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Preparation of Nitriles from Halides and Sodium Cyanide. An Advantageous Nucleophilic Displacement in Dimethyl Sulfoxide[1a]

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Reaction of primary and secondary chlorides with sodium cyanide in dimethyl sulfoxide occurs rapidly and efficiently to result in an improved general method for preparing nitriles. Advantages are also realized in conversion of primary and secondary bromides to their corresponding nitriles. Use of dimethyl sulfoxide allows preparative displacement of halides of the neophyl and neopentyl types by cyanide ion without rearrangement. Typical procedures which illustrate the various experimental methods are described.

Sodium or potassium cyanide reacts slowly (twenty-four to ninety-six hours) with primary chlorides in aqueous ethanol to give the corresponding nitriles in good yields, accompanied by alcohols, ethers, and olefins.[2] The procedure is unsatisfactory for low boiling nitriles[3] because of the difficulty of isolating the products from the solvent. The method has been improved by use of higher boiling solvents such as ethylene glycol,[3] methyl Cellosolve,[4a,b] tetrahydrofurfuryl alcohol,[4a] and dimethylformamide;[4b] however, the reaction is still slow because of the insolubility of the inorganic cyanides and offers disadvantages for the usual laboratory synthesis. Secondary chlorides give nitriles in only 30% yield in aqueous ethanol;[5] substitution also occurs slowly and in poor yield in methyl Cellosolve and dimethylformamide.[4b,6] Primary bromides are converted efficiently to nitriles in aqueous ethanol[7a] or ethylene glycol (better).[3,7b] Secondary bromides, however, in aqueous ethanol[8a] or ethylene glycol[3] give nitriles in unsatisfactory (27–39%) yields, and separation of the product from accompanying alcohols and ethers is difficult.[8b]

It is now reported that typical primary chloroalkanes (Table I) react rapidly and exothermically[9] with sodium cyanide in partial solution in dimethyl sulfoxide to give the corresponding nitriles in excellent yields. The nitriles are conveniently isolated from the reaction mixture by dilution with water followed by suitable extraction. At the preferred reaction temperatures of 120–140° the conversion of primary chlorides to nitriles may usually be completed in one half to two hours. The reaction is applicable to the slow conversion of 1-chloro-2-methyl-2-phenylpropane (neophyl chloride)[10] to 3-methyl-3-

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[2] (a) H. B. Hass and J. R. Marshall, *Ind. Eng. Chem.*, **23**, 352 (1931); (b) H. E. Fierz-David and W. Kuster, *Helv. Chim. Acta*, **22**, 82 (1939); (c) H. Suida and F. Drahowzal, *Chem. Ber.*, **75**, 991 (1942); (d) K. Ahmad and F. M. Strong, *J. Am. Chem. Soc.*, **70**, 1699 (1948); (e) K. Ahmad, F. M. Bumpus, and F. M. Strong, *J. Am. Chem. Soc.*, **70**, 3393 (1948).

[3] R. N. Lewis and P. V. Susi, *J. Am. Chem. Soc.*, **74**, 840 (1952).

[4] (a) A. O. Rogers, U. S. Patent **2,415,261**, Feb. 4, 1947; (b) H. B. Copelin, U. S. Patent **2,715,137**, Aug. 9, 1955.

[5] Ref. 2a; no experimental details were given.

[6] 2-Chlorobutane does not react with sodium cyanide in ethylene glycol.[3]

[7] (a) C. S. Marvel and E. M. McColm, *Org. Syntheses*, **5**, 103 (1925); (b) F. B. LaForge, N. Breen, and W. A. Gersdoff, *J. Am. Chem. Soc.*, **70**, 3709 (1948).

[8] (a) M. T. Rogers and J. D. Roberts, *J. Am. Chem. Soc.*, **68**, 843 (1946); (b) T. Moritsugu, M.S. Thesis, The Ohio State University, 1951.

