A new synthetic path to *peri*-naphthisoxazoles by oxidative intramolecular cyclization of some β,γ-unsaturated oximes

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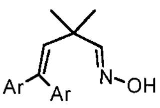
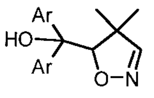
Some β,γ-unsaturated oximes undergo an unprecedented intramolecular cycloaddition to an aryl group to afford *peri*-naphthisoxazoles when they are irradiated in the presence of PhI(OAc)$_2$ and I$_2$ or HgO and I$_2$ in benzene or by thermal reaction with NaOCl and Et$_3$N in CH$_2$Cl$_2$.

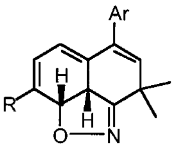
As part of a general study of the reactivity of β,γ-unsaturated oximes[1] we have examined their reactions in the presence of reagents known to yield free radicals. A survey of the literature on iminoxyl radicals suggests that such radicals have not been generated photochemically in solution previously. Therefore, the methodology for the generation of alkoxyl radicals was used as a model. Two methods, PhI(OAc)$_2$–I$_2$ in 1,2-dichloroethane[2] and HgO–I$_2$ in benzene[3] have been used extensively by several groups and these methods were utilised in this study. Thus we report the photochemical reactions of the β,γ-unsaturated oximes **1** with both these reagent systems.



1a Ar = Ph
b Ar = *p*-BrC$_6$H$_4$
c Ar = *p*-ClC$_6$H$_4$
d Ar = *p*-CH$_3$C$_6$H$_4$



2a Ar = Ph
b Ar = *p*-CH$_3$C$_6$H$_4$



3a Ar = Ph, R = H
b Ar = *p*-BrC$_6$H$_4$, R = Br
c Ar = *p*-ClC$_6$H$_4$, R = Cl
d Ar = *p*-CH$_3$C$_6$H$_4$, R = CH$_3$

The oximes **1** are readily prepared from the corresponding aldehydes. These are synthesised following the method originally reported by Zimmerman and co-workers[4] and more recently extended by Armesto *et al.*[1] Typically irradiation (λ > 280 nm) of the oxime **1a** in benzene in the presence of HgO–I$_2$ (3 equiv. of each) resulted in the formation of two products. The ^{13}C and ^{1}H NMR spectra of the more polar component showed it to be the known hydroxydihydroisoxazole **2a** (13%) previously reported by Armesto *et al.*[5]

The ^{1}H NMR spectrum of the less polar but major component of the mixture showed this to be considerably different from the hydroxydihydroisoxazole **2a**. The identification of this product was not easy by conventional means although the integral and the number of vinylic signals in the ^{1}H NMR spectrum suggested that addition to one of the aromatic rings had taken place. X-Ray diffraction† showed this product to be a *peri*-naphthisoxazole, 6-phenyl-8,8-dimethyl-10-aza-11-oxatricyclo[7.2.1^{1,9}.0^{5,12}]dodeca-2,4,6,9-tetraene **3a** (55%) (Fig. 1).

The irradiation of the oxime **1a** in 1,2-dichloroethane in the presence of PhI(OAc)$_2$–I$_2$ (1.2 equiv.), best carried out with a low wattage tungsten lamp, was more efficient and cleaner than in the presence of HgO–I$_2$, yielding only the *peri*-naphthisoxazole **3a** in 77% yield and recovered starting material. Other derivatives of the oxime behaved similarly and **1b** and **1c** were converted into the corresponding *peri*-naphthisoxazoles **3b** and **3c** in yields of 67 and 68%, respectively.

The formation of the *peri*-naphthisoxazole products from these irradiations suggests that they might arise from a conventional intramolecular 1,3-dipolar addition of a nitrile oxide to an arene. However, there appears to be no literature precedent for the addition of such a 1,3-dipole to a benzene moiety, although there are reports of additions to heteroarenes.[6] Neither are we aware of a precedent for the formation of a nitrile oxide *via* an iminoxyl radical. Thus it was important to verify whether or not the conventional route to nitrile oxides would also yield *peri*-naphthisoxazoles.

