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In situ Reduction in Photocycloadditions: A Method to Prevent Secondary Photoreactions

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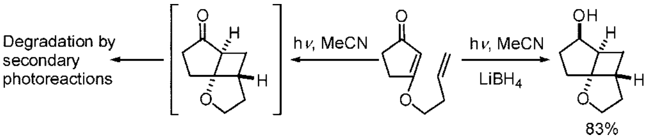
ABSTRACT



Secondary photoreactions are a common cause for the low yields often observed in photochemical reactions, preventing their widespread deployment in synthesis. In situ reductions which remove the chromophore from the product as it is formed provide a convenient method to prevent these secondary photoreactions.

Photochemical reactions are extremely powerful methods for application in organic synthesis. By accessing electronically excited states, modes of reactivity can be exploited that are not available to molecules in the ground state. An example is the [2+2] photocycloaddition, which provides convenient access to 4-membered rings that would otherwise be extremely challenging to synthesize by thermal means. However, despite the unique abilities of photochemical reactions these methods are still much underused in synthesis. One of the main reasons for this is the unpredictable yields associated with such reactions. In a number of cases this can be attributed to problems of secondary photoactivity, which can occur when the initial photoproducts retain a chromophore and undergo excitation leading to further reactions.[1]

In a few cases narrow-band light sources or filters have been reported to prevent secondary photoreactions by controlling the wavelengths of light that are incident on the solution such that only the starting material can absorb and not the product.[2,1f] However, the success of this method relies on the starting material and products absorbing in different regions of the spectrum, which is often not the case. Furthermore, such lamps and filters are only available for a few specific wavelength selections. It is clear that new methods to prevent secondary photoreactions would broaden the scope of viable photochemical reactions, leading to their greater deployment in synthesis.

We are proposing that the use of trapping agents that react with the desired photoproduct as it is formed, removing the chromophore, will serve to prevent secondary photoreactions and prove a valuable method. We are initially investigating this approach by considering the use of reducing agents in the [2+2] photocycloaddition of enones with alkenes. This photocycloaddition is an extremely useful method for the formation of cyclobutanes[2c,3] but suffers from the continued

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(1) (a) Mancini, I.; Cavazza, M.; Guella, G.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2181. (b) Matlin, A. R.; Turk, B. E.; McGarvey, D. J.; Manevich, A. A. *J. Org. Chem.* **1992**, *57*, 4632. (c) Williams, J. R.; Lin, C.; Chodosh, D. F. *J. Org. Chem.* **1985**, *50*, 5815. (d) Cantrell, T. S.; Solomon, J. S. *J. Am. Chem. Soc.* **1970**, *92*, 4656. (e) Cavazza, M.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1986**, 1480. (f) Demuth, M.; Pandey, B.; Wietfeld, B.; Said, H.; Viader, J. *Helv. Chim. Acta* **1988**, *71*, 1392. (g) Mazzocchi, P. H.; Khachik, F.; Wilson, P.; Highet, R. *J. Am. Chem. Soc.* **1981**, *103*, 6498. (h) Booker-Milburn, K. I.; Anson, C. E.; Clissold, C.; Costin, N. J.; Dainty, R. F.; Murray, M.; Patel, D.; Sharpe, A. *Eur. J. Org. Chem.* **2001**, 1473.

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(3) (a) Demuth, M.; Mikhail, G. *Synthesis* **1989**, 145. (b) Corey, E. J.; Lemahieu, R.; Mitra, R. B.; Bass, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

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photoactivity of the carbonyl in the product. Secondary photoreactions observed in such systems include Norrish type I[1b−d,4] and type II processes[5] and acyl shifts.[1a,e] We report herein on our initial results with the intramolecular [2+2] photocycloaddition of vinylogous ester **1** serving as the model system.

The photocycloaddition of vinylogous ester **1** is an apparently simple reaction that is conspicuous in its absence from the literature. We postulated that secondary photoactivity was likely to be the problem as other similar cycloadditions have been reported.[6] Indeed when we irradiated **1** for 1.5 h we observed complete consumption of starting material to afford a complex mixture from which the initial photocycloaddition product **2** could be isolated in just 13% yield (Figure 1a). This was found to be the maximum yield obtainable with variations in solvent (benzene, acetone, *i*-PrOH, MeOH) and concentration proving deleterious. To confirm that photochemical degradation was responsible for the low yield obtained we resubmitted the isolated ketone **2** to irradiation and observed complete degradation in 1.5 h to afford a complex mixture of unidentifiable products. We also confirmed that thermal decomposition of ketone **2** was not occurring by stirring it in acetonitrile in the dark and observing no change after 24 h.

