Copper-Catalyzed Direct Amination of Nitrobenzenes with *O*-Alkylhydroxylamines

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Direct amination of aromatic compounds remains as a challenging problem of practical importance in organic synthesis.[1] In particular, the amination of nitrobenzenes *via* the nucleophilic substitution of hydrogen has recently attracted considerable interest because it is an environmentally safer route to nitroanilines, since halogenated nitrobenzenes are not required as substrates. Two different approaches to this problem have recently been reported, i.e., the oxidative direct coupling of nitrobenzene and aniline[2] or amide[3] and a vicarious nucleophilic substitution of hydrogen (VNS)[4] using 4-amino-1,2,4-triazole[5] or sulfenamides[6] as aminating agents. However, both types of amination occur predominantly at the 4-position with respect to the nitro group of nitrobenzenes.[7] To our knowledge, general and simple or *ortho*-selective direct amination of nitrobenzenes has not been reported.[8] In this paper, we describe a new direct amination of nitrobenzenes with *O*-alkylhydroxylamines in the presence of a copper catalyst, producing predominantly *ortho*-nitroanilines.

The behavior of primary amines possessing an N−N, N−O, or N−S bond was examined for the direct amination of nitrobenzene. Consequently, *O*-methylhydroxylamine[9] was found to efficiently aminate nitrobenzene under basic conditions at room temperature to give nitroanilines (*o*/*p* = 65/35) in 60% yield. The yield was enhanced up to 93% (*o*/*p* = 71/29) by the addition of 10 mol % CuCl (Table 1, entry 1). A similar effect was observed with the addition of other copper catalysts such as $CuCl_2$, CuBr, CuI, $Cu(acac)_2$, $Cu(NO_3)_2$, and $Cu(OAc)_2$, whereas CuCN, $Cu(OH)_2$, and $CuSO_4$ were less effective. The results of the direct amination with various *O*-alkylhydroxylamines are shown in Table 1. *Ortho*-rich aminated products were obtained when using *O*-methylhydroxylamine, *O*-ethylhydroxylamine, and *O*-benzylhydroxylamine. However, the reactions with *O*-*tert*-butylhydroxylamine or *N*,*O*-dimethylhydroxylamine exhibited *para*-selectivity, an outcome attributed to steric effects. In contrast, no reaction occurred with unsubstituted hydroxylamine[8] under these conditions, and the starting material was recovered quantitatively (Table 1, entry 6).

Table 1. Direct Amination of Nitrobenzene with NHROR′[a]

	NHROR′		nitroanilines	
entry	R	R′	yield[b] (%)	o/p[c]
1	H	Me	93 (60)[d]	71/29 (65/35)[d]
2	H	Et[e]	68	68/32
3	H	Bn[e]	41	76/24
4	H	*t*-Bu[e]	40	27/73
5	Me	Me	22[f]	0/100
6	H	H[e]	0[g]	

[a] Unless otherwise noted, the reaction of nitrobenzene with NHROR′ (1.25 equiv) was performed in the presence of *t*-BuOK (3.00 equiv) and CuCl (0.1 equiv) in DMF at rt for 1−24 h. [b] GC yields. [c] The o/p ratio was determined by GC. [d] No CuCl was added. [e] Hydrochloric acid salt and an additional base (1.25 equiv) were used. [f] *N*-Methylnitroaniline was obtained. [g] Starting material was recovered.

The reaction of nitrobenzenes bearing various substituents with *O*-methylhydroxylamine gave the corresponding substituted nitroanilines in excellent yields.[10] Representative results are summarized in Table 2. In general, the preferential synthesis of a 1,2,3-trisubstituted aromatic compound from a 1,3-disubstituted aromatic compound by conventional intermolecular aromatic substitution of hydrogen, for example, through nitration,[11] Friedel−Crafts reaction,[12] VNS reaction,[4] etc., is extremely difficult because of steric hindrance. However, the reaction of *N*,*N*-dimethyl-3-nitroaniline with *O*-methylhydroxylamine in the presence of a copper catalyst surprisingly gave the most sterically congested **2** (R = NMe_2)[13] in 75% yield and **1** (R = NMe_2) and **3** (R = NMe_2) in 10% and 15% yields, respectively (Table 2, entry 5). Such regioselectivity was observed when using *meta*-substituted nitrobenzenes in which the substituent has a lone pair of electrons (Table 2, entries 2−4). This result does not appear to be due to coordination of an unshared electron pair of the substituent to copper because the addition of a copper catalyst has no effect on the orientation of the amination. The observed effects of the substituents on the reactivity of the 2-position lie in the order NMe_2 > OMe > F > Cl, which is consistent with the mesomeric effects (+M) in electrophilic aromatic substitution.[14] Hence, it is apparent that electronic factors must play a dominant role in this regioselectivity.

