88. *Reaction of α-Cyanobenzyl Bromide with Some Nucleophilic Reagents.*

By J. E. Banfield.

The outcome of such reactions depends on the reactivity of the nucleophile competing with the basicity of the reagent.

Synthesis of α-substituted benzyl cyanides and their derivatives by nucleophilic replacement of the halogen of α-cyanobenzyl chloride or bromide is restricted by the well-known reaction [1] of these halides with bases to yield *trans*-αβ-dicyanostilbene.[2] However, a number of such syntheses has been reported, *e.g.*, reactions with nitroso-compounds,[3] mercury,[4] thiourea,[5] ethyl xanthimide,[6] ammonium thiocyanate,[1] sodium hydrogen sulphide,[7] and sodium sulphide,[7] the products being frequently accompanied by the stilbene and in one case [6] by a derivative thereof.

Reaction of a number of thiophenols with α-cyanobenzyl bromide is now reported; the products were the aryl α-cyanobenzyl sulphides usually accompanied by the dicyanostilbene. The constitution of the phenyl derivative PhS•CHPh•CN was confirmed by hydrolysis to the known carboxylic acid. α-Cyanobenzyl *p*-tolyl sulphide was hydrolysed by ethanolic guanidine to α-carbamoylbenzyl *p*-tolyl sulphide $p\text{-}C_6H_4Me{\cdot}S{\cdot}CHPh{\cdot}CO{\cdot}NH_2$, and by alkali to the known acid. Sodium toluene-*p*-sulphinate reacted with α-cyanobenzyl bromide to yield α-cyanobenzyl *p*-tolyl sulphone which was also prepared by oxidation of the corresponding sulphide.

Neutral guanidine salts did not react with α-cyanobenzyl bromide in refluxing aqueous ethanol or under a variety of other conditions, whereas guanidine carbonate and the bromonitrile gave the dicyanostilbene. With an excess of ethanolic guanidine it yielded a substance apparently derived from αβ-dicyanostilbene, as indicated by its hydrolysis to diphenylmaleinimide, though satisfactory analyses were not obtained.

Thus it is apparent that the product of reaction of α-cyanobenzyl bromide with a nucleophile depends critically upon the nucleophilic reactivity on the one hand and the basicity of the reagent on the other; the mechanism [1] assumed for formation of the dicyanostilbene is the abstraction of a proton from the reactive α-position of the nitrile, the carbanion produced then competing with the nucleophile for carbonium ions formed from the bromo-nitrile in an S_N1-type reaction. Racemisation of α-cyanobenzyl chloride is known to be accelerated by alkali [8] which suggests that the formation of the anion involves rapid equilibration followed by rate- and product-determining steps.

9-Fluorenyl nitrate has been reported [9] to react (presumably by the S_N1 mechanism) with thiophenols and with sodium toluene-*p*-sulphinate, and with acetamide it gave *N*-9-fluorenylacetamide whereas under basic conditions the α-hydrogen was eliminated with the production of fluorenone.[9] Thus it seemed likely that the α-cyanobenzyl carbonium ion might react with acetamide under appropriate conditions; however, attempts to isolate α-acetamidobenzyl cyanide from the products of reaction of α-cyanobenzyl bromide with acetamide in dioxan or ethanol were abortive, the bromide being destroyed with the production of ammonium bromide and minute amounts of diphenylmaleinimide and (probably) αβ-diphenylsuccinodinitrile. Reaction of these components in formic

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[1] Coe, Gale, Linstead, and Timmons, *J.*, 1957, 123, and refs. 1—6 therein.

[2] Williams and Le Fèvre, *J.*, 1957, 2425.

[3] Barrow and Thornycroft, *J.*, 1934, 722; 1939, 775.

[4] Kretov and Abromov, *J. Gen. Chem.* (*U.S.S.R.*), 1937, **7**, 1572.

[5a] Miller, Sprague, Kissinger, and McBurney, *J. Amer. Chem. Soc.*, 1940, **62**, 2099; [b] Davies, Maclaren, and Wilkinson, *J.*, 1950, 3491; and [c] Chase and Walker, *J.*, 1955, 4443.

[6] Davies and Maclaren, *J.*, 1951, 1434.

[7] Kretov and Panchenko, *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 1975.

