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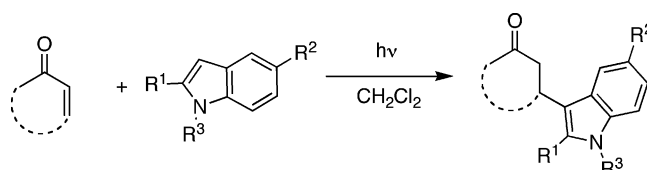
Photoinduced 1,4-Additions of Indoles to Enones

Joseph Moran, Tanya Suen, and André M. Beauchemin*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

andre.beauchemin@uottawa.ca

A photoinduced procedure for the 1,4-addition of indoles to enones is described. This reaction occurs with modest to excellent yield for cyclic and some acyclic enones. This reaction is experimentally simple, requiring only irradiation (UVA lamps, ca. 350 nm) of the reagents in a CH_2Cl_2 solution at room temperature, and avoids the necessity to use a Lewis acid. An important solvent effect was noticed, with CH_2Cl_2 and $CHCl_3$ being the optimal solvents. Various substituents are tolerated on the indole moiety and an electronic trend was noticed, as electron-withdrawing groups can suppress this reaction. A mechanism involving single electron transfer between the enone triplet excited state and the indole is proposed and accounts for all experimental observations.
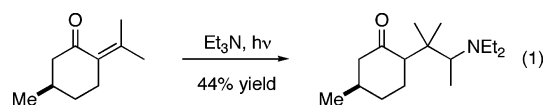
Introduction

The 1,4-addition of carbon nucleophiles is a powerful C—C bond forming strategy. While significant effort has focused on the development of general "thermal" processes, the parent photochemical processes have received less attention from the synthetic community. As part of a general program toward the activation of alkenes, we became interested in using UV irradiation to promote the addition of nucleophiles to α,β-unsaturated systems.

The prevalence of the indole motif in natural and bioactive products continues to be a vector for the development of new synthetic methods. The 1,4-addition of indoles to α,β-unsaturated systems is an efficient approach to indole-containing molecules. The ability of Lewis acids to promote 1,4-addition is well established[1] and recently led to the development of enantioselective versions of this reaction.[2] A related approach involves the use of organocatalysts to activate the α,β-unsaturated system toward nucleophilic attack.[3] In contrast, 1,4-addition of the indole nucleus could also occur via single electron transfer (SET) between the α,β-unsaturated system and

the indole ring system,[4] followed by coupling of the resulting radical ions, proton transfer, and tautomerization (Scheme 1). Herein, we disclose that UV light promotes such a process, leading to the 1,4-addition of indoles to enones, and we establish the scope and limitations of this transformation.

The ability of enones to act as electron acceptors in SET reactions is well established.[5] For example, the photolysis of enones and tertiary amines leads to a formal 1,4-addition of α-amino radical to the enone (eq 1).[6] Both intra- and intermo-

$$(1)$$

(1) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047 and references therein.

(2) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160. Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *105*, 10780. Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309. Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942.
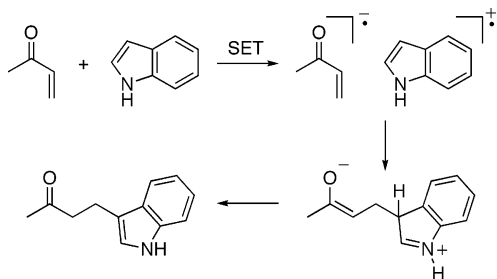
(3) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Ziao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482.

