Iron Catalyzed Oxidative Cyanation of Tertiary Amines

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**General.** All reactions were carried out under an atmosphere of dry nitrogen. $^1$H and $^{13}$C NMR spectra of solutions in CDCl$_3$ were recorded on 200, 300, or 400 MHz NMR spectrometers. Chemical shifts were expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals ($\delta_H$ 7.24 and $\delta_C$ 77.0 ppm). Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; m, multiplet. HRMS was performed on a Finnigan MAT 95Q mass spectrometer. Infrared spectra of neat substances were recorded on a Perkin-Elmer Spectrum BX II FT-IR spectrometer equipped with an ATR probe (diamond).

**Materials.** Commercially available tertiary amines were used as received. $N,N$-Dimethyl-$p$-anisidine, $S_1$ 1-phenylpiperidine, $S_2$ 2-phenyl-1,2,3,4-tetrahydroisoquinoline$^S_2$ and 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline$^S_2$ were prepared according to literature procedures. The following iron and copper salts were used: Iron(II) acetate (anhydrous, 97 %, Strem), iron(III) acetylacetonate (99.9 %, Aldrich), iron(III) bromide (99 %, ABCR), iron(II) chloride (98 %, Aldrich), iron(III) chloride (anhydrous, 97 %, Grüssing), iron(III) chloride hexahydrate (99 %), iron(II) fluoride (anhydrous, 99 %, Strem), iron(II) gluconate hydrate (purum p.a., Fluka), iron(II) sulfate (99 %), copper(I) bromide (98 %, Acros), and copper(II) bromide (> 99%, Acros).

Trimethylsilyl cyanide (98 %, Acros) and tert.-butyl hydroperoxide (5.5 M solution in decane, purum, Aldrich) were purchased.

**Typical Procedure for Iron-Catalyzed Cyanation of Tertiary Amines.** Under an atmosphere of dry N$_2$, a 25 mL Schlenk flask was charged with iron(II) chloride (10 mol-%, 13 mg). The tertiary amine (1.0 mmol), trimethylsilyl cyanide (2.0 mmol, 0.27 mL), and MeOH (2.0 mL) were added successively by syringe. To the mixture was added dropwise tert.-butyl hydroperoxide (2.5 mmol, 0.470 mL, 5.5 M solution in decane) over a period of 5 min. The mixture was stirred at room temperature for the indicated time. At the end of the reaction, the reaction mixture was poured into a saturated aqueous NaCl solution (20 mL) and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel ($n$-pentane/diethyl ether = 15:2, v/v).

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[(4-Methoxyphenyl)-methyl-amino]acetonitrile
Known compound; the NMR spectroscopic data agree with those given in lit.\textsuperscript{S3}. $\delta_{\text{H}}$(CDCl\textsubscript{3}, 400 MHz) 2.90 (s, 3 H), 3.76 (s, 3 H), 4.06 (s, 2 H), 6.86 ppm (s, 4 H); $\delta_{\text{C}}$(CDCl\textsubscript{3}, 100 MHz) 39.9, 43.9, 55.5, 114.7, 115.4, 117.8, 142.1, 154.3 ppm; HRMS m/z (EI) 176.0944, C\textsubscript{10}H\textsubscript{12}N\textsubscript{2}O requires 176.0950.

(Methyl-\textit{p}-tolyl-amino)acetonitrile
Known compound; the NMR spectroscopic data agree with those given in lit.\textsuperscript{S3}. $\delta_{\text{H}}$(CDCl\textsubscript{3}, 300 MHz) 2.29 (s, 3 H), 2.96 (s, 3 H), 4.12 (s, 2 H), 6.80 (d, J 8.5 Hz, 2 H), 7.12 ppm (d, J 8.5 Hz, 2 H); $\delta_{\text{C}}$(CDCl\textsubscript{3}, 100 MHz) 20.3, 39.4, 42.7, 115.3, 115.4, 129.9, 145.6 ppm; HRMS m/z (EI) 160.0990, C\textsubscript{10}H\textsubscript{12}N\textsubscript{2} requires 160.1001.

