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A Convenient Procedure for the Preparation of Alkyl Nitriles from Alkyl Halides. Acetone Cyanohydrin as an In Situ Source of Cyanide Ion

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A CONVENIENT PROCEDURE FOR THE PREPARATION OF ALKYL NITRILES FROM ALKYL HALIDES. ACETONE CYANOHYDRIN AS AN *IN SITU* SOURCE OF CYANIDE ION.

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Abstract: A convenient preparation of alkyl nitriles from alkyl halides is described. Acetone cyanohydrin is employed as the source of cyanide ion.

Replacement of halide by cyanide is a reaction of synthetic importance. It allows extension of the chain by one carbon atom and provides entry into the family of carboxylic acid derivatives.[1] In the classic procedure a mixture of the aliphatic halide and an aqueous alcoholic solution of sodium or potassium cyanide is kept under reflux. Under these conditions primary, benzylic and allylic halides give good yields of the corresponding nitriles while secondary halides react only in moderate yield. Newer variations of this conversion call for dipolar aprotic solvents,[2] phase-transfer catalysts,[3] or guanidinium[4] and tetraalkylammonium cyanides.[5]

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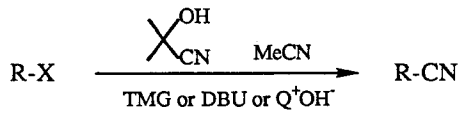
The latter provide an easy and efficient approach to the conversion of halides to nitriles. For example, ethyl 2-bromopropionate and tetraethylammonium cyanide in refluxing dichloromethane give ethyl 2-cyanopropionate (**1**) in 85% yield,[5] while the same conversion using aqueous ethanolic potassium cyanide at 78-100 °C gives only 12-20% yield.[6] However, both tetraethyl- and tetrabutylammonium cyanides are expensive, hygroscopic and toxic.

We report more convenient ways to convert alkyl halides to nitriles. In one approach a solution of quaternary ammonium hydroxide (Q^+OH^-)is treated with acetone cyanohydrin and the appropriate alkyl halide in acetonitrile (eq 1). In another, the hydroxide is replaced by a

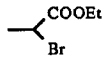
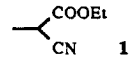
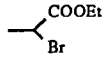
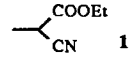
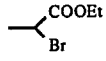
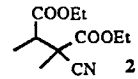
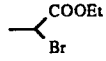
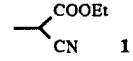
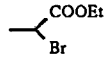
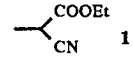
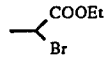
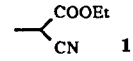
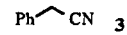
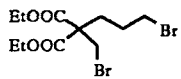
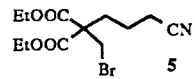
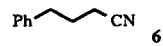


(1)

guanidine or amidine base such as 1,1,3,3-tetramethylguanidine (TMG) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (eq 1). The amidine reacts with acetone cyanohydrin forming the cyanide salt.[7] Acetone cyanohydrin is a convenient source of hydrogen cyanide. It was successfully used in the Gatterman reaction,[8] the Michael hydrocyanation of α,β-unsaturated systems,[7,9] preparation of cyanocarboxylic acids,[10] the Mitsunobu reaction[11] and regiospecific opening of epoxides.[12]

In the conversion of ethyl 2-bromopropionate to ethyl 2-cyanopropionate (**1**) we found that the course of the reaction depends on the conditions applied (Table). When no solvent was used diethyl 2,3-dimethyl-2-cyanosuccinate (**2**)[6,13] was the only product found (entry 3). Cyanosuccinate **2** accompanied **1** under the conditions employed in entries 2 and 4, but we found only traces of **2** when TMG was used (entry 6). Therefore we employed TMG or DBU to obtain good yields of pure cyanomalonate **1**, as determined by GC-MS, ^1H and ^{13}C nmr, as well as of the nitriles **3-6** (entry 6-11).

TABLE: Acetone Cyanohydrin Promoted Halide Displacement

Entry	Halide	Base	Nitrile	Yield %[a]
1		Bu_4NCN	 **1**	77[b]
2		Bu_4NOH	 **1**	68[c]
3		Bu_4NOH[d]	 **2**	59[e]
4		Bu_4NOH[f]	 **1**	44[g]
5		$BnNMe_3OH$	 **1**	79
6		TMG	 **1**	88
7		TMG	 **3**	92
8		TMG	 **3**	93
9		TMG	 **4**	71
10		TMG	 **5**	82
11		DBU	 **6**	90

a. Yield of isolated nitrile. b. See ref. 5. c. The crude reaction contained a 2:1 mixture of **1** and **2** (by GC-MS). d. No solvent was used. e. 1:1 mixture of diastereoisomers. f. A solution of tetrabutylammonium hydroxide and acetone cyanohydrin in acetonitrile was added to a solution of the bromoester in acetonitrile. g. The crude reaction contained a 0.85:1 mixture (determined by GC-MS) of **1** and **2**.

