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Reductive Monoalkylation of Aromatic and Aliphatic Nitro Compounds and the Corresponding Amines with Nitriles

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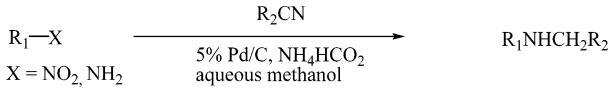
ABSTRACT

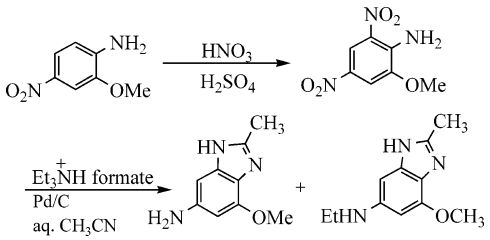


A simple, selective, rapid, and efficient procedure for the synthesis of secondary amines from the reductive alkylation of either aliphatic or aromatic nitro compounds and the corresponding amines is reported. Ammonium formate is used as the hydrogen source and Pd/C as the hydrogen transfer catalyst. The reaction is carried out at room temperature. The rate differences for the preferential formation of secondary over tertiary products are due to both steric and electronic factors.

Control over the synthesis of secondary amines is a problem of long standing in organic chemistry.[2] The problem of overalkylation has been solved in many instances either by the use of an excess of primary amine,[3] by special protecting groups,[4] or by special zeolyte[5] or other catalysts, including phase-transfer catalysts.[6−12] However, improvements in the efficiency of secondary amine formation have usually come at considerable cost. Thus, improved selective methods of secondary amine synthesis continue to be sought.

The present investigation began with the observation that aminobenzimidazole formation in a reduction reaction accompanying an imidazole cyclization reaction was complicated by a troublesome reductive N-ethylation of the isolated nitro group (Scheme 1).[13] In this instance, the undesired product was formed in 75% yield without any attempt to optimize. While the N-ethylation reaction could be avoided by substitution of the acetonitrile with acetic acid, the total absence of the tertiary diethylamine in this example suggested

Scheme 1



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(2) Salvatore, R. N.; Yoon, C. W.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785−7811.
(3) Mitsunobu, O. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 65.
(4) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 494−632.
(5) Siswanto, C.; Rathman, J. F. *J. Colloid Interface Sci.* **1997**, *196*, 99−102.
(6) Hayden, L.; Sauter, G.; Ore, F.; Pasillas, P.; Hoover, J.; Lindsay, G.; Henry, R. *J. Appl. Phys.* **1990**, *68*, 456−465.
(7) Bhattacharyya, A. K.; Nandi, D. K. *Ind. Eng. Chem. Prod. Res. Dev.* **1975**, *14*, 162−167.
(8) Narayanan, S.; Prabhu Prasad, B. *J. Mol. Catal. A: Chem.* **1995**, *96*, 57−64.
(9) Narayanan, S.; Kumari, V. D.; Rao, A. S. *Appl. Catal., A* **1994**, *111*, 133−142.
(10) Brown, A. B.; Reid, E. E. *J. Am. Chem. Soc.* **1924**, *46*, 1836−1839.
(11) Bayer, A. C.; Pittman, C. U.; Wang, L.; Alley, E. *Ger. Offen.* DE 4,013,613, 1990.

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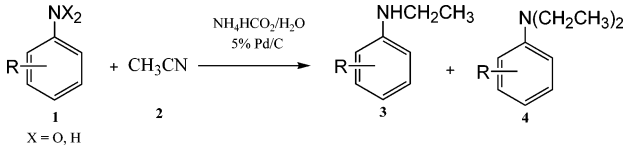
Table 1. Reductive N-Alkylation of Nitroarenes and Anilines with Acetonitrile



entry	1	1/2 ratio	3/4 ratio	time (h)	yield (%)
1	nitrobenzene	1:89	85:15	1.5	78
2	*p*-nitrotoluene	1:102	90:10	1.2	76
3	*o*-nitrotoluene	1:100	100:0	2.3	83
4	*m*-nitrotoluene	1:100	86:14	1.4	85
5	*p*-methoxynitro-benzene	1:115	86:14	0.4	93
6	*o*-methoxynitro-benzene	1:102	100:0	2.5	96
7	aniline	1:71	88:12	1.4	90
8	*p*-toluidine	1:79	81:19	1.2	95
9	*o*-toluidine	1:79	100:0	1.3	94
10	*m*-toluidine	1:78	88:12	0.8	100
11	*p*-anisidine	1:90	70:30	0.7	100
12	*o*-anisidine	1:90	100:0	2.2	98
13	*m*-anisidine	1:90	91:9	1.6	86

