Photochemistry

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First Higher-Order Photocycloaddition to a C=N Bond: 1,3-Diazepines from Maleimides**

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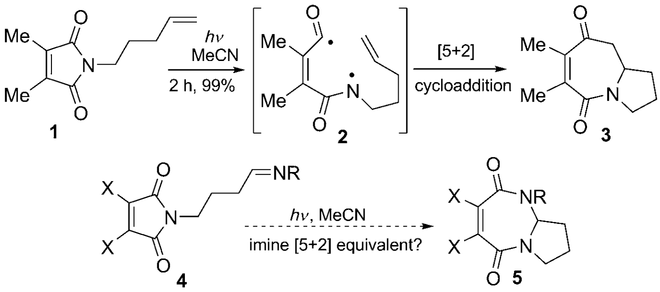
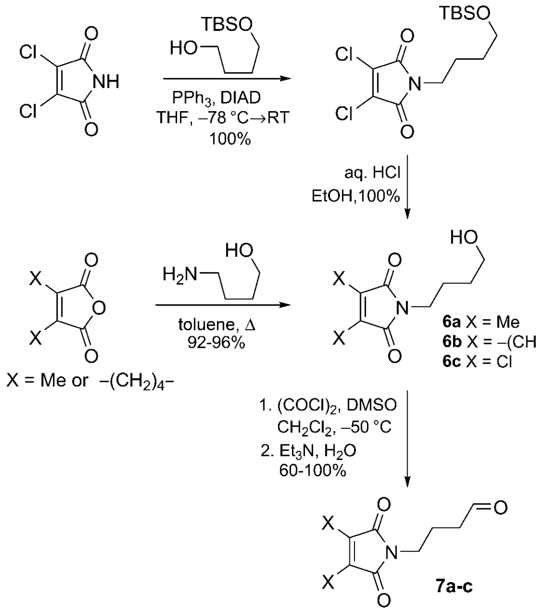
By comparison to C=O and C=C containing chromophores the photochemistry of the C=N bond has not received the same level of synthetic interest and mechanistic scrutiny. Excitation of the C=N bond is known to lead to isomerization, rearrangement, hydrolysis, oxidation, photoreduction, and photoalkylation.[1] Although olefins have been reported to undergo cycloaddition to photoexcited imines containing electron-withdrawing groups on the nitrogen atom,[1a–c,2] generally useful preparative examples of [2+2] photocycloadditions to C=N bonds are very rare. Furthermore, the reverse situation in which the imine is the ground-state partner during the cycloaddition with a photoexcited alkene has, to our knowledge, yet to be reported. Herein, we report our findings in an area of maleimide photochemistry which have resulted in the realization of a [5+2] photocycloaddition that utilizes oximes and hydrazones as ground-state C=N components in the reaction. These results constitute the first reported examples of a higher-order photocycloaddition to a C=N bond.

Previously we reported[3] the synthetic utility of the intramolecular [5+2] photocycloaddition[4] reaction of alkenyl-substituted maleimides **1** as a powerful method for the direct formation of the perhydroazaazulene ring system **3**, which is common to a number of alkaloids. After pursuing an in-depth study, we proposed a singlet mechanism involving n→π* excitation with subsequent C–N α cleavage to give the biradical **2**, which then underwent a [5+2] cycloaddition onto the alkene (Scheme 1).[5] Whereas the reaction is specific to the maleimide and phthalimide chromophores, a wide range of pendant alkene functionality can be used, including cyclic systems, a feature that we have exploited in alkaloid synthesis.[6] We were intrigued to see if similar reactivity would be displayed with maleimides using non-alkene substrates. Introducing a C=N based functionality to the maleimide photosubstrates **4** had the potential to extend the scope of the cycloaddition by enabling the formation of 1,3-diazepines **5**, a class of diazepine that has rarely been reported.[7]



Scheme 1. [5+2] Photocycloadditions of N-substituted maleimides.

We anticipated that an important factor when choosing the precursors **4** would be the stability of the C=N bond towards hydrolysis. Hydrazones and oximes were attractive as they are inherently more stable than imines with respect to isolation and additional manipulation. The preparation of the alcohols **6a–c** could be achieved by one of two routes (Scheme 2). Dimethylmaleimide and tetrahydrophthalimide derived alcohols **6a** and **6b** were prepared in excellent yield by condensation of the corresponding anhydrides with 4-aminobutanol under Dean Stark conditions. The dichloromaleimide derivative **6c** was more problematic and was best prepared by a two-step sequence involving a Mitsunobu



Scheme 2. Synthesis of aldehydes **7**, precursors to the oximes used for the [5+2] photocycloadditions. DMSO = dimethylsulfoxide, TBS = *tert*-butyldimethylsilyl, DIAD = diisopropylazodicarboxylate.

