Reactions of β-Azidostyrenes with Halogenoacetic Acid. A Novel Formation of Oxazoles

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The reaction of β-azidostyrene with trifluoro-, trichloro-, dichloro-, or monochloro-acetic acid gave 2-halogenomethyl-5-phenyloxazole *via* attack of halogenoacetate anion on a benzylic carbocation or a conjugate acid of the azide.

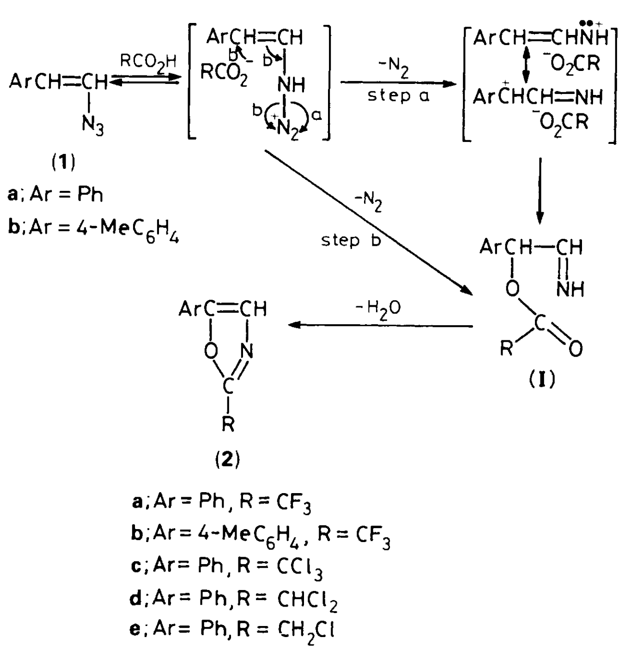
The thermal reaction of β-azidostyrene is known to give phenylacetonitrile together with indole *via* a vinylnitrene.[1] We have reported that phenylnitrenium ion generated from phenyl azide in the presence of trifluoroacetic acid (TFA) gives rise to an intermolecular aromatic *N*-substitution.[2] Considering this result, we expected that a vinylnitrenium ion formed from β-azidostyrene in the presence of TFA would provide indole in a high yield by an intramolecular aromatic *N*-substitution. However, the reaction produced oxazoles rather than indole. Several methods have been proposed for the formation of oxazole derivatives.[3] The present reaction provides a novel synthetic method, and is also of interest from a mechanistic point of view.

The reaction of β-azidostyrene (**1a**) with halogenoacetic acid gave 2-halogenomethyl-5-phenyloxazoles (**2a** and **2c**—**e**) (Scheme 1 and Table 1). The reaction of β-azido-4-methylstyrene (**1b**) with TFA also afforded the corresponding oxazole (**2b**). The azides were completely decomposed under the conditions shown in Table 1, and the oxazoles were isolated by preparative g.l.c. after work-up with aqueous $NaHCO_3$. The yields of (**2**) were 40—50%. Other products were tars.

The structures of the oxazoles were confirmed by i.r., ^1H and ^{13}C n.m.r., and mass spectroscopy, and elemental analysis.† The alternative 4-phenyl-5-halogenomethylisoxazole structures were ruled out by the following spectral data. The ^{13}C n.m.r. peak at δ *ca.* 122 can be attributed to C-4‡ of the oxazole ring, not C-3 (usually *ca.* δ 149)[4] in the isoxazole ring. A ^1H n.m.r. peak (1H, s) at δ 7.5 was clearly observed for (**2b**) (the corresponding peak for the other oxazoles overlaps with the phenyl multiplet peaks), at a position in good agreement with 4-H[3] of the oxazole ring§ [it is not consistent with that (*ca.* δ 7.2[5])¶ for 3-H of the isoxazole ring]. Further, the mass spectral peak at *m/z* 105 ($PhCO^+$) is best rationalised as resulting from the oxazoles (**2**),[6] not isoxazoles.

