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Strain-Release Electrophilic Activation via *E*-Cycloalkenones

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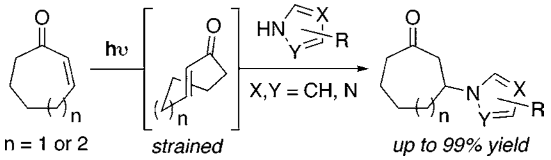
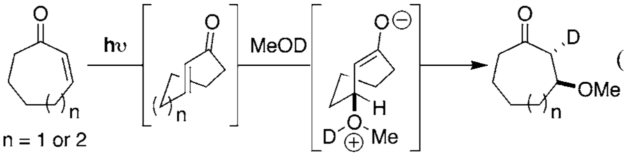
ABSTRACT



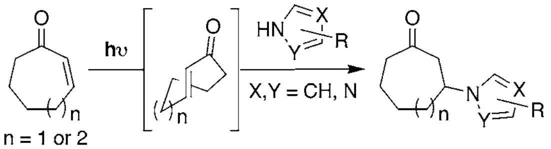
UVA irradiation (ca. 350 nm) of a mixture of cyclic enones and nitrogen heterocycles leads to efficient formation of the 1,4-adducts in a variety of solvents, at room temperature. These reactions likely proceed through strained *E*-cycloalkenone intermediates, as suggested by low-temperature generation/trapping experiments monitored by ^{1}H NMR. These results demonstrate that *E*-cycloalkenones are good electrophiles despite their known tendency to favor a conformation in which the carbonyl is not fully conjugated with the double bond.

Strained organic molecules often display high reactivity, consistent with high ground-state energy and low-activation energy for a variety of transformations.[1] Six- to eight-membered *E*-cycloalkenes[2] and *E*-cycloalkenones,[3] highly reactive yet readily accessible intermediates via photoisomerization, are representative examples. In seminal work on *E*-cycloalkenones, Corey and Eaton showed their unique dienophile reactivity in Diels−Alder additions.[3] Other examples have been documented over the years,[4] yet this reactivity remains largely unexploited by synthetic chemists. Notably, the ability of *E*-cycloalkenones to act as activated electrophiles has not been demonstrated, and in solution these enones favor a conformation in which the carbonyl is not fully conjugated with the double bond (i.e., their UV and IR spectroscopic data is consistent with saturated ketones).[3] Only MeOH (eq 1), EtOH, *i*-PrOH, and Et_2NH give the 1,4-adducts in moderate yield upon photoisomerization of the cycloalkenone in the presence of these reagents as *solvents*.[5]



(1)

As part of a program directed toward developing new reactivity of these strained intermediates, we suggest this approach could enable the 1,4-addition of a variety of nucleophiles under very mild conditions. Herein we report results demonstrating that efficient strain-release activation via *E*-cycloalkenones is possible, and leads to near stoichiometric 1,4-addition of various nitrogen heterocycles to cyclohept-2-enones and cyclooct-2-enone upon photoisomerization at room temperature in a variety of solvents (eq 2).



(2)

Initial experiments showed that benzimidazole (**2**) reacts efficiently with cyclohept-2-enone (**1**) upon irradiation with UVA lamps (ca. 350 nm) in a CH_2Cl_2/MeCN (8:1) mixture,

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[1] (a) Liebman, J. F.; Greenberg, A. A. *Chem. Rev.* **1976**, *76*, 311. (b) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312.

[2] (a) Kropp, P. J. *J. Am. Chem. Soc.* **1966**, *89*, 4091. (b) Marshall, J. A.; Carroll, R. D. *J. Am. Chem. Soc.* **1966**, *89*, 4092.

