Synthesis α-Aminonitrile through Anodic Cyanation of *N*-Benzylpiperidine

Ping Zhao[1], Ying-Wu Yin[1,2]

[1] Department of Chemistry, Tsinghua University, Beijing, China (100084)
[2]Beijing TH-UNIS Insight Co., Ltd. Beijing, China (100084)
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Six-membered cyclic α-aminonitrile has been prepared from anodic cyanation of *N*-benzylpiperidine. Good yields of α-aminonitriles could be obtained through potentiostatic electrolysis under different conditions. The results also explain why high yield α-aminonitriles could not be obtained under constant current electrolysis.

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Introduction.

α-Aminonitriles derived from piperidine derivatives have gained considerable attention during recent years, particularly because of their general utility in indole alkaloid synthesis [1-2]. According to the literatures, most of the piperidine alkaloids have substituents at the 2 and/or 6 positions, *i.e.* coniine, pinidine, and solenopsin A *etc*. These natural products may be isolated from both animals (*e.g.*, histrionicotonxin, solenopsin A) and plants (*e.g.*, sedinine, ponidine, carpaine) [3]. However, the yield from these sources is insufficient for practical uses. Moreover, most of the methods for preparing cyclic α-aminonitrile suffer from low yields [4-6] or from limited sources [7-10]. T. K. Yang *et al* reported that α-aminonitriles could be obtained through electro-oxidation α-cyanation of aza-ring compounds [11]. However, because their reaction was performed under constant cell voltage conditions, they obtained α-aminonitriles in low yields. In order to improve the yield and selectivity of this reaction, we initiated a study on the behavior of cyclic voltammetry and linear sweep voltammetry of tertiary cyclic amines [12]. As a result, some information was obtained about the mechanism and the range of the appropriate oxidation potentials of tertiary cyclic amines in potentiostatic electrolysis was confirmed.

Result and Discussion.

First, we carried out anodic cyanation of *N*-benzylpiperidine under constant current conditions. The result is summarized in Table 1. We found the yield and the CE (current efficiency) was low when the current was high and *vice versa*. A large amount of byproducts were produced through constant current electrolysis. Under high current electrolysis, the anodic potential increased to the point that α-aminonitriles were also oxidized. This phenomenon could be depressed to a large extent under low current electrolysis conditions. The reason for low CE is that the cyanide ion and its conjugate bases resulting from the equilibrium between CN^- and protic solvents discharged together with the organic substrate to produce a cyanide radical. The cyanide radical did not enter into organic products but, as found by Andreades and Zahnow [13], attacked the cyanide to form cyanogen anion radicals or dimerized to cyanogen. The excess current would thus be consumed by this inorganic electrode process as well as by the regeneration of the substrate as a consequence of homogeneous electron transfer between cation radicals and cyanide.

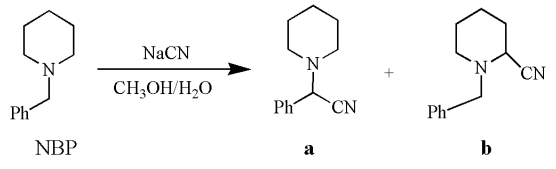

Figure 1. Anodic cyanation of *N*-benzylpiperidine.

Table 1

Anodic Cyanation of *N*-Benzylpiperidine Under Constant Current (Constant Quantity of Electric Charge 2.5F/mol)

Entry	Current (mA)	Time (s)	Substrate (%)	α-Aminonitrile Yield (%) **a+b**	Ratio **a/b**
1	10	33780	1.72	71.21	3.13
2	20	16890	19.05	69.90	3.70
3	50	6756	38.98	41.71	3.73
4	100	3378	79.07	16.98	3.05
5	200	1689	86.20	10.42	4.33

In order to elucidate the mechanism of the reaction, we monitored the process of the reaction under constant current (Table 2, Figure 2). We found that the yield of α-amino-

Table 2

Relationship Between Yield and Electrolysis Time of Anodic Cyanation *N*-Benzylpiperidine Under Constant Current Electrolysis (100 mA 8x5cm^2 Pt Electrode)

Entry	Reaction Time	Substrate (%)	α-Aminonitrile Yield (%) **a+b**	Ratio **a/b**	**a** (%)	**b** (%)
1	t=0	100	0	------	0	0
2	t=1	98.73	1.27	6.19	1.09	0.18
3	t=3	87.96	12.04	3.22	9.19	2.85
4	t=5	75.14	20.77	3.29	15.93	4.84
5	t=7	64.21	34.81	2.87	25.82	8.99
6	t=10	48.56	45.46	3.40	35.13	10.33
7	t=12	31.85	57.60	3.37	44.42	13.18
8	t=14	19.54	59.82	3.30	45.91	13.91
9	t=16	3.42	56.07	3.67	44.06	12.01
10	t=17	0	46.82	3.98	37.42	9.40

