Iranian Journal of Organic Chemistry 2 (2009) 88-91

One-Pot reductive amination of carbonyl compounds and reductive *N*-alkylation of amines with zirconium borohydride–piperazine complexes under mild conditions

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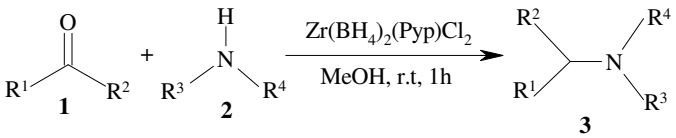
Abstract: Zirconium borohydride–piperazine(ZBPP) complex is a mild and highly efficient reagent for the direct reductive amination and reductive *N*-alkylation of amines. ZBPP is a nontoxic reagent with highly chemoselective and nonwater sensitive properties. The methodology can be applied to a variety of carbonyl compounds and amines.

Keywords: Reductive amination; Zirconium borohydride–piperazine; Reductive *N*-alkylation

Introduction

Secondary and Tertiary amino group is often embedded as a structural motif in various biologically active compounds [1,2] and are important intermediates in the synthesis of pharmaceutically active substances, dyes, and fine chemicals [3]. The direct reductive amination of aldehydes and ketones with metal hydride reagents is one of the most useful methods for the synthesis of secondary and tertiary amines [4]. Several reagents which effect reductive amination have been developed, including: catalytic hydrogenation [5], Et_3SiH–CF_3CO_2H [6], Zn–AcOH [7], Bu_3SnH–DMF [8], $NaBH_3CN$ [9a], $NaBH(OAc)_3$ [9b], pyridine–BH_3 [9c], $ZnCl_2$–$NaBH_4$ [9d], silica gel–$Zn(BH_4)_2$ [9e], $Ti(O\text{-}i\text{-}Pr)_4$–$NaBH_4$ [9f], $NiCl_2$–$NaBH_4$ [9g], $NaBH_4$–$ZrCl_4$ [9h], $NaBH_4$–H_2SO_4 [9i], $NaBH_4$–$H_3PW_{12}O_{40}$ [9j], $NaBH_4$–Guanidine.hydrochloride [9k], $NaBH_4$–wet clay-microwave [9l] and borohydride exchange resin [9m]. However, some of these preparations require relatively expensive reagents, harsh reaction conditions, sometimes tedious work-up, heavy metals as toxic waste, generation of toxic by-product, no chemoselectivity and some of those insoluble in most common organic solvents. Furthermore, direct reductive amination is performed under anhydrous conditions in order to avoid decomposition of the reducing agents or catalysts, and to enhance generation of the intermediate imines or iminium ions. Our recent endeavor of selective reduction of various important functionalities with zirconium borohydride–piperazine complex [10,11] prompted us to initiate a systematic study of this useful air and thermally stable reducing agent. In this paper, we report our results on the development of a highly practical method for the synthesis of amine derivatives by the direct reductive amination of carbonyl compounds and reductive *N*-alkylation of amines in the presence of zirconium borohydride–piperazine complex as a reducing agent and lewis acid in reagent grade methanol and THF (Scheme 1). Varieties of aldehydes and ketones were subjected to direct reductive amination by this procedure. The results appear in Table 1.



Scheme 1

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Table 1.

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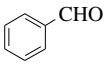
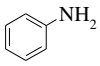
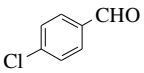
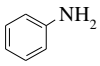
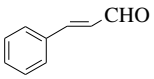
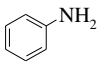
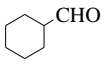
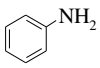
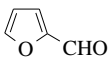
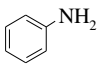
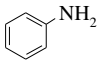
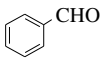
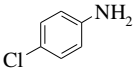
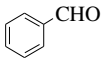
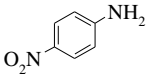
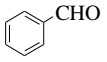
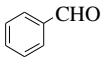
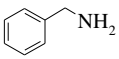
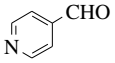
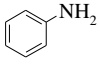
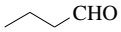
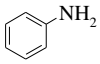
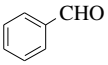
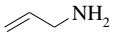
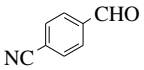
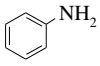
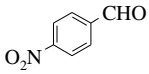
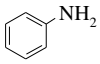
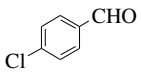
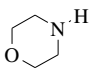
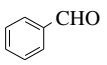
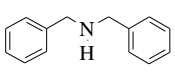
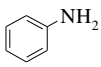
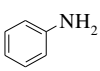
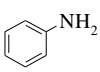
1			97
2			97
3			96
4			98
5			95
6			90
7			90
8			95
9			95
10			96
11			97
12			95
13			90
14			90
15			95
16			90
17			95
18			90
19			95
20			90

Table 1. Continued

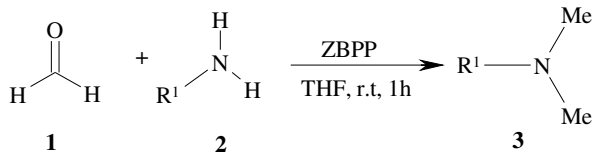
21			92
22			90
23			95
24			90

We initially studied the direct reductive amination of benzaldehyde with aniline in methanol in the presence of ZBPP, which afforded the corresponding imine which was then reduced to give *N*-benzylaniline in 98% isolated yield.

