Anodic Cyanation of 1-Arylpyrrolidines

Wei Liu, Yuan Ma, Yingwu Yin,* and Yufen Zhao

The Key Laboratory for Bioorganic Phosphorus
Chemistry and Chemical Biology, Ministry of Education,
Department of Chemistry, Tsinghua University,
Beijing 100084, P. R. China

Beijing TH-UNIS Insight Co., Ltd.,
Beijing 100084, P. R. China

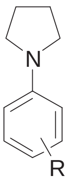
Received September 15, 2005; E-mail: liu-wei03@mails.tsinghua.edu.cn

The electrochemical cyanation of 1-arylpyrrolidines was carried out in methanol containing sodium cyanide at a platinum anode in a divided cell. The reaction gave the corresponding α-aminonitriles **2**, together with the unexpected 1-arylpyrrolidine-2-carboximidic acid methyl esters **3** as byproducts.

α-Aminonitriles derived from pyrrolidine derivatives have proven to be extremely versatile synthons in a number of synthetic applications.[1] These applications have stimulated further efforts for the development of the regiocontrolled synthesis of this class of compounds.

Anodic cyanation of organic compounds is expected to provide a promising method for the synthesis of nitriles by reason of its positional reactivity, clean reaction products, and mild reaction conditions.[2] However, few investigations on the anodic cyanation of pyrrolidine derivatives have been studied. Previously, Chiba et al.[3] reported anodic cyanation of tertiary heterocyclic amines involving several 1-alkylpyrrolidines in aqueous methanol containing sodium cyanide. They found steric hindrance around the nitrogen atom of amines affected product yields and regioselectivity. We herein investigate the anodic cyanation of 1-arylpyrrolidines and the effect of the aryl-substituents on both peak potentials and product yields. The structures of the title compounds are shown in Scheme 1.

The starting tertiary cyclic amines **1a**–**1j** were easily prepared by direct treatment of 2,5-dimethoxytetrahydrofuran with the requisite primary amines according to the procedure in Ref. 4. The oxidation potentials of 1-arylpyrrolidines were measured by cyclic voltammetry. Peak potentials, expressed in V vs SCE and ohmic drop has not been corrected, were collected in Table 1. These title compounds exhibited irreversible oxidation waves. 1-(2-Methylphenyl)pyrrolidine (**1b**) was here selected as the model compound. Three successive irreversible peaks were observed (Fig. 1) at $E_p\text{A} = +0.85$, $E_p\text{B} = +1.23$, and $E_p\text{C} = +1.60$ V vs SCE. It could be explained that the species (iminium cation) electrogenerated at peak A was trapped by cyanide anions leading to the α-aminonitrile **2b**, which could be further oxidized at E_pB. Indeed, a similar peak B′ was recorded on a cyclic voltammogram of a methanolic solution of the α-aminonitrile **2b** in the presence of eight equiv of sodium cyanide relative to the substrate. In the absence of substrate, no peak was observed in its CV (Fig. 1). Therefore, the remaining peak C is probably attributed to the oxidation of the product formed at peak B, not to the oxidation of the cyanide anion. As shown in Table 1, the 1-arylpyrrolidines **1a**–**1f** were oxidized at less positive potentials than those of **1g**–**1j**. The potential shift could be explained by the electron-withdrawing effect of the trifluoromethyl or nitro group. Taken together, these results indicated that selective transformations might be performed at the first oxidation peak of amines **1a**–**1j** during macroscale electrolyses.



1a R = H; **1b** R = *o*-CH_3; **1c** R = *m*-CH_3; **1d** R = *p*-CH_3
1e R = *p*-Cl; **1f** R = *p*-F; **1g** R = *o*-CF_3; **1h** R = *o*-NO_2
1i R = *m*-NO_2; **1j** R = *p*-NO_2

Scheme 1.

Controlled potential electrolysis was performed under the conditions described in Table 1. Results of the anodic cyanation are also given in Table 1. In each case, cyanation occurred exclusively at the carbon atom α to the nitrogen atom and the corresponding α-aminonitriles **2** were produced in moderate to good yields. A possible electrocyanation mechanism is shown in Scheme 2.[3]

It is interesting that the 1-arylpyrrolidine-2-carboximidic acid methyl esters **3** were also observed as byproducts in this electrolysis (GC-MS analysis). This surprising result could be explained by concomitant solvolysis of the aminonitriles **2** in a methanolic sodium cyanide solution at room temperature. In order to clarify the proposed mechanism, alkaline hydrolysis of the aminonitrile **2j** in a methanolic sodium cyanide solu-