[9] Cooling is sometimes required to keep the reaction under control.

[10] Halides of the neopentyl type are reported to be unreactive to cyanide ion; A. Franke, *Monatsh. Chem.*, **34**, 1893 (1913); F. C. Whitmore and G. H. Fleming, *J. Am. Chem. Soc.*, **55**, 4161 (1933).

phenylbutyronitrile (69% conversion, 29% yield). The secondary chloro compounds, 2-chlorobutane and chlorocyclopentane (Table I), react relatively slowly (*ca.* three hours) to give the corresponding nitriles in moderate yields (65–70%). As a general method for preparing nitriles from primary or secondary chlorides, the reaction in dimethyl sulfoxide is much superior to that in the previous solvents.

t-Butyl chloride and cyclohexyl chloride in dimethyl sulfoxide react either in the presence or absence of sodium cyanide to give olefins, malodorous decomposition products, and tars.[11] Benzyl chloride gave the corresponding nitrile (Table I) in excellent yield. Better yields of benzyl cyanide were obtained at lower temperatures because reaction between the halide and the solvent was minimized.[12] *p*-Nitrobenzyl chloride reacted with sodium cyanide in dimethyl sulfoxide to give 4,4′-dinitrostilbene.[13]

The reaction of sodium cyanide and alkyl halides was extended to representative bromides.[14] 1-Bromobutane reacts rapidly at 60–90° with sodium cyanide to give valeronitrile in excellent yield (Table I). The reaction is exothermic and, if the temperature is too high (>90°), the yield is lowered because of reaction of the halide with the solvent.[15,16] 2-Bromobutane reacts to give 2-methylbutyronitrile in 41% yield. The reaction mixtures are dark brown and noxious; the relatively poor yield and the complex products probably result from competing reactions with dimethyl sulfoxide. The yield with the secondary bromide is slightly superior, however, to those reported when ethanol and ethylene glycol are used as solvents, and there are experimental advantages in terms of reaction rate and isolation of products.

TABLE I

REACTION OF ALKYL AND CYCLOALKYL HALIDES WITH SODIUM OR POTASSIUM CYANIDE IN DIMETHYL SULFOXIDE

Halide	Cyanide[a]	Reaction Temp., °	Reaction Time, hr.[b]	Yield of Nitrile, %
1-Chlorobutane[c]	NaCN	140	0.25	93
1-Chlorobutane[c]	KCN	120–140	10	69
1-Chloro-2-methylpropane	NaCN	140[d]	0.5	88[e]
1-Chloro-3-methylbutane	NaCN	100–140	2	85[f]
1-Chloro-2-methyl-2-phenylpropane[c]	NaCN	120	24	26
Benzyl chloride	NaCN	35–40[g]	2.5	92[h]
p-Nitrobenzyl chloride	NaCN	35–40	1	0[i]
2-Chlorobutane	NaCN	120–145	3	64[j]
2-Chlorobutane	KCN	120–138[k]	24	42
Chlorocyclopentane[c]	NaCN	125–130	3	70
Chlorocyclohexane[l]	NaCN	130–80	4	0[l]
2-Chloro-2-methylpropane	NaCN	130–105	4	0[m]
1-Bromobutane[n]	NaCN	60–90[n]	0.6	92[o]
1-Bromo-2-methylpropane[c]	NaCN	70	2	62
2-Bromobutane	NaCN	70	6	41[p]

