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A novel photoinduced ring opening and isomerization of adamantane-2-spiro isoxazolines using $Mo(CO)_6$

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Abstract—The $Mo(CO)_6$-mediated photoinduced ring-opening reactions of adamantane isoxazolines involve novel rearrangement that provide enaminoketones as major products and β-hydroxy ketones as minor ones; in contrast, only β-hydroxy ketones and α,β-unsaturated ketones were obtained under thermal condition.

Isoxazolines are an interesting heterocyclic family because of their diverse biological applications. When treated with proper reducing reagents, isoxazolines can yield γ-amino alcohols, β-hydroxy ketones, α,β-unsaturated ketones, and β-hydroxy nitriles;[1] therefore, they are frequently used as precursors in the synthesis of various acyclic compounds.

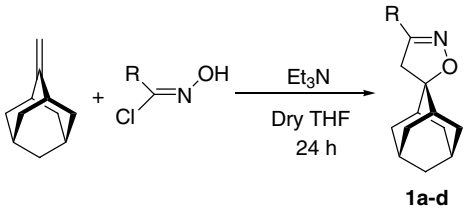
Photoinduced ring-opening reactions of five-membered heterocycles and their subsequent rearrangements have received much attention both as synthetic intermediates and in the study of their reaction mechanisms.[2–4] The photoreactions of 2-isoxazolines were studied by Schmid,[5] Matsuura,[6] and Mukai,[7] who showed that N–O bond fission occurs on irradiation. It has also been reported[8] that irradiation of 3-phenyl-2-isoxazoline gave isomeric 4-phenyl-2-oxazoline, ring opened β-amino aldehyde and benzonitrile. Nitta et al.[9] reported that the iron carbonyls induced an isoxazoline ring cleavage under thermal and photochemical conditions.

Based on these findings and our interest in the studies of adamantane containing five-membered heterocyclic ring systems,[10] we hereby report the ring-opening reactions of adamantane-2-spiro isoxazolines under thermal and photochemical conditions using $Mo(CO)_6$. Interestingly, a novel photoisomerization reaction of adamantane isoxazolines to enaminoketones was observed (vide infra).

The adamantane-isoxazolines **1a–d** were synthesized in moderate yields (Table 1) by refluxing a mixture of methyleneadamantane and the corresponding nitrile oxides in dry THF using the reported method of 1,3-dipolar addition reactions.[11] The structures of each adamantane-isoxazolines **1a–d** were confirmed by spectral data, in which **1a** has been reported previously.[11]

We performed the ring-opening reaction of **1c** initially under direct photolysis conditions; after irradiation for 16 h, however, only complex mixture of products along with starting material were observed; therefore, we sought an alternative approach. In addition to direct

Table 1. Synthesis of substituted adamantane-isoxazolines **1a–d**



1a-d

Compound	R	Yield (%)
1a	Phenyl	59
1b	*p*-Tolyl	55
1c	*p*-Anisyl	52
1d	5-Chlorofuran-2-yl	58

Keywords: Adamantane isoxazolines; Photorearrangement; Isomerization; Enaminoketones.
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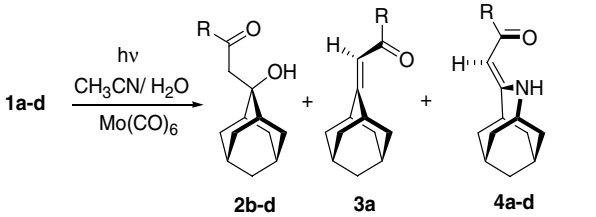
photolysis, several other methods are known for achieving N–O bond cleavage in an isoxazoline ring, including reduction with Raney Ni,[12] $LiAlH_4$,[13] H_2/Pd–C,[14] $TiCl_3$,[15] SmI_2,[16] and $Mo(CO)_6$.[17] Among these methods, the $Mo(CO)_6$-mediated ring opening of isoxazolines appears to be the most efficient one. To the best of our knowledge, $Mo(CO)_6$-mediated ring-opening reactions of adamantane isoxazolines have not been reported previously.

