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Efficient and Mild Procedure for Reductive Methylation of Amines Using N-Methylpiperidine Zinc Borohydride

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Efficient and Mild Procedure for Reductive Methylation of Amines Using *N*-Methylpiperidine Zinc Borohydride

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Abstract: A simple and efficient procedure for reductive methylation of primary and secondary amines using *N*-methylpiperidine zinc borohydride (ZBNMPP), giving tertiary amines, is described. The reaction is carried out in methanol at room temperature under neutral conditions.

Keywords: Amines, formaldehyde, reductive methylation, ZBNMPP

INTRODUCTION

Amines and their derivatives show biological activities and are important precursors used in pharmaceutical and agricultural industries.[1] The introduction of methyl groups into a primary or secondary amine by reductive alkylation with formaldehyde is a useful method for the preparation of tertiary methylated amines.[2]

A number of reagents have been used for this transformation, including $NaBH_3CN$,[3] $NaBH_4$ in neat liquid carboxylic acid media[4a] or in aqueous sulfuric acid,[4b] borane-methylsulfide,[5] zinc-modified cyanoborohydride,[6] $Ti(OiPr)_4$-$NaBH_4$,[7] and $Zr(BH_4)_2Cl_2(dabco)_2$.[8] However, most of these reagent have drawbacks. For example, the use of expensive and highly toxic $NaBH_3CN$ carries the risk of producing residual cyanide in the product as well

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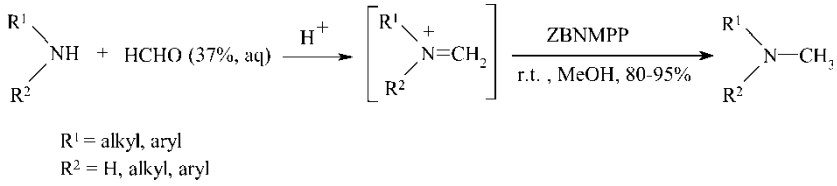

R1 = alkyl, aryl
R2 = H, alkyl, aryl

Scheme 1.

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as in the workup stream and generates a complex mixture of starting material and partially methylated products.[9] Sodium borohydride should be used in the presence of acid or in a protic solvent, reaction media that restrict its use for molecules containing acid-sensitive and easily solvolysed groups. These factors demonstrate the need for futher exploration beyond the existing reductive methylation synthetic repertoire. We expected from our pervious results for the reductive amination of aldehydes and ketones with *N*-methylpiperidine zinc borohydride (ZBNMPP)[10] that this reducing agent could be used effectively for reductive methylation of amines under mild conditions. ZBNMPP is an inexpensive, stable, and safe reducing agent.

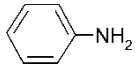
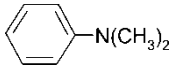
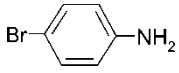
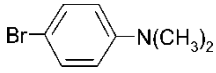
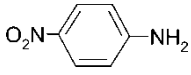
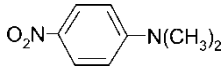
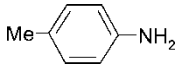
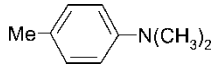
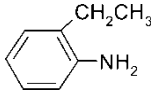
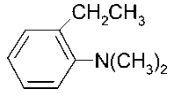
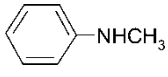
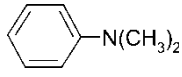
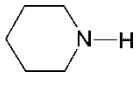
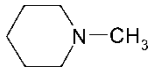
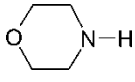
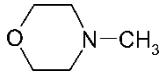
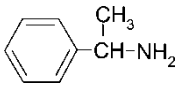
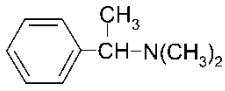
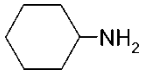
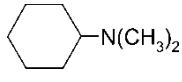
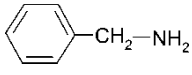
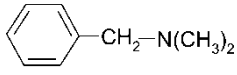
Therefore we herein report a mild and efficient method for the *N*-methylation of primary and secondary amines that affords tertiary amines (Scheme 1).

RESULTS AND DISCUSSION

The efficient and smooth reductive methylation of a variety of amines proceeded well in the presence of a 37% aqueous solution of formaldehyde using ZBNMPP under neutral conditions. The pH of the medium was adjusted to neutrality by addition of a 10% solution of HCl in methanol. Under such a condition, tertiary methylated amines were afforded in the absence of any other products. Complete chemoselectivity is observed in the reductive methylation of functionalized amines bearing other reducible functional groups. In general the reactions were carried out with 1 equivalent of amine, 5 equivalents of formaldehyde, and 1 equivalent of ZBNMPP in MeOH at room temperature under neutral conditions.

