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Novel photocyclization of β,γ-unsaturated oximes

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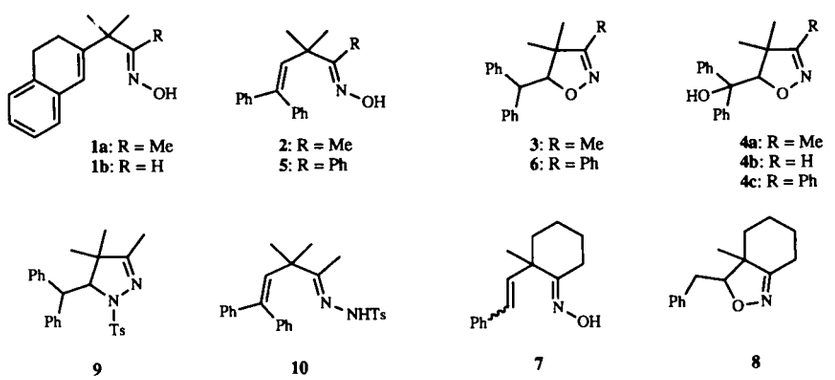
Abstract. Previously, β,γ-unsaturated oximes were thought to be photochemically unreactive. The present study reports the first three examples of photocyclization of β,γ-unsaturated ketoximes to yield 4,5-dihydroisoxazole derivatives. Typically, acetophenone-sensitized irradiation of 3,3-dimethyl-5,5-diphenylpent-4-en-2-one oxime (**2**) affords 5-(diphenylmethyl)-3,4,4-trimethyl-4,5-dihydroisoxazole (**3**) in 38% yield. A single-electron transfer (SET) mechanism is proposed to account for the cyclization.

For many years, it was considered that β,γ-unsaturated oximes and oxime ethers were photochemically unreactive, apart from *E,Z* isomerization around the CN double bond[1,2]. Recently, we have shown that, in some instances, β,γ-unsaturated aldoximes can undergo efficient aza-di-π-methane rearrangement (ADPM) on acetophenone-sensitized irradiation[3,4]. Our previous experience with the ADPM process[1,5] has shown that both imino and acetoxyimino derivatives of β,γ-unsaturated aldehydes react efficiently by this path but keto derivatives, in general, either fail to react or react with low efficiency. However, in one case we have demonstrated[4] an efficient ADPM rearrangement occurring with the ketoxime **1a**.

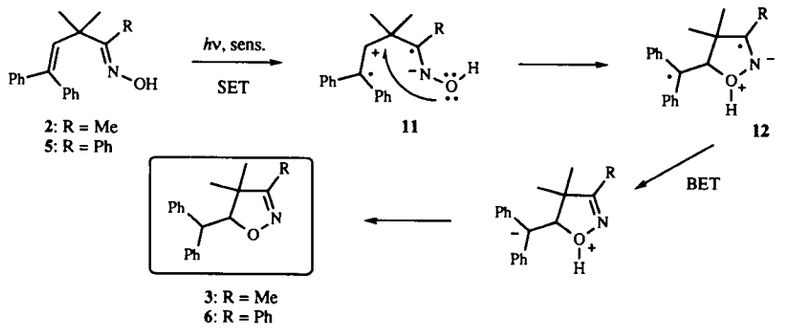
This result was a stimulus to seek other examples of the photoreactivity of such compounds. The logical starting point in a search for such reactivity in ketoximes was compound **2** since the corresponding oxime acetate was the one derivative that did react by the ADPM path in our earlier study[5].

The acetophenone-sensitized irradiation of the oxime **2** in methylene chloride for 30 min brought about the formation of a new compound in 15% yield. Phenanthrene sensitization was also effective, although the reaction was less efficient requiring 4 h of irradiation to produce 8% of the product. The new compound was identified as the dihydroisoxazole **3** using standard spectroscopic techniques. Identification was helped by comparison of the ^{13}C- and ^{1}H-NMR spectra of **3** with those of the dihydroisoxazole derivatives **4** which we obtained from the irradiation of the oximes **2** as a complex with boron trifluoride etherate. The identity of **4b** was unequivocally established by X-ray diffraction analysis[6]. A single-electron transfer (SET) mechanism was used to account for the formation of compounds **4**. Based on these precedents we propose that an SET mechanism might also be operative in the present case and such an interpretation is outlined in the Scheme. This is the first example of photocyclization of this type in a β,γ-unsaturated oxime.

The study was extended to include the phenyl-substituted derivative **5**, synthesized according to the method previously described[5]. Acetophenone-sensitized irradiation of **5** for only 10 min gave a new product, identified as **6**, in a yield of 38%. The reaction is qualitatively more efficient than that observed for **2**. Further information on the generality of the reaction was obtained with the oxime **7**. This compound was synthesized from 1-methyl-2-oxocyclohexanecarbaldehyde[7] by reaction with (phenylmethylene)triphenylphosphorane to yield 2-methyl-2-(2-phenyl-



Structure 1.