[a] The ratio of halide (moles), cyanide (moles), and DMSO (ml.) usually used was 1:1.1:250. [b] The reaction time listed is the sum of that for addition of the halide and subsequent reaction at the given temperature. [c] See Experimental. [d] The halide was added in 10 min. to the initial mixture at 80°. The reaction is mildly exothermic and was completed by heating to 140° until refluxing ceased. [e] B.p. 128°, n^{20}_{D} 1.3926; see ref. 23. [f] B.p. 151–155°, n^{20}_{D} 1.4047–1.4051; lit. b.p. 150–155°, H. Rupe and K. Glenz, *Helv. Chim. Acta*, **5**, 939 (1922). [g] The reaction mixture was cooled externally. [h] B.p. 90.5–91° (5 mm.), n^{20}_{D} 1.5237-1.5238; lit. b.p. 115–120° (10 mm.), n^{20}_{D} 1.5242; J. W. Bruhl, *Z. physik Chem.*, **16**, 218 (1895). [i] 4,4′-Dinitrostilbene is formed in 78% crude yield, m.p. 286–288°; lit. 288°; P. Ruggli and F. Lang, *Helv. Chim. Acta*, **21**, 42 (1938); R. Walden and A. Kernbaum, *Chem. Ber.*, **23**, 1959 (1890). [j] B.p. 123.5–124° (742 mm.), n^{20}_{D} 1.3898–1.3900; lit. b.p. 125°; M. Hanriot and L. Bouveault, *Bull. soc. chim. France*, (3) **1**, 172 (1889). [k] The halide was added dropwise in 6 hr. to the mixture at 120–125°; the mixture was then heated for 18 hr. until it reached 138°. [l] The reaction mixture became dark and gave cyclohexene, gases, and a black intractable product. [m] Upon initiating reaction at 130°, gases (2-methylpropene, hydrogen cyanide, and formaldehyde) were evolved, the temperature dropped to 105°, and black resinous materials were formed. The desired product was not obtained at lower reaction temperatures. [n] The bromide was added in 30 min. to the cyanide mixture at 60° while effecting cooling of the reaction; the mixture was then heated for 15 min. at 90°. [o] B.p. 138–139° (742 mm.), n^{20}_{D} 1.3970; see Ref. 19. [p] Upon addition of the 2-bromobutane, the temperature was maintained at 55–60° by intermittent cooling. In subsequent reaction gases were evolved and the mixture became progressively darker and malodorous.

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(11) (a) These results are consistent with current substitution theory, the results in related systems, and the effects of ionizing solvents on such halides. (b) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 319, 426. (c) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951). (d) S. Smith and J. Takahashi, unpublished work as quoted in ref. 12b.

(12) Reactions of halides with dimethyl sulfoxide have been investigated by (a) R. Kuhn and H. Trischmann, *Ann.*, **611**, 117 (1958); (b) S. G. Smith and S. Winstein, *Tetrahedron*, **3**, 317 (1958) and (c) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Am. Chem. Soc.*, **81**, 4113 (1959) and related previous paper.

(13) This reaction also occurs with cyanide ion in ethanol. Its mechanism has been discussed by C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956) and G. Hahn, *Chem. Ber.*, **62**, 2485 (1929).

(14) Reaction of 1-bromobenzocyclobutene with sodium cyanide in dimethyl sulfoxide to give 1-cyanobenzocyclobutene has been reported by our colleagues, M. P. Cava, R. L. Little, and D. R. Napier, *J. Am. Chem. Soc.*, **80**, 2260 (1958). Their use of dimethyl sulfoxide was based on suggestions and experimental details of prior observations by the present authors (Nov. 26–Dec. 21, 1955) on the advantageous use of the solvent in effecting conversions of chlorides and bromides to nitriles. The absence of any reference resulted from the fact that knowledge of the unpublished method was so common in this laboratory that it had assumed routine use. NOTE ADDED IN PROOF: R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25**, 257 (1960) have also described the advantageous use of dimethyl sulfoxide in preparing nitriles from alkyl chlorides.

(15) In the absence of sodium cyanide, extensive reaction of the bromide occurs with the solvent; see ref. 12.

