Photochemically Produced Aminocyclobutanes as Masked Dienes in Thermal Electrocyclic Cascade Reactions

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Supporting Information Placeholder

ABSTRACT: Cyclobutane products of a triplet sensitized enamide-alkene intramolecular [2+2] photocycloaddition have been shown to undergo fragmentation under acidic conditions. This lability has been exploited by inducing a complexity generating thermal electrocyclic cascade sequence involving the in situ formation of a cyclobutene, followed by electrocyclic ring opening, Diels-Alder cycloaddition and subsequent lactamization. This combination of excited state photochemistry and thermal electrocyclic cascade reactions allows simple planar molecules to be rapidly transformed into sp³ rich scaffolds.

Structural novelty and 3D molecules are generating increasing interest as potential library scaffolds in drug discovery as the pharmaceutical industry explores bioactivity beyond the constraints of flat polyaryl molecules.1,2 Excited state photochemistry is unparalleled in its ability to convert simple planar molecules into complex sp³ rich species.3 Photocycloadditions in particular, can give rise to exotic polycyclic species under ‘reagentless’ conditions with 100% atom economy. Although scalability is often cited as a limiting factor preventing the more widespread uptake of excited state photochemistry in pharma, we have recently demonstrated the scale-up of a wide range of photochemical reactions under research lab conditions to unprecedented quantities (≥ 1 kg/day) using novel flow reactors developed by us.4

The high energies involved in the formation of photochemically excited states means that the products often possess great strain.1c Thermal release of this strain often facilitates further ground state reactivity e.g. the de-Mayo reaction5; fragmentation of cyclobutanols from Norrish-Yang products6; 1,5-H shifts of photochemically produced aziridines7 and photoisomerization and trapping of trans cycloalkenes.8 The availability of complex photochemical products by flow-photochemistry means that they can now be considered as accessible feedstocks processing ‘masked reactivity’ due to their inherent high strain energy. The general application of these in synthesis has yet to be exploited. Herein we report an investigation into the cascade reactivity of one such structure from photochemically produced 2,4-methanopyrrolidine 2a on the kilogram scale[4c] in a standard fumehood (Scheme 1). Key to the success of the reaction was the use of an inexpensive organic triplet sensitizer isopropylthioxanthone (ITX) which has a strong UVA absorption and so can be used at low loadings (1%) whilst still harnessing the intense I-line emission at 365 nm of the medium pressure lamp used.

Scheme 1. Acid catalyzed fragmentation of 2,4-methanopyrrolidines and proposed capture of reactive intermediates

Pyrrolidine 2a appeared to be an ideal motif for fragment libraries being conformationally restricted and possessing favorable physiochemical properties.9 Unfortunately, attempts to deprotect the amide under acidic conditions10 resulted in significant degradation. On closer analysis of the reaction mixture traces of the alcohol 3 and cyclobutene 4 could be identified. This indicates that the strained nature of the molecule makes the
C-N bond particularly labile towards fragmentation upon protonation of the amide carbonyl. We reasoned that this inherent strain can be exploited by allowing the 2,4-methanopyrrolidine to undergo fragmentation to cyclobutane 4 which could then undergo electrocyclic ring opening to diene 5 under thermal conditions.\(^{13}\) In the presence of a dienophile, diene 5 should then be trapped out as a Diels-Alder adduct.\(^{13}\) Furthermore, in the case of maleic anhydride, the pendant amide is perfectly positioned to undergo lactamation to 7. This sequence should allow the formation of functionalized bicyclic lactams in a single operation from 2,4-methanopyrrolidines with exceptionally high efficiency and atom economy. Pyrrolidine and its derivatives are found in numerous natural products and APIs making this an attractive scaffold for drug discovery programs.

Whilst the key complexity generating step in the cascade is a Diels-Alder cycloaddition,\(^ {13}\) this sequence is unique in that the cascade begins with a photochemically produced cyclobutane which acts as a masked diene. It also provides the required functionality for lactam formation so each structural feature plays a vital role in the overall cascade.

