A novel photochemical synthesis of 5,6-dihydro-4*H*-1,2-oxazines by DCA-sensitized irradiation of γ,δ-unsaturated oximes

Diego Armesto,* Mark A. Austin, Owain J. Griffiths, William M. Horspool† and Mercedes Carpintero

Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, 28040 Madrid, Spain

On DCA-sensitized irradiation 6,6-diphenylhex-5-en-2-one oxime 5a, 5,5-diphenylpent-4-enal oxime 5b and 2,2-dimethyl-5-phenylpent-4-enal oxime 5c undergo a novel photochemical cyclization yielding 3-methyl-6-diphenylmethyl-5,6-dihydro-4*H*-1,2-oxazine 9a, 6-diphenylmethyl-5,6-dihydro-4*H*-1,2-oxazine 9b and 6-benzyl-4,4-dimethyl-5,6-dihydro-4*H*-1,2-oxazine 9c, respectively.

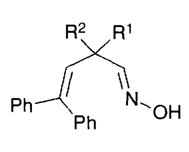
Previous studies carried out by us have shown that β,γ-unsaturated oximes undergo synthetically useful photochemical reactions on triplet sensitized irradiation.[1,2] Thus, β,γ-unsaturated aldoximes, such as **1**, undergo efficient azadi-π-methane rearrangement (ADPM) on acetophenone-sensitized irradiation yielding cyclopropane derivatives **2**.[1] However, under the same experimental conditions, β,γ-unsaturated ketoximes **3** afford the corresponding 4,5-dihydroisoxazoles **4**.[2] The results obtained with ketoximes **3** open the possibility of extending the reaction to other unsaturated oximes in which the two π-systems would be farther apart. Therefore, it was considered of interest to carry out a study on the photochemical reactivity of a series of γ,δ-unsaturated oximes aimed at observing cyclization to six-membered ring heterocycles.

The target molecules selected for this study were the γ,δ-unsaturated oximes **5**. The synthesis of **5a** was readily achieved from 4-bromo-1,1-diphenylbut-1-ene[3] which was converted into 5,5-diphenylpent-4-enonitrile by treatment with sodium cyanide. Reaction of this nitrile with methylmagnesium iodide yielded 6,6-diphenylhex-5-en-2-one which, by standard oximation, afforded ketoxime **5a** in 78% yield, as a mixture 1 : 2.7 of *E*/*Z* isomers. Oxime **5b** was synthesized by DIBAL-H reduction of 5,5-diphenylpent-4-enonitrile (see above) to yield 5,5-diphenylpent-4-enal, which was converted into **5b** by standard oximation procedures. The synthesis of oxime **5c** was carried out by reaction of commercially available cinnamyl bromide with *N*-butyl-*N*-isobutyl-2-methylprop-1-enamine[4] to yield, after hydrolysis, 2,2-dimethyl-5-phenylpent-4-enal. Oximation of this aldehyde affords **5c**. Compound **5d** was obtained by a modification of the procedure followed for **5c**. Thus, in this instance, treatment of commercially available 3-methylbut-2-enyl bromide with *N*-butyl-*N*-isobutyl-2-methylprop-1-enamine[4] yields, after hydrolysis, 2,2,5-trimethylhex-4-enal, which was converted into the oxime **5d** by standard procedures.

Direct and acetophenone-sensitized irradiations of **5a** afforded recovered starting material only. The lack of reactivity of oxime **5a** on sensitized irradiation was unexpected considering that the β,γ-unsaturated oximes **3** cyclize under similar conditions. The key step in the mechanism proposed by us to account for the photoreactivity of oximes **3** is the formation of the zwitterionic biradical **6**, resulting from intramolecular SET. Cyclization within **6** affords the cyclic intermediate **7**.[2] A similar process in oxime **5a** would generate the zwitterionic biradical **8**. This intermediate must undergo a conformational change in order to cyclize. The lack of reactivity of the γ,δ-unsaturated oxime **5a** could be due to efficient decay of **8** to the starting oxime by intramolecular back electron transfer, in a process that would compete favourably with the conformational change.

