Stereochemical and Mechanistic Aspects of the Base-promoted Cyclisation of *o*-Vinylphenylhydrazonyl Chlorides under Phase-transfer Conditions

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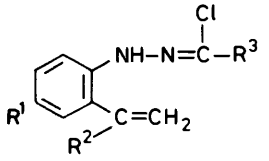
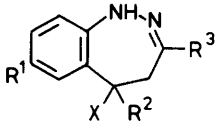
The title hydrazonyl chlorides react with sodium azide in benzene–water at 40 °C to give 1,2-benzodiazepines and/or cyclopropa[*c*]cinnolines, the product distribution being dependent on the substituents at the ethylenic bond. All products probably result from a common intermediate *via* different reaction paths.

ARYLHYDRAZONYL CHLORIDES with α,β-unsaturation at the *ortho*-position have been shown to undergo base-promoted cyclisation leading to 1,2-benzodiazepines and/or cyclopropa[*c*]cinnolines depending on the olefinic-bond substituents and the experimental conditions.[1-4] In a previous paper,[2] we reported that the reaction of hydrazonyl chlorides of type (1) with anionic nucleophiles under phase transfer conditions give directly 4,5-dihydro-1*H*-1,2-benzodiazepines (2) functionalised at the 5-position. The high efficiency of this reaction, particularly, with sodium azide as the nucleophilic reagent, makes it of synthetic importance; however, its stereochemical and mechanistic aspects merit a deeper exploration. In this context, we now describe some interesting new results an treating the hydrazonyl chlorides (3a–f) with sodium azide under phase-transfer conditions.



(1)



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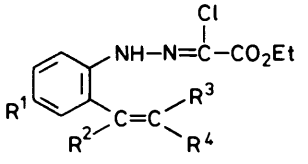


(3)

a ; $R^1 = R^2 = R^3 = H, R^4 = Me$

b ; $R^1 = R^2 = R^4 = H, R^3 = Ph$

c ; $R^1 = R^2 = R^3 = H, R^4 = Ph$

d ; $R^1 = Cl, R^2 = Ph, R^3 = Me, R^4 = H$

e ; $R^1 = Cl, R^2 = Ph, R^3 = H, R^4 = Me$

f ; $R^1 = H, R^2 = Ph, R^3 = R^4 = Me$

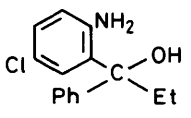
RESULTS AND DISCUSSION

The hitherto unknown compounds (3d) and (3e) were accessible from the substituted aniline (4) *via* diazotisation of the latter and coupling of the product with ethyl 2-chloroacetoacetate to give the hydrazonyl chloride (5). Dehydration of the latter either with phosphorus pentoxide or with toluene-*p*-sulphonic acid led to mixtures of (3d) and (3e), both of which could be obtained in the pure state after repeated fractional cyrstallisations. The assigned stereochemistry came from examination of the n.m.r. spectra of (3d) and (3e) and comparison of these with those of (3a) and (3f) as well as of a similar pair of olefinic isomers.[4]

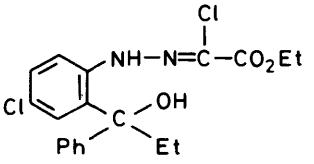
All the hydrazonyl chlorides (3a–f) were treated with 2 mol equiv. of sodium azide in benzene–water at 40 °C by using hexadecyltributylphosphonium bromide as a phase-transfer catalyst. Reaction times, products, and yields are shown in Table 1. While compound (6a) was recognized by comparison with an authentic sample,[1] the new structures (6b–d), (7a,b), (8a,b), and (9) were established on the basis of analytical and spectral data (see Table 2). The stereochemistry of (6d) was unequivocally shown by the n.m.r. signal at δ 0.39 which is only compatible with a methyl group located in the shielding region of the –N=N– moiety, *i.e.* in the *endo*-position. On the other hand, the distinction between the two stereoisomers (6b) and (6c) was easily made on the basis of both the chemical shifts and the coupling constants of the cyclopropyl protons: in fact, in accord with the literature data,[5] the *cis*-coupling constant is larger than the *trans*. For the stereoisomers (8a) and (8b), the assigned configurations were inferred from the following n.m.r. evidence: while the 4-H chemical shift is practically unchanged on going from (7a) to (8a), the analogous proton of (8b) resonates at much lower field; this marked influence by the phenyl group is justified for a *cis*-relationship. Unfortunately, because of the lack of a suitable model, the stereochemistry of (7a) and (7b) remains undetermined, though the identity of the vicinal coupling constants indicates that the spatial relationship between the hydrogens is the same in both cases.

