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An Improved Cyanoalkylation Method of Aldehydes Catalyzed by Electrogenerated Base in a DMF-H_2O System

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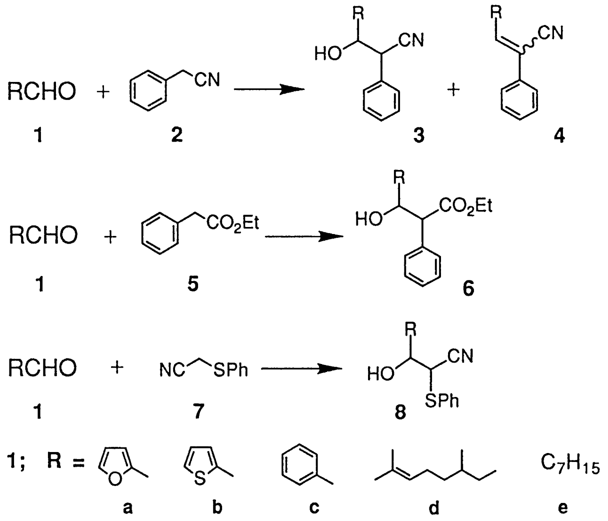
Synopsis. Electrogenerated base (EG base) formed in a DMF-H_2O (1.85 M)-Et_4NOTs (0.1—0.2 M)-(Pt) system is effective for condensation of phenylacetonitrile and its related compounds with aldehydes, giving the corresponding cyanoalkylation compounds in good yields, and the concomitant dehydration of the adducts is minimized.

Electroorganic reaction on a cathode can provide a reliable tool for generating versatile carbanions as bases and nucleophiles.[1] For example, cyanomethyl anions have been prepared by the following three alternative recipes: (1) the use of electrogenerated radical anions of aromatic ketones[2] or azobenzene dianions[3] as a base for deprotonation of acetonitrile, (2) the reductive cleavage reaction of α-hetero-substituted cyanomethyl derivatives,[4] and (3) the supply of high electrolytic current in MeCN solution containing ammonium salts.[5] Especially, the third method is essentially catalytic with respect to the electron used, yielding the cyanomethyl adduct of benzaldehyde in 88% by GC analyses. However, this method is notorious for being associated with competitive dehydration and the subsequent 1,4-addition of cyanomethyl anion to the resulting conjugated compounds. As the result of our continuing efforts in exploring electrocatalytic reactions on the cathode,[6] we report an improved procedure for the generation of a cyanoalkyl anion from phenylacetonitrile (**2**) and its homologues by using the EG base formed in a DMF/H_2O-Et_4NOTs-(Pt) system.[7]

We examined firstly the effect of solvent-electrolyte systems on realizing the electrogenerated base (EG base)-catalyzed carbon-carbon bond making reaction of phenylacetonitrile (**2**) and furfural (**1a**) as typical substrates. As shown in Entries 1—5, Table 1, the desired β-hydroxy nitrile **3a** was obtained in 67—84% yields in a DMF/H_2O (1.85 M) system containing appropriate electrolytes (0.1 M) by charging 0.047 F mol^{-1} of electricity (based on **1a** and it took for about 30 min) in a divided cell at −40 °C (1M=1 mol dm^{-3}). Especially, the electrolysis of **1a** and **2** in a DMF/H_2O (1.85 M)-Et_4NOTs (0.1 M) and a DMF/H_2O (1.85 M)-Et_4NClO_4 (0.1 M) systems gave favorable results (84 and 82% yields, Entries 1 and 2). The constant current of 5 mA was easily attained by addition of water in a DMF-Et_4NOTs (0.1 M) system during the electrolysis under an applied voltage of 18—40 V at −40 °C, which was essential for the smooth accumulation of EG base.[8] Furthermore, the desired β-hydroxy nitrile **3a** was isolated without the concomitant dehydration with prolonged stirring (0.5 h) in the electrolysis medium after the reaction. The presence of methanol (0.82 M) in a DMF-Et_4NOTs (0.1 M) system was also effective for a similar EG base-catalyzed reaction, giving the desired **3a** in 76% yield (Entry 6), but higher alcohols such as ethanol and 1-propanol were less useful. As a supporting electrolyte, tetrabutylammonium tetrafluoroborate (Bu_4NBF_4)



Scheme 1.