EXPERIMENTAL

General Methods. ^1H NMR spectra were determined in $CDCl_3$ on a Bruker IBM AF-300 (300.13 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ (7.26 ppm). ^{13}C NMR spectra were recorded in $CDCl_3$ at 75.46 MHz on a Bruker IBM-AF 300. Carbon chemical shifts are reported in parts per million (ppm) relative to $CDCl_3$ (77.09). Infrared spectra (IR) were obtained as thin films between sodium chloride plates on an IBM IR/32 FT-IR spectrophotometer, are reported in wave numbers (cm^{-1}) and are uncalibrated. High-resolution mass spectra (HRMS) were recorded on a Varian MAT CH-5DF spectrometer and were calibrated by peak matching. Gas chromatography-mass spectroscopy (GC-MS) was performed on a Hewlett Packard 5890 GC with an HP 5970 Mass Selective Detector (EI, 70 ev) using a 12 m x 0.2 mm I.D. x 0.33 μm fused silica capillary column of 100% dimethyl polysiloxane (HP-1, Hewlett-Packard). The GC-MS conditions were: initial temp. 70 °C, final temp. 300 °C, temp. rate 25 °C/min., inj. temp. 250 °C, det. temp. 280 °C. Flash chromatography was carried out on Merck 230-400 mesh silica gel with 9:1 v/v hexane-ethyl acetate. The alkyl halides and acetone cyanohydrin (Aldrich) were used as received. TMG, DBU, Triton B (40% solution in MeOH) and tetrabutylammonium cyanide were purchased from Aldrich and used as received.

General Procedure. Alkyl halide (10 mmol) was dissolved with acetone cyanohydrin (1.4 mL, 15 mmol) in acetonitrile (10 mL). A solution of the base (11 mmol) in acetonitrile (20 mL) was added from a dropping funnel within 20-30 min. The reaction mixture was stirred

for 14-24 hr in order to complete the conversion as followed by tlc (9 : 1 hexanes-ethyl acetate). Evaporation on a rotary evaporator gave a semisolid which was partitioned between water (10 mL) and ether (40 mL). The organic layer was washed with water (3 x 5 mL) and dried over anhydrous magnesium sulfate. After filtration to remove magnesium sulfate and evaporation of the ether, the crude product was subjected to flash chromatography on 10 g of silica gel.

The spectroscopic data for **1, 3, 4** and **6** were in agreement with those of authentic samples purchased from commercial sources. For analytical purposes, the diastereoisomers of **2**[6,13] were separated by flash chromatography (50 g of silica gel, 1% ethyl acetate in hexane).

2-I : GC-MS: t_r 7.4 min. (purity: 99%). ^{1}H-NMR δ 4.29 (q, J=7.1, 2H), 4.18 (q, J=7.1, 2H), 2.74 (q, J=7.2, 1H), 1.63 (s, 3H), 1.38 (d, J=7.1, 3H), 1.33 (t, J=7.2, 3H), 1.27 (t, J=7.2, 3H). ^{13}C-NMR δ 170.9 (s), 167.7 (s), 118.0 (s), 62.7 (t, J=149), 61.0 (t, J=148), 45.8 (s), 44.6 (d, J=136), 20.0 (q, J=133), 13.7 (q, J=127), 13.5 (q, J=129, two overlapping carbons). MS m/e (rel. intensity) 227 (1, M^+), 182 (26, M^+-OEt), 154 (37, M^+-COOEt), 126 (13), 110 (32), 82 (100). HRMS calc'd for $C_{11}H_{17}NO_4$ 227.1158; found 227.1158.

2-II : GC-MS: t_r 7.6 min. ^{1}H-NMR δ 4.28 (q, J=7.2, 2H), 4.18 (q, J=7.2, 2H), 3.03 (q, J=7.4, 1H), 1.61 (s, 3H), 1.42 (d, J=7.4, 3H), 1.33 (t, J=7.2, 3H), 1.26 (t, J=7.2, 3H). ^{13}C-NMR δ 171.8 (s), 168.9 (s), 117.9 (s), 62.4 (t, J=149), 61.0 (t, J=148), 45.6 (s), 44.6 (d, J=135), 22.0 (q, J=133), 13.5 (q, J=127), 13.4 (q, J=127), 12.1 (q, J=130). MS m/e (rel. intensity) 227 (1, M^+), 182 (33, M^+-OEt), 154 (43, M^+-COOEt), 126 (18), 110 (35), 82 (100). HRMS calc'd for $C_{11}H_{17}NO_4$ 227.1158; found 227.1158.

5 : ^{1}H-NMR δ 4.24 (q, J=7.1, 4H), 3.79 (s, 2H), 2.40 (t, J=7.2, 2H), 2.22-2.17 (m, 2H), 1.65-1.56 (m, 2H), 1.28 (t, J=7.1, 6H) (purity: 99%). ^{13}C-

NMR δ 168.4 (s), 118.9 (s), 62.6 (t, J=149), 58.1 (s), 32.8 (t, J=157), 30.8 (t, J=132), 20.2 (t, J=131), 17.2 (t, J=135), 14.0 (q, J=127). IR 2983, 2247, 1730, 1446, 1368, 1273, 1184, 1090, 1022, 858 cm^{-1}. MS m/e (rel. intensity) 319, 321 (1, M^+), 274, 276 (10, M^+-OEt), 251, 253 (5), 200 (20), 173 (65), 122 (100). HRMS calc'd for $C_{12}H_{18}BrNO_4$ 319.0419; found 319.0419.

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