Table 2 presents the products and yields of the $Mo(CO)_6$-mediated photochemical cleavages of the adamantane isoxazolines **1a–d**. The expected β-hydroxyketones **2b–d** and the α,β-unsaturated ketone **3a** were obtained as minor products (<18%); surprisingly, unexpected novel photorearrangements occurred to give the ring-expanded enaminoketones **4a–d** as major products (30–59% yields). For example, the irradiation (254 nm, Rayonet) of **1a** (R = Ph) in the presence of 1.5 equiv of $Mo(CO)_6$ in acetonitrile/water gave enaminoketone **4a** in 58% yield and α,β-unsaturated ketone **3a** in 10% yield (entry 1, Table 2).[18]

Although we eventually confirmed the structures of the photoproducts **2b–d**, **3a**, and **4a–d** spectroscopically, the determination of the major products was not straightforward. For example, in the ^1H NMR spectrum of **4c**, a broad singlet appears at δ 11.8, which is quite unusual for phenyl or adamantyl protons; we assign this signal to the enamine NH proton. In addition, a vinylic CH proton appears as a broad singlet at δ 5.6. It is noteworthy that these signals for the vinyl CH and enamine NH protons disappeared upon the addition of D_2O. The ^{13}C NMR spectrum of **4c** displays the characteristic signals of a carbonyl carbon atom at δ 187.4, a quaternary enamino carbon atom [$NH(CHR_2)C{=}CH–$] at δ 174.6, and a vinylic CH carbon atom at δ 89.3. The mass spectrum of **4c** exhibits the molecular ion at *m*/*z* 297, the same mass as that of its starting material **1c**. This finding implies that product **4c** is a geometrical isomer of **1c**, that is, no net addition or fragmentation occurred during photolysis. Taken together, these spectral data of **4c** are consistent with the enaminoketone structure. Gratifyingly, **4b** is a crystalline compound and we confirmed its structure through X-ray crystallography (Fig. 1).[19]

Table 2. $Mo(CO)_6$-Mediated photochemical ring-opening reactions of adamantane-isoxazolines



Compound	R	**2** Yield (%)[a]	**3** Yield (%)[a]	**4** Yield (%)[a]
1a	Phenyl	—	10	58
1b	*p*-Tolyl	12	—	59
1c	*p*-Anisyl	18	—	30
1d	5-Chlorofuran-2-yl	15	—	30

[a] Isolated yields based on recovered starting materials.

It is noteworthy that the enaminoketone **4a** has been reported previously by Eguchi and co-workers to arise through an interesting rearrangement that occurred from the unstable adduct of aldonitrone and phenylacetylene.[20] Our spectral data of **4a–d** support the previous structural assignment. We also performed the ring-opening reactions of **1a–d** with $Mo(CO)_6$ under thermal conditions to determine whether the enaminoketones **4a–d** are also obtained thermally. When we reacted **1a** with $Mo(CO)_6$ (3.5 equiv) in CH_3CN/H_2O at 80 °C, we obtained only the α,β-unsaturated ketone **3a** in 29% yield. Under the same reaction conditions, **1b** gave **3b** in 49% yield; in contrast, cycloadduct **1c** afforded both the β-hydroxyketone **2c** and the α,β-unsaturated ketone **3c** in 44% and 31% yields, respectively. Cycloadduct **1d** gave **2d** in 23% yield (Table 3).[21] In none of these cases did we observe even a trace amount of the corresponding enaminoketone.

In order to extend the scope of this novel photorearrangement with other sprio systems, the ring-opening reaction of isoxazoline-5-spiro cyclobutane **5**[22] was carried out. Irradiation of **5** with $Mo(CO)_6$ (1.5 equiv) in wet acetonitrile (Scheme 1) using 254 nm for 3 h gave the expected enaminoketone **6** and β-hydroxy ketone **7** in 32% and 15% yield, respectively. Whereas thermal reaction of **5** in wet acetonitrile containing $Mo(CO)_6$ (3.5 equiv) for 24 h gave only **7** (30%) with recovery of **5** (60%). No trace of spiro ring opened or rearranged product was observed in this condition (Scheme 1).