(4) To the best of our knowledge, 1,4-additions of indoles to enones occurring via SET have not been reported in the literature. For related, specific photoinduced additions of indoles, see the following. To 1-methyl-2-pyridone: (a) Ohmiya, S.; Noguchi, M.; Ina, S.; Kubo, H.; Otomasu, H. *Chem. Pharm. Bull.* **1992**, *40*, 854. (b) Sakurai, N.; Ohmiya, S. *J. Chem. Soc., Chem. Commun.* **1993**, 297. To 3-acetyl-6-nitrocoumarin (solid state): (c) Du, D.-M.; Wang, Y.-M.; Meng, J.-B.; Zhou, X.-Z.; Zhang, H.-P. *Gaodeng Xuexiao Huaxue Xuebao* **1996**, *17*, 252 (CAS 124:189184). (d) Wang, Y.-M.; Du, D.-M.; Li, X.-L.; Meng, J.-B.; Zhou, X.-Z. *Youji Huaxue* **1997**, *17*, 433 (CAS 128:28491). To 1,4-naphthoquinone (solid state): (e) Wang, Y.-M.; Wen, Z.; Chen, X.-M.; Du, D.-M.; Matsuura, T.; Meng, J.-B. *J. Heterocycl. Chem.* **1998**, *35*, 313.

(5) For a review of enone photochemistry, see: Schuster, D. I. in *The Chemistry of Enones*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons, Ltd.: Chichester, 1989; pp 623−756.

SCHEME 1. Single Electron Transfer Approach to 1,4-Addition of Indoles to Enones

lecular versions of this reaction have been reported. In addition, elegant work by Mariano has demonstrated the synthetic potential of the related reactions of α-silylamine substrates (eq 2).[7] The generally accepted reaction mechanism[8] involves
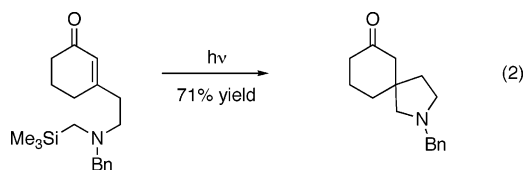
photoinduced electron transfer (PET) between the amine and the enone triplet, affording the parent amine radical cation and enone radical anion. Deprotonation (or desilylation, i.e., eq 2) of the amine radical cation affords the α-amino carbon-centered radical, which couples to the enone radical anion to afford the formal 1,4-addition product.

Indoles are generally compounds with rather low oxidation potentials. Therefore, indoles are prone to participate/react through electron-transfer processes. In biological systems, the redox properties of indole moieties (i.e., tryptophan residues) are key to the catalytic activity of certain enzymes.[9] Synthetically, it has also been established that a number of reactions of indoles involve SET and not ionic intermediates, as initially suggested.[10] An example of reactivity derived from PET is the trifluoromethylation of indole derivatives (eq 3).[11,12]

R[1] = H, R[2] = CF₃: 28% yield
R[1] = CF₃, R[2] = H: 18% yield
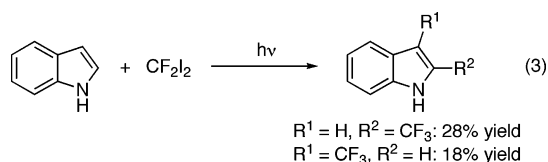
(6) (a) Cookson, R. C.; Hudec, J.; Mirza, N. A. *J. Chem. Soc., Chem. Commun.* **1968**, 180. (b) Pienta, N. J.; McKimmey, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 5501.

(7) Xu, W.; Jeon, Y. T.; Hasegawa, E.; Yoon, U. C.; Mariano, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 406. The scope of these reactions has also been extended through the use of sensitizers such as 9,10-dicyanoanthracene. For more examples and a detailed discussion, see: Jeon, Y. T.; Lee, C.-P.; Mariano, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 8847. Xu, W.; Zhang, X.-M.; Mariano, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 8863.

(8) Dunn, D. A.; Schuster, D. I.; Bonneau, R. *J. Am. Chem. Soc.* **1985**, *107*, 2802. Schuster, D. I.; Insogna, A. M. *J. Org. Chem.* **1991**, *56*, 1879.

(9) (a) Sivaraja, M.; Goodin, D. B.; Smith, M.; Hoffman, B. M. *Science* **1989**, *245*, 738. (b) Huyett, J. E.; Doan, P. E.; Gurbiel, R.; Houseman, A. L. P.; Sivaraja, M.; Goodin, D. B.; Hoffman, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 9033. (c) Bonagura, C. A.; Sundaramoorthy, M.; Pappa, H. S.; Patterson, W. R.; Poulos, T. L. *Biochemistry* **1996**, *35*, 6107.

