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# 4- $\pi$ -Photocyclization of 1,2-Dihydropyridazines: A Concise Route to Bicyclic 1,2-Diazetidines with Rich Synthetic Potential

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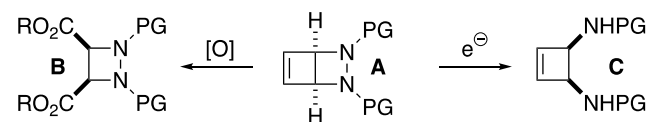
Supporting Information Placeholder

**ABSTRACT:** The 4- $\pi$ -photocyclization of a range of 1,2-dihydropyridazines is described. The bicyclic 1,2-diazetidine products were generally obtained in high yields, and the process was successfully scaled up to multigram scale. The key bicyclic 1,2-diazetidines are versatile synthetic intermediates and were easily converted into a range of novel derivatives, including functionalized 1,2-diazetidines, cyclobutenes, cyclobutanes, and dienes.

Despite growing interest in four-membered carbocycles and heterocycles,<sup>1</sup> their preparation remains challenging, especially when specific substituent patterns are required. Even established approaches (e.g. [2+2] photocycloaddition in the synthesis of cyclobutanes,<sup>2</sup> Staudinger reaction in the synthesis of  $\beta$ -lactams,<sup>3</sup> Paternò-Büchi reaction in the synthesis of oxetanes<sup>4</sup>) often cannot deliver the desired products selectively, in contrast to the synthesis of three-, five- and six-membered rings, which have been studied much more intensively. To fully exploit the potential of four-membered rings, new efficient and creative synthetic approaches are urgently required.

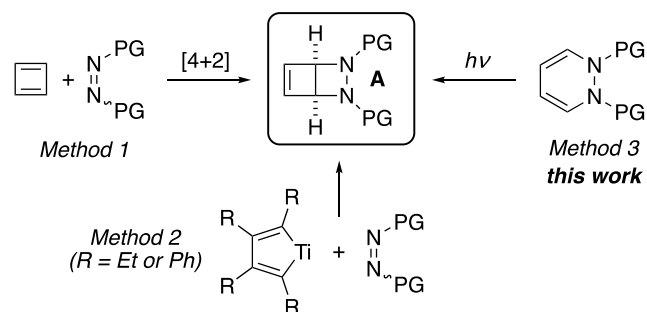
We envisioned bicyclic 1,2-diazetidines **A** as flexible intermediates that could be easily transformed into diverse four-membered molecular building blocks via standard functional group interconversions (Scheme 1). For example, N-N cleavage of **A** would lead to diaminocyclobutenes **B**, whilst oxidative C=C cleavage would furnish disubstituted 1,2-diazetidines **C**. Given their apparent simplicity and their obvious potential in synthetic/medicinal chemistry, it seemed surprising that scaffolds **B** and **C** have never been described before in the literature.

## Scheme 1. Proposed Synthetic Applications of Bicyclic 1,2-Diazetidines **A**



Meanwhile, bicyclic 1,2-diazetidines **A** have been reported only rarely, with only limited examples of three distinct synthetic approaches having been reported. First, the groups of Masamune,<sup>5</sup> Warrener,<sup>6</sup> and Carpenter<sup>7</sup> described the Diels-Alder reaction of cyclobutadiene with various azo compounds to furnish bicyclic 1,2-diazetidines **A** in low-moderate yields (Scheme 2, Method 1). Despite its efficiency, this approach is impractical on larger scales, since the required cyclobutadiene precursor (the corresponding iron tricarbonyl complex) is not commercially available, and its preparation is expensive and not atom-economical.<sup>8</sup> Nevertheless, two further reports describe the use of tetrasubstituted cyclobutadienes to give highly substituted versions of bicycles **A**.<sup>9,10</sup>

## Scheme 2. Known Synthetic Approaches to Bicyclic 1,2-Diazetidines **A**

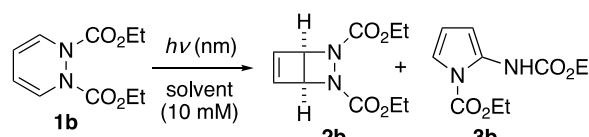


Alternatively, Feng and co-workers described the titanium-mediated conversion of tetrasubstituted 1,3-butadienes (Scheme 2, Method 2) into **A** in good yields, although only two examples were reported.<sup>11</sup> Finally, Altman and co-workers reported a single example of the 4- $\pi$ -photocyclization of a 1,2-dihydropyridazine (Scheme 2, Method 3; PG = CO<sub>2</sub>Me) to afford **A** in 61% yield, accompanied by a pyrrole side product (14%, vide infra).<sup>12</sup> Experimental details were scarce, and Warrener and co-workers later reported that they could obtain **A** only in low yield (~20%) using this approach.<sup>6</sup> Subsequently, Stearns and Ortiz de Montellano<sup>13</sup> reported a second example of this route (Scheme 1, Method 3; PG = CO<sub>2</sub>Et)