Control experiments on the stability of the tricyclic products (6a–d) under the above phase-transfer conditions showed some interesting features. In fact, while (6a) was totally unchanged after 2 days, (6b) and (6c) reacted within 4 and 3 h respectively, both giving the same azido-compound (7b). In the case of (6d), 80% of the starting substrate was still unchanged after 5 h; however, a slow reaction occurred during 3 days to afford a mixture of (8b) and (9) in the approximate ratio

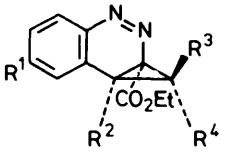
of 5 : 2. It was also ascertained that the reaction mixture arising from (3b) contained, after 2 h, some (6b). It was not possible to obtain similar evidence for the presence of cyclopropa[*c*]cinnolines for compounds (3a) and (3e).



(4)



(5)



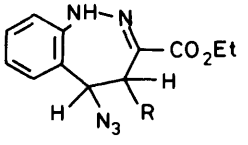
(6)

a ; R^1 = H, R^2 = Ph, R^3 = R^4 = Me

b ; R^1 = R^2 = R^4 = H, R^3 = Ph

c ; R^1 = R^2 = R^3 = H, R^4 = Ph

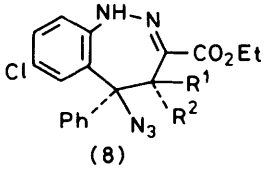
d ; R^1 = Cl, R^2 = Ph, R^3 = Me, R^4 = H



(7)

a ; R = Me

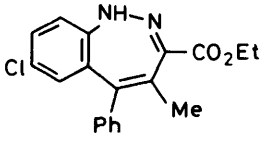
b ; R = Ph



(8)

a ; R^1 = H, R^2 = Me

b ; R^1 = Me, R^2 = H

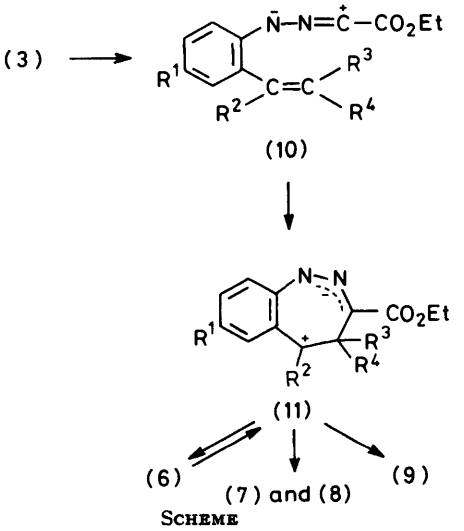


(9)

The results described above indicate an intriguing complexity and variability in chemical behaviour for the series of hydrazonyl chlorides (1) and (3). In an effort to reconcile all the experimental evidence within the frame of a common mechanistic picture, the following considerations and hypotheses will now be put forward. First, it seems very likely that the initial stage of the overall process is the formation of the nitrile imines (10).* These intermediates would undergo an intramolecular ring-closure, involving participation of the neighbouring ethylenic bond, which can be viewed as 1,7-electrocyclic change of an 8π-electron system. At present, while 1,5-electrocyclisations are common reactions of α,β-unsaturated 1,3-dipoles,[7] few reports deal with 1,7-electrocyclisations of 1,3-dipoles having both α,β- and γ,δ-unsaturation.[8]