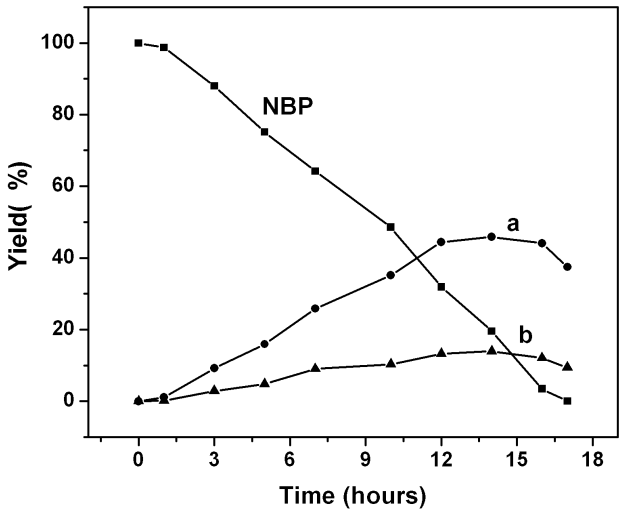

Figure 2. The relationship between yield and electrolysis time for anodic cyanation of *N*-benzylpiperidine under constant current electrolysis.

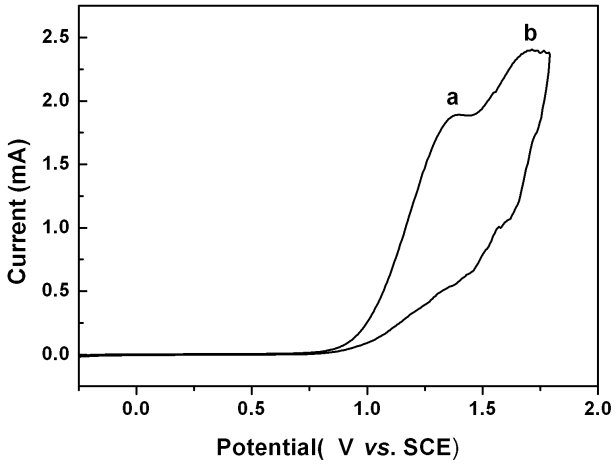

Figure 4. Cyclic voltammogram recorded in 0.15 *M N*-benzylpiperidine + 0.25 *M* sodium cyanide in 50 ml methanol + 50 ml water at room temperature (*ca*. 25 °C) v=50mVs^{-1}.

nitriles decreased with elapsed time, which can be explained by the fact that the electrode potential increases with elapsed time due to the polarization of the anode (Figure 3). The α-aminonitriles could be oxidize to α,α-aminodinitrile as well, which could be avoided through potentiostatic electrolysis. In order to confirm the appropriate oxidation potentials, we initiated a study on the behavior of cyclic voltammetry of *N*-benzylpiperidine in methanol-water (1:1) and sodium cyanide solution. We found that the system discharges at approximately at 0.87 V (*v s.* SCE) (Figure 4), and that the two successive irreversible peaks observed correspond to oxidation of the *N*-benzylpiperidine and oxidation of the α-aminonitrile formed at peak **a**.

We studied the anodic cyanation at potentiostatic electrolysis. The result is summarized in Table 3. We found

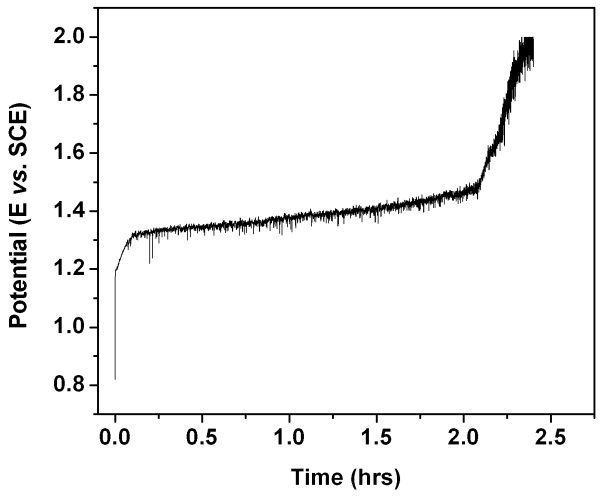

Figure 3. Anode potential-time curve under constant current electrolysis at 20mA.

