Tetrahedron Letters 50 (2009) 659–661

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Reductive amination of aldehydes and ketones to their corresponding amines with *N*-methylpyrrolidine zinc borohydride

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ARTICLE INFO

*Article history:*
Received 30 September 2008
Revised 16 November 2008
Accepted 25 November 2008
Available online 30 November 2008

*Keywords:*
Aldehydes
Ketones
Reductive amination
Amines
*N*-Methylpyrrolidine zinc borohydride

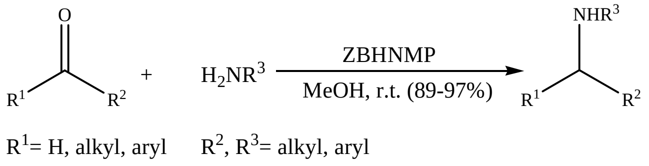
ABSTRACT

A simple and convenient procedure for reductive amination of aldehydes and ketones using *N*-methylpyrrolidine zinc borohydride (ZBHNMP) as a reducing agent is described. The reactions are carried out with 1 equiv of amine and 1 equiv of aldehyde or ketone using 1 equiv of ZBHNMP in methanol under neutral conditions at room temperature.

The reductive amination of aldehydes and ketones with primary and secondary amines is a very useful reaction in the synthesis of amines (Scheme 1). A variety of reducing agents, such as $NaBH_3CN$,[1] $NaBH(OAc)_3$,[2] pyridine-$BH_3$,[3] silica gel-$Zn(BH_4)_2$,[4] $Ti(O^i\text{-}Pr)_4$–$NaBH_4$,[5] $NiCl_2$–$NaBH_4$,[6] $Cu(PPh_3)_2BH_4$,[7] $NaBH_4$–$H_3PW_{12}O_{40}$,[8] $ZnCl_2$–$NaBH_4$,[9] $NaBH_4$–guanidine hydrochloride,[10] zinc borohydride *N*-methylpiperidine (ZBHNMP),[11] $Zr[(BH_4)_2(Cl)_2(dabco)_2]$,[12,13] Hantzch dihydropyridines,[14] and $NaBH_4$ in micellar media,[15] have been developed for this conversion. The most widely used reagents are (a) the expensive and highly toxic $NaBH_3CN$ that carries the risk of residual cyanide in the product as well as in the work-up, which makes this procedure less attractive. (b) $NaBH(OAc)_3$ reduces imines selectively over carbonyl compounds in 1,2-dichloroethane, however, solvents such as methanol or water are not suitable because of rapid reduction of the carbonyl compound or decomposition of the reducing agent in water.[16]

Here, we report an efficient and smooth reductive amination of a variety of carbonyl compounds in the presence of amines using *N*-methylpyrrolidine zinc borohydride (ZBHNMP) under neutral conditions. The pH of the media was adjusted to neutrality by addition of a 10% aqueous solution of HCl in methanol. Under such conditions, ZBHNMP did not reduce the carbonyl compounds in the reaction mixture, whereas the imine or iminium intermediates were converted easily to the corresponding amines.

The absence of formation of any hydroxy compound in these reactions suggests that the overall process would proceed successfully if a reasonable concentration of imine was available, and the reaction conditions could discriminate between the reduction of the imine intermediate and the carbonyl compound present in the reaction mixture. Complete chemoselectivity was observed in the reductive amination of α,β-unsaturated carbonyl compounds. In general, the reactions were carried out with 1 equiv of amine and with 1 equiv of aldehyde or ketone in the presence of 1 equiv of ZBHNMP in methanol under neutral conditions at room temperature (Scheme 1). The reductive amination of a wide variety of aldehydes and ketones with primary and secondary amines was successful and gave the desired products in good to excellent yields (89–97%) as summarized in Table 1.[17] We initially examined the reductive amination of benzaldehyde (1 mmol) with aniline (1 mmol) using ZBHNMP (1 mmol) in methanol (5 mL) and a 10% solution of HCl in methanol at room temperature for 2 h until TLC showed that the reaction was complete. Following work-up, *N*-benzylaniline was obtained in 95% yield (Table 1, entry 1). We also conducted this reaction on



**Scheme 1.**

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doi:10.1016/j.tetlet.2008.11.102