(10) Astolfi, P.; Greci, L.; Rizzoli, C.; Sgarabotto, P.; Marrosu, G. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1634.

(11) Chen, Q.-Y.; Li, Z.-T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 645.

TABLE 1. Solvent Effect in Photoinduced 1,4-Addition of Indole to Cyclohept-2-enone

entry	solvent	% conversion[a]
1	hexanes	23
2	C₆H₆	28
3	PhCF₃	23
4	CH₂Cl₂	84
5	CHCl₃	90
6	Et₂O	0
7	THF	0
8	MeCN	0
9	*i*-PrOH	0
10	DMSO	6

[a] Determined by ¹H NMR.

Results and Discussion

Early experiments focused on the photolysis of cyclohept-2-enone (**1**) and indole (**2a**) in CH₂Cl₂ at ca. 350 nm (UVA lamps). Gratifyingly, we observed quantitative formation of the conjugate addition product **3a** upon irradiation at 0.1 M in CH₂Cl₂ (¹H NMR analysis). This reaction is very dependent on the nature of the solvent utilized (Table 1). The use of nonpolar solvents results in modest conversion to the conjugate addition product (entries 1−3). Conversely, little or no reaction is observed with more polar solvents (entries 6−10). In contrast, halogenated solvents such as CH₂Cl₂ or CHCl₃ are uniquely effective for this reaction (entries 4 and 5), with CH₂Cl₂ being the solvent of choice. Overall, CH₂Cl₂ and CHCl₃ appear to significantly increase the concentration of the enone triplet excited state present in the flask at any given time, thereby allowing a more efficient single electron transfer process. Two possibilities could account for this. The first is the heavy-atom solvent effect,[13] which can promote singlet−triplet crossing (enone). Alternatively, the triplet lifetimes in CH₂Cl₂ and CHCl₃ could also be longer than in other solvents.[14] Experimentally, decreasing the concentration to 0.05 M in CH₂Cl₂ also led to quantitative conversion (¹H NMR analysis), but the TLC proved somewhat cleaner; these conditions appear to minimize the formation of an indole-derived byproduct. Therefore, these conditions were selected for the study of this transformation.

With suitable reaction conditions identified, various electrophiles were surveyed (Table 2). Methyl vinyl ketone (entry 1) and a number of cyclic enones (entries 2−5) are suitable substrates for the 1,4-addition of indole. The substrate scope of this transformation is limited, as a number of processes compete with this rather slow photoinduced reaction. In acyclic systems, the addition to methyl vinyl ketone occurred in a modest 46% yield (entry 1). The reaction could not be extended to other acyclic enones, as in these systems enone photodeconjugation and photoisomerization are known to be efficient processes.[15]

(12) For other examples of SET reactivity of indoles and related systems, see: (a) Yoshida, K. *J. Chem. Soc., Chem. Commun.* **1978**, 1108. (b) Yamasaki, K.; Matsuura, T.; Saito, I. *J. Chem. Soc., Chem. Commun.* **1974**, 944.

(13) Cowan, D. O.; Drisko, R. L. E. *J. Am. Chem. Soc.* **1970**, *92*, 6281.

(14) Natarajan, A.; Kaanumalle, L. S.; Ramamurthy, V. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W. M., Lanci, F., Eds.; CRC Press: Boca Raton, 2004; Chapter 107.

TABLE 2. Photoinduced 1,4-Addition of Indole to α,β-Unsaturated Systems

Entry	Enone	Product	Yield[a]
1	4	5	46
2	6	7	19
3	8	9	13
4	1	3a	98
5	10	11	66

[a] Isolated yield after column chromatography.