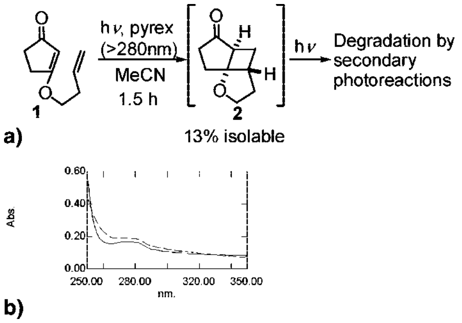
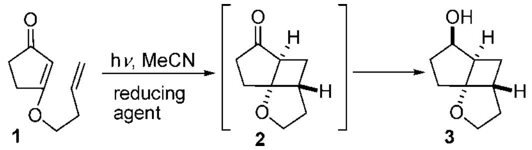


Figure 1. (a) Vinylogous ester **1** undergoes photocycloaddition followed by degradation of ketone **2** by secondary photoreactions. (b) UV spectra of the starting material **1** (solid line) overlaid with the product **2** (broken line).

UV spectra of the starting material **1** and the product **2** (Figure 1b) reveal the fundamental limitation with relying on filters to prevent secondary photoreactions. The $n-\pi^*$ absorbances involved have λ_{max} of 282 and 274 nm, respectively, and are clearly overlapping preventing selective excitation of just the starting material.

Having confirmed that secondary photoreactions were a major problem in this system we selected a range of reducing agents for trial as trapping agents. The conjugation in vinylogous ester **1** ensured that the starting material would be less reactive to reducing agents than the product, providing the necessary chemoselectivity. To confirm that reduction of the starting material **1** would be insignificant on the reaction time scale we treated it with either $NaBH_4$ or $LiBH_4$ in acetonitrile and observed negligible reduction (<5%) after 2 h. The trapping experiments were thus carried out by inclusion of reducing agents in the photochemical reaction (Table 1).

Table 1. Various Reducing Agents Included in the Photochemical Reaction to Trap Out the Ketone **2** As Alcohol **3**



entry	reducing agent	equiv	yield of **3** (%)
1	$NaBH_4$	1	36
2	$NaBH_4$	2	42
3	$LiBH_4$	1	57
4	$LiBH_4$	2	71
5	$LiBH_4$	3	60
6	$NaBH(OAc)_3$	2	40
7	$NaBH_3(OAc)$	2	0
8	$ZnBH_4$	2	19
9	$LiBH_4$[a]	2	13

[a] $LiBH_4$ added after irradiation.

With $NaBH_4$ the photocycloaddition−reduction sequence was complete in 1 h and 45 min and successfully afforded alcohol **3** in 36%, proving that removing the chromophore in the product could affect an increase in yield of product isolable. We postulated that this reagent was still not reducing ketone **2** fast enough and thus sought more reactive conditions. Two equivalents of $NaBH_4$ led to a small increase in the yield, but it was the use of 2 equiv of $LiBH_4$ that led to a significant improvement (Table 1, entry 4). Other reducing agents such as acetoxy borohydrides and zinc borohydride failed to improve on this. We also confirmed that the reducing agent needed to be present during the irradiation to prevent secondary photoreactions, by carrying out a reaction in which the $LiBH_4$ was only added at the end (entry 9). The 13% yield of alcohol **3** in this case matched the yield of ketone **2** that was obtained in the absence of reducing agent.

Interestingly, in this system only one diastereomer of the product is obtained, with the stereochemistry confirmed by NOESY analysis. The photocycloaddition forms three of the centers fixed as the cyclobutane must be *cis*-fused to both five-membered rings. The reduction is then remarkably selective with attack only taking place on the opposite face to the cyclobutane. Indeed a model of **2** shows the hydrogens protruding from the cyclobutane provide significant steric hindrance to this face and that the system lacks any conformational flexibility of note.

We also carried out a solvent and concentration screen to optimize the photocycloaddition−reduction sequence (Table

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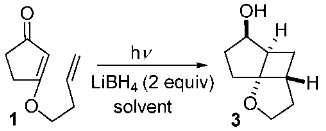
(5) Mal, J.; Venkateswaran, R. V. *J. Org. Chem.* **1998**, *63*, 3855.

(6) (a) Carreira, E. M.; Hastings, C. A.; Shepard, M. S.; Yerkey, L. A.; Millward, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6622. (b) Pirrung, M. C.; Webster, N. J. G. *J. Org. Chem.* **1987**, *52*, 3603.

Table 2. Solvent and Concentration Study to Optimize the Reaction Conditions



entry[a]	solvent	concn (M)	yield of **3** (%)
1	MeCN	0.04	71
2	dry MeCN	0.04	63
3	3:1 MeCN:H_2O	0.04	72
4	benzene	0.04	52
5	isopropanol	0.04	39
6	hexane	0.04	28
7	DCM	0.04	20
8	MeCN	0.01	78
9	MeCN	0.02	79
10	MeCN	0.08	12
11[a]	MeCN	0.02	83

[a] Column eluent includes NEt_3 (1%).