**Table 1**
Reductive amination of various aldehydes and ketones using ZBHNMP[a]

| Entry | Carbonyl | Amine | Product[b] | Time (h) | Yield[c] (%) |
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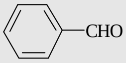
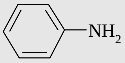
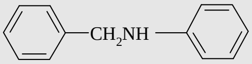
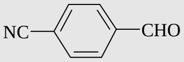
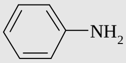
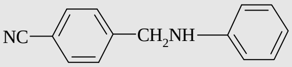
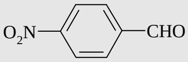
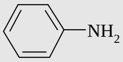
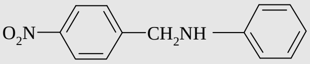
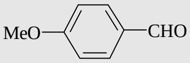
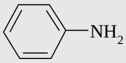
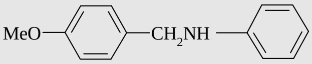
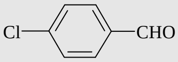
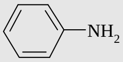
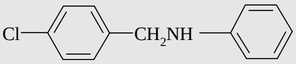
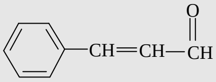
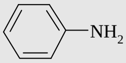
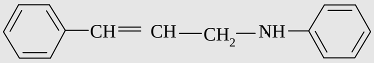
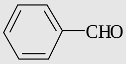
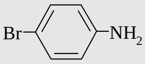
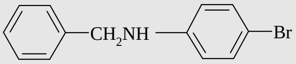
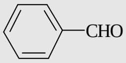
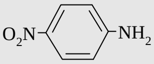
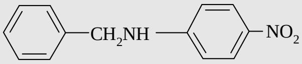
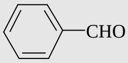
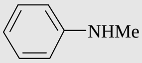
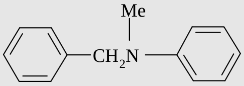
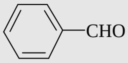
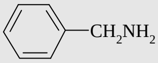
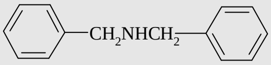
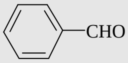
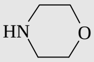
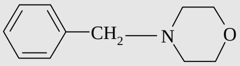
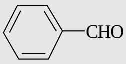
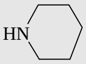
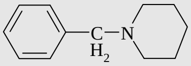
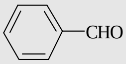
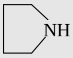
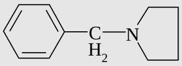
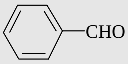
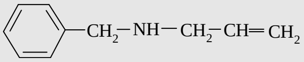
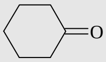
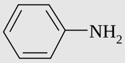
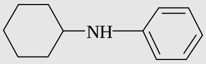
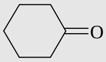
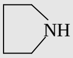
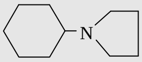
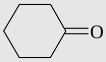
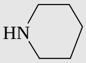
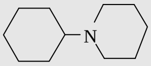
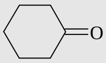
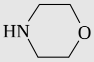
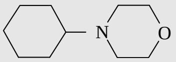
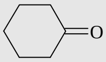
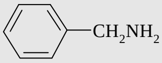
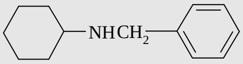
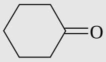
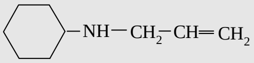
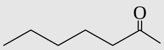
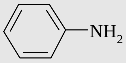
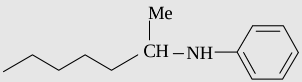
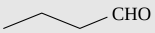
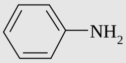
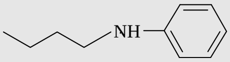
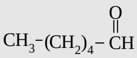
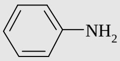
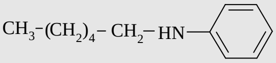
| 1 |  |  |  | 2 | 95[20] |
| 2 |  |  |  | 8 | 90[21] |
| 3 |  |  |  | 7 | 89[21] |
| 4 |  |  |  | 2.5 | 94[22] |
| 5 |  |  |  | 3 | 94[22] |
| 6 |  |  |  | 1.5 | 95[21] |
| 7 |  |  |  | 3 | 96[23] |
| 8 |  |  |  | 6 | 90[18] |
| 9 |  |  |  | 3 | 93[24] |
| 10 |  |  |  | 1.5 | 93[25] |
| 11 |  |  |  | 2 | 92[20] |
| 12 |  |  |  | 1.2 | 94[20] |
| 13 |  |  |  | 2 | 95[26] |
| 14 |  | $CH_2=CH-CH_2-NH_2$ |  | 1 | 92[27] |
| 15 |  |  |  | 1.5 | 96[20] |
| 16 |  |  |  | 1.5 | 95[26] |
| 17 |  |  |  | 1 | 97[20] |
| 18 |  |  |  | 2 | 95[25] |
| 19 |  |  |  | 1.5 | 93[20] |
| 20 |  | $CH_2=CH-CH_2-NH_2$ |  | 1.2 | 92[28] |
| 21 |  |  |  | 3 | 92[29] |
| 22 |  |  |  | 1.5 | 93[19] |
| 23 |  $CH_3{-}(CH_2)_4{-}\overset{\overset{O}{\|}}{C}H$ |  |  | 1.2 | 90[27] |

