Metalation of Nitroaromatics with in Situ Electrophiles

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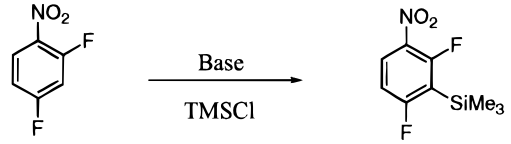
The directed ortho metalation (DoM) reaction of substituted aromatics is a powerful method of introducing functional groups to an aromatic nucleus.[1] One limitation of metalation chemistry is its incompatibility with the nitro group. Reduction of the nitro group by electron transfer from the alkyllithiums often used in metalations generally results in decomposition of the substrates. The preparation of (nitroaryl)lithium species by metal−halogen exchange reactions at low temperatures has been reported,[2] but these reactions are not general, and the resulting aryllithiums readily decompose by redox mechanisms.

Nitroaromatics are valuable synthetic intermediates due to their ease of synthesis, their ability to activate leaving groups in nucleophilic aromatic substitution, and their ready reduction to versatile amine derivatives. As a result, DoM chemistry compatible with nitro functionality would be a great advantage. This paper addresses the nitroaromatic metalation problem for electron-deficient substrates and reports observations pertinent to the mechanism of this reaction.

The apparent incompatibility of nitro groups and carbon-centered anions prompted us to explore methods of minimizing contact between these two species. The nitro group should significantly enhance the acidity of nearby aromatic protons, allowing the use of a base milder than the usual alkyllithiums. Lithium amide bases have been used for DoM chemistry in activated aromatic systems[3] and would be expected to avoid some of the redox problems associated with alkyllithium bases. An additional problem is posed by the inherent instability of the intermediate (nitroaryl)lithium species. This can be addressed by the use of an in situ electrophile[4] to minimize the lifetime of the (nitroaryl)lithium intermediate.

Our initial efforts focused on fluoro-containing nitroaromatics for three reasons. Fluorine has been reported to be a strong ortho-directing group,[5] it is a useful leaving group in nucleophilic aromatic substitution chemistry, and fluorobenzenes have been found to be optimal components of many new drug candidates. 2,4-Difluoronitrobenzene, **1**, was used as our standard substrate. As expected, attempted deprotonation with *n*-butyl- or *tert*-butyllithium led to dark reaction mixtures and multiple products. The use of an amide base such as LDA provided similar results. However, by introducing TMSCl prior to the addition of LDA, partial conversion to the desired silylated product was observed, the remaining material being recovered **1** or bis-silylated material. Reasoning that reaction between the base and TMSCl was competing with aromatic deprotonation,[6] we tried several other hindered bases (Table 1). LiTMP gave moderate results, while the very hindered lithium (*tert*-butyldimethysilyl)-*tert*-butylamide (LiBSBA)[7] gave a 70% yield of the desired product. LiHMDS also proved to be a suitable base for this reaction, giving a 78% yield of the silylated product **2**. We then explored NaHMDS and KHMDS and found that these bases were by far the best, giving 100% and 91% yields, respectively, with no bis-silylated product being observed, even when an excess of base was used. The use of sodium or potassium bases in DoM reactions has not been previously reported,[8] and the success of the reaction using these bases calls into question the mechanism of this particular metalation. Traditional DoM theory requires the lithium counterion[9] to act as a Lewis acid to coordinate the directing group and the base, effectively increasing the kinetic acidity of the aromatic proton in the ortho position.[10] The much lower coordinating ability of potassium relative to lithium implies that such coordination is not required for this substrate. The addition of 18-crown-6 to the KHMDS (Table 1, entry 7) had little effect, and again a high yield of the silylated product was obtained, reinforcing the notion that metal coordination is not important. Presumably, the electron-deficient nature of the aromatic ring of **1** sufficiently acidifies the proton in the 3-position through inductive effects such that direct abstraction of the proton by the base is possible.[11]

Table 1. Effect of the Base on Metalation



1 **2**

entry	base	yield[a] (%)
1	LDA	36
2	LiTMP	33
3	LiBSBA[b]	70
4	LiHMDS	78
5	NaHMDS	100
6	KHMDS	91
7	KHMDS/18-cr-6	87

[a] Isolated yields from reactions run in THF at −78 °C with 2 equiv of base in the presence of 3 equiv of TMSCl. [b] Lithium (*t*-butyldimethylsilyl)-*t*-butylamide.

Given the success of the NaHMDS deprotonation of **1**, we sought to explore the generality of this reaction with

(1) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (b) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306−312.

