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Reaction of the Electrogenerated Cyanomethyl Anion with Carbonyl Compounds: A Clean and Safe Synthesis of β-Hydroxynitriles

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The electrogenerated cyanomethyl anion reacts with carbonyl compounds to yield the corresponding β-hydroxynitriles in moderate to high yields. The reported methodology is very clean and safe, avoiding the use of any classical base or catalyst.

Introduction

β-Hydroxynitriles are useful and versatile synthetic intermediates in organic synthesis.[1] The nitrile group is a valuable precursor of both amino and carbonyl compounds[2] and β-hydroxynitriles can be easily converted into useful building blocks, such as β-hydroxycarboxylic acid derivatives and γ-amino alcohols.[3] β-Hydroxynitriles are usually prepared by ring-opening reactions of epoxides with cyanides (HCN,[4] NaCN,[1,5] KCN,[6] LiCN,[7] cyanide exchange resin,[8] TMSCN[9]) or with acetone cyanohydrin under basic conditions.[10] Cyanomethylation of carbonyl compounds is another useful method for the synthesis of β-hydroxynitriles. Simple alkylnitriles are among the least acidic carbon pronucleophiles, and the preparation of α-cyano carbanions from alkylnitriles usually requires more than stoichiometric amounts of a strong base in a separate process.[11] The reaction is also performed by using a proazaphosphatrane as a Brønsted base catalyst in the presence of magnesium sulfate.[12] Alternatively, the reaction was carried out by CuF-catalyzed cyanomethylation by $TMSCH_2CN$.[13] The Cu^I-catalyzed direct enantioselective cross-aldol-type reaction of acetonitrile has been recently reported.[14] All the reported methods suffer from several drawbacks including severe reaction conditions, high reaction temperatures, expensive and hazardous reagents, hygroscopic and nonrecyclable catalysts, and the use of volatile and toxic HCN. In addition, the above-mentioned ring-opening reactions of epoxides usually require protic solvents and additives and result in the formation of mixtures of regioisomers.[5a,6a,9a]

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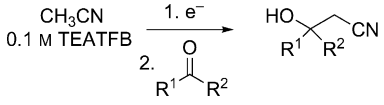
In order to avoid these limitations we have developed a new electrochemical methodology for the synthesis of β-hydroxynitriles under mild conditions, preventing the use of toxic and hazardous reagents. Among the different green methodologies recently reported, organic electrochemistry[15] could be rightly considered a powerful tool for clean and safe organic syntheses, providing a valuable alternative to the use of conventional reagents for fine chemical synthesis. In particular, the use of carbanions stabilized by electron-withdrawing groups has received, in the last years, great attention, especially because of their use in the formation of carbon–carbon bonds.

Results and Discussion

The cyanomethyl anion, usually obtained by deprotonation of acetonitrile (pK_a = 31.3) by suitable bases (alkali metal hydrides, amides, and alkoxides), has found wide application as a nucleophile in several reactions such as the addition reaction to carbonyl compounds and imines and Michael-type addition reactions. Recently, our research group reviewed the generation of the cyanomethyl anion by nonconventional electrochemical procedures.[16] In particular, we found that the cyanomethyl anion generated by direct electrolysis, under galvanostatic control, of CH_3CN/Et_4NBF_4 (TEATFB = tetraethylammonium tetrafluoroborate) solutions can be used as a base in a large number of organic reactions. In combination with carbon dioxide, the electrogenerated cyanomethyl anion proved to be a powerful carboxylating reagent for the synthesis of carbamates,[17] oxazolidine-2-ones,[18] and oxazolidine-2,4-diones.[19] In addition, it has proved to be effective, as a base, for the selective activation of amidic and aminic N–H[20] and C–H[21] bonds in cyclization reactions, leading to the formation of β-lactams,[22] butenolides, pyrrolin-2-ones,[23] indoles,[24] and so on.

