Electrolytic Oxidation of Ketones in a Methanolic Solution of NaCN in the Presence of Catalytic Amounts of KI

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The indirect electrolytic oxidation of ketones (1) in methanolic sodium cyanide was studied using iodide ion as a mediator. The product and the reactivity of ketone were dependent on the nature of the alkyl groups attached to the carbonyl group. Thus, 2-alkyl and 2,2-dialkyl ketones afforded the corresponding oxiranecarbonitriles **2** along with small amounts of methyl oxiranecarboximidate **3**, whereas acetophenones exclusively yielded benzoylpropanedinitriles **4**.

Introduction

The electrooxidation of carbonyl compounds by direct electron transfer to the anode involves some difficulties owing to the high oxidation potentials.[1,2] Therefore, the electrooxidative functionalization of the ketones and aldehydes has often been achieved by changing them to appropriate derivatives such as enol acetates or enol ethers which are more readily oxidizable than the parent carbonyl compounds[3] or by action of some active species anodically generated in situ, including indirect electrochemical methods.[4,5]

Previously, we reported the electrolytic oxidation of aldehydes in NaCN–MeOH,[6] NaOMe–MeOH–KI, and NH_3–NaOMe–MeOH–KI[7] electrolyte systems. In these electrolyses, aldehyde oxidized via a cyanohydrin, hemiacetal, or imine intermediate to yield the corresponding methyl esters or nitriles, respectively. As an extension of the above methods, we attempted the electrolytic oxidation of ketones **1** in an NaCN–MeOH–KI electrolyte system and found that although 2-alkyl and 2,2-dialkyl ketones underwent a cyanation at the carbonyl carbon atom involving a formation of an epoxy ring to yield oxiranecarbonitriles **2**, acetophenones were subject to dicyanation at the methyl group and converted into benzoylpropanedinitriles **4**.

Results and Discussion

Preparative-scale constant current electrolyses were performed at room temperature in a divided cell equipped with a platinum gauze anode, with a porous porcelain cup as the diaphragm. Most of the reactions were allowed to continue until the starting ketone **1** was almost wholly consumed.

The results of the oxidation of 2-alkyl and 2,2-dialkyl ketones are summarized in Table I. As can be seen from Table I, most of the 2-alkyl ketones readily underwent oxidation and converted into the corresponding oxiranecarbonitrile **2** in good yield at the stage where 2.2 F/mol of electricity had passed through the solution. In many cases, small amounts of methyl imidates **3** were formed as a byproduct.[8] Probably, the imidates were produced by methanolysis of **2** under the alkaline conditions. Indeed, the relative yield of **3** to **2** increased upon standing of the resulting electrolyte for a long time without passing current.

Compared to 2-alkyl ketones, 2,2-dialkyl ketones, such as diisopropyl ketone **1c** and isobutyrophenone **1e**, required an excess amount of electricity in order to complete the reaction. Upon adding an equimolar amount of sodium methoxide to the anolyte, however, the reaction proceeded

Scheme I

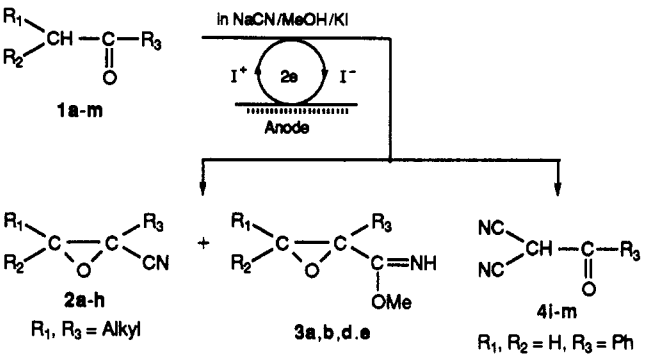

Table I. Electrochemical Oxidation of 2-Alkyl and 2,2-Dialkyl Ketones in NaCN/MeOH in the Presence of a Catalytic Amount of KI[a]

	ketones 1			current passed, F/mol	nitrile 2 (yield, %)[b]	imidate 3 (yield, %)[b]	total yield, %
	R_1	R_2	R_3				
1a	Et	H	n-Pr	2.5	**2a** (69)	**3a** (14)	83
1b	H		$-(CH_2)_4-$	2.6[c]	**2b** (12)	**3b** (57)	69
1c	Me	Me	i-Pr	5.2	**2c** (47)		47
				2.1[c]	**2c** (57)		57
1d	Me	H	Ph	2.1	**2d** (67)	**3d** (14)	81
1e	Me	Me	Ph	4.2	**2e** (47)	**3e** (18)	65
				2.2[c]	**2e** (51)	**3e** (32)	83
1f	Ph	H	Ph	2.2	**2f** (75)		75
1g	Ph	H	Me	2.1	**2g** (71)		71
1h	Ph	H	$PhCH_2$	2.2	**2h** (71)		71

