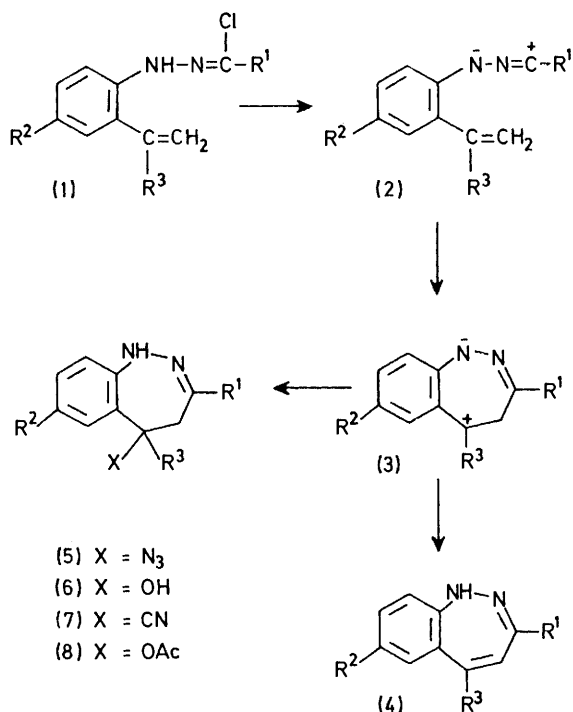


New Aspects in the Base-promoted Cyclisation of *o*-Vinylbenzohydrazonyl Chlorides

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Treatment of the title hydrazonyl chlorides with sodium azide, sodium cyanide, and sodium acetate in benzene–water (hexadecyltributylphosphonium bromide as phase-transfer catalyst, temperature 25–40 °C) gave 5-azido-, 5-cyano-, and 5-hydroxy-4,5-dihydro-1*H*-1,2-benzodiazepines; the related fully unsaturated 1*H*-1,2-benzodiazepines were also formed.

ARENOHYDRAZONYL chlorides (1) have been shown to react with triethylamine giving 1*H*-1,2-benzodiazepines (4) in preparative yields.^{1,2} Since the proposed mechanism involves (3) as transient intermediates, it was felt advisable to explore whether such dipolar species can be intercepted by external nucleophiles, thus providing 5-functionalised 1,2-benzodiazepine derivatives. New synthetic approaches to 1,2-benzodiazepines seem to be



- (5) X = N₃
 (6) X = OH
 (7) X = CN
 (8) X = OAc

- a; R¹ = CO₂Et, R² = R³ = H
 b; R¹ = CO₂Et, R² = Cl, R³ = Ph
 c; R¹ = COMe, R² = Cl, R³ = Ph
 d; R¹ = COPh, R² = Cl, R³ = Ph

desirable in view of the potential interest of this class of compounds in pharmacology.³ In this context, we now describe the reactions of (1) with anionic nucleophiles under phase-transfer conditions, which were found suitable for the above purpose.

† Treatment of (1) with sodium hydroxide (1 mol. equiv.) under the phase-transfer conditions led exclusively to (4).

‡ While the i.r. spectrum of this material has a significant band at 1720 cm⁻¹, its n.m.r. spectrum shows a set of broad signals of little diagnostic utility.

RESULTS AND DISCUSSION

Compounds (1) were reacted with sodium azide (2 mol. equiv.) in benzene–water in the presence of hexadecyltributylphosphonium bromide as phase-transfer catalyst. In all cases, a clean reaction was observed at moderate temperature giving 5-azido-4,5-dihydro-1*H*-1,2-benzodiazepines (5) in high yields (see Table 1). Treatment of (1) with sodium cyanide and with sodium acetate under similar conditions resulted in product mixtures which varied according to the substrate and the anionic reagent.

As summarised in Table 1, fully unsaturated 1*H*-1,2-benzodiazepines (4) were commonly obtained along with the desired 5-substituted-4,5-dihydro-1*H*-1,2-benzodiazepines, and this reveals competitive modes of evolution of the dipolar intermediates (3).† Furthermore, in the reaction of (1) with sodium acetate, the hydroxy-derivatives (6) were the usual products in addition to (or rather than) the acetoxy-derivatives (8), thus indicating that hydroxide ion strongly rivals (or predominates over) acetate ion in capturing (3). Such nucleophilic attack by the hydroxide ion was also observed in a few cases when compounds (1) were treated with sodium cyanide. Control experiments showed that the different products are not interconverted under the conditions of their formation.

