Improved Procedure for the Synthesis of Substituted β-Hydroxynitriles

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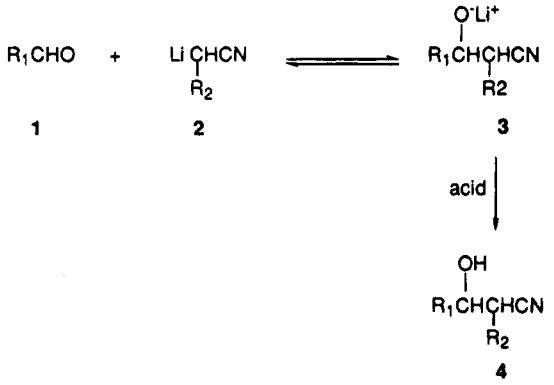
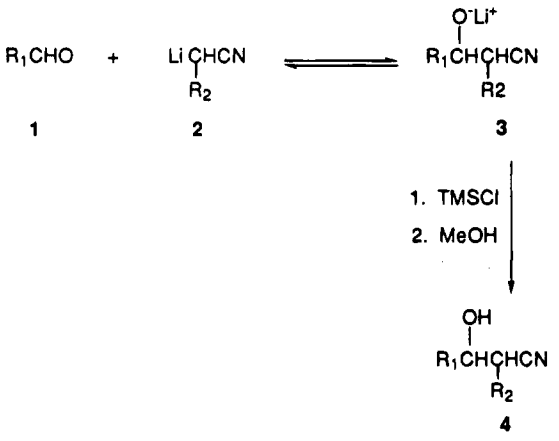
β-Hydroxynitriles **4** can be made by the condensation of carbonyl compounds with alkali acetonitriles, prepared by α-deprotonation of suitable nitriles with LDA or *n*-butyllithium.[1–3]



However, in certain instances the yields of this type of condensation are not satisfactory, because the reactions are reversible, and the structures of both the carbonyl compounds and the α-alkali nitriles have significant influences over the position of the equilibrium.[4,5] Generally, in the cases of hindered carbonyl compounds or hindered α-alkali nitriles, which may form more strained alkoxide intermediates, the yields are lower. For example, Kaiser and Hauser[4] showed that under the same conditions the reaction of lithioacetonitrile with benzophenone afforded the addition product in good yields, whereas alkali phenylacetonitrile, which is more sterically hindered, did not add satisfactorily to benzophenone. However, its magnesium and aluminum halide derivatives did undergo the addition to benzophenone to give the desired products in 40–60% yields. It was rationalized that the greater coordinating capacities of magnesium and aluminum ions played an important role in shifting the equilibrium to the right. Another major reason for low yields in these reactions is the decomposition of the alkoxide intermediate during quenching of the reaction. It has been shown by Kaiser and Hauser[5] that the neutral β-hydroxynitrile can be reversed to the starting carbonyl compounds and nitriles on treatment with only a catalytic amount of strong base such as *n*-butyllithium. They suggested that inverse quenching, pouring the reaction mixture into a large amount of aqueous acidic solution, should be applied to minimize reversions. Inverse quenching is successful in many cases; however, there are limitations to this technique. For instance, how fast the reaction mixtures can diffuse into the aqueous solution is highly critical, which depends upon the solubility of the product and the scale of the reaction. In our experiments with two water-insoluble aldehydes, 2-naphthalenecarboxaldehyde and 1-pyrenecarboxaldehyde, we followed the inverse quenching procedure reported in the literature,[5] but we found that the yields of the desired products were always below 40% and large amounts of unreacted starting aldehyde compounds were recovered. Rathke and Lindert[6] reported that addition of trimethyl borate in Reformatsky reactions increased the stability of the zinc alkoxide intermediate and, therefore, improved the yields of the condensation reactions. Since the "chelating" ability of the countercation is important to the position of the equilibrium of condensation reactions between lithioacetonitrile and carbonyl compounds, we added trimethyl borate to the reaction of lithioacetonitrile with 2-naphthalenecarboxaldehyde in the hope of increasing the yield of the condensation product by shifting the equilibrium. This, however, was not successful. Apparently, the trimethyl borate does not stabilize the lithium alkoxide intermediate as effectively as it does zinc analogues.

It is well known that chlorotrimethylsilane acts as a scavanger of alkoxide ions to form trimethylsilyl ethers.[7–10] In his studies on the properties of alkali acetonitriles, Krüger[9] used chlorotrimethylsilane to convert the alkali alkoxide intermediates into their trimethylsilyl ethers. Gornowicz and West[10] used chlorotrimethylsilane similarly in their studies on polylithiated acetonitriles. However, their purpose for trapping the alkoxide ions with chlorotrimethylsilane was not to improve the yields of condensation reactions.

