Alkylation of Acetonitrile

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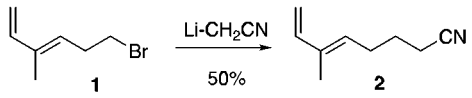
We recently needed to homologate bromide **1**[1] to nitrile **2**. Although multistep procedures for effecting this transformation have been established,[2] the straightforward alkylation of lithioacetonitrile had not been optimized.[3,4] We now report that this direct alkylation can in fact be effected in reasonable yield.



The inherent difficulty with this alkylation is that the product (e.g., **2**) is *more* acidic than acetonitrile. Once the alkylation has proceeded to partial conversion, the acetonitrile anion can act either as a nucleophile, to convert the alkylating agent to the product, or as a base, to deprotonate the product that has already been formed. The anion resulting from the latter process then reacts with the alkylating agent to give the dialkylated nitrile.

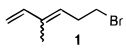
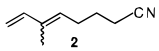
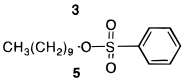
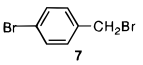
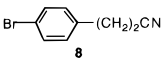
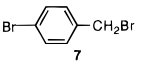
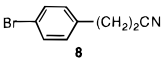
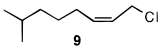
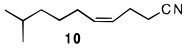
To solve this problem, we have developed two experimental protocols (Table 1). In procedure A, we add the alkylating agent all at once to an excess of lithioacetonitrile (prepared by the addition of *n*-BuLi in hexane to acetonitrile in THF at −78 °C) at low temperature. In procedure B, we add lithioacetonitrile slowly, via cannula, to the alkylating agent at 0 °C. While both protocols are effective, procedure B works for a broader range of alkylating agents. With both procedures, the major competing side reaction is dialkylation.

We believe that this direct alkylation of lithioacetonitrile will be a useful addition to the armamentarium of organic synthesis.

Experimental Section[5]

Preparation of 6-Methyl-5,7-octadienenitrile (2) (Method A). A solution of acetonitrile (6.00 mL, 115 mmol) in 140 mL of dry THF was added to *n*-BuLi (48.1 mL, 2.39 M in hexanes) at −78 °C under N_2. The mixture was stirred at −78 °C for 1 h, after which a solution of bromide **1** (8.07 g, 46.1 mmol) in 57 mL of dry THF was added all at once. The temperature was kept at −78 °C for 1 h, and then 50 mL of water was added and the mixture partitioned between 20% MTBE/petroleum ether and water. The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed to give **2** as a colorless oil (3.12 g, 50% yield): TLC R_f (5% MTBE/petroleum ether) = 0.33; IR (film) 2937, 2246, 1607, 1451 cm^{-1}; ^1H NMR δ 6.74 (dd, 1/3H, J = 10.7 Hz, 17.5 Hz), 6.36 (dd, 2/3H, J = 10.7 Hz, 17.5 Hz), 5.22 (m, 3H), 2.32 (m, 4H), 1.77 (m, 5H); ^{13}C NMR δ u 135.6, 134.0, 119.2, 114.1, 111.2, 26.5, 25.7, 25.2, 24.9, 16.1, 16.0 d 140.6, 132.7, 129.5, 127.6, 19.4, 11.3; MS *m*/*z* (rel inten) 135 (41), 134 (11), 120 (13), 107 (11), 106 (9.5), 95 (39), 81 (100); exact mass calcd for $C_9H_{13}N$ 135.1048, found 135.1052.

Table 1

Entry	Substrate	Method	Product	Yield[a]
1	 **1**	A	 **2**	50%
2	$CH_3(CH_2)_{10}CH_2Br$ **3**	A	$CH_3(CH_2)_{11}CH_2CN$ **4**	79%
3	 **5**	B	$CH_3(CH_2)_9CH_2CN$ **6**	72%
4	 **7**	A	 **8**	50%
5	 **7**	B	 **8**	64%
6	 **9**	B	 **10**	52%
7	$BrCH_2(CH_2)_6CH_2Br$ **11**	B[b]	$BrCH_2(CH_2)_7CH_2CN$ **12**	74%

[a] Yields are for isolated products. [b] Only 1 equiv of lithioacetonitrile was used. The yield is based on starting material not recovered (conversion was 50%).