(2) Kobrich, G.; Buck, P. *Chem. Ber.* **1970**, *103*, 1412−1419.

(3) (a) Krizan, T. D.; Martin, J. C. *J. Org. Chem.* **1982**, *47*, 2681−2682. (b) Mao, Y.; Boekelheide, V. *J. Org. Chem.* **1980**, *45*, 2746−2749.

(4) (a) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155−6157. (b) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, 495−498.

(5) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, 7495−7498.

(6) This possibility was confirmed in the case of KHMDS by control experiments in which the base and TMSCl were allowed to interact in the absence of substrate. A significant amount of $(TMS)_3N$ was formed.

(7) Prieto, J. A.; Suarez, J.; Larson, G. L. *Synth. Commun.* **1988**, *18*, 253−257.

(8) Ortho magnesiation has previously been reported: Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016−8018. LICKOR bases contain both lithium and potassium counterions: Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett* **1991**, 731−732.

(9) Slocum, D. W.; Moon, R.; Thompson, J.; Coffey, D. S.; Li, J. D.; Slocum, M. G.; Siegel, A.; Gayton-Garcia, R. *Tetrahedron Lett.* **1994**, *35*, 385−388.

(10) (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1−360. (b) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191−7198. (c) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356−363.

(11) This "acid−base" mechanism has previously been postulated: ref 10a.

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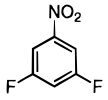
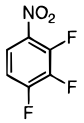
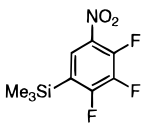
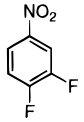
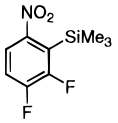
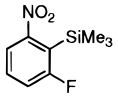
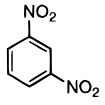
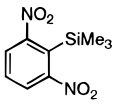
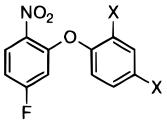
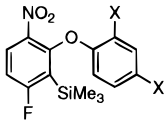
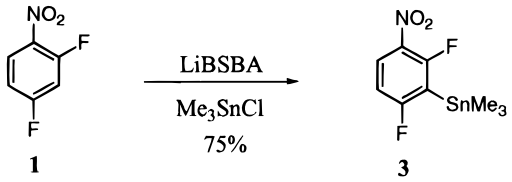
Table 2. Substituent Effects: in Situ Trimethylsilylation with NaHMDS

Entry	Substrate	Product	Yield (%)
8			100
9			100
10			100
11			10
12			61
13	 X=F		60
14	X=Cl		66
15	X=H		25

other fluorinated nitroaromatics (Table 2). Whenever a metalation position was available between two fluorine substituents, the reaction proceeded extremely well. If the aromatic ring was particularly electron deficient, regiospecific proton abstraction directed by a single fluorine substituent in the ortho position was sufficient to give high yields (Table 2, entries 9 and 10). However, in the case of 3-fluoronitrobenzene, only a 10% yield the 2-silyl derivative was observed. 4-Fluoronitrobenzene was found to be unreactive under these conditions. In the systems we examined without a fluorine-directing group present, reactions were usually unsuccessful. An exception to this was 1,3-dinitrobenzene, which gave a 61% yield of the desired 2-silylated product (Table 2, entry 12). Even molecules containing "excellent" directing groups, 3-(diethylamido)nitrobenzene and 4-(dimethylamido)nitrobenzene, proved unreactive and provided only recovered starting material. It would appear from these results that this methodology is restricted to very electron-deficient aromatic systems. Some interesting reactivity was found in the case of difluorophenyl ether (Table 2, entry 13). Here, given a choice of a proton between two fluorine substituents on a relatively electron-rich ring and a proton ortho to a single fluorine on an electron-deficient ring, NaHMDS is strongly selective for the electron-deficient ring. A 60% yield of the desired monosilylated product is observed, the remaining material being recovered starting material. The use of KHMDS improves this yield to 82%, but in this case, competition from the difluoro ring begins to emerge as 15% of the bis-silylated product is also obtained.

The role of the fluorine atoms on the phenyl ether in this reaction was addressed by submitting the analogous 2,4-dichlorophenyl ether. A similar result was observed, and a 66% yield of the desired monosilylated product was obtained on reaction with NaHMDS. The unsubstituted phenyl ether (Table 2, entry 15), however, was found to be considerably less reactive, and only a 25% yield of the monosilylated product was obtained. It would appear that the main factor involved with reactivity is the inductive effect of the substituents on the ring bearing the reactive hydrogen.