We thought that the addition of chlorotrimethylsilane to the reaction mixture of lithioacetonitriles and aldehydes would trap the alkoxide intermediate and prevent reversal of the addition reaction; mild hydrolysis of the TMS ethers would give the desired β-hydroxynitriles in one pot. In fact, chlorotrimethlysilane quenching of the



reactions of lithioacetonitrile and either 2-naphthalenecarboxaldehyde or 1-pyrenecarboxaldehyde, followed by mild hydrolysis of the TMS ether with methanol, gave significantly higher yields of the desired products than

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Table 1. Condensations of Lithioacetonitriles with Aldehydes To Form β-Hydroxynitriles

entry	aldehyde	nitrile	TMSiCl	product[a] (yield, %)
1	1-pyrene-carboxaldehyde	CH_3CN	−	**4a** (30)
			+	**4a** (91)
2	2-naphthalene-carboxaldehyde	CH_3CN	−	**4b** (35)
			+	**4b** (96)
3	2,5-dimethoxy-benzaldehyde	CH_3CN	+	**4c** (95)
4	benzaldehyde	$PhCH_2CN$	+	**4d** (97)
5		CH_3CH_2CN	+	**4e** (91)
6	pivalaldehyde	$PhCH_2CN$	+	**4f** (91)
7		CH_3CH_2CN	+	**4g** (75)

[a] Key: (a) R_1 = pyrenyl, R_2 = H; (b) R_1= naphthyl, R_2 = H; (c) R_1 = dimethoxyphenyl, R_2 = H; (d) R_1 = R_2 = phenyl; (e) R_1 = phenyl, R_2 = methyl; (f) R_1 = *tert*-butyl, R_2 = phenyl; (g) R_1 = *tert*-butyl, R_2 = methyl.

when aqueous acid was used to quench the reaction (Table 1, entries 1 and 2). In comparison with the reported aqueous workup procedure,[5] this method is more efficient and easier to use. We have tested the generality of this improved procedure by varying the structures of the aldehydes and nitriles, and in all cases, excellent yields were obtained (Table 1). This simple, modified procedure is not only complementary to the routinely used procedures but also can substitute for aqueous workup when it is not satisfactory.

Experimental Section

All starting materials were purchased from Aldrich and used without further purification. Melting points were obtained with a Fisher-Johns melting point apparatus and are uncorrected. Column chromatography was performed with Merck silica gel (230–400 mesh). THF was distilled freshly from sodium benzophenone ketyl. All reactions were carried out in an atmosphere of inert gas (nitrogen or argon).

General Procedure for the Condensation Reactions of Lithioacetonitrile with Aldehydes. To a stirred solution of *n*-butyllithium in hexanes (2.55 M, 3.5 mL, 8.93 mmol) at −78 °C under nitrogen was added 4 mL of anhydrous THF followed immediately by the addition of acetonitrile (0.5 mL, 9.57 mmol). A white suspension formed. After being stirred for 1 h at −78 °C, a solution of 1-pyrenecarboxaldehyde (2.04 g, 8.8 mmol) in THF (10 mL) was added via cannula at −78 °C. The resulting yellow-brown mixture was stirred at −78 °C for 30 min, and then chlorotrimethylsilane (1.8 mL, 14.2 mmol) was added via syringe at −78 °C. Ten min later, methanol (2 mL) was added. The reaction mixture was warmed to room temperature, most of the THF was removed *in vacuo*, and the residue was taken up with EtOAc, washed with water, and dried with $MgSO_4$. Concentration to dryness afforded a yellow solid, which was recrystallized from toluene to afford 2.16 g (91%) of the β-hydroxylnitrile product (**4a**) as a crystalline material: mp 146–147 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16–8.32 (m, 6 H), 8.02–8.14 (m, 3 H), 6.17 (m, 1 H), 3.07 (m, 2 H); IR (KBr) ν 3400 (br), 3042, 2264, 1603, 1589, 1413, 1386, 1081, 854 cm^{-1}; MS (EI, *m/z*) 271 (M^+, 50), 232 (26), 231 (100) 230 (32), 229 (24),203 (64), 202 (89), 201 (44), 200 (35); HRMS calcd for $C_{19}H_{13}NO$ 271.0997, found 271.0992. Anal. Calcd for $C_{19}H_{13}NO$: C, 84.18; H, 4.83; N, 5.17. Found: C, 83.84; H, 4.76; N, 5.16.

4b. The crude reaction mixture was purified by column chromatography (silica gel, hexane:ethyl acetate = 2:1, R_f = 0.30, yield = 96%): mp 84–85 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (m, 4 H), 7.52 (m, 3 H), 5.24 (dd, 1 H), 2.87 (d, 2 H, *J* = 6.5 Hz); IR (KBr) ν 3384 (br), 3050, 2272, 1073, 825 cm^{-1}; MS (EI, *m/z*) 197 (M^+, 59), 157 (100), 129 (97), 128 (43), 127 (35); HRMS calcd for $C_{13}H_{11}NO$ 197.0841, found 197.0856. Anal. Calcd for $C_{13}H_{11}NO$: C, 79.23; H, 5.63; N, 7.11. Found: C, 79.17; H, 5.57; N, 7.05.