[a] Anolyte: ketone (25 mmol), NaCN (100 mmol), KI (1.5 mmol), and MeOH (90 mL). Strength of constant current: 1.0 A. Temperature: approximately 15 °C. [b] Isolated yield. [c] Electrolyzed by adding an equimolar amount of NaOMe to the anolyte.

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(8) **2** and **3** were readily separated by treating the mixture with dilute hydrochloric acid, as **3** is soluble in acid. From the water phase, the imidate **3** was regenerated by making it alkaline.

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Scheme II

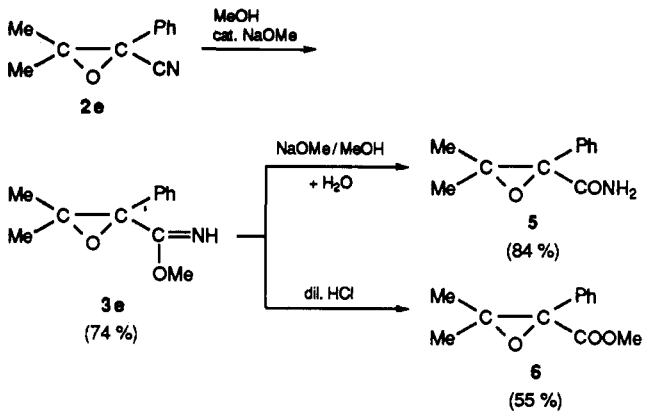


Table II. Electrochemical Oxidation of Acetophenones in NaCN/MeOH in the Presence of a Catalytic Amount of KI[a]

	acetophenone 1 R_3	current passed, F/mol	propanedinitrile 4 (yield, %)[b]
1i	C_6H_5	4.0	4i (70)
1j	4-MeC_6H_4	4.4	4j (67)
1k	4-$MeOC_6H_4$	10	4k (55)
		4.0[c]	4k (54)
1l	4-ClC_6H_4	4.0	4l (82)
1m	4-$NO_2C_6H_4$	3.7	4m (89)

[a] Anolyte: ketone (25 mmol), NaCN (100 mmol), KI (1.5 mmol), and MeOH (90 mL). Strength of constant current: 0.5 A. Temperature: approximately 15 °C. [b] Isolated yield. [c] Electrolyzed by adding an equimolar amount of NaOMe to the anolyte.

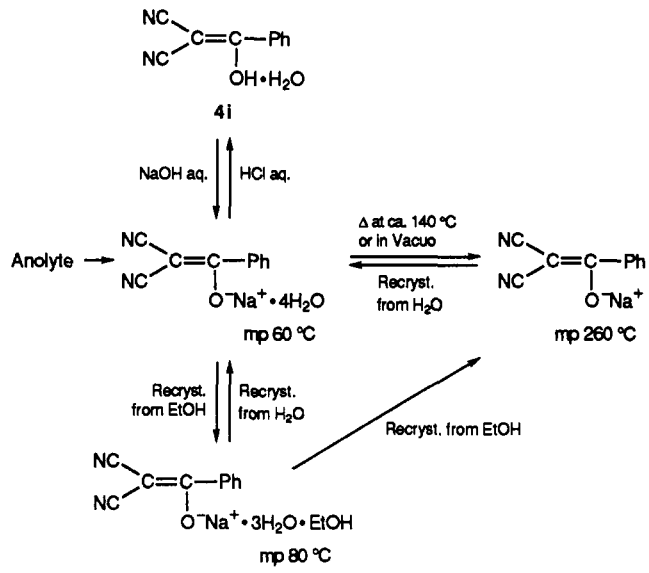
smoothly, while the relative yield of 3 to 2 increased. This suggested that ketones are oxidized through the enolic form.