At this point an alternative way of generating oxonium ions that could undergo electrophilic attack to the alkene moiety of oxime **5a** and, therefore, to promote the cyclization, was envisaged by carrying out the reaction using 9,10-dicyanoanthracene (DCA) as an electron acceptor sensitizer.‡ Irradiation of **5a** under these conditions for 30 min gave a single photoproduct in 53% yield, in addition to 41% of recovered starting material, after chromatography on silica gel.§ This product was identified as the 1,2-oxazine **9a** based on spectroscopic and microanalytical evidence.¶

DCA-sensitized irradiation of **5b** for 20 min, under the same conditions used for **5a**, yielded the corresponding 1,2-oxazine **9b** (21%) and recovered starting material (57%), after chromatography on silica gel. This result shows that the reaction is not limited to ketoxime derivatives, such as **5a**, but can also be extended to γ,δ-unsaturated aldoximes.



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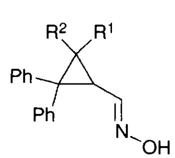

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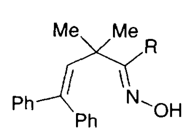
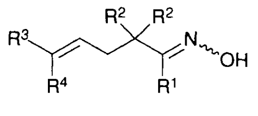
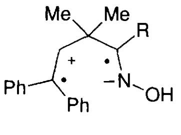
1a, **2a** R¹ = R² = Ph
1b, **2b** R¹ = Me; R² = vinyl



3a R = Me
b R = Ph



5a R^1 = Me; R^2 = H; R^3 = R^4 = Ph
5b R^1 = R^2 = H; R^3 = R^4 = Ph
5c R^1 = R^4 = H; R^2 = Me; R^3 = Ph
5d R^1 = H; R^2 = R^3 = R^4 = Me



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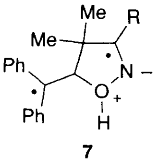

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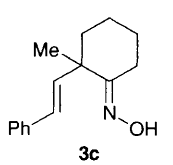
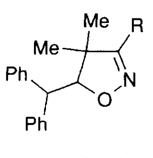
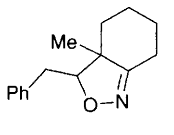


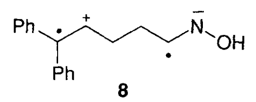
3c



4a R = Me
b R = Ph



4c



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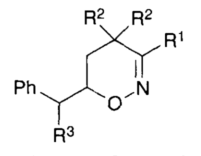


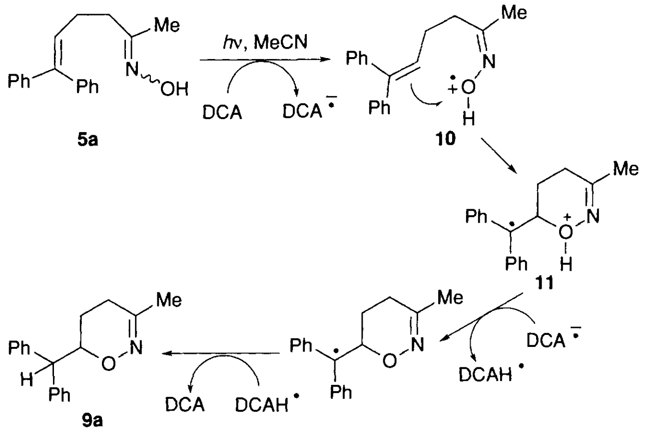
9a R^1 = Me; R^2 = H; R^3 = Ph
9b R^1 = R^2 = H; R^3 = Ph
9c R^1 = R^3 = H; R^2 = Me

DCA-sensitized irradiation of **5c** for 30 min brought about the formation of the 1,2-oxazine **9c** (52%) and recovered starting material (29%), after chromatography on silica gel. This result clearly demonstrates that dimethyl substitution at the α-position and monophenyl substitution at the δ-position of the γ,δ-unsaturated oxime are not detrimental to the success of the cyclization.

