



## Highly chemoselective reductive amination-coupling by one-pot reaction of aldehydes, HMDS and NaBH<sub>4</sub>

Najmedin Azizi<sup>b</sup>, Elham Akbari<sup>a</sup>, Alireza Khejeh Amiri<sup>b</sup>, Mohammad R. Saidi<sup>a,\*</sup>

<sup>a</sup>Department of Chemistry, Sharif University of Technology, PO Box 11465-9516, Tehran 11365, Iran

<sup>b</sup>Chemistry and Chemical Engineering Research Center of Iran, PO Box 14335-186, Tehran, Iran

### ARTICLE INFO

#### Article history:

Received 29 June 2008

Revised 31 August 2008

Accepted 10 September 2008

Available online 13 September 2008

### ABSTRACT

An efficient and highly chemoselective synthesis of symmetrical secondary amines via reductive amination of aldehydes with inexpensive and commercially available HMDS and sodium borohydride in high to quantitative yields is reported.

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Secondary amines and their derivatives exist in many biologically important molecules, and are important intermediates in the synthesis of pharmaceutically active substances, dyes, and fine chemicals.<sup>1</sup> In addition, optically active secondary amines have important applications in organic asymmetric synthesis as chiral auxiliaries,<sup>2</sup> catalysts,<sup>3</sup> and resolving agents.<sup>4</sup> Consequently, synthesis of amines is an active field in medicinal chemistry and modern organic synthesis.

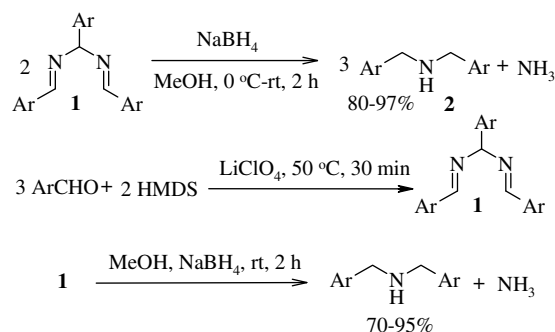
The direct reductive amination of aldehydes and ketones with metal hydride reagents is one of the most useful methods for the synthesis of secondary and tertiary amines, and different methods have been developed to carry out this transformation.<sup>5,6</sup> However, some of these procedures are complicated by the formation of tertiary amines (when secondary amines are required) and by the reduction of carbonyl compounds to alcohols. They often require a large excess of nitrogen and hydrogen sources to achieve good yields. Furthermore, in many of these procedures, primary amines, as well as high pressure or precious metals, are used for reductive amination. Recently, two Letters<sup>7</sup> reported the first reductive amination of aldehydes with ammonia using molecular hydrogen and water-soluble catalysts with excellent results. However, the reactions were performed at high temperature and pressure. A literature survey shows that there are no reports on the selective synthesis of secondary amines via reductive amination of aldehydes with inexpensive and commercially available hexamethyldisilazane, HMDS. Thus the development of a mild direct reductive amination using HMDS as the source of amine is an important research goal.

In continuation of our interest in developing organic transformations, using simple reagents, catalysts and reaction media,<sup>8</sup> herein, we report the first direct reductive amination of aromatic aldehydes with HMDS. In this procedure, HMDS is used as the

source of amine. This completely acid-free reaction was carried out in the presence of catalytic amounts of lithium perchlorate as a simple and readily available catalyst in a one-pot reaction with NaBH<sub>4</sub> in methanol as reducing agent. The general applicability of this method for the direct and indirect synthesis of a wide variety of diverse amines is demonstrated in Scheme 1.

We initially examined indirect reductive amination of *N,N*-bis(phenylmethylidene)phenylmethanediimine<sup>9</sup> (**1**) with sodium borohydride. After examining different procedures, it was determined that slow addition of a NaBH<sub>4</sub> (3 equiv) to a cold solution of **1** (1 equiv) in methanol at 0 °C resulted in formation of secondary amine **2**. The reaction was carried out by mixing compound **1** with sodium borohydride in methanol under normal atmosphere, until TLC showed complete disappearance of diimine **1**.