Table 1. Effect of Solvent-Electrolyte System on the EG Base-Catalyzed Reaction of **1a** and **2**[a)]

Entry	Co-solvent in DMF (ml, M)[b)]	Electrolyte	Isomer ratio[c)]	Products, Yield/%[d)]		
				3a	4a	1a
1	H_2O (0.5, 1.85)	Et_4NOTs	46/54	84	3	1
2	H_2O (0.5, 1.85)	Et_4NClO_4	40/60	82	—	4
3	H_2O (0.5, 1.85)	Bu_4NBF_4	47/53	67	—	7
4	H_2O (0.5, 1.85)	Et_4NBr	51/49	70	—	7
5	H_2O (0.5, 1.85)	$LiClO_4$	53/47	70	1	7
6	MeOH (0.5, 0.82)	Et_4NOTs	47/53	76	—	5

a) Carried out by using **1a** (2.0 mmol) and **2** (2.0 mmol) at 5 mA (0.047 F mol^{-1}) for 30 min. b) M=mol dm^{-3}. c) ^{1}H NMR (500 MHz) peak areas at δ=4.96 and 5.04. d) Based on isolated products.

Table 2. EG Base-Catalyzed C-C Bond Making Reaction of Alkanenitriles **2** and **7**, and Alkanoate **5**[a)]

Entry	RCHO	Nucleophile	Time/F mol^{-1}[b)]	Products (Yield/%[c)])
1	**1b**	**2**	80/0.124	**3b** (52)+**1b** (43)
2	**1c**	**2**	30/0.047	**3c** (75)+**1c** (8)
3	**1d**	**2**	26/0.040	**3d** (90)
4	**1e**	**2**	30/0.047	**3e** (83)
5	**1a**	**5**	30/0.047	**6a** (73)+**1a** (1)
6	**1c**	**5**	30/0.047	**6c** (72)+**1c** (22)
7	**1d**	**5**	30/0.047	**6d** (73)+**1d** (14)
8	**1c**	**7**	30/0.047	**8c** (65)+**1c** (29)

a) Unless otherwise noted, **1** (2 mmol) and **2** (2 mmol) were reacted in DMF (14.5 ml)-H_2O (0.5 ml) at −40 °C. b) Passed electricity based on **1**. c) Based on isolated products.

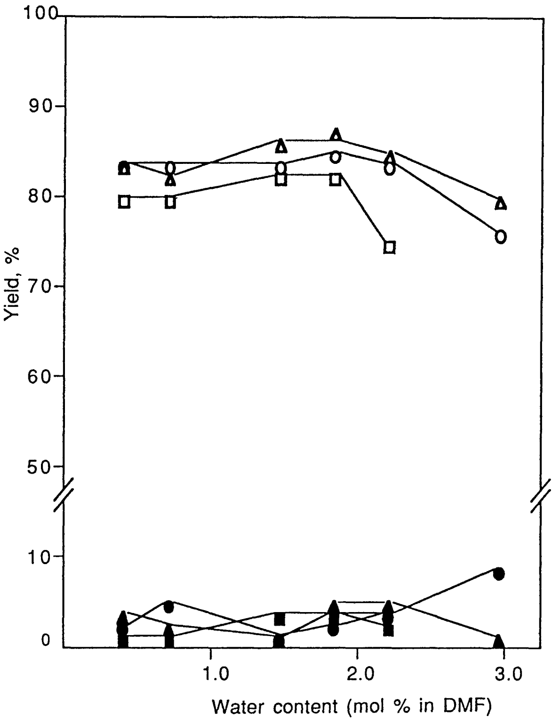


Fig. 1. Effect of water content on the formation of the hydroxyalkanenitrile **3a** and **4a**. Symbols: Et_4NOTs, 0.05 M (□ ■); 0.1 M (○ ●); 0.2 M (△ ▲).

and tetraethylammonium bromide (Et_4NBr) were less effective (Entries 3 and 4) in comparison with tetraethylammonium tosylate (Et_4NOTs) and tetraethylammonium perchlorate (Et_4NClO_4). Considerable amount of the starting **1a** was remained when lithium perchlorate was used (Entry 5).

In order to clarify the role of water in the electrolysis, we studied the relationship between the amount of water and the concentration of tetraethylammonium tosylate (Et_4NOTs) in a DMF solution for producing **3a** and **4a**. As shown in Fig. 1 obtained under three different concentrations of Et_4NOTs (0.05, 0.1, and 0.2 M), the yields of **3a** are favored at the point of 1.85 M of water in all electrolyte concentrations (82, 84, and 87% yields). It is likely that higher electrolyte concentration in DMF is advantageous for the formation of **3a**.