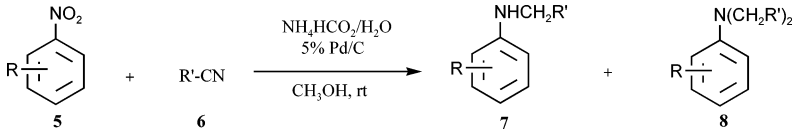
that reductive N-monoalkylation with alkyl nitriles to form the secondary amine in high yield might be developed more generally.

Thus, the reaction was investigated for a number of simpler substrates.[14] Table 1[15] shows the results for a number of nitrobenzene derivatives and for the corresponding anilines. The progress of the reaction was monitored by GC-MS. Very high yields or exclusive formation of secondary amine products are shown for reaction with acetonitrile. The large molar excess of acetonitrile used in the original example as both reactant and solvent could be significantly reduced to minimal concentrations required for formation of the secondary amine product at a reasonable rate, while substituting the removed acetonitrile with methanol. Thus, when higher alkyl analogues of acetonitrile (Table 2) were employed, use of methanol as a co-solvent maintained the solubility of both the nitro or amino arene and the alkyl nitrile.

For the cases shown in Tables 1 and 2 reduction of the nitro group to the corresponding amine appeared to occur rapidly in a preliminary step, as use of the amine directly gave similar high ratios of secondary to tertiary products (Table 3). This was in conformity with the analysis that showed rapid formation of the amine in most cases, especially for the nitroarenes with electron-donating activating groups. For small increases in the size and steric encumberance of the alkyl group in the nitrile as well as the presence of the ortho groups in the nitroarene or aniline, the formation of the tertiary amine was reduced or eliminated completely.

Table 4 shows several examples using the procedure for the formation of secondary amines starting from either nitroalkanes or aminoalkanes. In these instances, the secondary amine products were always formed first, and in some cases, it was relatively easy to discriminate kinetically

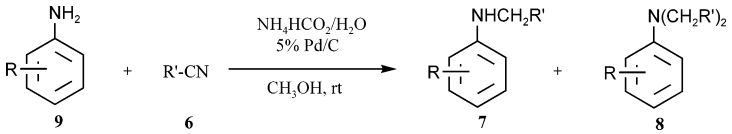
Table 2. Reductive N-Alkylation of Nitroarenes with Various Organic Nitriles



entry	5	R′	5/6 ratio	7/8 ratio	time (h)	yield (%)
1	nitrobenzene	CH_3-	1:89[a]	85:15	1.5	85
2	nitrobenzene	CH_2CH_2-	1:8	89:11	16.6	87
3	nitrobenzene	$CH_2(CH_2)_2-$	1:8[a]	99:1	19.2	71
4	*p*-nitrotoluene	CH_3-	1:102[a]	90:10	1.16	76
5	*p*-nitrotoluene	CH_2CH_2-	1:8	90:10	3.9	100
6	*p*-nitrotoluene	$CH_2(CH_2)_2-$	1:8	90:10	5.9	100
7	*o*-nitrotoluene	CH_3-	1:100[a]	100:0	2.3	83
8	*o*-nitrotoluene	CH_2CH_2-	1:8	97:2[b]	3.4	100
9	*o*-nitrotoluene	$CH_2(CH_2)_2-$	1:8	100:0	4.0	100
10	*m*-nitrotoluene	CH_3-	1:100[a]	86:14	1.4	85
11	*m*-nitrotoluene	CH_2CH_2-	1:8	95:5	3.0	89
12	*m*-nitrotoluene	$CH_2(CH_2)_2-$	1:8	97:3	3.3	100
13	*p*-methoxynitrobenzene	CH_3-	1:115[a]	86:14	0.4	93
14	*p*-methoxynitrobenzene	CH_2CH_2-	1:8	90:10	4.0	99
15	*p*-methoxynitrobenzene	$CH_2(CH_2)_2-$	1:8	90:10	4.5	100
16	*p*-methoxynitrobenzene	$CH_2(CH_2)_4-$	1:4	71:0[b]	29.0	75
17	*o*-methoxynitrobenzene	CH_3-	1:102[a]	100:0	2.5	96
18	*o*-methoxynitrobenzene	CH_2CH_2-	1:8	95:5	3.1	100
19	*o*-methoxynitrobenzene	$CH_2(CH_2)_2-$	1:8	100:0	3.1	100

[a] In the absence of CH_3OH, with CH_3CN as the solvent. [b] Balance is starting material.