To explore the generality and scope of this process, the reactions of a range of diimines were studied, and the results are summarized in Table 1. Generally, excellent yields of secondary amines with different aryl groups were obtained under the optimized reaction conditions, including those bearing electron-withdrawing- or electron-donating groups, and the corresponding products were obtained in excellent yields in all cases.<sup>10</sup>

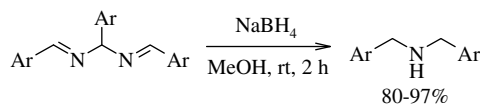


**Scheme 1.** Reductive amination of aromatic aldehydes.

\* Corresponding author. Tel.: +98 2166 165303; fax: +98 2166 012983.

E-mail address: [saidi@sharif.edu](mailto:saidi@sharif.edu) (M. R. Saidi).

**Table 1**  
Synthesis of secondary amine from diimines

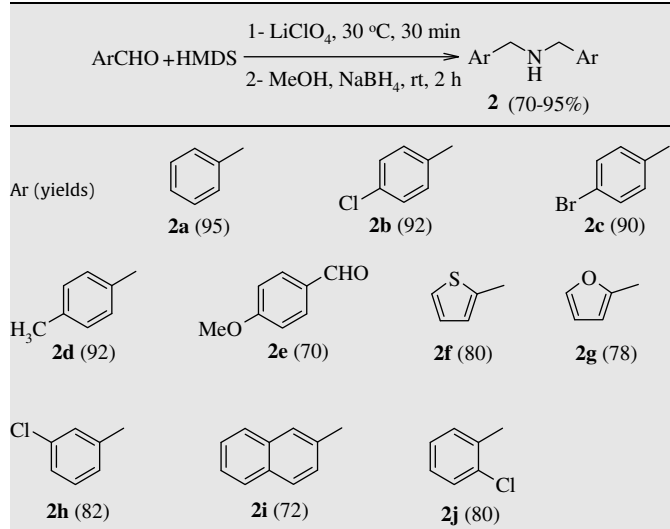


Entry	Aryl group	Products	Yield (%)
1			97
2			97
3			97
4			95
5			80
6			85
7			92
8			80
9			88
10			84

Next, we explored the possibility of developing this new protocol into a one-pot three-component reaction, using an aldehyde, HMDS, and  $\text{NaBH}_4$ , Scheme 1. The reaction of benzaldehyde was chosen as a model, and several sets of reaction conditions were examined. The aldehyde (1.0 equiv) and HMDS (1.3 equiv) were mixed at 50 °C in the presence of solid  $\text{LiClO}_4$  (1.0 equiv) as Lewis acid for 30 min. Then the reaction mixture was cooled to room temperature, and  $\text{NaBH}_4$  in methanol was added. The reaction mixture was stirred at room temperature for 120 min to give the corresponding secondary amines in good to excellent yields. To show the generality and scope of this method, various aromatic aldehydes were successfully transformed into their corresponding secondary amines in high yields. The results are summarized in Table 2. The presence of electron-withdrawing- or electron-donating substituents on the aromatic ring was not effective on the reactivity. Sensitive aldehydes well tolerated under these reaction conditions, which are very mild. Secondary amines formed exclusively without the formation of reduced aldehyde.<sup>11</sup> In most cases, after the normal work-up, the crude products did not need any further purification. However, aliphatic aldehydes, such as isobutyl aldehyde, did not give the desired products.

