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Photochemically Produced Aminocyclobutanes as Masked Dienes in Thermal Electrocyclic Cascade Reactions

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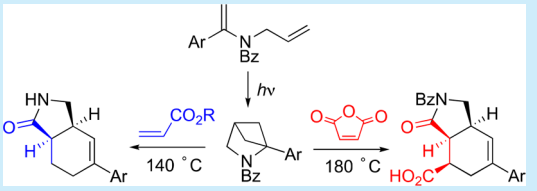
Supporting Information

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 sp^3-rich scaffolds.

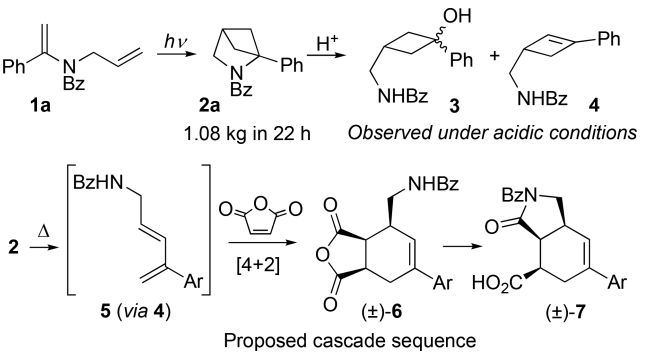


Structural novelty and 3D molecules are generating increasing interest as potential library scaffolds in drug discovery as the pharmaceutical industry explores bioactivity beyond the constraints of flat polyaryl molecules.[1,2] Excited state photochemistry is unparalleled in its ability to convert simple planar molecules into complex sp^3-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.[3c] Thermal release of this strain often facilitates further ground state reactivity, e.g. the de-Mayo reaction;[5] fragmentation of cyclobutanols from Norrish−Yang products;[6] 1,5-H shifts of photochemically produced aziridines;[7] 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-methanopyrrolidines.

As part of a program involving the scale-up of photochemistry for drug discovery, we were able to synthesize 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%) while 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 conditions[10] 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 toward 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 cyclobutene **4** which could then undergo electrocyclic ring opening to diene **5** under thermal conditions.[11] In the presence of a dienophile, diene **5** should then be trapped out as a Diels−Alder adduct.[12] Furthermore, in the case of maleic anhydride, the pendant amide is perfectly positioned to undergo lactamization to **7**. This sequence should allow the formation

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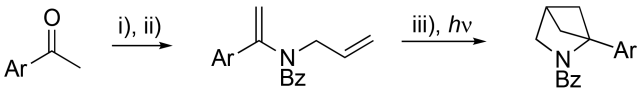
Org. Lett. XXXX, XXX, XXX−XXX

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.

While 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 cyclo*butane* 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 acetophenones (Table 1).

Table 1. Preparation of 2-Aryl-2,4-methanopyrrolidines by Crossed [2 + 2] Photocycloaddition[a]



8a-j **1a-j** **2a-j**

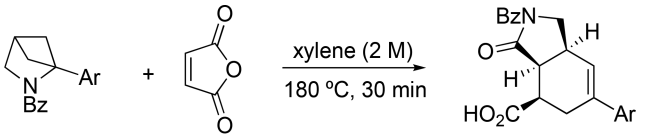
entry	ketone	Ar	**1**(a–j) yield % (g)[b]	**2**(a–j) yield % (g)[b]
1	**8a**	C_6H_5-	81 (426)	89 (93)
2	**8b**	3-$MeOC_6H_4$-	80 (426)	87 (102)
3	**8c**	4-$MeOC_6H_4$-	85 (125)	88 (10.4)
4	**8d**	4-FC_6H_4-	78 (441)	75 (170)
5	**8e**	3-FC_6H_4-	78 (158)	82 (9.2)
6	**8f**	2-FC_6H_4-	95 (48)	88 (9.9)
7	**8g**	4-$CF_3C_6H_4$-	77 (488)	94 (249)
8	**8h**	3-$CF_3C_6H_4$-	69 (121)	79 (21)
9	**8i**	4-MeC_6H_4-	72 (74)	73 (8.1)
10	**8j**	3-BrC_6H_4-	77 (528)	86 (103)

[a]Conditions: (i) Allylamine (1.5 equiv), 3 Å mol. sieves, cyclohexane; (ii) BzCl (1.0 equiv), Et_3N (1.0 equiv), 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 mol while 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 h, 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 lactamization from the initial [4 + 2] adduct to form (±)-**7a** (Table 2). The structure and relative configuration were 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/lactamization sequence. Reaction times were reduced from 4 h to just 30 min 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/ Lactamization Cascade Reactions of 2(a–j) with Maleic Anhydride



2a-j 1.2 equiv (±)-**7a-j**

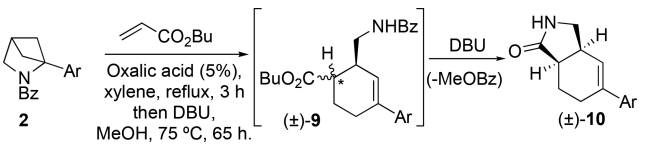
entry	lactam	Ar	yield (%)[a]
1	**7a**	C_6H_5-	64
2	**7b**	3-$MeOC_6H_4$-	55
3	**7c**	4-$MeOC_6H_4$-	12
4	**7d**	4-FC_6H_4-	52
5	**7e**	3-FC_6H_4-	65
6	**7f**	2-FC_6H_4-	59
7	**7g**	4-$CF_3C_6H_4$-	57
8	**7h**	3-$CF_3C_6H_4$-	48
9	**7i**	4-MeC_6H_4-	42
10	**7j**	3-BrC_6H_4-	66

[a]All reaction performed on a 20 mmol scale in a sealed tube.