to afford **A** in reasonable yield, again accompanied by a pyrrole side product, with low selectivity (6:4 **A**:side product). The cyclization is analogous to the 4- $\pi$ -photocyclization of 2-pyrones to give bicyclic  $\beta$ -lactones, which has recently been exploited by Maulide to access a variety of cyclobutene products.<sup>14</sup> Having recently developed an efficient synthesis of 1,2-dihydropyridazines,<sup>15</sup> we chose to pursue the 4- $\pi$ -photocyclization approach to bicycles **A**. Herein, we describe the development of a robust photocyclization procedure capable of producing multigram quantities of bicycles **A**, as well as the conversion of **A** into varied novel molecular building blocks.

First, the 4- $\pi$ -photocyclization of 1,2-dihydropyridazine **1b** was studied (Table 1). Upon irradiation at 300 nm in diethyl ether, **1b** was reported to yield bicyclic 1,2-diazetidene **2b**, accompanied by pyrrole **3b** (**3b** is assumed to result from initial photochemical 6- $\pi$  electrocyclic ring opening to form a diimine, followed by cyclisation to **3b**).<sup>12</sup> As **1b** exhibits an absorption band in the UV-B region ( $\lambda_{\text{max}} = 298$  nm; 0.2 mM in acetonitrile), we started by irradiating a solution of **1b** in acetonitrile at 300 nm in a Rayonet photoreactor (Table 1, entry 1), which furnished **2b** (56% yield) and **3c** (9% yield), in line with Altman's report.<sup>12</sup> Varying the solvent did not lead to any improvement in the selectivity for **2b** over **3b** (Table 1, entries 1-5), thus acetonitrile was retained to study the effect of the irradiation wavelength on the product distribution.

**Table 1. Optimisation of the 4- $\pi$ -Photocyclization of 1,2-Dihydropyridazine 1b**



entry	solvent	$\lambda$ (nm)	time <sup>a</sup> (h)	yield <b>2b</b> (%) <sup>b</sup>	yield <b>3b</b> (%) <sup>b</sup>
1	MeCN	300	1	56	9
2	PhMe	300	1	39	29
3	EtOAc	300	1	42	35
4	TBME	300	1	45	24
5	C <sub>6</sub> H <sub>12</sub>	300	1	38	14
6	MeCN	254	2.5	15	7
7	MeCN	350	20	77	traces
8	MeCN	419	20	0	0

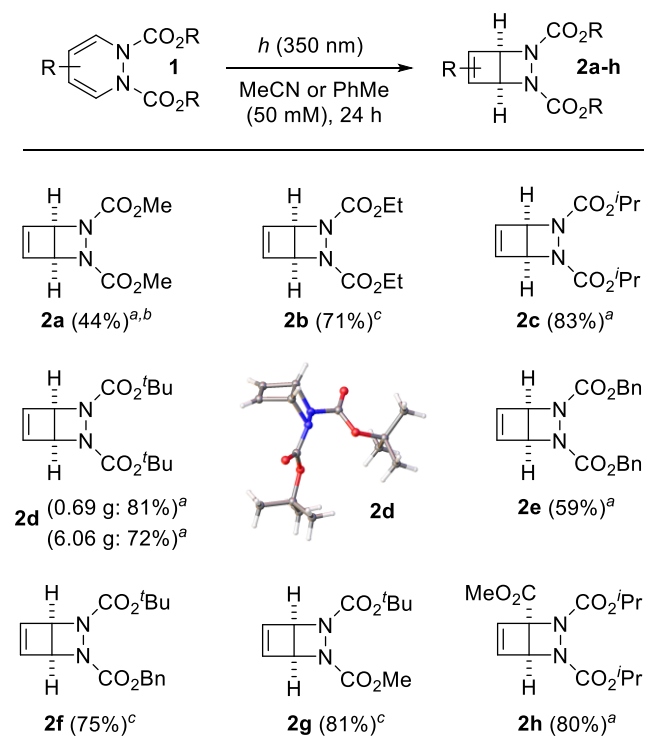
<sup>a</sup> Time taken for the complete consumption of the starting 1,2-dihydropyridazine <sup>b</sup> Isolated yields of 1,2-diazetidene after chromatography. TBME = *tert*-butyl methyl ether.