In the present electrolysis, oxidation occured sufficiently even when 2 mol % of KI was used for 1, but little or no 2 was formed in the absence of the catalyst. Another halide ion, such as bromide or chloride, showed no effect on the formation of 2. The required amount of NaCN was four times greater for ketone in order to yield 2 effectively. Decreasing the amount of NaCN resulted in the formation of methoxyoxirane.

Since, unlike the epoxy ring of α-methoxy oxiranes,[9] that of α-cyano oxiranes is stable under acid or alkaline environments, the resulting products could readily be transformed into the oxiranecarboxylic acid derivatives, such as ester or amide, without causing ring opening. For instance, 2e was converted into 3e in a yield of 74% upon standing in methanol in the presence of a catalytic amount of NaOMe.[10] When 3e is dissolved in methanol containing an equimolar amount of NaOMe and allowed to stand overnight in an open dish in contact with moisture, the corresponding amide 5 could be obtained in a yield of 84%. The treatment of 3e with concentrated hydrochloric acid gave the methyl ester 6 in 55% yield.

Acetophenones gave a quite different type of product from 2-alkyl and 2,2-dialkyl ketones. They underwent dicyanation at the methyl group, affording sodium salts of benzoylpropanedinitriles 4. To the best of our knowledge, this is the first example of dicyanation at C-2 of ketones in one step. Usually, compounds of type 4 are

Scheme III



prepared by acylation of malonodinitrile with benzoyl chloride or cyanide in the presence of a base.[11,12]

The reactivity of acetophenones toward the dicyanation was different upon the substituents on the benzene ring. Electron-withdrawing groups promoted the cyanation while electron-donating groups interfered with the substitution. For example, chloro- and nitroacetophenone (1l and 1m) were almost wholly consumed by the time 4 F/mol of electricity had passed through the solution and converted into 4 in good yield, whereas methoxyacetophenone 1k required more than 10 F/mol of electricity in order to complete the reaction. In the latter case, the presence of NaOMe in the anolyte greatly promoted the reaction, as in the case of the electrolysis of 2,2-dialkyl ketones.

The product 4 showed an interesting property.[13] 4i sodium salt tetrahydrate, which is primarily obtained in the electrolysis of 1i from the resulting anolyte, liberated crystal water at 60 °C and solidified at approximately 140 °C to form anhydrous salt which decomposed at 260 °C. The crystal water was also released easily in vacuo. In addition, recrystallization of 4i sodium salt tetrahydrate from ethanol resulted in replacement of one molecule of the crystal water by one molecule of the alcohol to give fine needle crystals with a melting point of 80 °C. Upon treatment with ethanol again, this salt crystallized as the anhydrous salt.

The benzoylpropanedinitriles 4 which are precipitated on addition of acid to the aqueous solution of the sodium salt were such strong acids that carbon dioxide was liberated from sodium hydrogen carbonate. The IR spectra of 4 showed no C=O but did show OH absorption, and the ^1H NMR spectra exhibited a broad singlet absorption in the vicinity of 11–13 ppm in CD_3COCD_3, indicating the presence of an OH group. Therefore, 4 must exist as the enol, and the high acidity may be attributed to the strong electron-withdrawing character of the two cyano groups.[14]

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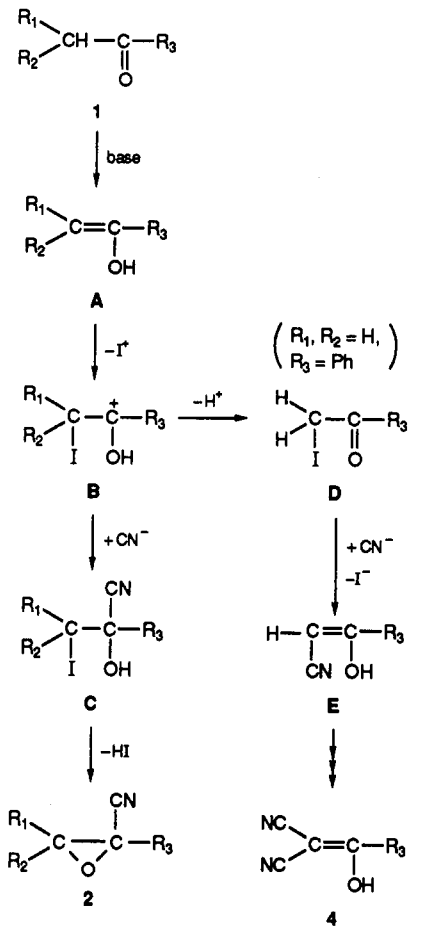
(14) Friedrich, K. *Angew. Chem.* **1967**, *79*, 980.