Table 1. Anodic Cyanation of 1-Arylpyrrolidines: Voltammetric Data and Products

Substrate R	E_p[a)]/V	E[b)]/V	Product yield/% **2**[c)]	**3**[d)]
H	0.818, 1.152, 1.595	0.7	41	5
o-CH_3	0.846, 1.228, 1.602	0.7	70	—
m-CH_3	0.755, 1.081, 1.469	0.6	79	3
p-CH_3	0.666, 0.990, 1.388	0.6	81	3
p-Cl	0.810, 1.148, 1.565	0.7	71	11
p-F	0.785, 1.115, 1.511	0.6	75	10
o-CF_3	1.048, 1.492	0.9	83	2
o-NO_2	1.158, 1.498	1.0	30	37
m-NO_2	1.033, 1.385	1.0	39	46
p-NO_2	1.089, 1.403	1.1	41	42

a) Peak potential from cyclic voltammetry. Pt anode, CH_3OH, 0.16 M NaCN. SCE reference. Scan rate is $0.1\,V\,s^{-1}$. Values are obtained on first scan from 0.00 to 2.00 V. Substrate concentration is 0.02 M. b) Potential for preparative electrolysis. c) Isolated yield. d) Determined yield by GC-MS.

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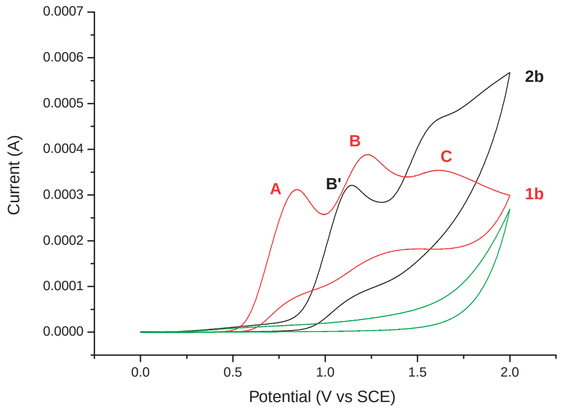
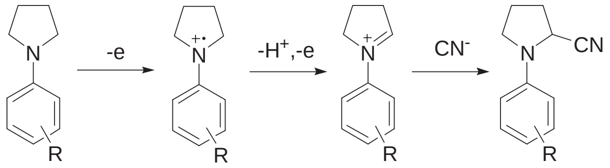
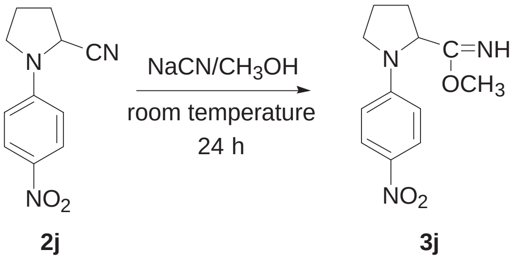


Fig. 1. Voltammetric investigations in the amine **1b**, aminonitrile **2b**, and MeOH + NaCN, respectively. Scan rate = 100 mV s^{-1}.



Scheme 2.



Scheme 3.

tion was investigated at room temperature. The same ester product **3j** was obtained in reasonable yield (Scheme 3).

This side reaction is favored for the structure of the substrate, the 1-arylpyrrolidines **1** bearing an electron-withdrawing group on the aromatic ring. Moderate yields of the imidates **3** were observed when a strongly electron-withdrawing group, such as a nitro group, was employed, while the use of an electron-donating group, such as a methyl group, resulted in a significant decrease in the yield (Table 1). It is worth noting that when a trifluoromethyl substituent was located at the ortho position as an electron-withdrawing group, the desired aminonitrile **2g** was obtained in 83% yield with only a trace amount of the byproduct **3g**. In addition, when ortho-substituted 1-arylpyrrolidines (**1b** and **1h**) were used, the byproduct yields were lower than those of para- or meta-substituted substrates [(**1c** and **1d**) and (**1i** and **1j**)]. These results suggested that the steric hindrance of the ortho-substituents on the aromatic ring could probably suppress the side reaction.

Experimental

General. Methanol and reagent-grade sodium cyanide were used without further purification.

NMR spectra were recorded on a JEOL JNM-A300 spectrometer. HRMS spectra were taken with the Bruker APEX II FT-ICR MS. The cyclic voltammetric experiments were performed by a CHI 660B analyzer.

