presence of water in the reaction mixture however led to
significant rate increase compared the reaction completed in pure methanol. Completing the reaction “on perfluorohexane” only led to a modest rate increase relative to the neat reaction, indicating that heterogeneity alone was not the reason for the rate enhancements.

Table 14: Reaction of quadricyclane 169 with dimethyl azodicarboxylate 170 in various solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Concentration</th>
<th>Time to Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>2</td>
<td>&gt; 120 hours</td>
</tr>
<tr>
<td>MeOH</td>
<td>2</td>
<td>18 hours</td>
</tr>
<tr>
<td>Neat</td>
<td>4.53</td>
<td>48 hours</td>
</tr>
<tr>
<td>On perfluorohexane</td>
<td>4.53</td>
<td>36 hours</td>
</tr>
<tr>
<td>On water</td>
<td>4.53</td>
<td>10 min</td>
</tr>
<tr>
<td>MeOH/H$_2$O (3:1 homogeneous)</td>
<td>4.53</td>
<td>4 hours</td>
</tr>
<tr>
<td>MeOH/H$_2$O (1:1 heterogeneous)</td>
<td>4.53</td>
<td>10 min</td>
</tr>
<tr>
<td>MeOH/H$_2$O (1:3 heterogeneous)</td>
<td>4.53</td>
<td>10 min</td>
</tr>
</tbody>
</table>

In 2007, Marcus and Jung\textsuperscript{99} proposed that the rate accelerations associated with “on water” reactions are due to the reactions occurring at the oil-water interface in the aqueous suspensions. In an “on water” reaction, vigorous stirring of the reaction mixture disperses the reactants in the form of oil droplets surrounded by water molecules. Approximately 25\% of water molecules at the surface of the oil-water boundary have a free (or “dangling”) -OH group oriented into the organic phase (Figure 58). These groups play key role in catalyzing reactions through the formation of H-bonds.

The structural arrangement of water around a small hydrophobic solute in homogenous solution is different as “dangling” –OH groups are no longer found at the boundary. Instead the water molecules are arranged such that H-bonds are formed laterally along the boundary, and so there is no catalytic effect (Figure 58). A rate increase\textsuperscript{99} of approximately $1.5 \times 10^{-5}$ fold was estimated for the reaction of
quadricyclane 169 with dimethyl azodicarboxylate 170 (Scheme 54) due to the effects of Marcus trans-phase H-bonding.

**Figure 58:** Depiction of the on water catalysis in comparison to the neat and aqueous homogeneous reactions

Our long standing interest in the impact of water on 1,3-dipolar reactions led us to explore the phthalazinium-2-dicyanomethanide 1,3-dipole 45 dipole system in more detail. The phthalazinium-2-dicyanomethanide 1,3-dipole 45 has been extensively studied in these laboratories. It has been determined that dipole 45 is a Sustmann type II dipole. It can react via normal or inverse electron demand. The change in mechanism is accompanied by a change in regiochemistry (Section 1.4.2, Scheme 11). Reactions between 1,3-dipole 45 and electron rich dipolarophiles are LUMO dipole controlled while reactions with electron poor dipolarophiles are HOMO dipole controlled.

Extensive kinetic studies have also revealed the beneficial impact of water on the reaction rates of 1,3-dipole 45. The introduction of water as cosolvent into cycloaddition reactions of phthalazinium-2-dicyanomethanide 45 in acetonitrile gave small initial rate enhancements followed by larger rate increases as the mole fraction of the solvent mixture approached that of pure water. The influence of water on the rates was about 10 times larger for some dipolarophiles than for others, and these dipolarophiles, which were mainly vinyl ketones, were classified as water-super because of this. Other dipolarophiles, such as vinyl esters and vinyl nitriles showed smaller water effects and were classed as water-normal.
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This chapter deals with the influence of water on the reactions of 1,3-dipole 45 with various dipolarophiles. Mechanistically, we were interested in determining if water influenced the polarity of cycloaddition transition states involving 1,3-dipole 45. We were also interested in investigating the “on water” reactions of 1,3-dipole 45, particularly those involving water-insoluble solids.

3.2 Synthesis of phthalazinium-2-dicyanomethanide 1,3-dipole 45

A process similar to that used to generate the azolium 1,3 dipoles discussed in Chapter 2 was used to produce compound 45. A cooled solution of phthalazine 172 in ethyl acetate was treated dropwise with a cooled solution of TCNEO 8 in ethyl acetate (Scheme 55). The temperature of the reaction was maintained below 12 °C. When the addition was complete the bright yellow compound 45 precipitated from solution in 92% yield. The structure was supported by IR, \(^1\)H and \(^{13}\)C NMR spectra.

\[
\begin{array}{c}
\text{172} \quad \text{8} \quad \text{45}
\end{array}
\]

Scheme 55

The IR spectrum showed two strong cyano signals at 2191 and 2159 cm\(^{-1}\). NMR analysis was carried out using hexadeuteriомethyl sulfoxide (DMSO-d\(_6\)) at 80 °C due to the low solubility of 45 in other solvents. The proton adjacent to the quaternised nitrogen was the most deshielded in the H\(^1\) NMR spectrum and appeared at δ 9.60 (Figure 59).

In the \(^{13}\)C NMR spectrum only one cyano group was observed at 117.2 ppm, the two cyano groups being NMR chemical shift equivalent, similar to the azolium dicyanomethanide 1,3-dipoles (Section 2.2). A very weak signal at 63.5 ppm was observed in the \(^{13}\)C NMR for the methanide carbon. A pulse delay of 10 seconds was used when the spectrum was being measured.
3.3 Synthetic study of the reactions of phthalazinium-2-dicyanomethanide 1,3-dipole 45 with \( p \)-substituted benzyldiene acetone dipolarophiles in acetonitrile

The benzyldiene acetone molecule (systematic name: 4-arylbut-3-en-2-one) can be looked upon as comprising of two separate fragments- a styrene and an alkyl vinyl ketone. Styrene 173 is a water-normal dipolarophile while methyl vinyl ketone 157 is a water-super dipolarophile.\(^{34, 44}\) The synthetic course\(^ {43}\) of the separate reactions of 45 with styrene 173 and methyl vinyl ketone 157 is summarized below (Scheme 56).
When both of the styrene and vinyl ketone features are included in a single dipolarophile (benzylidene acetone), the products 176 and 177 (Figure 60) might be expected from transition states comparable to those by which 174 and 175 are formed (Scheme 56). However activation energies calculated in collaboration with Prof. Luke Burke predicted that the regiochemistry would be reversed. The phthalazinium-2-dicyanomethanide 1,3-dipole 45 was reacted with a number of p-substituted benzylidene acetones in order to determine the regiochemistry of the reaction.

![Figure 60](image)

**3.3.1 Cycloaddition reaction of phthalazinium-2-dicyanomethanide 1,3-dipole 45 with benzylidene acetone 178**

A suspension of the phthalazinium-2-dicyanomethanide 1,3-dipole 45 in acetonitrile was treated with benzylidene acetone (4-phenyl-3-buten-2-one) 178 and then stirred under reflux for 4.5 h (Scheme 57). The solvent was subsequently removed under vacuum and resulting residue taken up in ice-cold ether. This caused the major product 179 to separate as a yellow solid. The ethereal filtrate contained further 179, the minor product 180, excess dipolarophile 178 and unreacted 1,3-dipole 45. Some intractable gum was also generated. The major product 179 was formed in 60% yield, the minor 180 in 6% yield. The expected products, based on the individual fragment reactions, 176 and 177, were not observed. The structural assignment of the major compound 179 was supported by IR, $^1$H NMR and $^{13}$C NMR spectroscopy.
The IR spectrum of compound 179 contained a carbonyl band at 1720 cm$^{-1}$. The pyrrole ring protons were instrumental in determining the regiochemistry of the product. The lowest field signal of the three protons was assigned to H-10b, the highest to H-1, leaving H-2 in between. These pyrrole ring protons displayed a distinctive pattern in the $^1$H NMR spectrum (Figure 61). H-C(10b) showed as a doublet at $\delta$ 5.24, H-C(1) as a doublet of doublets at $\delta$ 3.94 and H-C(2) as a doublet at $\delta$ 4.27. The structural assignment was found to be in agreement with calculations completed with ACD labs software (Figure 61). The $^{13}$C NMR spectrum (Figure 61) included two signals at 111.3 and 112.2 ppm corresponding to the two cyano groups present.
The stereochemistry of 179 was supported by NOEDS. A strong NOE (12-15%) between H-C(10b) and H-C(1), and the absence of an NOE from either of these to H-C(2), indicated that the aryl and the acetyl substituents were in the endo- and exo-positions, respectively (Figure 62).

**Figure 61:** $^1$H NMR and $^{13}$C NMR assignments for compound 179

**Figure 62:** NOEDS enhancements of compound 179 in CDCl$_3$
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Analysis of the ethereal filtrate provided the key pyrrole ring proton signals of the minor product (Figure 63). H-C(10b) showed as a doublet at δ 4.64, H-C(1) as a doublet of doublets at δ 3.80 and H-C(2) as a doublet at δ 4.21. The minor product’s H-C(10b) proton was shifted upfield relative to the major product due to shielding from the exo-aryl group at C(1). The ratio of 179/180 generated in the reaction mixture was ~10:1. No interconversion or changes in the products took place under the reaction and workup conditions.

