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ON THE REACTION BETWEEN NITRILE OXIDES AND ARYLACETYLENES*

S. Morrocchi, A. Ricca and A. Zanarotti
Istituto di Chimica del Politecnico di Milano
G. Bianchi, R. Gandolfi and P. Grünanger
Istituto di Chimica Organica, Università di Pavia, Italy

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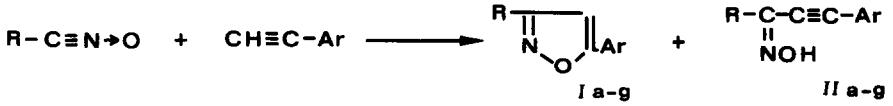
Nitrile oxides are long[1] known to react with arylacetylenes to yield 3,5-disubstituted isoxazoles (I). The reaction falls within the general pattern of 1,3-dipolar cycloadditions[2] and kinetic data[3,4] seem to support a one-step concerted mechanism. No intermediate or by product has to our knowledge ever been mentioned in the vast literature regarding this isoxazole synthesis[5].

We wish now to report that consistent yields of the open-chain acetylenic oximes (II) could be isolated, in addition to the 3,5-disubstituted isoxazoles (I), from the reaction mixture of both aliphatic and aromatic nitrile oxides with arylacetylenes:



a: R=Me; Ar=Ph
b: R=Et; Ar=Ph
c: R=Ar=Ph
d: R=Mesityl; Ar=Ph
e: R=Ph; Ar= α-Naphthyl
f: R=p-BrC_6H_4; Ar= α-Naphthyl
g: R=Ph; Ar=Mesityl

When equimolecular amounts of a nitrile oxide, either isolated as in lit.[6,7] (Method A) or prepared *in situ* from hydroxamyl chloride and triethylamine[8,9] (Method B) and an arylacetylene were treated in standard conditions (3 hr at room temperature, ether as solvent), a residual oily mixture was obtained after cautious concentration of the solution. Analysis of the mixture on TLC plates revealed the presence of two products, possibly accompanied by variable amounts of unreacted arylacetylene and of diarylfuroxan, the dimer of nitrile oxide. The isoxazoles I a-d and the α-acetylenic oximes II a-d could be separated by speedy working up on preparative TLC (Silicagel H, benzene as eluent), compounds

* The present paper summarizes experimental work independently carried out by two research groups.

I e-g[10] and II e-g by eluting through a Silicagel H column (Tab. I)*.

Oximes II a-d, even though characterized by spectroscopic and chemical tests, were too unstable to be purified and therefore yields could not be calculated.

The structures of the α-acetylenic oximes II a-g, hitherto unknown, could be deduced from the following evidence:

(i) the products readily cyclize to the corresponding 3,5-disubstituted isoxazoles (I) either by heating or simply by standing, especially in neutral or alkaline solution; the isomerization can be easily followed by UV spectroscopy;

(ii) reaction of IIe with acetic anhydride (in excess, 2 hr, room temperature) led to 86% yield of a monoacetylderivative, m.p. 118-119° (from $isoPr_2O$), which is now stable under the above conditions (IR: 2205 (C≡C), 1770 (C=O), 1198 (C-O) cm^{-1}; the acetylderivative of IIb is liquid and less stable; NMR: 1.3 δ 3H-triplet ($\underline{CH_3}CH_2$), 2.22 δ 3H-singlet (CH_3CO), 2.6δ 2H-quartet ($CH_3\underline{CH_2}$), 7.3-7.6 δ 5H-multiplet (Ph);

(iii) IR spectra show broad OH bands at 3100-3300 cm^{-1} and triple bond bands at 2190-2220 cm^{-1}; UV spectra significantly differ from those of the isoxazoles; NMR spectra ($CDCl_3$) show a low-field 1H-singlet, which exchanges with D_2O; mass spectra are identical with those of the corresponding 3,5-disubstituted isoxazoles;

TABLE 1

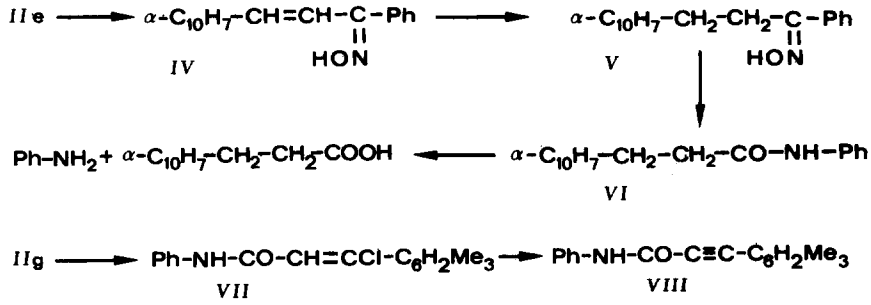
Product	Method	Yields % I	Yields % II	II : M.p.	IR(cm^{-1}) ν_{OH}	IR(cm^{-1}) $\nu_{C\equiv C}$	UV(mμ) λ_{max}^{EtOH}	UV(mμ) (log ε)
e	A/B	35/59	8/18	118°	3300	2188	230	(4.33)
							321	(4.29)
							339	(4.23)
f	A/B	27/23	15/13	127-131°	3300	2203	228	(4.62)
							286	(4.17)
							323	(4.19)
							342	(4.16)
g	B	38.5	24	127-131°	3100	2193	sh230	(4.27)
							254	(4.28)
							295	(4.16)
							312	(4.13)