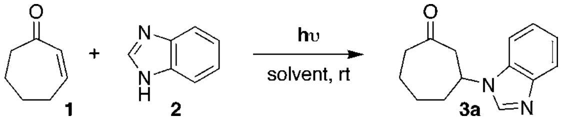
[3] (a) Eaton, P. E.; Lin, K. *J. Am. Chem. Soc.* **1964**, *86*, 2087. (b) Corey, E. J.; Tada, M.; LaMahieu, R.; Libit, L. *J. Am. Chem. Soc.* **1965**, *87*, 2051. (c) Eaton, P. E.; Lin, K. *J. Am. Chem. Soc.* **1965**, *87*, 2052.

[4] For selected examples, see: Nazarov: (a) Crandall, J. K.; Haseltine, R. P. *J. Am. Chem. Soc.* **1968**, *90*, 6251. (b) Noyori, R.; Katô, M. *Tetrahedron Lett.* **1968**, 5075. (c) Photodeconjugation: Noyori, R.; Inoue, H.; Katô, M. *J. Am. Chem. Soc.* **1970**, *92*, 6699. (d) Intramolecular [2+2]: Noyori, R.; Inoue, H.; Katô, M. *J. Chem. Soc., Chem. Commun.* **1970**, 1695. (e) Intramolecular Diels-Alder: Dorr, H.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 10229. For a recent application of in synthesis, see: Davies, H. M. L.; Loe, Ø.; Stafford, D. G. *Org. Lett.* **2005**, *7*, 5561.

10.1021/ol701496b CCC: $37.00

affording the 1,4-adduct in 94% isolated yield. To our delight, the reactivity proved general in a variety of solvents (Table 1), with little or no thermal reaction observed in samples not exposed to UV light. The use of a 8:1 mixture of CH_2Cl_2/MeCN was selected for substrate scope determination as these conditions allow solubilization of most heterocycles while minimizing the likelihood of a thermal reaction involving the cis form of the cycloalkenone.

Table 1. Solvent Effect

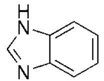
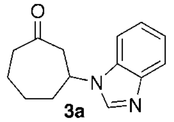
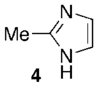
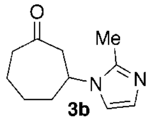
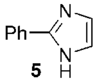
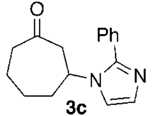
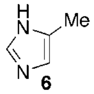
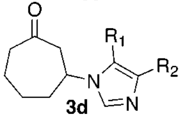
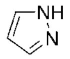
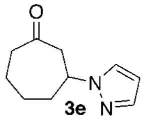
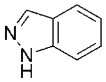
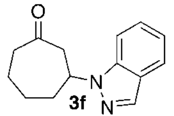
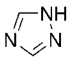
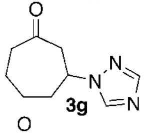
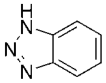
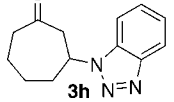


entry	solvent	conversion (%)[a]
1	$PhCF_3$	37
2	Et_2O	58
3	THF	86
4	EtOAc	91
5	CH_2Cl_2/MeCN (8:1)	94
6	MeCN	94
7	*i*-PrOH	71
8	DMSO	55

[a] Samples not subjected to UVA irradiation showed no conversion, except in *i*-PrOH (11%) and THF (<5%)

The substrate scope with respect to various nitrogen heterocycles is shown in Table 2.[6,7] Various imidazoles reacted to afford the 1,4-adducts in good yield (entries 1−4).[8] Substitution at the 2 and 4 positions was tolerated (entries 2−4), and a 7:1 selectivity is observed for 4-methylimidazole, favoring attack from the least hindered nitrogen atom (entry 4). This reaction is also efficient with pyrazoles, with pyrazole and benzopyrazole affording the desired product in 99 and 92% yield, respectively (entries 5−6). Triazoles also add efficiently under the reaction conditions (entries 7−8). The observed selectivity for the reaction of benzotriazole (entry 8) is in agreement with that typically observed for related reactions.[9]

Table 2. Nucleophile Scope

entry	nucleophile	product(s)	yield[a]
1	 **2**	 **3a**	94
2	 **4**	 **3b**	70
3	 **5**	 **3c**	44
4	 **6**	 **3d**	73[b]
5	 **7**	 **3e**	99
6	 **8**	 **3f**	92
7	 **9**	 **3g**	66
8	 **10**	 **3h**	53[c]

[a] Isolated yield after column chromatography. [b] 7 (R_1 = H, R_2 = Me):1 (R_1 = Me, R_2 = H) inseperable mixture of isomers. [c] 11% of the parent N2 isomer was also isolated.