![Figure 63: Key 1H NMR signals of compound 180 in CDCl3](image)

**Figure 63:** Key 1H NMR signals of compound 180 in CDCl3

### 3.3.2 Cycloaddition reaction of phthalazinium-2-dicyanomethanide 1,3-dipole 45 with p-chlorobenzylidene acetone 181

A suspension of the phthalazinium-2-dicyanomethanide 1,3-dipole 45 in acetonitrile was treated with p-chlorobenzylidene acetone (4-(4-chlorophenyl)-3-buten-2-one) 181 and then stirred under reflux for 4 h (Scheme 58). The solvent was subsequently removed under vacuum to afford a gummy orange solid. The residue was taken up in ice-cold ether causing the major product 182 to separate as a white solid. The ethereal filtrate contained further 182, the minor product 183, excess dipolarophile 181 and unreacted 1,3-dipole 45. Some intractable gum was also generated. The major product 182 was formed in 52% yield, the minor 183 in 5% yield. The assignment of the major compound 182 was supported by IR, 1H NMR and 13C NMR spectroscopy.
The IR spectrum of compound 182 contained a carbonyl band at 1725 cm$^{-1}$. The key pyrrole ring protons displayed a similar pattern in the $^1$H NMR spectrum (Figure 64) to that observed for compound 182. H-C(10b) appeared as a doublet at $\delta$ 5.25, H-C(1) as a doublet of doublets at $\delta$ 3.86 and H-C(2) as a doublet at $\delta$ 4.26. The regiochemistry of the product was assigned with reference to 182. The $^{13}$C NMR spectrum (Figure 64) included two signals at 111.2 and 111.9 ppm corresponding to the two cyano groups present.
**1H NMR (CDCl₃)**

A strong NOE (10-15%) between H-C(10b) and H-C(1), combined with the absence of an NOE from either of these protons to H-C(2), indicated that the aryl and the acetyl substituents were in the endo- and exo- positions, respectively (Figure 65).

**13C NMR (CDCl₃)**

Analysis of the ethereal filtrate provided the key pyrrole ring proton signals of the minor product 183 (Figure 66). H-C(10b) showed as a doublet at δ 4.66, H-C(1) as a doublet of doublets at δ 3.67 and H-C(2) as a doublet at δ 4.19. The minor product’s H-C(10b) proton was shifted upfield relative to the major product due to shielding from the exo-aryl group at C(1). The stereochemistry of 183 was supported by NOEDS. An NOE of 7-9% was observed between H-C(2) and H-C(10b), indicating that the aryl and the acetyl substituents were in the exo- and endo- positions, respectively. The ratio of 182/183 produced in the reaction mixture was ~10:1.
3.3.3 Cycloaddition reaction of phthalazinium-2-dicyanomethanide 1,3-dipole 45 with \( p \)-tolylbenzylidene acetone 184

A suspension of the phthalazinium-2-dicyanomethanide 1,3-dipole 45 in acetonitrile was treated with \( p \)-tolylbenzylidene acetone (4-(4-methylphenyl)-3-buten-2-one) 184 and then stirred under reflux for 5 h (Scheme 59). The solvent was subsequently removed under vacuum to afford a brown gummy residue. The residue was taken up in ice-cold ether causing the major product 185 to separate as a yellow solid. The ethereal filtrate contained further 185, the minor product 186, excess dipolarophile 184 and unreacted dipolarophile 45. Some intractable gum was also generated. The major product 185 was formed in 69% yield, the minor 186 in 8% yield. The assignment of the major compound 185 was supported by IR, \(^1\text{H} \) NMR and \(^{13}\text{C} \) NMR spectroscopy.
The IR spectrum of compound 185 contained a carbonyl band at 1725 cm\(^{-1}\). The key pyrrole ring protons were clearly visible in the \(^1H\) NMR spectrum (Figure 67). H-C(10b) appeared as a doublet at \(\delta 5.22\), H-C(1) as a doublet of doublets at \(\delta 3.93\) and H-C(2) as a doublet at \(\delta 4.23\). The regiochemistry of the product was assigned with reference to 182. The \(^{13}C\) NMR spectrum (Figure 67) included two signals at 111.3 and 112.3 ppm corresponding to the two cyano groups.
The assignment of 185 was supported by NOEDS. A strong NOE (13-18%) was observed between H-C(10b) and H-C(1). There was no NOE from either of these protons to H-C(2). This supports the assignment of the aryl and the acetyl substituents in the endo- and exo- positions respectively (Figure 68).

Analysis of the ethereal filtrate provided the key pyrrole ring proton signals of the minor product (Figure 69). H-C(10b) showed as a doublet at δ 4.63, H-C(1) as a doublet of doublets at δ 3.69 and H-C(2) as a doublet at δ 4.11. The minor product’s H-C(10b) proton was shifted upfield relative to the major product due to shielding from the exo-aryl group at C(1). The ratio of 185/186 generated in the reaction mixture was ~10:1.
3.4 Kinetic study of the reactions of phthalazinium-2-dicyanomethanide 1,3-dipole 45 with \( p \)-substituted benzylidene acetone dipolarophiles

The rates of reaction of 1,3-dipole 45 with a number of benzylidene acetone dipolarophiles were measured by following the disappearance of the dipole using UV-Vis spectroscopy. The wavelength of maximum absorbance (\( \lambda_{\text{max}} \)) was 423 nm in acetonitrile and 411 nm in (9:1 mole ratio) water/acetonitrile. The dipolarophile concentration ranged from 20 to 600 molar excess depending on the dipolarophile used. The rates were measured under pseudo-first order conditions at 37 °C for all reactions. Three different concentrations of dipolarophile were used in order to determine the second order rate constant. All kinetic measurements were repeated three times.

Table 15: Rate data for \( p \)-substituted benzylidene acetones with 1,3-dipole 45 in acetonitrile and aqueous acetonitrile at 37 °C (\( k_2 \): dm\(^3\)mol\(^{-1}\)s\(^{-1}\))

<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>( k_2 ) CH(_3)CN</th>
<th>( k_2 ) H(_2)O/CH(_3)CN (0.9/0.1)</th>
<th>( k_2 ) ratio(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzylidene acetone 178</td>
<td>7.20 x 10(^{-4})</td>
<td>2.40 x 10(^{-2})</td>
<td>33</td>
</tr>
<tr>
<td>( p )-chlorobenzylidene acetone 181</td>
<td>9.20 x 10(^{-4})</td>
<td>9.98 x 10(^{-3})</td>
<td>11</td>
</tr>
<tr>
<td>( p )-tolylbenzylidene acetone 184</td>
<td>6.35 x 10(^{-4})</td>
<td>7.52 x 10(^{-3})</td>
<td>12</td>
</tr>
</tbody>
</table>

\(^a\) Measured \( k_2 \) H\(_2\)O/CH\(_3\)CN (9.0:1.0 mole ratio) / \( k_2 \) CH\(_3\)CN
Chapter 3

The benzylidene acetone dipolarophile was chosen for study as it contains two distinctive structural fragments- an alkyl vinyl ketone and a styrene. These fragments share the same double bond. Individually, both of these fragments are accelerated in water, but to differing extents. A ketone conjugated to a double bond is a common feature of water-super dipolarophiles.\(^44\) Styrenes are water-normal dipolarophiles.\(^34\) The benzylidene acetones therefore contain elements of both water-super and water-normal dipolarophiles.

The reaction rate measurements indicate that the benzylidene acetones are water-super dipolarophiles\(^34, 63\) as there is a <10 fold increase in rate on switching from pure acetonitrile to (9:1 mole ratio) water/acetonitrile. Despite containing a water-normal structural fragment, the presence of a ketone conjugated to a double bond is sufficient to ensure that reactions of the benzylidene acetones are strongly accelerated in the presence of water.

### 3.4.1 Water and polarity of the transition state: Hammett plots

Previous studies on the reactions of the 1,3-dipole \(^{45}\) in water indicate that the growth of water clusters plays a significant role in accelerating the reactions of water-super dipolarophiles.\(^34, 44\) In addition to the pervasive hydrophobic effect and special hydrogen bonding effects, transition state polarity changes may contribute to rate accelerations in water. We were therefore interested to see if there was an increase in polarity of the cycloaddition transition states for the reactions of 1,3-dipole \(^{45}\) and the benzylidene acetones on completing the reactions in water. We wished to explore the possibility that there was a cooperative increase in the polarity of the transition state as each bridging water molecule bound to the growing water cluster.

The Hammett rho value (\(\rho\)) has been used extensively to quantify the effect of electron donating and electron withdrawing groups on the transition states of various reactions. This allows the measurement of polarity or charge development in the transition state of a reaction. Hammett plots were measured for the reactions.
between 1,3-dipole 45 and the benzylidene acetones in order to identify any changes in transition state polarity on completing the reaction in the presence of water. 

