Intramolecular 1,3-Cycloadditions of Aryl Azides with Alkynyl Substituents: a Kinetic Investigation

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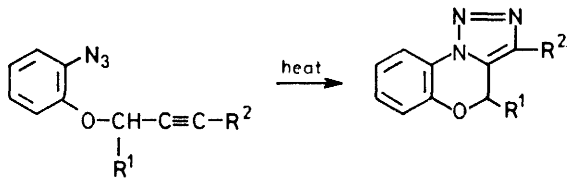
The formation of 4*H*-*v*-triazolo[5,1-*c*][1,4]benzoxazines (IIa—c) by thermal reaction of 2-(2-alkynyloxy)phenyl azides (Ia—c) has been studied kinetically in toluene and 3-methylbutan-1-ol at different temperatures. The solvent effect on the rate is small; activation enthalpies are of the order of 22—23 kcal mol^{-1}; activation entropies range from −8 to −14 cal mol^{-1} K^{-1}.

AMONG the well known 1,3-dipolar cycloadditions, the intramolecular reactions are the object of growing interest as they represent a general method for constructing multi-ring heterocyclic systems. The experimental evidence in this field[1,2] shows that intramolecular cycloadditions of 1,3-dipoles may vary from the usual intermolecular patterns; for instance, they can occur smoothly even though involving poor dipolarophiles such as nitrile groups or unactivated carbon–carbon multiple bonds. However, while several investigations have been devoted to the stereo- and regiochemical aspects of intramolecular 1,3-dipolar cycloadditions,[1,2] kinetic analyses are still lacking for this type of reaction. In this context, we now report a kinetic study of the formation of 4*H*-*v*-triazolo[5,1-*c*]-[1,4]benzoxazines (IIa—c) by thermal reaction of 2-(2-alkynyloxy)phenyl azides (Ia—c).



(I) (II)

a; $R^1 = R^2 = H$
b; $R^1 = H, R^2 = Ph$
c; $R^1 = Me, R^2 = Ph$

RESULTS AND DISCUSSION

The reactions under study were carried out in two different solvents, toluene and 3-methylbutan-1-ol, with a 0.02M concentration of the substrate. It was found that, in all the experimental conditions, evaporation of the solvent gave the cycloaddition product (II) in >90% yield.

Kinetic measurements were performed by following the decrease of the strong i.r. absorption at *ca.* 2 100 cm^{-1} due to the azido group. Linear first-order plots were obtained in all cases, at least up to the investigated conversion (75—85%). Rate constants as a function of solvent and temperature are collected in Table 1; each value given is the average of three independent measurements, probable errors being of the order of 1%. Correlation of the rate constants by standard methods gave the activation parameters reported in Table 2.

These results merit some comment. It is common to indicate 1,3-dipolar cycloadditions as generally characterized by moderate activation enthalpies and large negative activation entropies.[3-5] This is not true for the reactions here studied, which in fact present, with respect to the analogous intermolecular reactions, a higher enthalpy barrier and a much less negative entropy of activation.† Although these changes are not surprising on going from bimolecular to monomolecular processes,

TABLE 1

Rate constants for the reaction (I) ⟶ (II)

Azide	Solvent	T/°C	$10^5k/s^{-1}$
(Ia)	Toluene	30.0	0.630
		40.0	2.11
		50.0	6.30
	3-Methylbutan-1-ol	30.0	0.514
		40.0	1.65
		50.0	5.69
(Ib)	Toluene	55.0	0.903
		63.1	2.06
		69.9	4.25
		77.0	8.17
	3-Methylbutan-1-ol	55.1	0.901
		65.0	2.47
		76.9	8.42
(Ic)	Toluene	50.1	1.39
		60.0	4.03
		75.1	18.9
	3-Methylbutan-1-ol	50.1	1.26
		60.0	4.04
		70.0	11.1

TABLE 2

Relative rates and activation parameters for the reaction (I) ⟶ (II)

Azide	Solvent	Relative rate (at 50 °C)[a]	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal mol^{-1} K^{-1}
(Ia)	Toluene	12.6	21.8 ±0.2	−10.5 ±0.5
	3-Methylbutan-1-ol	11.0	22.7 ±0.5	−7.8 ±1.8
(Ib)	Toluene	1.03	22.3 ±0.2	−13.8 ±0.6
	3-Methylbutan-1-ol	1	22.8 ±0.3	−12.5 ±1.0
(Ic)	Toluene	2.70	22.7 ±0.2	−10.7 ±0.4
	3-Methylbutan-1-ol	2.52	23.3 ±0.5	−8.9 ±1.4

[a] Ratio of rate constants evaluated by the Arrhenius plots.