Table 3. Reductive N-Alkylation of Aromatic Amines with Various Organic Nitriles



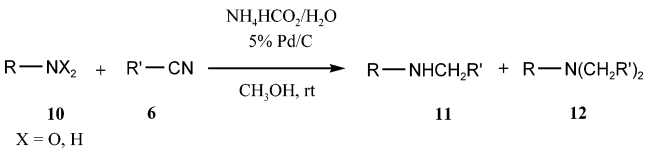
entry	9	R′	**9/6** ratio	**7/8** ratio	time (h)	yield (%)
1	aniline	CH_3-	1:8	98:0[b]	4.3	83
2	aniline	CH_2CH_2-	1:8	94:6	6.7	100
3	aniline	$CH_2(CH_2)_2-$	1:8	97:3	8.6	100
4	*p*-toluidine	CH_3-	1:79[a]	81:19	1.2	95
5	*p*-toluidine	CH_2CH_2-	1:8	90:10	4.2	100
6	*p*-toluidine	$CH_2(CH_2)_2-$	1:8	95:5	5.5	100
7	*o*-toluidine	CH_3-	1:79[a]	100:0	1.3	94
8	*o*-toluidine	CH_2CH_2-	1:8	97:3	2.8	100
9	*o*-toluidine	$CH_2(CH_2)_2-$	1:8	98:2	4.5	100
10	*m*-toluidine	CH_3-	1:78[a]	88:12	1.2	100
11	*m*-toluidine	CH_2CH_2-	1:8	88:12	2.4	100
12	*m*-toluidine	$CH_2(CH_2)_2-$	1:8	96:4	2.5	100
13	*p*-anisidine	CH_3-	1:90[a]	70:30	0.7	100
14	*p*-anisidine	CH_2CH_2-	1:8	83:17	2.5	99
15	*p*-anisidine	$CH_2(CH_2)_2-$	1:8	90:10	3.9	100
16	*o*-anisidine	CH_3-	1:90[a]	100:0	2.2	98.0
17	*o*-anisidine	CH_2CH_2-	1:8	92:8	3.1	100
18	*o*-anisidine	$CH_2(CH_2)_2-$	1:8	98:2	3.5	100
19	*m*-anisidine	CH_3-	1:90[a]	91:9	1.6	86
20	*m*-anisidine	CH_2CH_2-	1:8	94:6	3.0	100
21	*m*-anisidine	$CH_2(CH_2)_2-$	1:8	99:1	4.5	100

[a] In the absence of CH_3OH, with CH_3CN as the solvent. [b] Balance is starting material.

between the formation of the secondary product and the tertiary one. It was also possible to form asymmetric tertiary products by forming the secondary amine first and then subsequently forming the tertiary amine by addition of a larger concentration of a nitrile with a smaller R group to the medium. Thus, while the selective, high yield formation of both aryl−alkyl and alkyl−alkyl secondary amines occurred, this method was also applicable to the formation of tertiary amines with three different alkyl substituents, provided their total steric bulk was small.

In one example, cyclohexylamine was converted first to N-propylcyclohexylamine in 78% yield with propionitrile (8 equivalents, 2 h, rt). Subsequent addition of acetonitrile (90 equivalents) at 60 °C for 28 h, gave a 70% yield of N-ethyl-N-propylcyclohexylamine with less than 10% each of N-propyl-, N,N-diethyl-, and N,N-dipropylcyclohexylamines.

Table 4. Reductive N-Alkylation of Nitroalkanes and Aliphatic Amines



entry	10	R′	**10/6** ratio	**11/12** ratio	time (h)	yield (%)
1	$CH_3(CH_2)_5NO_2$	CH_3-	1:89[a]	4:96	2.3	ND[c]
2	$CH_3(CH_2)_5NO_2$	CH_2CH_2-	1:8	70:30	0.3	51
3	cyclohexylamine	CH_3-	1:80[a]	86:14	0.4	39
4	cyclohexylamine	CH_2CH_2-	1:8	76:22[b]	1.0	77
5	cyclohexylamine	$CH_3(CH_2)_2$	1:8	85:6[b]	2.0	85

[a] In the absence of MeOH, with CH_3CN as the solvent. [b] Balance is starting material. [c] ND = not determined.