On plotting the log of the rate constant against the Hammett $\sigma^+$ values, the $\rho$ value in acetonitrile was found to be +0.35. This $\rho$ value is in good agreement with this reaction being a HOMO_dipole controlled process where electron withdrawing groups enhance the rate by lowering the LUMO_dipolarophile energy. The magnitude of this $\rho$ value suggests little charge build up in the transition state. This indicates that the reaction proceeds via a concerted orbital controlled cycloaddition mechanism.

The $\rho$ value in water/acetonitrile (9:1 mole ratio) was found to have increased slightly to +0.58. This minor change does not suggest a significant increase in the polarity of the transition state in the presence of water. Therefore the rate accelerations associated with completing these reactions in water are not related to an increase in transition state polarity. Further measurements were hampered by the availability of suitable dipolarophiles, and so a theoretical study was completed to explore this area further.

![Figure 70: Hammett plot of 1,3-dipole 45 and p-substituted benzylidene acetones in acetonitrile and aqueous acetonitrile at 37 °C](image-url)
3.5 Computational study

3.5.1 Calculations with 0-water and 4-water clusters

A theoretical study was completed in conjunction with Prof. Luke A. Burke of Rutgers University. Calculations were completed with the Gaussian 03 suite of programs using the B3LYP DFT method and the 6-31G(d) basis set. Calculations were carried out on the reactants and the transition state, each with 0 or 4 water molecules in a cage-like structure. Care was taken that the aryl substituents were internally oriented the same way in the reactants and the transition state structures.

The activation energies \( (E_a) \), activation entropies \( (S_a) \) and activation free energies \( (G_a) \) were calculated for the reactions of 1,3-dipole \( 45 \) with a series of \( p \)-substituted benzylidene acetones (Table 16). The rate ratios reported are based on the following equation:

\[
k_Y/k_H = e^{(Ea1/RT)}e^{(Ea2/RT)}
\]

The activation energy \( (E_a) \), rather than activation free energy \( (G_a) \), was used in these calculations as the rate ratios were required for the construction of a Hammett plot.

The results indicate that the reactions of dipolarophiles with electron withdrawing substituents have lower activation energies than those with electron donating substituents. This is consistent with the reaction being a HOMO dipole controlled process where electron withdrawing groups lower the LUMO dipolarophile energy. Activation energies are further reduced when the 4-water cluster is included in the calculations. A water dimer was originally chosen, but the optimisation procedures brought the dimer from a higher energy structure, where two H-atoms of the dimer were bonded to the oxygen of the carbonyl, to another structure in which the dimer fitted in to the notch between the oxygen of the carbonyl and the benzylidene CH group. This structure was not predominant in a previous theoretical study with MVK.\(^{44}\) The 4-water cluster remained attached to the oxygen of the carbonyl group throughout the optimization process.
Table 16: Theoretical calculations for \( p \)-substituted benzylidene acetones. Activation energy \( E_a \) in kJ mol\(^{-1} \), activation entropy \( S_a \) in J mol\(^{-1} \) K\(^{-1} \), free energy of activation \( G_a \) in kJ mol\(^{-1} \).  

<table>
<thead>
<tr>
<th>Y</th>
<th>Keto Position</th>
<th>0-Water</th>
<th>4-Water</th>
<th>4-Water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( E_a )</td>
<td>-( S_a )</td>
<td>( G_a )</td>
</tr>
<tr>
<td></td>
<td>2-endo</td>
<td>67.71</td>
<td>214.15</td>
<td>134.68</td>
</tr>
<tr>
<td></td>
<td>1-endo</td>
<td>74.85</td>
<td>207.13</td>
<td>138.96</td>
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<tr>
<td></td>
<td>2-exo</td>
<td>73.34</td>
<td>204.40</td>
<td>136.64</td>
</tr>
<tr>
<td></td>
<td>1-exo</td>
<td>74.31</td>
<td>203.89</td>
<td>137.45</td>
</tr>
<tr>
<td>Me(_2)N</td>
<td>2-endo</td>
<td>74.54</td>
<td>217.86</td>
<td>142.05</td>
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<td>73.90</td>
<td>212.55</td>
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<td>70.57</td>
<td>213.46</td>
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<tr>
<td>Me</td>
<td>2-endo</td>
<td>68.90</td>
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<tr>
<td></td>
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<td>75.04</td>
<td>203.69</td>
<td>138.10</td>
</tr>
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<td></td>
<td>2-exo</td>
<td>74.06</td>
<td>211.16</td>
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</tr>
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<td></td>
<td>1-exo</td>
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<td>207.00</td>
<td>138.01</td>
</tr>
<tr>
<td>MeO</td>
<td>2-endo</td>
<td>70.66</td>
<td>211.35</td>
<td>136.59</td>
</tr>
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<td></td>
<td>1-endo</td>
<td>75.14</td>
<td>203.84</td>
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<td></td>
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<td></td>
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<td>202.27</td>
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<td>F</td>
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<td>69.31</td>
<td>213.76</td>
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<td>Cl</td>
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<td>68.16</td>
<td>210.78</td>
<td>133.91</td>
</tr>
<tr>
<td></td>
<td>1-endo</td>
<td>74.44</td>
<td>206.37</td>
<td>138.20</td>
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<tr>
<td></td>
<td>2-exo</td>
<td>72.98</td>
<td>207.84</td>
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<td></td>
<td>1-exo</td>
<td>74.08</td>
<td>204.79</td>
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<td>212.81</td>
<td>131.61</td>
</tr>
<tr>
<td>Ac</td>
<td>2-endo</td>
<td>65.30</td>
<td>212.77</td>
<td>131.86</td>
</tr>
<tr>
<td>CF(_3)</td>
<td>2-endo</td>
<td>66.22</td>
<td>215.27</td>
<td>133.33</td>
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<tr>
<td>CN</td>
<td>2-endo</td>
<td>66.09</td>
<td>213.30</td>
<td>132.65</td>
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<tr>
<td>NO</td>
<td>2-endo</td>
<td>64.99</td>
<td>212.28</td>
<td>131.20</td>
</tr>
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<td>NO(_2)</td>
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<td>65.29</td>
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<td>130.79</td>
</tr>
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<td></td>
<td>1-exo</td>
<td>70.77</td>
<td>207.38</td>
<td>135.1</td>
</tr>
</tbody>
</table>
3.5.2 Plot of activation energy versus Hammett constants

A plot of activation energy versus Hammett constants further illustrates the effect of the substituents on the reactions of 1,3-dipole 45 with p-substituted benzylidene acetones (Figure 71). The best correlation was achieved when the substituents were grouped into $\sigma^+$ and $\sigma^-$ Hammett constants. Electron donating groups by resonance (including $p$-Cl and $p$-F) were assigned $\sigma^+$ values while electron withdrawing substituents were assigned $\sigma^-$ Hammett constants. Both groups gave rise to negative slopes, however the electron donating groups gave larger absolute values.

![Graph showing plot of activation energy versus Hammett constants](image)

Note 1: ED and EWD refer to electron donating and electron withdrawing groups (by resonance) respectively

Note 2: 0W and 4W refers to water clusters comprised of zero and four water molecules, respectively

Note 3: Pluses (+) represent electron donating groups, triangles (Δ) electron withdrawing groups

Figure 71: Plot of activation energy ($E_a$) versus Hammett constants for the reaction of 1,3-dipole 45 with p-substituted benzylidene acetones

The plot demonstrates that the presence of the 4-water cluster leads to a reduction in the activation energy of the reaction. Therefore the rate enhancement observed on completing these reactions in water is associated with the presence of H-bonded water clusters attached to the carbonyl group.
3.5.3 Theoretical Hammett plot

A theoretical Hammett plot was also created using calculated reaction rates for a variety of \( p \)-substituted benzylic acetones (Figure 72). Once again, both \( \sigma^+ \) and \( \sigma^- \) Hammett constants were used depending on the nature of the dipolarophile. This leads to four separate \( \rho \) values, two for the reactions with 0 water molecules present and two for the reactions with the 4-water cluster present (Table 17).

Note 1: ED and EWD refer to electron donating and electron withdrawing groups (by resonance) respectively.

Note 2: 0W and 4W refers to water clusters comprised of zero and four water molecules respectively.

Note 3: Crosses (X) represent electron donating groups, triangles (Δ) electron withdrawing groups.

Figure 72: Theoretical Hammett plots for the reaction of 1,3-dipole 45 with \( p \)-substituted benzylic acetones.

In all cases the \( \rho \) values are positive and quite small. The magnitude of the \( \rho \) value suggests little charge build up in the transition state. There are slight increases in the \( \rho \) values in the presence of the 4-water cluster, however these increases are minor in nature and do not suggest a significant increase in polarity of the transition state. The
Theoretical results are in good agreement with the experimentally derived results. Therefore it is concluded that increased polarity of the cycloaddition transition state is not responsible for the rate accelerations observed in the presence of water.