Scheme 1.

vinyl)cyclohexanone that was converted to the oxime by the standard oximation route. Oxime **7** was obtained as a 1 : 1 mixture of the *E* and *Z* isomers of the alkene moiety. Acetophenone-sensitized irradiation of **7** for 25 min yielded the dihydroisoxazole **8** in 20% yield. Qualitatively, the efficiency of the reaction with this oxime is similar to that observed for oxime **2**. Clearly the change on the vinyl moiety from diphenyl substitution in **2** to monophenyl in **7** does not markedly affect the efficiency of the photoreaction.

The results obtained in the present study are surprising and can be explained by two different mechanisms. The first would involve *E–Z* isomerization of the oximino group, abstraction of the oxime hydrogen by the sensitizer, and cyclization of the resulting radical on the diphenylvinyl moiety. Upon hydrogen abstraction this species would then afford the observed product. Our previous studies with acetophenone sensitization of other oximes have provided no evidence for this type of hydrogen abstraction steps[3,4]. In fact, the energy transfer from the triplet acetophenone to the diphenylvinyl moiety is extremely efficient. Thus, it seems unlikely in these examples that a hydrogen abstraction/cyclization mechanism would be operative, and this mechanism is therefore rejected in favour of our second proposal involving SET, outlined in the Scheme. Excitation of the molecule is followed by intramolecular SET from the diphenylvinyl group to the oxime, cyclization within this yielding a zwitterionic intermediate, followed by back electron transfer (BET) as illustrated to afford the final product. This mechanism can also be used to explain the formation of the dihydropyrazole **9** obtained on irradiation of the hydrazone derivative **10**[8]. If our mechanistic interpretation is correct, the higher efficiency observed in the cyclization of **5** can be explained, by the stabilizing effect that the change of substitution on C1 from methyl in **2** to phenyl in **5** can have on the zwitterionic biradical intermediates **11** and **12**.

The novelty of the present results is that the SET takes place without any need to enhance the electron-accepting ability of the oxime. Previously, as mentioned above[6], we have used BF_3 etherate to complexate the oximino group to achieve such an effect. However, that reaction involves direct irradiation with light absorption by the complexed imino group, while the excitation of the non-complexed oximes is achieved by acetophenone sensitization of the diphenylvinyl moiety. The fact that a similar result can be brought about by these two different excitation pathways involving different chromophores and even different excited states is surprising and, as far as we are aware, unprecedented.

Our previous research with β,γ-unsaturated oximes identified the first examples of the ADPM rearrangement in such systems. That type of excited state reactivity is observed when the intermediate biradicals leading to the ADPM product are highly stabilized[3,4]. Moreover, β,γ-unsaturated ketoxime **1a** and the corresponding aldoxime **1b**, in which deactivation of the excited state by rotation of the alkene double bond is suppressed, also undergo efficient ADPM rearrangement[4]. The present work has identified a new reaction mode of β,γ-unsaturated oximes where SET from the vinyl substituent to the CN double bond takes place. In fact this appears to be the favoured reaction mode with the ketoximes studied herein. Cyclization within the resulting zwitterionic biradical affords the 4,5-dihydroisoxazoles. Currently work is in progress to establish the scope of this process.

Experimental

Melting points were determined on a Buchi 530D apparatus in open capillaries and are uncorrected. IR spectra were recorded as liquid films unless otherwise stated, on a Perkin-Elmer 781 spectrophotometer and band positions are reported in wavenumbers (cm^{-1}). ^{1}H-NMR spectra were recorded on a Varian VXR-300S (300 MHz) and Bruker AC-250F (250 MHz) using $CDCl_3$ as solvent, and TMS as internal standard. Coupling constants *J* are given in Hz. ^{13}C-NMR spectra were recorded on a Varian VXR-300S (75 MHz) and Bruker AC-250F (62 MHz) using $CDCl_3$ as internal standard. UV/vis spectra were recorded in CH_2Cl_2 or ethanol solution using a Perkin Lambda 3B spectrophotometer. Mass spectra were run at the Chemistry Department, University of Dundee, using a VG 11-250J mass spectrometer. Combustion analyses were carried out by the Servicio de Microanálisis de la Universidad Complutense de Madrid. Column chromatography was performed using silica gel 60 (40–63 mm) from Merck. Commercially available starting materials and reagents were purchased from Aldrich Chemical Co.