As shown in Table 3, the enone substrate scope is consistent with that of other reactions involving *E*-cycloalkenones.[3,4] For entries 1−6, benzimidazole was selected as nucleophile as only a very slow thermal reaction, if any, is observed at room temperature in a CH_2Cl_2/MeCN mixture with these substrates. However, upon irradiation, a very clean conversion to the 1,4-adducts is observed. Cyclohept-2-enone and cyclooct-2-enone afford these products in 94 and 90% yield, respectively (entries 1−2). Substituted cyclohept-2-enones also react efficently (entries 3−4), and cycloheptadienone affords the monoadduct in 51% yield (entry 5), despite the possibility of double addition or Nazarov cyclization.[10] In addition, substitution at the 4 position is also tolerated, and affords the 1,4-adducts as mixtures of diastereoisomers (entries 6−7). Notably, irradiation of a cyclohex-2-enone and benzimidazole mixture under identical reaction conditions does not lead to any photoinduced reactivity, in agreement with the expected propensity of the highly strained *E*-cyclohex-2-enone to isomerize back to *Z*-cyclohex-2-enone (if formed).[11] Similarly, no photoinduced

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(5) MeOH: (a) Hart, H.; Dunkelblum, E. *J. Am. Chem. Soc.* **1978**, *100*, 5141. For precedence, see: (b) Nozaki, H.; Kurita, M.; Noyori, R. *Tetrahedron Lett.* **1968**, 2025. Et_2NH: (c) Noyori, R.; Katô, M. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1460. For related studies, see: (d) Dunkelblum, E.; Hart, H.; Jeffares, M. *J. Org. Chem.* **1978**, *43*, 3409.

(6) Typical experimental procedure: 3-(2-methylimidazol-1-yl)cycloheptanone (Table 2, entry 2). A borosilicate tube was charged with a stir bar, cyclohept-2-enone (0.050 g, 0.45 mmol), and 2-methylimidazole (0.112 g, 1.38 mmol). A volume of 8.0 mL of CH_2Cl_2 and 1.0 mL of MeCN was added to the mixture. The tube was capped with a septum and was sparged with a nitrogen balloon and an outlet for 10 minutes while stirring. The tube was then placed in a Rayonet photoreactor equipped with eight 8W UV-A bulbs for 18 hours. The reaction was monitored by TLC. The crude mixture was then transferred to a round bottom flask and concentrated under reduced pressure. The resulting oil was purified by column chromatography (6% MeOH/CH_2Cl_2), affording the product as a yellow oil (61 mg, 70%).

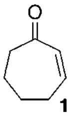
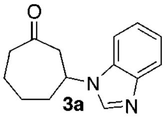
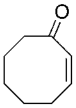
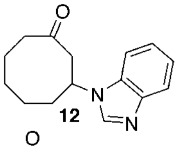
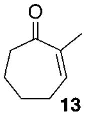
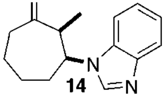
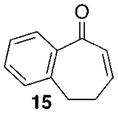
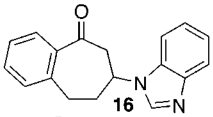
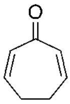
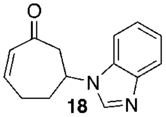
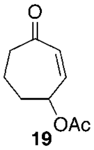
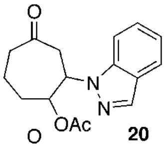
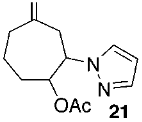
(7) In control experiments, no 1,4-addition was observed with **2**, **4**, **5**, **7**-**10** under identical conditions but in the absence of UV light. In contrast, **6** led to 53% conversion (vs >99% conversion upon UV irradiation).