Table 3

Electrolysis at Different Electrode Potentials

Entry	V (*vs.* SCE)	Substrate (%)	Product **a**+**b** (%)	Product **a**/**b**
1	0.8	100	0	------
2	0.9	3.65	82.40	2.75
3	1.3	4.77	89.30	3.11
4	1.4	low	90.26	3.90
5	1.6	3.44	71.86	3.04

that the yield of α-aminonitrile was increased to 90% when the oxidation potential was suitable. *N*-benzylpiperidine was not oxidized when the electrode potential was lower than 0.9V. This meant that the anodic cyanation only took place at potentials higher than 0.87 V. When the electrode potential was higher than 1.6 V overoxidation and other reactions such as the decomposition of α-aminonitrile **b**, which lowers yield, took place. The selectivity could not be affected greatly by the electrode potential, and the yield of α-aminonitrile increased under potentiostatic electrolysis relative to constant current electrolysis.

Electrolysis at different substrate concentrations, different sodium cyanide concentrations, different temperatures and different ratios of CH_3OH and H_2O at controlled potential electrolysis was all studied in this paper. Table 4 shows the effects of temperature on anodic cyanation of *N*-benzylpiperidine at a potential of 1.4 V. From these results, it can be seen that the yield of α-aminonitrile is very low when the temperature is low. High temperature promoted an increase in the yield of α-aminonitrile. However, when the temperature is increased decomposition of **b** also increases. Thus the selectivity increased with the temperature.

Table 4

Electrolysis at Different Temperature at 1.4 V (*vs.* SCE)

Entry	T (°C)	Substrate (%)	Product **a+b** (%)	Product **a/b**
1	-15	74	23.47	2.16
2	0	low	91.82	2.44
3	r.t (~20)	low	90.26	3.90
4	35	1.4	90.47	4.87
5	50	1.79	83.61	7.84

Table 5

Electrolysis at Different Substrate Concentration at 1.4 V (*vs.* SCE)

Entry	Concentration (mol/l)	Substrate (%)	Product **a+b** (%)	Product **a/b**
1	0.05	low	91.09	5.18
2	0.1	low	90.26	3.90
3	0.15	9.81	76.60	3.78
4	0.2	5.62	82.42	3.52
5	0.25	3.85	90.80	3.03

Table 6

Electrolysis at Different concentrations of Sodium Cyanide at 1.4 V(*vs.* SCE)

Entry	Concentration of NaCN (mol/l)	Substrate (%)	Product **a+b** (%)	Product **a/b**
1	0.1	19.73	65.82	4.60
2	0.2	6.53	82.58	3.59
3	0.25	0.47	90.26	2.99
4	0.4	5.0	85.9	3.89
5	0.6	19.13	76.03	3.66

Table 7

Electrolysis at Different Ratios of CH_3OH to H_2O at 1.4 V

Entry	CH_3OH:H_2O (volume ratio)	Substrate (%)	Product **a+b** (%)	Product **a/b**
1	1:3	24.78	68.30	4.27
2	1:2	8.78	69.18	3.02
3	1:1	0.47	90.26	2.99
4	2:1	low	89.93	4.70
5	3:1	low	75.82	4.36

Increasing the concentration of *N*-benzylpiperidine resulted in increased reaction time with the same quantity of electric charge consumed (Table 5). This implied that the current decreased because the large concentration *N*-benzylpiperidine decreased the conductivity of the solution. Long electrolysis times contributed to the decomposition of **b**. Thus the reaction selectivity also decreased with an increase in substrate concentration. In short, a low concentration of substrate was good for electrolysis.

N-Benzylpiperidine could not be completely converted to α-aminonitriles if the concentration of sodium cyanide was too low although the selectivity was good (Table 6). The result was the same as when the concentration of sodium cyanide was too high. The reason being that the α-aminonitrile would be cyanated to α,α-aminodinitrile if the concentration of sodium cyanide was too high. Thus the concentration range of sodium cyanide was 0.2-0.4 *M*.

At a low ratio of CH_3OH to H_2O, the yield of the reaction is low (Table 7) with a large amount of substrate remaining. At high ratio of CH_3OH to H_2O, the yield is low but the remaining substrate is also low. This shows that not only sodium cyanide but also *N*-benzylpiperidine must be dissolved in solution. Sodium cyanide can be dissolve in methanol but *N*-benzylpiperidine can not be dissolve in water. Thus the yield was not affected greatly when the quantity of methanol was large, but the observed yield was low when excess water was present in solution.

Conclusion.

In conclusion, low current resulted in high yield under constant current electrolysis. Long electrolysis times led to a decrease in the yield of α-aminonitrile under constant current electrolysis. Anode potential was the key factor for the synthesis. Under potentiostatic electrolysis, low substrate concentration, high temperature was propitious to electrolysis. The concentration range of sodium cyanide was 0.2-0.4 *M* and the best ratio of CH_3OH to H_2O was1:1 or 2:1.

EXPERIMENTAL

General.

