

Reductive amination of carbonyl compounds using NaBH_4 in a Brønsted acidic ionic liquid

P. Srinivasa Reddy, Sanjit Kanjilal, S. Sunitha and Rachapudi B. N. Prasad*

Lipid Science and Technology Division, Indian Institute of Chemical Technology, Uppal Road, Hyderabad 500 007, India

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Abstract—Reductive amination of carbonyl compounds using sodium borohydride is conducted in the Brønsted acidic ionic liquid, 1-methyl imidazolium tetrafluoroborate $[(\text{HMIm})][\text{BF}_4]$. The ionic liquid plays the dual role of solvent as well as catalyst for efficient conversion of aldehydes and ketones to amines in excellent yields without the formation of side products.

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1. Introduction

Functionalized amines are important organic intermediates and have wide applications in synthetic and combinatorial chemistry.¹ Reductive amination of aldehydes and ketones is a convenient method for the synthesis of functionalized amines. There are several reagents and catalysts reported in the literature for reductive amination, following direct as well as indirect approaches.^{1–7} Most are associated with expensive and flammable reagents, utilization of complex catalysts and low product yield even though conversion of the aldehyde is high in some cases.^{7–9} In many instances, a large excess of amine was used to improve the yield and also to prevent reduction of the aldehydes to alcohols.⁹

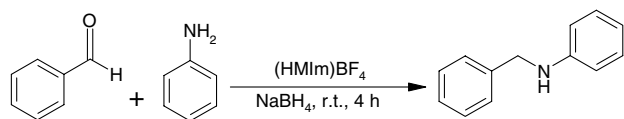
In an effort to develop a mild and efficient procedure for reductive amination of carbonyl compounds, we focused our attention on ionic liquids (IL). The potential of IL as green solvents for several chemical and biochemical transformations has already been established.¹⁰ They are non-volatile, have excellent chemical and thermal solubility and can solubilize a variety of substrates. Imao et al. first reported the use of the IL, 1-butyl-3-methyl imidazolium tetrafluoroborate $[(\text{BMIm})\text{BF}_4]$ as reaction medium for the direct reductive amination

(DRA) of carbonyl compounds with hydrogen catalyzed by an iridium complex.³ High temperatures, long reaction times and low yields were the drawbacks associated with this method. A report by Nagaiah et al. described a combination of IL and water as solvent and sodium borohydride as the reducing agent for the one pot reductive amination of aldehydes and ketones.¹¹ However, low yields and the requirement of a large excess of IL (10 equiv) were the disadvantages. Moreover, there was no mention of the possibility of reduction of aldehydes to alcohols, which can be a major side reaction in DRA. NaBH_4 has been utilized with various Brønsted acids to facilitate initial formation of the imine leading to successful reductive amination.⁷ Most of these Brønsted acidic catalysts are toxic, corrosive and difficult to separate from the reaction mixture. Attempts have been made to substitute these acids with non-corrosive environmentally friendly solid acid catalysts to carry out reductive amination alongside the reducing agent.⁷ There is no report available in the literature for the generation of an imine in an IL, wherein the Brønsted acidic nature of the IL is responsible for imine formation. In the present work, we report the use of the Brønsted acidic IL, 1-methylimidazolium tetrafluoroborate $[(\text{HMIm})\text{BF}_4]$ as a recyclable medium for efficient conversion of carbonyl compounds to imines followed by reduction using NaBH_4 for the synthesis of functionalized amines.

1-Methylimidazolium tetrafluoroborate has been exploited as an efficient Brønsted acid promoter IL in various organic transformations.^{12–14} The preparation of this IL is simple compared to other imidazolium

Keywords: Brønsted acidic ionic liquid; Carbonyl compound; Reductive amination; Sodium borohydride.

* Corresponding author. Tel.: +91 40 27193179; fax: +91 40 27193370; e-mail: rbnprasad@iict.res.in



Scheme 1.