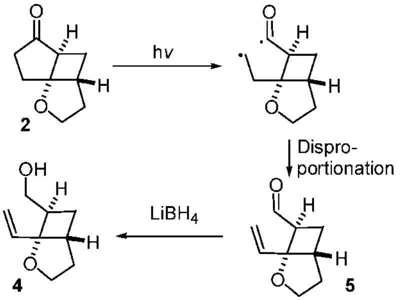
2). It was difficult to predict the conditions that would be favored as such photocycloadditions can variously be favored in polar or nonpolar solvents.[2c] Furthermore, while the $LiBH_4$ reduction would be faster in polar protic solvents,[7] competing reaction of the reducing agent with the solvent would occur. We found that acetonitrile or an acetonitrile−water mix yielded the best results with no improvement shown by other solvents. The water likely serves to solubilize and increase the reactivity of the $LiBH_4$. The ideal concentration was found to be 0.02 M. Notably by 0.08 M the yield drops off substantially, which is likely due to competing intermolecular reactions.

We observed that column purification was leading to some degradation of the product by an unknown mechanism, likely to involve cleavage of the strained cyclobutane. We were able to limit this by using NEt_3 (1%) in the column eluent resulting in an improved 83% yield (entry 11, Table 2).

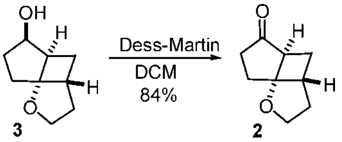
It is notable that in these reactions a small amount (∼1%) of an impure compound was commonly isolated, which we have tentatively assigned as alcohol **4** by ^1H NMR analysis (Scheme 1). This compound is formed by a well-precedented Norrish type 1 cleavage−disproportionation sequence followed by reduction of the resulting aldehyde **5** by the reducing agent. This was the first clear indication of the nature of the secondary photoreactions that were occurring in this system.

To show that ketone **2** could be accessed in good overall yield for the first time using this methodology, we reoxidized alcohol **3** (Scheme 2) to afford the ketone in good yield.

Scheme 1. Postulated Norrish Type I pathway for the Formation of Alcohol **4**



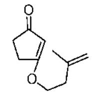
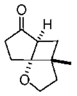
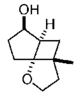
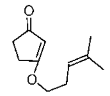
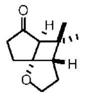
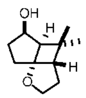
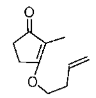
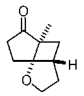
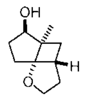
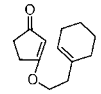
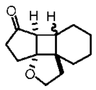
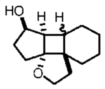
Scheme 2. Reoxidation of Alcohol **3** Providing the First Viable Route to Ketone **2**



To illustrate the scope of this in situ reduction methodology we tried it on a number of related substrates (Table 3). Each substrate was irradiated initially in the absence of reducing agent, to attempt to isolate the ketones (method A), and then in the presence of $LiBH_4$ (method B) to give the alcohol. We found that in all cases the ketones were being consumed by secondary photoreactions, leading to poor yields of the ketone isolable, if any at all. The inclusion of $LiBH_4$ (method B) then led to the prevention of secondary

Table 3. Photocycloaddition−Reduction Sequence in More Complex Examples

$$\text{Ketone} \xleftarrow[\text{Method A}]{h\nu,\ \text{MeCN}} \text{Vinylogous ester} \xrightarrow[\text{LiBH}_4\ \text{(2 equiv)}\ \text{Method B}]{h\nu,\ \text{MeCN}} \text{Alcohol}$$

entry	vinylogous ester	ketone *via* method A		alcohol *via* method B	
1			0%		71%
2			0%		78%
3			50%		72%
4			13%[a]		72%[b]

[a] 13% of a de-Mayo fragmentation product also isolated. [b] 1:1 ratio of diastereomers obtained.

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(7) Brown, H. C.; Mead, E. J.; Rao, B. C. S. *J. Am. Chem. Soc.* **1955**, *77*, 6209.

photoreactions with the alcohol being obtained in good yields. Single diastereomers were obtained in all cases with the exception of entry 4 in which the triplet nature of these photocycloadditions is revealed by the loss of stereochemical control at one center. This example still shows the power of photochemistry to form complex strained structures in a single step from a simple starting material.

In conclusion we have illustrated that in situ reduction can be effectively employed in photochemical reactions to prevent undesired secondary photoreactions. A protocol with $LiBH_4$ in the intramolecular [2+2] photocycloaddition of vinylogous esters has been developed. We are currently investigating the application of a variety of trapping agents, and envisage that this methodology will be widely employed to broaden the scope of viable photochemical reactions.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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