## 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 <sup>1</sup>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.<sup>1</sup> Six- to eightmembered *E*-cycloalkenes<sup>2</sup> and *E*-cycloalkenones,<sup>3</sup> 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.<sup>3</sup> Other examples have been documented over the years,<sup>4</sup> 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).<sup>3</sup> Only MeOH (eq 1), EtOH, *i*-PrOH, and Et<sub>2</sub>NH give the 1,4-

(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.

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adducts in moderate yield upon photoisomerization of the cycloalkenone in the presence of these reagents as *solvents*.<sup>5</sup>

$$\underbrace{\bigcap_{n=1}^{O} \underbrace{h_{\upsilon}}_{n} \underbrace{\left(\bigcap_{n}^{O}\right)}_{n=1 \text{ or } 2} \underbrace{MeOD}_{\text{MeOD}} \underbrace{\left(\bigcap_{n}^{O\ominus}\right)}_{\text{MeOD}} \underbrace{\left(\bigcap_{n}^{O\ominus}\right)}_{\text{MeOD}} \underbrace{\left(\bigcap_{n}^{O\ominus}\right)}_{\text{MeOD}} \underbrace{\left(\bigcap_{n}^{O\ominus}\right)}_{n} \underbrace{\left(\bigcap_{n}^{O}\right)}_{n} \underbrace{\left(\bigcap_{n}^{$$

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).



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,

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

<sup>(2) (</sup>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.

<sup>(3) (</sup>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.

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



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

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.

The substrate scope with respect to various nitrogen heterocycles is shown in Table 2.<sup>6,7</sup> Various imidazoles reacted to afford the 1,4-adducts in good yield (entries 1-4).<sup>8</sup> 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.<sup>9</sup>

(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.

Table 2.	Nucleophile Scope	
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<sup>*a*</sup> Isolated yield after column chromatography. <sup>*b*</sup> 7 ( $R_1 = H, R_2 = Me$ ):1 ( $R_1 = Me, R_2 = H$ ) inseperable mixture of isomers. <sup>*c*</sup> 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.<sup>3,4</sup> 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<sub>2</sub>Cl<sub>2</sub>/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-2enones also react efficiently (entries 3-4), and cycloheptadienone affords the monoadduct in 51% yield (entry 5), despite the possibility of double addition or Nazarov cyclization.<sup>10</sup> 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).<sup>11</sup> Similarly, no photoinduced

<sup>(5)</sup> 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<sub>2</sub>NH: (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.

<sup>(6)</sup> 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<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub>), affording the product as a yellow oil (61 mg, 70%).

<sup>(10)</sup> Nozaki, H.; Kurita, M.; Noyori, R. Tetrahedron Lett. 1968, 3635.





<sup>*a*</sup> Isolated yield after column chromatography. <sup>*b*</sup> Diastereomeric ratio = 12:1 (cis/trans). <sup>*c*</sup> Diastereomeric ratio = 1.3:1 (cis/trans). <sup>*d*</sup> 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).<sup>5a</sup>



Despite a substrate scope consistent with the reactivity of a *E*-cycloalkenone intermediate, more conclusive evidence was needed.<sup>12</sup> Therefore, we performed low-temperature generation/trapping experiments,<sup>13</sup> 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.



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



**Figure 1.** <sup>1</sup>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.

occurred, leading to the appearance of *E*-cyclooctenone (**B**, diagnostic  $J_{\text{CH}=\text{CH}} = 18.0 \text{ Hz}$ ),<sup>3a</sup> and only traces of 1,4-adduct

<sup>(11)</sup> 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.<sup>14</sup>

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.<sup>14</sup>

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

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<sup>(12)</sup> *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.

<sup>(13)</sup> 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).

<sup>(14)</sup> 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.