Higher-energy irradiation (254 nm) led to extensive degradation, with very low yields of bicycle **2b** and pyrrole **3b** obtained (Table 1, entry 6). In contrast, we were delighted to observe that irradiation at 350 nm led to almost complete selectivity: **2b** was generated in 77% yield, with only traces of pyrrole **3b** (Table 1, entry 7). Conversely,

irradiation at even longer wavelength only returned starting material (419 nm; Table 1, entry 8), which was expected due to its lack of absorption at this wavelength. The optimal reaction observed at 350 nm was unexpected, given the low absorbance of **1b** at this wavelength. Indeed, conversion is much less efficient at 350 nm than at 300 nm (20 h for complete consumption of **1b** at 350 nm compared to 1 h at 300 nm; Table 1, entries 1 and 7). We postulate that the enhanced selectivity at 350 nm results from selective excitation into a second, low-intensity absorption band that is obscured at the long-wavelength edge of the main absorption band. Although it has not yet been possible to observe this suggested second band experimentally, this explanation for the observed selectivity seems the most plausible, particularly as the photocyclization is not reversible upon irradiation at 300 or 350 nm (both in the presence and absence of pyrrole **3b**).

The methodology was next applied to a range of other 1,2-dihydropyridazine substrates **1** (Table 2). A variety of different carbamate protecting groups can be employed, with bicyclic 1,2-diazetidines **2** generally being produced in high yields and with excellent selectivity (in all cases, only traces of pyrroles **3** were observed). A substrate concentration of 50 mM was chosen, as it led to the best compromise between throughput and reaction time. In some cases, a slightly higher yield of bicycle **2** was obtained in toluene than in acetonitrile, which we attribute to the small bathochromic absorption shift observed in the UV/Vis spectra of 1,2-dihydropyridazines **1** in less polar solvents; see the Supporting Information).

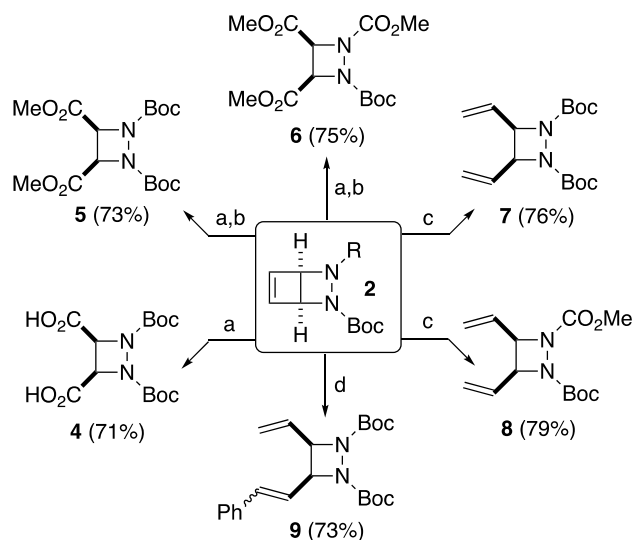
**Table 2. 4- $\pi$ -Photocyclization of 1,2-Dihydropyridazines 1**



(a) Reaction performed in MeCN; (b) Irradiation for 44 hours; (c) Reaction performed in PhMe.

1,2-Dihydropyridazines bearing two different carbamate groups (**1f** and **1g**) were successfully employed, producing bicyclic 1,2-diazetidines carrying orthogonal protecting groups, and ester-substituted 1,2-dihydropyridazine **1h** also underwent successful cyclisation in high yield. The scale-up of the photocyclization to produce multi-gram quantities of bicycles **2** was also investigated. Mindful of the strained nature of these products, an initial safety assessment was first carried out using differential scanning calorimetry (DSC; see the Supporting Information). The DSC data for **2d** exhibited a complex, broad exotherm starting at around 95 °C, which corresponds to a rearrangement reaction of **2d** (vide infra), followed by a sharp exotherm starting at around 185 °C. Based on these data, we concluded that scale-up/storage under the standard conditions (i.e. 35-40 °C in the photoreactor) did not pose a significant safety risk. Gratifyingly, the scaled-up procedure proceeded smoothly, generating 6.1 grams of **2d** from 8.5 grams of **1d** in a single run (Table 2; 72% yield). Meanwhile, the use of a flow photoreactor was also explored, but due to the low rate of the photocyclization at 350 nm, very slow flow rates were required for full conversion, even at low substrate concentrations.