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† The literature data[3-6] for intermolecular cycloadditions of aryl azides to multiple bonds show $\Delta H^{\ddagger}$ values in the range 10—17 kcal mol^{-1} and $\Delta S^{\ddagger}$ values between −26 and −36 cal mol^{-1} K^{-1}.

the present results prove that intramolecular 1,3-dipolar cycloadditions essentially profit from steric constraints favourable to bonding contact between the reacting functions. The role of such steric factors appears to be predominant since compound (Ia) reacts much faster than (Ib and c) despite the lack of conjugation of the acetylenic bond. Actually, in intermolecular cycloadditions, conjugated acetylenes have been amply shown to be better dipolarophiles than unconjugated ones.[3,7] The greater reactivity of (Ic) by comparison with (Ib), which rests on entropy grounds, could be the consequence of some steric congestion forcing the approach of the dipolarophile to the π orbital region of the azido group.

In view of the difference in polarity between toluene and 3-methylbutan-1-ol,* the observed solvent effects upon the rate are very small. This finding is in line with the general features of 1,3-dipolar cycloadditions which occur through a concerted pathway without substantial charge separation. However, it is noteworthy that the solvent change from toluene to 3-methylbutan-1-ol causes some increase of the activation enthalpy, which happens to be compensated over the temperature range of the experiments by a more favourable activation entropy. This may indicate slightly greater solvation of the ground with respect to the transition state.

EXPERIMENTAL

N.m.r. spectra were recorded on a Varian A-60A instrument with tetramethylsilane as an internal standard. I.r. spectra were measured on a Perkin-Elmer 377 spectrophotometer equipped with KBr cells (path 0.5 mm). For kinetic runs, commercial solvents were purified by usual methods.[9]

3-(2-Nitrophenoxy)-1-phenylbut-1-yne.—Treatment of 2-nitrophenol (7.2 g) with 3-bromo-1-phenylbut-1-yne [10] (9.7 g) according to a standard procedure [11] gave the title *ether* (10.9 g), m.p. 68—69° (from cyclohexane) (Found: C, 72.1; H, 4.8; N, 5.1. $C_{16}H_{13}NO_3$ requires C, 71.9; H, 4.9; N, 5.2%); $\delta(CDCl_3)$ 1.77 (3 H, d, *J* 7 Hz, Me), 5.12 (1 H, q, *J* 7 Hz, CH), and 6.8—7.8 (9 H, m, ArH).

3-(2-Aminophenoxy)-1-phenylbut-1-yne.—A solution of tin(II) chloride dihydrate (5.1 g) in concentrated hydrochloric acid (30 ml) was slowly added to a solution of 3-(2-nitrophenoxy)-1-phenylbut-1-yne (6.0 g) in acetic acid (100 ml) with cooling at 13—15°. Zinc powder (14.7 g) was then added in portions under stirring and cooling. After 0.5 h, solid material was filtered off and the solution was adjusted to pH 5 with ammonia and partly evaporated under reduced pressure. The residue was made alkaline with aqueous ammonia and extracted with chloroform, and the organic layer was dried (Na_2SO_4) and evaporated. The oily residue was dissolved in anhydrous ether and treated with ethereal hydrogen chloride to afford the title *amine hydrochloride* (3.8 g), m.p. 184—186° (from ethanol–di-isopropyl ether) (Found: C, 70.0; H, 6.1; N, 4.9. $C_{16}H_{16}ClNO$ requires C, 70.2; H, 5.9; N, 5.1%); $\delta(CD_3CO_2D)$ 1.80 (3 H, d, *J* 6.5 Hz, Me), 5.31 (1 H, q, *J* 6.5 Hz, CH), and 7.0—7.7 (9 H, m, ArH).