Synthesis of 2-methyl-2-(2-phenylvinyl)cyclohexanone

To a solution of 16.3 g (0.042 mol) of benzyltriphenylphosphonium chloride in 80 ml of anhydrous THF was added, under argon atmosphere, 27 ml (0.043 mol) of *n*-butyllithium (solution 1.6 M in hexane) at 0°C. The mixture was refluxed for 2 h. After cooling the red reaction mixture, a solution of 3 g (0.021 mol) of 1-methyl-2-oxocyclohexanecarbaldehyde[7] in 20 ml of THF was added at room temperature. The mixture was stirred for 12 h, hydrolyzed with a saturated solution of ammonium chloride, extracted with diethyl ether and dried over magnesium sulfate. The desiccant was filtered off and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel using hexane/diethyl-ether (9/1) as eluent. The titled ketone was obtained as a yellow oil (3.4 g, 75%), consisting of a 1 : 1 mixture of the *Z* and *E* isomer. ^{1}H-NMR (300 MHz): δ 1.19, s, CH_3, *E* isomer, 1.21, s, CH_3, *Z* isomer; 1.4–2.6, m, 4 CH_2; 5.6, d, *J* 12.4 Hz, CH, *Z* isomer; 6.2, 6.3, AB, *J* 16.5 Hz, CHPh, *E* isomer; 6.5, d, *J* 12.5 Hz, CHPh, *Z* isomer; 7.0–7.3, m, ArH. ^{13}C-NMR (62 MHz): δ 21.7, 22.0 (CH_2), 24.1, 24.3 (CH_3), 27.4, 29.0, 39.2, 39.7, 40.1, 44.8 (CH_2), 51.3, 52.0 (quaternary C), 125.9–137.1 (Ar and vinyl-C), 212.7 (C=O), 213.9 (C=O). IR: 1710 cm^{-1}. UV (CH_2Cl_2) λ_{max}/nm (ε/mol·m^{-2}) 247 (10000). MS *m/z* (%, fragment): 214 (79, M^+), 129 (95, $C_{10}H_9^+$), 95 (100, $C_6H_7O^+$). Found: 214.1347; $C_{15}H_{18}O$ requires M, 214.1353.

Oximes **2** *and* **5** These were synthesized by the method previously described[5]. For **2**, UV (CH_2Cl_2) λ_{max}/nm (ε/mol·m^{-2}): 252 (11400). For **5**, UV (CH_2Cl_2) λ_{max}/nm (ε/mol·m^{-2}): 249 (14400).

Oxime **7** The oxime **7** was prepared by refluxing 2-methyl-(2-phenylvinyl) cyclohexanone (1 g, 4.7 mmol) with hydroxylamine hydrochloride (0.38 g, 5.6 mmol) and pyridine (1 ml) in ethanol (50 ml) for 6 h. After conventional work-up, the oxime was isolated and purified by flash chromatography using hexane/diethyl-ether (9/1) as eluent. Oxime **7** (0.98 g, 91%) was obtained as a white solid consisting of a 1:1 mixture of the *Z* and *E* isomers; m.p. 60–63°C (from hexane). Anal. calcd. for $C_{15}H_{19}NO$ (229.32): C 78.61, H 8.29, N 6.10; found: C 78.0, H 8.0, N 6.1%. ^{1}H-NMR (300 MHz): δ 1.3, s, CH_3; 3.1–3.3, m, 4 CH_2; 5.6, d, *J* 12.6 Hz, CH, *Z* isomer; 6.3, 6.4, AB, *J* 16.3 Hz, CH, *E* isomer; 6.6 d, *J* 12.6 Hz, CHPh, *Z* isomer; 7.1–7.4, m, ArH; 9.7, br s, OH, *Z* isomer; 10.2, br s, OH, *E* isomer. ^{13}C-NMR (62 MHz): δ 21.6, 22.1, 22.2, 22.4 (CH_2), 25.5, 25.7 (CH_3), 25.9, 26.4, 40.4 (CH_2), 43.4 (quaternary C), 43.8 (CH_2), 44.3 (quaternary C), 126.1–138.0 (Ar and vinyl-C), 163.3 (C=N), 163.4 (C=N). IR (KBr): 3260 cm^{-1} (OH), 1600 cm^{-1} (C=N). UV (CH_2Cl_2) λ_{max}/nm (ε/mol·m^{-2}): 247 (12240). MS *m*/*z* (%, fragment) 212 (68, $M^+ - 17$), 187 (100, $M^+ - C_3H_6$), 91 (74, $C_7H_7^+$).

Preparative photolyses

The photolyses were carried out in an immersion-well apparatus with a Pyrex filter and a 400-W medium-pressure Hg arc lamp. Solutions of the compounds and the sensitizer in methylene chloride (420 ml) were purged with argon for 1 h and irradiated under a positive pressure of argon for the times shown. After completion of the irradiation the solvent and the sensitizer were removed under reduced pressure and the products were separated by flash chromatography.