We applied the conditions of Entry 1 in Table 1 to the addition reactions of alkanenitriles or alkanoate to other aldehydes. As shown in Table 2, the reaction of aliphatic or aromatic aldehydes **1** with **2** and **7** (Entries 1—4 and 8) or ethyl phenylacetate (**5**) (Entries 5—7) proceeded smoothly. However, the addition of **2** to ketones were unsuccessful.

In connection with the amount of electricities consumed in this reaction, we can assume the chain process catalyzed by the EG base. EG base generated in this system is capable of initiating the C-C bond making reaction of nitrile derivatives of pK_a 20—25, while not being capable of promoting the reaction of aliphatic nitriles of pK_a 30. As shown in Fig. 1, the increase of yield of **3a** at a higher electrolyte concentration suggests generation of strong base such as tetraalkylammonium hydroxide from the electrolyte, which requires appropriate amount of water as a possible precursor of hydroxide ion. These EG base-catalyzed cyanoalkylation in DMF can be favored at the expense of the concomitant dehydration by buffering effect of water. Easy controlling of the electrolysis in the range of 5—10 mA of the electric current at −40 °C encourages us to engage in the another application to proton donors of pK_a less than 25, which is under investigations in our laboratory.

Experimental

Apparatus and Procedures. Melting and boiling points indicated by an air-bath temperature are uncorrected. IR spectra were recorded on a Hitachi 215 grating or a JASCO FT-8000 spectrometers. ^{1}H NMR spectra were taken in $CDCl_3$ (Me_4Si as a standard) on a JEOL FX-90A (90 MHz), Varian VXR-500, or -200 instruments. Column chromatographies were carried out with a Merck Kieselgel 60, Art. 7734 (silica gel) with hexane-AcOEt as an eluent.

EG Base-Catalyzed Reaction of Furfural (1a) and Phenylacetonitrile (2), Typical Procedure. Electrolysis was carried out in an H-shaped cell divided by a glass frit, which was equipped with two platinum foils (3 cm^2) as a cathode and an anode. Into both compartments were charged two DMF-H_2O solutions (14.5 ml—0.5 ml) containing 450 mg of Et_4NOTs. To the cathodic cell were added furfural (**1a**, 192 mg, 2 mmol) and phenylacetonitrile (**2**, 234 mg, 2 mmol). The mixture was electrolyzed under a constant current density of 1.7 mA cm^{-2} at −40 °C for 30 min (0.047 F mol^{-1}). The catholyte was poured into cold water and taken up in AcOEt. Extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude products were purified by a column chromatography on SiO_2 (hexane-AcOEt=5 : 1) to yield **3a** (358 mg, 84%), **4a** (12 mg, 3 %), and **1a** (2 mg, 1%). **3a** (a 46 : 54 mixture of stereoisomers): bp 147 °C/1 Torr (1 Torr≈133.322 Pa); IR (neat) 3425 (OH), 2230 (CN), 1490, 1450, 880, 750, 700 cm^{-1}; ^{1}H NMR (500

MHz) δ=2.55 (brs, 1H, OH), 4.32, 4.33 (d, 1H, J=6.5, 6.0 Hz), 4.96, 5.04 (d, 1H, J=6.5, 6.0 Hz), 6.27, 6.31, 6.34 (m, 2H), 7.23—7.27, 7.32—7.36 (m, 5H, PhH), 7.41 (d, 1H, J=8.0 Hz). Found: C, 73.10; H, 5.15; N, 6.45%. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57%. **4a**; mp 39—40 °C; IR (neat) 3065, 3036, 1595, 1026, 885, 756, 698 cm^{-1}; ^{1}H NMR (500 MHz) δ=6.75 (dd, 1H, J=3.4, 1.6 Hz), 7.20 (d, 1H J=3.4 Hz), 7.38 (s, 1H), 7.83 (d, 1H, J=1.7 Hz), 7.34—7.64 (m, 5H).

Physical properties along with spectral data of products listed in Table 2 are as follows.

