

Anodic Cyanation of 1-(1-Methoxycarbonyl ethyl) piperidine

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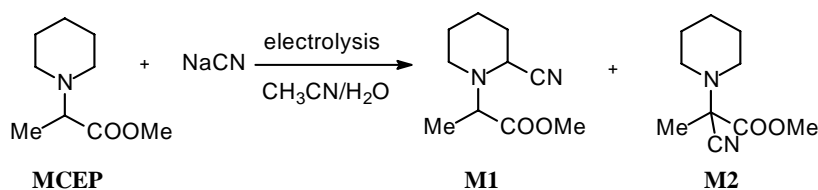
Abstract: α -Aminonitriles were prepared efficiently from anodic cyanation of α -amino ester. The effect of different solvents and electrolytes was studied. The other byproducts were analyzed.

Keywords: α -Aminonitriles, 1-(1-methoxycarbonyl ethyl) piperidine, anodic cyanation, electrolysis.

α -Aminonitriles derived from piperidine have proven to be extremely versatile synthons and gained much attention due to their general utility in indole alkaloid synthesis^{1,2}. They are generally obtained from tertiary amines by the Polonovsky-Potier³ reaction *i.e.* treatment of tetrahydropyridine N-oxides with trifluoroacetic anhydride followed by trapping with cyanide anions. A. Koskinen *et al.* reported the synthesis of α -aminonitriles from the corresponding α -amino ester *via* the modified Polonovsk-Potier reaction⁴. They obtained α -aminonitriles with the yield of 30-60%. Herein, we studied the electro-oxidation of α -amino ester to prepare α -aminonitrile.

The electro-oxidative α -cyanation was carried out in a breaker-type undivided cell, fitted with two platinum plate type electrodes ($1 \times 3 \text{ cm}^2$). Typical electrolysis procedure is described as follows: 1.6 mmol α -amino ester and 4 mmol NaCN dissolved in 16 mL $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1) solution in 30 mL beaker. Electrolysis was carried out under a constant current at 10 mA. Total consumed current was 2.5 F/mol. The resulted mixture was concentrated *in vacuo* and the products were analyzed by GC-MS and NMR. The results of this electro-oxidative substitution at the α -nitrogenous carbon (**Scheme 1**) under various electrolytes are summarized in **Table 1**.

Scheme 1 Anodic cyanation of MCEP.



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Table 1 Constant current (10 mA) electrolysis of MCEP in CH₃CN/H₂O with different electrolytes

Entry	electrolyte	Substrate	Yield (%)	Yield (%)	Others
1	NaCN	low	21.09	24.61	54.3
2	Bu ₄ NBr/ NaCN	low	20.86	25.43	53.71
3	LiClO ₄ / NaCN	low	26.95	28.35	44.7
4	polyglycol (400) / NaCN	low	11.97	13.25	74.78
5	Et ₄ NOTs/ NaCN	5.51	20.69	27.30	46.50
6	C ₁₂ H ₂₅ SO ₃ Na/ NaCN	32.04	12.67	18.10	37.19
7	Bu ₄ NI/ NaCN	19.52	---	---	80.48

According to the above results, the cyanation took place not only on the ring but also on the side chain. α -Aminonitriles was obtained no matter what electrolyte was used except the Bu₄NI because of the I⁻ is easy to be oxidized to iodine. The yield of α -aminonitriles is much lower than others when polyglycol (400) was used as electrolyte because of the high viscosity and low conductance of the polyglycol (400). A mass of substrate was left and low yield of α -aminonitriles were obtained when C₁₂H₂₅SO₃Na was used as electrolyte indicated that C₁₂H₂₅SO₃Na is not suitable as electrolyte in this system because of its foam and emulsification.

The results of electrolysis of MCEP in different solvent are summarized in **Table 2**. Good yield α -aminonitriles can be obtained when only methanol was used as solvent with no other electrolytes or CH₃COOLi·2H₂O used as electrolyte only.

Table 2 Constant current (10 mA) electrolysis of MCEP in different solvent

Entry	Solvent	Electrolyte	substrate (%)	Yield (%) M1	Yield (%) M2	Others (%)
1	CH ₃ OH/H ₂ O	NaCN	Low	10.88	19.69	69.43
2	CH ₃ OH	NaCN /CH ₃ COOLi·2H ₂ O	Low	35.74	36.78	27.48
3	CH ₃ OH	NaCN	2.98	35.62	44.71	16.69
4	CH ₃ CN/H ₂ O	LiClO ₄ / NaCN	Low	26.95	28.35	44.7
5	CH ₃ CN	LiClO ₄ / NaCN	3.85	24.91	22.55	48.69
6	CH ₂ Cl ₂ /H ₂ O	LiClO ₄ / NaCN	36.72	31.34	19.67	12.27
7	THF	LiClO ₄ / NaCN	63.71	8.52	6.40	21.37
8	CH ₃ NO ₂ /H ₂ O	LiClO ₄ / NaCN	32.28	29.34	24.06	14.32

Sodium cyanide is soluble only in methanol and not in other solvents. Thus other solvents must be used with water in order to dissolve sodium cyanide. Methanol and acetonitrile are both most used solvents because of their high dielectric constant, a wide, usable potential range and good electrochemical properties.

