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Iron-Catalyzed Oxidation of 4-Substituted *N*,*N*-Dimethylanilines with Molecular Oxygen in the Presence of Benzoyl Cyanide

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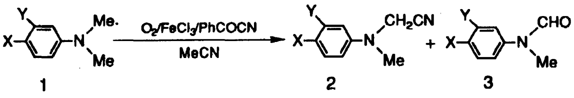
Synopsis. The oxidation of 4-substituted *N*,*N*-dimethylanilines with molecular oxygen using a catalytic amount of iron(III) chloride efficiently proceeded in the presence of benzoyl cyanide to give the corresponding *N*-cyanomethyl-*N*-methylanilines along with *N*-methylformanilides.

Oxidative functionalization of amines at the position α to the nitrogen including alkoxylation and cyanation is a useful tool for synthesis of various nitrogen-containing compounds.[1] Another important feature of amine oxidation, especially in using transition metal catalysts, is of relevance to oxidative degradation of nitrogen-containing drugs in biological systems, and tertiary amines have been subjected to reaction in a variety of model oxidizing systems.[2] We have recently reported that 4-substituted *N*,*N*-dimethylanilines (**1**) are readily oxidized by molecular oxygen in the presence of a catalytic amount of several transition metal salts and complexes to give the corresponding *N*-methylformanilides together with *N*-methylanilines.[3] In the presence of acetic anhydride and alkyl vinyl ethers, *N*-methylacetanilides and *N*-methyl-4-alkoxy-1,2,3,4-tetrahydroquinolines, respectively, are produced as the predominant products.

We herein report that the reaction using iron(III) chloride in the presence of benzoyl cyanide also proceeds efficiently to give *N*-cyanomethyl-*N*-methylanilines (**2**) along with *N*-methylformanilides (**3**) (Eq. 1).



(1)

When a mixture of *N*,*N*-dimethyl-*p*-toluidine (2 mmol), benzoyl cyanide (2 mmol), and $FeCl_3$ (0.1 mmol, 5 mol%) in acetonitrile (10 cm^3) was stirred under oxygen (1 atm) at 50°C for 16 h, *N*-cyanomethyl-*N*,4-dimethylaniline was produced in a yield of 63% (60% after isolation) along with *N*,4-dimethylformanilide (25%) (Table 1, Run 1). The benzoyl moiety in benzoyl cyanide was found to be transformed into benzoic acid (85%) and into a small amount of *N*-benzoyl-*N*,4-dimethylaniline (2%). The reaction using 1 mol% of $FeCl_3$ at 30°C also proceeded similarly, consuming 1.8 mmol of oxygen (Run 2). Without $FeCl_3$, the conversion of the aniline was very low (Run 3) and the reaction did not occur under nitrogen. Cobalt(II) chloride could be used in place of $FeCl_3$, but with $MnCl_2$ and CuCl the formanilide was formed preferentially (Runs 5—8). Potassium hexacyanoferrate(III) and potassium cyanide in place of $FeCl_3$ and benzoyl cyanide, respectively, were far less effective (Runs 9 and 10).[4]

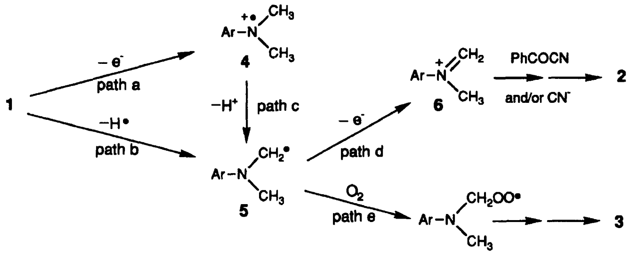
4-Methoxy- and 4-ethoxy-*N*,*N*-dimethylanilines as well as *N*,*N*,3,4-tetramethylaniline also reacted with benzoyl cyanide in the presence of $FeCl_3$, as did the 4-methyl substrate (Runs 11—13). In the reaction of the 4-chloro derivative, *N*-methyl-4-chloroaniline was formed in a considerable amount together with **2** and **3** (Run 14).