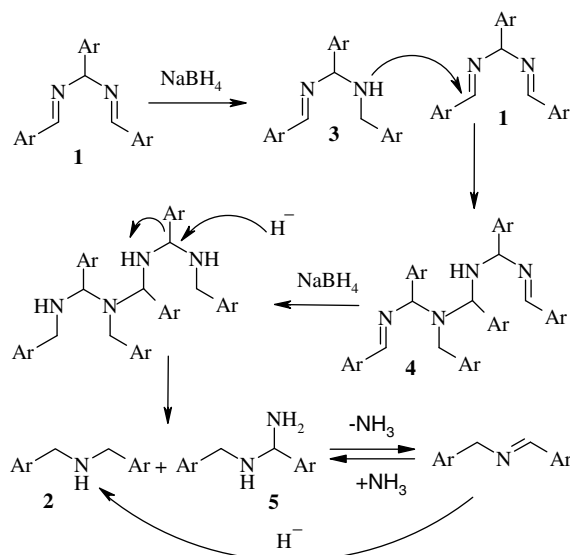
The following mechanistic postulate may be invoked to rationalize the formation of the secondary amines from the aldehyde

**Table 2**  
One-pot synthesis of secondary amines from an aldehyde and HMDS



and HMDS. Initially, the nucleophilic nitrogen in **3**, generated from reduction of the imine, adds to another molecule of diimine **1** to form the intermediate **4**, which can then undergo further reduction and fragmentation to form the secondary amine **2** and intermediate **5**. Although we have no direct evidence for this mechanistic pathway, the detection of  $\text{NH}_3$  as a byproduct and the failure to detect any deuterium in the secondary amines **2**, when the reaction was carried out in  $\text{D}_2\text{O}$  instead of MeOH, may validate the proposed mechanism in Scheme 2. Detection of ammonia was tested qualitatively by HCl gas (formation of  $\text{NH}_4\text{Cl}$  powder) and by pH indicator paper.

In summary, we have described a novel, highly efficient and simple protocol for the synthesis of secondary amines from aldehydes and HMDS in the presence of  $\text{NaBH}_4$ . Furthermore, the procedure offers several advantages including improved yields, cleaner reactions, simple experimental procedure, and use of readily available and inexpensive starting materials, which make it a useful and attractive strategy in multicomponent reactions in combinational chemistry.



**Scheme 2.** Possible mechanism for the formation of secondary amine **2**.

## Acknowledgments

Financial support of this work by the Chemistry and Chemical Research Center of Iran and Sharif University of Technology is gratefully appreciated.

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- General procedure for the one-pot preparation of a secondary amine*: A mixture of aldehyde (2 mmol), HMDS (4 mmol), and LiClO<sub>4</sub> (2 mmol) was heated for 30 min at 50 °C. Then the reaction mixture was cooled to 0 °C, and methanol (5 mL) and NaBH<sub>4</sub> (6 mmol) were added over a period of 5 min. The reaction mixture was warmed to room temperature and stirred for 120 min. Methanol was removed under reduced pressure, and reaction mixture was quenched with a saturated aqueous solution of NaHCO<sub>3</sub> (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> or ether (2 × 5 mL). The combined organic extract was washed with saturated aqueous NaCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude products were purified in some cases by a flash column chromatography on silica gel (petroleum ether and ethyl acetate). All compounds were characterized on the basis of their spectroscopic data (IR, NMR) and by comparison with those reported in the literature. *Caution*: Although we did not have any accident while using lithium perchlorate, it is advisable to dry LiClO<sub>4</sub> in a fume hood using a lab-shield.
- Indirect methods*: *N,N*-Bis(phenylmethylidene)phenyl-methanediamine,<sup>9</sup> **1** (Ar = phenyl), (1 mmol) in MeOH (5 mL) was treated carefully with solid NaBH<sub>4</sub> (3 mmol) over a period of 5 min at 0 °C. The reaction mixture was warmed to room temperature, stirred for 120 min, and quenched with 1 M NaHCO<sub>3</sub>. The product was extracted with ether or CH<sub>2</sub>Cl<sub>2</sub>. The solvent extract was washed with saturated aqueous NaCl and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated to give the crude product. Further, purification was carried out by column chromatography on silica gel eluting with petroleum ether/ethyl acetate, if needed.