Relative rates for the halogenoacetic acids were determined by using an equimolar mixture of two acids, where the molar ratio of acid to azide (**1a**) was more than 10. The relative rate obtained increased with an increase in acidic strength, except trichloroacetic acid; $CF_3CO_2H : CCl_3CO_2H : HCCl_2CO_2H : ClCH_2CO_2H = 114 : 1.0 : 68 : 11$. These results suggest that the oxazoles (**2**) are formed *via* a conjugate acid of the azide.|| The unusual low reactivity of trichloroacetic acid cannot be unambiguously explained, but the bulky trichloromethyl group presumably hinders an attack of trichloroacetate anion on the benzylic carbocation or on the conjugate acid of the azide (see step a or b in Scheme 1).

The reaction order of TFA for the decomposition of azide (**1a**) was obtained as follows. Pseudo first-order rate constants were measured at three different concentrations (2.3, 3.8, and 5.3 M) of TFA at 2.0 °C, and plots of the rate constants against



Scheme 1

Table 1. Reactions of β-azidostyrenes ($ArCH{=}CHN_3$) with halogenoacetic acid (RCO_2H).

Ar of $ArCH{=}CHN_3$	R of RCO_2H	Azide/ mmol	Acid/ mmol	CH_2Cl_2 ml	*T*/°C	*t*/h	Yield (**2**)/%
Ph	CF_3	4	35	5	20	0.5	48
4-MeC_6H_4	CF_3	6	30	10	20	3	45
Ph	CCl_3	7	30	7	20	3	40
Ph	$CHCl_2$	7	38	7	20	3	51
Ph	CH_2Cl	8	35	10	80	3	42

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† *Spectral data* for (**2a**) (m.p. 2—4 °C): ν_{max} (neat) 3130 and 3060 (C–H), 1590 (C=C of Ph), 1565 (C=C or C=N), 1490 (Ph), 1455 (C=N or C=C), 1380 (C–F), 1210 and 1110 (C–O), 1150 (CF_3), and 770 and 695 cm^{-1} (monosubstituted Ph); δ_H (CCl_4–$CDCl_3$) 7.0—8.2 (6H, m, Ph and oxazole protons); δ_C (CCl_4–$CDCl_3$) 122.1, 126.2, and 139.6 (C-4, -5, and -2 of oxazole) and 124.7, 128.9, and 129.6 (C-2, -3, and -4 of Ph); *m/z* 213 (M^+), 121, 110, 105, 77, 69, and 51. Satisfactory elemental analyses (C, H, N) were obtained.

‡ Comparing ^{13}C n.m.r. spectra of (**2b**) with those of other oxazoles, the peak at *ca.* δ 122 can be attributed to C-4 of the oxazole ring.

§ We can estimate the chemical shift of (**2**) as δ 7.5 on the basis of that of 5-alkyloxazole, reported by Jacobi *et al.* in ref. 3.

¶ The chemical shift is predicted to be δ *ca.* 7.2, from consideration of the N=CH proton in a five-membered imine in ref. 5.

|| The structure of the conjugate acid of azide may be written with the more customary protonation of the inner nitrogen instead of the terminal nitrogen of the azide.

the concentration of TFA were linear. This means that the decomposition of azide is first-order in TFA. Thus, the mechanism for the reaction is as shown in Scheme 1; only one molecule of TFA is involved in the denitrogenation of the azide, and a benzylic carbocation (having a small contribution to the vinylnitrenium ion structure) is formed by spontaneous denitrogenation from the conjugate acid (step a in Scheme 1). The carbocation interacts with halogenoacetate anion, forming an intermediate (**I**); ring-closure then gives (**2**) after deprotonation and dehydration. There is an alternative route by which the haloacetate anion attacks the conjugate acid of the azide to form (**I**) (see step b in Scheme 1).

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