In order to exploit the reactivity of the electrogenerated cyanomethyl anion as a nucleophile, we considered the possible reaction of CH_2CN^- with carbonyl compounds (aldehydes and ketones) for the synthesis of β-hydroxynitriles. The electrolysis of carbonyl compounds (acetophenone, benzaldehyde, and benzophenone) in dry CH_3CN (1.0 M in TEATFB) solution was first reported by Bellamy.[25] The reaction gave significant yield of different cyanomethylation products not including β-hydroxynitriles. The author excluded the generation of the cyanomethyl anion by direct or indirect reduction of the solvent. Bellamy also studied the indirect electrogeneration of the cyanomethyl anion by reduction of a probase (azobenzene) in CH_3CN or by reduction of cyanomethyl phosphonium or arsonium salts in super-dry DMF[26] and its reaction with carbonyl compounds. Alternatively, Troupel[27] indirectly obtained the cyanomethyl anion by using the electrogenerated base (EGB) phenyl anion by using a sacrificial magnesium anode. Moderate to high yields of β-hydroxynitriles were obtained. The electrochemical synthesis of 3-phenylcinnamonitrile by reduction of benzophenone in acetonitrile was also reported. The cyanomethyl anion was obtained by benzophenone radical anion that acted as the EGB.[28]

Here we report a clear and safe method for the synthesis of several β-hydroxynitriles by nucleophilic addition of the electrogenerated cyanomethyl anion to carbonyl compounds in moderate to very high yields. The anion was simply obtained, according to the usual way, by electrochemical reduction, under galvanostatic control, of CH_3CN/TEATFB solutions (Scheme 1). 3-Aminocrotonitrile was also produced in small amounts during the electrolysis. Concerning the reaction mechanism, a mechanistic hypothesis has been proposed.[18b]



Scheme 1. Reaction of the electrogenerated cyanomethyl anion with carbonyl compounds: synthesis of β-hydroxynitriles.

In order to optimize the reaction conditions, benzaldehyde was used as a model compound in a series of experiments that showed that better reaction yields were obtained at room temperature by using method B and an amount of electricity of 2.0 F mol^{-1} relative to the starting benzaldehyde (R^1 = Ph, R^2 = H; Table 1, Entry 5).

Electrolysis of 0.1 M CH_3CN solutions in TEATFB were carried out, under galvanostatic control, in a divided cell equipped with platinum electrodes at 0 °C. Reaction yields are related to the amount of electricity supplied to the cathode. Best yields were obtained when Q = 2.0 F mol^{-1} of aldehyde were used. Another interesting factor that affects the reaction yield was the rate of aldehyde addition. Two methods are reported: method A, in which benzaldehyde dissolved in anhydrous CH_3CN was added in "one-portion" to the catholyte containing electrogenerated $^-CH_2CN$, and method B that consists of the dropwise addition of the aldehyde solution to the catholyte over 30 min. Reactions carried out with method B provided higher reaction yields than those obtained with method A. In addition, temperature also played an important role: in method A raising the temperature from room temperature to 80 °C gave an increase in the reaction yields. Conversely, method B did not seem to be affected by temperature variation; reaction yields were very good even when low temperatures were used. Only an increase in reaction time was observed.

Table 1. Reaction of benzaldehyde with the electrogenerated cyanomethyl anion under different reaction conditions.[a]

Entry	Q [F mol^{-1}][b]	Method[c]	T [°C]	t [h]	Yield [%][d]
1	1.2	A	20	24	64 (25)
2	2.0	A	20	24	71 (18)
3	3.0	A	20	24	67 (23)
4	2.0	A	80	20	77
5	2.0	B	20	0.5	87
6	2.0	B	0	2	87
7	2.0	B	–20	4	81

[a] The electrolyses were carried out, under galvanostatic control, in a divided cell equipped with Pt electrodes at 0 °C. [b] The value Q refers to the amount of benzaldehyde (0.5 mmol) used in the experiment. [c] Method A: benzaldehyde in anhydrous MeCN (3.0 mL) was added in "one-portion" to the cathodic solution of 0.1 M MeCN in TEATFB (2.0 mL); Method B: benzaldehyde in anhydrous MeCN (2.0 mL) was added dropwise over 30 min to the cathodic solution of 0.1 M MeCN in TEATFB (3.0 mL). [d] Yields refer to isolated products. Yields in parentheses refer to the recovered benzaldehyde.