**Table 17:** Experimental and theoretical $\rho$ values for the reaction of 1,3-dipole 45 with $p$-benzylidene acetones

<table>
<thead>
<tr>
<th></th>
<th>Experimental ($\rho^+$)</th>
<th>Theoretical ($\rho^+$)</th>
<th>Theoretical ($\rho^-$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Absent</td>
<td>+ 0.35 $^a$</td>
<td>+ 0.62 $^c$</td>
<td>+ 0.31 $^c$</td>
</tr>
<tr>
<td>Water Present</td>
<td>+ 0.58 $^b$</td>
<td>+ 1.03 $^d$</td>
<td>+ 0.53 $^d$</td>
</tr>
</tbody>
</table>

$^a$) Measured in acetonitrile. $^b$) Measured in 0.9 mole fraction water/acetonitrile, $^c$) Calculated based on 0-water cluster, $^d$) Calculated based on 4-water cluster.

### 3.5.4 Regiochemistry

The regiochemistry of a number of these cycloadditions was determined theoretically, the outcome agreeing with the experimentally observed regiochemistry in all cases. All four potential isomers were investigated for $Y= H, Me, MeO, Cl, NO_2$. In all cases there was a clear energetic preference for the keto group of the dipolarophile adding in the 2-position. The calculations do not reflect the relative endo/exo ratios observed synthetically. The calculations predict that the 2-endo-acetyl isomer should be preferentially formed whereas the synthetic reactions completed demonstrated that the major product formed was the 2-exo-acetyl isomer in all cases. This may be due to the operation of a solvophobic effect which favours the endo-arrangement for the aryl substituent.

Transition state structures were calculated for the four possible isomers derived from 45 and 4-phenyl-3-buten-2-one 178 (Figure 73). In all cases the C(2)-C(3) bond is the shorter of the two new bonds being formed, indicating a concerted asynchronous transition state.
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Note 1: Distances of bonds to be formed given in Å
Note 2: Isomer takes its abbreviated name from the position of keto substituent

**Figure 73:** Calculated transition state structures for the reaction of 1,3-dipole 45 with benzylidene acetone 178

Calculations also indicated that a dipolar interaction along the developing C(2)-C(3) bond was a key feature of the concerted transition state. Strong resonance electron donating substituents are therefore expected to inhibit the rate by reducing the positive charge at C(2) in the transition state (Scheme 60). Conversely electron withdrawing substituents should speed up the reaction.
3.5.5 Ionisation potential

The ionisation potential of a molecule has traditionally been used as a measure of the energy of the highest occupied molecular orbital. When the measured rates of cycloaddition of a series of dipolarophiles were plotted against the calculated ionisation potential a U-shaped curve was obtained (Figure 74).\(^{43}\) This placed the 1,3-dipole 45 in the Sustmann Type II class (normal or inverse demand). Reactions on the left hand side of the curve are \(\text{LUMO}_{\text{dipole}}-\text{HOMO}_{\text{dipolarophile}}\) controlled in the transition state. On the right hand side of the curve the reactions are \(\text{HOMO}_{\text{dipole}}-\text{LUMO}_{\text{dipolarophile}}\) controlled. The reaction mechanism of the phthalazinium-2-dicyanomethanide 1,3-dipole 45 therefore changes depending on the type of dipolarophile involved in the reaction, leading to variation in the regiochemistry of products.\(^{33, 43}\)

The ionisation potential of benzylidene acetone 178 (6.35 eV) was calculated by Prof. Luke Burke of Rutgers University at Camden using methods incorporated into the Gaussian 03 A7 series\(^{101}\) of programs. When combined with a measured reaction constant of 7.2 \(\times 10^{-4}\) dm\(^3\) mol\(^{-1}\) s\(^{-1}\), benzylidene acetone 178 is found to sit on the lower left hand side of the curve at point number 27 (Figure 74). The position of benzylidene acetone 178 is therefore very close to the point of mechanism change over. Both the experimental and theoretical Hammett plots indicate that the 1,3-dipole 45 reacts with the benzylidene acetones via a \(\text{HOMO}_{\text{dipole}}-\text{LUMO}_{\text{dipolarophile}}\) controlled process.
Figure 74: Experimental rates versus calculated (DFT) ionisation potentials for the reactions of phthalazinium-2-dicyanomethanide 1,3-dipole 45 with various dipolarophiles. Points 1-26 correspond to the dipolarophiles listed in reference 43. Benzylidene acetone plotted as point 27.

3.6 Synthetic study of “on water” cycloaddition reactions of phthalazinium-2-dicyanomethanide 1,3-dipole 45

Breslow’s discovery of the acceleration of the Diels-Alder reaction in water has prompted increased interest in the use of water as a medium for organic reactions. There are both cost and environmental benefits associated with the use of water rather than organic solvents. As indicated previously, Sharpless has suggested that the term “on water” be applied to reactions between insoluble reactants which are suspensions in water. Non-polar liquids that separate from water into a clear organic phase are considered to be good candidates for these reactions. It has been...
suggested that solids can also be used in these reactions provided one reactant is a liquid.\textsuperscript{98}

The solid phthalazinium-2-dicyanomethanide 1,3-dipole 45 is quite water insoluble ($\leq 5 \times 10^{-6} \text{ mol L}^{-1}$ at 37 °C). This limit was measured\textsuperscript{34} from the UV spectra of saturated neat water solutions using the $\lambda_{\text{max}}$ of 413 nm and the extinction coefficient for the solutions of 45 in H$_2$O-MeCN (9:1 v/v), which were used previously for kinetic studies. The synthetic reactions between aqueous suspensions of compound 45 and insoluble liquid alkene and alkyne dipolarophiles\textsuperscript{44, 63} give high yields of cycloadducts through reactions which can occur in an oily phase at the water-organic interface, or at the solid-liquid interface in the stirred mixture.

It was decided to investigate the impact of reacting phthalazinium-2-dicyanomethanide 1,3-dipole 45 with solid dipolarophiles of decreasing water solubility in water. The water solubilities of the dipolarophiles were obtained from SciFinder. These values were calculated using ACD Labs software\textsuperscript{102} and provide a good assessment of the solubilities in water. The dipolarophile $N$-phenylmaleimide 131 has a water solubility in the order of $10^{-3} \text{ mol L}^{-1}$, which we considered to be “sparingly soluble”. The compound $p$-chlorobenzylidene acetone 181 has a water solubility in the order of $10^{-4} \text{ mol L}^{-1}$, which we considered to be “very sparingly soluble”. Both dipolarophiles give the appearance of insoluble suspensions in water.

3.6.1 “On water” cycloaddition of phthalazinium-2-dicyanomethanide 1,3-dipole 45 with $N$-phenylmaleimide 131

Phthalazinium-2-dicyanomethanide dipole 45 was stirred with an equimolar amount of $N$-phenylmaleimide 131 in Millipore water for 24 h at ambient temperature. The highly yellow coloured suspension changed to white/off-white as the dipole 45 was consumed and replaced by product. The insoluble water-wet product stuck to the insides of the flask but could be collected with care. The mixture was filtered to yield compound 187 (Scheme 61) as a pale yellow solid. The structural assignment of the product 187 was supported by IR, $^1$H NMR and $^{13}$C NMR spectroscopy.
The IR spectrum showed two bands at 1715 and 1795 cm\(^{-1}\) corresponding to the two carbonyl groups. NMR spectra were measured in DMSO-\(d_6\). The H-1 signal appeared as a doublet of doublets at \(\delta 4.41\) (Figure 75). The H-2 signal occurred as a doublet at \(\delta 4.77\) while H-10b appeared as a doublet at \(\delta 5.19\). In the \(^{13}\)C NMR, the C-10b signal appeared at 59.7 ppm (Figure 75). The two cyano groups occurred at 110.8 and 112.4 ppm. The C-6 signal appeared at 146.8 ppm. The two carbonyl groups appeared at 170.4 and 172.4 ppm. An X-ray crystal structure of the product obtained from the reaction of 45 with \(N\)-(t-butyl) maleimide has previously been obtained in these labs (Figure 10, Section 1.4.3).

**Figure 75:** \(^1\)H NMR and \(^{13}\)C NMR assignments for compound 187
The stereochemistry of 187 was determined by NOEDS. Irradiation of the H-1 signal resulted in enhancement of both the H-10b and H-2 signals. Irradiation of the H-10b signals caused enhancement of the H-1 signal. Therefore the maleimide ring was determined to be in the \textit{endo} position.

\begin{center}
\textbf{Figure 76:} NOEDS enhancements for compound 187 in DMSO-d$_6$
\end{center}

The compound \textit{N}-phenylmaleimide 131 has a melting point of 89-90 °C and a calculated$^{102}$ water solubility of $4.4 \times 10^{-3}$ mol L$^{-1}$. The reaction was completed at ambient temperature, well below the melting point of the dipolarophile. Therefore in this case it is not necessary to liquefy a “sparingly soluble” solid dipolarophile in order to allow it to react with a “very sparingly soluble” solid dipole in water.