In the case of *p*-chloronitrobenzene, the Cl atom is susceptible to conventional nucleophilic aromatic substitution (S_NAr) since it is activated by the *p*-nitro group. Nevertheless, no **7** from a typical S_NAr could be detected,

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(2) Stern, M. K.; Hileman, F. D.; Bashkin, J. K. *J. Am. Chem. Soc.* **1992**, *114*, 9237−9238.

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(7) For *ortho*-amination of 1-nitronaphthalene, see ref 6.

(8) For direct aminations of 1,3-dinitroarenes or bicyclic nitroarenes with hydroxylamine, see: (a) Möler, F. In *Houben-Weil Methoden der Organische Chemie*; Müller, E., Ed.; G. Thieme: Stuttgart, 1957; Vol. 11/1, pp 17−19. (b) Baumgarten, H. E. *J. Am. Chem. Soc.* **1955**, *77*, 5109−5112. (c) Nasielski-Hinkens, R.; Kotel, J.; Lecloux, T.; Nasielski, J. *Synth. Commun.* **1989**, *19*, 511−514.

(9) Bissot, T. C.; Parry, R. W.; Campbell, D. H. *J. Am. Chem. Soc.* **1957**, *79*, 796−800.

(10) Typical procedure: A solution of NH_2OMe (2.5 mmol) and a nitroarene (2 mmol) in DMF (3 mL) was added dropwise to a stirred solution of *t*-BuOK (6 mmol) and CuCl (0.2 mmol) in DMF (7 mL) over 5 min at room temperature. Then, formation of a deep red color was observed. After 1 h at room temperature, the reaction was quenched in saturated NH_4Cl, and the products were extracted with CH_2Cl_2 and purified by silica gel thin layer chromatography.

(11) Pearson, D. E.; Buehler, C. A. *Synthesis* **1971**, 455−477.

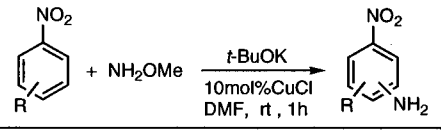
(12) *Friedel Crafts and Related Reactions*; Olah, G. A., Ed.; John Wiley & Sons: New York, 1964; Vols. II and III.

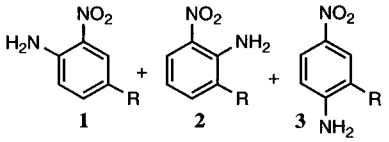
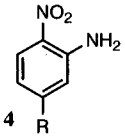
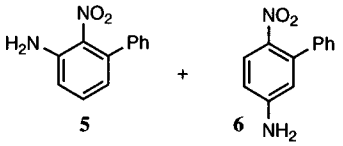
(13) New compound (see supporting information).

(14) Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley & Sons: Chichester, 1990.

0022-3263/96/1961-0442$12.00/0

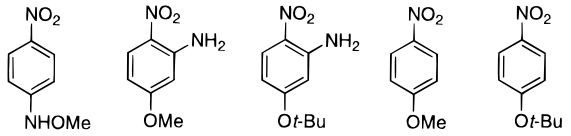
Table 2. Copper-Catalyzed Direct Amination of Nitroarenes with *O*-Methylhydroxylamine[a]



entry	R	ratios of products[b]	%yields[c]
			