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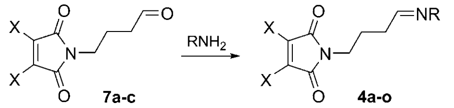
coupling[3a] of dichloromaleimide with TBSO(CH$_2$)$_4$OH and subsequent deprotection. Conversion of the alcohols **6a–c** into the aldehydes **7a–c** could be achieved in moderate to excellent yields by Swern oxidation. The aldehydes were then condensed with a variety of substituted hydrazines and oximes to produce a range of potential C=N photosubstrates (Table 1). The formation of **4** generally resulted in a mixture of inseparable *E* and *Z* isomers. Their ratios, however, could be calculated by using ^{1}H NMR analyses wherein a distinct difference in chemical shift of the HC=NR proton ($\delta_Z > \delta_E$; $\approx$1 ppm) is observed.[8]

Table 1: Preparation of C=N tethered imide photoprecursors **4**.

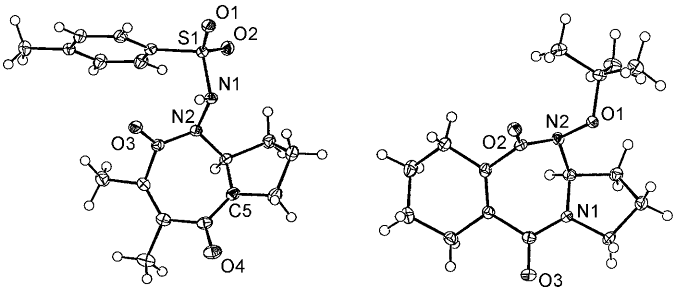


Entry	RNH$_2$[a]	X	R	4	Yield [%][b]	*E*/*Z* ratio
1	H$_2$NNHSO$_2$tol	Me	NHSO$_2$tol	**4a**	68	1:4.4
2	H$_2$NOH·HCl	Me	OH	**4b**	21	1:2.3
3	H$_2$NOMe·HCl	Me	OMe	**4c**	73	1:1.6
4	H$_2$NO*t*Bu·HCl	Me	O*t*Bu	**4d**	74	1:1.7
5	H$_2$NOTHP	Me	OTHP	**4e**	74	1:1
6	H$_2$NNMe$_2$	Me	NMe$_2$	**4f**	78	*E* only
7	H$_2$NNPh$_2$	Me	NPh$_2$	**4g**	42	*E* only
8	H$_2$NNHCOPh	Me	NHC(O)Ph	**4h**	61	*E* only
9	H$_2$NNHSO$_2$tol	-(CH$_2$)$_4$-	NHSO$_2$tol	**4i**	84	1:3.5
10	H$_2$NOH·HCl	-(CH$_2$)$_4$-	OH	**4j**	85	1.4:1
11	H$_2$NOMe·HCl	-(CH$_2$)$_4$-	OMe	**4k**	80	1:1.6
12	H$_2$NO*t*Bu·HCl	-(CH$_2$)$_4$-	O*t*Bu	**4l**	89	1:1.6
13	H$_2$NOH·HCl	Cl	OH	**4m**	44	1.3:1
14	H$_2$NOMe·HCl	Cl	OMe	**4n**	69	1:1.6
15	H$_2$NO*t*Bu·HCl	Cl	O*t*Bu	**4o**	91	1:1.6

[a] Solvent: 10 mol% pyridine/CH$_2$Cl$_2$ (1:9) with entries **b–d** and **j–o**; THF with entries **a** and **e–i**. [b] Yield of isolated product. THP = tetrahydropyranyl, tol = tolyl.