The method selected was reaction of the oxime **1b** (250 mg, 0.94 mmol) with NaOCl (0.21 ml of an 8% solution, 1.68 mmol) and Et$_3$N (10 mg, 0.1 mmol) in CH$_2$Cl$_2$ (10 ml).[7] The mixture was stirred at room temperature for 4 days. This indeed yields the same *peri*-naphthisoxazole **3b** obtained by the photochemical route. However, in this instance the yield is only 44% and the reaction time is much longer (4 days). Similar thermal reactivity was observed with the oxime **1d**, which gave the *peri*-naphthisoxazole **3d** in 47%. Interestingly the irradiation of oxime **1d** using either HgO–I$_2$ or PhI(OAc)$_2$–I$_2$ failed to yield a *peri*-naphthisoxazole and gave only the corresponding hydroxydihydroisoxazole **2b** in yields varying from 24–45%. Thus there appears to be a difference between the photochemical and the thermal cyclization.

It is most likely that both of the photochemical reactions involve the homolytic fission of OI bonds. There are many literature examples of hypoiodites formed from alcohols using both of the methods utilised here.[2,3] It is reasonable to assume that oximes will also yield hypoiodites and, therefore, these should also undergo OI bond fission with the formation of, in this instance, iminoxyl radicals such as **4**. The cycloaddition could involve this species with the formation of an intermediate such as **5**.

Final cycloaddition and loss of a hydrogen would yield the product. Alternatively the iminoxyl radical could lose a hydrogen to afford the nitrile oxide **6** that would then undergo cycloaddition. We have not resolved this dilemma since it is clear that the conventional path to nitrile oxides also affords the cycloadducts. The one thing that is obvious is that the paths appear to be subtly different. This is seen by the failure of **1d** to undergo the photochemical cyclization while the thermal reaction of **1d** affords **3d**. Currently experiments are in hand to try to resolve this difference.

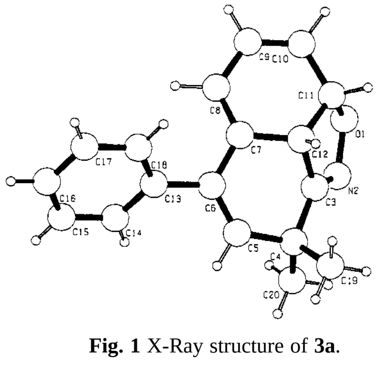
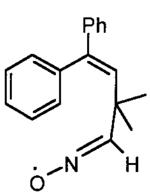


Fig. 1 X-Ray structure of **3a**.



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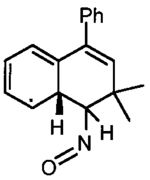

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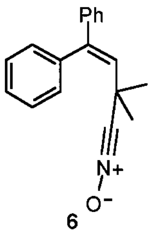

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Notes and references

† *Crystal data* for **3a**: $C_{18}H_{17}NO$, M = 263.33, orthorhombic, $P2_12_12_1$, a = 8.6306(7), b = 10.610(2), c = 15.119(4) Å, V = 384.4(5) Å^3, Z = 4, D_c = dimensions 0.18 × 0.14 × 0.14 mm was used. Reflections collected / unique 5768 / 2125 [R(int) = 0.0686] collected on the EPSRC FAST system at University of Wales, Cardiff. Structure solved by direct methods (SHELXS-97) (ref. 8) and refined anisotropically using full-matrix least-squares based on F^2 (SHELXL-97/2). Hydrogen atoms of the tricyclic portion located and refined, other hydrogen atoms placed on calculated positions, all isotropic. Largest difference peak and hole 0.225 and −0.159 e Å^{-3}, R_1 = 0.030, wR_2 = 0.068 for 1792 independent observed reflections [$|F_o| > 4\sigma_F$, $2\theta \leq 50°$]. The absolute chirality of **3a** could not be unambiguously determined. CCDC 182/1156. Crystal data are available in CIF format from the RSC web site, see: http://www.rsc.org/suppdata/cc/1999/425

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