The structures of compounds **6** and **7** were confirmed by spectral data (see Supplementary data). From the formation of enaminoketone **6** it is clear that, in addition to the N–O bond cleavage of the isoxazoline ring, C_1–C_2 bond cleavage of spiro cyclobutane ring was also involved in the photolysis of **5** mediated by $Mo(CO)_6$. The rearrangement of isoxazoline-5-spiro cyclobutanes[22] and cyclopropanes,[23] via N–O bond cleavage, under flash vacuum pyrolysis conditions and irradiation conditions has already been reported; however, their observed products are different from ours. $Mo(CO)_6$ mediated ring-opening reaction of isoxazoline-5-spiro cyclopropane to enaminoketone has also been reported.[18a]

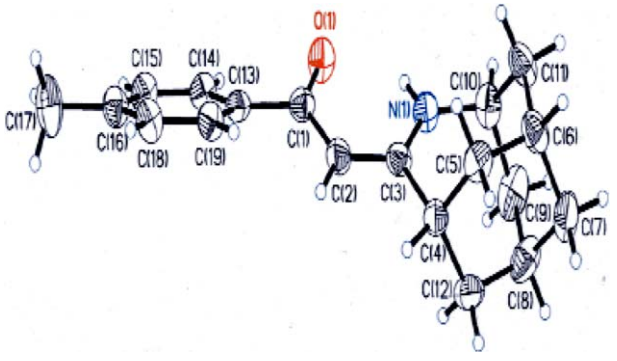
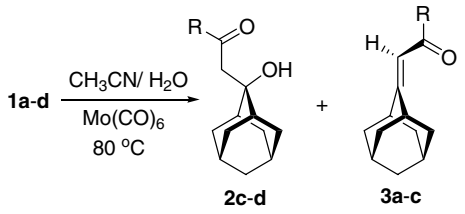


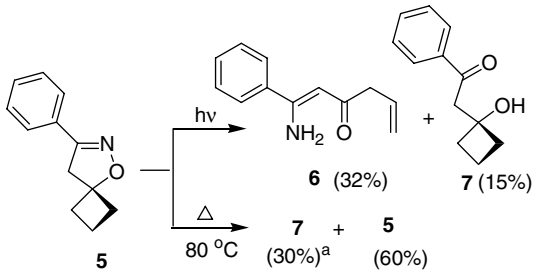
Figure 1. ORTEP plot of the solid state structure of **4b**.

Table 3. $Mo(CO)_6$-Mediated thermal ring-opening reactions of adamantane-isoxazolines



Compound	R	**2** Yield (%)[a]	**3** Yield (%)[a]
1a	Phenyl	—	29
1b	*p*-Tolyl	—	49
1c	*p*-Anisyl	44	31
1d	5-Chlorofuran-2-yl	23	—

[a] Isolated yields based on recovered starting material.

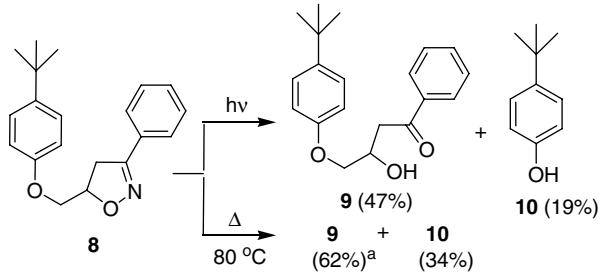


Scheme 1. $Mo(CO)_6$-Mediated ring-opening reactions of isoxazoline **5**. ([a]Isolated yield based on recovered starting material.)