The initial photochemical studies were carried out using **4a** as a test substrate on a 1 mmol scale, using a 100 mL Pyrex immersion well and a 125 W medium pressure mercury lamp. After some optimization it was found that a relatively short irradiation time (1.75 h) led to the clean formation of a new photoproduct, which was assigned as the desired [5+2] adduct **5a** (Table 2). For the majority of examples it was found that UV irradiation of **4a–o** resulted in the formation of the anticipated 1,3-diazepines in good yields and generally without the occurrence of side reactions (Table 2). X-ray crystallographic analyses of **5a** and **5l** (Figure 1) confirmed the structures of the photoproducts formed by this novel mode of cycloaddition. We have previously observed that dichloroazepines derived from alkene [5+2] cycloadditions are susceptible to photo-decomposition if over-irradiated.[3a] The same trend was seen with the products **5m–o**, and as a consequence the irradiation time for oximes **4m–o** was chosen so as to maintain an acceptable balance of conversion versus yield.

Interestingly, no reaction was observed when the disubstituted hydrazones **4f** and **4g** were irradiated. One possible explanation was the assumption that this cycloaddition was *Z* specific. Significantly, (apart from **4h**) **4f** and **4g** were the only photoprecursors that existed solely as the *E* isomers (confirmed by nOe). A post-irradiation analysis of recovered **4f** showed only the *E* isomer to be present, giving no evidence of *E*/*Z* photoisomerization.



5a **5l**

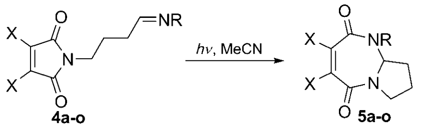
Figure 1. Molecular structures of **5a** and **5l** (thermal ellipsoids at 50% probability).[10]

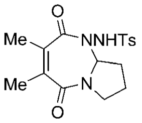
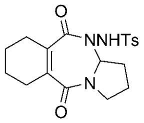
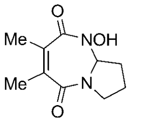
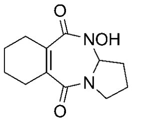
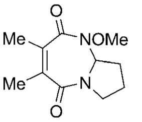
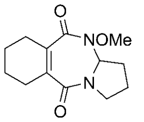
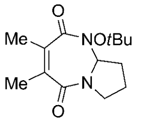
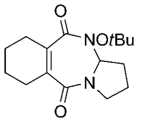
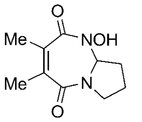
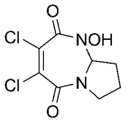
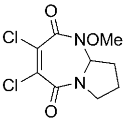
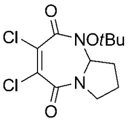
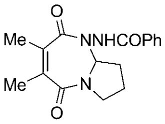
In comparison to all the other photoprecursors, **4f** and **4g** have distinctively different ^{13}C NMR chemical shifts for the C=N carbon atom. For example, all the successful cycloaddition substrates have ^{13}C chemical shifts for C=N within the $\delta = 149–152$ ppm range, whereas the corresponding peak for **4f** and **4g** each fall at significantly lower shifts ($\delta = 137$ ppm). This important information suggests that if the C=N bond is too electron rich, then cycloaddition of the photoexcited maleimide chromophore will not occur. An additional, in-depth mechanistic study will be required to confirm this assertion.[9]

Having developed a general reaction, we turned our attention to the mechanism of the cycloaddition. It was assumed that the [5+2] photocycloaddition of maleimide/C=N substrates would follow the same α-cleavage sequence we have previously demonstrated for maleimide/C=C systems (Scheme 1).[5] Compelling evidence for this stepwise mechanism was obtained from a combined study involving tunable laser measurements of quantum yields and time-dependent DFT (TD-DFT) calculations of photochemically excited states of maleimide **1**. From these studies it was shown that the maximum quantum yield (Φ) for the formation of **3** occurred at wavelengths that were 50 nm red-shifted from the $\lambda_{\max}$ of a minor feature (270 nm) in the UV spectrum of **1**. Deconvolution of the UV/Vis spectrum and TD-DFT calculations determined this peak ($\approx$320 nm) to correspond to an n→π* transition for the S$_1$ excited state.

An identical laser study was carried out with **4c** over the wavelength range of 266 to 355 nm. This system was chosen because conversion into the product is straightforward to monitor accurately by ^{1}H NMR analysis of the photolysate, and there are no complications from side reactions. The UV spectrum of **4c** in solution (Figure 2) is dominated by a strong absorption maximum around 230 nm and a significantly smaller feature at 265 nm, which extends to approximately 345 nm (very similar to that of **1**). The quantum yields (Φ) of the [5+2] cycloaddition of **5c** were measured at wavelengths spanning the transmission spectrum of Pyrex glassware used and the data are presented in Figure 2.