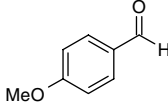
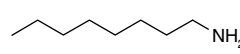
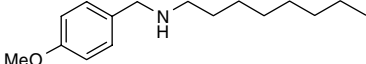
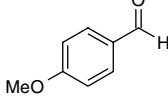

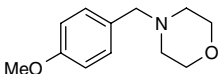
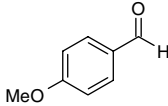

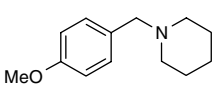
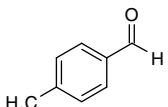
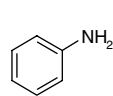
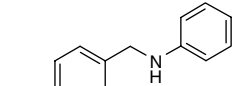
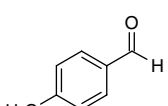
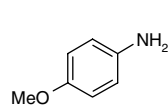
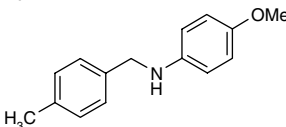
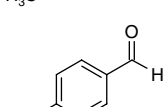
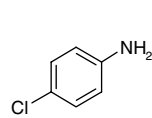
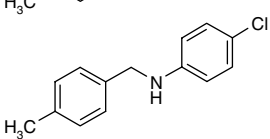
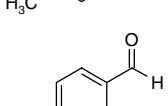
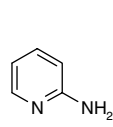
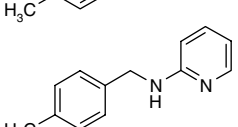
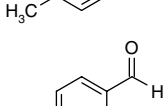
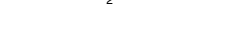
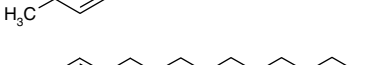
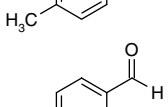

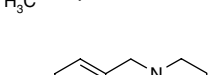
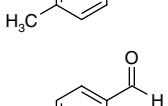

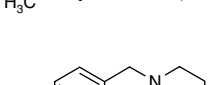
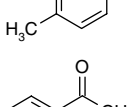
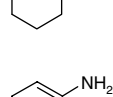
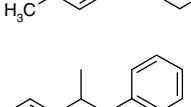
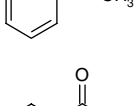
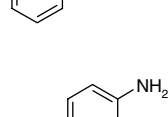
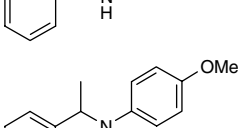
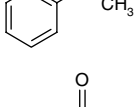
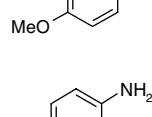
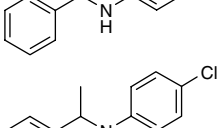
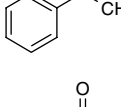
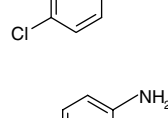
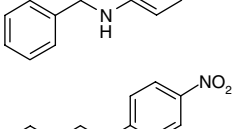
based ILs. The DRA of benzaldehyde and aniline was conducted initially to optimize the reaction conditions. Aniline (1.0 mmol) and benzaldehyde (1.2 mmol) were taken in (HMIm)BF₄ (1.0 mmol) followed by the addi-

tion of sodium borohydride (1.5 mmol) and the reaction mixture was stirred at 30 °C (Scheme 1). The reaction progress was monitored by GC–MS. Considerable formation of benzyl alcohol was observed within 30 min due to the almost simultaneous addition of the reducing agent. The final yield of *N*-benzylaniline was 70%. It was then decided to monitor the conversion of aldehydes to imines initially in (HMIm)BF₄ without the addition of NaBH₄. It was observed that the conversion of benzaldehyde was >98% complete within 30 min. After 30 min, sodium borohydride was added to achieve a 94% yield of *N*-benzylaniline within 4 h.

Table 1. Reductive amination of carbonyl compounds using NaBH₄ in (HMIm)BF₄

Entry	Aldehyde	Amine	Product	Time ^a (h)	Isolated yield (%)
1				4 (30)	94
2				2 (45)	94
3				4 (60)	93
4				3 (90)	68
5				4 (60)	70
6				3 (30)	92
7				4 (60)	75
8				4 (60)	90
9				2 (60)	96
10				2 (60)	97
11				6 (60)	72

Table 1 (continued)

Entry	Aldehyde	Amine	Product	Time ^a (h)	Isolated yield (%)
12				3 (60)	85
13				2 (60)	95
14				4 (60)	87
15				3 (60)	98
16				4 (60)	96
17				4 (60)	96
18				4 (60)	70
19				4 (60)	85
20				3 (60)	93
21				4 (60)	86
22				6 (60)	82
23				4 (60)	92
24				4 (60)	92
25				3 (60)	84

^a Value in parenthesis indicates the time (in min) of imine formation.