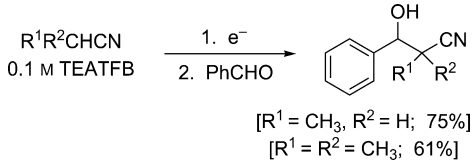
The procedure was then tested over a large number of aliphatic and aromatic aldehydes and ketones. Results are reported in Table 2. Beside sterically hindered 2-naphthaldehyde (57% yield), both aromatic and aliphatic aldehydes provided very good yields of hydroxynitriles (67–92% isolated yield). Method B is preferred over method A, as it provides better reaction yields and the formation of byproducts (double substitution and aldolic condensation products; Table 2, Entries 2 and 5, respectively) that appear when the reaction is carried out at high temperature is avoided. Cyclic ketones usually react very well even when method A is adopted (Table 2, Entries 13–16); only with substituted cyclohexanones (Table 2, Entries 17–20) was method B preferred to method A, although the reactions needed to be carried out at room temperature. Aromatic and linear ketones (Table 2, Entries 20–22) provided only moderate yields of the corresponding β-hydroxynitriles.

A further investigation was carried out by using different nitriles than acetonitrile. Results are reported in Scheme 2. Benzaldehyde was used as the starting compound. Both linear propionitrile and branched 2-methylpropionitrile reacted with benzaldehyde to yield the corresponding β-hydroxynitriles in quite good yields. This result opens the way to an effective method for the synthesis of α-branched β-hydroxynitriles. Further improvements in this methodology are now under study.

Table 2. Reaction of different carbonyl compounds with the electrogenerated cyanomethyl anion: synthesis of β-hydroxynitriles.[a]

Entry	R^1	R^2	Method[b]	T [°C]	t [h]	Yield [%][c]
1	2-furyl	H	A	20	20	77
2	2-furyl	H	A	80	1	62[d]
3	2-furyl	H	B	–20	1	82
4	*n*-heptyl	H	A	20	20	61
5	*n*-heptyl	H	A	80	1	53[e]
6	*n*-heptyl	H	B[f]	–20	2	73
7	4-$CH_3OC_6H_4$	H	A	20	16	67
8	4-$CH_3OC_6H_4$	H	B	–20	2	92
9	2-naphthyl	H	A	20	4	11
10	2-naphthyl	H	B	–20	4	57
11	4-$CH_3C_6H_4$	H	B	–20	2	81
12	4-ClC_6H_4	H	B	–20	4	67
13	$(CH_2)_5$		A	20	2	90
14	$(CH_2)_4$		A	20	48	70
15	$(CH_2)_4$		B	–20	24	76
16	$(CH_2)_6$		A	20	48	81
17	$(CH_2)_2CH(C_6H_5)(CH_2)_2$		A	20	24	51
18	$(CH_2)_2CH(C_6H_5)(CH_2)_2$		B	20	24	73
19	$(CH_2)_2CH(t\text{Bu})(CH_2)_2$		A	20	24	49
20	$(CH_2)_2CH(t\text{Bu})(CH_2)_2$		B	20	24	78
21	C_6H_5	CH_3	A	20	8	35 (49)
22	C_6H_5	CH_3	B[f]	–20	15	76 (12)

