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Reductive and Catalytic Monoalkylation of Primary Amines Using Nitriles as an Alkylating Reagent

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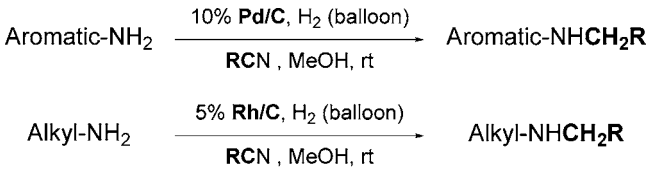
ABSTRACT



A selective and catalytic mono-*N*-alkylation method of both aromatic and aliphatic amines using nitriles as an alkylating agent with Pd/C or Rh/C as a catalyst is described. This method is particularly attractive to provide an environmentally benign and applicable alkylation method of amines without using toxic and corrosive alkylating agents such as alkyl halides and carbonyl compounds.

The selective alkylation of primary amines to secondary amines represents an important class of chemical transformations that have found extensive use in the construction of a vast range of natural products, bioactive molecules, and industrial materials.[1] This broad utility has made secondary amines important synthetic targets, and traditional routes to their preparation are mainly classified into three categories, i.e., direct base-promoted mono-*N*-alkylation,[2] reductive amination,[3] and alkylative amination.[4] In these cases, the use of toxic and corrosive alkylating reagents[5] or carbonyl compounds and the frequent generation of wasteful salts as byproducts are undesirable in view of environmental concerns.[6] Besides, these methods are not always selective for monoalkylation of primary amines,[7,8] which leads to mixtures of secondary and tertiary amines that are quite difficult to separate.[1] To prevent overalkylation, troublesome and expensive multistep methods have been devised such as partial protection of primary amines[8] and reduction of mono-*N*-substituted amides.[9,10] However, the reaction conditions are often drastic (high temperature, basic conditions, etc.) or reagents are not readily available. To overcome these difficulties, highly selective, environmentally benign, and convenient mono-*N*-alkylation of primary amines is an important synthetic goal. We report an entirely new Pd/C and Rh/C-catalyzed selective monoalkylation of amines using nitriles as alkylating reagents.

(1) (a) Patai, S. *The Chemistry of Amino, Nitroso, Nitro and Related Groups*; Wiley: New York, 1996. (b) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785−7811.

(2) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; pp 789−792.

(3) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; pp 835−846.

(4) (a) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651−673. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (c) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946.

(5) Ono, Y. *Pure Appl. Chem.* **1996**, *68*, 367−375.

(6) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998.

(7) For some recent papers on selective and direct mono-*N*-alkylation of primary amines, see: (a) Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359−3363. (b) Blackburn, L.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 1637−1639. (c) Zhang, J.; Chang, H.-M.; Kane, R. R. *Synlett* **2001**, 643−645. (d) Fujita, K.-i.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* **2003**, *44*, 2687−2690.

(8) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2001**, *66*, 677−680 and references therein.

(9) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; pp 869−874.

(10) Recently, Petrini et al. reported an interesting synthetic method of secondary amines by reduction of α-aminoalkylphenyl sulfones using $NaBH_3OAc$. Mataloni, M.; Petrini, M.; Profeta, R. *Synlett* **2003**, 1129−1132.

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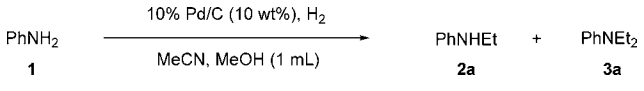
Initially, we examined 10% Pd/C-catalyzed *N*-ethylation of aniline (**1**), aromatic amine, with MeCN under various conditions. Amazingly, mono-*N*-ethylaniline (**2a**) was obtained at ambient temperature and under hydrogen pressure in MeCN as a solvent although the formation of a minimal amount of overalkylated *N*,*N*-diethylaniline (**3a**) was observed (Table 1, entry 1). The effect of MeOH as a solvent

Table 1. Reductive Mono-*N*-alkylation of Aniline Using MeCN



entry	MeCN (equiv)	solvent	time (h)	**1/2a/3a**[a]
1	38[b]		24	0:98:2
2	5	MeOH	24	0:89:11
3	2	MeOH	25	0:100 (85)[c]:0
4	1.5	MeOH	24	8:92:0

[a] Determined by ^{1}H NMR. [b] MeCN was used as a solvent. [c] Isolated yield.

is essential for this reaction, and the use of only 2 equiv of MeCN versus aniline gave a thoroughly selective result as shown in Table 1, entry 3.