The necessity of using of an in situ electrophile clearly limits the choice of electrophiles for nitroaromatic metalation. However, a number of electrophiles suitable for such reactions have been published.[4a,12] TMSCl is without doubt the most convenient, although it has limited synthetic potential. However, trimethyltin chloride works in a similar fashion, providing entry to palladium-catalyzed coupling reactions. We have noticed that the trimethyltin chloride is more readily attacked by the base than the corresponding silicon derivative, thus demanding excess reagents or a very hindered base. While NaHMDS provides a 38% yield of the desired stannylated product, we have found that the more hindered LiBSBA gives higher yields (eq 1).



1 **3** (1)

A method of nitroaromatic metalation has been successfully developed in which in situ Me_3SiCl or Me_3SnCl traps an intermediate metalated aromatic generated by a hindered amide base. While the generality of this reaction appears to be limited to electron-deficient nitroaromatics, other bases may be found to provide more general reactivity. For the first time, sodium and potassium bases have been found to be useful in aromatic metalation. This observation implies that, for these substrates, the "directing" effect of the ortho substituents is the result of an inductive acidification of the adjacent hydrogen rather than a more traditional coordination mechanism between the base and the directing group.

Experimental Section

All reactions were run under nitrogen in flame-dried glassware. THF solvent was Adrich anhydrous grade. The biphenyl ethers were prepared by nucleophilic aromatic displacement on **1**.[13] (*tert*-Butyldimethylsilyl)-*tert*-butylamine was prepared according to the literature procedure.[7] All other starting materials and reagents were obtained commercially and used as received.

2,4-Difluoro-3-(trimethylsilyl)nitrobenzene (2). To a −78 °C solution of 0.30 mL (2.74 mmol) of 2,4-difluoronitrobenzene in THF (10 mL) was added 1.03 mL (8.21 mmol) of chlorotrimethylsilane. NaHMDS (5.47 mL, 1 M in THF) was then added dropwise to maintain an internal temperature below −75 °C. The resulting mixture was stirred for 30 min at −78 °C and then partitioned between 1 M HCl and Et_2O. The aqueous phase was separated and extracted with ether. The combined organic phases were washed with 1 M HCl (3×) and brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (10% acetone/hexane) provided 634 mg (100%) of the title compound: IR (film) 3083, 2958, 1610, 1530, 1350, 1255, 1000,

(12) Beak, P.; Lee, B. *J. Org. Chem.* **1989**, *54*, 458−464.
(13) Bamkole, T. O.; Hirst, J.; Udoessien, E. *J. Chem. Soc., Perkin Trans. 2* **1973**, *15*, 2114−2119.

845 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 8.08 (dt, J = 8.9, 5.8 Hz, 1H), 6.93 (ddd, J = 7.87, 6.41, 1.46 Hz, 1H), 0.42 (t, J = 0.15 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (dd, J = 253, 15.5 Hz), 159.7 (dd, J = 259, 17 Hz), 134.3 (d, J = 9.0 Hz), 129.0 (d, J = 11.7 Hz), 117.3 (t, J = 35.4 Hz), 111.9 (dd, J = 29, 3.6 Hz), −0.1(s); MS (CI, CH_4) m/z 232, 215, 97, 79. Anal. Calcd for $C_9H_{11}F_2NO_2Si$: C, 46.74; H, 4.79; N, 6.06. Found: C, 46.69; H, 4.80; N, 6.12.

Using the same general procedure, the following compounds were prepared in the yields indicated in Table 2 and gave the following analytical data.

3,5-Difluoro-4-(trimethylsilyl)nitrobenzene (Table 2, entry 8): IR (film) 3100, 2960, 1605, 1532, 1405, 1350, 1250,1168, 1090, 845 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 7.78 (dt, J = 7.0, 2.1 Hz, 2H), 0.42 (t, J = 3.5 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (dd, J = 246, 15.8 Hz), 150.0 (t, J = 12.0 Hz), 122.2 (t, J = 35.0 Hz), 106.9 (dd, J = 35.0, 3.1 Hz), −0.3 (t, J = 2.5 Hz); MS (CI, CH_4) m/z 232, 216, 202. Anal. Calcd for $C_9H_{11}F_2NO_2Si$: C, 46.74; H, 4.79; N, 6.06. Found: C, 46.65; H, 4.92; N, 5.99.