[a] The electrolyses were carried out, under galvanostatic control, in a divided cell equipped with Pt electrodes at 0 °C. An amount of electricity of 2.0 F mol^{-1} was supplied to the electrodes; 0.5 mmol of carbonyl compound was used in each experiment. [b] Method A: substrate in anhydrous MeCN (3.0 mL) was added in "one-portion" to the cathodic solution of 0.1 M MeCN in TEATFB (2.0 mL); Method B: substrate in anhydrous MeCN (2.0 mL) was added dropwise over 30 min to the cathodic solution of 0.1 M MeCN in TEATFB (3.0 mL). [c] Yields refer to isolated products. Yields in parentheses refer to recovered starting material. [d] 3-(2-Furyl)pentanedinitrile was isolated in 28% yield as a byproduct. Substrate was added dropwise over 30 min. [e] 2-Hexylnon-2-enal was isolated as a byproduct in 18% yield. [f] Substrate was added dropwise over 60 min.



Scheme 2. Reaction of benzaldehyde with propionitrile and 2-methylpropionitrile. Reactions were carried out according to method A.

Conclusions

In conclusion, we have developed a new application of the electrogenerated cyanomethyl anion in organic synthesis. $^-CH_2CN$ was used as a nucleophile in the synthesis of β-hydroxynitriles, by addition reaction to carbonyl compounds. The proposed approach is very clean and safe, as it avoids the use of toxic cyanides or any base or metal catalysts. The described method provides β-hydroxynitriles in moderate to very good yields and represents a valuable and competitive alternative to the reported procedures.

Experimental Section

General Procedure for Electrochemical Addition of Cyanomethyl Anion to Carbonyl Compounds

Method A: A solution of anhydrous CH_3CN (0.1 M in TEATFB, 10.0 mL) was electrolyzed in a divided cell under galvanostatic control [Pt electrodes; J = 50 mA cm^{-2}; Q = 2.0 F mol^{-1} (t = 33 min) relative to carbonyl compound] at 0 °C under an atmosphere of argon. At the end of electrolysis the carbonyl compound (0.5 mmol) in anhydrous CH_3CN (1.0 mL) was added to the cathodic compartment, and the reaction was prolonged at the temperature and for the time reported in Table 2. The solvent was then evaporated under reduced pressure, and the crude reaction mixture was purified by flash chromatography on silica gel (ethyl acetate/hexane).

Method B: A solution of CH_3CN (0.1 M in TEATFB) was electrolyzed according to the conditions reported in method A. At the end of electrolysis, the carbonyl compound (0.5 mmol) in CH_3CN (5.0 mL) was added to the cathodic solution over 30 min. The reaction mixture was allowed to stand at the temperature and for the time reported in Table 2, after which the mixture was subjected to the work up procedure reported in method A.

2-(1-Hydroxy-4-phenylcyclohexyl)acetonitrile: Yield: 79 mg, 73%. M.p. 105–106 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.41–2.08 (m, 8 H, CH_2CCH_2), 2.15–2.30 (br. s, 1 H, OH), 2.55 (s, 2 H, CH_2CN), 7.22–7.35 (m, 5 H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.8, 32.2, 35.8, 42.3, 68.2, 116.3, 125.2, 125.7, 127.4, 145.2 ppm. MS (EI): *m/z* (%) = 215 (28) [M$^+$], 91 (98), 73 (100). $C_{14}H_{17}NO$ (215.29): calcd. C 78.10, H 7.96, N 6.51; found C 77.88, H 7.77, N 6.44.

2-(1-Hydroxycycloheptyl)acetonitrile: Yield: 62 mg, 81%. M.p. 41–42 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.11–1.33 (m, 2 H, CHCCH), 1.38–1.73 [m, 10 H, $CH(CH_2)_4CH$], 2.47 (s, 2 H, CH_2CN), 2.63–2.68 (br. s, 1 H, OH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.7, 25.0, 31.7, 36.8, 69.9, 117.6 ppm. MS (EI): *m/z* (%) = 98 (85), 81 (100), 57 (63). $C_7H_{11}NO$ (125.17): calcd. C 70.55, H 9.87, N 9.14; found C 69.23, H 9.71, N 9.19.

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