The reaction of (1a) with sodium cyanide is a particular case in that it provided, beside some hydroxy-derivative (6a), a sizeable amount of a solid of low solubility in common solvents, whose elemental analysis corresponds to C_{6n}H_{6n}N_nO_n. The molecular weight, determined by the ebullioscopic technique, is consistent with an oligomeric structure.‡

The following points help to rationalize the above results. The dipolar species (2) and (3), which have been proposed for the reaction of (1) with triethylamine in benzene,^{1,2} are plausible intermediates.§ Conversion of (3) into stable compounds can occur in principle by proton elimination or by reaction with an external nucleophile. The total suppression of the former pathway with sodium azide is in line with the well established ability of the azide ion to trap carbocationic species.⁵⁻⁷ With less efficient trapping agents, the capture is still complete for (3a), but not for (3b–d). This is reasonable

§ That compounds (1) are capable of generating (2) under our conditions is reasonable on considering that the hydrolysis of hydrazonyl halides in the presence of sodium azide has been shown to proceed *via* nitrile imides.⁴

since the phenyl substituent on the electrophilic centre, while hindering nucleophilic attack, favours the elimination pathway because of the gain in conjugation. As to the competition between the hydroxide ion and

(2 H, q), 5.38 (1 H, d, *J ca.* 1 Hz), 5.84 (1 H, d, *J ca.* 1 Hz), 7.1–7.7 (8 H, m), and 8.2br (1 H, s).

Reaction of (1) with Sodium Azide.—A solution of (1) (3 mmol) in benzene (45 ml) was treated under vigorous stirring

TABLE 1
Reactions of hydrazoneyl chlorides (1) with NaX

| Substrate | NaX | Temp. (°C) | Time (h) | Products ^a | Yield (%) | Eluant |
|-----------|------------------|------------|----------|-----------------------|-------------|--------------------------------------|
| (1a) | NaN ₃ | 25 | 3 | (5a) | 77 | |
| | NaCN | 25 | 1 | (6a) ^b | 10 | Et ₂ O |
| (1b) | NaOAc | 40 | 5 | (8a) + (6a) | 36 + 27 | Et ₂ O |
| | NaN ₃ | 40 | 5 | (5b) | 67 | |
| | NaCN | 25 | 2 | (4b) + (7b) + (6b) | 20 + 8 + 46 | Et ₂ O–chloroform (1 : 1) |
| (1c) | NaOAc | 40 | 12 | (4b) + (6b) | 33 + 40 | Et ₂ O–hexane (2 : 1) |
| | NaN ₃ | 40 | 5 | (5c) | 78 | |
| | NaCN | 25 | 2 | (4c) + (7c) | 40 + 36 | Et ₂ O–hexane (1 : 1) |
| (1d) | NaOAc | 40 | 12 | (4c) + (6c) | 60 + 21 | Et ₂ O–hexane (3 : 1) |
| | NaN ₃ | 40 | 5 | (5d) | 85 | |
| | NaCN | 25 | 3 | (4d) + (7d) | 5 + 73 | Et ₂ O–hexane (1 : 1) |
| | NaOAc | 40 | 8 | (4d) + (6d) | 42 + 28 | Et ₂ O–hexane (1 : 1) |

^a In order of elution. ^b See text.

other anions in capturing (3), it is probable that an interplay of electronic and steric factors may determine the observed product distribution.

EXPERIMENTAL

M.p.s. were taken on a Büchi apparatus and are uncorrected. I.r. spectra were determined on a Perkin-Elmer 377 spectrophotometer. N.m.r. spectra were recorded on a Varian HA-100 instrument with Me₄Si as an internal standard. Organic solutions were dried (Na₂SO₄).

with a solution of sodium azide (6 mmol) and catalyst (0.15 mmol) in water (20 ml) as indicated in Table 1. The organic layer was washed with water, dried, and evaporated. The residue was taken up with a small amount of di-isopropyl ether and filtered to afford (5) (see Tables 1 and 2).

Reaction of (1) with Sodium Cyanide.—A solution of (1) (5 mmol) in benzene (75 ml) was treated under vigorous stirring with a solution of sodium cyanide (10 mmol) and catalyst (0.25 mmol) in water (35 ml) as indicated in Table 1. The mixture was worked up as above and the residue was