		1 : 2 : 3	
1	3-CF_3	50 (48) : 26 (31) : 24 (21)	93 (25)
2	3-OMe	15 (15) : 61 (61) : 24 (24)	94 (57)
3	3-Cl	18 : 48 : 34	85
4	3-F	15 : 55 : 30	88
5	3-NMe_2	10 (10) : 75 (73) : 15 (17)	>99 (65)
			
		4	
6	4-OPh		70
7	4-SMe		92
8	4-*t*-Bu		91
9	4-Cl		86
10	4-F		17
			
		5 6	
11	2-Ph	70 : 30	86

[a] See ref 10 for typical procedure. Results when no CuCl was used are in parentheses. [b] All isomers were isolated. [c] Total yields of all isolated products.

and **4** (R = Cl) was obtained in 86% yield along with **8** (8%) (Table 2, entry 9). On the other hand, with *p*-fluoronitrobenzene, the yield of the desired aminated product **4** (R = F) was only 17%, and **8** (37%), **9** (14%), **10** (25%), and **11** (7%) were obtained *via* nucleophilic

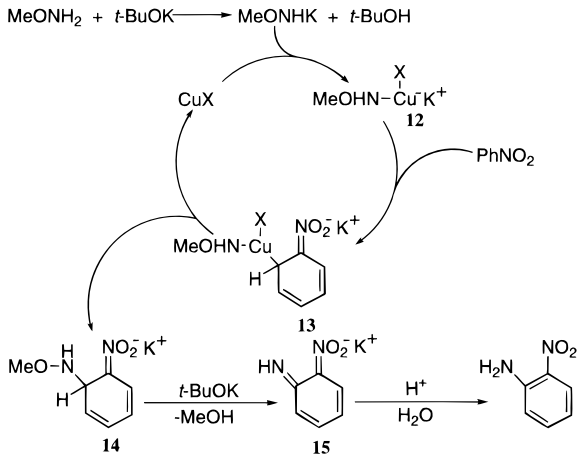


7 8 9 10 11

substitution of fluorine by *t*-BuO^- derived from the base or MeO^- generated in situ after the amination (Table 2, entry 10). Again, however, **7** was also apparently not produced in this case, which does not agree with the amination with sulfenamide reported by Makosza.[6] The fact that **7** is not produced in both cases clearly indicates that the direct amination with *O*-methylhydroxylamine is faster than S_NAr with *O*-methylhydroxylamine under these conditions, even when *p*-fluoronitrobenzene is used as a substrate.

A proposed copper-catalyzed mechanism is illustrated in Scheme 1. The oxidative addition of copper amide ate

Scheme 1



complex **12**[15] derived from a potassium amide and a copper salt to nitrobenzene is thought to produce **13**, which readily undergoes reductive elimination to give the Meisenheimer complex **14**. Finally, base-induced β-elimination gives the red-colored quinoid intermediate **15**, which is protonated through workup to give the nitroaniline. We assume that the role of the copper catalyst differs from that proposed by Nilsson,[16] who previously described stoichiometric copper-mediated vicarious nucleophilic substitution, because a catalytic amount of copper salt is sufficient for this amination. The details of this mechanism, particularly the role of the copper catalyst and the observed regioselectivity, remain to be explored.

In conclusion, the copper-catalyzed direct amination of nitrobenzenes with *O*-alkylhydroxylamine, in particular *O*-methylhydroxylamine, has been demonstrated. The reaction with *O*-methylhydroxylamine generates methanol as a byproduct that is easier to treat in large-scale production than the byproducts of the other known methods.[5,6] Since the reaction affords predominantly *o*-amino compounds, we believe that this method will greatly facilitate the synthesis of *o*-nitroaniline derivatives which are important intermediates in the preparation of numerous pharmaceuticals and agricultural chemicals containing a benzimidazole moiety. Further studies along these lines are currently underway.

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Supporting Information Available: Spectral and analytical data for nitroaniline derivatives (12 pages).

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(15) ^{1}H-NMR spectrum (DMSO-d_6) of the mixture of NH_2OMe, *t*-BuOK, and CuCl exhibited two singlets for the methoxy groups of two different species at δ 3.35 and δ 3.22, although in the absence of CuCl it indicated only one singlet for the methoxy group at δ 3.34.

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