(8) In contrast with the nucleophiles shown in Table 2, imidazole underwent a high yielding thermal addition with *Z*-cycloheptenone.

(9) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.

(10) Nozaki, H.; Kurita, M.; Noyori, R. *Tetrahedron Lett.* **1968**, 3635.

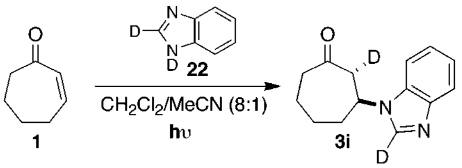
Table 3. Electrophile Scope

entry	electrophile	product	yield[a]
1	 **1**	 **3a**	94
2	 **11**	 **12**	90
3	 **13**	 **14**	66[b]
4	 **15**	 **16**	92
5	 **17**	 **18**	51
6	 **19**	 **20**	79[c]
7	**19**	 **21**	87[d]

[a] Isolated yield after column chromatography. [b] Diastereomeric ratio = 12:1 (cis/trans). [c] Diastereomeric ratio = 1.3:1 (cis/trans). [d] Diastereomeric ratio = 1.1:1 (cis/trans).

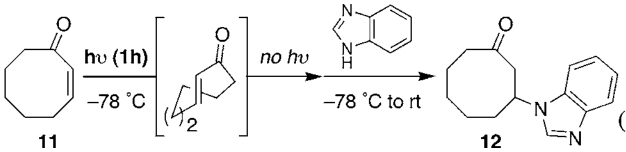
reactivity is observed upon irradiation of a mixture of methyl vinyl ketone and benzimidazole.

Interestingly, the addition of deuterated benzimidazole **22** to cyclohept-2-enone is stereospecific (eq 3). This result is in good agreement with the stereochemical outcome of solvolysis reactions outlined in eq 1. A plausible mechanism for the formation of **3i** involves the 1,4-addition to *E*-cycloheptenone, forming a zwitterionic intermediate analogous to that shown in eq 1. After conformational relaxation, intermolecular deuteration (likely involving **22**) and subsequent proton-transfer would provide adduct **3i** selectively. A similar rationale has been proposed by Hart and Dunkelblum (eq 1).[5a]



(3)

Despite a substrate scope consistent with the reactivity of a *E*-cycloalkenone intermediate, more conclusive evidence was needed.[12] Therefore, we performed low-temperature generation/trapping experiments,[13] which involved generation of the strained ground-state intermediate upon UV irradiation of a cyclooct-2-enone solution in CH_2Cl_2 at −78 °C. After 1 h, the irradiation was stopped, the flask was covered with aluminum foil, benzimidazole was added, and the mixture was allowed to warm to room temperature. A modest 18% conversion to the 1,4-adduct **12** was observed, suggesting that a long-lived strained *E*-cycloalkenone ground-state intermediate is involved in this transformation (eq 4). In the absence of irradiation, no conversion to the 1,4-adduct was observed under similar conditions.



(4)

Seeking a more definitive proof for the likely ground-state intermediate, we repeated the reaction shown in eq 4 in CD_2Cl_2/CD_3CN and monitored the reaction by low-temperature NMR. Following enone irradiation at −75 °C in an NMR tube, benzimidazole was added, and the sample was inserted in the NMR probe (precooled to −20 °C). An initial spectra (ii, Figure 1) confirmed that photoisomerization had occurred, leading to the appearance of *E*-cyclooctenone (**B**, diagnostic $J_{CH=CH} = 18.0$ Hz),[3a] and only traces of 1,4-adduct