It is well-known that the hydrogenation of nitriles under relatively vigorous hydrogenation conditions over platinum metal catalysts is favorable for the formation of symmetrical secondary and tertiary amines.[11] While it is quite expected that the hydrogenation of nitriles in the presence of amines can produce unsymmetrical amines,[12] only a few examples of selective mono-*N*-alkylation of amines have been reported in the literature because nitriles are not so reactive under hydrogenation conditions and the regulation of the selective reaction is very difficult.[11,13] Such conventional procedures are all limited to the substrate and require large excess amount of amines and elevated hydrogen pressure and/or higher temperature.[14]

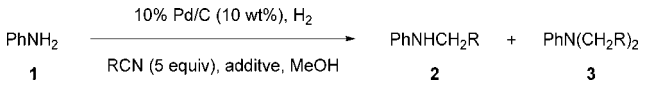
(11) (a) Rylander, P. N. *Hydrogenation Methods*; Academic Press: London, 1985; pp 94−103. (b) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley-Interscience: New York, 2001; pp 270−285.

(12) Kindler, K.; Hesse, F. *Arch. Pharm. (Weinheim, Ger.)* **1933**, *271*, 439−445.

(13) (a) Rylander, P. N.; Hasbrouck, L.; Karpenko, I. *Ann. New York Acad. Sci.* **1973**, *214*, 100−109. (b) Fülöp, F.; Huber, I.; Bernáth, G.; Höenig, H.; Seufer-Wasserthal, P. *Synthesis* **1991**, 43−46. (c) Rosowsky, A.; Mota, C. E.; Wright, J. E.; Queener, S. F. *J. Med. Chem.* **1994**, *37*, 4522−4528. (d) Gavagan, J. E.; Fager, S. K.; Fallon, R. D.; Folsom, P. W.; Herkes, F. E.; Eisenberg, A.; Hann, E. C.; DiCosimo, R. *J. Org. Chem.* **1998**, *63*, 4792−4801. (e) Graffner-Nordberg, M.; Kolmodin, K.; Aqvist, J.; Queener, S. F.; Hallberg, A. *J. Med. Chem.* **2001**, *44*, 2391−2402. (f) Gangjee, A.; Adair, O. O.; Queener, S. F. *J. Med. Chem.* **2003**, *46*, 5074−5082. (g) Ananthan, S.; Kezar, H. S.; Saini, S. K.; Khare, N. K.; Davis, P.; Dersch, C. M.; Porreca, F.; Rothman, R. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 529−532.

(14) Recently, an attractive example of mono-*N*-alkylation of primary amines using cyanohydrin and Pd/C accompanied by cyclization was investigated; see: Vink, M. K. S.; Schortinghuis, C. A.; Mackova-Zabelinskaja, A.; Fechter, M.; Pöchlauer, P.; Marianne, A.; Castelijns, C. F.; van Maarseveen, J. H.; Hiemstra, H.; Griengl, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2003**, *345*, 483−487.

Table 2. Reductive Mono-*N*-alkylation of Aniline Using Various Nitriles



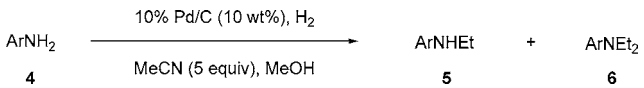
entry	RCN	additive (1 equiv)	time (h)	**1/2/3**[a]
1	MeCN[b]		25	0:100 (85)[c]: 0
2	EtCN		29	2:98:0
3	PrCN		42	5:95:0
4	dist. PrCN		19	0:99:1
5	^{i}PrCN		24	100:0:0
6	dist. ^{i}PrCN		28	0:100 (88)[c]:0
7	BuCN		48	0:100 (89)[c]:0
8	dist.^{i}BuCN		49	5:95:0
9	dist. ^{t}BuCN		56	81:19:0
10[d]	dist. ^{t}BuCN	NH_4OAc	24	0:100 (80)[c]:0
11	dist. $Me(CH_2)_{10}CN$		72	72:28:0
12[d]	dist. $Me(CH_2)_{10}CN$		48	0:100: 0
13	dist. CyCN	NH_4OAc	24	0:100 (quant)[c]: 0
14	$HO(CH_2)_2CN$		53	0:100 (81)[c]: 0
15	$(CH_2CN)_2$		27	0:100 (86)[c,f]: 0
16	$(MeO)_2CH(CH_2)_2CN$		24	0:100: 0
17	BnCN		27	1:99:0

[a] Determined by ^{1}H NMR. [b] 2 equiv of MeCN was used. [c] Isolated yield. [d] 20 wt % of 10% Pd/C was used. [e] Cy = cyclohexyl. [f] *N*-(3-Cyanopropyl)-aniline was isolated as a sole product.