\subsection*{3.6.2 “On water” cycloaddition of phthalazinium-2-dicyanomethanide 1,3-dipole 45 with \textit{p}-chlorobenzylidene acetone 181}

The phthalazinium-2-dicyanomethanide 1,3-dipole 45 reacts with \textit{p}-chlorobenzylidene acetone 181 in acetonitrile to yield tetrahydropyrrolo[2,1-a]phthalazine products (Scheme 58). The \textit{p}-chlorobenzylidene acetone 181 dipolarophile has a melting point of 58-62 °C and a calculated$^{102}$ water solubility of $1.2 \times 10^{-4}$ mol L$^{-1}$. The solubility of 181 in water is therefore an order of magnitude lower than \textit{N}-phenylmaleimide 131, and so we termed it a “very sparingly soluble” dipolarophile.

The phthalazinium-2-dicyanomethanide 1,3-dipole 45 was treated with a slight excess of \textit{p}-chlorobenzylidene acetone 181 in Millipore water at ambient
temperature, similar to procedure used with \( N \)-phenylmaleimide 131. However, in this case the reaction was unsuccessful. There was no visible change in the appearance of the reaction mixture despite the age time being doubled to 48 hours. The yellow suspension was filtered and the resulting precipitate analyzed by \(^1\)H NMR. The precipitate contained unreacted dipole 45, \( p \)-chlorobenzylidene acetone 181 and a small amount (<1%) of the expected major product 182. (Table 18)

Increasing the reaction temperature to 40 °C had a minor beneficial impact, as the yield of the major product 182 increased to 3.5 % after stirring for 48 h (Table 18). However the appearance of the reaction mixture did not change, remaining a yellow suspension during the course of the reaction. It was only when the reaction temperature was raised above the melting point of \( p \)-chlorobenzylidene acetone 181 that the expected products 182 and 183 were formed in high yield after stirring for 24 h (Table 18). A change in the reaction mixture appearance was observed over the course of the reaction. As the reaction mixture was heated to 75 °C, the yellow suspension became oily. Product began to precipitate from solution, adhering to the inside of the reaction flask and the stir-bar. The reaction mixture was filtered and analyzed by \(^1\)H NMR spectroscopy. A small amount of unreacted dipole 45 and \( p \)-chlorobenzylidene acetone 181 remained, however the majority of the precipitate was made up of the expected products 182 and 183. These products were formed in overall 86% yield and in a ratio of 6.2:1 (Table 19). The endo/exo product ratio was reduced relative to the reaction in acetonitrile.

<table>
<thead>
<tr>
<th>Reaction Time (h)</th>
<th>Reaction Temperature (°C)</th>
<th>Total Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>20</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>48</td>
<td>40</td>
<td>3.5</td>
</tr>
<tr>
<td>24</td>
<td>75</td>
<td>86 (^a)</td>
</tr>
</tbody>
</table>

\(^a\) Major/minor product ratio (182:183) - 6.2:1
Therefore, when both solid reactants are very sparingly soluble, liquefaction of one allows a reaction to occur as expected for an oily-phase process. The solid 1,3-dipole 45 has an intense yellow colour and even trace quantities present in a solution show a yellow colouration. In the reactions at temperatures where the dipolarophile was liquefied the oily phase showed yellow colouration, suggesting that compound 45 was present in this phase.

The reduction in the endo/exo ratio for the reaction of 1,3-dipole 45 with p-chlorobenzylidene acetone 181 was somewhat unexpected. Breslow\textsuperscript{83, 84} has demonstrated that the endo/exo ratio for the Diels-Alder reaction is enhanced when the reaction is completed in water. The same endo-effect was expected to occur for the 1,3-dipolar cycloadditions of 45 in water. This effect is suggested to be due to the hydrophobic effect, which favours the more compact transition state associated with the endo-transition state. Smaller contributions may also come from polarity effects on the endo-favouring secondary orbital interactions and charge transfer contributions to the transition state.\textsuperscript{86, 87}

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Major Isomer 182 Yield (%)</th>
<th>Minor Isomer 183 Yield (%)</th>
<th>endo/exo (182/183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>52</td>
<td>5</td>
<td>10.4:1</td>
</tr>
<tr>
<td>Water</td>
<td>74</td>
<td>12</td>
<td>6.2:1</td>
</tr>
</tbody>
</table>

The results suggest that the reaction of the 1,3-dipole 45 with the sparingly soluble dipolarophile N-phenylmaleimide 131 is passing through the water at low concentrations. When the solubilities of both reactants are well below the millimolar threshold, as in the reaction of 1,3-dipole 45 with p-chlorobenzylidene acetone 181, liquefaction of one reactant is necessary. This allows the reaction to pass through a water-penetrated oily phase. In both cases the reactions are subject to the pervasive hydrophobic effect which (i) accelerates the reaction of sparingly soluble reactants.
and (ii) immediately expels the more insoluble cycloadducts with larger organic surface areas from the medium as soon as they are formed (when they appear to stick to available surfaces). Hence the entire reaction is rapidly shuttled through the water medium or the oily-phase medium by hydrophobic driven equilibria.

The reduction in the endo/exo ratio for the reaction of p-chlorobenzylidene acetone 181 with 1,3-dipole 45 in water relative to the reaction in acetonitrile suggests that the hydrophobic effect does not play a significant role in determining the stereochemistry of the reaction. The hydrophobic effect is expected to be strongest when a reaction is occurring within the bulk water medium, and so the reactants are surrounded by water molecules. This suggests therefore the reaction of 1,3-dipole 45 and p-chlorobenzylidene acetone 181 is a true “on water” rather than “in water” reaction.

The influence of water on product endo/exo ratios is a useful tool in determining if a reaction is proceeding via “in water” or “on water” mode. The hydrophobic effect has a significant impact on reactions that proceed “in water”. This results in an increased preference for the endo-isomer. Reactions that proceed “on water” are not subject to such a strong hydrophobic effect, and so the endo-isomer is not as favoured.

3.7 Comparison with substituted styrenes

The reaction of 1,3-dipole 45 and substituted styrenes are generally LUMO_dipole controlled. Typically two products are formed, both with the aryl substituent in the C-2 position. The main product 188 contains the aryl substituent in the exo position, while the minor product 189 has the aryl group in the endo position (Scheme 62).
However, a second minor product was encountered when a strongly electron withdrawing substituent ($m$-$\text{NO}_2$) was investigated.\textsuperscript{63} This product \ref{192} has the opposite regiochemistry to the major product \ref{190} and the typical minor product \ref{191} (Figure 77). This is the same regiochemistry observed when electron-poor dipolarophiles react with 1,3-dipole \ref{45} in HOMO\textsubscript{dipole} controlled reactions. This is also the regiochemistry (aryl group attached to C1) observed for the reactions of 1,3-dipole \ref{45} with the benzylidene acetones.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure77}
\caption{Figure 77}
\end{figure}
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The experimentally measured Hammett plot\(^\text{62}\) (Figure 78) for the reaction of 1,3-dipole 45 with substituted styrenes is \(v\)-shaped, indicating that a changeover in mechanism, from \(\text{LUMO}_{\text{dipole}}\) to \(\text{HOMO}_{\text{dipole}}\) control, occurs for this reaction.

![Hammett plot](image)

**Figure 78:** Hammett plot of 1,3-dipole 45 and \(p\)- and \(m\)- substituted styrenes in acetonitrile and aqueous acetonitrile at 37 °C

This \(v\)-shape indicates a change in mechanism on going from dipolarophiles with electron donating substituents to dipolarophiles with electron withdrawing substituents. The plot of experimental rates versus calculated DFT ionisation potentials (Figure 74) for 1,3-dipole 45 with various electron-rich and electron-poor dipolarophiles is a U-shaped curve. A U-shaped curve indicates that dipole 45 is a Sustmann type II dipole. Styrene appears at the bottom of the curve on the left hand side effectively on the borderline for the mechanistic changeover.
From the Hammett plot (Figure 78) it is clear that a change of mechanism from \( \text{LUMO}_{\text{dipole}} \) to \( \text{HOMO}_{\text{dipole}} \) control occurs as the substituents are changed. The changeover in mechanism is reflected in a change in regiochemistry. The changeover in mechanism from \( \text{LUMO}_{\text{dipole}} \) to \( \text{HOMO}_{\text{dipole}} \) control occurs once the substituent on the phenyl ring is sufficiently electron withdrawing. The presence of the carbonyl group in the benzylidene acetone dipolarophiles has a similar effect, causing their reactions with 1,3-dipole 45 to be \( \text{HOMO}_{\text{dipole}} \) controlled. Substituted styrenes react equally well with 1,3-dipole 45 in water and acetonitrile (Table 20). The reactants appear visually insoluble in water, but react smoothly to generate the expected cycloadducts. There is a slight decrease in the \text{endo/exo} \) ratio for the reactions completed using water as solvent. The styrene dipolarophiles listed (Table 20) all have solubilities in the range of \( 10^{-3} \) mol L\(^{-1} \), and so react “on water”.