[8] Smith, *Ber.*, 1938, **71**, 634.

[9] Cheeseman, *J.*, 1959, 448; see also *J.*, 1958, 117 for S_N1 reaction of amides with diphenylmethyl nitrate, and *J.*, 1959, 452 for that with triphenylmethyl nitrate.

acid (known to be a good ionising solvent for S_N1 reactions [10]) gave a substantial recovery of the bromide and no α-acetamidobenzyl cyanide was isolated.

EXPERIMENTAL

Crude α-cyanobenzyl bromide (Defence Research Laboratories, Maribyrnong, Victoria) decomposed extensively when precise fractionation on a large scale was attempted under moderate vacuum. Accordingly the crude material was distilled rapidly and the fraction of b. p. 125—138°/20 mm. was collected. This material, to which quantities given below refer, contained benzyl cyanide as the main impurity and was of *ca.* 50% purity (by bromine analysis).

α-Cyanobenzyl Phenyl Sulphide.—A mixture of thiophenol (5 ml.), α-cyanobenzyl bromide (15 ml.), ethanol (40 ml.), and a drop of phenolphthalein solution was stirred under nitrogen whilst aqueous 2N-sodium hydroxide was added at such a rate that the mixture remained colourless. The mixture was stirred for 2 hr., then the pale yellow oil was separated and crystallised by trituration with small portions of ethanol. Extraction of the solid (9·3 g.) with ethanol left a residue of *trans*-αβ-dicyanostilbene, m. p. 161—162° (from light petroleum). The extract was diluted with water to yield, after repeated recrystallisation from light petroleum, *α-cyanobenzyl phenyl sulphide* in tabular crystals, m. p. 51·5—52° (Found: N, 6·3; S, 14·7; 13·8. $C_{14}H_{11}NS$ requires N, 6·2; S, 14·2%).

The sulphide (1 g.) was refluxed with water (5 ml.), sulphuric acid (5 ml.), and acetic acid (5 ml.) for 3 hr., the mixture was diluted with water, the precipitated solid was collected and extracted with alkali, and the extract was acidified, to give α-carboxybenzyl phenyl sulphide in needles, m. p. 101—102° (from 20% aqueous ethanol) (lit.,[11] 102—103°).

α-Cyanobenzyl p-*Tolyl Sulphide.*—*p*-Thiocresol (5 g.) reacted with α-cyanobenzyl bromide (10 ml.) by the above method to give the *sulphide* (6·1 g.) (from 50% ethanol), repeated recrystallisation of which from 30% acetic acid yielded a sample, m. p. 64·5—66° (Found: C, 75·5; H, 5·9; N, 5·9; S, 13·2. $C_{15}H_{13}NS$ requires C, 75·3; H, 5·5; N, 5·85; S, 13·4%). Less pure sulphide was obtained from the aqueous-ethanolic mother-liquors.

The sulphide (3 g.) was hydrolysed as above to α-carboxybenzyl *p*-tolyl sulphide (1·6 g.), m. p. 130—131·5° (lit.,[12] 128°) (from aqueous ethanol) (Found: S, 11·9. Calc. for $C_{15}H_{14}O_2S$: S, 12·4%).

α-Cyanobenzyl *p*-tolyl sulphide (6 g.) was refluxed with guanidine (2 g.) in ethanol for 2 hr. The cold mixture deposited *α-carbamoylbenzyl* p-*tolyl sulphide* (1·5 g.), m. p. 200·5° (from ethanol) (Found: C, 70·2; H, 5·8; N, 5·4; S, 12·5. $C_{15}H_{15}ONS$ requires C, 70·0; H, 5·9; N, 5·4; S, 12·5%), which was not readily soluble in hot hydrochloric acid or hot sodium hydroxide solution.

α-Cyanobenzyl p-*Tolyl Sulphone.*—(*a*) A mixture of sodium toluene-*p*-sulphinate (16 g.), water (40 ml.), ethanol (80 ml.), and α-cyanobenzyl bromide (20 ml.) was refluxed for a short time to yield the *sulphone*, m. p. 152—153° (from ethanol) (Found: N, 4·93. $C_{15}H_{13}O_2NS$ requires N, 5·16%).

(*b*) α-Cyanobenzyl *p*-tolyl sulphide in acetic acid with 30% hydrogen peroxide under reflux for a few seconds gave the sulphone, m. p. and mixed m. p. 146—149°.

