

Visible Light Induced Photocatalytic Conversion of Enamines into Amides

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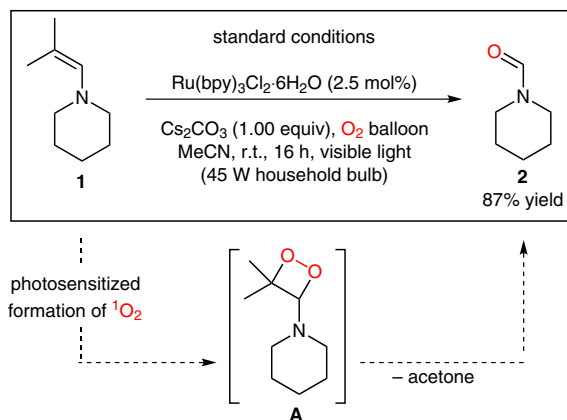
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Abstract: A series of enamines were photocatalytically cleaved to produce amide products under simple visible-light irradiation from a 45 W household light bulb. Mechanistically, the reactions appear to involve photosensitized formation of a singlet oxygen intermediate and a subsequent [2+2] cycloaddition event.

Key words: photochemistry, catalysis, enamines, amides

There has been a recent increase in the appreciation of visible light induced photoredox catalysis by the chemical community.¹ Among the extensive range of reactivities that have been described, most rely mechanistically on the single-electron oxidant nature of the catalyst that is most frequently used: tris(bipyridyl)dichlororuthenium hexahydrate [Ru(bpy)₃Cl₂·6H₂O]. This oxidant is capable of initiating electron abstraction, thereby generating reactive radical species that undergo subsequent synthetic events.² Conceivably, if new reaction modes could be strategically merged with visible-light photoredox catalysis, then the range of synthetic applications of the latter would be significantly broadened and enriched. In this context, we were particularly motivated by the possibility of combining photoredox catalysis with the rich chemistry of singlet oxygen chemistry³ to realize some new reactivities. It is clear that a visible light induced entry to singlet oxygen intermediates would represent a change in the conventional protocol, which uses UV radiation from, for example, high-pressure mercury lamps,³ thereby providing unusually benign reaction conditions and an improvement in efficiency.

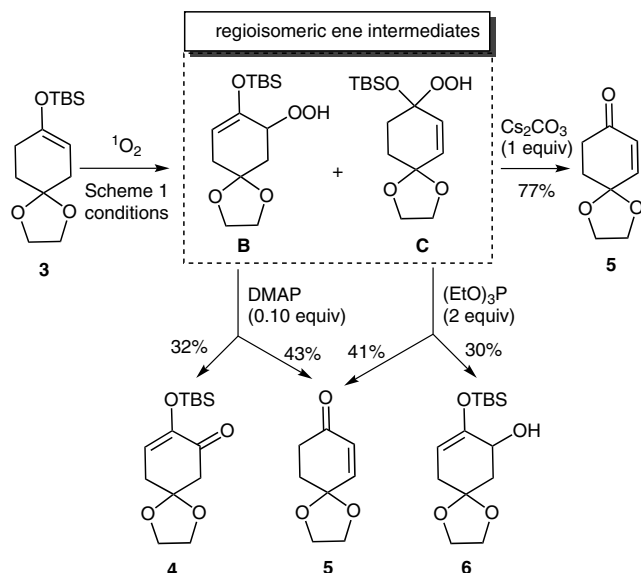
After numerous attempts, we discovered that the synergistic action of 2.5 mol% of Ru(bpy)₃Cl₂·6H₂O photocatalyst, one equivalent of cesium carbonate base, and visible light irradiation from a 45 W household light bulb for 16 hours at room temperature in acetonitrile as the solvent under an oxygen atmosphere supplied by a balloon (hereafter referred as the standard conditions), enamine **1** (Scheme 1) was smoothly converted into the formamide product **2** in 87% yield (quantitative if determined by ¹H NMR spectroscopy with naphthalene as an internal reference). We confirmed that the reaction did not occur in the absence of either visible-light irradiation or the photocatalyst, and was retarded when an atmosphere of dry air was used in place of oxygen from the balloon.



Scheme 1 Visible light induced photocatalytic cleavages of enamine **1** to give formamide **2**, and a possible [2+2] cycloaddition pathway involving singlet oxygen