The cyclic intermediates (11) would then evolve according to one or more of the following concurrent pathways: (i) intramolecular reorganisation by way of a disrotatory 1,6-electrocyclic collapse resulting in cyclopropa[*c*]cinnolines; (ii) intermolecular reaction with the azide ion to provide 5-azido-4,5-dihydro-1*H*-1,2-benzodiazepines; or (iii) prototropic rearrangement to fully unsaturated 1*H*-1,2-benzodiazepines. The relative extents of these pathways would be mainly dictated by the stability of the tricyclic products (6), a property strongly dependent on the degree of substitution on the cyclopropane ring; this would be similar to the results obtained for norcaradienes [9-11] and diazanorcaradienes.[9,12] Since the first pathway is *a priori* reversible, by analogy with the valence isomerisation of diazanorcaradienes to 1,2-diazepines,[9,12] the formation of cyclopropa[*c*]cinnolines may well be favoured on kinetic, but not thermodynamic grounds; this has actually been found for compounds (3b) and (3c). Since complete planarity near the carbocationic centre of (11) implicates steric strain, particularly in the case of encumbering substituents, it seems reasonable to assume that some energy barrier opposes the flipping motion of the seven-membered ring. Thus, any further reaction of compound (11) could occur either, with retention of configuration if it were faster or loss if it were slower than the ring flipping. The observed changes on going from one substrate to another may, therefore, be plausibly rationalised.

In conclusion, the results here presented point to a general pattern of behaviour in which, as outlined in the Scheme, all nitrile imines (10) generate the cyclic species (11), irrespective of the nature of the final products. The alternative hypothesis that formation of cyclo-



SCHEME

* It is known that sodium azide is capable of promoting the formation of nitrile imines from hydrazonyl halides.

propa[*c*]cinnolines might represent the primary mode of evolution of (10), eventually followed by ring enlargement to 1,2-benzodiazepines, is not in harmony with our findings, being contradicted by the proven inertness of (6d). The latter mechanism has, however, been recently shown to operate in the reaction of a few hydrazonyl chlorides of type (3) with silver carbonate in benzene.[4]

EXPERIMENTAL

M.p.s were taken with a Büchi apparatus and are uncorrected. N.m.r. and i.r. spectra were recorded with Varian EM-90 and Perkin-Elmer 377 instruments, respectively. Chemical shifts are given in p.p.m. relative to internal $SiMe_4$.

Compounds (3a), (3c), and (3f) were prepared as previously described.[1]

Preparation of the Hydrazonyl Chloride (3b).—Sodium nitrite (1.75 g) in water (15 ml) was added dropwise to a solution of (*Z*)-2-aminostilbene [13] (3.9 g) in 1 N-hydrochloric acid (60 ml) with vigorous stirring and ice-cooling. After 15 min, the solution was adjusted to pH 4 with sodium acetate and ethyl 2-chloroacetoacetate (3.5 g) in methanol (15 ml) was added slowly with stirring at 0—5 °C. The mixture was stirred at room temperature for 2 h, and then extracted with chloroform. The organic solution was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on a silica gel column with light petroleum–diethyl ether (1 : 1) as eluant to give the *chloride* (3b) in 25% yield; m.p. 72—73 °C (from n-pentane) (Found: C, 65.5; H, 5.3; N, 8.4. $C_{18}H_{17}ClN_2O_2$ requires C, 65.7; H, 5.2; N, 8.5%), δ($CDCl_3$) 1.36 (3 H, t), 4.35 (2 H, q), 6.53, 6.82 (2 H, AB AB type, *J* 12 Hz), 6.9—7.7 (9 H, m), and 8.5 (1 H, br s).