(Methyl-\textit{m}-tolyl-amino)acetonitrile
Known compound; the NMR spectroscopic data agree with those given in lit.\textsuperscript{S3}. $\delta_{\text{H}}$(CDCl\textsubscript{3}, 300 MHz) 2.31 (s, 3 H), 2.98 (s, 3 H), 4.25 (s, 2 H), 6.66-6.68 (m, 2 H), 6.74 (d, J 6.0 Hz, 1 H), 7.16-7.22 ppm (m, 1 H); $\delta_{\text{C}}$(CDCl\textsubscript{3}, 100 MHz) 21.8, 39.2, 42.3, 112.0, 115.5, 115.6, 121.1, 129.2, 139.2, 147.8 ppm; HRMS m/z (EI) 160.0990, C\textsubscript{10}H\textsubscript{12}N\textsubscript{2} requires 160.1001.

(Methyl-\textit{o}-tolyl-amino)acetonitrile
Known compound; the NMR spectroscopic data agree with those given in lit.\textsuperscript{S3}. $\delta_{\text{H}}$(CDCl\textsubscript{3}, 300 MHz) 2.29 (s, 3 H), 2.85 (s, 3 H), 3.84 (s, 2 H), 7.03-7.09 (m, 1 H), 7.17-7.22 ppm (m, 3 H); $\delta_{\text{C}}$(CDCl\textsubscript{3}, 100 MHz) 17.7, 41.0, 45.0, 115.6, 120.6, 124.9, 126.8, 131.3, 132.8, 148.4 ppm; HRMS m/z (EI) 160.0995, C\textsubscript{10}H\textsubscript{12}N\textsubscript{2} requires 160.1001.

(Methyl-phenyl-amino)acetonitrile
Known compound; the NMR spectroscopic data agree with those given in lit.\textsuperscript{S3}. $\delta_{\text{H}}$(CDCl\textsubscript{3}, 300 MHz) 3.00 (s, 3 H), 4.16 (s, 2 H), 6.85-6.94 (m, 3 H), 7.28-7.33 ppm (m, 2 H); $\delta_{\text{C}}$(CDCl\textsubscript{3}, 100 MHz) 39.3, 42.3, 114.9, 115.4, 120.2, 129.4, 147.7 ppm; HRMS m/z (EI) 146.0841, C\textsubscript{9}H\textsubscript{10}N\textsubscript{2} requires 146.0844.

[(4-Bromophenyl)-methyl-amino]acetonitrile. The reaction mixture was heated to reflux. Known compound; the NMR spectroscopic data agree with those given in lit.\textsuperscript{S3}. $\delta_{\text{H}}$(CDCl\textsubscript{3}, 300 MHz) 2.98 (s, 3 H), 4.13 (s, 2 H), 6.72 (d, $J = 9.0$ Hz, 2 H), 7.37-7.40 ppm (m, 2 H); $\delta_{\text{C}}$(CDCl\textsubscript{3}, 100 MHz) 39.3, 42.2, 112.6, 115.1, 116.4, 132.2, 146.7 ppm; HRMS $m/z$ (EI) 223.9943, C\textsubscript{9}H\textsubscript{9}BrN\textsubscript{2} requires 223.9949.

[(2-Bromophenyl)-methyl-amino]acetonitrile Viscous oil; $\nu_{\text{max}}$(neat/ATR probe)/cm$^{-1}$ 2956, 2887, 2802, 2232 (C≡N), 1586, 1473, 1439, 1415, 1337, 1325, 1222, 1177, 1111, 1023, 987, 919, 871, 766, 752, 272, 722 and 653; $\delta_{\text{H}}$(CDCl\textsubscript{3}, 300 MHz) 2.92 (s, 3 H), 4.07 (s, 2 H), 6.98-7.04 (m, 1 H), 7.25-7.35 (m, 2 H), 7.55-7.58 ppm (m, 1 H); $\delta_{\text{C}}$(CDCl\textsubscript{3}, 100 MHz) 40.6, 44.8, 115.1, 119.7, 122.8, 126.3, 128.5, 133.9, 147.3 ppm; HRMS $m/z$ (EI) 223.9942, C\textsubscript{9}H\textsubscript{9}BrN\textsubscript{2} requires 223.9949; Anal. Calcd for C\textsubscript{9}H\textsubscript{9}BrN\textsubscript{2}: C, 48.03; H, 4.03; N, 12.45. Found: C, 48.10; H, 3.70; N, 12.41.