3-Hydroxy-3-(2-thienyl)-2-phenylpropanenitrile (3b). (less polar component): mp 89—90 °C; IR (neat) 3503 (OH), 3090, 2251 (CN), 1493, 1455, 754, 698 cm^{-1}; ^{1}H NMR (500 MHz) δ=4.14 (d, 1H, J=6.0 Hz, CHCN), 5.23—5.25 (m, 1H, OCH), 6.87—6.94 (m, 2H), 7.25—7.35 (m, 6H). Found: C, 67.91; H, 4.97; N, 6.25%. Calcd for $C_{13}H_{11}NOS$: C, 68.10; N, 4.84; H, 6.11%.

3b. (polar component): mp 61—63 °C; IR (neat) 3400 (OH), 2240 (CN), 1493, 1450, 738, 698 cm^{-1}; ^{1}H NMR (500 MHz) δ=4.20 (d, 1H, J=6.5 Hz, CHCN), 5.25 (d, 1H, J=6.5 Hz, OCH), 6.97—7.03 (m, 2H), 7.26—7.38 (m, 6H). Found: C, 68.09; H, 4.70; N, 6.00%. Calcd for $C_{13}H_{11}NOS$: C, 68.10; H, 4.84; N, 6.11%.

3-Hydroxy-2,3-diphenylpropanenitrile (3c). (less polar component): mp 101—102 °C; IR (neat) 3441, 3335, 2245 (CN), 1455, 762, 700 cm^{-1}; ^{1}H NMR (500 MHz) δ=4.06 (d, 1H, J=6.0 Hz, CHCN), 4.98 (d, 1H, J=6.0 Hz, OCH), 7.21—7.34 (m, 10H, PhH). Found: C, 80.59; H, 6.14; N, 5.99%. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27%.

3c. (polar component): mp 78—80 °C; IR (neat) 3380 (OH), 2230 (CN), 1482, 1450, 753, 698 cm^{-1}; ^{1}H NMR (500 MHz) δ=2.21 (brs, 1H, OH), 4.14 (d, 1H, J=6.5 Hz, CHCN), 4.99 (d, 1H, J=6.5 Hz, OCH), 7.20—7.35 (m, 10H, PhH). Found: C, 80.55; H, 5.99; N, 6.06%. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27%.

5,9-Dimethyl-3-hydroxy-2-phenyl-8-decenenitrile (3d). (less polar component): IR (neat) 3463 (OH), 2255, 1672, 1455, 887, 756, 704 cm^{-1}; ^{1}H NMR (500 MHz) δ=0.89, 0.96 (d, 3H, J=7.0, 6.5 Hz), 1.08—1.43 (m, 3H), 1.55—1.60 (m, 1H), 1.59 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.69—1.74 (m, 1H), 1.88 (brs, 1H, OH), 1.91—2.05 (m, 2H), 3.84, 3.86 (d, 1H, J=4.5, 4.0 Hz), 3.97 (m, 1H, OCH), 5.07 (m, 1H, HC=C), 7.36—7.38 (m, 3H, PhH), 7.40—7.43 (m, 2H, PhH).

3d. (polar component): IR (neat) 3400 (OH), 2225 (CN), 1440, 1367, 840, 750, 695 cm^{-1}; ^{1}H NMR (500 MHz) δ=0.86, 0.94 (d, 3H, J=7.0 Hz), 0.87—1.49 (m, 3H), 1.53—1.73 (m, 2H), 1 .58 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.80 (brs, 1H, OH), 1.83—2.04 (m, 2H), 3.83—3.85 (m, 1H), 3.94—4.50 (m, 1H, OCH), 5.20—5.90 (m, 1H, HC=C), 7.35—7.38 (m, 3H, PhH), 7.39—7.43 (m, 2H, PhH). Found: C, 79.45; H, 9.49; N, 5.06%. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16%.

3-Hydroxy-2-phenyldecanenitrile (3e): bp 138 °C/1 Torr; IR (neat) 3470 (OH), 2250 (CN), 1600, 1459, 760, 705 cm^{-1}; ^{1}H NMR (500 MHz) δ=0.85—0.89 (m, 3H, CH_3), 1.27 (m, 10H, CH_2), 1.45—1.66 (m, 2H, CH_2), 2.27 (brs, 1H, OH), 3.83—3.90 (m, 2H, CH, OCH), 7.33—7.41 (m, 5H, PhH). Found: C, 78.10; H, 9.63; N, 5.55%. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71%.