All reagents were obtained commercially and used without further purification. NMR spectra were recorded on a Bruker DPX300 (300MHz, $CDCl_3$). Mass spectra were obtained with a GC/MS-QP5050A instrument. The electrochemical experiments were performed on an electrochemical interface (EG&G Potentiostat/Galvanostat model 283) controlled by a personal computer.

Cyclic voltammogram of *N*-benzylpiperidine was recorded on Potentiostat/Galvanostat. All potentials were refereed to saturated calomel electrode (SCE). Prior to each measurement, the electrolyte was saturated with pure nitrogen for five minutes in order to remove oxygen from the solution. The electrode was activated by cathodic and anodic potential cycles between 1.4 V and -0.25 V at the rate of 50 mV/s in 0.5 *M* H_2SO_4 until the cyclic voltammogram was the same as authentic.

General Procedure for Constant Current Electrolysis of *N*-Benzylpiperidine.

The mixed solution of *N*-benzylpiperidine 0.245 g (1.4 mmol), sodium cyanide 0.1719 g (2.5 mmol), water (7 ml) and methanol (7 ml) was used as electrolyte. The current was controlled at 10 mA, 20 mA, 50 mA, 100 mA and 200 mA, respectively. Anode and cathode are smooth Pt plate with area 3 cm^2. The electrolysis time was calculated according to Faraday law. The consumed electric charge was 2.5 F/mol in each experiment. The final solutions were extracted three times with dichloromethane. The organic layers were dried using anhydrous magnesium sulfate, evaporated at 40 °C, and the liquid crude products with yellow color were obtained.

The crude product was purified by column chromatograph on silica gel (hexane/ethyl acetate 10:1, Et_3N 1%).

General Procedure for Potentiostatic Electrolysis of *N*-Benzylpiperidine.

The potential of working electrode was controlled at 0.8 V, 0.9 V, 1.3 V,1.4 V, 1.6 V (*vs*. SCE), respectively. The same quantity of electric charge was consumed in each experiment (2.5 F/mol). The final solutions were extracted three times with dichloromethane. The organic layers were dried using anhydrous magnesium sulfate, evaporated at 40 °C, and the liquid crude products with yellow color were obtained. The crude product was purified by column chromatograph on silica gel (hexane/ethyl acetate 10:1, Et_3N 1%).

The yields of α-aminonitriles in Tables 1-4 were determined by GC, and the ratio of **a**/**b** was determined by the chemical shift of α-H of α-aminonitriles **a** and **b**.

N-Benzylpiperidine.

A solution of benzyl bromide (5.9 mL, 5.0 mmol) in 1,2-dichloroethane (2.0 mL) was dropped into a solution of piperidine (9.9 mL, 10.0 mmol) and an equivalent amount of triethylamine in 1,2-dichloroethane (18.0 mL). The mixture was stirred at room temperature for six hours. The reaction was complete as indicated by the disappearance of the benzyl-bromide signal in the ^1H NMR spectrum (δ 3.5 ppm). The solution was filtrated twice to remove the triethylammmonia hydrobromide salt. The filtrate was washed with deionized water, dried and evaporated. The residue was distilled under reduced pressure to give **a** (0.796 g, 91%). The purity was 99.1% as determined by a gas chromatography. bp 50 ºC/85Pa; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.2-1.6 (m, 6H), 2.38 (m, 4H), 3.48 (s, 2H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 53.7, 25.3, 23.7, 25.3, 53.7, 63.0, 138.1, 128.4, 127.8, 126.1; MS *m*/*z* (%): 175 (M^+, 35%), 174 (42%), 98 (50%), 91 (100%), 84 (46%), 65 (26%).

1-Benzylpiperidine-2-carbonitrile (**a**).

This compound was obtained as colorless liquid; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.49-1.89 (m, 6H), 2.42 (dt, 1H, J =11.5 Hz), 2.79 (m, 1H, J = 13.0 Hz), 3.52 (d, 1H, J = 13.0 Hz), 3.69 (d, 1H, J = 13.0 Hz), 3.72 (t, 1H, J = 3 Hz), 7.25-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 20.5, 20.5, 28.6, 49.7, 52.1, 60.7, 116.7, 127.6, 128.5, 129.0, 127.0; MS *m*/*z* (%): 200 (M^+, 18%), 173 (23%), 109 (67%), 91 (100%).

1-(1-Cyanobenzyl)piperidine (**b**).

This compound was obtained as colorless crystals; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.10-1.95 (m, 6H), 2.20-2.65 (m, 4H), 4.82 (s, 1H), 7.10 - 8.00 (m, 5H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 50.8, 25.7, 23.8, 25.7, 50.8, 62.8, 115.4, 127.6, 128.5, 128.9, 134.5; MS *m*/*z* (%): 200(M^+, 45%), 199 (40%), 116 (80%), 84 (100%).

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