Preparation of tetradecanenitrile (4) (method A): TLC R_f (5% MTBE/petroleum ether) = 0.30; bp $(bath)_{0.5mm}$ = 100−110 °C; IR (film) 2924, 2854, 2246, 1466 cm^{-1}; ^1H NMR δ 2.33 (t, 2H, J = 7.1 Hz), 1.64 (pentet, 2H, J = 7.2 Hz), 1.44 (m, 2H), 1.26 (bs, 18H), 0.88 (t, 3H, J = 6.6 Hz); ^{13}C NMR δ u 119.7, 31.8, 29.5, 29.4, 29.2, 28.7, 28.6, 25.3, 22.6, 17.0 d 14.0; MS *m*/*z* (rel inten) 194 (0.95), 180 (14), 166 (26), 152 (22), 138 (26), 125 (11), 124 (50), 111 (41), 110 (76), 97 (100); exact mass calcd for $C_{14}H_{28}N^+$ (M + 1) 210.2222, found 210.2227.

Preparation of Dodecanenitrile (6) (Method B). A solution of acetonitrile (0.26 mL, 5.0 mmol) in 6.5 mL of dry THF was added to *n*-BuLi (2.25 mL, 2.40 M in hexanes) at −78 °C under N_2. The mixture was stirred at −78 °C for 1 h and then transferred by cannula to a solution of benzenesulfonate **5** (597 mg, 2.00 mmol) in 2.5 mL of dry THF at 0 °C over 20 min. The mixture was stirred for an additional 15 min and then was quenched with 10 mL of water. The mixture was partitioned between 50% MTBE/petroleum ether and saturated brine. The combined organic extract was dried (Na_2SO_4), concentrated, and distilled bulb-to-bulb to give **8** as a colorless oil (261 mg, 72% yield): bp $(bath)_{0.5mm}$ = 80−90 °C; TLC R_f (10% MTBE/petroleum ether) = 0.55; IR (film) 2927, 2922, 2239, 1460 cm^{-1}; ^1H NMR δ 2.33 (t, 2H, J = 7.0 Hz), 1.62 (pentet, 2H, J = 7.2 Hz), 1.40 (m, 16H), 0.88 (t, 3H, J = 6.4 Hz); ^{13}C NMR δ u 119.5, 31.7, 29.31, 29.28, 29.1 (2), 28.5, 28.4, 25.1, 22.4, 16.8 d 13.8; MS *m*/*z* (rel inten) 182 (M + 1) (4.2), 180 (4.8), 152 (31), 138 (57), 125 (15), 124 (65), 111 (48), 110 (84), 98 (15), 97 (100); exact mass calcd for $C_{12}H_{23}N$ 181.1831, found 181.1842.

Preparation of 3-(4-bromophenyl)propanenitrile (8) (method A or B): TLC R_f (25% MTBE/petroleum ether) = 0.30; IR (film) 3027, 2936, 2246, 1592, 1488 cm^{-1}; ^1H NMR δ 7.45 (d, 2H, J = 8.3 Hz), 7.10 (d, 2H, J = 8.3 Hz), 2.90 (t, 2H, J = 7.3 Hz), 2.59 (t, 2H, J = 7.3 Hz); ^{13}C NMR δ u 136.9, 121.0, 118.7, 30.8, 19.0 d 131.8, 129.9; MS *m*/*z* (rel inten) 211 (54), 209 (55), 171 (100), 169 (97), 129 (3.7), 128 (4.1), 103 (9.7), 102 (9.2); exact mass calcd for $C_9H_8N^{81}Br$ 210.9819, found 210.9793, $C_9H_8N^{79}Br$ 208.9840, found 208.9826. Anal. Calcd for C_9H_8BrN: C, 51.46; H, 3.84. Found: C, 51.47; H, 4.04.