Table 2: [5+2] Photocycloaddition of stabilized imines **5a–o**.



Entry	Substr. **4**	Irrad. time [h][a]	Yield [%]	Product **5**	Entry	Substr. **4**	Irrad. time [h][a]	Yield [%]	Product **5**
1	**4a**	1.75	60	 **5a**	9	**4i**	1.5	85	 **5i**
2	**4b**	2.5	78	 **5b**	10	**4j**	1.8	81	 **5j**
3	**4c**	3.5	78	 **5c**	11	**4k**	1.7	74	 **5k**
4	**4d**	3.5	69	 **5d**	12	**4l**	1.5	90	 **5l**
5	**4e**	2.5	60[b]	 **5e**	13	**4m**	2.0	62	 **5m**
6	**4f**	2.0	0	n.r. **5f**	14	**4n**	2.0	60	 **5n**
7	**4g**	4.0	0	n.r. **5g**	15	**4o**	2.0	40	 **5o**
8	**4h**	4.5	48	 **5h**					

[a] All reactions carried out on a 1 mmol scale using a 125 W medium-pressure mercury lamp in a 100 mL Pyrex immersion well; [b] hν MeCN, 2.5 h then TsOH, EtOH, RT, 30 min. n.r. = no reaction, Ts = *p*-tolylsulfonyl.

From the plot, the key observation to note is that the quantum yield reaches a maximum at a wavelength of 310 nm ($\Phi = 0.12$) which, like that of maleimide **1**, is red-shifted (90 nm) from the λ_{max} in the 260–270 nm region. As no quenching of the cycloaddition of **4c** was observed in the presence of isoprene, the reactions in this study are likely to proceed by a singlet manifold. Direct excitation and additional reaction of the C=N chromophore is highly unlikely as λ_{max} oxime = 205 nm (beyond the spectral window of Pyrex). We therefore conclude that the cycloaddition proceeds from a maleimide singlet state (see Scheme 1) rather than via a maleimide sensitized C=N triplet state.

In summary a new photochemically mediated intramolecular [5+2] photocycloaddition of maleimides to C=N bonds has been described. To the best of our knowledge the present study represents the first example of a preparative cycloaddition sequence where the C=N bond is the ground-state partner. The reaction is tolerant of a wide range of C=N systems and proceeds efficiently even with bulky substituted hydrazones and oximes (see **4l** to **5l**). The reaction realizes a new method for the synthesis of fused polycyclic 1,3-diazepines and as such should find general application in their synthesis.

Experimental Section

4l: *tert*-Butoxyamine hydrochloride (565 mg, 4.5 mmol) and pyridine (36 μL, 0.45 mmol) were added to a solution of the aldehyde **7b**

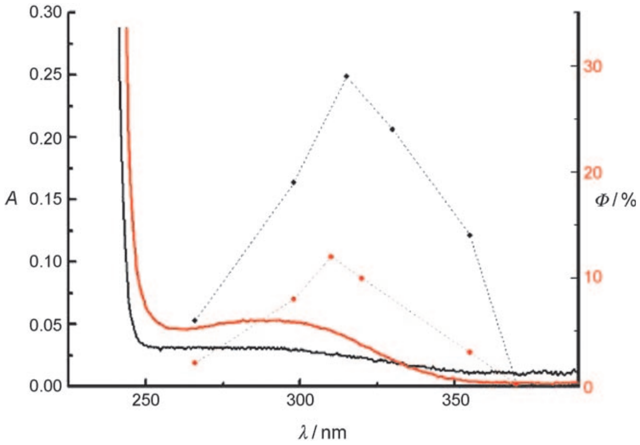


Figure 2. Plot of quantum yield (Φ) versus wavelength for irradiation of **1** and **4c** (—— UV spectrum of **1**; —— UV spectrum of **4c**; ● = Φ of **1**→**3**; ● = Φ of **4c**→**5c**).