Reaction of α-Cyanobenzyl Bromide with Some Thiols.—*p*-Methoxythiophenol (5 ml.) with α-cyanobenzyl bromide (11 ml.) gave by the above method a solid (3·6 g.) which, purified from light petroleum, gave *α-cyanobenzyl* p-*methoxyphenyl sulphide*, m. p. 53—54° (Found: C, 70·5; H, 5·1; N, 5·7. $C_{15}H_{13}ONS$ requires C, 70·6; H, 5·1; N, 5·5%). 3,4-Dimethoxythiophenol (2 g.) with α-cyanobenzyl bromide (4 ml.) gave an oil which solidified when triturated with ethylene glycol. The solid (2·3 g.) had m. p. 48—52° and was repeatedly recrystallised from light petroleum to yield *α-cyanobenzyl 3,4-dimethoxyphenyl sulphide*, m. p. 67·5—68° (Found: C, 67·2; H, 5·4; N, 4·7; S, 11·0; OMe, 21·6. $C_{16}H_{15}O_2NS$ requires C, 67·4; H, 5·3; N, 4·9; S, 11·2; 2OMe, 21·8%).

p-*NN*-Dimethylaminothiophenol [13,14] had b. p. 162—168°/25 mm. and was conveniently obtained in 70% yield when *p*-dimethylaminophenyl thiocyanate (20 g.) was refluxed with sodium sulphide (nonahydrate; 40 g.), sodium hydroxide (5 g.), and ethanol (200 ml.) under

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[10] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 321.

[11] Fuchs, *Monatsh.*, 1929, **53/54**, 441.

[12] Arventi and Robn-Burnuz, *Ann. Sci. Univ. Jassy*, 1940, **26**, 3025.

[13] Leuckart, *J. prakt. Chem.*, 1890, **41**, 208.

[14] Gilman and Fullhart, *J. Amer. Chem. Soc.*, 1949, **71**, 1428.

nitrogen for 4 hr., the mixture poured on ice, ammonium chloride (100 g.) added, and the mixture extracted with ether. This thiophenol (4 ml.) and α-cyanobenzyl bromide (6 ml.) in ethanol (30 ml.) gave by the above method (4 hr.) a solid (3·2 g.) which was collected and stirred with hot 2N-hydrochloric acid. The mixture was cooled and the residual *trans*-αβ-dicyanostilbene (m. p. and mixed m. p. 160—162°; from ethyl acetate; 0·8 g.) was collected and the filtrate was basified, to give *α-cyanobenzyl* p-*dimethylaminophenyl sulphide*, m. p. 90·5—91° (from light petroleum) (Found: C, 71·6; H, 5·8; N, 10·2; S, 12·1. $C_{16}H_{16}N_2S$ requires C. 71·6; H, 6·0; N, 10·4; S, 12·0%).

A warm solution of β-thionaphthol (8 g.), and α-cyanobenzyl bromide (11 ml.) in ethanol (40 ml.), treated under nitrogen with sodium hydroxide solution and then stirred for 2 hr., deposited *α-cyanobenzyl 2-naphthyl sulphide*, m. p. 88—90° (11·5 g.) which, recrystallised from acetic acid and then ethanol, formed pale yellow crystals, m. p. 94·5—96° (Found: C, 78·2; H, 4·8; N, 4·8. $C_{18}H_{13}NS$ requires C, 78·5; H, 4·8; N, 5·1%).

α-Cyanobenzyl bromide reacted with *o*-thiocresol, *m*-thiocresol, *p*-nitrothiophenol, and 2,4-dinitrothiophenol severally to give *trans*-αβ-dicyanostilbene, viscous oils also being obtained in the reactions with *o*- and *m*-thiocresols. Toluene-ω-thiol (5 ml.), α-cyanobenzyl bromide (10 ml.), and ethanol (30 ml.) with sodium hydroxide gave *trans*-αβ-dicyanostilbene (1·2 g.) and an oil which decomposed extensively on distillation. Sodium methyl sulphide and α-cyanobenzyl bromide in boiling aqueous ethanol gave *trans*-αβ-dicyanostilbene and unchanged bromide.

