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ABSTRACT

Nicotine-based task specific ionic liquid has been used as a carrier of boron hydride instead of pyridine borane and other related reagents. Borohydride complex of Nicotine-IL has been used for reductive amination of variety of carbonyls and amines with encouraging results. The same reagent has the potential of other applications. The reactions were conducted under pyridine free odorless conditions. The improved results were obtained in terms of enhanced yields, with minimal work up.

INTRODUCTION

Borane-Lewis base complexes such as borane-tetrahydrofuran (THF-BH_3) and borane-dimethyl sulfide (DMS-BH_3) have different stabilities and chemical reactivities as reducing agents, hydroborating agents.[1] and relatively safer to handle. The THF-BH_3 on reaction with amines forms complex which is indefinitely stable when stored under nitrogen at room temperature DMS-BH_3 is more stable than THF-BH_3 but has an unpleasant odor. They offer highly useful applications in the reduction of various functional groups.[2] such as direct reduction of carboxylic acids to alcohols (DMS-BH_3) and amides to amines (THF-BH_3).[3] Hydroboration and oxidation of alkenes and alkynes.[4] The pyridine-boron complex is more stable than other complexes of boron (Figure 1). When Pyridine is added to a THF solution of borane-THF, the result is *N*-complexation of pyridine with boron hydride.

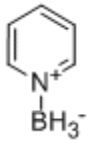


Fig. 1

The pyridine imparts considerable stability to boron hydride thus making it easier for handling, application and storage. The pyridine-borane is a valuable reagent for the reduction of selected functional groups.[5] One of the very useful applications of amine-boranes is the reduction of imines and oximes to corresponding amino compounds called reductive amination.[6] In case of polyfunctional compound, the imine group is reduced by pyridine-borane to an amine, while leaving a wide variety of other functionalities of the compound unaffected.[7] The sterically hindered aromatic ketones can be aminated quite easily with pyridine-borane. The reduction proceeds rapidly when conducted in glacial acetic acid to giving secondary amines in excellent yields[8] and oximes can be reduced presence of CbZ and BOC protecting groups.[9]

In this paper we focus on the use of borane complex reagents as reagents for reductive amination Different kinds of hydroborating reagents have been designed and further modified to improve their efficiency and scope for these reactions. Reductive amination is one classical organic reaction which is still used unabated and finds its application in various organic transformations.[10] The boron reagents have been shown be superior to other inorganic reagents as reducing agents.[11] However each of these reagents possess merits and demerits and the major factor among them is toxicity, high cost and tedious working procedure. In this context some ease of handling and relatively cleaner protocol for reductive aminations has been achieved by using pyridine complexes pyr-BH_3 and methanolic pyr-BH_3.[12] However Pyridine-borane has this reagent is quite unstable to heat and may explode, therefore, extreme care must be used if this reagent is handled in large quantities. To avert such threats some modifications have been suggested by Sato *et al.*[13] They used thermally stable 2-picoline-borane for the efficient reductive amination of variety of amines and carbonyls yet these reagents are air and moist sensitive. The disadvantages of various complexes stir more efforts for devising further efficient alternatives which must be devoid of all of such demerits. The emergence of ionic liquids especially task specific or functional ionic liquids have added new dimensions to the science of

catalysis in general and organocatalysis is particular. Task specific ionic liquids contain an organocatalyst attached to imidazolium ring through few carbon spacings. In this way different chemists have developed the ionic liquid versions of many useful organocatalysed reactions.[14] This methodology enables to perform routine tedious and cumbersome organocatalysis under clean, and efficient ionic liquid conditions which lead to procedural convenience, rapid reaction rates, better yields of products, easy recovery of products and recycling of ionic liquid-based catalysts and thus making the reuse of catalyst possible. Hullio *et al* has introduced a novel concept in the field of functional ionic liquids and reported a first kind of functional ionic liquid which was not task specific rather multipurpose in its applications and named it multipurpose DMF-like ionic liquid.[15] This multipurpose ionic liquid is first example of functional ionic liquids and has been used to accomplished variety of diverse type of organic transformations.[16,17] Apart from this our group is working on other functional ionic liquids which can be turned into multipurpose ionic liquids by exploring their scope of applications. One of such example is nicotine-based functional ionic liquids introduced by Handy *et al* [18] which was shown as as a green alternative reagent for toxic pyridine for acylation of different types of alcohols and the results obtained were highly encouraging. Our group decided to check the potential of same nicotine-based ionic liquid for other pyridine-dependent reactions like pyridine-catalyzed Huisgen cycloaddition and other reactions catalyzed by reagents containing nucleophillic nitrogen such as Morita-Baylis-Hillman Reaction.[19] The nicotine-based functional ionic liquid has shown encouraging results and motivated by such findings we intend to find more applications we are reporting the ionic liquid version of pyridine-borane complex by preparing the complex of borane with pyridine unit of nicotine-based ionic liquid and it has been investigated for its potential as suitable substitute of pyridine-borane complex for reductive amination. The use of ionic liquid nicotine-borane eliminates the problems associated with pyridine-borane such as heat instability, air and water sensitivity. Ncotine-IL-BH_3 (Figure 2) has been found to be reasonable ionic liquid which air and water resistant and has been found to be more stable to heat than pyr-BH_3 and pic-BH_3. Ncotine-IL-BH_3 can be recyclable for any number of periods without noticeable decomposition.