The reductive methylation of a variety of primary and secondary amines was successful and gave the desired tertiary methylated products in good to excellent yields (80–95%), as shown in Table 1. Initially we examined the reductive methylation of aniline (1 mmol) with 37% aqueous formaldehyde (5 mmol) in methanol (5 mL) under neutral conditions, using ZBNMPP (1 mmol) at room temperature. After 30 min, thin-layer chromatography (TLC) showed complete disappearance of aniline. After the usual workup, *N,N*-dimethylaniline was obtained in high yield (Table 1, entry 1). The secondary amines reacted faster than the primary amines and steric

Table 1. Reductive methylation of amines with ZBNMPP[a]

Entry	Compound	Product[b]	Time (min)	Yield (%)[c]	Ref.
1			30	88	[12]
2			40	92	[12]
3			90	85	[12]
4			18	95	[6]
5			120	82	[13]
6			15	88	[11]
7			6	89	[14]
8			6	80	[14]
9			15	97	[12]
10			24	90	[12]
11			18	91	[6]

(*continued*)

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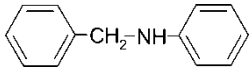
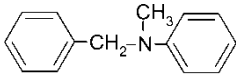
Table 1. Continued

Entry	Compound	Product[b]	Time (min)	Yield (%)[c]	Ref.
12			45	84	[15]
13	CH_3-CH_2-CH_2-CH_2-NH_2	CH_3-CH_2-CH_2-CH_2-$N(CH_3)_2$	20	89	[16]

[a]All reactions were carried out at room temperature; the molar ratio of amine/formaldehyde/reagent was 1 : 5 : 1.

[b]All products were characterized spectroscopically (^{1}H NMR, IR) and showed physical and spectral data in accordance with their expected structures and those of authentic samples.

[c]Yields refer to pure isolated products.

hindrance posed no problem; the hindered amines *N*-methylaniline and piperidine underwent clean and complete methylation (Table 1, entries 6, 7), although morpholine reacted in lower yield (Table 1, entry 8). We also employed the same methodology to examine the chemoselective reductive methylation of functionalized amines bearing other reducible functional groups. As shown in Table 1, anilines having a nitro group underwent reductive methylation to give the corresponding *N,N*-dimethylaniline in good yield without reduction of the nitro group (Table 1, entry 3). The effect of the nature of the substituted groups on the aromatic ring of aniline is quite clear: electron-releasing groups such as methyl increase the rate of reaction in relation to electron-withdrawing groups such as nitro and bromo (Table 1, entries 2–4).

To show the advantages and drawbacks of our method, we have compared some of our results with those reported in the literature in Table 2. This shows that our method in most cases gives lower reaction times and higher yields of the corresponding amines.

In conclusion, ZBNMPP is a good substitute for $NaBH_3CN$, $NaBH_3CN/ZnCl_2$, and zinc-modified cyanoborohydride for the preparation of tertiary methylated amines. Moreover, the mildness, ease of reaction workup, efficiency, chemoselectivity, high yields, and lack of need for an inert atmosphere make this reagent a useful addition to the group of reagents that can be used for the reductive methylation of amines.

EXPERIMENTAL

Materials were purchased from Fluka and Merck companies. The reactions were monitored by TLC using silica-gel plates. The products were purified

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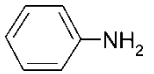
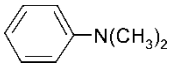
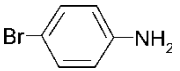
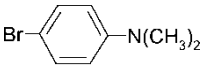
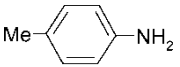
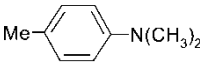
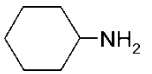
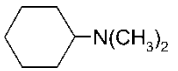
Table 2. Comparison of the results obtained by ZBNMPP with other reducing agents for reductive methylation of amines

			ZBNMPP		$NaBH_3CN$		$NaBH_3CN/ZnCl_2$		Zinc-modified cyanoborohydride		$Zr(BH_4)_2Cl_2(dabco)_2$	
Entry	Amine	Product	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1			30	86	120	92	120	86	—	—	—	—
2			40	92	60	87	—	—	—	0	—	—
3			18	95	—	—	—	—	120	83	18	87
4			24	90	120	84	—	—	—	—	6	81

by flash-column chromatography on silica gel (Merck; 230–400 mesh) and identified by comparison of their spectral and physical data with those of authentic samples. ^{1}H NMR spectra were measured at 300 MHz on a JEOL spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent. IR spectra were recorded on Pye-unicam SP1100 spectrophotometer.

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Preparation of *N*-Methylpiperidine Zinc Borohydride (ZBNMPP)

To a freshly prepared ethereal solution of zinc borohydride (200 ml, 0.03 mol), *N*-methylpiperidine (2.97 g, 0.03 mol) was added dropwise over 20 min. Then the mixture stirred at room temperature for 1 h under a nitrogen atmosphere. The precipitate was filtered off and washed with Et_2O (10 mL), and the resulting white powder was dried in a vacuum desicator to produce 4.5 g (85% yield).

Typical Procedure for Reductive Methylation of Amines with ZBNMPP

The preparation of *N,N*-dimethyl-*p*-toluidine is representative. A stirred solution of *p*-toluidine (0.107 g, 1 mmol) and 37% aqueous formaldehyde (0.4 mL, 5 mmol) in methanol (5 mL) was prepared, and the pH was adjusted to neutral conditions by addition of a 10% solution of HCl in MeOH. ZBNMPP (0.194 g, 1 mmol) was added, and the mixture was stirred at room temperature (18 min). Silica gel (2 g) was added when no amine remained (TLC). The solvent was evaporated, and the resulting material was applied on a silica-gel column and eluted with hexane/EtOAc 10/1 (100 mL). After evaporation of solvent, pure *N,N*-dimethyl-*p*-toluidine was obtained (0.128 g, 95% yield; Table 1, entry 4).

ACKNOWLEDGMENT

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