### Scheme 3. Functionalized 1,2-Diazetidines Available from Bicycles **2d** and **2g**



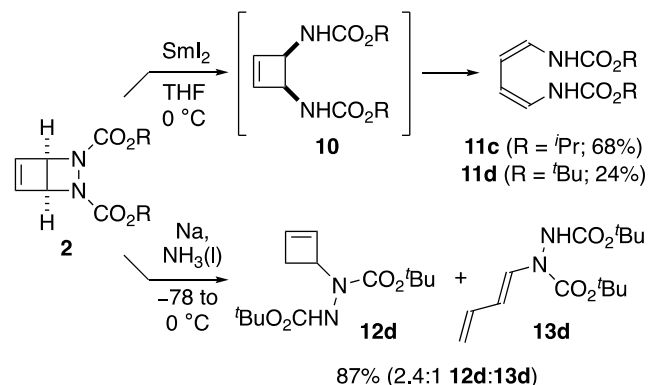
(a)  $\text{RuO}_2 \cdot \text{H}_2\text{O}$ ,  $\text{NaIO}_4$ ,  $\text{EtOAc}/\text{H}_2\text{O}$ , 0 °C to rt, 48 h; (b)  $\text{TMSCHN}_2$ ,  $\text{MeOH}$ , 1 h; (c) Hoveyda-Grubbs II, ethylene (1 atm),  $\text{CH}_2\text{Cl}_2$ , 1 h; (d) Hoveyda-Grubbs II, styrene,  $\text{CH}_2\text{Cl}_2$ , reflux, 30 min.

The synthetic potential of bicyclic 1,2-diazetidines **2** was next examined, and we were delighted to observe that bicycles **2** could be selectively transformed into a wide range of novel building blocks, including functionalized 1,2-diazetidines, cyclobutenes, cyclobutanes, and dienes. Thus,  $\text{RuO}_4$ -mediated oxidative cleavage of **2d** led to the expected diacid **4**, which could be cleanly converted to the corresponding diester **5** (Scheme 3). The same oxidation was also successfully applied to bicycle **2g**, to give diester **6** bearing two orthogonal protecting groups. In addition, a ring-opening metathesis/cross metathesis sequence allowed cleavage of the cyclobutene moiety to

yield divinyl diazetidines **7/8** (using ethylene) and **9** (using styrene) in high yields. This work represents a conceptually new approach to substituted monocyclic 1,2-diazetidines (for which there is no generally applicable synthetic route),<sup>16</sup> and promises easy access to varied related derivatives (e.g. 1,2-diamines) by manipulation of the novel 1,2-diazetidines shown in Scheme 3.

We also sought to access cyclobutene products from **2** through the cleavage of the N-N bridge. Reduction of **2c** with samarium(II) iodide did indeed lead to N-N cleavage, but cyclobutene **10** was not obtained. Instead, diene (*Z,Z*)-**11c** was obtained in 68% yield (Scheme 4; structure conformed by X-ray diffraction), presumably resulting from a thermal 4- $\pi$ -electrocyclic ring-opening of the putative cyclobutene **10** (to give (*E,Z*)-**11**) followed by isomerization (to give (*Z,Z*)-**11**). A lower yield of diene **11d** was obtained than with **11c**, likely due to the sensitivity of the Boc protecting groups to the Lewis acidic samarium(III) by-product. That these electrocyclic ring-opening processes should proceed at ambient temperature is predicted in computational work carried out by Maryasin and Maulide,<sup>16</sup> and by Sheikh;<sup>17</sup> in particular, amino substituents were reported to substantially lower the barrier to ring-opening. In contrast, reduction of bicycle **2d** under dissolving metal conditions led to complementary selectivity, in that C-N cleavage rather than N-N cleavage was observed. Cyclobutene **12d** was isolated from the reaction, but underwent relatively slow thermal 4- $\pi$ -electrocyclic ring-opening at ambient temperature to give a 2.4:1 mixture of **12d** and diene **13d** in 87% yield (Scheme 4).