Acetophenone-sensitized irradiation of oxime **2** This compound (246 mg, 0.88 mmol) and acetophenone (6 ml, 51 mmol) were irradiated for 30 min. After removal of the solvent and the sensitizer, flash chromatography using hexane/diethyl-ether (9/1) gave 169 mg (69%) of unreacted **2**. Further elution with methylene chloride gave 37 mg (15%) of isoxazole **3** as a white solid, and 50 mg of highly polar polymeric material; m.p. 205–206°C (ethanol). ^{1}H-NMR (300 MHz): δ 0.8, s, CH_3; 1.0, s, CH_3; 1.8, s, CH_3; 4.2, d, *J* 12.0 Hz, CH; 4.8, d, *J* 12.0 Hz, O-CH; 7.2–7.4, m, ArH. ^{13}C-NMR (62 MHz): δ 9.8, 18.5, 23.7 (CH_3), 50.9 (quaternary C), 51.4, 88.8 (CH), 126.6–142.2 (Ar), 164.8 (C=N). IR (KBr): 1600 cm^{-1}. MS *m*/*z* (%; fragment): 279 (3, M^+), 167 (100, $C_{13}H_{11}^+$) (Found: M^+, 279.1622. $C_{19}H_{21}NO$ requires M^+, 279.1618).

m-Methoxyacetophenone-sensitized irradiation of oxime **2** This compound (241 mg, 0.86 mmol) and *m*-methoxyacetophenone (2 g, 13 mmol) were irradiated in methylene chloride for 4 h. After removal of the solvent, flash chromatography using hexane/diethyl-ether (9/1), gave *m*-methoxyacetophenone (2 g) and 160 mg (66%) of the oxime **2**. Further elution with methylene chloride gave 23 mg (10%) of isoxazole **3**, and 40 mg of highly polar polymeric material.

Acetophenone-sensitized irradiation of oxime **5** This compound (350 mg, 1.03 mmol) and acetophenone (7 ml, 60 mmol) were irradiated for 10 min. After removal of the solvent and the sensitizer, flash chromatography using hexane/diethyl-ether (9/1) gave 148 mg (42%) of unreacted **5** and 134 mg (38%) of isoxazole **6**: m.p. 139–141°C (from ethanol). Anal. calcd. for $C_{24}H_{23}NO$ (341.45): C 84.45, H 6.74, N 4.10; found: C 84.7, H 6.8, N 3.9%. ^{1}H-NMR (300 MHz): δ 0.8, s, CH_3; 1.3, s, CH_3; 4.3; d, *J* 10.0 Hz, $CHPh_2$; 5.0, d, *J* 10.0 Hz, O-CH; 7.2–7.6, m, ArH. ^{13}C-NMR (62 MHz): δ 19.3, 24.3 (CH_3), 51.0 ($CHPh_2$), 51.4 (quaternary C), 90.6 (CH-O), 126.4–141.9 (Ar), 166.1 (C=N). IR (KBr): 1585 cm^{-1} (C=N). Further elution with dichloromethane gave 60 mg of a mixture of polymeric material.

Acetophenone-sensitized irradiation of oxime **7** This compound (400 mg, 1.75 mmol) and acetophenone (11.7 ml, 100 mmol) were irradiated for 25 min. After removal of the solvent and the sensitizer, flash chromatography using hexane/diethyl-ether (98/2) gave 185 mg (46%) of oxime **7** as a mixture of *Z*,*E* isomers. Further elution using hexane/diethyl-ether (9/1) gave 84 mg (21%) of isoxazole **8** as a white solid, and 90 mg of highly polar polymeric material; m.p. 90–91°C (from hexane). Anal. calcd. for $C_{15}H_{19}NO$ (229.33): C 78.61, H 8.29, N 6.10; found: C 78.3, H 8.5, N 6.1. ^{1}H-NMR (300 MHz): δ 1.5, s, CH_3; 1.7–2.4, m, 4 CH_2; 2.9, dd, J_{AY} 6.2 and J_{XY} 14.3 Hz, 1H, Y of AXY, CH_2; 3.2, dd, J_{AX} 7.7 and J_{XY} 14.3 Hz, 1H, X of AXY, CH_2; 4.2, dd, J_{AY} 6.2 and J_{AX} 7.7 Hz, 1H, A of AXY, CH; 7.0–7.3, m, ArH. ^{13}C-NMR (62 MHz) δ 15.9 (CH_3), 21.4, 23.3, 25.2, 34.3, 38.1 (CH_2), 50.1 (quaternary C), 90.8 (CH), 126.5–129.4, 137.7 (Ar), 166.1 (C=N). IR ($CHCl_3$) 1640 cm^{-1}. MS *m*/*z* (%; fragment): 212 (68, $M^+ - 17$), 187 (100, $M^+ - 42$), 91 (74, $C_7H_7^+$).

Acknowledgments

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