Formation of 2-Isoxazoline Derivatives and 3,5-Diarylisoxazoles from 2,4,6-Triarylpyrylium Salts. Norrish Type II Photoeliminations

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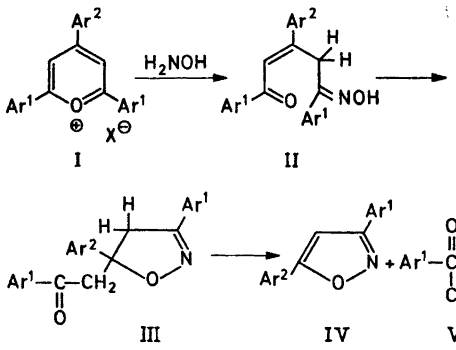
The recent paper by Balaban [1] concerning the reaction of 2,4,6-triphenylpyrylium perchlorate with hydroxylamine prompts us to report similar independent findings from our laboratory.

Balaban found that 2,4,6-triphenylpyrylium perchlorate (Ia, $X=ClO_4$), when treated with hydroxylamine, gave the monoxime (IIa) of the pseudobase, which isomerized easily to the 2-isoxazoline IIIa. This isoxazoline was converted to the 3,5-diarylisoxazole IVa and acetophenone (Va) by treatment with 70 % perchloric acid.

We have observed the same reaction sequence for a series of 2,4,6-triarylpyrylium salts. Thus, reaction of the salts Ia-e ($X=BF_4$) with hydroxylamine in ethanol led to the formation of the corresponding 2-isoxazolines IIIa-e in good yield (see Table 1).*



a) $Ar^1 = Ar^2 = C_6H_5$

b) $Ar^1 = p\text{-}BrC_6H_4$; $Ar^2 = C_6H_5$

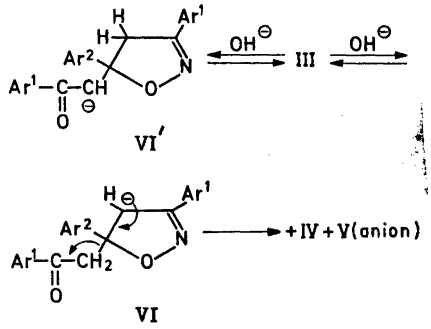
c) $Ar^1 = C_6H_5$; $Ar^2 = p\text{-}ClC_6H_4$

d) $Ar^1 = C_6H_5$; $Ar^2 = m\text{-}NO_2C_6H_4$

e) $Ar^1 = p\text{-}CH_3C_6H_4$; $Ar^2 = p\text{-}CH_3OC_6H_4$

The structures of the isoxazolines were assigned on the basis of elemental analyses and infrared, ultraviolet and NMR spectra (see Tables 1 and 2). The observed spectral properties are in excellent agreement with those reported by Balaban.[1]

In the previous work [1] conversion of the isoxazoline IIIa to the 3,5-diarylisoxazole IVa and acetophenone (Va) was brought about under strongly acidic conditions. We have found that this same transformation can be carried out under basic conditions or by photolysis. For example, refluxing the isoxazoline IIIa in alcoholic sodium hydroxide led to isolation of the isoxazole IVa in high yield (for other examples see the experimental section). The presence of acetophenone (Va) in the reaction mixture was detected by NMR spectroscopy (see experimental). A reasonable mechanism for this transformation can be presented.



In the presence of base, the isoxazolines III are undoubtedly in equilibrium with two possible anions, VI and VI′. The equilibrium concentration of VI is expected to be smaller than that of VI′, but elimination of the phenacyl substituent at C_5 as the enolate of acetophenone, with concomitant formation of the stable isoxazole nucleus, is the driving force for the indicated sequence. The possibility that elimination of the phenacyl substituent takes place simultaneously with the removal of the C_4 proton cannot, however, be eliminated.

As additional support for the isoxazoline structure III, it was predicted that the

*In some cases the monoxime was detected in the crude reaction mixture before recrystallization.

Table 1. Yields and physical properties of 2-isoxazolines IIIa-e.

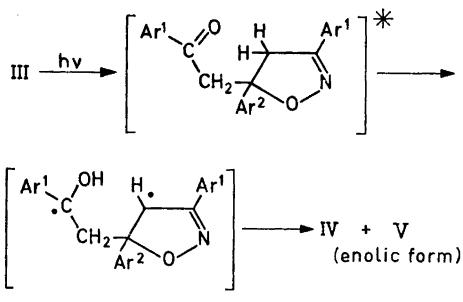
Compound	M.p.[a]	% Yield	Formula	Analysis							
				% C		% H		% N		% Halogen	
				Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
IIIa	123–124°[b] (A)	76	$C_{23}H_{19}NO_2$	80.91	80.95	5.61	5.90	4.10	4.02		
IIIb	161–162°[c] (A)	48[d]	$C_{23}H_{17}NO_2Br_2$	55.33	55.30	3.43	3.46	2.81	2.71	32.02 (Br)	32.12
IIIc	102–104° (B)	40[d]	$C_{23}H_{18}NO_2Cl$	73.50	73.55	4.83	4.89	3.73	3.70	9.43 (Cl)	9.37
IIId	124–125° (B)	35[d]	$C_{23}H_{18}N_2O_4$	71.49	71.49	4.69	4.84	7.25	7.30		
IIIe	124–128° (B)	70	$C_{26}H_{25}NO_3$	78.17	78.20	6.31	6.44	3.51	3.50		

[a]Recrystallization solvent given in parentheses; A, benzene-hexane; B, ethanol. [b]Ref. 1 gives m.p. 124°. [c]This compound exhibits a double melting point with the lower m.p. 131–132° probably due to the isomeric form IIb. [d]No attempt was made to maximize this yield.

