

Reductive Amination of Aldehydes and Ketones with 2-(Tributylamino)-ethoxyborohydride

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Summary. A new ionic liquid is presented as a medium and reducing agent for the reductive amination of aldehydes and ketones.

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Introduction

An important method of preparing amines is to treat ammonia or an amine with aldehyde or ketone in the presence of a suitable reducing agent. These reducing agents are usually hydrogen and a catalyst [1] or a hydride reducing agent, particularly sodium cyanoborohydride (NaBH_3CN) [2]. Other reported reductive amination reagents include borane-pyridine [3], $\text{Ti}(\text{O}-i\text{-Pr})_4/\text{NaBH}_3\text{CN}$ [4], borohydride exchange resin [5], Zn/AcOH [6], $\text{NaBH}_4/\text{Mg}(\text{ClO}_4)_2$ [7], $\text{NaBH}(\text{OAc})_3$ [8], $\text{Et}_3\text{SiH}/\text{CF}_3\text{COOH}$ [9], $\text{Bu}_3\text{SnH}/\text{DMF}$ [10], $\text{ZnCl}_2/\text{NaBH}_4$ [11], silica gel/ $\text{Zn}(\text{BH}_4)_2$ [12], $\text{ZrCl}_4/\text{NaBH}_4$ [13], $\text{NiCl}_2/\text{NaBH}_4$ [14], and $\text{H}_2\text{SO}_4/\text{NaBH}_4$ [15]. Though some of the above-mentioned reagents provide good yields of amines, they also involve the use of hazardous reagents or organic solvents. Reductive amination with NaBH_4 and Lewis acids requires an excess of the amine (up to five-fold) in order to drive the reaction to completion, since carbonyl compounds themselves are also reduced under the conditions used. Thus, the devel-

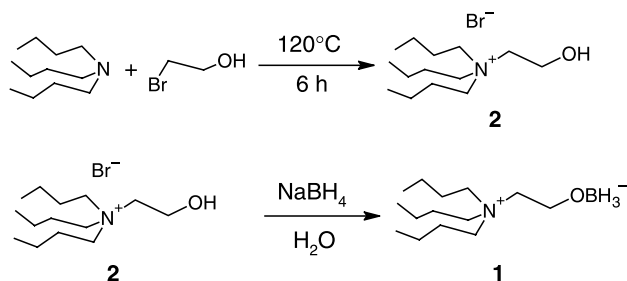
opment of an efficient, safe, and environmentally friendly method to accomplishing the reductive amination is an important challenge.

Room temperature ionic liquids (RTILs) are recognized as green recyclable alternatives to the traditional volatile organic solvents because of their unique chemical and physical properties [16]. They have emerged as alternative reaction media for the immobilization of transition metal based catalysts, Lewis acids, and enzymes [17]. They are referred to as “designer solvents” as their properties such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity, and density can be altered by changing the cation and the counter anions. Their high polarity and ability to solubilize both organic and inorganic compounds can result in enhanced reaction rates and can provide higher selectivity compared to conventional solvents. As results of their green credentials and potential to enhance rates and selectivity ionic liquids are finding increasing applications in organic synthesis [18].

Results and Discussion

However, we discovered that a task-specific ionic liquid, 2-(tributylamino)ethoxyborohydride (**1**), efficiently promotes the reductive amination of aldehydes and ketones with amines without requiring any other catalyst and solvent. 2-Hydroxy-*N,N,N*-tributylethanaminium bromide (Scheme 1, **1**) was

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Scheme 1

obtained from reaction of tributylamine and 2-bromoethanol at 120°C for 6 h. 2-(Tributylamino)ethoxyborohydride (Scheme 1, **1**) was prepared from **2** by reaction with sodium borohydride in water. This reagent is soluble in chloroform, dichloromethane, acetone, and ethanol. It is insoluble in water, diethyl ether, and *n*-hexane. The resulting ionic liquid is very stable at room temperature and could be stored as a bench-top reagent for months without appreciable change in its reactivity.

In a typical procedure the aldehyde or ketone and amine are mixed with the ionic liquid at room temperature for the time specified in Table 1. At the end of the reaction, ether was added. The organic layer was separated, washed with water, dried with Na₂SO₄, and filtered. The filtrate was evaporated to leave the crude product. It was purified on a short column of silica gel. The bromide salt of ionic liquid **2** was

generated by mixing the separated ionic liquid with 5% HBr for 20 min, decanting, and heating at 80°C under vacuum for 30 min.