[a] All reactions were carried out at room temperature, and the molar ratio of reagent/carbonyl compound/amine was 1:1:1).

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

[c] Yield refers to pure isolated products.

10 mmol scale and a similar yield was obtained. We also examined the chemoselective reductive amination of functionalized benzaldehydes bearing other reducible functional groups employing the same methodology. As shown in Table 1, reductive amination of aromatic aldehydes possessing nitro and cyano groups proceeded to give the corresponding *N*-phenylamines in good yields without reduction of the cyano or nitro groups (Table 1, entries 2 and 3). In the case of $\alpha,\beta$-unsaturated aldehydes, such as cinnamaldehyde, reductive amination was achieved successfully in excellent yield without reduction of the carbon–carbon double bond (Table 1, entry 6). We found that both 4-bromo- and 4-nitroaniline reacted efficiently with benzaldehyde in the presence of ZBHNMP to produce the corresponding amines (Table 1, entries 7 and 8). However, in order to examine a greater range of amines to better illustrate the scope and limitations of the method, we investigated the reactions with aniline, *N*-methylaniline, benzylamine, morpholine, piperidine, pyrrolidine, and allylamine using benzaldehyde as a representative aldehyde, and cyclohexanone as a representative ketone (Table 1, entries 8–20). Excellent yields of the expected amines were obtained. Reductive amination of aliphatic ketones such as cyclohexanone and heptan-2-one, and aldehydes such as butanal and hexanal with aniline gave excellent yields of the corresponding amines (Table 1, entries 21–23).

*N*-Methylpyrrolidine zinc borohydride was prepared according to the literature procedure.[18] All the products are known compounds, and were identified by comparison of their spectra and physical data with those of authentic samples.

In conclusion, ZBHNMP is a stable and versatile bench-top reducing agent which is prepared easily from commercially available starting materials. It is a white powder and unlike its parent compound $Zn(BH_4)_2$, is thermally stable and can be stored for several months without appreciable loss of its reducing ability. ZBHNMP is a good substitute for $Na[BH_3CN]$ for reductive amination of carbonyl compounds. Moreover, the simple reaction procedure, easy work-up, selectivity, high reaction rates and yields, and lack of requirement of an inert atmosphere or neutral conditions make this stabilized transition-metal tetrahydroborate a useful addition to the category of reagents used for the reductive preparation of amines.

## Acknowledgments

Financial support of this work from the Research Council of Mazandaran University is gratefully acknowledged.

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17. *Typical procedure for the reductive amination of aldehydes and ketones with ZBHNMP*: To a stirred solution of aldehyde or ketone (1 mmol) and amine (1 mmol) in 5 mL of methanol was added the reducing agent (1 mmol) under neutral conditions (pH 7). The pH was adjusted by addition of a 10% aqueous solution of HCl in MeOH. The mixture was stirred, and the progress of the reaction was followed by TLC (eluent: *n*-hexane/EtOAc 4:1). After completion, water (10 mL) was added and the reaction mixture was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography with *n*-hexane/EtOAc as the eluent to afford the pure amine.
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