**Table 20:** Comparison of yields (%) and \text{endo/exo} isomer ratios for the reaction of 1,3-dipole 45 with substituted styrenes

<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>Acetonitrile</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Major (exo)</td>
<td>Minor (endo)</td>
</tr>
<tr>
<td>Styrene 173</td>
<td>74</td>
<td>13</td>
</tr>
<tr>
<td>( p )-MeO styrene</td>
<td>63</td>
<td>8</td>
</tr>
<tr>
<td>( m )-F styrene</td>
<td>76</td>
<td>15</td>
</tr>
<tr>
<td>( m )-NO(_2) styrene</td>
<td>68</td>
<td>11</td>
</tr>
</tbody>
</table>

The reactions of 1,3-dipole 45 and substituted styrenes are accelerated in water and fall into the category of water-normal dipolarophiles (Table 21). Water-normal dipolarophiles typically have esters, ethers, sulfones, nitriles or aryl rings conjugated to an alkene or alkyne. In general these give enhancements < 6 in water/acetonitrile (0.9 mole fraction). Therefore reactions of 1,3-dipole 45 with \( p \)-substituted benzylidene acetones are accelerated in water to a greater extent than the reactions of 1,3-dipole 45 with substituted styrenes. This is due to the presence of the carbonyl group conjugated to the double bond in the \( p \)-substituted benzylidene acetones. The
presence of this group allows special H-bonding to play a significant role in water reactions, and so ensures that the benzylidene acetones are water-super dipolarophiles.

**Table 21:** Kinetic data for the reaction of 1,3-dipole 45 with substituted styrenes in acetonitrile and aqueous acetonitrile mixtures at 37 °C (k_2: dm^3 mol^{-1} s^{-1})^{63}

| Dipolarophile     | k_2 CH_3CN | k_2 H_2O/CH_3CN 0.9 : 0.1 | k_2 Ratio
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Styrene 173</td>
<td>2.92 x 10^{-3}</td>
<td>15.1 x 10^{-3}</td>
<td>5.2</td>
</tr>
<tr>
<td>p-MeO styrene</td>
<td>5.55 x 10^{-3}</td>
<td>37.8 x 10^{-3}</td>
<td>6.8</td>
</tr>
<tr>
<td>p-EtO styrene</td>
<td>4.98 x 10^{-3}</td>
<td>42.3 x 10^{-3}</td>
<td>8.7</td>
</tr>
<tr>
<td>p-Me styrene</td>
<td>3.77 x 10^{-3}</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>m-F styrene</td>
<td>3.56 x 10^{-3}</td>
<td>22.9 x 10^{-3}</td>
<td>6.4</td>
</tr>
<tr>
<td>p-Cl styrene</td>
<td>3.34 x 10^{-3}</td>
<td>20.4 x 10^{-3}</td>
<td>6.1</td>
</tr>
<tr>
<td>p-F styrene</td>
<td>3.15 x 10^{-3}</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a) mole fraction b) measured k_2 H_2O-CH_3CN (0.9:0.1)/ k_2 in CH_3CN

3.8 **Comparison with alkyl vinyl ketones**

The reactions of 1,3-dipole 45 and the alkyl vinyl ketones methyl vinyl ketone 157 and ethyl vinyl ketone 193 are HOMO_dipole controlled.^{34, 43} The unsubstituted terminus of the dipolarophile attaches to the 1-CH terminus of the 1,3-dipole. The major products 161 and 194 contain the ketone group in the endo-position (Scheme 63) (Table 22). The minor products 162 and 195 have the same regiochemistry, however the ketone group is in the exo-position.
Table 22: Comparison of yields (%) and endo/exo isomer ratios for the reaction of 1,3-dipole 45 with vinyl ketones 157 and 193 in acetonitrile and water at ambient temperature [73]

<table>
<thead>
<tr>
<th>Dipolarophile</th>
<th>Acetonitrile</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Major (endo)</td>
<td>Minor (exo)</td>
</tr>
<tr>
<td>Methyl vinyl ketone 157</td>
<td>72</td>
<td>23</td>
</tr>
<tr>
<td>Ethyl vinyl ketone 193</td>
<td>71</td>
<td>23</td>
</tr>
</tbody>
</table>

The reaction behaves similarly in water and acetonitrile (Table 23). The yields and reaction times are comparable when acetonitrile and water are used as the reaction solvent. However a significant change occurs to the endo/exo ratio when the reaction is completed in water. A large increase in the endo isomer is observed. This is similar to results obtained by Breslow [86, 87] for the Diels-Alder reaction. The preference for the endo transition state could be due to the fact that it is more
compact than the *exo* transition state, and so is favoured in water. It also indicates that these reactions are taking place “in water”, and so is greatly influenced by the hydrophobic effect.

**Table 23:** Kinetic data for the reaction of 1,3-dipole 45 with alkyl vinyl ketones 157 and 193 in acetonitrile and aqueous acetonitrile mixtures at 37 °C (k₂: dm³mol⁻¹s⁻¹)

| Dipolarophile            | k₂ CH₃CN | k₂ H₂O/CH₃CN | k₂ Ratio
|--------------------------|----------|--------------|-----------
| Methyl vinyl ketone 157  | 62.0 x 10⁻³ | 1079 x 10⁻³  | 17.4      |
| Ethyl vinyl ketone 193   | 76.9 x 10⁻³ | 1044 x 10⁻³  | 13.6      |

*a*mole fraction  
*b*measured k₂ H₂O-CH₃CN (0.9:0.1)/ k₂ in CH₃CN

Both methyl vinyl ketone 157 and ethyl vinyl ketone 193 experience large rate accelerations in aqueous acetonitrile and so are considered water-super dipolarophiles. In general water-super dipolarophiles give rate enhancements > 10 in water/acetonitrile (0.9 mole fraction).³⁴ Water-super dipolarophiles typically feature a ketone C=O conjugated to an alkene or alkyne. The *p*-substituted benzyldiene acetones also contain a carbonyl group conjugated to an alkene and so display similar water-super behaviour.
3.9 Conclusion

We have explored the cycloaddition reaction of the phthalazinium-2-dicyanomethanide 1,3-dipole 45 with benzylidene acetone dipolarophiles. New 1,2-substituted tetrahydropyrrolo[2,1-a]phthalazine derivatives have been synthesised. The reactions produce two products, both with the aryl substituent on the C-2 position. This regiochemistry was not expected based on the individual reactions of styrenes and alkyl vinyl ketones with the 1,3-dipole 45. The major product has the aryl substituent in the endo-position.

The kinetics of the cycloaddition reaction of 1,3-dipole 45 with benzylidene acetone dipolarophiles was also explored. Large rate accelerations were observed when the reactions were completed in aqueous acetonitrile as opposed to pure acetonitrile. The dipolarophiles are considered to be water-super dipolarophiles, as they experience a rate enhancement of over eleven fold when the reactions are completed in 0.9 mole fraction water/acetonitrile rather than acetonitrile. The water-super nature of these dipolarophiles is associated with the presence of a double bond conjugated to a ketone. This facilitates rate acceleration due to special hydrogen bonding effects. Clusters of water become attached to the carbonyl resulting in stabilization of the transition state relative to the ground state.

A DFT study was completed by Prof. Luke A. Burke of Rutgers University at Camden in a collaborative investigation. The results support a concerted non-synchronous 1,3-dipolar cycloaddition reaction and account for the observed regiochemistry. The theoretical calculations indicate that a dipolar interaction along the developing C(2)-C(3) bond is a key feature of the concerted transition state.

The potential for increases in transition state polarity to contribute to the rate enhancements observed in aqueous acetonitrile was investigated through the use of Hammett plots. The experimental Hammett plots for the reaction of 1,3-dipole 45 with the benzylidene acetones in aqueous acetonitrile and pure acetonitrile had small $\rho$ values of +0.35 and +0.58 respectively. This suggests that little charge build up in
the transition state occurs in either solvent. Theoretical calculations were also completed with a wide variety of benzylidene acetone dipolarophiles to generate a theoretical Hammett plot for this reaction. The theoretical results are in good agreement with the experimentally derived results. Therefore it is concluded that increased polarity of the cycloaddition transition state is not responsible for the rate accelerations observed in the presence of water.

A natural progression of this study was to examine the reactions of 1,3-dipole 45 in pure water. The solid 1,3-dipole 45 was reacted with the solid dipolarophiles p-chlorobenzylidene acetone 181 and N-phenylmaleimide 131 in pure water. The dipolarophile p-chlorobenzylidene acetone required liquefaction to achieve reaction. The N-phenylmaleimide 131 dipolarophile has superior solubility in water and so did not need to be liquefied to react. This indicates that successful synthetic reactions can be achieved between two insoluble organic compounds via the “on water” methodology if one is liquefied to provide an oily layer in the water mixture. Liquefaction is not required if one of the reactants has sufficient solubility in water to generate an oil layer.

3.10 Future work
The impact of water on endo/exo product ratios for the reactions of 45 with benzylidene acetones remains an area of interest. Comparison of the “on water” product ratios with reactions completed in water/acetonitrile solutions would provide additional insight into the factors that influence reaction selectivity. The reactions of the imidazolium 1,3-dipoles have yet to be completed using water as a reaction solvent. Water would be expected to accelerate the cycloaddition reactions through a combination of the hydrophobic effect and hydrogen bonding, though its polar nature may provide additional stability for the ylide intermediate during the rearrangement step. Finally, advances in process analytical technology, particularly in-line NIR, may also prove to be useful in tracking the cycloaddition reactions and subsequent rearrangements.
3.11 Experimental

Experimental: synthesis

Melting points were measured on an Electrothermal apparatus. IR spectra were measured on a Perkin-Elmer Spectrum 1000 spectrophotometer. Microanalyses were measured on a Perkin-Elmer Model 240 CHN analyser. NMR spectra were measured on a JEOL GXFT 400 instrument with tetramethysilane as an internal reference. Deuteriochloroform, hexadeuteriomiethyl sulphoxide and acetonitrile-d$_3$ were used as solvents. $^1$H NMR assignments were supported by selective proton decoupling and COSY spectra. $J$ values are given in Hz. $^{13}$C NMR assignments were supported by DEPT spectra. The stereochemistry of the cycloadducts was determined using NOEDS. Acetonitrile was HPLC grade and was used without purification.

