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Asymmetric Reductive Amination of Carbonyl Compounds by Using *N*,*N*,*N*-Tributylpropanaminium Based Novel Chiral Ionic Liquid

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ABSTRACT

Asymmetric reductive amination of carbonyl compounds was carried out using a novel class of aliphatic quarternary ammonium based chiral ionic liquid. S-(+)-2,3-dihydroxy-*N*,*N*,*N*-tributylpropanaminum bromide chiral ionic liquid has been synthesized, characterized and used for asymmetric reductive amination of carbonyl compounds in the presence of sodium borohydride. These preliminary results are encouraging and advocate dual role of novel ionic liquid as a medium and reducing agent for proficient conversion of ketones to amines, however, reductive amination reaction needs to be established for other substituents.

Keywords: Ionic Liquid; Asymmetric Reductive Amination; Chiral; Carbonyl Compounds

1. Introduction

Functionalized chiral amines are considered as building blocks for the construction of pharmaceuticals [1,2] and agrochemicals. Asymmetric reductive amination of carbonyl compounds [3] and direct asymmetric reductive amination [4] are convenient methods to synthesize chiral amines. The reducing agents in these methods are usually hydrogen and a catalyst [5,6] or hydride as a reducing a agent which includes $NaBH_3CN$ [7], borohydride exchange resin [8], silica gel/Zn (BH_4) [9], Et_3SiH/CF_3COOH [10] and $H_2SO_4/NaBH_4$ [11]. Most of these reagents deliver good yields of amines; however, their hazardous nature creates complications. There is a chance of alcohol formation in reductive amination reaction using $NaBH_4$ in the presence of Lewis acid. To achieve the minimum use of the hazardous reagents and improved selectivity of reductive amination reaction, there has been emphasis on green chemistry. Green chemistry implies the use of environmental caring chemicals and avoids the use of halogenated solvents, etc. Room temperature ionic liquids occupy a prominent place and are recognized as green solvents for organic synthesis [12,13] in view of their unique physical and chemical, non-toxic properties and the possibility of their recycling. Also ionic liquids have been used as an alternative reaction media for several reactions [14,15] including electrolytes for batteries [16]. Among the room temperature ionic liquids, chiral ionic liquids are known to be attractive and important for their potential applications to chiral recognition such as asymmetric synthesis and optical resolution of racemates [17]. Room temperature ionic liquids have become the choice of chemists for green synthesis and also employed in a variety of reactions [18,19], including organometallic reactions [20] and bio- catalyzed reactions [21,22].

Keeping in view of the responsibility of a chemist in designing, the ecofriendly solvents to carry out the reactions, we have undertaken the synthesis of novel task specific chiral ionic liquid. Herein we report synthesis, characterization and applications of novel aliphatic quarternary ammonium based chiral ionic liquid. The reaction of S-(+)-3-chloro-1,-2-propanediol and tri-n-butylamine followed by reduction is the key step in designing a new chiral ionic liquid, which plays a dual role as a solvent and a catalyst for reductive amination reaction.

2. Results and Discussion

Two novel chiral ionic liquids were prepared and found to be efficient in promoting the reductive amination of

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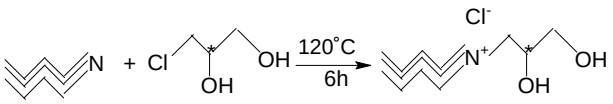
carbonyl compounds with aromatic amines to afford chiral secondary amines. These reactions are highly stereoselective in nature. The first ionic liquid, S-(+)-2-3-dihydroxy-*N*,*N*,*N*-tributylpropanaminum chloride (**1**) was obtained by the reaction of tributylamine and S-(+)-3-chloro-1,-2-propanediol at 120˚C for 6 h (**Scheme 1**). S-(+)-2-3-dihydroxy-*N*,*N*,*N*-tributylpropanaminum chloride ionic liquid is soluble in chloroform, dichloromethane, acetone and ethanol. It is insoluble in water, diethyl ether and n-hexane. The resulting chiral ionic liquid is very stable at room temperature. The other ionic liquid, S-(+)-3-(tributylamino)-1-hydroxy-2-propoxyborohydride (**2**) was prepared by the reaction of **1** with sodium borohydride in water (**Scheme 2**).

In a typical procedure of the asymmetric reductive amination of aniline and 4-fluoro-propeophenone in ionic liquid, **1** was carried out to standardize the reaction procedure (**Scheme 3**). Interestingly, the reaction afforded in 72% yield over a period of 30 minutes. The same reaction was carried out in the presence of ionic liquid **2** at room temperature for ~30 minutes to secure 60% yield of the same product. In the present investigation, an extremely efficient method has been developed for the synthesis of novel chiral amine, 4-fluoropropeophenyl-N-benzyl-3-(2-amino-4-thiazolyl) coumarin using one pot, three component reaction using ionic liquids **1** and **2** as efficient reusable catalyst. This method has several merits such as high stereo selectivity, cost efficiency, taskspecific, and simple work up and usage in the synthesis of complex amines.