TABLE 2
Physical, spectral, and analytical data of compounds (5)–(8)^a

| Compound | M.p. (°C) | $\nu_{\max.}/\text{cm}^{-1}$ ^b | ¹ H N.m.r. (δ) ^{c-e} | Required (%) | | | Found (%) | | |
|----------|-----------|---|--|--------------|-----|------|-----------|-----|------|
| | | | | C | H | N | C | H | N |
| (5a) | 145 | 3 310, 2 120, 1 715 | 2.82 (1 H, dd, <i>J</i> 15 and 1.5 Hz), 3.62 (1 H, dd, <i>J</i> 15 and 7 Hz), 5.03 (1 H, dd, <i>J</i> 7 and 1.5 Hz) | 55.6 | 5.0 | 27.0 | 55.5 | 4.9 | 26.8 |
| (5b) | 133 | 3 320, 2 120, 1 715 | 3.19, 4.08 (each 1 H, AB type, <i>J</i> 15 Hz) | 58.5 | 4.3 | 18.9 | 58.7 | 4.3 | 18.8 |
| (5c) | 150 | 3 330, 2 120, 1 675 | 2.98, 4.28 (each 1 H, AB type, <i>J</i> 15 Hz) | 60.1 | 4.1 | 20.6 | 60.3 | 4.2 | 20.4 |
| (5d) | 163 | 3 330, 2 120, 1 650 | 3.14, 4.28 (each 1 H, AB type, <i>J</i> 15 Hz) | 66.0 | 4.0 | 17.4 | 65.9 | 4.1 | 17.6 |
| (6a) | 160 | 3 380–3 300, 1 715 | 2.3br (1 H, s), 2.95 (1 H, dd, <i>J</i> 15 and 1.5 Hz), 3.42 (1 H, dd, <i>J</i> 15 and 7 Hz), 5.0–5.2 (1 H, m) | 61.5 | 6.0 | 12.0 | 61.5 | 5.8 | 12.1 |
| (6b) | 132 | 3 500, 3 330, 1 690 | 2.9br (1 H, s), 3.06, 4.04 (each 1 H, AB type, <i>J</i> 15 Hz) | 62.7 | 4.9 | 8.1 | 62.9 | 4.9 | 8.0 |
| (6c) | 172 | 3 380–3 300, 1 660 | 2.7br (1 H, s), 2.85, 4.16 (each 1 H, AB type, <i>J</i> 15 Hz) | 64.9 | 4.8 | 8.9 | 64.7 | 4.9 | 8.9 |
| (6d) | 93 | 3 380–3 300, 1 630 | 2.9br (1 H, s), 3.00, 4.28 (each 1 H, AB type, <i>J</i> 15 Hz) | 70.1 | 4.5 | 7.4 | 70.3 | 4.4 | 7.5 |
| (7b) | 203 | 3 340, 1 730 | 3.34, 4.16 (each 1 H, AB type, <i>J</i> 15 Hz) | 64.5 | 4.5 | 11.9 | 64.8 | 4.6 | 12.0 |
| (7c) | 158 | 3 350, 1 670 | 3.28, 4.38 (each 1 H, AB type, <i>J</i> 15 Hz) | 66.8 | 4.3 | 13.0 | 66.7 | 4.2 | 12.8 |
| (7d) | 185 | 3 350, 1 630 | 3.37, 4.50 (each 1 H, AB type, <i>J</i> 15 Hz) | 71.6 | 4.2 | 10.9 | 71.7 | 4.4 | 10.9 |
| (8a) | 158 | 3 320, 1 740, 1 720 | 1.94 (3 H, s), 2.78 (1 H, dd, <i>J</i> 15 and 1.5 Hz), 3.62 (1 H, dd, <i>J</i> 15 and 7 Hz), 6.14 (1 H, dd, <i>J</i> 7 and 1.5 Hz) | 60.9 | 5.8 | 10.1 | 60.9 | 5.6 | 10.2 |

^a All compounds listed gave correct molecular peaks in the mass spectra. ^b Nujol. ^c Deuteriochloroform. ^d The signals of the aromatic protons and the R³ substituent are not given. ^e The signal for NH is a broad singlet at δ 8–9.

Compounds (1a),¹ (1c),² and (1d)² were prepared as previously reported.

Ethyl Chloroglyoxylate 4-Chloro-2-(1-phenylvinyl)phenylhydrazone (1b).—This compound was prepared from 1-(5-chloro-2-aminophenyl)-1-phenylethanol⁸ according to the general procedure described previously,² yield 42%; m.p. 142° (Found: C, 59.8; H, 4.4; N, 7.5. C₁₈H₁₆Cl₂N₂O₂ requires C, 59.5; H, 4.4; N, 7.7%), $\nu_{\max.}$ (Nujol) 3 320 and 1 720 cm⁻¹, δ (CDCl₃) 1.34 (3 H, t), 4.32

chromatographed on a silica gel column to give pure products (see Tables 1 and 2). In the case of (1a), the treatment of the crude product mixture with diethyl ether left a solid material (0.60 g), m.p. 210–220° (Found: C, 66.6; H, 5.7; N, 12.7%), $\nu_{\max.}$ (Nujol) 1 720 cm⁻¹; molecular weight (Hitachi-Perkin-Elmer molecular weight apparatus; chlorobenzene as solvent) 1560.

Reaction of (1) with Sodium Acetate.—A solution of (1) (5 mmol) in benzene (75 ml) was treated under vigorous

stirring with a solution of sodium acetate (10 mmol) and catalyst (0.25 mmol) in water (35 ml) as indicated in Table 1. After the usual work-up, the residue was chromatographed on a silica gel column to afford pure products (see Tables 1 and 2).

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