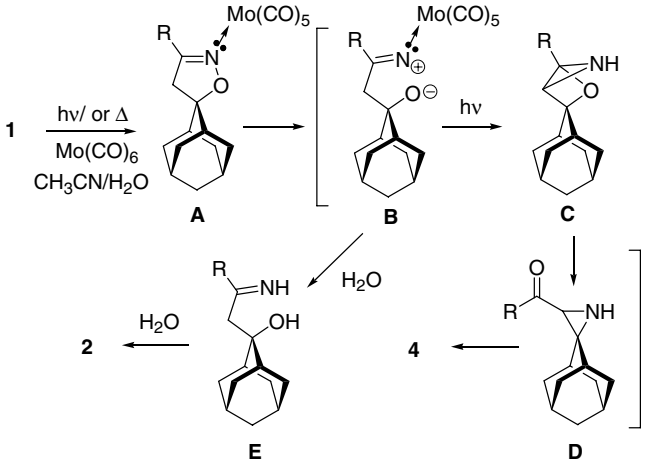
Further, we investigated the ring-opening reaction of 3,5-disubstituted isoxazoline **8** (containing no 5-spiro group) using $Mo(CO)_6$. Compound **8** was synthesized by 1,3-dipolar cycloaddition reaction of 1-allyloxy-4-*tert*-butyl benzene with phenyl nitrile oxide, using the reported method.[11] The reaction of **8** with $Mo(CO)_6$ (1 equiv) in CH_3CN/H_2O, under photochemical condition for 2 h gave the expected β-hydroxy ketone **9** in 47% yield, in addition to cleaved *t*-butyl phenol **10** (19% yield) (Scheme 2). Thermal ring-opening reaction of **8** with $Mo(CO)_6$ (3 equiv) under similar condition for 36 h also gave β-hydroxy ketone **9** in 62% yield with recovered **10** (34% yield). The structures of compounds **8**–**10** were confirmed by spectral data. Furthermore, compound **10** was compared with the authentic sample.

From these observations, it is clear that the ring-opening reactions of isoxazolines **1a**–**d**, **5** and **8** were mediated by $Mo(CO)_6$ under both the reaction conditions. The readily occurred rearrangement of isoxazolines **1a**–**d** and **5** to the corresponding enaminoketones **4a**–**d** and **6** under photolysis is mainly due to the 5-spiro substituents: adamantane and cyclobutane moieties.

Based on our experimental results and literature evidences, we proposed a plausible mechanism for the formation of β-hydroxyketones **2** and the enaminoketones **4** (Scheme 3). Complex **A**, formed initially between the isoxazoline and $Mo(CO)_6$, undergoes N–O bond cleavage to provide a nitrene complex **B**. In the presence of



Scheme 2. $Mo(CO)_6$-Mediated ring-opening reactions of isoxazoline **8**. ([a]Isolated yield based on recovered starting material.)



Scheme 3. A plausible mechanism of the $Mo(CO)_6$-Mediated ring opening reactions of **1**.

water complex **B** gave β-iminoalcohol **E**, which hydrolyzes subsequently to form β-hydroxyketone **2**. Similar mechanisms for the formation of β-hydroxyketones from isoxazolines under thermal[9,24] and photochemical[9] reaction conditions have been reported previously. The photochemical formation of **4** came from complex **A**[25] via the aziridine intermediates **D** (itself obtained from complex **B** via **C**[26]) and was followed by a homologous Beckmann rearrangement.[27] Although such a rearrangement may seem strange, a related but different rearrangement from an adamantane oxaziridine intermediate to an amide has been reported.[28]

In summary, we report here a convenient method for the $Mo(CO)_6$-mediated ring-opening reactions of adamantane-2-spiro isoxazolines under photochemical and thermal conditions. This cycloaddition-cleavage protocol provides a novel isomerization pathway for the synthesis of substituted enaminoketones under photochemical conditions.[29]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.156.