Cyclic voltammetry was performed in a three-compartment cell. The working electrode was a platinum disk electrode, 2 mm in diameter, and the counter electrode was a platinum sheet. All potentials were referred to a saturated calomel electrode (SCE) and ohmic drop was not corrected. Prior to each measurement, the solution was saturated with pure nitrogen for five minutes in order to remove oxygen. The electrode was activated by anodic and cathodic potential cycles between 1.4 and −0.25 V at a rate of 0.05 V s^{-1} in 0.5 M H_2SO_4 until the cyclic voltammogram was the same as the standard curve. The E_p values are shown in Table 1.

General Procedure for Constant Potential Electrolysis of the 1-Arylpyrrolidines 1. The preparative-scale electrolysis was performed in an H-type cell with a glass frit separating two compartments fitted with Pt sheet electrodes having an area of 3 cm^2. The anolyte was made up of the pyrrolidines **1** (0.02 M) in methanolic sodium cyanide solution (0.16 M) and was stirred magnetically. The catholyte was a methanolic solution of sodium cyanide. The reaction was carried out at controlled anode potentials as indicated in Table 1 at 25 °C. The electrolysis was stopped when 2 F mol^{-1} of electricity was passed. The final anolyte was concentrated under reduced pressure; a saturated aqueous sodium chloride solution was then added and the mixture was extracted with ether. The organic layer was dried over sodium sulfate and concentrated. The products were purified by column chromatography on silica gel using ethyl acetate/petroleum ether (1:5) as the eluent. Elemental analyses of the α-aminonitriles **2** are uncertain because they easily eliminate HCN under combustion conditions.[3] The byproducts **3** were unstable for chromatographic purification and resulted in partial decomposition. **3a**–**3d** and **3g** were not isolated due to trace amounts.

1-Phenyl-2-pyrrolidinecarbonitrile (2a): Oil; IR (KBr) ν 2922, 2851, 2230 (CN), 1600, 1505, 1360, 750, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08–2.47 (m, 4H), 3.42 (m, 2H), 4.44 (d, $J = 6.9$ Hz, 1H), 6.70 (d, $J = 8.3$ Hz, 2H), 6.82 (t, $J = 7.2$ Hz, 1H), 7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.1, 31.7, 47.6, 49.2, 112.8, 118.3, 119.4, 129.6, 145.3; HRMS (ESI) calcd for $C_{11}H_{13}N_2$ $[M + H]^+$ 173.1078, found 173.1079.

1-(2-Methylphenyl)-2-pyrrolidinecarbonitrile (2b): Oil; IR (KBr) ν 2955, 2879, 2225 (CN), 1600, 1493, 1301, 1143, 1106, 962, 762, 721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95–2.20 (m, 2H), 2.24–2.51 (m, 2H), 2.31 (s, 3H), 3.17 (m, 1H), 3.48 (m, 1H), 4.40 (dd, $J = 7.9$, 3.8 Hz, 1H), 7.01–7.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.9, 22.8, 30.8, 50.1, 52.1, 119.2, 119.8, 124.2, 126.9, 131.5, 132.2, 144.9; HRMS (ESI) calcd for $C_{12}H_{15}N_2$ $[M + H]^+$ 187.1235, found 187.1238.

1-(3-Methylphenyl)-2-pyrrolidinecarbonitrile (2c): Oil; IR (KBr) ν 2951, 2873, 2229 (CN), 1605, 1496, 1360, 1179, 1023, 768, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15–2.47 (m, 4H), 2.37 (s, 3H), 3.31 (m, 2H), 4.43 (d, $J = 6.9$ Hz, 1H), 6.52 (s, 2H), 6.66 (d, $J = 7.6$ Hz, 1H), 7.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.9, 24.0, 31.7, 47.6, 49.2, 110.0, 113.5, 119.3, 119.5, 129.4, 139.4, 145.4; HRMS (ESI) calcd for $C_{12}H_{15}N_2$ $[M + H]^+$ 187.1235, found 187.1234.

1-(4-Methylphenyl)-2-pyrrolidinecarbonitrile (2d): Light yellow solid; mp 50–51 °C; IR (KBr) ν 2922, 2852, 2229 (CN), 1623, 1522, 1360, 1161, 809, 516 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.19–2.43 (m, 4H), 2.30 (s, 3H), 3.40 (m, 2H), 4.42 (d, $J = 7.2$ Hz, 1H), 6.62 (d, $J = 8.6$ Hz, 2H), 7.11 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 20.4, 24.0, 31.6, 47.7, 49.4, 112.9, 119.5, 127.6, 130.1, 143.2; ESI-MS (+): $m/z = 186.8$ $[M+H]^+$.