The Pd/C-catalyzed reductive mono-*N*-alkylation of aniline (**1**) using various nitriles is summarized in Table 2. The present mono-*N*-alkylation system could be applied to a variety of primary, secondary, and tertiary nitriles while the use of 5 equiv of nitriles gave better results except only MeCN (entry 1). When PrCN, ^{i}PrCN, ^{i}BuCN, ^{t}BuCN, $Me(CH_2)_{10}CN$, or cyclohexanecarbonitrile was used as an alkylating reagent, the alkylation was incomplete (see entries 3 and 5). This drawback can be overcome by the use of distilled reagents (entries 4, 6, 8, 10, 12, and 13, see the Supporting Information). If the yield was still lower (entries 9 and 11), the multiplication of 10% Pd/C (20 wt %) and/or the addition of 1.0 equiv of NH_4OAc as an additive gave complete results (entries 10, 12, and 13). *N*-Alkylation of aniline (**1**) with nitriles bearing alcohol and acetal proceeded to give the corresponding mono-*N*-alkylated anilines (**2**) in excellent yields (entries 14 and 16). For the alkylation using succinonitrile under the same conditions, *N*-(3-cyanopropyl)-aniline was isolated as the sole product (entry 15).

We next examined the mono-*N*-alkylation of other aromatic amines (**4**). Mono-*N*-alkylation of aniline derivatives with MeCN bearing electron-donating (OMe, NHCOMe) and electron-withdrawing (Ph, F, CO_2H, CF_3) substituents at the aromatic ring smoothly and selectively proceeded to give the corresponding mono-*N*-alkylated aniline derivatives (**5**) in nearly quantitative yields (Table 3, entries 1−6). Although the reaction of 4-trifluoromethylaniline with MeCN did not give a satisfactory result (entry 7), the addition of 1.0 equiv of NH_4OAc is very efficient for the selective mono-*N*-alkylation of 4-trifluoromethylaniline (entry 8). Other aro-

Table 3. Reductive Mono-*N*-alkylation of Various Aromatic Amines Using MeCN

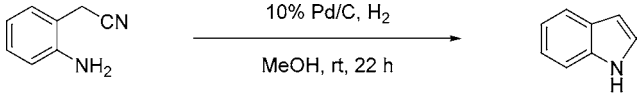


entry	$ArNH_2$	time (h)	**4/5/6**[a]
1[b]	$3,4,5\text{-}(MeO)_3C_6H_2NH_2$	22	0:100 (100)[c]:0
2	$4\text{-}MeCONHC_6H_4NH_2$	12	0:99 (97)[c]:1
3[d]	$2\text{-}PhC_6H_4NH_2$	24	0:98 (95)[c]:2
4[e]	$4\text{-}FC_6H_4NH_2$	12	0:100 (95)[c]:0
5	$4\text{-}HO_2CC_6H_4NH_2$	10	0:100 (94)[c]:0
6[f]	$2\text{-}HO_2CC_6H_4NH_2$	26	0:100 (91)[c]:0
7	$4\text{-}CF_3C_6H_4NH_2$	54	65:35:0
8[g]	$4\text{-}CF_3C_6H_4NH_2$	24	0:100 (99)[c]:0
9[d,f]	β-naphthylamine	47	0:97:3
10[h]	3-aminopyridene	58	11:89:0

[a] Determined by ^1H NMR. [b] 2 equiv of MeCN was used. [c] Isolated yield. [d] MeCN was used as a solvent. [e] AcOEt was used as a solvent. [f] 20 wt % of 10% Pd/C was used. [g] 1.0 equiv of NH_4OAc was used as an additive. [h] 30 wt % of 10% Pd/C was used.

matic primary amines, β-naphthylamine and 3-aminopyridine, were also applicable to this alkylation (entries 9 and 10).

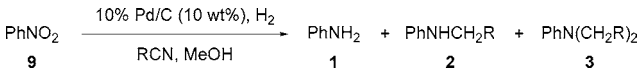
Scheme 1



As illustrated in Scheme 1, this process can also be useful for indole (**8**) synthesis[15] via Pd/C-catalyzed intramolecular cyclization under quite mild reaction conditions.

To expand this methodology, the one-pot synthesis of mono-*N*-alkylanilines (**2**) starting from nitrobenzene (**9**) with nitriles was attempted (Table 4). Indeed, the desired mono-*N*-alkylanilines (**2**) can be readily and selectively obtained

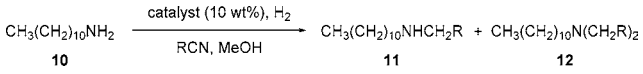
Table 4. Preparation of Mono-*N*-alkylaniline Delivatives from Nitrobenzene (9)



entry	RCN	time (h)	**1/2/3**[a]
1	dist. PrCN	20	0:100 (71)[b]:0
2[c]	dist. ^{i}PrCN	19	0:100 (quant)[b]:0
3	dist. BuCN	20	0:100 (69)[b]:0
4[d]	dist. ^{i}BuCN	24	0:100 (85)[b]:0
5	dist. $Me(CH_2)_{10}CN$	66	0:100 (90):0

[a] Determined by ^1H NMR. [b] Isolated yield. [c] 20 wt % of 10% Pd/C was used. [d] 1.0 equiv of NH_4OAc was used as an additive. [e] 30 wt % of 10% Pd/C was used.