Preparation of Azides (Ia—c).—Sodium nitrite (7.3 mmol) was added portionwise to a suspension of 3-(2-aminophenoxy)-1-phenylbut-1-yne hydrochloride (3.65 mmol) in 1N aqueous hydrochloric acid (22 ml) under stirring and ice-cooling. A little undissolved material was filtered off, cold ether was added (150 ml), and sodium azide (18.7 mmol) was then added in portions with vigorous stirring and cooling at 5°. After 0.5 h, the ethereal layer was separated, washed with aqueous sodium hydrogencarbonate, and dried (Na_2SO_4). Evaporation of the solvent at reduced pressure gave *3-(2-azidophenoxy)-1-phenylbut-1-yne* (Ic) as a viscous oil (3.2 mmol); $\nu_{max.}$ (toluene) 2 110 cm^{-1}; $\delta(CDCl_3)$ 1.75 (3 H, d, *J* 7 Hz, Me), 4.95 (1 H, q, *J* 7 Hz, CH), and 6.7—7.3 (9 H, m, ArH). No impurities were detected by t.l.c. and n.m.r. analyses. Following the same procedure, azides (Ia and b) [12] were obtained from the corresponding anilines in a practically pure state.

Thermal Reaction of Azide (Ia).—A solution of (Ia) (0.50 g) in toluene (150 ml) was heated at 100° for 0.5 h. After removal of the solvent at reduced pressure, the residue (0.48 g) was practically pure (IIa) [12] (n.m.r.). The same result was obtained by using 3-methylbutan-1-ol as solvent.

Thermal Reaction of Azide (Ib).—A solution of (Ib) (0.50 g) in toluene (100 ml) was heated at 100° for 1.5 h. Evaporation of the solvent at reduced pressure gave practically pure (IIb) [12] (0.47 g). When the reaction was carried out in 3-methylbutan-1-ol, the product was (IIb) in 90—95% purity (n.m.r.).

Thermal Reaction of Azide (Ic).—(A) A solution of (Ic) (0.80 g) in toluene (150 ml) was heated at 100° for 1.5 h. Evaporation of the solvent and recrystallization from n-hexane–benzene gave *4-methyl-3-phenyl-4*H*-v-triazolo*[5,1-c][1,4]*benzoxazine* (IIc) (0.64 g), m.p. 102° (Found: C, 72.9; H, 5.1; N, 16.0. $C_{16}H_{13}N_3O$ requires C, 73.0; H, 5.0; N, 16.0%); $\delta(CDCl_3)$ 1.60 (3 H, d, *J* 7 Hz, Me), 5.90 (1 H, q, *J* 7 Hz, CH), and 7.0—8.1 (9 H, m, ArH).

(B) A solution of (Ic) (0.50 g) in 3-methylbutan-1-ol (100 ml) was heated at 100° for 1.5 h. Evaporation of the solvent at reduced pressure gave practically pure (IIc) (0.48 g).

Kinetic Procedure.—Runs were carried out in sealed tubes each containing *ca.* 0.5 ml of 0.02M solution of the substrate, in a thermostat accurate to ±0.05 °C. After quenching by cooling, the 1 950—2 300 cm^{-1} region of the i.r. spectrum was recorded and the absorbance (*D*) at 2 110 cm^{-1} was measured. Preliminary measurements in the concentration range 0.003—0.020M had given linear plots of log *D* against concentration in both the solvents used. Rate constants (k) were evaluated by the equation $\ln D = -kt +$ constant by the least-squares procedure, all correlation coefficients being better than 0.998 5. Activation enthalpies ($\Delta H^{\ddagger}$) and entropies ($\Delta S^{\ddagger}$) were obtained from the rate constants by a standard computer program.

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* Dielectric constants are 2.4 and 15.2 and Dimroth's E_T values are 33.9 and 47.0 for toluene and 3-methylbutan-1-ol respectively.[8]

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