The reaction condition is very mild and can tolerate the presence of acid sensitive functional groups such as ketals. For example, the reductive amination of cyclohexanedione monoethylene ketal with primary and secondary amines afforded good isolated yields of the corresponding amines (Table 1, entries 11, 12).

In conclusion, the present procedure using an easily accessible and inexpensive ionic liquid as reagent for the reductive amination of amines with aldehydes or ketones provides a novel protocol for the synthesis of amines. This procedure offers marked improvements with regard to operational simplicity, isolated yields of products, considerably faster reaction times (20–30 min), and mild and neutral conditions.

Experimental

2-Hydroxy-*N,N,N*-tributylethanaminium bromide (**2**, C₁₄H₃₂BrNO)

In a round bottomed 50 cm³ flask equipped with a condenser and magnetic stirrer, 9.25 g tributylamine (0.05 mol) and 6.25 g 2-bromoethanol (0.05 mol) were mixed at 120°C for 6 h. The reaction mixture was washed with 2 × 30 cm³ diethyl ether. After drying in vacuum for 30 min, 10.8 g (70%) of product were isolated as a pure oily liquid. ¹H NMR (90 MHz, DMSO-

Table 1. Reductive amination of aldehydes and ketones

Entry	Aldehyde/ketone	Amine	Time min	Yield ^a %	Ref. ^b
1	benzaldehyde	aniline	30	92	[20]
2	benzaldehyde	benzylamine	20	93	[21]
3	benzaldehyde	<i>o</i> -toluidine	30	85	[22]
4	4-chlorobenzaldehyde	aniline	30	93	[23]
5	4-nitrobenzaldehyde	benzylamine	20	93	[24]
6	3-chlorobenzaldehyde	<i>o</i> -toluidine	30	83	[25]
7	propanal	aniline	20	91	[26]
8	acetophenone	aniline	90	75	[27]
9	cyclohexanone	aniline	45	85	[28]
10	cyclohexanone	morpholine	45	88	[29]
11	cyclohexanedionemonoethylene ketal	benzylamine	45	85	[8]
12	cyclohexanedionemonoethylene ketal	piperidine	60	87	[8]

^a Comparison of spectral data (IR, NMR) and thin layer chromatography with an authentic sample also confirmed structure and purity of the reported amines. ^b References for products

δ_6): δ = 6.1 (s, 1H), 3.8–4.1 (t, 2H), 3.1–3.7 (m, 8H), 1.2–1.9 (m, 12H), 0.86–1.1 (br, d, 9H) ppm.

2-(Tributylamino)ethoxyborohydride (1, C₁₄H₃₄BNO)

In a round bottomed 100 cm³ flask, 15.5 g compound **2** (0.05 mol), 40 cm³ H₂O, and 2.28 g sodium borohydride (0.06 mol) were mixed at room temperature. The mixture was stirred rapidly for 2 min and extracted with 3 × 50 cm³ CH₂Cl₂. The organic layer was dried (Na₂SO₄) and the solvent was evaporated in reduced pressure. After drying in vacuum for 2 h, 11.3 g (93%) **1** were obtained as a colorless oily liquid. ¹H NMR (90 MHz, DMSO-d₆): δ = 3.4–4.0 (t, 2H), 2.9–3.4 (m, 8H), 1.2–1.9 (m, 12H), 0.8–1.1 (br. d, 9H) ppm; Anal. calcd (%) for C₁₄H₃₄BNO (234.24): C, 69.13; N, 5.758; B, 4.444; H_{total}, 14.08; H_{active}, 1.243; O, 6.577; found: C, 68.01; N, 6.27; B, 4.41; H_{total}, 13.88; H_{active}, 1.22; B/H_{active} 1/3. Active hydrogen was determined by a standard method [19] and nitrogen by the *Dumas* method.

Reductive Amination of Benzaldehyde and Aniline, Typical Procedure

Benzaldehyde (1.06 g, 0.01 mol) and aniline (0.93 g, 0.01 mol) are mixed in 5.13 g (0.015 mol) ionic liquid **1**, at room temperature for 30 min. At the end of the reaction, 20 cm³ diethyl ether were added. The organic layer was separated, washed with water, dried (Na₂SO₄), and filtered. The filtrate was evaporated to leave the product. Crystallization from ethanol afforded 1.68 g (62%) benzylaniline. Mp 36.5–37.5°C (Ref. [20] 36–37.2°C).

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