EXPERIMENTAL

Preparation of Nicotine-based IL boron-complex reagent

The required nicotine-based ionic liquid (Figure 2) was prepared according to the procedure employed by Handy *et al.* [20]

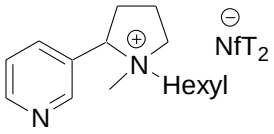
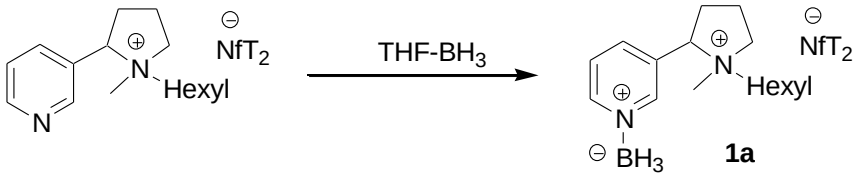


Fig. 2

The major and crucial step in synthesis was for selective alkylation of the pyrrolidine moiety leaving nitrogen of pyridine active as reported by Shibagaki. [21] The complete re-synthesis of the nicotine based task specific ionic liquid has been achieved by our groups and has been reported in previous papers and thus there is no need to repeat here. After the preparation of desired Nicotine-based ionic liquid according to known procedure, we proceeded to prepare its unreported borohydride complex (Scheme 1).



Scheme-1

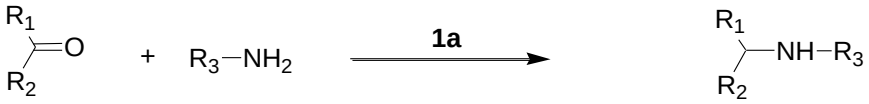
The Ncotine-IL-BH_3 **1a** was prepared by boronation of nicotine-based ionic liquid treating the nicotine based ionic liquid with tetrahydrofuran complex of hydroborane (THF-BH_3). The stirring of Nicotine-IL with (THF-BH_3) at – 25 ^oC in THF for 30-40 minutes yielded quantitative amounts of **1a**.

General procedure for reductive amination under ionic liquid protocol

Benzaldehyde (**1**) (200 mg, 1.88 mmol) and aniline (**2**) (176 mg, 1.88 mmol) in MeOH (5.5 mL) was added Nicotine-based-IL-BH_3 (50 mg, 1.88 mmol) and the reaction mixture was stirred for 3 h at room temperature. The progress of reactions was monitored by thin layer chromatography (TLC). Upon completion of the reaction, the product was simply extracted with diethyl ether (3 × 5 mL). The organic extract was then combined and concentrated under reduced pressure to give the desired products in high purity. After isolation of the product, methanol solvent was removed under vacuum and the residue the remainder of the nicotine-based ionic liquid was freeze dried to remove water. Then recovered nicotine-based ionic liquid was again converted into its boron hydride complex and reused for next run and every reaction was performed under identical reaction conditions.

RESULTS AND DISCUSSIONS

The Borohydride complex of ionic liquid thus formed was tested for its potential for reductive amination (Scheme 2). Variety of aldehydes and ketones were treated with different primary amines leading to successful preparation of corresponding *N*-alkylation products.



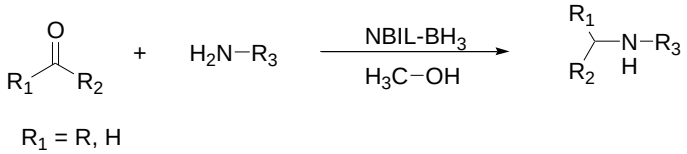
Scheme-2

After successful formation of our Nicotine-IL-borane, we proceeded to investigate its potential for reductive amination of variety of carbonyls compounds and amines. We initially focused to find the optimal conditions for effective reductive power of our ionic liquid. In order to find a workable system for the reductive amination, we started with equimolar amounts of amine, carbonyl compounds, and treated the resulting mixture with using nicotine-based borane (NBIL-BH_3) as a reducing agent in MeOH. First, we carried out the reductive amination of cyclohexanone (200 mg, 2.04 mmol) with aniline (190 mg, 2.04 mmol) using NBIL-BH_3 (50 mg, 2.04 mmol) in MeOH (5 mL) at room temperature for 1 h. the reaction occurred in the homogeneous phase, and on completion of reaction the product cyclohexylphenylamine (334 mg, 94%) was simply extracted with diethyl ether in high yield of 97% (Table 1, entry 1). Several carbonyl compounds and amines reacted in this way and the results are presented in Table 1.