A possible mechanism for the reaction is illustrated in Scheme 1. It is similar to that proposed previously for the reaction with acetic anhydride.[3b] It should be noted that addition of a radical inhibitor, 2,6-di-*t*-butyl-4-methylphenol (BHT), to the reaction of the 4-methyl substrate resulted in the selective formation of the cyanide **2**, while the conversion was considerably decreased (Run 4).[5] This may suggest that the reaction involves both initial one-electron oxidation (path a) and hydrogen abstraction (path b) to give amine cation radical **4** and aminomethyl radical **5**, respectively.[6] In the presence of BHT, the oxidation seems to proceed predom-

Table 1. Oxidation of *N*,*N*-Dimethylanilines **1** with Molecular Oxygen in the Presence of Benzoyl Cyanide[a)]

		1		Yield/%[b)]		Recovery
Run	Catalyst (mmol)	X	Y	**2**	**3**	of **1**/%[b)]
1	$FeCl_3$ (0.1)	Me	H	63(60)	25	7
2[c)]	$FeCl_3$ (0.02)	Me	H	56	23	10
3	None	Me	H	12	5	80
4[d)]	$FeCl_3$ (0.1)	Me	H	37		35
5	$CoCl_2$ (0.1)	Me	H	53	36	6
6	$CoCl_2$ (0.02)	Me	H	28	2	68
7	$MnCl_2$ (0.1)	Me	H	12	53	4
8	CuCl (0.1)	Me	H	8	77	4
9	$K_3Fe(CN)_6$ (0.1)	Me	H	16	2	77
10[e)]	$FeCl_3$ (0.1)	Me	H	1		97
11	$FeCl_3$ (0.02)	MeO	H	53(48)	27	6
12	$FeCl_3$ (0.02)	EtO	H	62(57)	27	7
13	$FeCl_3$ (0.02)	Me	Me	54(50)	28	13
14	$FeCl_3$ (0.02)	Cl	H	11	29	24[f)]

a) The reaction of **1** (2 mmol) was carried out using benzoyl cyanide (2 mmol) in acetonitrile under oxygen at 50°C for 16 h. b) Yield based on **1** charged was determined by GLC analysis. The value in parentheses is the yield after isolation by column chromatography on silica gel. *N*-Benzoyl-*N*-methylanilines (2—4%) were formed in most of the reactions. c) At 30°C. d) In the presence of BHT (0.2 mmol). e) With KCN (2 mmol). f) *N*-Methyl-4-chloroaniline (17%) was also produced.



Scheme 1.

inantly via paths a, c, and d followed by the reaction of the iminium cation **6** with benzoyl cyanide and/or cyanide ion generated in situ to afford **2**,[7] while the free radical chain process including paths b and e is suppressed by the radical inhibitor.[8]

The different observed product ratio of **2** to **3** depending on the metal species employed may be attributable to the change of the relative rate of path d to path e.

Experimental

^{1}H NMR spectra were obtained with a JEOL JNM-GSX-400 spectrometer for $CDCl_3$ solutions. GC-MS spectra were obtained with a JEOL JMS-DX-303 spectrometer. GC analysis was carried out on a Shimadzu GC-8APF gas chromatograph with a silicone OV-17 column (ϕ 2.6 mm×1.5 m) or with a CBP-1 capillary column (ϕ 0.5 mm×25 m).

General Procedure for Oxidation of *N*,*N*-Dimethylanilines (1) with Molecular Oxygen in the Presence of Benzoyl Cyanide. A mixture of **1** (2 mmol), benzoyl cyanide (2 mmol, 262 mg), and $FeCl_3$ (0.1 mmol, 16 mg) in acetonitrile (10 cm^3) was stirred under oxygen (1 atm) at 50°C for 16 h. The resulting mixture was poured into water (100 cm^3) and extracted with ether (100 cm^3×2). The organic layer was dried over sodium sulfate and evaporated. Product identification and quantification were made by GC-MS and GC analyses. Authentic samples were prepared by the reported methods.[3b] The cyanomethylanilines **2** were also isolated by column chromatography on silica gel using ethyl acetate–hexane as eluant.

***N*-Cyanomethyl-*N*,4-dimethylaniline:** Mp 55—56°C; ^{1}H NMR δ=2.21 (3H, s, ArC$\underline{H}_3$), 2.88 (3H, s, NC$\underline{H}_3$), 4.04 (2H, s, NC$\underline{H}_2$CN), 6.72 (2H, d, J=8.6 Hz, aromatic), and 7.04 (2H, d, J=8.6 Hz, aromatic); MS m/z 160 (M$^+$). Found: C, 74.94; H, 7.55; N, 17.14%. Calcd for $C_{10}H_{12}N_2$: C, 74.96; H, 7.55; N, 17.49%.

***N*-Cyanomethyl-4-methoxy-*N*-methylaniline:** Colorless oil; ^{1}H NMR δ=2.92 (3H, s, N–C$\underline{H}_3$), 3.78 (3H, s, ArOC$\underline{H}_3$), 4.08 (2H, s, NC$\underline{H}_2$CN), and 6.88 (4H, brs, aromatic); MS m/z 176 (M$^+$). Found C, 67.90; H, 6.82; N, 15.86%. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90%.