Scheme IV



The present reaction seems to proceed through α-halo ketone or its cyanohydrin, while quite different behavior between 2-alkyl and 2,2-dialkyl ketones and acetophenones was observed. Such behavior has been reported in the chemical reaction of α-halo ketones with cyanide ions, in which the former gives oxiranecabonitriles, whereas the latter gives 3-oxo-3-phenylpropionitriles.[15] Accordingly, the reaction process can be explained as shown in Scheme IV.

The principle mechanism of formation of **2** appears to be similar to that of transformation of ketone into the corresponding α-hydroxy acetal via the methoxylated oxirane by anodic oxidation carried out in methanol containing KI and KOH,[5] except that cyanide ion attacks the carbonyl carbon instead of the methoxide ion. Namely, enol **A** derived from ketone **1** initially undergoes an electrophilic addition of positive iodide species to form cation **B**. The resulting cation is attacked by cyanide anion, followed by elimination of HI to give oxiranecabonitriles **2**.

In the case of acetophenones, replacement of iodide by cyanide following deprotonation of **B** leading to **E** would be favorable. The electronegative character of the cyano group makes the α-hydrogen atoms which remain more readily replaceable by iodine, and thus substitution on the same carbon atom occurs to lead to **4** according to the route (A → B → D), as in the case of haloform reaction. Since in the base-catalyzed halogenation of ketones at the α position to the carbonyl carbon the rate-determing step is enolization of the ketone, the readiness of formation of **4** seems to depend on that of enolization of starting ketone. Substituted acetophenones with an electron-withdrawing group on the benzene ring more readily enolize than those with an electron-attracting group, since the former α hydrogen is more acidic than the latter one. Consequently, the electron-withdrawing group on the benzene ring of acetophenones promoted the formation of **4**.

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Experimental Section

General. Melting and boiling points are uncorrected. The ^{1}H NMR spectra were measured at 200 MHz in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in ppm downfield (δ) from internal Me_4Si. GC/MS analyses were performed using a 25-m capillary column (0.25 mm in diameter; liquid phase, FFAP). Ionization potential was 70 eV. FD-mass spectra and elemental analyses were performed by Instrumental Analyses Laboratories at Hokkaido University, Sapporo.

Materials. Starting ketones **1d**, **1e**, **1j**, **1k**, and **1l** were prepared from an appropriate acyl chloride and an aromatic compound by Friedel–Crafts reaction.[16] **1f**[17] and **1g**[18] were prepared by using the literature procedure, respectively. **1a**, **1b**, **1c**, **1h**, **1i**, and **1m** were commercial products and were used without further purification.

Preparative-Scale Electrolyses. All electrolyses were performed in a 100-mL divided cell by using a circular platinum gauze anode (33 mm in diameter, 40-mm high) and a platinum coil cathode (5 mm in diameter, 50-mm high). A porcelain porous cup (20-mm diameter, 50-mm high, 1.5-mm wall thickness) served as the cathode compartment, and the cathode was placed inside the cup. The cell was cooled with running water and the anolyte was stirred magnetically. The progress of the reaction was monitored by either GLC or TLC.

Electrolysis of Ketones (1a-g). General Procedure. A solution of **1** (25 mmol), NaCN (100 mmol), and KI (1.5 mmol) in MeOH (90 mL) was electrolyzed by passing a constant current of 1.0 A. The terminal voltage ranged from 5 to 7 V. After 2.2 F/mol of electricity had passed, the anolyte was concentrated on the rotary evaporator at rt, and the residue was treated with brine. The liberated oily layer was extracted with ether (25 mL × 3). The combined extracts were washed with ice-cold 3 N hydrochloric acid (15 mL), with concentrated aqueous sodium thiosulfate solution, and with water, dried (Na_2SO_4), and concentrated in vacuo at rt. The distillation of the residue gave oxiranecarbontrile **2**. In the cases of **2f** and **2h**, the product was isolated by column chromatography on silica gel using benzene as eluent. On the other hand, the washing of hydrochloric acid was made alkaline with 3 N NaOH (20 mL), and the liberated organic layer was extracted with ether (20 mL × 3). The combined extracts were dried (Na_2SO_4) and distilled to give imidate **3**. The isolated yields of **2** and **3** are given in Table I. Analytical samples were obtained by redistillation or recrystallization.

