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SAFE AND EFFICIENT REDUCTIVE METHYLATION OF PRIMARY AND SECONDARY AMINES USING *N*-METHYLPYRROLIDINE ZINC BOROHYDRIDE

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An efficient, general procedure for reductive methylation of primary and secondary amines with 37% formaldehyde using* N*-methylpyrrolidine zinc borohydride (ZBHNMP) as a reducing agent gave the corresponding tertiary amines in excellent yields. The reaction was carried out in tetrahydrofuran under neutral conditions at 0–10°C.

Keywords: Amine; formaldehyde; reductive methylation; ZBHNMP

Synthesis of amines is an objective of high priority from the perspective of drug discovery.[1] The synthesis of tertiary amines by the reductive methylation of primary and secondary amines with formaldehyde has been often used as a synthetic tool in organic chemistry.[2] Because the reduction of imine or enamine, generated in situ by the reaction of amine with formaldehyde, can compete with the reduction of the starting compound, the reducing agents must reduce the imine or enamine with high selectivity. Sodium or potassium hydridotetracarbonylferrate in ethanol or tetrahydrofuran,[3] $NaBH_4$ in methanol,[4] and $NaBH_3CN$ in acetonitrile[5] are the most commonly used agents for this transformation. However, most of these reagents have drawbacks such as tedious workup, use of expensive and highly toxic reagents, and residual cyanide in the product as well as in the workup stream.

Other methods such as $NaBH_4$-$ZnCl_2$,[6] and $NaBH_4$ in tetrahydrofuran (THF),[7] borane–methylsulfide,[8] zinc-modified cyanoborohydride,[9] $Zr(BH_4)_2$-$Cl_2(DABCO)_2$,[10] and *N*-methylpyrrolidine zinc borohydride (ZBNMPP)[11] have been used for this purpose.

ZBHNMP is an inexpensive, stable, and safe-to-handle reducing agent for reduction of a variety of organic compounds such as aldehydes, ketones, acid chlorides, and esters.[12] Recently, we reported the reductive amination of aldehydes and ketones using this reducing agent.[13] In continuation, we expected that ZBHNMP could be used effectively for reductive methylation of amines under neutral conditions. Here, we report the reductive methylation of primary and secondary amines for the preparation of methylated tertiary amines (Scheme 1).

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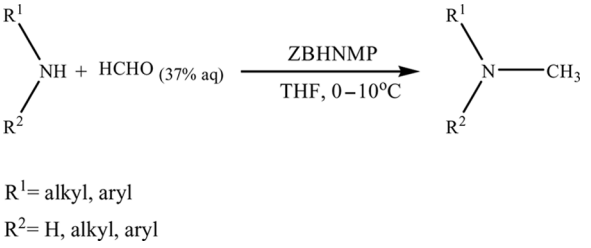


Scheme 1. Reductive methylation of amines using *N*-methylpyrrolidine zinc borohydride (ZBHNMP).

To find the optimum condition for reductive methylation of amines with ZBHNMP, we chose aniline as a model compound. Reductive methylation of aniline was first investigated in different solvents such as THF, CH_3OH, CH_2Cl_2, and *n*-hexane. We observed that THF was best solvent for this purpose. The amount of ZBHNMP in this reaction was also examined with different molar ratios of reductant to substrate in the presence of formaldehyde (37% aq) under neutral conditions in THF at 0 to 10 °C. A molar ratio of reductant to aniline to formaldehyde of 2:1:4 was found to be ideal for complete conversion to *N,N*-dimethyl aniline; the reaction remained incomplete with lesser amounts of reducing agent, for example, 1 or 1.5. Table 1 summarizes the reductive methylation of various aliphatic and aromatic amines with formaldehyde by using this procedure to furnish the corresponding *N,N*-dimethyl amines in good to excellent yields.

As indicated in Table 1, reductive methylation of aromatic amines with different substituents gives excellent yields of the corresponding amines (Table 1, entries 1–11). We did not encounter any problem in the methylation of low basicity amines such as *p*-nitroaniline and *o, m, p*-chloroanilines. Also, *o*-ethylaniline and *o*-toluidine, which might exhibit steric hindrance to *N*-substitution, were converted into the *N,N*-dimethyl derivatives. We also found that reductive methylation of aliphatic amines such as cyclohexylamine, pyrrolidine, morpholine, and benzylamine was performed in less time and gave better yields (Table 1, entries 12–15).

We compare some of the results obtained by ZBHNMP with other methods used for this purpose in Table 2. This shows that our method is a good substitute for $NaBH_3CN$ and zinc-modified cyanoborohydride for the preparation of tertiary methylated amines, and also in most cases it gave better yields of the corresponding amines in less reaction time.