1-(4-Chlorophenyl)-2-pyrrolidinecarbonitrile (2e): Light yellow solid; mp 83–84 °C; IR (KBr) ν 2904, 2862, 2229 (CN), 1601, 1497, 1360, 1094, 808, 713 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.18–2.46 (m, 4H), 3.38 (m, 2H), 4.39 (dd, $J = 7.2$, 2.4 Hz, 1H), 6.60 (d, $J = 9.3$ Hz, 2H), 7.23 (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 24.0, 31.7, 47.8, 49.3, 113.9, 119.0, 123.4, 129.4, 143.9; HRMS (ESI) calcd for $C_{11}H_{12}ClN_2$ $[M+H]^+$ 207.0689, found 207.0686.

1-(4-Fluorophenyl)-2-pyrrolidinecarbonitrile (2f): Light yellow solid; mp 54–55 °C; IR (KBr) ν 2923, 2853, 2224 (CN), 1512, 1233, 1151, 961, 822 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.11–2.43 (m, 4H), 3.40 (m, 2H), 4.36 (d, $J = 7.2$ Hz, 1H), 6.62 (m, 2H), 7.00 (t, $J = 9.0$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 24.0, 31.6, 48.0, 49.7, 113.6, 113.7, 115.9, 116.2, 119.3, 142.0, 154.7, 157.8; HRMS (ESI) calcd for $C_{11}H_{12}FN_2$ $[M+H]^+$ 191.0984, found 191.0982.

1-[2-(Trifluoromethyl)phenyl]-2-pyrrolidinecarbonitrile (2g): Oil; IR (KBr) ν 2962, 2844, 2226 (CN), 1604, 1496, 1318, 1139, 962, 767 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.01–2.22 (m, 2H), 2.23–2.47 (m, 2H), 3.21 (m, 1H), 3.47 (m, 1H), 4.34 (dd, $J = 7.6$, 3.0 Hz, 1H), 7.30 (t, $J = 6.5$ Hz, 1H), 7.60 (m, 2H), 7.76 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.0, 31.2, 51.6, 54.5, 119.1, 122.2, 125.2, 125.7, 127.5, 133.1, 145.1; HRMS (ESI) calcd for $C_{12}H_{12}F_3N_2$ $[M+H]^+$ 241.0952, found 241.0963.

1-(2-Nitrophenyl)-2-pyrrolidinecarbonitrile (2h): Light yellow solid; mp 64–65 °C; IR (KBr) ν 2977, 2886, 2244 (CN), 1605, 1515, 1361, 1178, 741 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.99–2.55 (m, 4H), 3.25 (m, 1H), 3.42 (m, 1H), 4.57 (t, $J = 7.2$ Hz, 1H), 7.01 (t, $J = 8.1$ Hz, 1H), 7.13 (d, $J = 8.7$ Hz, 1H), 7.51 (t, $J = 8.1$ Hz, 1H), 7.79 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 24.1, 31.4, 50.2, 50.4, 118.2, 118.5, 120.3, 126.6, 133.6, 139.7, 140.4; HRMS (ESI) calcd for $C_{11}H_{12}N_3O_2$ $[M+H]^+$ 218.0929, found 218.0927.

1-(3-Nitrophenyl)-2-pyrrolidinecarbonitrile (2i): Yellow solid; mp 105–107 °C; IR (KBr) ν 2920, 2866, 2233 (CN), 1618, 1518, 1340, 856, 730, 667 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.21–2.54 (m, 4H), 3.41–3.59 (m, 2H), 4.51 (d, $J = 7.2$ Hz, 1H), 6.98 (dd, $J = 8.3$, 2.8 Hz, 1H), 7.44 (m, 2H), 7.66 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 24.0, 31.7, 48.0, 49.2, 107.2, 112.9, 118.4, 118.4, 130.3, 145.9, 149.4; HRMS (ESI) calcd for $C_{11}H_{12}N_3O_2$ $[M+H]^+$ 218.0929, found, 218.0935.

1-(4-Nitrophenyl)-2-pyrrolidinecarbonitrile (2j): Yellow solid; mp 114–115 °C; IR (KBr) ν 2924, 2878, 2229 (CN), 1601, 1486, 1307, 1108, 965, 826, 751 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.27–2.52 (m, 4H), 3.50 (m, 2H), 4.53 (d, $J = 7.1$ Hz, 1H), 6.67 (d, $J = 9.1$ Hz, 2H), 8.20 (d, $J = 9.1$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 24.1, 31.6, 48.0, 48.9, 111.8, 117.9, 126.2, 139.2, 149.7; HRMS (ESI) calcd for $C_{11}H_{12}N_3O_2$ $[M+H]^+$ 218.0929, found 218.0937.