The reaction of alkyl chlorides and bromides with potassium cyanide in partial solution in dimethyl sulfoxide is of significance with respect to preparative purposes in that displacement occurs much more slowly when compared with sodium cyanide.[17] The reason for this difference was not investigated. The synthesis of nitriles from halides and cyanides was also attempted in dimethylformamide, sulfolane, and dimethyl sulfolane. Because the yields are lower and longer reaction times are required, these solvents are not as advantageous as dimethyl sulfoxide.

EXPERIMENTAL[18]

Reaction of 1-chlorobutane and sodium or potassium cyanide. Valeronitrile. (*Sodium Cyanide*). 1-Chlorobutane (93 g., 1 mole) was added in 10–15 min. to a rapidly stirred partially-soluble mixture of sodium cyanide (53 g., 1.08 moles, Reagent) in dimethyl sulfoxide (250 ml., technical; Stepan Chemical Company) at 80°. The temperature of the mixture rose rapidly and was kept at 140 ± 5° by cooling with water when necessary. During the reaction the mixture became more fluid, and the insoluble salts more crystalline. After the 1-chlorobutane had been added, the temperature dropped rapidly, and the reaction was apparently complete. The brown reaction mixture was cooled, diluted with water to a volume of *ca.* 1000 ml., and extracted with ether (3 × 150 ml.). The pale yellow ether extracts were washed with 6*N* hydrochloric acid (to hydrolyze the small amount of noxious isocyanide) and water, and dried over calcium chloride. After removal of ether, the residue was rectified over phosphorus pentoxide to give forerun (6.0 ml.), b.p. 110–138° (747 mm.), and valeronitrile (77 g., 0.93 mole, 93%), b.p. 138–139° (747 mm.), n_D^{20} 1.3970–1.3972; lit., b.p. 140.75°,[19a] n_D^{15} 1.3990.[19b]

In a similar manner, 1-chlorobutane (465 g., 5 moles), sodium cyanide (95% purity, 265 g., 5.5 moles) and dimethyl sulfoxide (475 ml.) gave valeronitrile (388 g., 4.7 moles), b.p. 138–139°, in 94% yield. In large runs the relative volume of dimethyl sulfoxide was thus lowered.

(*Potassium cyanide*). 1-Chlorobutane (93 g., 1.0 mole) was added *dropwise* in 2 hr. to a stirred suspension of potassium cyanide (70 g., 1.06 moles) in dimethyl sulfoxide (250 ml.) maintained at 120–125°. The mixture was then heated until the pot temperature rose to 140° (8 hr.) and refluxing ceased. The dark-brown evil-smelling mixture was diluted with water and worked up as described in the preceding experiments to give a small forerun (4.0 g., b.p. 110–138°) and valeronitrile (57.5 g., 0.69 mole, 69%), b.p. 138–139° (747 mm.).

Reaction of 1-chloro-2-methyl-2-phenylpropane and sodium cyanide. 3-Methyl-3-phenylbutyronitrile. A stirred mixture of 1-chloro-2-methyl-2-phenylpropane (neophyl chloride, 84.39 g., 0.5 mole, b.p. 110–112° (12 mm.), n_D^{25} 1.5216), sodium cyanide (40.0 g., 0.82 mole) and dimethyl sulfoxide (250 ml.) was heated at 120° for 24 hr. The resulting dark-brown mixture was cooled, diluted with water and worked up for product. Rectification gave 1-chloro-2-methyl-2-phenylpropane (28.0 g., 0.163 mole, 32.6%; b.p. 115–135° (18 mm.), n_D^{25} 1.5216–1.5200) and *3-methyl-3-phenylbutyronitrile* (14.1 g., 0.089 mole, 26% yield, 69% conversion of neophyl chloride), b.p. 135–137° (18 mm.), n_D^{25} 1.5130–1.5132. The physical constants of an analytical sample are b.p. 136° (18 mm.), n_D^{25} 1.5130.

Anal. Calcd. for $C_{11}H_{13}N$: N, 8.80. Found: N, 8.83.