4c. The crude reaction mixture was purified by column chromatography (silica gel, hexane:ethyl acetate = 2:1, R_f = 0.52, yield = 95%): mp 89–90 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.00 (m, 1 H), 6.81 (m, 2 H), 5.17 (dd, *J* = 4.8 Hz, *J* = 7.5 Hz, 1 H), 3.82 (s, 3 H), 3.77 (s, 3 H), 3.18 (br, 1 H), 2.85 (dd, 1 H, *J* = 4.8 Hz, *J* = 12 Hz), 2.75 (dd, 1 H, *J* = 16.8 Hz, *J* = 7.5 Hz); IR (KBr) ν 3533 (br) 2942, 2833, 2233, 1283, 1217, 1050 cm^{-1}; MS (EI, *m/z*) 207 (M^+, 59), 167 (100), 152 (23), 139 (56), 137 (31), 124 (26); HRMS calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0894. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.80; H, 6.33; N, 6.76. Found: C, 63.71; H, 6.27; N, 6.77.

4d. The crude reaction mixture was purified by column chromatography (silica gel, hexane:ethyl acetate = 4:1, yield = 97%): mp 101–102 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.40 (m, 10 H), 4.96 (q, 1 H), 4.05 (d, 1 H), 2.68 (d, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5, 132.5, 129.0, 128.8, 128.6, 128.5, 118.9, 76.3, 47.4 (d); IR (KBr) ν 2253 cm^{-1}; MS (EI, *m/e*) 223 (M^+, 10), 206 (100), 117 (81), 107 (100), 79 (50); HRMS calcd for $C_{15}H_{13}NO$ 223.0997, found 223.0974. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.77; H, 5.91; N, 6.41.

4e. The crude reaction mixture was purified by column chromatography (silica gel, dichloromethane:ethyl acetate = 25:1, yield = 91%): mp 67.5–68 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.21–7.45 (m, 5 H), 4.05 (d,1 H), 3.42 (d, 1 H), 2.05 (d, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.9, 129.2, 128.2, 127.9, 119.1, 82.3, 39.9(d), 36.0, 26.2; IR (KBr) ν 2240 cm^{-1}; MS (EI, *m/z*) 204 ($(M + 1)^+$, 4), 117 (100). [xa1] Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.62; H, 8.50; N, 6.95.

4f. The crude reaction mixture was purified by column chromatography (silica gel, hexane:ethyl acetate = 3:1, yield = 91%, diastereomers ratio **A**:**B** = 3:1).

A: oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.45 (m, 5 H), 4.83 (q, 1 H), 3.02 (m, 1 H), 2.40 (d, 1 H), 1.28(d, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.8, 128.7, 128.7, 126.5, 121.2, 74.1, 34.0, 13.5; IR (KBr) ν 2245 cm^{-1}; MS (EI, *m/z*) 162 ($(M + 1)^+$, 6), 144 (10), 107 (100), 79 (58); HRMS calcd for $C_{10}H_{11}NO$ 161.0841, found 161.0834. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 73.94; H, 6.99; N, 8.67.

B: oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.45 (m, 5 H), 4.74 (q, 1 H), 2.96 (m, 1 H), 2.30 (d, 1 H), 1.25 (d, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.1, 128.9, 128.9, 126.4, 121.1, 74.2, 34.6, 14.8; IR (KBr) ν 2245 cm^{-1}; MS (EI, *m/z*) 162 ($(M + 1)^+$, 6), 144 (10), 107 (100), 79 (58); HRMS (M + 1) calcd for $C_{10}H_{12}NO$ 162.0919, found 162.0915. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 72.38; H, 6.77; N, 8.49.

4g. The crude reaction mixture was purified by column chromatography (silica gel, hexane:ethyl acetate = 5:1, yield = 75%, diastereomers ratio **C**:**D** = 1:1).[11]

C: oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.50 (t, 1 H), 2.76 (m,1 H), 2.29 (d, 1 H), 1.39 (d, 3 H), 1.00 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 123.4, 78.5, 36.1, 27.3, 26.4, 14.9; IR (KBr) ν 2244 cm^{-1}; MS (EI, *m/z*) 142 (M + 1^+, 2), 126 (5), 87 (42), 71 (28), 58 (50), 57 (100), 41 (37); HRMS (M + 1) calcd for $C_8H_{16}NO$ 142.1232, found 142.1237. Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.12; H, 10.58; N, 9.81.

D: mp 53.5–55 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.15 (d, 1 H), 2.87 (m, 1 H), 2.09 (d, 1 H), 1.46 (d, 3 H), 1.02 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 121.3, 80.8, 35.8, 27.7, 26.0, 18.3; IR (KBr) ν 2249 cm^{-1}; MS (EI, *m/z*) 142 (M + 1^+, 5), 126 (5), 87 (45), 71 (25), 58 (49), 57 (100), 41 (39); HRMS (M + 1) calcd for $C_8H_{16}NO$ 142.1232, found 142.1215. Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.92; H, 10.66; N, 9.94.

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(11) Compound **4g** has been made by another method in lower yield; see: Gardner, D. V.;. M., D. E. *Can. J. Chem.* **1970**, *48*, 2110.