Based on this result, a series of reactions were conducted by reacting benzaldehyde, anisaldehyde and tolualdehyde with a series of amines: aromatic amines (primary and secondary), aliphatic amines (cyclic and acyclic) and aromatic amines with different substituents. For each type of substrate, the time for maximum formation of imines was monitored and NaBH₄ was added after the optimized time, see Table 1. All the substrates reacted smoothly to afford the corresponding amines in good to excellent yields. The methodology was also extended for the reductive amination of ketones (Table 1; entries 22–24). The reusability of an IL is always an advantage for the commercial viability of the process. The recovered ionic liquid was recycled for four consecutive runs for the reductive amination of benzaldehyde over a period of 4 h affording 93%, 85%, 83% and 76% yields of *N*-benzylaniline.

In conclusion, an efficient protocol for reductive amination of carbonyl compounds using a variety of amines in a Brønsted acidic IL (HMIm)BF₄ has been reported. The reported protocol is mild, efficient and user and environmentally friendly. An important aspect of this protocol is the selectivity of the reducing agent towards imines without the formation of any side product.

2. Experimental

The IL, (HMIm)BF₄ was prepared following the reported procedure.¹²

2.1. General procedure for reductive amination

Amine (1.0 mmol) and carbonyl compound (1.2 mmol) were taken in (HMIm)BF₄ (0.17 g; 1.0 mmol) and the reaction mixture was stirred at 30 °C for 30–60 min followed by the addition of sodium borohydride (0.057 g; 1.5 mmol). After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried over anhydrous Na₂SO₄ and evaporated. The crude was purified by silica gel column chromatography eluting with 2–10% EtOAc in hexane. The IL was solubilized in acetonitrile and filtered to separate sodium borohydride. The organic layer was evaporated and the IL dried under vacuum for further reuse. All products were characterized by IR, NMR, mass spectrometry and elemental analysis and compared with those reported in the literature.^{1–9,11,15,16} All new compounds gave satisfactory spectroscopic data in accordance with their structures.

2.1.1. 2-(*N*-Benzyl)aminopyridine (entry 4). Yellow oil; IR (neat): ν 3377 (NH) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.52 (2H, *J* = 6.04 Hz, d), 6.50 (1H, *J* = 8.3 Hz, d), 6.78–6.90 (1H, br s), 6.55 (1H, *J* = 6.04 Hz, t), 7.21–7.28 (5H, m), 7.50 (1H, *J* = 6.79 Hz, t), 8.20 (1H, *J* = 5.28 Hz, d); ¹³C NMR (75 MHz, CDCl₃): δ 46.41, 106.92, 113.17, 127.37,

127.48, 127.54, 128.75, 128.78, 137.67, 139.31, 148.13, 158.79; Anal. Calcd for C₁₂H₁₂N₂: C, 78.23; H, 6.57, N, 15.21. Found: C, 78.69; H, 6.31, N, 15.42; EI-mass: *m/z* 184 [M]⁺, 106 [M–78]⁺, 91, 79.

2.1.2. 4-Chlorophenyl-4-methoxybenzylamine (entry 10). Yellow solid; mp: 78–81 °C; IR (KBr): ν 3409 (NH), 1166 (OCH₃) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.72 (3H, s), 3.81–3.91 (1H, br s), 4.18 (2H, s), 6.5 (2H, *J* = 9.06 Hz, d), 6.80 (2H, *J* = 9.06 Hz, d), 7.0 (2H, *J* = 9.06 Hz, d), 7.22 (2H, *J* = 8.30 Hz, d); ¹³C NMR (75 MHz, CDCl₃): δ 47.75, 55.54, 113.55, 113.99, 114.34, 114.53, 121.87, 129.05, 129.43, 130.60, 130.94, 132.00, 146.77, 158.95; Anal. Calcd for C₁₄H₁₄ClNO: C, 67.88; H, 5.70; N, 5.65. Found: C, 68.75; H, 5.39; N, 5.64; EI-mass: *m/z* 247 [M]⁺, 121 [M–126]⁺, 91, 77.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.094.

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