The following chemicals were purchased from:

**Sigma-Aldrich:** DMSO-d$_6$, phthalazine, N-phenylmaleimide, *trans*-4-phenyl-3-buten-2-one, 4-(4-chlorophenyl)-3-buten-2-one, 4-(4-methylphenyl)-3-buten-2-one.

**Flourochem:** chloroform-d$_1$.
Chapter 3

The numbering and naming system below is used in this chapter and has been accepted for publication.

phthalazinium-2-dicyanomethanide 1,3-dipole 45

endo-1,2-(dicarboxy-N-phenylimido)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo-[2,1-a]phthalazine 187

1-endo-2-exo-2-acetyl-1,2,3,10b-tetrahydro-1-phenylpyrrolo [2,1-a]phthalazine-3,3-dicarbonitrile 179
Synthesis of phthalazinium-2-dicyanomethanide 1,3-dipole 45
A solution of phthalazine (0.91 g, 7.0 mmol) in ethyl acetate (40 cm³) was cooled to below 0 °C in an ice-bath. This was treated dropwise with a cooled ethyl acetate solution (5 cm³) of TCNEO (1.00 g, 7.0 mmol) such that the reaction temperature was maintained below 12 °C. The yellow product precipitated immediately and was collected by filtration (1.25 g, 92%), mp 263-265 °C (acetonitrile); (Found C, 67.9, H, 3.1; N, 28.7. C₁₁H₆N₄ requires C, 68.0; H, 3.1; N, 28.9%); ν_max (mull)/cm⁻¹ 2191, 2159 (C≡N); δH (DMSO-d₆, 80 °C), 7.92-7.96 (m, 1H, H-5), 8.02-8.06 (m, 1H, H-8), 8.18-8.24 (m, 2H, H-6 and H-7), 9.40 (s, 1H, H-4), 9.60 (s, 1H, H-1); δC (DMSO-d₆, 80 °C), 63.5 (methanide C), 117.2 (C≡N), 117.2 (C-8a), 126.4, 128.0 (C-6 and C-7), 129.8 (C-4a), 129.7 (C-8), 132.8 (C-5), 135.4 (C-1), 153.9 (C-4).

Cycloaddition reactions of the phthalazinium-2-dicyanomethanide 1,3-dipole 45 with p-substituted benzylidene acetones

Phthalazinium-2-dicyanomethanide 1,3-dipole (0.30 g, 1.54 mmol) was added to a solution of trans-4-phenyl-3-buten-2-one (0.62 g, 4.62 mmol) in acetonitrile (25 cm³) and stirred under reflux for 4.5 h. After this time the solvent was removed under reduced pressure and the residue was taken up in ice-cold ether which caused the major product 179 to separate as a yellow solid. The ethereal filtrate contained further 179, the minor product 180, excess benzylidene acetone, unreacted dipole 45 and some intractable gum. Proton NMR analysis of this mixture gave the reported yields for the products. Compound 179 (0.31 g, 60%), white solid, mp 174-176 °C (from ethanol); (Found: C, 73.6; H, 4.7; N, 16.1. C₂₁H₁₆N₄O requires C, 74.1; H, 4.75; N, 16.45%); ν_max/cm⁻¹ 694, 770 (-Ph) 1720 (C=O); δ_H (CDCl₃) 1.91 (s, 3H, CH₃), 3.94 (dd, J 7.8, 8.7, 1H, H-1), 4.27 (d, 1H, J 7.8, H-2), 5.24 (d, 1H, J 8.7, H-
10b), 7.19 (d, 1H, J 7.3, H-10), 7.34 (d, 1H, J 7.3, H-7), 7.40-7.53 (m, 7H, H-8, H-9 and Ph), 7.64 (s, 1H, H-6); δ_C (CDCl_3) 31.4 (CH_3), 57.6 (C-10b), 58.5, 59.4 (C-1, C-2), 65.8 (C-3), 111.3, 112.2 (C=NH), 124.5 (C-10a), 126.0 (C-10), 127.4 (C-9), 128.8 (C-2'), 129.6 (C-3') 129.8 (C-4'), 129.9 (C-8), 131.9 (C-6a), 132.0 (C-7), 144.6 (C-6), 204.8 (C=O) (phenyl C-1' signal overlapped).

Compound 180 (0.03 g, 6%), δ_H (CDCl_3) (from mixture) key signals: 3.80 (dd, 1 H, J 9.2, 7.3, H-1), 4.21 (1H, J 7.3, H-2), 4.64 (d, 1H, J 9.2, H-10b). Other signals overlapped in the mixture.

**Synthesis of 1-endo-2-exo-2-acetyl-1-(4-chlorophenyl)-1,2,3,10b-tetrahydro pyrrolo[2,1-a]phthalazine-3,3-dicarbonitrile 182 and 1-exo-2-endo-2-acetyl-1-(4-chlorophenyl)-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine-3,3-dicarbonitrile 183**

A suspension of phthalazinium-2-dicyanomethanide 1,3-dipole (0.20 g, 1.03 mmol) in acetonitrile (20 cm^3) was treated with 4-(4-chlorophenyl)-3-buten-2-one (0.56 g, 3.10 mmol) and the resulting mixture stirred under reflux for 4 h. The solvent was removed under reduced pressure to afford an orange gummy residue. The residue was taken up in ice-cold ether which caused the major product 182 to separate as a white solid. The ethereal filtrate contained further 182, the minor product 183, unreacted dipole 45 and some intractable gum. Proton NMR analysis of this mixture gave the reported yields for the products. Compound 182 (0.19 g, 52%), white solid, mp 162-163 °C (from ethanol); (Found: C, 67.0; H, 3.9; N, 15.4. C_{21}H_{15}ClN_{4}O requires C, 67.3; H, 4.0; N, 14.95%); ν_max/cm^{-1} 1725 (C=O); δ_H (CDCl_3) 1.87 (s, 3H, CH_3), 3.86 (dd, J 7.8, 7.3, 1H, H-1), 4.26 (d, 1H, J 7.8, H-2), 5.25 (d, 1H, J 7.3, H-10b), 7.21 (d, 1H, J 7.3, H-10), 7.34 (d, 1H, J 7.3, H-7), 7.41-7.47 (m, 6H, H-8, H-9 and H-2', H-3'), 7.63 (s, 1H, H-6); δ_C (CDCl_3) 31.6 (CH_3), 57.2 (C-10b), 58.9, 59.4 (C-1, C-2), 65.9 (C-3), 111.2, 111.9 (C=NH), 124.3 (C-10a), 126.2 (C10), 127.5 (C-9), 129.3 (C-1'), 129.8 (C-2'), 129.9 (C-8), 130.1 (C-3'), 130.4 (C-6a), 132.1 (C-7), 136.1 (C-4'), 144.6 (C-6), 204.5 (C=O).
$^1$H and $^{13}$C NMR spectra for product 179 in CDCl$_3$
Compound 183 (0.02 g, 5%) $\delta_H$ (CDCl$_3$) (from mixture) key signals: 3.67 (dd, 1 H, $J$ 7.1, 9.1 H-1), 4.19 (1H, $J$ 7.1, H-2), 4.66 (d, 1H, $J$ 9.1, H-10b). Other signals overlapped in the mixture.