Preparation of (*Z*)-9-Methyl-4-decenenitrile (10) (Method B). The (*Z*)-allylic chloride was prepared by the literature route:[6] TLC R_f (5% MTBE/petroleum ether) = 0.33; bp $(bath)_{0.5mm}$

(1) Julia, M.; Julia, S.; Stalla-Bourdillon, B.; Descoins, C. *Bull. Soc. Chim. Fr.* **1964**, 2533.

(2) For previous reports of the direct alkylation of acetonitrile, see: (a) Barrett, G. C.; Grattan, T. J. *Tetrahedron Lett.* **1979**, 4237. (b) Larcheveque, M.; Mulot, P.; Cuvigny, T. *J. Organomet. Chem* **1973**, *C33*. (c) Horner, L.; Gusten, H. *Justus Liebigs Ann. Chem.* **1962**, *652*, 99. (d) Savoia, D.; Trombini, C.; Umani-Ronchi, A. *Tetrahedron Lett.* **1977**, 653. (e) Zhou, S.-E.; Anne, S.; Vandewalle, M. *Tetrahedron Lett.* **1996**, 37, 7637.

(3) For a review of nitrile alkylations, see: Arseniyadis, S.; Kyler, K. S; Watt, D. S. *Organic Reactions*; John Wiley & Sons, Inc.: New York, 1984; Vol. 31, p 1.

(4) (a) For the displacement of allylic and benzylic halides with the organocopper derivative of acetonitrile, see: Corey, E. J.; Kuwajima, I. *Tetrahedron Lett.* **1972**, 487. (b) For the displacement of halides, most efficiently allylic and benzylic, with the organozinc derivative of acetonitrile, see: Orsini, F. *Synthesis* **1985**, 500.

(5) For general experimental procedures, see: Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.

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= 75−80 °C; IR (film) 2953, 2923, 2246, 1633, 1462 cm^{-1}; ^1H NMR δ 5.56 (m, 1H), 5.36 (m, 1H), 2.37 (m, 4H), 2.03 (dd, 2H, J = 7.3 Hz), 1.53 (m, 1H), 1.37 (m, 2H) 1.18 (m, 2H), 0.87 (d, 6H, J = 6.5 Hz); ^{13}C NMR δ u 119.1, 38.3, 27.2, 27.0, 23.0, 17.2 d 133.3, 124.8, 27.6, 22.3 (2); MS m/z (rel inten) 150 (43), 137 (7.7), 136 (13), 123 (7.1), 122 (50), 110 (15), 108 (17), 69 (100); exact mass calcd for $C_{11}H_{19}N$ 165.1517, found 165.1502.

Preparation of 1-bromodecanenitrile 12 (method B): TLC R_f (5% MTBE/petroleum ether) = 0.26; IR (film) 2929, 2855, 2245, 1463, 1427 cm^{-1}; ^1H NMR δ 3.41 (t, 2H, J = 6.8 Hz), 2.34 (t, 2H, J = 7.0 Hz), 1.86 (pentet, 2H, J = 7.0 Hz), 1.66 (pentet, 2H, J = 7.2 Hz), 1.40 (m, 10H); ^{13}C NMR δ u 119.7, 33.9, 32.6, 29.0, 28.53, 28.48 (2), 28.0, 25.2, 17.0; MS m/z (rel inten) 232 (9.3), 230 (6.6), 204 (40), 202 (40), 191 (6.8), 190 (100), 189 (7.1), 188 (97); exact mass (CI) calcd for $C_{10}H_{19}{}^{79}BrN^+$ 232.0700, found 232.0688, $C_{10}H_{19}{}^{81}BrN^+$ 234.0680, found 234.0689.

Acknowledgment. We thank D. S. Watt and R. C. Larock for helpful discussions.

Supporting Information Available: ^1H and ^{13}C spectra for compounds **2**, **4**, **6**, **8**, **10**, and **12** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(6) Trost, B. M.; Taber, D. F.; Alper, J. B. *Tetrahedron Lett.* **1976**, 3857.