Table 5. Reductive *N*-Alkylation of Aliphatic Amines



entry	RCN (equiv)	catalyst	time (h)	**10/11/12**[a]
1	MeCN (3)	10% Pd/C	24	0:0:100 (94)[b]
2[c]	PrCN (5)	10% Pd/C	29	0:0:100 (quant)[b]
3	BuCN (5)	10% Pd/C	29	0:0:100 (90)[b]
4	MeCN (2)	5% Rh/C	24	0:100 (96)[b]:0
5	PrCN (2)	5% Rh/C	34	3:97 (82)[b]:0
6	BuCN (2)	5% Rh/C	13	3:97 (71)[b]:0

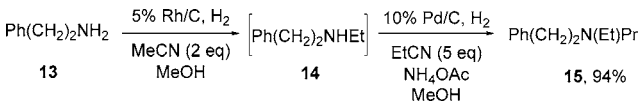
[a] Determined by ^1H NMR. [b] Isolated yield. [c] 1.0 equiv of NH_4OAc was used as an additive.

by a one-pot process without isolation of the intermediary aniline (**1**) and the overalkylated product (**3**).

On the basis of the successful demonstration of Pd/C-catalyzed reductive mono-*N*-alkylation of aromatic amines, we next explored the applicability of this procedure to the mono-*N*-alkylation of aliphatic primary amines (**10**). Unfortunately, quantitative formation of tertiary amines (**12**) (selective di-*N*-alkylation) is observed with 10 wt % of 10% Pd/C as a catalyst in the presence of 3−5 equiv of nitriles in MeOH as a solvent at ambient temperature and under hydrogen pressure (Table 5, entries 1−3). While the increased nucleophilicity of the aliphatic amine may lead to the formation of tertiary amines, thereby making the control of the monoselectivity of the reaction difficult during the course of our continuous investigation, we have found the excellent catalytic activity of 5% Rh/C toward selective mono-*N*-alkylation of aliphatic primary amines.[16] In each reaction, a secondary amine (**11**) was formed nearly quantitatively when the reaction was performed at ambient temperature and under H_2 pressure in the presence of 10 wt % of 5% Rh/C and 2 equiv of nitriles (Table 5, entries 4−6).

A useful application of these results in Table 5 is to transform a primary amine (**13**) into tertiary amine (**15**) possessing all different substituents via 5% Rh/C-catalyzed mono-*N*-alkylation of 13 with accompanying subsequent 10% Pd/C-catalyzed *N*-alkylation of intermediary 14 as shown in Scheme 2.

Scheme 2

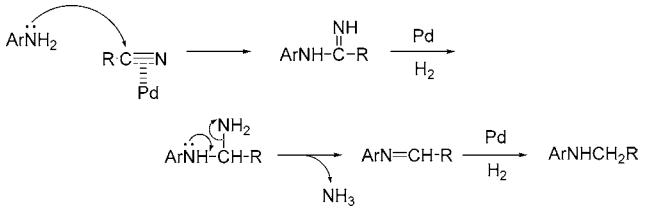


The simple reduction of aliphatic nitriles scarcely proceeded under the present reaction conditions and appropriate

(15) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662−5663.

(16) Rylander et al. reported the hydrogenation of valeronitrile in the presence of butylamine gives butylpentylamine selectively with 5% Rh/C in octane as a solvent under 50 psi of H_2 although the reaction required 6.6 equiv of butylamine to avoid the formation of dipentylamine.[13a]

Scheme 3



nucleophilicity of amines and catalyst activity of Pd/C or Rh/C are plausibly important for achievement of the selective alkylation. On the basis of these results, amidine formation by the nucleophilic attack of amines on the nitrile carbon suitably activated by the mild coordination of Pd or Rh is a key step for the selective alkylation (Scheme 3); however, the exact intermediate is not known yet.

In summary, we have developed a selective and reductive mono-*N*-alkylation method of both aromatic and aliphatic amines using nitriles as an alkylating reagent. This method is particularly attractive to provide alkyl halides or carbonyl compounds and is environmentally benign and applicable alkylation of amines.

Supporting Information Available: Experimental procedure and ^{1}H NMR and ^{13}C NMR spectra for the new and known product compunds. This material is available free of charge via the Internet at http://pubs.acs.org.

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