The structure of the 3-methyl-3-phenylbutyronitrile was confirmed by its conversion (99%) to 3-methyl-3-phenylbutyric acid, m.p. 54–56°, by saponification in refluxing aqueous ethylene glycol (12 hr.) and subsequent acidification; m.p. 58–59° (from carbon tetrachloride-hexane); lit.,[20] m.p., 58–59.5°. The mixed melting point with an authentic sample was undepressed.

Reaction of chlorocyclopentane and sodium cyanide. Cyclopentanecarbonitrile. Chlorocyclopentane (210 g., 2.0 moles) was added in 20 min. to a stirred mixture of sodium cyanide (110 g., 2.25 moles) in dimethyl sulfoxide (530 ml.) at 115°. The reaction was mildly exothermic. The mixture was heated at 125–130° for 3 hr. and low boiling material began to reflux. A portion was collected and identified as cyclopentene, b.p. 44–46°, n_D^{20} 1.4208; lit.,[21] b.p. 44.24°, n_D^{20} 1.4224. The dark-brown reaction mixture was cooled and worked up for product. Rectification gave cyclopentanecarbonitrile (133 g., 1.4 moles, 70%), b.p. 74–74.5° (28 mm.), n_D^{20} 1.4429; lit.[8a] b.p. 74.5–75° (30 mm.), n_D^{25} 1.4404.

Reaction of 1-bromo-2-methylpropane and sodium cyanide. 3-Methylbutyronitrile. 1-Bromo-2-methylpropane (137 g., 1 mole) was added in 20 min. to a warm (60°) stirred mixture of sodium cyanide (55 g., 1.12 moles) in dimethyl sulfoxide (400 ml.); the temperature was maintained between 55 and 60° by intermittent cooling. Sodium bromide began to gel near the end of the addition. The mixture was then maintained at 70° for 2 hr. to allow completion of the reaction. During this period gases were evolved and the mixture became progressively darker and malodorous. Isolation of the product in the usual manner gave 3-methylbutyronitrile (51 g., 0.615 mole, 62%), b.p. 128° (743 mm.), n_D^{20} 1.3927; lit.,[22] b.p. 128–129°.

When the reaction was effected at 90–100°, more 1-bromo-2-methylpropane reacted with dimethyl sulfoxide, and the yield of nitrile dropped to 48%.

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(16) T. Dougherty, Ph.D. Thesis, The Ohio State University, 1959 has found that 1,3-dibromo-2,2-dimethylpropane (neopentyl dibromide) reacts with equivalent amounts of sodium cyanide in dimethyl sulfoxide in 66 hr. at 90–95° to give 4-bromo-3,3-dimethylbutanenitrile (23% conversion) and 2,2-dimethyl-1,3-propanedinitrile (26–30% conversion). The initial dibromide recovered ranged from 35–50%. The details of this experiment will be published elsewhere.

(17) (a) In using potassium cyanide with chlorides, the temperature of the mixture had to be maintained above 120° in order to effect reaction. Low boiling halides thus had to be added dropwise to a heated mixture of potassium cyanide in dimethyl sulfoxide at a rate such that the temperature is not significantly lowered. (b) Sodium and potassium cyanides are appreciably soluble in warm DMSO; the actual solubilities at various temperatures were not determined.

(18) The preparative examples described are representative of the various experimental procedures summarized in Table I.

(19) (a) G. Lievens, *Bull. soc. chem. Belges*, **33**, 126 (1924); (b) S. Sugden, *J. Chem. Soc.*, **125**, 1186 (1924).

(20) F. C. Whitmore, C. A. Weissgerber, and A. C. Shabica, Jr., *J. Am. Chem. Soc.*, **65**, 1471 (1943).

(21) *Selected Values of Properties of Hydrocarbons*, API Research Project 44, 1958, Table 58a.

(22) H. Rupe and E. Hodel, *Helv. Chim. Acta*, **7**, 1023 (1924).