(iiii) treatment of oximes IIa and IIb with 2,4-dinitrophenylhydrazine in sulfuric acid solution yielded the corresponding 2,4-dinitrophenylhydrazones (R=Me, Ar=Ph: m.p. 195-196°; R=Et, Ar=Ph: m.p. 167-168°), whose open-chain structures are deduced from their NMR spectra, which show a 11.90 δ 1H-singlet exchangeable with D_2O, and from the 2200 cm^{-1} band in their IR-spectra. Under the

* Satisfactory analyses were obtained for all compounds reported in this paper hitherto unknown.

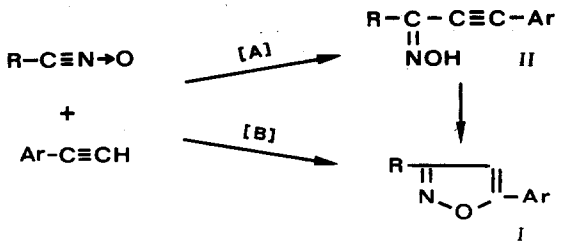
same conditions the corresponding isoxazoles were perfectly stable.

In order to establish the configuration of the oxime, IIe was treated with PCl_5 in ether, but unsatisfactory results were obtained owing to difficulties in purifying the products. Better yields could be achieved through a two-step catalytic hydrogenation: passing through the α,β -unsaturated oxime IV, m.p. 140-144°, the saturated oxime V, m.p. 128-129°, was obtained and its anti-phenyl configuration was demonstrated through Beckmann rearrangement. Treatment of V with PCl_5 in ether furnished a 73% yield of a product, m.p. 142-143°, whose structure VI was assured by acidic hydrolysis to 3-(α.naphthyl)propionic acid[12] and aniline. Treatment of IIg with PCl_5 in ether gave a 46% yield of VII, m.p. 157-158°. Boiling for 3 hr with 10% NaOH dehydrohalogenated VII to VIII, m.p. 230°, and heating for further 15 hr completely hydrolysed the amide to mesitylpropiolic acid[13] and aniline. Since the starting acetylenic oximes (II) appear to be



homogeneous on thin-layer chromatoplates and by NMR spectroscopy, it is reasonable to assign to them an anti-R configuration, in accordance with their high tendency to cyclization.

These results demonstrate that the reaction between nitrile oxides and aryl acetylenes does not proceed exclusively through a 1,3-dipolar concerted cycloaddition, as so far generally assumed[2-4]. Preliminary studies on the behaviour



of acetylenic oximes in acidic media showed that oximes II e-g are stable in ether solution at r.t. for more than 24 hr in the presence of traces of anhydrous HCl. If the oximes were in fact the actual intermediates in the formation of the isoxazoles (pathway A), then overwhelming or exclusive isolation of the oximes should occur under acidic conditions. Such was not the case. Repetition of the reaction between nitrile oxides and arylacetylenes in the presence of HCl gave yield ratios oxime/isoxazole quite similar as under neutral conditions. Therefore the 1,3-addition to oximes should be simultaneous and concurrent to the cyclo addition to isoxazoles (pathway B).

Cyclization of the oximes II is promoted by bases and steric factors are not without influence. Whereas under comparable conditions (24 hr, r.t., ether as solvent, 2-3% NEt_3) IIg did not cyclize appreciably, 30-40% of IIe or IIf cyclized to isoxazoles. Cyclization was faster in more polar solvents (e.g. ethanol) and was immediate with stronger bases (e.g. KOH).

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10. If: hitherto unknown, m.p. 122,5-123°; Ig, m.p. 66-67°,(a not unambiguous phenylmesitylisoxazole, m.p. 76°, has been obtained (ref.11) by oximation of the β-diketone); our product was further prepared in 35% yield by N-bromo succinimide oxidation of 3-phenyl-5-mesityl-2-isoxazoline, m.p. 106-107°(UV: λ_{max}^{EtOH} 267 mμ ; log ε 4.20), which was in turn prepared with 60% yield by cycloaddition of benzonitrile oxide to vinylmesitylene. NMR spectrum (CCl_4) of Ig: singlets at 2.18 (6H) and 2.28 δ (3H) (methyl groups), at 6.41 δ (1H, isoxazole 4-proton), 6.85 (2H, mesityl aromatic protons) and multiplets at 7.2-7.4 (3H) and 7.7-7.9 (2H) (phenyl aromatic protons).
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