[(4-Ethynylphenyl)-methyl-amino]acetonitrile. The reaction mixture was heated to reflux. Viscous oil; $\nu_{\text{max}}$(neat/ATR probe)/cm$^{-1}$ 3279 (=C-H), 3042, 2916, 2823, 2240 (C≡N), 2101 (C≡C), 1671, 1605, 1512, 1360, 1332, 1246, 1181, 1113, 997, 924 and 819; $\delta_{\text{H}}$(CDCl\textsubscript{3}, 200 MHz) 2.99 (s, 1 H), 3.03 (s, 3 H), 4.18 (s, 2 H), 6.75 (d, $J = 9.0$ Hz, 2 H), 7.42 ppm (d, $J = 9.0$ Hz, 2 H); $\delta_{\text{C}}$(CDCl\textsubscript{3}, 100 MHz) 37.7, 40.5, 76.0, 84.7, 113.5, 113.9, 115.1, 133.5, 148.5 ppm; HRMS $m/z$ (EI) 170.0839, C\textsubscript{11}H\textsubscript{10}N\textsubscript{2} requires 170.0844.

[Methyl-(4-nitrophenyl)-amino]acetonitrile. The reaction mixture was heated to reflux. Known compound; the NMR spectroscopic data agree with those given in lit.\textsuperscript{S4}. Solid, mp 112.5-113.4 °C (lit.,\textsuperscript{S4} 114 °C); $\delta_{\text{H}}$(CDCl\textsubscript{3}, 400 MHz) 3.17 (s, 3 H), 4.26 (s, 2 H), 6.79 (d, $J = 8.0$ Hz, 2 H), 8.19 ppm (d, $J = 8.0$ Hz, 2 H); $\delta_{\text{C}}$(CDCl\textsubscript{3}, 100 MHz) 39.3, 41.1, 112.3, 114.5, 126.0, 139.9, 152.0 ppm; HRMS $m/z$ (EI) 191.0691, C\textsubscript{9}H\textsubscript{9}N\textsubscript{3}O\textsubscript{2} requires 191.0695.

[Methyl-(3-nitrophenyl)-amino]acetonitrile Solid, mp 99.3-99.5 °C (from Et\textsubscript{2}O/pentane); $\nu_{\text{max}}$(neat/ATR probe)/cm$^{-1}$ 3099, 3042, 2920, 2240 (C≡N), 1617, 1520, 1337, 1259, 1221, 1132, 1015, 881, 860, 789, 782, 737 and 667; $\delta_{\text{H}}$(CDCl\textsubscript{3}, 300 MHz) 3.11 (s, 3 H), 4.25 (s, 2 H), 7.09-7.13 (m, 1 H), 7.45 (t, $J = 8.3$ Hz, 1 H), 7.68 ppm (m, 2 H); $\delta_{\text{C}}$(CDCl\textsubscript{3}, 100 MHz) 39.3, 41.1, 112.3, 114.5, 126.0, 139.9, 152.0 ppm; HRMS $m/z$ (EI) 191.0691, C\textsubscript{9}H\textsubscript{9}N\textsubscript{3}O\textsubscript{2} requires 191.0695.

7.65-7.76 ppm (m, 2 H); δ(C(CDCl₃, 100 MHz) 39.3, 41.7, 108.7, 114.4, 114.7, 119.6, 130.3, 148.3, 149.3 ppm; HRMS m/z (EI) 191.0689, C₉H₉N₃O₂ requires 191.0695; Anal. Calcd for C₉H₉N₃O₂: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.40; H, 4.73; N, 21.45.

2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile

Known compound; the NMR spectroscopic data agree with those given in lit.⁵³. δ(H(CDCl₃, 200 MHz) 2.91-3.24 (m, 2 H), 3.41-3.55 (m, 1 H), 3.71-3.82 (m, 1 H), 5.50 (s, 1 H), 6.97-7.10 (m, 3 H), 7.24-7.39 ppm (m, 6 H); δ(C(CDCl₃, 100 MHz) 28.1, 44.1, 53.4, 117.6, 117.7, 121.9, 126.8, 127.1, 128.8, 129.3, 129.5, 129.6, 134.1, 148.1 ppm; HRMS m/z (EI) 234.1146, C₁₆H₁₄N₂ requires 234.1157.