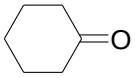
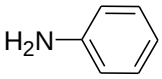
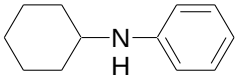
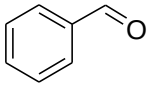
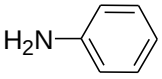
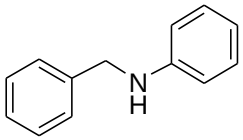
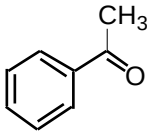
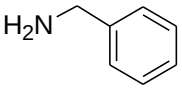
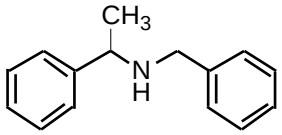
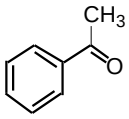
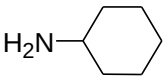
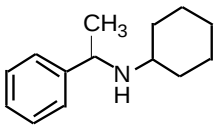
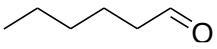
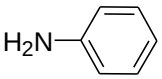
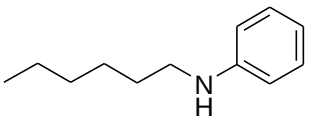
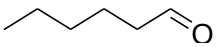
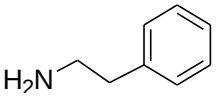
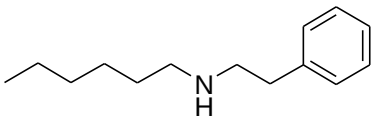
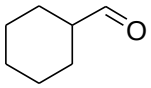
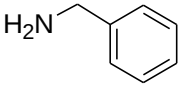
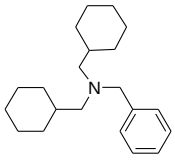
Widely varying structural variants of both carbonyls and amines were tested to gauze the scope of novel reductive system. Apart from the quick and effective formation of *N*-alkylated products, easy recovery of the product and minimized work up were additional advantages. The tabulated data (Table 1) indicates that aliphatic aldehydes and primary amine were highly response to the novel conditions and furnished excellent amount of the products. However aromatic ketones were poor substrates for reductive amination protocols. The reductive amination of acetophenone with benzylamine is under different protocols is often reported to be quite dismal, however under this procedure, yields of desired product was found to be much better (Table 1, entry 3). In previous reported procedure, the acetophenone did not exhibit the reductive amination from the reactions of aliphatic amines using pyr-BH_3 and acetic acid. However, it did undergo reductive amination using pic-BH_3 as a reducing agent, the corresponding amines in good yields after taking very long time of 72 h. The same acetophenone was found to undergo quantitative amination with cyclohexyl amine in just 15 h. (Table 1, entry 4).

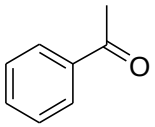
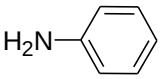
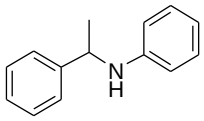
Under these conditions it was possible to reductively aminate electron rich aldehydes with deactivated heterocyclic amines, such as 2-aminopyridine and 2-amino-5-bromopyridine (Table 1, entries 13 and 14). Likewise, the reaction proceeded in good yields with sterically hindered 2-aminotoluene (Table 1, entry 15) or with deactivated 4-nitroaniline (Table 1, entry 16). Both ester and amide functionalities remained safe under the new reaction conditions (Table 1, entries 17–18) giving 72–76% yields. For most ketones, reactions were improved by the addition of AcOH. However, for hexanal, a better result was obtained without addition of AcOH (Table 1, entry 5-6). *N*-benzyl-2-amino pentane was obtained from 2-aminopentane and benzaldehyde in a one-pot operation in 84% yield (Table 1, entry 9).