Reaction of α-Cyanobenzyl Bromide with Guanidine Carbonate.—Guanidine carbonate (1 g.), α-cyanobenzyl bromide (2 ml.), ethanol (15 ml.), and water (1 ml.) were refluxed for 0·5 hr. The cold mixture deposited *trans*-αβ-dicyanostilbene (0·4 g.), m. p. and mixed m. p. 162—163° (from ethanol); when the filtrate was basified and treated with benzenesulphonyl chloride, benzenesulphonylguanidine (m. p. and mixed m. p. 214·5—215·5°) separated. Details of similar unsuccessful experiments are in the Ph.D. thesis of J. E. B. (University of Melbourne, 1951).

Reaction of α-Cyanobenzyl Bromide with Guanidine.—A mixture of guanidine nitrate (100 g.) potassium hydroxide (55 g.), and ethanol (250 ml.) was stirred for 0·5 hr., filtered, and stirred during the addition of α-cyanobenzyl bromide (50 ml.) in ethanol (100 ml.) in 0·5 hr. The mixture was set aside for several days, whereupon yellow crystals (21 g.), m. p. *ca.* 207° (decomp.), were deposited. This substance was insoluble in the usual solvents; it was hydrolysed in boiling 50% sulphuric acid (5 min.) to diphenylmaleinimide (2·6 g. from 5 g.), m. p. and mixed m. p. 216—217·5° (Found: C, 76·8; H, 4·2. Calc. for $C_{16}H_{11}O_2N$: C, 77·1; H, 4·4%), which with sodium hydroxide gave diphenylmaleic anhydride, m. p. and mixed m. p. 158—159·5°.

Reaction of α-Cyanobenzyl Bromide with Acetamide.—(*a*) The bromide (10 ml.) and acetamide (7 g.) in dioxan (20 ml.) were refluxed until a portion, diluted with water, extracted with ether, and washed with water, was free from bromine (8 hr.). The mixture was diluted, and material extracted with benzene was chromatographed on alumina. Benzene eluted a red oil which deposited crystals (0·1 g.) of probably *meso* + DL-αβ-diphenylsuccinodinitrile, m. p. 214—221°, undepressed by the sample mentioned below (from benzene; Found: N, 12·3%) (lit.,[15] 224°; Gale, Linstead, and Timmons [1] give m. p. 225° for the *meso*-compound and note that Chalanay and Knoevenagel [16] give m. p. 240° for the *meso*-compound completely free from the racemic form), and ether eluted diphenylmaleinimide (0·08 g.), m. p. and mixed m. p. 215—216° (Found: N, 5·8. Calc. for $C_{16}H_{11}O_2N$: N, 5·6%). α-Acetamidobenzyl cyanide had m. p. 114—114·5° (Found: C, 68·95; H, 5·60; N, 16·03. Calc. for $C_{10}H_{10}ON_2$: C, 69·0; H, 5·8; N, 16·1%) (lit.,[17] 113°) and was sparingly soluble in cold benzene and was readily eluted by benzene from alumina.

(*b*) Reaction of the above components in ethanol gave ammonium bromide and a little αβ-diphenylsuccinodinitrile, m. p. 210° (from ethanol) [Found: C, 82·4; H, 5·2; N, 12·1%; *M* (Rast), 187. Calc. for $C_{16}H_{12}N_2$: C, 82·8; H, 5·2; N, 12·1%; *M*, 232].

(*c*) In absence of solvents, at 97°, gave similar results.

(*d*) Acetamide (10 g.), 98—100% formic acid (20 ml.), α-cyanobenzyl bromide (3 ml.), and sodium acetate (1·5 g.), kept at 55—60° for 48 hr. yielded, after chromatography, a yellow lachrymatory oil (1·05 g.), b. p. *ca.* 120°/8 mm. [Found: Br (by saponification and Volhard),

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[15] Tronov and Aksenenko, *Zhur. obshchei Khim.*, 1956, **26**, 1393.

[16] Chalanay and Knoevenagel, *Ber.*, 1892, **25**, 285.

[17] Reihlen, Von Hessling, Hühn, and Weinbrenner, *Annalen*, 1932, **493**, 20.

14·4%; corresponding to 35% of α-cyanobenzyl bromide]. Reaction at 90—95° for 8 hr. gave a similar oil (1·55 g.; Found: Br, 11·8%).

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