Synthesis of 1-endo-2-exo-2-acetyl-1,2,3,10b-tetrahydro-1-(4-methylphenyl) pyrrolo[2,1-a]phthalazine-3,3-dicarbonitrile 185 and 1-exo-2-endo-2-acetyl-1,2,3,10b-tetrahydro-1-(4-methylphenyl)pyrrolo[2,1-a]phthalazine-3,3-dicarbonitrile 186

Phthalazinium-2-dicyanomethanide 1,3-dipole (0.20 g, 1.03 mmol) was added to a solution of 4-(4-methylphenyl)-3-buten-2-one (0.50 g, 3.09 mmol) in acetonitrile (20 cm$^3$) and stirred under reflux for 5 h. After this time the solvent was removed under reduced pressure to afford a brown gummy residue. The residue was taken up in ice-cold ether which caused the major product 185 to separate as a yellow solid. The ethereal filtrate contained further 185, the minor product 186, unreacted dipole and some intractable gum. Proton NMR analysis of this mixture gave the reported yields for the products. Compound 185 (0.25 g, 69%), yellow solid, mp 175-176 °C (from ethanol); (Found: C, 74.4; H, 4.8 N, 15.85. C$_{22}$H$_{18}$N$_4$O requires C, 74.6; H, 5.1; N, 15.8%); $\nu$$_{max}$/cm$^{-1}$ 1725 (C=O); $\delta_H$ (CDCl$_3$) 1.92 (s, 3H, COCH$_3$), 2.37 (s, 3H, CH$_3$ of p-tolyl), 3.93 (dd, $J$ 7.8, 8.9, 1H, H-1), 4.23 (d, 1H, $J$ 7.8, H-2), 5.22 (d, 1H, $J$ 8.9, H-10b), 7.18 (d, 1H, $J$ 6.9, H-10), 7.26 (d, 2H, $J$ 7.8, H-3'), 7.34 (d, 1H, $J$ 7.1, H-7), 7.39-7.46 (m, 4H, H-8, H-9, H-2'), 7.64 (s, 1H, H-6); $\delta_C$ (CDCl$_3$) 21.3 (CH$_3$ of p-tolyl), 31.3 (COCH$_3$), 57.3 (C-10b), 58.4, 59.3 (C-1, C-2), 65.3 (C-3), 111.3, 112.3 (C=N), 124.5 (C-10a), 125.9 (C-10), 127.4 (C-9), 128.7 (C-2'), 128.9 (C-1'), 129.7 (C-8), 130.0 (C-6a), 130.3 (C-3'), 132.0 (C-7), 140.0 (C-4'), 144.6 (C-6), 204.9 (C=O).

186 (0.03 g, 8%), $\delta_H$ (CDCl$_3$) (from mixture) key signals: 3.69 (dd, 1H, $J$ 9.2, 7.3, H-1), 4.11 (1H, $J$ 7.3, H-2), 4.63 (d, 1H, $J$ 9.2, H-10b). Other signals overlapped in the mixture.
$^1$H and $^{13}$C NMR spectra for product 185 in CDCl$_3$
Cycloaddition reactions of the phthalazinium-2-dicyanomethanide 1,3-dipole 45 in water

Synthesis of endo-1,2-(dicarboxy-N-phenylimido)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine 187
A suspension of phthalazinium-2-dicyanomethanide 1,3-dipole (0.30 g, 1.54 mmol) in water (20 cm³, Millipore grade) was treated with N-phenylmaleimide (0.26 g, 1.54 mmol) and stirred at ambient temperature for 24 hours. During this time the product precipitated from solution as a pale yellow solid and was collected by direct filtration to give compound 187 (0.56 g, 96 %); mp 252-253 °C (ethanol); (Found: C, 62.9; H, 3.7 N, 23.2. C₂₁H₂₃N₅O₂ requires C, 62.9; H, 3.6; N, 22.9%); νmax/cm⁻¹ 1715, 1795 (C=O); δH (DMSO-d₆) 4.41 (dd, 1H, J 7.8, 7.6 H-1), 4.77 (d, 1H, J 7.8, H-2), 7.19 (d, 2H, J 7.1, H-2' of N-Ph, 7.51-7.66 (m, 6H, H-3' and H-4' of N-Ph and H-7 to H-9), 7.82 (d, 1H, J 7.8, H-10), 8.07 (s, 1H, H-6); δC (DMSO-d₆) 45.3 (C-2), 51.3 (C-1), 59.2 (C-3), 59.7 (C10-b), 110.8, 112.4 (C=N), 123.9 (C-10a), 128.9 (C-1’ of N-Ph), 129.6 (C-6a), 131.9 (C-7), 126.5 (C-8), 127.1 (C-9), 127.8 (C-10), 129.2 (C-2’ of N-Ph), 131.5 (C-3’ of N-Ph), 146.8 (C-6), 170.4, 172.4 (C=O).

Synthesis of 1-endo-2-exo-2-acetyl-1-(4-chlorophenyl)-1,2,3,10b-tetrahydro pyrrolo[2,1-a]phthalazine-3,3-dicarbonitrile 182 and 1-exo-2-endo-2-acetyl-1-(4-chlorophenyl)-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine-3,3-dicarbonitrile 183
A suspension of phthalazinium-2-dicyanomethanide 1,3-dipole (0.20 g, 1.03 mmol) and 4-(4-chlorophenyl)-3-buten-2-one (0.19 g, 1.05 mmol) in water (10 cm³, Millipore grade) was stirred vigorously at 75 °C for 24 h. During this time the suspended solids compacted into a sticky mass surrounding the stir bar and the interior of the reaction flask. The solids were collected by filtration and scraping from the stir bar and flask to give a mixture of compounds 182 and 183; (0.35 g, 86% total yield); (ratio 182: 183 determined by ¹H NMR spectroscopy, 6.2:1).
$^1$H and $^{13}$C NMR spectra for product 182 in CDCl$_3$
Chapter 3

**Experimental: kinetics**

The phthalazinium-2-dicyanomethanide 1,3-dipole 45 was recrystallized from ethanol before use. The dipolarophiles 4-phenyl-3-buten-2-one (Sigma-Aldrich, ≥99%), 4-(4-chlorophenyl)-3-buten-2-one (Sigma-Aldrich, 97%) and 4-(p-tolyl)-3-buten-2-one (Sigma-Aldrich, 97%) were used as purchased. Acetonitrile was of spectrophotometric grade (Sigma-Aldrich, >99.9%) and used without further purification. Water was of Millipore grade. The rate constants were measured by recording the disappearance of the phthalazinium-2-dicyanomethanide 1,3-dipole 45 at its maximum wavelength in the solvent mixture. The $\lambda_{\text{max}}$ was 423 nm in acetonitrile and 411 nm in 0.9 mole fraction water / acetonitrile.

Spectra were measured using a Hewlett Packard Agilent Technologies 8453 UV-Vis spectrophotometer featuring an automatic changer for up to 8 glass cuvettes of path length 1 cm. The temperature (± 0.2 °C) was maintained by means of a thermostat (Haake DC10) controlled water bath, with a separate calibrated thermometer check. The reaction was monitored using pseudo-first-order conditions. The initial concentration of 1,3-dipole 45 was $3.2 \times 10^{-5}$ M and the dipolarophile concentrations were in excesses ranging from 20 to 600 fold. Kinetic runs were performed at three different concentrations of dipolarophiles and repeated three times. The length of time for the reaction ranged from 36 to 96 h depending on the dipolarophile and conditions. The solution changed from yellow to colourless as the reaction progressed.

In a typical kinetic run 2 cm$^3$ of the dipole solution was placed in a tightly capped cuvette of path length 1 cm and left to equilibrate to the temperature for 10 min. The dipolarophile solution (1 cm$^3$) was added and the mixture was shaken, allowed to equilibrate and the absorbance (A) measured. A plot of $\ln (A_t - A_\infty)$ versus time for more than 3 half-lives, gave a line whose slope gave the pseudo-first-order rate constant. These lines typically gave r values of ≥ 0.999. Plots of the measured pseudo-first-order rate constants, with the origin as an extra point, versus the molarity of the dipolarophile, gave lines where slopes which were the second-order
rate constants quoted. All second-order rate constants were measured at least three times and were reproducible to $\pm 5.0\%$.

**Computational Methods**

A number of computational methods incorporated into the Gaussian 03 series of programs\textsuperscript{101} were used in this study. All geometry optimisations were carried out with B3LYP\textsuperscript{103, 104} DFT method. The standard split valence plus polarisation 6-31G(d) basis set was used in all cases. Normal mode analysis was used to ascertain the nature of all structures identified as stationary points. All dipolarophiles were optimised and their lowest energy conformations were used in this study. The geometries of all carbonyl groups were optimised to a *cis* or quasi *cis* configuration to the C=C bond in the transition states as these configurations give lower energies than the *trans* configurations in the separated dipolarophiles. Transition state structures were calculated for all four stereo (*endo*/*exo*) and regioisomeric products from C=C bond dipolarophiles. In many of the dipolarophiles used in this study there is a possibility for one or more lone pair orbitals to be the HOMO(s). As we are dealing with cycloaddition reactions the highest $\pi$-C=C molecular orbital should be considered for the frontier orbital interactions. All dipolarophile LUMO in this study are $\pi$-C=C molecular orbitals. It was verified that the HOMO and the LUMO of the 1,3-dipole 45 are composed mainly of the three dipole atoms and do not involve a lone pair of the benzo system.\textsuperscript{63}
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Publications
Publications

1. Water and the Huisgen cycloaddition reaction: A focus on polar contributions to the transition state in the reactions of dicyano(phthalazinium)methanide with substituted styrenes and benzylidene acetones.

2. Spirally twisted ylide structures from 1,2-rearrangements in reactions of imidazolium dicyanomethanide 1,3-dipoles with maleic anhydride: new perspectives on the Boekelheide-Fedoruk ring expansions

3. Organic synthesis in water: 1,3-dipolar cycloaddition reactions at ambient temperature with aqueous suspensions of solid reactants

4. Water and organic synthesis: A focus on the in-water and on-water border. Reversal of the in-water Breslow hydrophobic enhancement of the normal endo-effect on crossing to on-water conditions for Huisgen cycloadditions with increasingly insoluble organic liquid and solid 2π-Dipolarophiles