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile

Solid; ν_max(neat/ATR probe)/cm⁻¹ 2996, 2933, 2837, 2221 (C≡N), 1647, 1510, 1465, 1454, 1259, 1245, 1206, 1179, 1030, 829 and 733; δ(H(CDCl₃, 400 MHz) 2.91-2.96 (m, 1 H), 3.12-3.21 (m, 1 H), 3.40-3.47 (m, 1 H), 3.55-3.59 (m, 1 H), 3.80 (s, 3 H), 5.36 (s, 1 H), 6.90-6.94 (m, 2 H), 7.07-7.11 (m, 2 H), 7.22-7.33 ppm (m, 4 H); δ(C(CDCl₃, 100 MHz) 28.7, 44.9, 55.5, 55.6, 114.8, 117.6, 121.0, 126.7, 127.1, 128.6, 129.4, 129.6, 134.3, 142.6, 155.7 ppm; HRMS m/z (EI) 264.1250, C₁₇H₁₆N₂O requires 264.1263; Anal. Calcd for C₁₇H₁₆N₂O: C, 77.25; H, 6.10; N, 10.60. Found: C, 76.88; H, 6.51; N, 10.43.

1-Phenylpiperidine-2-carbonitrile from the reaction without methanol.

Known compound; the NMR spectroscopic data agree with those given in lit.⁵³,⁵⁵. δ(H(CDCl₃, 400 MHz) 1.66-1.73 (m, 2 H), 1.84-1.87 (m, 2 H), 1.99-2.03 (m, 2 H), 3.00-3.06 (m, 1 H), 3.46 (d, J 12 Hz, 1 H), 4.63 (s, 1 H), 6.98-7.02 (m, 3 H), 7.25-7.34 ppm (m, 2 H); δ(C(CDCl₃, 100 MHz) 20.1, 25.0, 29.1, 46.4, 51.9, 117.1, 118.1, 122.0, 129.2, 149.6 ppm; HRMS m/z (EI) 186.1153, C₁₂H₁₄N₂ requires 186.1157.

Additional NMR signals of unidentified byproducts: δ(H(CDCl₃, 400 MHz) 1.3-1.5 (m), 5.93 (s), 6.80-6.82 (m); δ(C(CDCl₃, 100 MHz) 16.0, 21.6, 22.3, 69.4, 86.9, 113.1, 117.4, 121.9, 129.4, 146.5, 150.6 ppm. One of the byproducts is tentatively assigned to the dicyanation product 1-phenylpiperidine-2,6-dicarbonitrile⁵⁶ based on HRMS [m/z (EI) 211.1106,


C$_{13}$H$_{13}$N$_{3}$ requires 211.1109]. Because of superimposition of resonances, however, an unambiguous assignment of the signals in the NMR spectra was not possible.

**1-Phenylpyrrolidine-2-carbonitrile** from the reaction without methanol.

Known compound; the NMR spectroscopic data agree with those given in lit.$^{S7}$. $\delta_{HH}$(CDCl$_3$, 200 MHz) 2.07-2.34 (m, 4 H), 3.26-3.38 (m, 2 H), 4.33-4.37 (m, 1 H), 6.58-6.63 (m, 2 H), 6.74 (t, $J$ 7.4 Hz, 1 H), 7.16-7.25 ppm (m, 2 H); $\delta_{C}$(CDCl$_3$, 100 MHz) 23.9, 31.5, 47.4, 49.0, 112.6, 118.1, 119.2, 129.4, 145.1 ppm; HRMS $m/z$ (EI) 172.0991, C$_{11}$H$_{12}$N$_{2}$ requires 172.1000.

**1-Phenylpyrrolidine-2,5-dicarbonitrile** from the reaction in the presence of TMSCN (4.0 mmol). The Typical Procedure was followed to obtain the crude product which was purified by column chromatography (SiO$_2$, $n$-pentane/diethyl ether = 3:1, v/v).

Known compound (lit.$^{S8}$); $\nu_{\text{max}}$(neat/ATR probe)/cm$^{-1}$ 3075, 3050, 3003, 2930, 2233, 1597, 1504, 1347, 1338, 1323, 1269, 1251, 1180, 1160, 966, 818, 745 and 693; $\delta_{HH}$(CDCl$_3$, 400 MHz) 2.56-2.63 (m, 4 H), 4.57 (t, $J$ 2.8 Hz, 2 H), 6.78-6.81 (m, 2 H), 6.96-6.99 (m, 1 H), 7.35-7.39 ppm (m, 2 H); $\delta_{C}$(CDCl$_3$, 100 MHz) 30.4, 48.9, 113.4, 117.9, 120.5, 129.9, 141.8 ppm. Attempts to elucidate the stereochemistry of the product were not made.