2,3,4-Trifluoro-5-(trimethylsilyl)nitrobenzene (Table 2, entry 9): IR (film) 2860, 1612, 1540, 1440, 1250, 1056, 846 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 8.00 (ddd, J = 8.1, 4.8, 2.6 Hz, 2H), 0.42 (t, J = 1.0 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8 (ddd, J = 251.8, J = 6.2, 2.4 Hz), 146.9 (ddd, J = 268.7, 7.6, 5.1 Hz), 140.0 (ddd, J = 257.6, 14.2, 5.6 Hz), 134.3, 124.8 (dt, J = 13.7, 3.6 Hz), −1.7. Anal. Calcd for $C_9H_{10}F_3NO_2Si$: C, 43.38; H, 4.04; N, 5.62. Found: C, 43.32; H, 4.09; N, 5.55.

3,4-Difluoro-2-(trimethylsilyl)nitrobenzene (Table 2, entry 10): IR (film) 3100, 2950, 1535, 1530, 1455, 1298, 1270, 1251, 835 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 7.89 (ddd, J = 8.9, 5.8, 1.6 Hz, 1H), 7.60 (dt, J = 9.1, 8.9 Hz, 1H), 0.39 (d, J = 2.4 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 (dd, J = 246.5, 12.3 Hz), 153.3 (dd, J = 258.5, 17.9 Hz), 150.6 (d, J = 8.9 Hz), 125.6 (d, J = 29.9 Hz), 120.9 (dd, J = 7.4, 6.5 Hz), 117.9 (d, J = 18.8 Hz), −0.2 (d, J = 7.7 Hz); MS (CI, CH_4) m/z 232, 216, 160. Anal. Calcd for $C_9H_{11}F_2NO_2Si$: C, 46.74; H, 4.79; N, 6.06. Found: C, 46.47; H, 4.48; N, 5.95.

3-Fluoro-2-(trimethylsilyl)nitrobenzene (Table 2, entry 11): IR (film) 3100, 2980, 2953, 1607, 1535, 1441, 1358, 1235, 1109, 850 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 7.65 (dd, J = 8.0, 1.0 Hz, 1H), 7.48 (dt, J = 8.2, 5.5 Hz, 1H), 7.50 (dt, J = 8.6, 1.1 Hz, 1H), 0.39 (d, J = 2.3 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0 (d, J = 245.6 Hz), 156.4, 131.3 (d, J = 9.5 Hz), 122.3 (d, J = 34.3 Hz), 119.8 (d, J = 28.3 Hz), 119.4 (d, J = 3.1 Hz), 0.2 (d, J = 4.4 Hz); MS (CI, CH_4) m/z 214, 198. Anal. Calcd for $C_9H_{12}FNO_2Si$: C, 50.68; H, 5.67; N, 6.67. Found: C, 50.90; H, 5.69; N, 6.52.

2-(Trimethylsilyl)-1,3-dinitrobenzene (Table 2, entry 12): mp 94−95 °C; IR (film) 3090, 2970, 1538, 1355, 1287, 1256, 1047, 905, 840, 713 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 8.03 (d, J = 7.7 Hz, 2H), 7.62 (t, J = 7.7 Hz, 1H), 0.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 131.7, 130.4, 126.8, −0.63; MS (CI, CH_4) m/z 241, 225. Anal. Calcd for $C_9H_{12}N_2O_4Si$: C, 44.97; H, 5.03; N, 11.70. Found: C, 45.30; H, 4.66; N, 11.54.

2-(2,4-Difluorophenoxy)-4-fluoro-3-(trimethylsilyl)nitrobenzene (Table 2, entry 13): IR (film) 3083, 2958, 1595, 1547,1505, 1345, 1250, 1205, 845 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 8.20 (dd, J = 9.0, 6.0 Hz, 1H), 7.30 (dd, J = 9.0, 8.0 Hz, 1H), 7.23 (ddd, J = 11.1, 7.9, 3.2 Hz, 1H), 6.86 (m, 1H), 6.78 (dt, J = 9.1, 4.9 Hz, 1H), 0.39 (d, J = 2.1 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5 (d, J = 252.0 Hz), 158.2 (dd, J = 245.1, 10.0 Hz), 152.6 (dd, J = 252.3, 12.2 Hz), 141.8 (dd, J = 252.3, 12.2 Hz), 138.5, 129.5 (d, J = 12.4 Hz), 123.9 (d, J = 33.6 Hz), 115.3 (d, J = 9.4 Hz), 113.2 (d, J = 29.6 Hz), 110.8 (dd, J = 23.1, 3.7 Hz) 105.7 (dd, J = 27.2, 21.9 Hz), 104.8 (d, J = 25.2 Hz), 0.2; MS (CI, CH_4) m/z 342, 326, 212, 199. Anal. Calcd for $C_{15}H_{14}F_3NO_3Si$: C, 52.78; H, 4.13; N, 4.10. Found: C, 52.71; H, 4.22; N, 4.07.