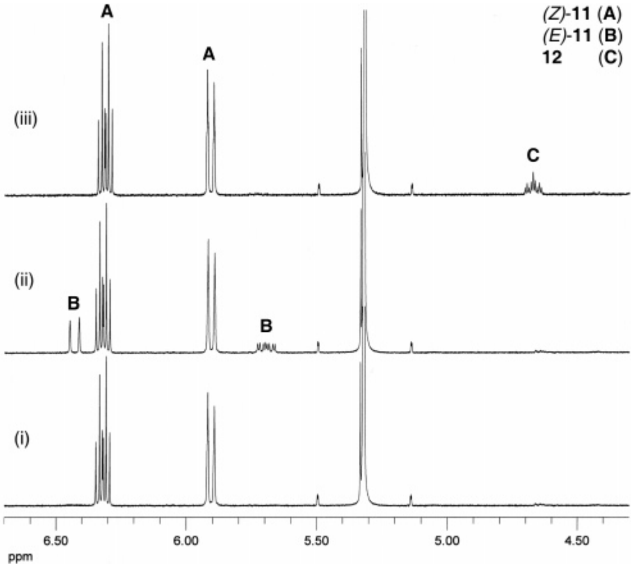


Figure 1. ^{1}H NMR monitoring of low-temperature generation/trapping experiments (eq 4): (i) spectrum before photoisomerization (350 nm) at −78 °C; (ii) spectrum after photoisomerization, but before addition of benzimidazole (**2**); (iii) spectrum after addition of excess **2** and warming to 10 °C.

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(11) *E*-Cyclohex-2-enones have been invoked as intermediates in a number of reactions. However, they have not been observed directly by low temperature laser flash photolysis and are expected to be very short lived, if formed. For a discussion, see: Schuster, D. I. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P.-S., Eds.; CRC Press: Boca Raton, FL, 1995; Chapter 48.

12 were observed at that temperature. Upon warming to 10 °C (over ca. 10 min), *E*-cycloalkenone (*E*)-**11** reacted efficiently to afford **12**, as judged by the similar ratios relative to *Z*-cyclooctenone [**B**/**A** = 0.29 in spectra ii vs **C**/**A** = 0.28 in spectra iii]. This finding suggests that only little unproductive *E* to *Z* thermal isomerization occurred under the reaction conditions. Overall, these results support the involvement of highly strained *E*-cycloalkenone ground-state intermediates under the reaction conditions.[14]

In summary, we have demonstrated that significant electrophilic activation can be achieved via *E*-cycloalkenones, leading to near stoichiometric 1,4-addition of imidazoles, pyrazoles, and triazoles upon UV irradiation of seven- and eight-membered cycloalkenones. Studies toward new reactivity of these strained intermediates in other reactions are underway and will be reported in due course.[14]

Acknowledgment. We thank the NSERC for generous support through the discovery grants and research tools and instrumentation programs, the University of Ottawa for startup funds, the Canadian Foundation for Innovation and the Ontario Ministry of Research and Innovation. J.M. also thanks NSERC for CGS-M and PGS D postgraduate scholarships and the University of Ottawa for a SAD award. P.D. thanks NSERC for an Undergraduate Student Research Award.

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

OL701496B

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(12) *E*-Cyclohept-2-enone has been observed by laser flash photolysis: Bonneau, R.; Fornier de Violet, P.; Joussot-Dubien, J. *Nouv. J. Chim.* **1977**, *1*, 31.

(13) For other low temperature generation/trapping experiments, see references 3b, 4b, and 5c. Such experiments are based on the longer lifetimes of ground-state intermediates compared to excited states, which are known to rapidly decay to the ground state (typically $\ll$ 1 s).

(14) Over the course of these studies, we discovered that indoles react with enones, likely via a photoinduced electron transfer mechanism: Moran, J.; Suen, T.; Beauchemin, A. *J. Org. Chem.* **2006**, *71*, 676.