TABLE 3. Photoinduced 1,4-Addition of Indoles to Cyclohept-2-enone

entry	R^1	R^2	2a−j (equiv)	% yield[a]
1	H	H	2a (1.1)	98
2	Me	H	2b (1.1)	58
3	Ph	H	2c (3.0)	50
4	H	OMe	2d (3.0)	75
5	H	Me	2e (3.0)	49
6	H	Br	2f (3.0)	43
7	H	F	2g (3.0)	33
8	H	CO_2Me	2h (3.0)	22
9	H	CN	2i (3.0)	0
10	H	NO_2	2j (3.0)	0

[a] Isolated yield after column chromatography.

**TABLE 4. Effect of Nitrogen Substitution in Photoinduced 1,4-Addition of Indoles to Cyclohept-2-enone**

entry	R	2a−o (equiv)	% yield[a]
1	H	2a (1.1)	98
2	Me	2k (1.0)	51
3	Allyl	2l (1.0)	53
4	Bn	2m (1.0)	33
5	Ac	2n (1.2)	0
6	Boc	2o (1.2)	0

[a] Isolated yield after column chromatography.

In cyclic systems, the addition of indole to cyclopent-2-enone (entry 2) and cyclohex-2-enone (entry 3) occurs in low yield due to competing dimerization of the enones.[16] In larger ring systems, the dimerization is slower and the formal 1,4-addition is efficient, resulting in addition to cyclohept-2-enone and cyclooct-2-enone in 98% and 66% yield, respectively (entries 4 and 5). The increased efficiency observed in cyclic systems can be explained by the suppression of known nonproductive pathways, as photodeconjugation is impossible due to geometrical constraints and photoisomerization is disfavored (or impossible) due to strain.

Thus, cyclohept-2-enone was selected as substrate to determine the nucleophile scope (Table 3), as its reaction with indole occurs in 98% yield (entry 1). Substitution at the 2 position is tolerated, affording the desired product in 58% and 50% yield for methyl and phenyl substituents, respectively (entries 2 and 3). Unfortunately, substitution at the 3 position is not tolerated, and only enone dimerization is observed.[17] Substitution at the 5 position is tolerated, affording the desired products in modest to good yields (entries 4−8). From these entries, it is clear that the reaction is more efficient with electron-donating substituents. This reaction is even suppressed with indoles bearing strong electron-withdrawing substituents such as nitro or cyano groups (entries 9 and 10). This trend is consistent with electron-withdrawing substituents retarding the PET process and allowing enone dimerization to occur competitively. In general, even indoles bearing electron-donating substituents (entry 4) lead to a lower isolated yield compared to the reaction with indole itself (entry 1). This observation is consistent with the increased

stability (diminished reactivity) of the substituted indole radical cations.

Experiments aimed at determining the scope with respect to nitrogen substitution were then performed (Table 4). N-H substitution is optimal for a clean 1,4-addition to proceed (entry 1). However, methyl, benzyl, and allyl substitution is tolerated, affording the desired adducts in 51%, 33%, and 53% yield, respectively (entries 2−4). In contrast, electron-withdrawing nitrogen protecting groups such as Boc or Ac suppress 1,4-addition (entries 5 and 6), which is consistent with a mechanism involving SET (destabilization of the indole radical cation).

Finally, attempts were made to extend the scope of this transformation to other 1,4-acceptors such as unsaturated esters and lactones, with no success. Other nitrogen heterocycles were also poor substrates for this reaction. For example, photolysis of a mixture of cyclohept-2-enone (1) and pyrrole (12) led only to a modest 7% yield of adduct 13 (eq 4).
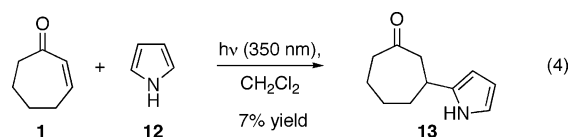
Proposed Mechanism. A photoinduced electron-transfer mechanism such as shown in Scheme 2 is in good agreement with all of our experimental findings. As discussed in the

(15) Pete, J. P. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P.-S., Eds.; CRC Press: Boca Raton, 1995; pp 593−606.