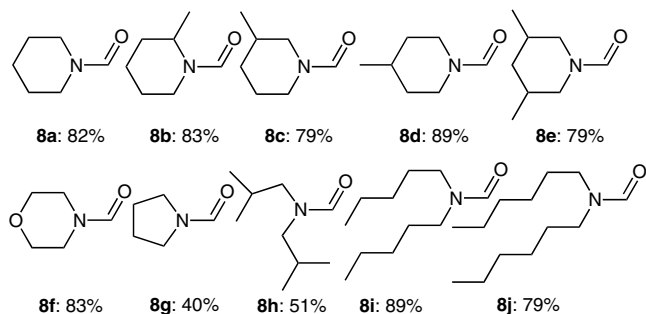
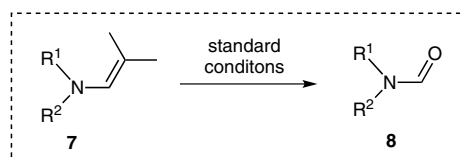
The possibility that the reaction might have proceeded through a singlet oxygen (¹O₂)-initiated [2+2] cycloaddition via intermediate **A** emerged from a set of interesting experimental observations outlined below (Scheme 2). Although direct attempts to isolate or to intercept intermediate **A** failed in the enamine system described above, we were able to identify the corresponding intermediate in the protected silyl enol ether structure **3** when this was subjected to the standard reaction conditions described above. The reaction of **3** progressed cleanly in the presence of cesium carbonate to give the enone product **5** in 77% isolated yield and, notably, no C=C bond-cleavage product was found to be present. We surmised the involvement of a regioisomeric mixture of ene-type allylic hydroperoxide products **B** and **C**, formed through participation of singlet oxygen, echoing a recent report in the literature on the formation of singlet oxygen under visible-light stimulation, and we probed this reaction by using 4-(*N,N*-dimethylamino)pyridine as an alternative base or triethyl phosphite as an alternative reductant in place of cesium carbonate.⁴ The reaction in the presence of 4-(*N,N*-dimethylamino)pyridine resulted in the formation of enone **5** in 43% yield and the new enone **4** in 32% yield, whereas the reaction in the presence of triethyl phosphite gave enone **5** in 41% yield together with allylic alcohol **6** in 30% yield. Strikingly, the structural footprints of **4** and **6** are strongly indicative of their formation from the corresponding allylic hydroperoxide precursor **B**, whereas the formation of enone **5** appears to be directly attributable to the other precursor **C**. Furthermore, the reaction ceased to work when 1,4-diazabicyclo[2.2.2]octane (DABCO), known to be an

effective quencher of singlet oxygen,⁵ was deliberately added to the system under otherwise identical conditions.⁶ Note that Friedrich⁷ and Turro⁸ and their respective co-workers have previously demonstrated similar reaction pathways with a high-pressure mercury lamp as the UV source; the current discovery therefore represents a significantly improvement in terms of operational safety and practical usefulness.



Scheme 2 Experimental observations supporting the visible light stimulated formation of singlet oxygen species

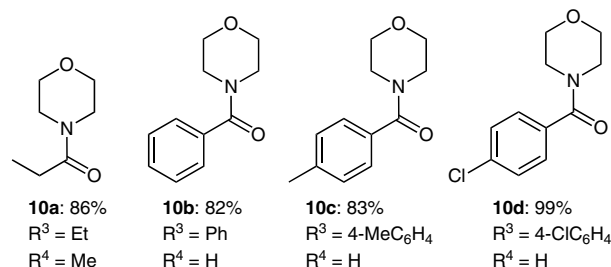
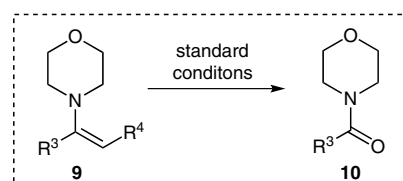
Next, we examined the reaction of a range of enamines **7a–g** under the standard conditions (Scheme 3). All underwent smooth C=C bond-cleavage reactions to give the corresponding formamides **8** in good isolated yields.⁹ Both the cyclic enamines **8a–g** and the acyclic enamines **8h–j** were suitable substrates. The piperidine-derived en-



Scheme 3 Formation of formamides by means of visible light induced C=C bond cleavage of enamines

amine **7a** and its various analogues **7b–e** bearing methyl substituents on each of the three regioisomeric α -, β -, and γ -positions were converted into the corresponding formamides **8a–e** in 79–89% yield. The lone pair on the oxygen of the morpholine ring did not appear to impede the reaction, as the morpholine derivative **8f** was obtained in 83% yield. The pyrrolidine group, presumably because of its allylic strain, showed a significantly reduced reactivity, and the corresponding product **8g** was obtained in 40% yield. The presence of linear aliphatic groups in formamides **8i** and **8j** appeared to be advantageous in comparison with the branched substitution in **8h**, possibly as a result of the difference in bulk.

Next, we applied the protocol to the ketone-derived enamine substrates **9a–d**, and in each case we obtained the corresponding amide **10a–d** in high isolated yield (82–99%) under the standard conditions. Both, the aliphatic keto amide **10a** and the aromatic keto amides **10b–d** could be used as substrates without loss of reaction efficiency. These results, in conjunction with those shown in Scheme 3 illustrate the ability of this new method to provide a simple route for amide synthesis. Note that such transformations have previously relied on promotion by metal-based oxidants.¹⁰



Scheme 4 Formations of amides by means of visible light enabled C=C bond cleavage of ketone-derived enamines

In summary, we have developed direct enamine-to-amide conversion facilitated by visible-light photoredox catalysis. The method is fairly simple and can be readily implemented on widely available materials. It constitutes a very useful formal functionality metathesis from a C=C bond to a C=O bond, synthetically connecting significant enamine and amide structures. The transformation has been shown to proceed through an interesting visible light sensitized formation of a singlet oxygen species that subsequently initiates a [2+2] cycloaddition event and ring fragmentation. Given the usefulness of this new method and the importance of amide-bond formation, the work should contribute to the arsenal of the practicing chemist.

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Supporting Information for this article is available online at <http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083>.

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