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Short Communication

Reductive amination of aldehydes and ketones catalyzed by deep eutectic solvent using sodium borohydride as a reducing agent ☆

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ABSTRACT

Different derivatives of aldehydes/ketones were subjected under reductive amination reaction in the presence of ChCl/Urea as a green and biocompatible catalyst. Sodium borohydride was used as a reducing agent. Secondary amines were achieved with high selectivities and yields.

Using the non-toxic and environmentally friendly reagents is one of the goals of green chemistry. One of the main components of most organic reactions is catalyst. The use of green and non-toxic catalyst is an important issue in a chemical reaction and of particular interested to researchers. Employment of heterogeneous or heterogenized homogeneous catalytic systems, with the ability to recycle and re-use, utilization of organic compounds, organocatalysts, as catalyst instead of toxic and expensive metals and designing the catalytic systems based on environmentally friendly compounds such as ionic liquids are among the attempts that have been made in recent years to bring the catalysts closer to the aims of green chemistry. Recently, deep eutectic solvents (DESs) have emerged. DESs are peers of the conventional ionic liquids (ILs) and as they have low vapor pressure and low flammability [1]. The main difference between these two families of compounds is that ILs are neither biodegradable nor cost-effective but DESs are biodegradable, non-toxic, and inexpensive. DESs are easily prepared by combining two components, a hydrogen acceptor (mainly choline chloride) and a hydrogen donor. The easiest component of this family is the combination of choline chloride and urea (ChCl/Urea) which are very cheap and non-toxic compounds. The occurrence of these compounds dates back to 2003, and so, their ability to serve as catalysts as well as solvents, has received little attention [2].

Due to their presence in natural products, pharmaceutical, and many biologically active molecules, as well as their role as intermediates in the synthesis of fine chemicals and dyes, amine structure has become an important component in chemistry [3]. Despite the development of several synthetic methods for the preparing of these compounds in recent years [4], the direct reductive amination of carbonyl compounds is still the powerful tool for this purpose. Several reducing methods for these conversions such as $NiCl_2$–$NaBH_4$ [5], Ti(Oi-Pr)$_4$–$NaBH_4$ [6], $NaBH_4$–$H_3PW_{12}O_{40}$ [7], $ZnCl_2$–$NaBH_4$ [8], $NaBH_4$–guanidine hydrochloride [9], $Cu(PPh_3)_2BH_4$ [10], pyridine-BH_3 [11], $Zr[(BH_4)_2(Cl)_2(dabco)_2]$ [12], *N*-methylpyrrolidine zinc borohydride (ZBHNMP) [13], $LiClO_4$-(Ppyz) $Zr(BH_4)_2Cl_2$ [14], $[NaBAr^{F}_{4}]$-hydrio-iridium(III) complex [15], $[(HMIm)BF_4]$-$NaBH_4$ [16], $NaBH_3CN$ [17], $NaBH(OAc)_3$ [18], oxo-rhenium complex-$PhSiH_3$ [19], Hantzsch ester [20], $Fe(OTf)_3$-$NaBH_4$ [21], Li-4,4′-di-tert-butylbiphenyl [22], H_2-Pd/C [23], Hantzsch ester-S-benzylisothiouronium chloride [24], PdO/Fe_3O_4-polymethylhydrosiloxane [25], $Ni(OAc)_2$-TMDS [26], nBu_3SnH–SiO_2 [27], Cl_3SiH–DMF [28], Et_3SiH–CF_3CO_2H [29], Bu_3SnH–DMF or HMPA [30], Zn–AcOH [31] and PMHS–BuSn(OCOR)$_3$ [32] have been developed. However, most of them may have one or more of the following drawbacks: the harsh reaction conditions, the generally poor yields, the low chemical selectivities, the use of toxic metals, and the generation of toxic by-products. Given the importance of reductive amination reaction in the synthesis of secondary amines, the development of the green, selective and metal-free catalytic systems is still required for this reaction.

In this study, we are going to report the synthesis of secondary amines by reductive amination of aldehydes/ketones in the presence of DES (ChCl/Urea) as catalyst and $NaBH_4$ as a reducing agent in MeOH. The ChCl/Urea was prepared according to the procedures reported in literature [33] simply by heating mixture of choline chloride and urea with a molar ratio of 1:2 at 80 °C until a homogeneous liquid was formed.

☆ This article is dedicated to memory of Mehdi Bakeri.

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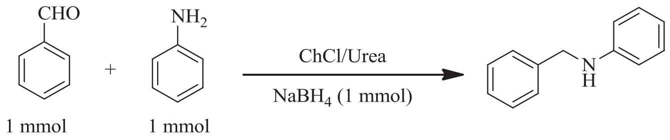


Scheme 1. Synthesis of *N*-benzylaniline in ChCl/Urea.