To explore the scope of the initial triplet sensitized photochemical reaction a series of 2,4-methanopyrrolidines (2a-j) were prepared from some readily available acetonophenones (Table 1)

**Table 1. Preparation of 2-aryl-2,4-methanopyrrolidines by crossed [2+2] photocycloaddition\(^ a\)**

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone</th>
<th>Ar</th>
<th>1(a-j) yield (%)*</th>
<th>2(a-j) yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td>C(_6)H(_4)</td>
<td>81 (426)</td>
<td>89 (93)</td>
</tr>
<tr>
<td>2</td>
<td>8b</td>
<td>3-MeOC(_6)H(_4)</td>
<td>80 (426)</td>
<td>87 (102)</td>
</tr>
<tr>
<td>3</td>
<td>8c</td>
<td>4-MeOC(_6)H(_4)</td>
<td>85 (125)</td>
<td>88 (10.4)</td>
</tr>
<tr>
<td>4</td>
<td>8d</td>
<td>4-FC(_6)H(_4)</td>
<td>78 (441)</td>
<td>75 (170)</td>
</tr>
<tr>
<td>5</td>
<td>8e</td>
<td>3-FC(_6)H(_4)</td>
<td>78 (158)</td>
<td>82 (9.2)</td>
</tr>
<tr>
<td>6</td>
<td>8f</td>
<td>2-FC(_6)H(_4)</td>
<td>95 (48)</td>
<td>88 (9.9)</td>
</tr>
<tr>
<td>7</td>
<td>8g</td>
<td>4-CF(_3)C(_6)H(_4)</td>
<td>77 (488)</td>
<td>94 (249)</td>
</tr>
<tr>
<td>8</td>
<td>8h</td>
<td>3-CF(_3)C(_6)H(_4)</td>
<td>69 (121)</td>
<td>79 (21)</td>
</tr>
<tr>
<td>9</td>
<td>8i</td>
<td>4-MeC(_6)H(_4)</td>
<td>72 (74)</td>
<td>73 (8.1)</td>
</tr>
<tr>
<td>10</td>
<td>8j</td>
<td>3-BrC(_6)H(_4)</td>
<td>77 (528)</td>
<td>86 (103)</td>
</tr>
</tbody>
</table>

\(^a\)Conditions: i) Allylamine (1.5 eq.), 3Å mol. sieves, cyclohexane; ii) BzCl (1.0 eq.), Et\(_2\)N (1.0 eq.), DCM; iii) 400 W Hg lamp, ITX (1%), MeCN. \(^b\)Isolated mass of product

The photochemical precursors and product could all be formed in similar yield and efficiency for both electron withdrawing and electron donating substituents at meta and para positions. Enamides 1(a-j) were prepared on scales up to 2 moles whilst the photochemical step could produce around 100 g of 2,4-methanopyrrolidine in 24 h with a conventional batch reactor and 400 W mercury lamp. These results demonstrate how an optimized photochemical reaction driven by a carefully selected triplet sensitizer can be scaled-up using traditional batch apparatus.

To test the proposed electrocyclic cascade sequence pyrrolidine 2a was heated in xylene at reflux with maleic anhydride. Full conversion was observed after 4 hours and a new compound was isolated. To our delight, this was confirmed to be the expected *endo* Diels-Alder adduct 6 which had undergone further lactamation from the initial [4+2] adduct to form (+)-7a (Table 2). The structure and relative configuration was confirmed by single crystal X-ray crystallography. This single diastereomer was the product of four sequential reactions and required no additional reagents or catalysts – essentially 90% yield for each of the four steps. The full range of 2,4-methanopyrrolidines were then heated in the presence of maleic anhydride to explore the scope of the proposed fragmentation / electrocyclic rearrangement / addition / lactamation sequence. Reaction times were reduced from 4 hours to just 30 mins by heating at 180°C in a sealed tube. Remarkably no added acid was required as it was likely provided by a small amount of maleic acid present in the corresponding anhydride.