2-Ethyl-3-*n*-propyl-3-oxiranecarbonitrile (2a): bp 88–89 °C (18 mm) (lit.[19] bp 190–195 °C). GLC analysis (silicone SE 30, 2 m, at 120 °C) revealed that the product consists of two stereoisomers with the retention times of 1.5 and 1.8 min. The area ratio was 10:3. From the ^{1}H NMR data, the former was assumed to be trans form and the latter was cis. This was characterized as a mixture: IR (neat) ν 2230, 1455, 1220 cm^{-1}; ^{1}H NMR δ 0.90–1.2 (m, 6 H), 1.5–1.9 (m, 6 H), 2.92 and 3.29 (t, t, J = 6 Hz each, total 1 H, trans:cis = 10:3); MS m/e (relative intensity) 42 (100), 110 (30), 139 (M^+, 3).

Methyl 2-ethyl-3-*n*-propyl-3-oxiranecarboximidate (3a): bp 86–88 °C (18 mm); IR (neat) ν 3300, 1660, 1440, 1090 cm^{-1}; ^{1}H NMR δ 0.92 (t, J = 7 Hz, 3 H), 0.98 (t, J = 7 Hz, 3 H), 1.17–2.24 (m, 6 H), 2.91 (t, J = 6 Hz, 1 H, C*H*), 3.80 (s, 3 H),

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6.5–7.3 (broad s, 1 H); MS *m/e* (relative intensity) 73 (100), 142 (M^+ – 29, 19). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.00; N, 8.18. Found: C, 63.07; H, 10.02; N, 7.88.

2,2-Dimethyl-3-phenyl-3-oxiranecarbonitrile (2e): bp 118–121 °C (13 mm) [lit.[15] bp 110–112 °C (10 mm)]; IR (neat) ν 2220, 1455 cm^{-1}; ^1H NMR δ 1.09 (s, 3 H), 1.75 (s, 3 H), 7.42 (broad s, 5 H); MS *m/e* (relative intensity) 115 (100), 173 (M^+, 19).

Methyl 2,2-dimethyl-3-phenyl-3-oxiranecarboximidate (3e): bp 124–125 °C (15 mm); IR (neat) ν 3300, 1660, 1440, 1080 cm^{-1}; ^1H NMR δ 1.04 (s, 3 H), 1.39 (s, 3 H), 3.78 (s, 3 H), 7.22–7.60 (m, 5 H), 7.60 (broad s, 1 H); MS *m/e* (relative intensity) 73 (100), 105(60), 205 (M^+, 3). Anal. Calcd for $C_{12}H_{15}N\,O_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.20; H, 7.40: N, 6.54.

Alkaline-Induced Addition of MeOH to 2e. A solution of **2e** (3.46 g, 20 mmol) in 0.1 M NaOMe–MeOH (20 mL) was allowed to stand overnight in a stoppered flask. The resulting solution was worked up as usual to give **3e** (3.03 g, 74%).

Hydrolysis of 3e to Amide. A solution of **3e** (2.05 g, 10 mmol) in 1 M NaOMe–MeOH (10 mL) was placed in a crystallizing dish and permitted to stand overnight. A white solid that was left behind was treated with water and isolated by filtration. Almost pure **5** was obtained (1.60 g, 84%).

2,2-Dimethyl-3-phenyl-3-oxiranecarbamide (5): mp 156–157 °C (from MeOH); IR (KBr) ν 3370, 3140, 1630, 1410, 1080 cm^{-1}; ^1H NMR δ 1.06 (s, 3 H), 1.53 (s, 3 H), 5.7 (broad s, 1 H), 6.4 (broad s, 1 H), 7.3–7.4 and 7.6–7.7 (m, 5 H). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.20; H, 6.91: N, 7.35.