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19. Crystal structure data for **4b**: $C_{19}H_{23}NO$, $M = 281.38$, triclinic, $a = 9.8122(1)$ Å, $\alpha = 106.8226(9)°$, $b = 12.9988(2)$ Å, $\beta = 101.9080(8)°$, $c = 13.1727(2)$ Å, $\gamma = 94.8232(9)°$, $V = 1554.97(4)$ Å^3, $T = 295(2)$ K, space group $P\bar{1}$, $Z = 4$, $\mu = 0.073$ mm^{-1}, 29,260 reflections collected ($R1 = 0.0495$, $wR2 = 0.1329$), 7122 independent reflections ($R(int) = 0.0393$, $R1 = 0.0879$, $wR2 = 0.1572$). Crystallographic data for the structure in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 299771. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: data_request@ccdc.cam.ac.uk].
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29. *Procedures for the photochemical ring-opening reaction of* **1b**: An acetonitrile (18 mL) solution of isoxazoline **1b** (0.09 mmol) and molybdenum hexacarbonyl (0.135 mmol) containing water (three drops) was irradiated by using a Rayonet multilamp reactor (254 nm) for 4 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography to give **1b** (20%), in addition to **2b** and **4b** (yields are summarized in Table 2). *Procedures for the thermal ring-opening reaction of* **1c**: A mixture of **1c** (0.105 mmol) and molybdenum hexacarbonyl (0.105 mmol) in acetonitrile (18 mL) containing water (three drops) was refluxed at 80 °C for 48 h. After removing the solvent, the residue was purified over silica gel column to give **1c** (43%), in addition to **2c** and **3c**. *Spectral data of some selected compounds:* For **2b**: colorless solid; mp 88–90 °C; $R_f = 0.60$ (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48–1.91 (m, 12H), 2.29–2.35 (m, 2H), 2.42 (s, 3H, CH_3), 3.36 (s, 2H, 4′-CH_2), 4.42 (s, 1H, OH), 7.26–7.29 (m, 2H, ArH), 7.85–7.89 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.3 (CH_3), 28.0 (CH), 28.6 (CH), 33.2 (CH_2), 35.4 (CH_2), 37.5 (CH), 40.0 (CH_2), 44.3 (CH_2), 75.6 (C_q), 129.1 (CH), 130.0 (CH), 135.8 (C_q), 145.1 (C_q), 202.7 (C_q); MS (EI) *m/z* (%): 284 (M^+, 5), 266 (40), 265 (50), 251 (20), 134 (50), 119 (100), 91 (50); HRMS calcd for $C_{19}H_{24}O_2$ 284.1776; found 284.1780. For **3c**: colorless solid; mp 97–99 °C; $R_f = 0.63$ (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88–2.05 (m, 12H), 2.54 (br s, 1H), 3.87 (s, 4H), 6.56 (s, 1H), 6.91–6.95 (m, 2H, ArH), 7.94–7.98 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 28.0 (CH), 33.6 (CH), 36.9 (CH_2), 39.3 (CH_2), 40.4 (CH_2), 41.8 (CH), 55.4 (CH_3), 113.5 (CH), 114.3 (CH), 130.5 (CH), 132.4 (C_q), 162.9 (C_q), 170.4 (C_q), 191.2 (C_q); MS (EI) *m/z* (%): 283 (M^++1, 5), 282 (M^+, 40), 254 (10), 251 (30); HRMS calcd for $C_{19}H_{22}O_2$ 282.1620; found 282.1628.
For **4c**: colorless solid; mp 96–98 °C; $R_f = 0.25$ (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.72–1.97 (m, 10H), 2.09 (br s, 2H), 2.55 (br s, 1H), 3.66 (br s, 1H), 3.81 (s, 3H, OCH_3), 5.59 (s, 1H), 6.88 (d, $J = 8.7$ Hz, 2H, ArH), 7.84 (d, $J = 8.7$ Hz, 2H, ArH), 11.83 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 27.0 (CH), 32.9

(CH_2), 34.9 (CH_2), 36.0 (CH_2), 40.4 (CH), 48.9 (CH), 55.3 (CH_3), 89.3 (CH), 113.3 (CH), 128.6 (CH), 133.4 (C_q), 161.4 (C_q), 174.6 (C_q), 187.4 (C_q); MS (EI) *m*/*z* (%): 297 (M^+, 15), 296 (100), 280 (10), 190 (10), 162 (5), 135 (18), 91 (7); HRMS calcd for $C_{19}H_{23}NO_2$ 297.1729; found 297.1715.