(12) Chen, P. Y.; Chen, M. C.; Chu, H. Y.; Chang, N. S.; Chuang, T. K. *Stud. Surf. Sci. Catal.* **1986**, *28*, 73−7469.

(13) Fouchard, D. M. D.; Tillekeratne, L. M. V.; Hudson, R. A. *Synthesis* **2004**, 17−18.

(14) During the preparation of this manuscript, we became aware of an analogous study of the reductive alkylation of amines with nitriles using a direct catalytic hydrogenation procedure (Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 4977−4980) reporting many examples of selective secondary amine formation using direct hydrogenation with hydrogen over palladium or rhodium on carbon catalysts. The formation of the secondary amine dominates for examples where aromatic amines are alkylated by aliphatic nitriles and selective formation of secondary amines is less easily controlled for alkylation of aliphatic amines with aliphatic nitriles. Reaction rates using these conditions are much slower than those employing the transfer hydrogenation procedure we used, though the net result in both cases is the same. In some cases reported by Sajiki et al., the rate of the hydrogenation reaction was shown to increase using ammonium acetate as an additive. This procedure also improved the selective formation of the secondary amine. In the report given here, the use of ammonium formate as the hydrogen transfer source may also be consistent with an interesting rate-accelerating effect due to added ammonium acetate that was observed by Sajiki et al. yet remains to be explained.

(15) Yields reported in Tables 1−4 are based on weight of isolated products; product ratios are based on GC-MS analysis of the isolated products.

The use of a transfer hydrogenation procedure appeared to be much faster compared to direct reduction with hydrogen over palladium or other types of catalysts. Indeed, there were a number of reports of intramolecular nitrile-mediated reductive alkylations that have been conducted with hydrogen as a reductant at various pressures and over various types of catalysts.[16−20] Also, using active rhodium catalysts, Galan et al.[21] have demonstrated direct reductive coupling of aliphatic nitriles to form the corresponding secondary amines in high yield. In these instances, direct reduction of nitrile led to the corresponding amine, which then reacted with nitrile leading to a secondary amine product in a process likely identical to that reported here. The products formed in both those cases as well as here were consistent with the intermediacy of an amidine[22] reduced first to a geminal diamine, from which ammonia was then eliminated to form a Schiff's base. A final reduction then led to the secondary amine.

This reductive coupling of nitriles to form secondary amines represented a useful model for understanding the observations presented here. However, the hydrogenation conditions employed for reductively alkylating nitriles with amines, or nitro compounds that have to be first converted to an amine, cannot in our case directly reduce the nitrile. Thus, our conditions support nitro group but not nitrile reduction. It is the apparent interaction of the nitrile with the amine that leads to intermediates from which one of the nitrogens must be eliminated and eventually reduced to yield the observed secondary amine products.

The planar intermediates required for secondary amine formation clearly would make it easier to form a secondary rather than a tertiary product. In the carbon−nitrogen double-bond character of the presumed intermediates formed during reductive alkylation of the amine, the presence of a third alkyl group in the formation of a tertiary product can clearly become a steric problem. Whereas the secondary product can still avoid steric difficulties, the carbon−nitrogen double-bond intermediates formed on the way to the tertiary products cannot. These steric effects are clearly more important for the reductive alkylation of nitriles than in the analogous nucleophilic substitution reactions.

Supporting Information Available: Experimental procedures and ^{1}H NMR and ^{13}C NMR data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Somei, M.; Tsuchiya, M. *Chem. Pharm. Bull.* **1981**, *29*, 3145−3157.
(17) Sasai, H.; Yamada, Y.; Suzuki, T.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 12313−12318.
(18) Czeskis, B.; Clodfelter, D.; Wheeler, W. *J. Label. Compd. Radiopharm.* **2002**, *45*, 1143−1152.
(19) Makosza, M.; Stalewski, J.; Maslennikova, O. *Synthesis* **1997**, 1131−1133.
(20) Zhou, L.; Zhang, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2399−2402.
(21) Galan, A.; Mendosa, J.; Prados, P.; Rojo, J.; Echavarren, A. M. J. *Org Chem.* **1991**, *56*, 452−454.
(22) Zhang, J. Chang, H.-M.; Kane, R. R. *Synlett* **2001**, 643−645.