Preparation of the Hydrazonyl Chloride (5).—The amine (4) [14] was diazotised and coupled with ethyl 2-chloroacetoacetate according to the procedure described in the preceding preparation. Recrystallisation of the crude product from chloroform–ethanol gave the *chloride* (5) (79%), m.p. 174 °C (Found: C, 57.8; H, 5.2; N, 6.9. $C_{19}H_{20}Cl_2N_2O_3$ requires C, 57.7; H, 5.1; N, 7.1%); δ($CDCl_3$) 0.90 (3 H, t), 1.35 (3 H, t), 2.31 (2 H, q), 2.8 (1 H, br s), 4.38 (2 H, q), 5.9 (1 H, br s), and 7.2—7.6 (8 H, m).

Preparation of the Hydrazonyl Chloride (3d).—A solution of compound (5) (9.8 g) in toluene (250 ml) was treated with phosphorus pentoxide (15 g) and stirred overnight at room temperature. The undissolved material was filtered off and the solution was washed with water, dried (Na_2SO_4), and evaporated to give a 3 : 1 mixture of (3d) and (3e) (4.3 g). Recrystallisation from n-pentane afforded a 1 : 1 isomeric mixture (2.0 g). The residue from the mother-liquor was recrystallised twice from n-pentane to give the pure *chloride* (3d) (1.3 g), m.p. 101 °C (Found: C, 60.7; H, 5.0; N, 7.4. $C_{19}H_{18}Cl_2N_2O_2$ requires C, 60.5; H, 4.8; N, 7.4%); δ($CDCl_3$) 1.33 (3 H, t), 1.69 (3 H, d), 4.33 (2 H, q), 6.48 (1 H, q), 7.0—7.8 (8 H, m), and 8.3 (1 H, br s).

Preparation of the Hydrazonyl Chloride (3e).—A solution of (5) (8.2 g) in benzene (200 ml) was treated with toluene-*p*-sulphonic acid (2 g) and refluxed under a Dean-Stark apparatus for 1 h. The mixture was washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to give a 2 : 1 mixture of (3e) and (3d). Two fractional recrystallisations from n-pentane-di-isopropyl ether afforded the pure *chloride* (3e) (3.3 g), m.p. 135 °C (Found: C, 60.7; H, 4.9; N, 7.3. $C_{19}H_{18}Cl_2O_2$ requires C, 60.5; H, 4.8; N,

TABLE 1

Reaction of hydrazonyl chlorides (3) with sodium azide in benzene–water at 40 °C

Compound	Time (h)	Products	Yields (%)	Isolation procedure [a]
(3a)	7	(7a)	85	A
(3b)	5	(7b)	73	A
(3c)	2	(6b) + (6c)	34 [b]	B
		(7b)	43	
(3d)	3	(6d)	7	B
		(9)	10	
		(8b)	52	
(3e)	5	(9)	12	B
		(8a)	67	
(3f)	12	(6a)	69	A

[a] A, treatment of the crude product with di-isopropyl ether and subsequent filtration; B, column chromatography on silica gel with 50 : 45 : 5 light petroleum–diethyl ether–triethylamine as eluant [products are given in order of elution]. [b] Overall yield of a mixture of compounds (6b) and (6c) in the approximate ratio of 1 : 1.

TABLE 2

Physical, spectral, and analytical data of compounds (6)—(9)