**Table 2. Reagent-Free thermal fragmentation / electrocyclic ring-opening / [4+2] cycloaddition / lactamation cascade reactions of 2(a-j) with maleic anhydride**

\[
\text{\begin{align*}
\text{entry} & \quad \text{lactam} & \quad \text{Ar} & \quad \text{yield (%)*} \\
1 & 7a & \text{C}_6\text{H}_5- & 64 \\
2 & 7b & 3-\text{MeOC}_6\text{H}_4- & 55 \\
3 & 7c & 4-\text{MeOC}_6\text{H}_4- & 12 \\
4 & 7d & 4-\text{FC}_6\text{H}_4- & 52 \\
5 & 7e & 3-\text{FC}_6\text{H}_4- & 65 \\
6 & 7f & 2-\text{FC}_6\text{H}_4- & 59 \\
7 & 7g & 4-\text{CF}_3\text{C}_6\text{H}_4- & 57 \\
8 & 7h & 3-\text{CF}_3\text{C}_6\text{H}_4- & 48 \\
9 & 7i & 4-\text{MeC}_6\text{H}_4- & 42 \\
10 & 7j & 3-\text{BrC}_6\text{H}_4- & 66
\end{align*}}
\]

\(^*\)All reaction performed on a 20 mmol scale in a sealed tube

The Diels-Alder products were all formed in isolated yields that represented greater than 80% yield for each of the four steps involved in the cascade. Only entry 3, a pyrrolidine with a para electron donating aryl substituent, showed a reduced yield due to formation of an unidentified resinous material. The only actual reagent used in the whole sequence from commercially available starting materials is Et\(_2\)N in the initial reactions of acetonophenones 8 with allyl amine and BzCl. The only by-products are water and Et\(_2\)N.HCl. The subsequent [2+2] and 4-step cascade sequence are mediated by light and heat alone. Apart from 1f all products were isolated by trituration and no chromatography was needed for the entire sequence from the starting acetonophenones.
We then investigated the reaction of pyrrolidines 2 with butyl acrylate in order to ascertain the reactivity of the diene 5 with a mono-activated dienophile (Table 3). Initially the reaction proved ineffective in xylene at reflux and so a catalytic amount of oxalic acid was added (5%) based on its similar pKa to maleic acid. During the reaction, NMR analysis showed the Diels-Alder adduct 9 was formed as a mixture of diastereomers (endo : exo = 2:1) but as a single regioisomer. When the crude reaction mixture was refluxed in methanol with DBU, epimerization occurred (C*) and the endo isomer consequently underwent concurrent lactamization and methanol mediated debenzylation. The overall sequence from 2 to (+)-10 could be carried out as a single one-pot procedure whereby 6 discreet reaction steps are telescoped together. Furthermore, these complex sequences could be carried out on significant scale producing the final products in 14-76g quantities.

Table 3. One-pot, 6-reaction cascade sequence reactions of 2-aryl-2,4-methanopyrrolidines 2 with butyl acrylate

<table>
<thead>
<tr>
<th>entry</th>
<th>lactam</th>
<th>Ar</th>
<th>yield (%)</th>
<th>mass (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>C6H5</td>
<td>71</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>10b</td>
<td>3-BrC6H5-</td>
<td>61</td>
<td>14.7</td>
</tr>
<tr>
<td>3</td>
<td>10d</td>
<td>4-FC6H5-</td>
<td>66</td>
<td>15.4</td>
</tr>
<tr>
<td>4</td>
<td>10f</td>
<td>2-BrC6H5-</td>
<td>64</td>
<td>14.9</td>
</tr>
<tr>
<td>5</td>
<td>10j</td>
<td>3-BrC6H5-</td>
<td>49</td>
<td>14.3</td>
</tr>
</tbody>
</table>