Various aldehydes and amines were subjected to direct reductive amination using this procedure. Acyclic and conjugated carbonyl compounds underwent successful reductive amination with aniline derivatives or morpholine to produce the corresponding secondary or tertiary amines in good to excellent yields. Under our standard conditions, direct reductive amination of *p*-cyano- or *o*-nitrobenzaldehydes with aniline proceeded smoothly giving good yields of the desired alkylated anilines (Table 1, entries 14 and 15). With these results in hand, we next studied the regioselective one-pot reductive amination of trans-cinnamaldehyde with aniline or diethylamine. The expected substituted cinnamyl amines were obtained in high isolated yields. The use of our procedure also enabled the reductive amination of ketones (Table 1, entries 18-23). *N,N*-dimethyl amines are important intermediates in the production of pharmaceuticals, agrochemicals and fragrance compounds [1,2]. They can be produced by the *N*-alkylation with alkyl halides [12], the reductive amination with carbonyl compounds [13] and The *N*-alkylation of amines with alcohols [14]. In order to investigate *N*-alkylation of amines to dialkylated products we used formaldehyde and ZBPP as a methylating agent and reducing agent. On the basis of the encouraging results obtained on the regioselective reductive amination of carbonyl compounds, it seemed logical to investigate the possibility of extending this method to the preparation of dialkylated products via reductive amination of formaldehyde and amine derivatives. The results appear in Table 2.

We first examined the direct reductive amination of formaldehyde with aniline in THF in the presence of ZBPP, which was then reduced to give *N,N*-dimethylaniline in 96% isolated yield (Scheme 2).

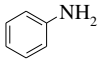
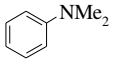
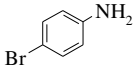
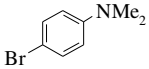
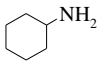
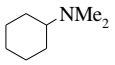
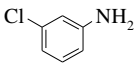
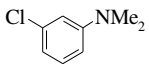
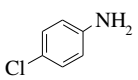
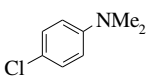
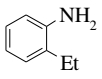
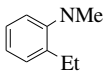
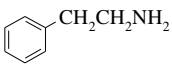
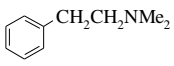
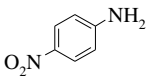
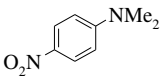
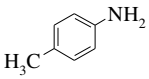
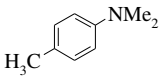
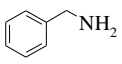
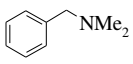
Various amines were subjected to direct reductive alkylation using this procedure (Table 2).



1 **2** **3**

Scheme 2

Table 2.

Entry	**2**	**3**	Yield%
1			96
2			97
3			96
4			98
5			95
6			90
7			90
8			95
9			95
10			96
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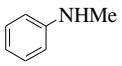
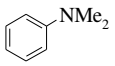
12			97

This reaction has been performed in different organic solvents such as diethyl ether, CH_2Cl_2, $CHCl_3$, MeCN, THF, dioxane, and methanol. The best result obtained when reaction has been performed in THF. In summary, we have established zirconium borohydride–piperazine complex promoted direct reductive *N*-alkylation methodology, which is selective and efficient. High selectivity of the converting primary and secondary amine, mono-*N*-alkylations has been clearly demonstrated. This methodology proves to be a general protocol for the synthesis of the *N,N*-dialkylated amines, offering a wide applications.

General procedure:

Preparation of amines and amine derivatives

A solution of carbonyl compound (2 mmol) and amine (2.2 mmol) in reagent grade MeOH (4 mL), was vigorously stirred for 15 min at room temperature. After this time, zirconium borohydride–piperazine complex (104 mg, 2 mmol, 1.0 equiv) was added and stirred for an additional 1 h. The reaction mixture was washed with water followed by brine solution and then extracted with CH2Cl2, dried over Na2SO4, concentrated under vacuum, and the crude mixture was purified by column chromatography on silica gel (hexane:ethylacetate, 2:1) to afford pure products. When aniline, formaldehyde were used as the amine and carbonyl compound, the procedure was the same, but THF was used as a solvent. All products were identified by comparing their NMR and IR spectra with those of authentic samples.

Acknowledgments

Financial support for this work by the Research Council of Islamic Azad University, Qaemshahr Branch, is gratefully acknowledged.

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