Compd.	M.p. (°C)	$\nu_{max.}$(Nujol)/cm^{-1}	δ($CDCl_3$) [a,b]	Elemental analysis (%) Found (required) C	H	N
(6b)	93 [c]	1 740	3.60 (1 H, d, *J* 9), 4.10 (1 H, d, *J* 9), 6.6—7.6 (8 H, m), 7.8—8.0 (1 H, m)	74.1 (73.9)	5.4 (5.5)	9.5 (9.6)
(6c)	105 [d]	1 750	1.79 (1 H, d, *J* 6.5), 3.79 (1 H, d, *J* 6.5), 7.2—7.6 (8 H, m), 8.2—8.4 (1 H, m)	73.8 (73.9)	5.7 (5.5)	9.6 (9.6)
(6d)	108 [c]	1 735	0.39 (3 H, d, *J* 6.5), 3.73 (1 H, q, *J* 6.5), 6.7—7.7 (7 H, m), 8.27 (1 H, d, *J* 8)	66.8 (67.0)	5.1 (5.0)	8.1 (8.2)
(7a)	148 [c]	3 300, 2 100, 1 715	0.90 (3 H, d, *J* 7), 3.90 (1 H, dq, *J* 7 and 6), 4.74 (1 H, d, *J* 6), 6.9—7.5 (4 H, m), 9.1 (1 H, br s)	57.0 (57.1)	5.6 (5.5)	25.4 (25.6)
(7b)	134 [c]	3 280, 2 090, 1 710	4.93 (1 H, d, *J* 6), 5.18 (1 H, d, *J* 6), 6.6—7.3 (9 H, m), 9.5 (1 H, br s)	64.7 (64.5)	5.0 (5.1)	20.8 (20.9)
(8a)	169 [c]	3 280, 2 090, 1 710	1.02 (3 H, d, *J* 7), 3.88 (1 H, q, *J* 7), 7.0—7.6 (8 H, m), 9.5 (1 H, br s)	59.3 (59.4)	4.8 (4.7)	18.0 (18.2)
(8b)	176 [c]	3 280, 2 090, 1 710	0.98 (3 H, d, *J* 7), 4.60 (1 H, d, *J* 7), 6.8—7.6 (7 H, m), 7.85 (1 H, d, *J* 2.5), 8.7 (1 H, br s)	59.5 (59.4)	4.5 (4.7)	18.1 (18.2)
(9)	161 [c]	3 310, 1 720	1.87 (3 H, s), 6.65 (1 H, d, *J* 2.5), 6.78 (1 H, d, *J* 8), 6.9 (1 H, br s), 7.0—7.6 (6 H, m)	66.9 (67.0)	5.1 (5.0)	8.1 (8.2)

[a] The signals of the ethyl group are not given. [b] *J* in Hz. [c] From di-isopropyl ether. [d] From n-pentane. [e] From n-hexane–chloroform.

7.4%); δ($CDCl_3$) 1.32 (3 H, t), 1.95 (3 H, d), 4.35 (2 H, q), 6.06 (1 H, q), 7.1—7.6 (8 H, m), and 8.3 (1 H, br s).

Treatment of the Hydrazonyl Chlorides (3) *with Sodium Azide*.—A solution of compound (3) (5 mmol) in benzene (100 ml) was treated with a solution of sodium azide (10 mmol) and hexadecyltributylphosphonium bromide (0.25 mmol) in water (50 ml) at 40 °C with vigorous stirring for the time given in Table 1. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated. The residue was then worked up as indicated in Table 1. Both isomers (6b) and (6c) were obtained in the pure state by chromatography on a silica-gel column and fractional recrystallisations. Chromatographic separations without triethylamine in the eluant mixture caused partial decomposition of compounds (6).

Treatment of the Cyclopropa[c]*cinnolines* (6b) *and* (6c) *with Sodium Azide*.—Compounds (6b) and (6c) were treated with sodium azide according to the phase-transfer conditions described above (4 and 3 h, respectively). In both cases, the usual work-up procedure gave practically pure compound (7b) (n.m.r. analysis).

Treatment of Cyclopropa[c]*cinnoline* (6d) *with Sodium Azide*.—Compound (6d) was treated with sodium azide under the above phase-transfer conditions (60 h). After the usual work-up procedure, the product mixture was chromatographed on a silica-gel column with chloroform–diethyl ether (4 : 1) as eluant to give compounds (9) (21%) and (8b) (49%).

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