To further understand the cascade sequence the individual steps were studied. Treatment of pyrrolidine 2a with p-toluene sulphonic acid (10%) in CHCl3 at 60°C resulted in the expected fragmentation to cyclobutene 4 (89%). This was stable when purified but degraded in solution over a period of days on standing at room temperature. When heated in a sealed tube at 180°C, low levels of the diene 4 (Ar = Ph, Scheme 1) were observed by 1H-NMR but the main product was the Diels-Alder homodimer14 (+)-20 as a mixture of diastereomers (Scheme 2). Although Diels-Alder cycloaddition of α-quinoindimethanes15 generated in situ from the thermolysis of benzocyclobutenes is well known, examples of non-aromatic systems, where the ring opened diene is trapped in situ remain scarce.16 More commonly the diene obtained from ring opening is isolated before further reaction with dienophile.17 To the best of our knowledge this is the first example of a Diels-Alder cascade sequence in which the starting material is an alkyl cyclobutane. Although it may be possible to synthesize the key reactive diene 5 by conventional means, it is hard to envisage a more efficient and scalable route than the one disclosed.

In order to assess the scope of the reactivity of the in situ formed diene 5, the isolated cyclobutene 4 was then heated in the presence of a wide range of dienophiles (Scheme 2). Maleimide adducts ((±)-11 and (+)-12) were formed with complete endo selectivity. All acrylates gave approximately 2:1 selectivity and tolerated α-substitution well ((±)-14 and (+)-15), however β-substituents proved problematic as in the case of crotonates and cinnamates which gave no isolable products. To telescope the process with non-acidic dienophiles a further screen of additives was carried out. This identified 5% tetra butylammonium bromide (TBAB) as a mild and effective additive to initiate the fragmentation (Conditions B).

Excellent yields were obtained for other electron deficient alkenes such acrylonitrile and methyl vinyl ketone, with exclusive regioselectivity observed for the Diels-Alder step ((±)-16 and (+)-17). Electron deficient alkenes also performed well with no aromatized products observed ((±)-19 and (+)-21). Although styrene was found to undergo reaction to the cyclohexene (+)-18, the presence of the dimer (+)-20, indicated that homo Diels-Alder of diene 5 was competitive with reaction of styrene.

Scheme 2. Thermal electrocyclic cascade reactions of cyclobutene 4 and 2,4-methanopyrrolidine 2a with a range of dienophiles*

*Conditions: A (cyclobutene 4, no additive); B (2a, 5% TBAB); C (2a, 5% oxalic acid); endo:exo ratio in parentheses

Regioselectivity was exclusive in all relevant cases although all mono-activated dienophiles gave epimeric mixtures of initial Diels-Alder adducts. However, this is conveniently overcome by epimerization to the more stable exo isomer under basic conditions. For example, treatment of the crude reaction mixture of (+)-16 with 10% DBU gave the exo isomer which precipitated out of MeOH solution when stirred at room temperature overnight (Scheme 3).
The crude butyl acrylate adduct mixture (±)-9a can similarly be epimerized to the exo isomer by heating with DBU in ethanol rather than methanol (cf. Table 3). The isolated product had undergone full transesterification to the corresponding ethyl ester (±)-13. This result is presumably due to a slower rate of lactamization of an intermediate ethyl ester over the methyl ester and so the reaction outcome can be controlled by solvent choice.

Scheme 3. Epimerization to exo isomers

In summary, we have reported a new and efficient sequence for the formation of bicyclic lactams and highly substituted cyclohexenyl-amines. The reaction proceeds from a novel fragmentation of labile 2,4-methanopyrrolidine derivatives and involves the in situ formation of cyclobutenes, electrocyclic ring-opening to dienes followed by Diels-Alder cycloaddition. The reactions have been carried out on scales of over 70g and the 2,4-methanopyrrolidine [2+2] adducts can be prepared on scales of up to 1 kg. In the case of many of the examples no added acid is required which renders the sequence ‘reagentless’ as well as highly atom-economic.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental details and full spectroscopic data for all new compounds.

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