The Diels–Alder products were all formed in isolated yields that represented a 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_3N in the initial reactions of acetophenones **8** with allyl amine and BzCl. The only byproducts are water and Et_3N·HCl. The subsequent [2 + 2] and four-step cascade sequence reactions 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 acetophenones.

We then investigated the reaction of pyrrolidines **2** with butyl acrylate in order to ascertain the reactivity of the diene **5** with a monoactivated 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 pK_a

Table 3. One-Pot, Six-Step Cascade Sequence Reactions of 2-Aryl-2,4-methanopyrollidines 2 with Butyl Acrylate



2 (±)-**9** (±)-**10**

entry	lactam	Ar	yield (%)	mass (g)
1	**10a**	C_6H_5	71	76
2	**10b**	3-$MeOC_6H_4$-	61	14.7
3	**10d**	4-FC_6H_4-	66	15.4
4	**10f**	2-FC_6H_4-	64	14.9
5	**10j**	3-BrC_6H_4-	49	14.3

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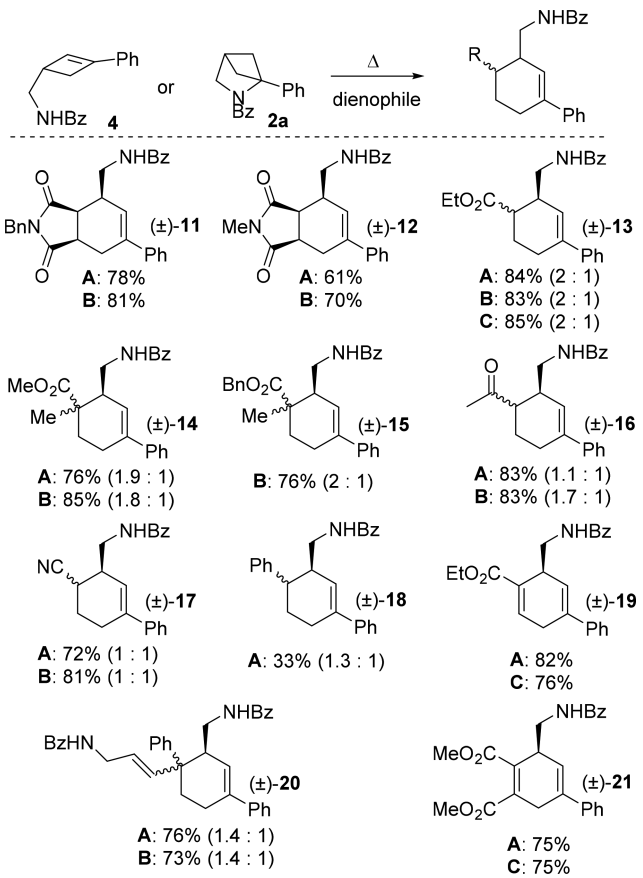
Org. Lett. XXXX, XXX, XXX–XXX

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 conveniently underwent concurrent lactamization and methanol mediated debenzoylation. The overall sequence from **2** to (±)-**10** could be carried out as a single one-pot procedure whereby six discrete reaction steps are telescoped together. Furthermore, these complex sequences could be carried out on significant scale producing the final products in 14–76 g quantities.

To further understand the cascade sequence the individual steps were studied. Treatment of pyrrolidine **2a** with *p*-toluenesulfonic acid (10%) in $CHCl_3$ 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 **5** (Ar = Ph, Scheme 1) were observed by ^{1}H NMR but the main product was the Diels–Alder homodimer[14] (±)-**20** as a mixture of diastereomers (Scheme 2). Although Diels–Alder cycloaddition of *o*-quinodimethanes[15] generated *in situ* from the thermolysis of benzocyclobutenes is well-known, examples of nonaromatic 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 the 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.

Scheme 2. Thermal Electrocyclic Cascade Reactions of Cyclobutene 4 and 2,4-Methanopyrollidine 2a with a Range of Dienophiles[a]



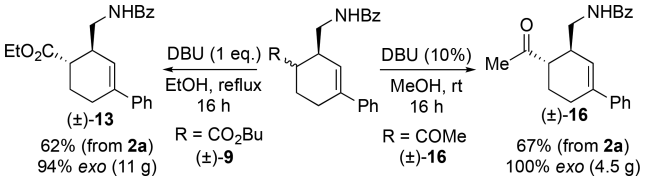
[a]Conditions: **A** (cyclobutene **4**, no additive); **B** (**2a**, 5% TBAB); **C** (**2a**, 5% oxalic acid); *endo*/*exo* ratio in parentheses.

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 nonacidic dienophiles, a further screen of additives was carried out. This identified 5% tetrabutylammonium 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 alkynes 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 the reaction of styrene.

Regioselectivity was exclusive in all relevant cases although all monoactivated 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).

Scheme 3. Epimerization to *exo* Isomers



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.

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 and electrocyclic ring opening to dienes followed by Diels–Alder cycloaddition. The reactions have been carried out on scales of over 70 g, and the 2,4-methanopyrrolidine [2 + 2] adducts can be prepared

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Org. Lett. XXXX, XXX, XXX–XXX

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 at DOI: 10.1021/acs.orglett.9b00211.

Experimental details and full spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1891842 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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