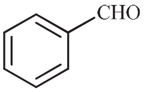
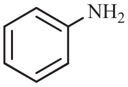
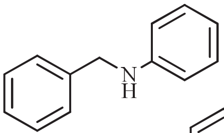
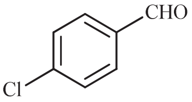
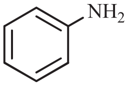
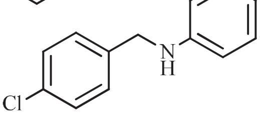
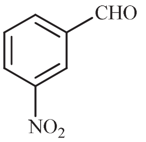
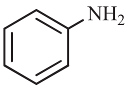
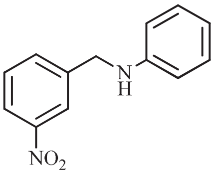
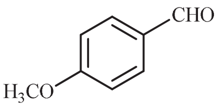
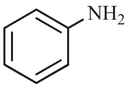
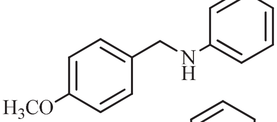
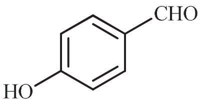
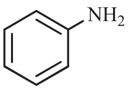
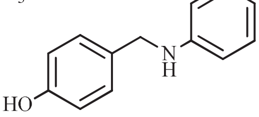
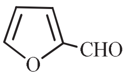
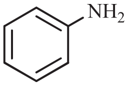
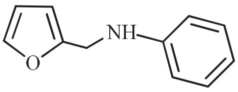
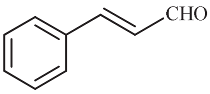
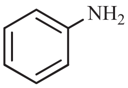
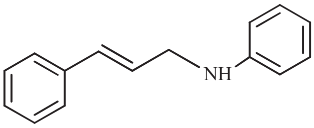
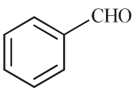
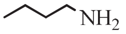
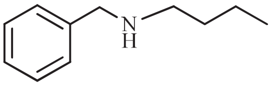
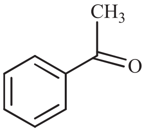
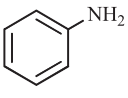
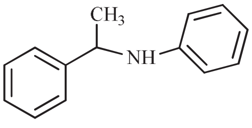
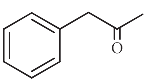
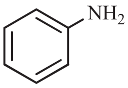
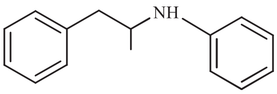
Initially, the synthesis of *N*-benzylaniline in ChCl/Urea (2 ml) as the solvent as well as catalyst and in the presence of $NaBH_4$ as a reducing agent was studied (Scheme 1).

Under these conditions, the product was obtained in only 20% yield. Low yield was probably due to the low solubility of $NaBH_4$ in ChCl/Urea. In another experiment, methanol (2 mL), a suitable solvent for dissolving of $NaBH_4$, was added to the reaction mixture and after 45 min of reaction time, 92% of product was obtained. In MeOH and in the absence of ChCl/Urea, the reaction yield was low, and this indicates that the reaction is catalyzed by which. By reducing the amount of ChCl/Urea to 50 mg, there was no change in the efficiency of reaction. However, the following conditions were used for the diversity of ChCl/Urea catalyzed reductive amination reaction to synthesis of secondary amines: aldehyde/ketone (1 mmol), amine (1 mmol), $NaBH_4$ (1 mmol), MeOH (2 mL), ChCl/Urea (50 mg), and at room temperature.

A variety of products, synthesized by this method [34], are shown in Table 1. As can be seen in this table, different derivatives of benzaldehyde were well coupled with aniline and $NaBH_4$ to give the corresponding product. Other aldehydes such as furfural and cinnamaldehyde had the same situation. The aliphatic amine, butylamine, gave a high yield of

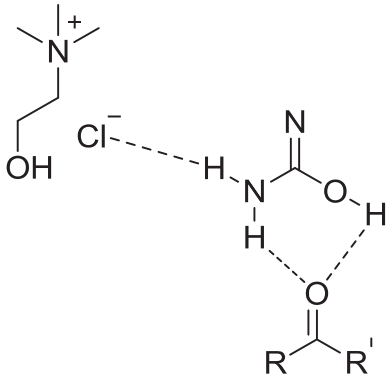
Table 1

ChCl/Urea catalyzed reductive amination of aromatic aldehydes/ketones with amines using $NaBH_4$ as a reducing agent.[a]

Entry	Aldehyde/ketone	Amine	Product	Time (min)	Yield[b] (%)
1				45	98
2				35	95
3				30	96
4				60	92
5				60	94
6				45	95
7				55	90
8				50	90
9				60	89
10				60	90

[a] Reaction conditions: aldehyde/ketone (1 mmol), amine (1 mmol), $NaBH_4$ (1 mmol), and ChCl/Urea (50 mg), at room temperature.

[b] Isolated yield.



Scheme 2. Formation of hydrogen bond between carbonyl compound and ChCl/Urea.

product in the reaction with benzaldehyde and NaBH$_4$ (Table 1, entry 8). By applying these conditions to ketones such as acetophenone and phenylacetone, the corresponding products were obtained in good yields. The results showed that the nature of the applied reagents and the type of substituent on the aromatic ring has no profound influence on the reactivity. In all reactions secondary amines were isolated with high yield in the short reaction time.

According to the previously reported ChCl/Urea catalyzed reactions [35], it seems that this reagent catalyze the reaction through the formation of hydrogen bonds with carbonyl compound and followed with imine results in increased electrophilicity of carbon (Scheme 2).

In conclusion, the reductive amination catalyzed by biodegradable ammonium deep eutectic solvent based on choline chloride and urea as the catalysts provides an efficient and green method for the synthesis of secondary amines. The use of metal-free and non-toxic catalytic system and the formation of products with high yields provide a good and practical alternative to existing methods.

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[34] *Typical procedure for the reductive amination of aldehydes/ketones in the presence of ChCl/Urea*: To a stirred solution of aldehyde or ketone (1 mmol) and amine (1 mmol) in 2 mL of methanol was added ChCl/Urea (50 mg). The mixture was stirred for 5 min and then NaBH$_4$ (1 mmol) was added to it. 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 CH$_2$Cl$_2$ (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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