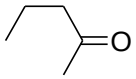
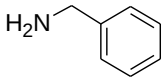
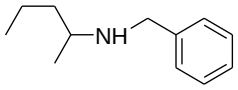
Table 1: Reductive Amination using ionic liquid-based nicotine-borane (NBIL-BH_3) complex as reducing agent

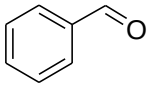
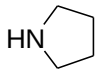
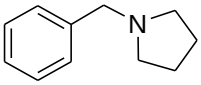


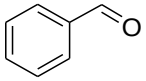
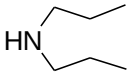
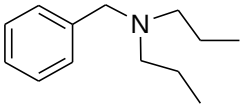
R_1 = R, H

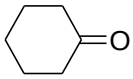
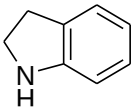
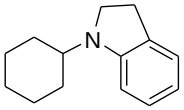
Entry	Carbonyl	Amine	Product	Yield%
1				97
2				90
3				65
4				65
5				86
6				67
7	2x 			92

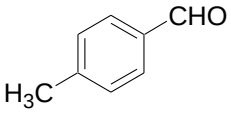
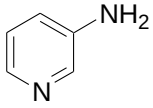
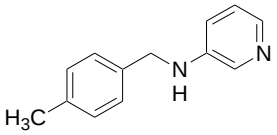
8    78

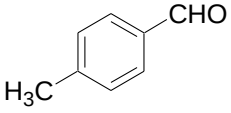
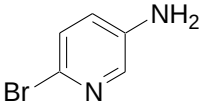
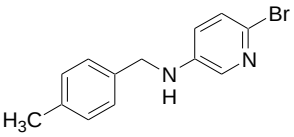
9    84

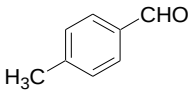
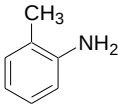
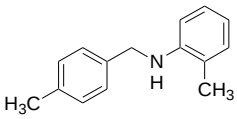
10    87

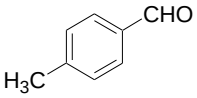
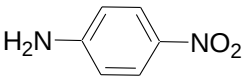
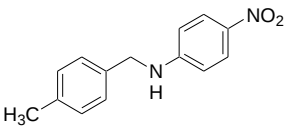
11    79

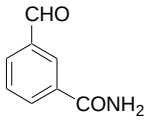
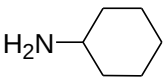
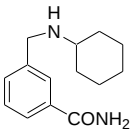
12    81

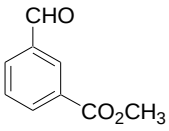
13    87

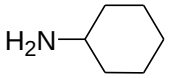
14    91

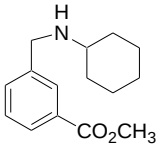
15    57

16    60

17    72







18 76

Yield(%) (GC analysis)

Ionic liquid being hydrophobic in nature provides anhydrous conditions which are necessary not only for stability of hydroboron complex but for the reductive amination as well. This is because strict anhydrous conditions are often found to be favorable to generate imines or iminium ions, which are subsequently reduced by the reducing agents. Use of present methodology has provided the easier, facile and convenience operational procedure. In case of reported ordinary situations, the reducing agents are used along with drying agents like molecular sieves or anhydrous $MgSO_4$ or Na_2SO_4[20] or titanium(IV) isopropoxide have been for safe formation of water-sensitive imine or iminium ions which are subsequently reducted to yield secondary and tertiary amines. Since it is operationally troublesome to maintain the anhydrous conditions during a reaction our water phobic ionic liquid will be a milestone in achieving the greater convenience for reductive amination. The reductive amination in ionic liquid conditions has offer clean protocol because it eliminates the use of many organic solvents which are ecologically harmful. Ionic liquid conditions for reductive amination seems to hold promise to be a highly useful technique, especially for industry. The major merit is minimal work up isolation of clean product by simple extraction thus avoiding which use ecologically harmful solvents and toxic reagents.

Like pyridine, picoline and other related nitrogen complexes of boron hydride, the nicotine-based ionic liquid complex of boron hydride (NBIL-BH_3), the boron hydride is consumed during the reductive amination. Therefore re-complexation with borohydride is required for each reaction. Our recycling study suggest that nicotine based ionic liquids can be recycled more than dozen times without any significant loss of the activity of the reagent. The recycling studies were done with equimolar amounts of benzaldehyde and aniline; the results obtained are shown in (Table 2). Recycling from one to six gave invariably same yields under same condition. Detectable loss in activity can be seen from recycling number ten and onwards.

Table 2: The recycling profile of ionic liquid-based nicotine-borane (NBIL-BH_3) complex

Number of Recyclings	1	2	3	4	5	6	7	8	9	10	11	12
Yield(%) (GC analysis)	97	97	96	96	96	95	95	94	92	89	85	82

CONCLUSION

Nicotine-based ionic liquid has been developed as carrier of boron hydride (BH_3). This novel reagent found to have many advantages over its other competent Boron hydride carriers like pyridine, picoline and DMAP. The proposed reagent is a thermally stable free of any toxic aspects. It has facilitated the one pot reductive amination with more efficiency than other reagents. Ionic liquid aspects of the reagent favor the easy recovery of product by eliminating the cumbersome work up. In summary, we have developed an expeditious, easy-to-handle and environmentally friendly approach to the synthesis of a variety of amines through a three-component one-pot reaction of carbonyl compounds, amines.

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