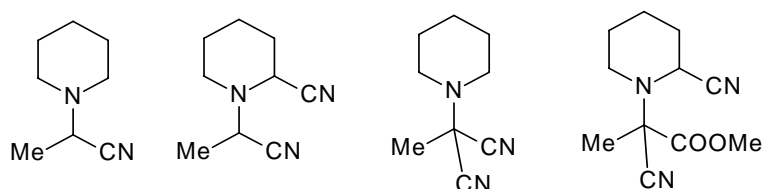
LiClO₄ can dissolve in nitromethane and about 3V potential can be reached at a platinum electrode. When CH₃NO₂/H₂O used as solvent, a lot of substrate was remained. The cathode was passivated by layers of unknown compound which formed in electrolysis.

Since the dielectric constant of THF is very low, LiClO_4 was added as electrolyte. The cathode in THF was passivated likely to that in $\text{CH}_3\text{NO}_2/\text{H}_2\text{O}$.

$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ is a system of two immiscible solvent, the dielectric constant of methylene chloride is low and LiClO_4 and NaCN are both insoluble in methylene chloride. This is the reason that the yield of α -aminonitriles and conversion ratio of the substrate are not high.

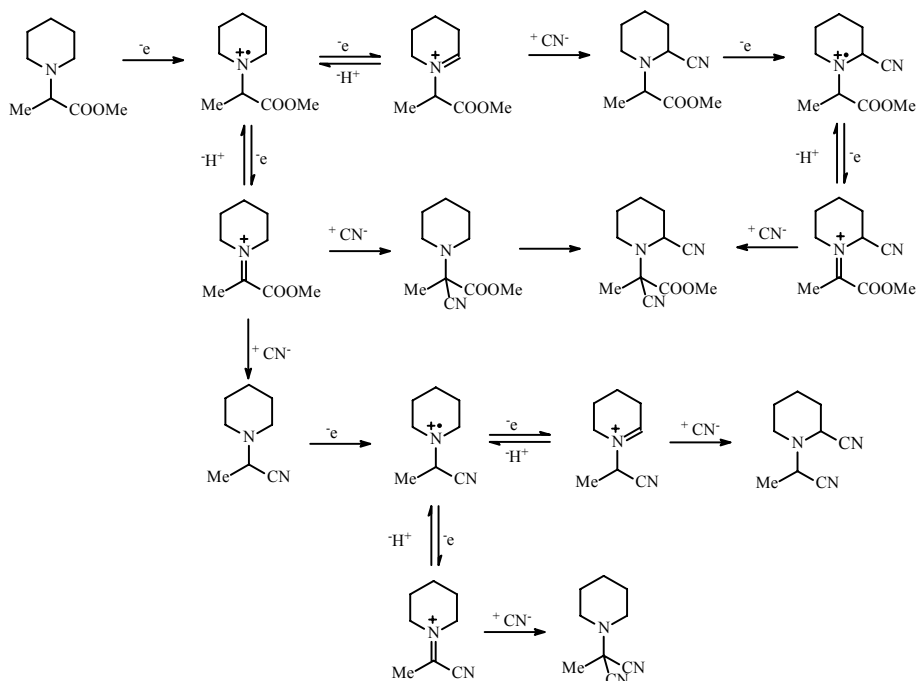
No matter what solvent and electrolyte was chosen, certain extent byproducts were formed for reaction of MCEP in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ under constant current electrolysis (**Scheme 2**).

Scheme 2 The byproducts of anodic cyanation of MCEP



The mechanism of the cyanation is shown in **Scheme 3**. The substrate transferred an electron to form a cation radical which then deprotonated and transferred an electron again to give iminium cation. The iminium cation reacted with cyanide ion to give α -aminonitriles. The α -aminonitriles could be oxidized to form the corresponding double-cyanated products.

Scheme 3 The mechanism of anodic cyanation of MCEP



Acknowledgments

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References and Notes

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3. A. Koskinen, M. Lounasmaa, *Tetrahedron*, **1983**, 39 (9), 1627.
4. P. Potier, *Rev. Latinoamer. Quim.*, **1978**, 9,47.
5. **M1**: pale yellow oil. MS m/z (rel. int.): 196(2, M^+), 169(9), 154(0.40), 137(100), 121(0.45), 110(76), 94(3), 82(14), 67(12), 55(23), 41(27). $^1\text{H NMR}$ (CDCl_3 , 300MHz) δ 1.34(d, 3H, $J=7\text{Hz}$), 1.3-2.1(m, 6H), 2.55-2.95(m, 2H), 3.48(q, 1H, $J=7\text{Hz}$), 3.73(s, 3H), 3.90(m, 1H)
6. **M2**: pale yellow oil. MS m/z (rel. int.): 196(2, M^+), 181(0.33), 169(7), 154(0.39), 137(100), 121(0.43), 110(69), 94(3), 82(13), 67(12), 55(22), 41(27). $^1\text{H NMR}$ (CDCl_3 , 300MHz) δ 1.50(m, 6H), 2.24(m, 4H), 1.73(s, 3H), 3.67(m, 3H).

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