Table 2. Spectral properties of 2-isoxazolines IIIa-e.

Compound	IR[a]	UV[b]		NMR[c]					
	C=O	λ_{max}	log ε	H_A[d]	H_B[d]	J_{AB}	CO-CH_2[e]	Aromatic[e]	Other
IIIa	1690	254[f]	4.36	6.24	5.84	17.0	6.23(2H)	1.9–2.8(15H)	
IIIb	1670	263	4.63	6.35	5.92	17.0	6.35(2H)	2.0–2.9(13H)	
IIIc	1680	253	4.45	6.28	5.93	17.0	6.27(2H)	1.9–2.9(14H)	
IIId	1685	253	4.53	6.18	5.90	17.0	6.17(2H)	1.4–2.9(14H)	
IIIe	1680	260	4.56	6.30	5.95	16.5	6.30(2H)	2.0–3.3(12H)	Ar-CH_3 7.63 Ar-OCH_3, 6.23

[a]Spectra recorded in KBr. [b]Spectra recorded in 96 % ethanol. [c]60 Mc/s, $CDCl_3$ solution, Me_4Si internal reference; chemical shifts in τ values and coupling constants (J) in cps. [d]Calculated position of the A or B part of the AB quartet; H_A+H_B equivalent to two protons. [e]Relative intensity given in parentheses. [f]Spectra recorded in $CHCl_3$.



compounds should undergo the well-known Norrish "Type II" photoelimination reaction of ketones possessing at least one γ-hydrogen atom.[2] In agreement with this prediction, photolysis of the 2-isoxazolines IIIa-c and e (ether solution, wavelength> 3000 Å) resulted in formation of the 3,5-diarylisoxazoles IVa-c, and e in good yield. The nitro-substituted 2-isoxazoline IIId, although photoactive, is not converted to the corresponding isoxazole IVd. We assume that the mechanism of the photoelimination involves abstraction of one of

the hydrogens at C_4 by an excited state of the ketone,* *via* a six-membered ring transition state, followed by cleavage to the enol form of the acetophenone derivative V and the 3,5-diarylisoxazole IV.

Experimental. Pyrylium salts. These were prepared according to the method of Lombard and Stephan.[3]

Reaction of pyrylium salts with hydroxylamine. This was performed (Table 1) analogously to the following procedure. 2,4,6-Triphenylpyrylium fluoroborate (200 mg) was suspended in ethanol (10 ml). To the stirred suspension was added an aqueous solution of hydroxylamine hydrochloride (5 molar equivalents) and excess sodium hydroxide. The suspension was stirred for 18 h at room temperature. The 2-isoxazoline IIIa (130 mg, 76 %, m.p. 123–124°) was removed by filtration. This material was homogeneous by thin layer chromatography (TLC) and was recrystallized from benzene-hexane for analysis.

Preparation of 3,5-diarylisoxazoles (IV). a) *Base-catalyzed method.* A sample of 2-isoxazoline IIIa (392 mg) was refluxed for 24 h in ethanol (200 ml) and aqueous 2 N sodium hydroxide (20 ml). The ethanol was removed on a rotary evaporator and 3,5-diphenylisoxazole (223 mg, 86 %, homogeneous by TLC) was removed by filtration. Recrystallization from hexane gave colourless needles, m.p. 142.5–143° (lit.[4] m.p. 140–141°), identical (m.p., mixture m.p., infrared spectrum) with an authentic sample of 3,5-diphenylisoxazole prepared from dibenzoylmethane and hydroxylamine.[4] The filtrate above was extracted with $CHCl_3$, and the organic phase was dried over Na_2SO_4. The residue after evaporation of the solvent exhibited an NMR spectrum that indicated the presence of acetophenone (sharp singlet at 7.42 τ in $CDCl_3$).

By the above method, 3-(*p*-bromophenyl)-5-phenylisoxazole (IVb) was prepared in 67 % yield (see physical properties below).

b) *Photochemical method.* A sample of 2-isoxazoline IIIb (200 mg) was dissolved in 250 ml of ether in a Pyrex flask and photolyzed in a Rayonet reactor, type RPR-208, using the RUL-3500 lamps. After 38 h of irradiation the solvent was evaporated and the residue was separated by preparative layer chromatography on silica gel. In addition to an unidentified crystalline substance (21 mg) and recovered starting material (93 mg), 3-(*p*-bromophenyl)-5-phenylisoxazole (IVb, 53 mg) was isolated (83 % yield based on reacted starting material). This sample had m.p. 179–180° (lit.[5] m.p. 178–179°) and was identical (m.p., mixture m.p., infrared spectrum, TLC) with the sample prepared by base-catalyzed elimination from IIIb (see above).

By the above procedure, the following isoxazoles were prepared (yields are based upon reacted starting material):

IVa: 48 %, m.p. 141–142° (lit.[4] m.p. 140–141°).
IVc: 55 %, m.p. 177–178° (lit.[6] m.p. 178–179°).
IVe: 48 %, m.p. 128–129° (lit.[8] m.p. 130°).

Acknowledgements. We thank the *Carlsberg Foundation* for a grant to purchase the Rayonet reactor. One of us (P.L.K.) is indebted to the *North Atlantic Treaty Organization* for a N.A.T.O. Postdoctoral Fellowship.

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Received September 10, 1968.

* For a discussion of the multiplicity (*i.e.* singlet *vs.* triplet) of the excited state responsible for the hydrogen abstraction process see Ref. 2c, pp. 384–385.