(1.10 g, 4.5 mmol) in anhydrous CH_2Cl_2 (50 mL) with activated 3 Å molecular sieves (2.5 g). The reaction was stirred at RT and under a N_2 atmosphere for 16 h. The reaction was then filtered under gravity, diluted with CH_2Cl_2 (100 mL), and washed with H_2O (100 mL). The organic fraction was dried ($MgSO_4$), concentrated in vacuo and purification by column chromatography (EtOAc/*n*-hexane 1:5) gave oxime **41** (1.3 g, 89 %) as a mixture of *E*/*Z* isomers (1:1.6). Yellow oil: R_f 0.63 (EtOAc/*n*-hexane 1:1); (270 MHz, $CDCl_3$): $\delta_H = 7.34$ (1 H, t, $J = 5.6$ Hz, N=CH, *Z* isomer), 6.63 (1 H, t, $J = 5.4$ Hz, N=CH, *E* isomer), 3.56–3.45 (4 H, m, NCH_2, *E*/*Z* isomers), 2.37–2.25 (10 H, m, $N{=}CHCH_2$, *E* isomer & $CH_2C{=}C$, *E*/*Z* isomers), 2.19 (2 H, td, $J = 7.6$ Hz, $J = 5.6$ Hz, $N{=}CHCH_2$, *Z* isomer), 1.84–1.65 (12 H, m, NCH_2CH_2 & $CH_2CH_2C{=}C$, *E*/*Z* isomers), 1.26 ppm (18 H, s, CH_3, *E*/*Z* isomers); (68 MHz, $CDCl_3$): $\delta_C = 171.2$ (CO), 148.9 (CH), 147.8 (CH), 141.5 (C), 77.9 (C), 37.1 (CH_2), 37.0 (CH_2), 27.4 (CH_3), 27.4 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 23.1 (CH_2), 21.3 (CH_2), 20.0 ppm (CH_2); (EtOH): $\nu_{max} = 2937$ (m), 1768 (w), 1705 (s), 1435 (w), 1400 (m), 1363 (m), 1194 (m), 942 cm^{-1} (m); CI-HRMS: *m*/*z* 293.1865 (MH^+ $C_{16}H_{25}N_2O_3$ requires 298.1787).

51: A solution of oxime **41** (292 mg, 1.0 mmol) in degassed MeCN (100 mL) was irradiated using a 125-W medium pressure lamp in a water-cooled Pyrex immersion well for 1.5 h. Upon completion of the reaction, the solvent was removed in vacuo and purification by column chromatography ($MeCN/CH_2Cl_2$ 1:4) afforded photoproduct **51** (271 mg, 90 %). White solid: R_f 0.14 (SiO_2, $MeCN/CH_2Cl_2$ 1:4); m.p. 183–184 °C; (400 MHz, $CDCl_3$): $\delta_H = 5.59$ (1 H, dd, $J = 7.7$ Hz, $J = 2.1$ Hz, CH), 3.63–3.55 (1 H, m, NCHH), 3.52–3.43 (1 H, m, NCHH), 2.90–2.78 (2 H, m, $CHHC{=}C$), 2.57–2.50 (1 H, m, NCH_2CH_2CHH) 2.28–2.05 (4 H, m, $NCH_2CHHCHH$ & $CH_2C{=}C$), 1.98–1.88 (1 H, m, NCH_2CHH), 1.81–1.61 (4 H, m, $CH_2CH_2C{=}C$), 1.36 ppm (9 H, s, CH_3); (100 MHz, $CDCl_3$): $\delta_C = 170.4$ (CO), 166.9 (CO), 139.0 (C), 135.8 (C), 84.3 (C), 72.3 (CH), 45.4 (CH_2), 29.0 (CH_2), 27.8 (CH_3), 27.5 (CH_2), 25.2 (CH_2), 23.4 (CH_2), 21.6 (CH_2), 21.2 ppm (CH_2); (neat): $\nu_{max} = 2931$ (w), 1680 (s), 1644 (s), 1623 (s), 1413 (s), 1353 (s), 1281 (s), 1207 (w), 1159 (s), 1103 (w), 967 (m), 927 (m), 818 cm^{-1} (m); CI-HRMS: *m*/*z* 293.1865 (MH^+ $C_{16}H_{25}N_2O_3$ requires 298.1787).

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Keywords: cycloaddition · heterocycles · hydrazones · oximes · photochemistry · quantum yield

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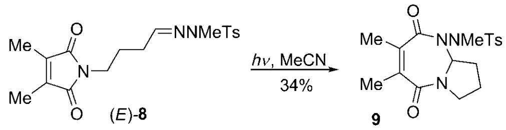
[9] Although **4f** and **4g** were the only disubstituted photoprecursors in Table 2, successful cycloaddition of (*E*)-**8** illustrated that disubstitution is not a barrier to cycloaddition (see the Supporting Information).



[10] CCDC 719475 (**5a**) and CCDC 719476 (**51**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.