Hydrolysis of 3e to Ester. A solution of **3e** (3.46 g, 20 mmol) in ether (20 mL) was vigorously stirred with 4 mL of concd HCl. The organic layer was separated, washed with water, and dried with Na_2SO_4. The distillation gave **6** (2.26 g, 55%). **Methyl 2,2-dimethyl-3-phenyl-3-oxiranecarboxylate (6)**: bp 132–134 °C (14 mm); IR (neat) ν 1740, 1080 cm^{-1}; ^1H NMR δ 1.04 (s, 3 H), 1.45 (s, 3 H), 3.77 (s, 3 H), 7.3–7.4 and 7.5–7.6 (m, 5 H); MS *m/e* relative intensity) 73 (100), 77 (20), 105 (M^+ – 77, 19). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.90; H, 6.91.

Electrooxidation of Acetophenone (1i-m). General Procedure. A solution of 1 (25 mmol), NaCN (100 mmol), and KI (1.5 mmol) in MeOH (90 mL) was electrolyzed by passing a constant current of 0.5 A. After 4 F/mol of electricity had been passed, the solvent was removed at rt in vacuo. Upon addition of 20 mL of water to the sludgy residue, the sodium salt of **4** was precipitated as the hydrate. After being cooled in an ice bath, the solid was isolated by suction and washed with ether in order to remove the unreacted ketone. The resulting cake was acidified with 3 N hydrochloric acid, and a liberated **4** was isolated by suction and washed thoroughly with cold water. The isolated yields are given in Table II. Analytical samples of **4** were obtained by recrystallization from water with activated charcoal.

Benzoylpropanedinitrile monohydrate (4i): mp 130 °C dec (lit.[11,12] mp 127 °C, mp 130 °C); IR (KBr) ν 3350, 2220, 1550, 1340 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 6.67 (broad s, total 3 H, O*H*, H_2O), 7.5–7.7 (m, 3 H), 7.7–7.8 (m, 2H); FD-MS *m/e* 170 (M^+ – H_2O). Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.87; H, 4.33; N, 14.77.

Recrystallization of sodium salt of **4i** from a small amount of cold water gave fine powder crystals. **Benzoylpropanedinitrile sodium salt tetrahydrate (7)**: mp 62–63 °C dec (from H_2O); ^1H NMR (CD_3COCD_3) δ 3.13 (s, 8 H, 4H_2O), 7.25–7.4 (m, 3 H), 7.65–7.8 (m, 2H). Recrystallization of the sodium salt tetrahydrate from EtOH gave colorless needle-like crystals.

Benzoylpropanedinitrile sodium salt trihydrate solvated by ethanol (8): mp 79–81 °C dec; ^1H NMR (CD_3COCD_3) δ 1.12 (t, 3 H, CH_3), 2.98 (s, 6 H, 3H_2O), 3.45–3.65 (m, 3 H, CH_2, O*H*), 7.25–7.4 (m, 3 H), 7.65–7.8 (m, 2H).

Both sodium salt hydrates **7** and **8** readily released the crystal water and alcohol to give the anhydrous salt upon heating or under reduced pressure. Consequently, combution analysis gave unsatisfactory results for C and H. Analytical data of Na by the ashing method[20] and of N by the Kjeldahl method were in fair agreement with the calculated values. **7**. Anal. Calcd for $C_{10}H_{13}N_2O_5Na$: N, 10.60; Na, 8.70. Found: N, 10.67; Na, 8.62. **8**. Anal. Calcd for $C_{12}H_{17}N_2O_5Na$: N, 9.59; Na, 7.87. Found: N, 9.57; Na, 8.10. The weight loss in vacuo (0.1 mmHg) after 4 h at 35 °C was 27.8% for **7** and 33.5% for **8** (theoretical value is 27.3 and 34.3%, respectively). **Benzoylpropanedinitrile anhydrous sodium salt**: mp 260 °C dec; IR (KBr) ν 3300, 2170, 1480, 1370 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 7.3–7.4 (m, 3 H), 7.6–7.8 (m, 2 H); FD-MS *m/e* 192, (M^+).

Anal. Calcd for $C_{10}H_5N_2ONa$: C, 62.51; H, 2.62; N, 14.58; Na, 11.96. Found: C, 62.52; H, 2.43; N, 14.41; Na, 11.91.

Supplementary Material Available: Experimental data for **2b–d,f–h, 3b,d,** and **4j–m** (3 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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