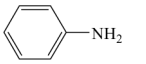
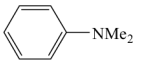
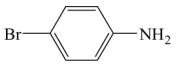
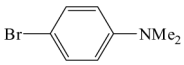
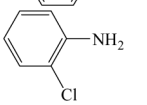
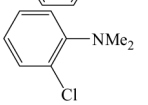
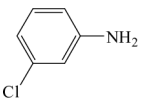
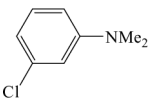
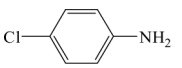
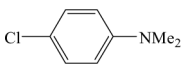
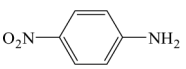
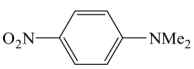
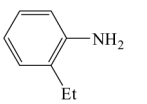
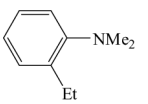
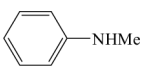
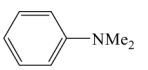
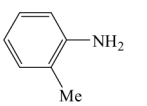
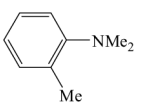
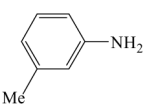
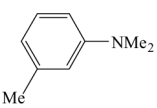
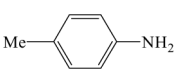
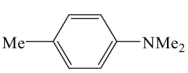
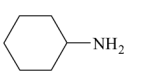
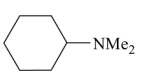
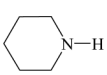
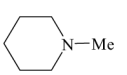
In conclusion, a new, efficient, reductive methylation method was developed using ZBHNMP as a mild reducing agent and formaldehyde (37% aq) in one-pot method with excellent yields. Notable advantages of the present method include the mildness, ease of reaction workup, efficiency, excellent yields, neutral conditions, and no need for an inert atmosphere.

EXPERIMENTAL

General

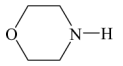
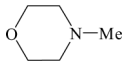
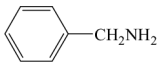
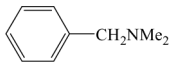
The ZBHNMP used in this study was prepared easily in good yield from commercially available starting materials.[12] Amines were purchased from Merck.

Table 1. Reductive methylation of primary and secondary aromatic and aliphatic amines with ZBHNMP in THF[a]

Entry	Substrate	Product[b]	Time (min)	Yield (%)[c]	Ref.
1			10	90	[5]
2			15	93	[5]
3			20	92	[14]
4			20	90	[5]
5			20	90	[14]
6			20	89	[5]
7			25	88	[15]
8			20	88	[7]
9			15	90	[7]
10			15	92	[7]
11			15	92	[9]
12			10	92	[5]
13			10	89	[16]

(*Continued*)

Table 1. Continued

Entry	Substrate	Product[b]	Time (min)	Yield (%)[c]	Ref.
14			10	88	[16]
15			10	94	[9]

[a]All reactions were carried out in THF at 0–10 °C, and the molar ratio of amine/formaldehyde/reductant was 2:1:4.

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

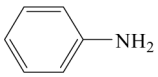
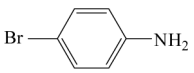
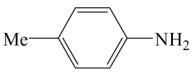
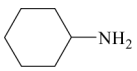
[c]Yields refer to pure isolated products.

Reaction monitoring and purity determination of the products were accomplished by thin-layer chromatography (TLC) or gas chromatography (GC). All the products are known compounds and were identified by comparison of their spectra and physical data with those of the authentic samples. Infrared (IR) spectra were recorded on a Bruker Vector 22 spectrometer. ^{1}H NMR spectra were measured on Bruker DRX 500 Avance (500-MHz) and GNM-EX90A (90-MHz) spectrometers, using $CDCl_3$ as solvent.

Typical Procedure for the Reductive Methylation of Amines with ZBHNMP

The preparation of *N,N*-dimethylaniline is representative. In an Erlenmeyer flask, a solution of the aniline (0.093 g, 1 mmol) and 37% aqueous solution of formaldehyde (4 mmol) in THF (5 mL) was prepared, and ZBHNMP (0.36 g, 2 mmol) was added. The pH was adjusted to neutral conditions with 10% aqueous solution of

Table 2. Comparison of ZBHNMP with the other reducing agents in reductive methylation of amines

		ZBHNMP		ZBNMPP		$NaBH_3CN$		Zn-$NaBH_3CN$		ZrBDC	
Entry	Substrate	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1		10	90	30	88	120	92	120	86	6	80
2		15	93	40	92	60	87	—	—	45	95
3		15	92	18	95	—	—	120	83	18	87
4		10	89	24	90	120	84	—	—	6	81

sulfuric acid. The mixture was stirred at 0 to 10 °C, and progress of the reaction was followed by TLC (eluent: *n*-hexane/EtOAc 4:1). After completion of the reaction, the mixture was diluted with water (10 mL) and then extracted with diethyl ether (2×20 mL). The combined organic layers were dried on anhydrous $MgSO_4$ and evaporated. The crude product was purified by column chromatography on silica gel and eluted with 2% solution of ethyl acetate in *n*-hexane to afford pure *N,N*-dimethylaniline (0.114 g, 94%).

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