Ethyl 3-(2-Furyl)-3-hydroxy-2-phenylpropanoate (6a). (a 81 : 19 mixture of stereoisomers): mp 74—76 °C; IR (neat) 3470 (OH), 3154, 3121, 1713 (CO), 1601, 1227, 1180, 884, 743, 700 cm^{-1}; ^{1}H NMR (500 MHz) δ=1.12, 1.21 (t, 3H, J=7.0 Hz, CH_3), 3.38 (brs, 1H, OH), 3.99—4.27 (m, 3H, CH_2O, CH), 5.18, 5.31 (d, 1H, J=8.9, 8.4 Hz, OCH), 6.03, 6.26 (d, 1H, J=3.3 Hz), 6.17, 6.31 (dd, 2H, J=3.3, 1.7 Hz), 7.18—7.39 (m, 5H, PhH). Found: C, 68.97; H, 6.44%. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20%.

Ethyl 2,3-Diphenyl-3-hydroxypropanoate (6c). (less polar component): mp 77—78 °C; IR (neat) 3399 (OH), 1721 (CO), 1267, 1238, 885, 760, 704 cm^{-1}; ^{1}H NMR (200 MHz) δ=1.01 (t, 3H, J=7.1 Hz, CH_3), 2.49 (brs, 1H, OH), 3.85 (d, 1H, J=7.8 Hz, CHCO), 3.89—4.09 (m, 2H, CH_2O), 5.25 (d, 1H, J=7.8 Hz, OCH), 7.23—7.48 (m, 10H, PhH). Found: C, 75.33; H, 6.82%. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%.

6c. (polar component): mp 76—77 °C; IR (neat) 3517 (OH), 1713 (CO), 1291, 1200, 1181, 760, 702 cm^{-1}; ^{1}H NMR (200 MHz) δ=1.20 (t, 3H, J=7.1 Hz, CH_3), 3.18 (brs, 1H, OH), 3.86 (d, 1H, J=9.3 Hz, CH), 4.03—4.30 (m, 2H, CH_2O), 5.16 (d, 1H, J=9.3 Hz, OCH), 7.03—7.19 (m, 10H, PhH).

Ethyl 5,9-Dimethyl-3-hydroxy-2-phenyl-8-decenoate (6d). (less polar component, diastereomeric mixtures): bp 120 °C/1.5 Torr; IR (neat) 3530 (OH), 2900, 1730 (CO), 1190, 1170, 1150, 738, 700 cm^{-1}; ^{1}H NMR (200 MHz) δ=0.92 (d, 3H, J=6.6 Hz, CH_3), 1.03—1.51 (m, 5H), 1.21 (t, 3H, J=7.1 Hz, CH_3), 1.58 (d, 3H, J=5.0 Hz, CH_3) 1.67 (dd, 3H, J=4.3, 1.0 Hz, CH_3), 1.85—2.05 (m, 2H), 2.27, 2.42 (brs, 1H, OH), 3.52 (dd, 1H, J=6.1, 2.1 Hz, CH), 4.15—4.22 (m, 2H, CH_2O), 4.28 (m, 1H, OCH), 5.07 (m, 1H, HC=C), 7.27—7.40 (m, 5H, PhH).

6d. (polar component, diastereomeric mixtures): bp 90 °C/0.5 Torr; IR (neat) 3490 (OH), 2900, 1735 (CO), 1190, 1170, 1150, 735, 702 cm^{-1}; ^{1}H NMR (200 MHz) δ=0.78, 0.85 (d, 3H, J=6.7 Hz, CH_3), 0.88—1.47 (m, 5H), 1.20 (t, 3H, J=7.2 Hz, CH_3), 1.56 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.75—1.99 (m, 2H), 2.71 (brs, 1H, OH), 3.52 (d, 1H, J=8.8 Hz, CH), 4.00—4.30 (m, 3H, CH_2O, OCH), 5.04 (m, 1H, HC=C), 7.21—7.38 (m, 5H, PhH). Found: C, 75.27; H, 9.67%. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50%.

3-Hydroxy-3-phenyl-2-(phenylthio)propanenitrile (8c). (diastereomeric mixtures): bp 134 °C/1.5 Torr; IR (neat) 3450 (OH), 2240 (CN), 740, 702 cm^{-1}; ^{1}H NMR (200 MHz) δ=2.61 (brs, 1H, OH), 3.87, 3.98 (d, 1H, J=8.3, 5.0 Hz, CH), 4.71, 4.97 (d, 1H, J=8.3, 5.0 Hz, OCH), 7.35—7.47 (m, 8H), 7.52—7.67 (m, 2H). Found: C, 70.41; H, 5.41; N, 5.20%. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49%.

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