1-(4-Chlorophenyl)-2-pyrrolidinecarboximidic Acid Methyl Ester (3e): ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.85–2.20 (m, 4H), 3.20 (m, 1H), 3.59 (t, $J = 6.4$ Hz, 1H), 3.84 (s, 3H), 3.95 (d, $J = 8.3$ Hz, 1H), 6.44 (d, $J = 9.0$ Hz, 2H), 7.16 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.8, 31.1, 49.3, 54.0, 62.0, 113.8, 122.5, 129.1, 145.7, 173.5; HRMS (ESI) calcd for $C_{12}H_{16}ClN_2O$ $[M+H]^+$ 239.0951, found 239.0947.

1-(4-Fluorophenyl)-2-pyrrolidinecarboximidic Acid Methyl Ester (3f): ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.84–2.21 (m, 4H), 3.17 (m, 1H), 3.57 (t, $J = 7.2$ Hz, 1H), 3.83 (s, 3H), 3.90 (d, $J = 8.9$ Hz, 1H), 6.49 (m, 2H), 8.13 (t, $J = 9.0$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.9, 31.2, 49.6, 53.8, 62.3, 113.2, 113.3, 115.6, 115.9, 143.8, 154.3, 157.4, 173.8; HRMS (ESI) calcd for $C_{12}H_{16}FN_2O$ $[M+H]^+$ 223.1247, found 223.1250.

1-(2-Nitrophenyl)-2-pyrrolidinecarboximidic Acid Methyl Ester (3h): ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.81–2.08 (m, 3H), 2.50 (m, 1H), 2.83 (t, $J = 7.5$ Hz, 1H), 3.66 (m, 1H), 3.81 (s, 3H), 4.30 (t, $J = 7.8$ Hz, 1H), 6.75–6.87 (m, 2H), 7.35 (t, $J = 8.6$ Hz, 1H), 7.54 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 25.6, 32.0, 52.8, 53.9, 61.8, 116.5, 118.2, 126.6, 133.2, 139.2, 141.8, 172.7; HRMS (ESI) calcd for $C_{12}H_{16}N_3O_3$ $[M+H]^+$ 250.1192, found 250.1185.

1-(3-Nitrophenyl)-2-pyrrolidinecarboximidic Acid Methyl Ester (3i): ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.95–2.30 (m, 4H), 3.33 (m, 1H), 3.70 (t, $J = 6.9$ Hz, 1H), 3.86 (s, 3H), 4.10 (d, $J = 7.5$ Hz, 1H), 6.76 (d, $J = 8.3$ Hz, 1H), 7.35 (m, 2H), 7.58 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.7, 31.2, 49.4, 54.3, 61.9, 106.9, 112.2, 118.5, 129.9, 147.6, 149.4, 173.0; HRMS (ESI) calcd for $C_{12}H_{16}N_3O_3$ $[M+H]^+$ 250.1192, found 250.1190.

Synthesis of 1-(4-Nitrophenyl)-2-pyrrolidinecarboximidic Acid Methyl Ester (3j). The aminonitrile **2j** (0.2 mmol) was dissolved in methanolic sodium cyanide solution (0.16 M, 10 mL). The mixture was stirred for 24 h at room temperature. The solvent was removed. Then, saturated aqueous sodium chloride solution was added and the mixture was extracted with ether. The organic layer was concentrated. The product was purified by column chromatography on silica gel using dichloromethane/methanol as the eluent (20:1). **3j** as a yellow solid; yield 77%; mp 119–121 °C; IR (KBr) ν 3309, 2950, 2872, 1667, 1606, 1517, 1488, 1358, 1071, 817, 750 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.99–2.26 (m, 4H), 3.39 (m, 1H), 3.70 (t, $J = 8.0$ Hz, 1H), 3.84 (s, 3H), 4.19 (d, $J = 7.7$ Hz, 1H), 6.49 (d, $J = 9.0$ Hz, 2H), 8.13 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.4, 30.9, 49.0, 53.8, 61.7, 111.5, 126.0, 138.2, 151.2, 171.6; ESI-MS (+): $m/z = 271.8$ $[M+Na]^+$; Found: C, 57.83; H, 6.09; N, 17.11%. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86%.

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