(16) For a good discussion on the differences in the photochemistry of various cyclic enones, see: Eaton, P. E. *Acc. Chem. Res.* **1968**, *1*, 50.

(17) See Experimental Section for details.

SCHEME 2.   Proposed Photoinduced Electron Transfer Mechanism for 1,4-Addition of Indoles to Enones
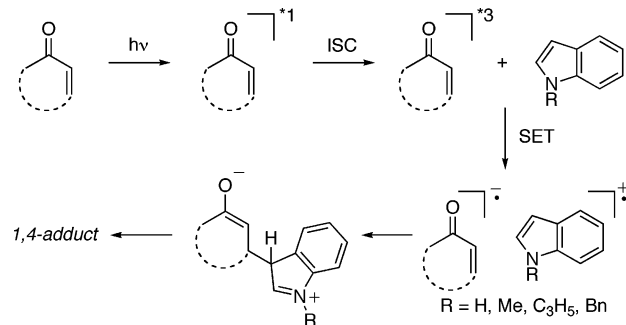
Introduction, there is ample evidence present in the literature for the participation of enones in PET reactions, for example, with tertiary amines.[6−8] It is also well established that indoles can react through pathways involving SET. The strong solvent dependence and restricted substrate scope are consistent with the proposed mechanism. Furthermore, the long reaction times (typically 18 h) suggest a low quantum yield, consistent with forbidden intersystem crossing (ISC) leading to the formation of the triplet enone. Single electron transfer between the triplet enone excited state and indole affords the radical ions, which combine to form the C−C bond. Intramolecular deprotonation at C3 of the indole (*N*-alkyl substitution is tolerated) followed by tautomerization affords the 1,4-adduct. A similar mechanism was proposed for 1,4-additions of indoles to 1-methyl-2-pyridone,[4a−b] and this mechanism is likely operating in reported photoinduced 1,4-additions of indole to 3-acetyl-6-nitrocoumarin and 1,4-naphthoquinone in the solid state.[4c−e] We also noted that reactions exposed to air did not lead to any 1,4-adduct formation, consistent with oxygen quenching of the enone triplet required for the electron-transfer step.[17,18]

Conclusion

   We have developed a photoinduced procedure for the 1,4-addition of indoles to enones. This reaction occurs with modest to excellent yield for cyclic and some acyclic enones. This reaction is experimentally simple, requiring only irradiation (UVA lamps) of the reagents in a CH_2Cl_2 solution at room temperature and avoids the necessity to use a Lewis acid. A mechanism involving single electron transfer between the enone triplet excited state and the indole is proposed and accounts for all experimental observations.

Experimental Section

   General Procedure for Photoinduced 1,4-Addition of Indoles (Tables 2−4). 3-(1*H*-Indol-3-yl)cycloheptanone (Table 2, entry 4). A borosilicate tube was charged with a stir bar, cyclohept-2-enone (0.105 g, 0.949 mmol), and indole (0.117 g, 0.999 mmol). A volume of 18.0 mL of CH_2Cl_2 was added to the mixture and the volume was marked on the tube. An excess of 1−2 mL of solvent was then added to the tube. The tube was capped with a septum and was purged with stirring using a nitrogen balloon and an outlet until the solvent evaporated to the volume marked. The reaction mixture was then placed on a stir-plate and allowed to stir between two exposure panels each equipped with four 8W UV-A bulbs for 18 h to obtain the crude mixture as a dark red liquid.[19] The reaction was monitored by TLC and the product was found to have TLC R_f of 0.51 on silica gel (40% EtOAc/hexanes). The crude mixture was concentrated under reduced pressure to a few milliliters and was purified by flash chromatography using CH_2Cl_2. The purified product was a clear, colorless oil (0.211 g, 98% yield).

   Supporting Information Available: Typical experimental procedures, experimental details, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) A more detailed mechanistic discussion can be found in the Supporting Information.

(19) The described transformations were typically accompanied by a change in color from a clear to a red or an amber solution.