The mechanism shown in Scheme 1 for compound **5a** is proposed to account for these results. Excitation of DCA, followed by SET from the oxime group to the sensitizer, generates the radical cation intermediate **10**. Cyclization within this affords a new radical cation **11** which, by proton transfer to the radical anion of DCA, followed by hydrogen abstraction, yields the observed product.

Finally, DCA-sensitized irradiation of the all-alkyl substituted oxime **5d** for variable times up to three hours, under the same conditions used for **5a–c**, gave recovered starting material only. This result shows that in the absence of phenyl substitution at the δ-position of the γ,δ-unsaturated oxime, that stabilizes the reaction intermediates such as **11**, the reaction does not take place. However, the successful cyclization of the γ,δ-unsaturated oximes **5a**, **b** and **c** opens a new synthetic route to differently substituted 1,2-oxazines in reasonable yields by a simple path and from readily accessible starting materials.

Some 1,2-oxazines have been reported to have interesting pharmacological properties.[5] A number of methods have been reported in the literature for the preparation of 5,6-dihydro-4*H*-1,2-oxazines,[6–9] including their preparation from 1-chloro-4-nitrobutane,[6] the reaction of nitrosonium hexafluorophosphate with alkenes[7] and the photolysis of azidopyridine-1-oxides.[8] However, these reactions have limited scope due to the need for appropriately substituted starting materials. The most general method for the synthesis of these oxazines is the hetero-Diels–Alder reaction of transient nitroso alkenes with different dienophiles,[9] although, this reaction has the usual limitations regarding the nature of the substituents that can be present in both the heterodiene and the dienophile. None of these methods would allow access to the 1,2-oxazines obtained by this new photochemical route. Furthermore, this is the first report on the photoreactivity of γ,δ-unsaturated oximes. Until very recently the only photoreaction reported for α,β- and β,γ-unsaturated oximes was *E*/*Z* isomerization.[10] However, in recent times we have described the efficient ADPM rearrangement[1] and the cyclization to dihydroisoxazoles[2] in the triplet sensitized irradiation of β,γ-unsaturated oximes. The novel synthesis of 1,2-oxazines by DCA-sensitized irradiation of γ,δ-unsaturated oximes described herein, increases the synthetic utility of the photochemical reactivity of unsaturated oximes.



Scheme 1

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Footnotes

† Permanent address: Department of Chemistry, The University, Dundee, UK DD1 4HN.

‡ The irradiations were carried out in acetonitrile with DCA as sensitizer in an immersion well apparatus with a Pyrex filter and a 400 W medium pressure Hg arc lamp. The solutions were purged for 1 h with argon and irradiated under a positive pressure of argon.

§ The yields of photoproducts have not been optimized.

¶ All new solid products gave satisfactory microanalytical results. High resolution MS were obtained for oils. *Selected spectroscopic data* for 1,2-oxazine **9a**: mp 147–149 °C; ν_{max}(KBr)/cm^{-1} 1620; δ_H(300 MHz; CDCl$_3$) 1.29 (1 H, m), 1.78 (3 H, s), 2.01–2.34 (3 H, m), 4.71 (1 H, m), 5.25 (1 H, d, *J* = 2.3 Hz), 7.05–7.36 (10 H, m); δ_C(75 MHz, CDCl$_3$) 12.8, 19.8, 31.6, 49.2, 75.2, 126.8, 127.3, 128.1, 128.6, 128.7, 129.7, 139.4, 140.8, 146.3; IR 1620; *m*/*z* 265 (M$^+$, 96%), 191 (68), 167 (100), 115 (56) and 91 (51).

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