***N*-Cyanomethyl-4-ethoxy-*N*-methylaniline:** Colorless oil; ^{1}H NMR δ=1.39 (3H, t, J=7.0 Hz, OCH$_2$C$\underline{H}_3$), 2.91 (3H, s, NC$\underline{H}_3$), 3.99 (2H, q, J=7.0 Hz, OC$\underline{H}_2$CH$_3$), 4.07 (2H, s, NC$\underline{H}_2$CN), and 6.86 (4H, brs, aromatic); MS m/z 190 (M$^+$). Found: C, 69.04; H, 7.33; N, 14.68%. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73%.

***N*-Cyanomethyl-*N*,3,4-trimethylaniline:** Colorless oil; ^{1}H NMR δ=2.19 (3H, s, ArC$\underline{H}_3$), 2.25 (3H, s, ArC$\underline{H}_3$), 2.95 (3H, s, NC$\underline{H}_3$), 4.12 (2H, s, NC$\underline{H}_2$CN), 6.64 (1H, dd, J=8.3 and 2.9 Hz, aromatic), 6.69 (1H, d, J=2.9 Hz, aromatic), and 7.06 (1H, d, J=8.3 Hz, aromatic); MS m/z 174 (M$^+$). Found: C, 75.55; H, 8.07; N, 15.70%. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08%.

4-Chloro-*N*-cyanomethyl-*N*-methylaniline: Colorless oil; ^{1}H NMR δ=2.91 (3H, s, NC$\underline{H}_3$), 4.07 (2H, s, NC$\underline{H}_2$CN), 6.71 (2H, d, J=9.0 Hz, aromatic), and 7.19 (2H, d, J=9.0 Hz, aromatic); MS m/z 180 and 182 (M$^+$). Found: C, 59.75; H, 4.91; N, 15.47%. Calcd for $C_9H_9N_2Cl$: C, 59.87; H, 5.02; N, 15.51%.

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1) See, e.g.: T. Shono, Y. Matsumura, and K. Tsubata, *Org. Synth.*, **63**, 206 (1985); C. -K. Chen, A. G. Hortmann, and M. R. Marzabadi, *J. Am. Chem. Soc.*, **110**, 4829 (1988); S. -I. Murabashi, T. Naota, and K. Yonemura, *J. Am. Chem. Soc.*, **110**, 8256 (1988); T. Naota, T. Nakato, and S. -I. Murahashi, *Tetrahedron Lett.*, **31**, 7475 (1990); J. Santamaria, M. T. Kaddachi, and J. Rigaudy, *Tetrahedron Lett.*, **31**, 4735 (1990); T. Shono, Y. Matsumura, S. Katoh, K. Takeuchi, K. Sasaki, T. Kamada, and R. Shimizu, *J. Am. Chem. Soc.*, **112**, 2368 (1990).

2) The relevant literature is cited in Ref. 3.

3) a) S. Murata, M. Miura, and M. Nomura, *J. Chem. Soc., Chem. Commun.*, **1989**, 116; *J. Org. Chem.*, **54**, 4700 (1989); b) S. Murata, A. Tamatani, K. Suzuki, M. Miura, and M. Nomura, *Chem. Lett.*, **1990**, 757; *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1387; c) S. Murata, K. Teramoto, M. Miura, and M. Nomura, *Heterocycles*, **34**, 1177 (1992).

4) Treatment of *N*,*N*-dimethyl-*p*-toluidine with an equimolar amount of $K_3Fe(CN)_6$ under nitrogen gave no cyanated product, the aniline being quantitatively recovered. This indicates that the cyanide can not oxidize the aniline.

5) A similar trend was also observed in the reaction with acetic anhydride where the corresponding acetanilides were formed selectively in the presence of BHT.[3b]

6) In the oxidation in the presence of acetic anhydride, the common initiation step (path a) was found to be synergistically promoted by both the catalyst and the anhydride.[3b] In the present reaction, benzoyl cyanide is also considered to act as the promoter as well as the cyanide source.

7) On the other hand, the presence of an excess of cyanide ion, which may coordinate to the iron catalyst, seems to hamper the catalyst activity to suppress the initiation reaction (see Runs 9 and 10 in Table 1).

8) The possibility that the iminium cation **6** is also formed from the radical cation **4** by hydrogen abstraction can not be excluded.[9]

9) L. T. Burka, F. P. Guenrerich, R. J. Billard, and T. L. Mcdonald, *J. Am. Chem. Soc.*, **107**, 2549 (1985).