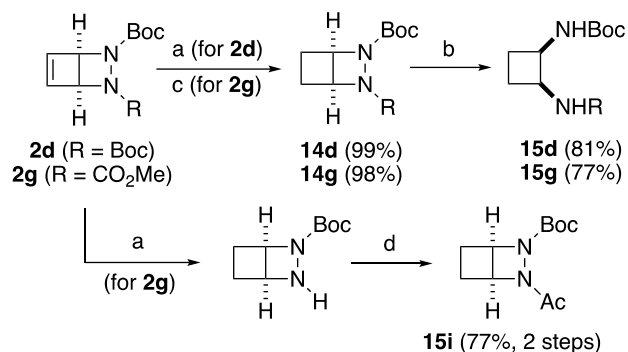
### Scheme 4. Synthesis of Functionalized Cyclobutenes and Dienes from Bicycle **2c/2d**



Mindful of the sensitivity of the cyclobutene products derived from bicycles **2** towards ring-opening, we next chose to target functionalized cyclobutane products through hydrogenation of bicycles **2** to give the corresponding saturated bicycles **14**, followed by cleavage of the N-N bridge. Initial attempts at catalytic hydrogenation of **2d** led mainly to over-reduction (to the hexahydropyridazine product), but the use of diimide led to smooth reduction, furnishing **14d** in quantitative yield (Scheme 5). For the reduction of bicycle **2g**, judicious choice of the diimide precursor allowed the selective retention or deprotection of the methyl carbamate protecting group,

giving bicycle **14g** or **14i** (after acetylation) respectively. Subsequent N-N bond cleavage under dissolving metal conditions gave the target diamines **15d** and **15g** in high yields (Scheme 5), which, despite their apparent simplicity, have never been reported before.<sup>18</sup>

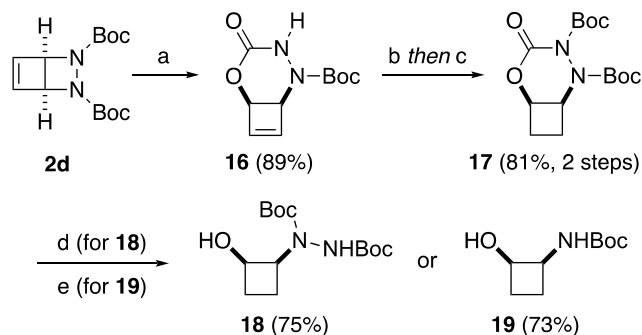
### Scheme 5. Synthesis of Functionalized Cyclobutanes from Bicycles



(a) H<sub>2</sub>N-NH<sub>2</sub> · H<sub>2</sub>O, H<sub>2</sub>O<sub>2</sub>, EtOH, 0 °C; (b) Na, NH<sub>3</sub>, THF, -78 °C then NH<sub>4</sub>Cl (s); (c) KO<sub>2</sub>C-N=N-CO<sub>2</sub>K, AcOH, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt; (d) Ac<sub>2</sub>O, pyridine.

Finally, a second series of cyclobutene/cyclobutane derivatives can be accessed through rearrangement of **2d**. Upon moderate heating followed by the addition of dilute hydrochloric acid, bicycle **2d** was converted into cyclobutene **16**, likely via a [3,3]-sigmatropic rearrangement involving one of the Boc protecting groups (Scheme 6). In analogy to the reactions of bicycle **2d**, diimide reduction of bicycle **16** followed by Boc protection gave cyclobutane **17**, which was easily converted to the novel cyclobutanols **18** (upon ring-opening with lithium hydroxide) or **19** (upon dissolving metal reduction).

### Scheme 6. Thermal Rearrangement of Bicycle 2d; Synthesis of Functionalized Cyclobutanes from 16



(a) 1,4-dioxane, 100 °C, 24 h; 1N HCl (aq); (b) H<sub>2</sub>N-NH<sub>2</sub> · H<sub>2</sub>O, H<sub>2</sub>O<sub>2</sub>, EtOH, 0 °C; (c) Boc<sub>2</sub>O, Et<sub>3</sub>N, THF, 48 h; (d) LiOH, THF, H<sub>2</sub>O; (e) Na, NH<sub>3</sub>, THF, -78 °C, then NH<sub>4</sub>Cl (s).

In summary, a robust procedure for the 4- $\pi$ -photocyclization of 1,2-dihydropyridazines has been developed, which can be conveniently run on multigram scale to produce a range of bicyclic 1,2-diazetidines. The products are extremely versatile synthetic intermediates that can be easily converted to a variety of novel molecular building blocks, including functionalized diazetidines, cyclobutenes, cyclobutanes and dienes. The new building

blocks are deceptively simple, in that they have never been reported before, and are now available for further applications (e.g. as new scaffolds in drug discovery, as ligands with a rigid backbone, or precursors to a wider range of derivatives, such as 1,2-diamines). Further work towards extending the photochemical methodology and applications of the interesting bicyclic products is underway, and will be reported in due course.

## ASSOCIATED CONTENT

### Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, characterization/spectral data (PDF)

X-ray crystallographic data for **2d** (CCDC: XXX), **11d** (CCDC: XXX) and **16** (CCDC: XXX). (being deposited)

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### Notes

The authors declare no competing financial interests.

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