2-(2,4-Dichlorophenoxy)-4-fluoro-3-(trimethylsilyl)nitrobenzene (Table 2, entry 14): IR (film) 3083, 2958, 1595, 1547,1505, 1345, 1250, 1205, 845 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 8.24 (dd, J = 9.0, 5.8 Hz, 1H), 7.62 (d, J = 2.5 Hz, 1H), 7.33 (dd, J = 9.0, 8.0 Hz, 1H), 7.24 (dd, J = 8.9, 2.6 Hz, 1H), 6.72 (d, J = 8.9 Hz 1H), 0.33 (d, J = 1.9 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4 (d, J = 252.2 Hz), 152.5, 152.3 (d, J = 6.3 Hz), 138.4 (d, J = 3.5 Hz), 130.9, 129.7 (d, J = 12.3 Hz), 128.1, 127.6, 124.4, 123.7 (d, J = 20.0 Hz) 113.8 (d, J = 7.2 Hz), 113.3, 0.27 (d, J = 3.3 Hz); MS (CI, CH_4) m/z 374, 358, 344, 249, 232, 212. Anal. Calcd for $C_{15}H_{14}Cl_2FNO_3Si$: C, 48.14; H, 3.77; N, 3.76. Found: C, 48.26; H, 3.50; N, 3.85.

2-Phenoxy-4-fluoro-3-(trimethylsilyl)nitrobenzene (Table, entry 15): IR (film) 3090, 2980, 1596, 1570,1527, 1489, 1440, 1395, 1345, 1255, 1213, 1110, 875, 845 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 8.15 (dd, J = 9.0, 5.8 Hz, 1H), 7.33 (m, 1H), 7.26 (dd, J = 5.8, 4.9 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.84 (m, 2H), 0.30 (d, J = 1.9 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (d, J = 253.1 Hz), 157.5, 153.1 (d, J = 17.3 Hz), 139.3, 130.2, 129.6, 129.0 (d, J = 12.1 Hz), 122.8, 114.8, 112.5 (d, J = 29.7 Hz), 0.2 (d, J = 3.5 Hz); MS (CI, CH_4) m/z 306, 290, 249, 232. Anal. Calcd for $C_{15}H_{16}FNO_3Si$: C, 58.99; H, 5.28; N, 4.61. Found: C, 59.18; H, 5.11; N, 4.56.

2,4-Difluoro-3-(trimethylstannyl)nitrobenzene (3). To a −78 °C solution of 0.83 mL (3.46 mmol) of (*tert*-butyldimethylsilyl)-*tert*-butylamine in THF (5 mL) was added 2.14 mL (3.29 mmol) of *n*-BuLi (1.54 M in hexane), and the solution was allowed to warm to 0 °C to provide a solution of LiBSBA. In a separate flask, a solution of 0.3 mL (2.74 mmol) of 2,4-difluoro-1-nitrobenzene in THF (10 mL) was cooled to −78 °C, and 1.64 mL (4.11 mmol) of Me_3SnCl (2.5 M in THF) was added. The LiBSBA solution was then added dropwise to maintain an internal temperature below −74 °C. The resulting mixture was stirred for 30 min at −78 °C and then partitioned between 1 M HCl and Et_2O. The aqueous phase was separated and extracted with ether. The combined organic phases were washed with 1 M HCl (3×) and brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (10% acetone/hexane) provided 636 mg (75%) of the title compound: IR (film) 3090, 2990, 1600, 1580, 1525, 1445, 1345, 995, 745 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 8.17 (dt, J = 8.8, 5.9 Hz, 1H), 7.16 (dd, J = 8.97, 5.8 Hz, 1H), 0.50 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7 (dd, J = 321.8, 19.2 Hz), 159.7 (dd, J = 252.9, 21.1 Hz), 133.8 (d, J = 10.1 Hz), 128.8 (dd, J = 10.7, 2.1 Hz), 118.1 (dd, J = 51.2, 48.9 Hz), 111.4 (dd, J = 26.8, 3.6 Hz), −7.7 (s, with tin satellites at 185 Hz); MS (CI, CH_4) m/z 324, 322, 320, 160. Anal. Calcd for $C_9H_{11}F_2NO_2Sn$: C, 33.59; H, 3.44; N, 4.37. Found: C, 33.48; H, 3.43; N, 4.40.

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