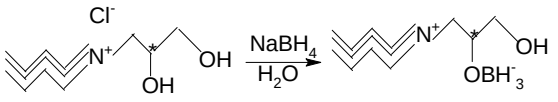
3. Experimental Section

3.1. General Consideration

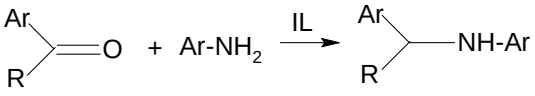
Chemicals and solvents used in the experiment were commercially available. Homogeneity/purity of all the products was assayed by thin-layer chromatography (TLC) on alumina-coated plates (Merck). Product samples in methanol (MeOH) were loaded on TLC plates and developed in $CHCl_3$: MeOH (9.5:0.5, v/v). When slight impurities were detected by iodine vapor/UV light visualization, compounds were further purified by chromatography on silica gel columns (100 - 200 mesh size, CDH). Purity of the compounds was finally re-checked by TLC. Infrared (IR) spectra were recorded in KBr medium using a Perkin-Elmer Fourier Transform-IR spectrometer, whereas ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ medium on a JNM ECX-400P (JEOL, USA) spectrometer with tetramethylsilane (TMS) as internal reference. Chemical shifts are expressed in ppm (δ-scale) and coupling constants (J) in Hz. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m).



Scheme 1. Synthesis of S-(+)-2-3-dihydroxy-N, N, N-tributylpropanaminum chloride (1).



Scheme 2. Synthesis of S-(+)-3-(tributylamino)-1-hydroxy-2-propoxyborohydride (2).



Scheme 3. General reaction for asymmetric reductive amination.

3.2. S-(+)-2-3-Dihydroxy-N, N, N-Tributylpropanaminum Chloride (1)

In a round bottomed 50 cm_3 flask equipped with a condenser and magnetic stirrer, 5 g tributylamine (0.02 mole) and 3 g S-(+)-3-Chloro-1, 2-propanediol (0.02 mole) were mixed and heated at 120˚C for 12 h. The reaction mixture was washed with 2 × 30 cm^3 diethyl ether. The drying of organic layer under vacuum afforded **1** in 70% yield as a pure oily liquid. ^{1}H NMR (400 MHz, DMSO-d_6, 25˚C, ppm): δ 0.90 (q, 9H), 1.28 (m, 6H, 2'CH_2), 1.61 (m, 6H, 2'CH_2), 3.34 (m, 6H, CH_2-N), 4.75 (b, 1H, 2'OH), 4.00 (b, 1H, 1'OH), 3.28 (m, 1H, CH-N), 2.92 (m, 1H, CH-N), 3.62 (m, 2H, 1'CH_2), 3.40 (m, 1H, *CH). ^{13}C NMR (100 MHz, $CDCl_3$, 25˚C, ppm): δ 77.3, 77.0, 76.7, 59.5, 23.8, 19.6 and 13.7.

3.3. S-(+)-3-(Tributylamino)-3-Hydroxy-1-Propoxyborohydride (2)

In a round bottomed 100 cm^3 flask, 1 g of compound **1** (0.003 mole), 40 cm^3 H_2O and 0.14 g of sodium borohydride (0.0037 mole) were mixed at room temperature. The contents were stirred rapidly for 2 min and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. After drying under vacuum for 2 h, the product 2 was obtained in 65% yield as a colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 25˚C, ppm): δ 0.93 (t, 9*H*), 1.32 (m 12*H*), 2.33 (m, 0.98*H*), 2.57 (m, 0.82*H*), 3.37 (m, 5.92*H*), 3.41 (m, 3*H*); ^{13}C NMR (400 MHz, $CDCl_3$, 25˚C, ppm): δ 77.3, 77.0, 76.7, 59.5, 23.8, 19.6, and 13.7.

3.4. Reductive Amination of 4-Fluoropropeo-Phenone and Aniline: Typical Procedure

4-fluoropropeophenone (0.192 g, 0.0012 mole) and ani-

line (0.07 g, 0.0008 mole) are mixed in 0.25 g (0.0008 mol) ionic liquid **1** at room temperature for 30 minutes followed by the addition of $NaBH_4$. At the end of the reaction, diethyl ether was added. The organic layer was separated, washed with water, dried (Na_2SO_4), and filtered. The filtrate was evaporated to afford the product. Crystallization from ethanol afforded 1.68 g (72%) 4-fluorobenzylaniline. ^{1}H NMR (400 MHz, DMSO-d_6, 25˚C): δ 6.65-7.27 (m, 9H, Ar-H), 6.70 (merged 1H, NH), 0.86 (t, 3H), 1.75 (m, 2H), 4.10 (m, 1H, *CH).

3.5. 4-Fluoropropeophenyl-N-Benzyl-3-(2-Amino-4-Thiazolyl) Coumarin

3-(2-amino-4-thiazolyl) Coumarin (0.39 g, 0.0016 mole) and 4-fluoropropeophenone (0.48 g, 0.0032 mole) are mixed in 0.25 g (0.0008 mole) of ionic liquid **1** at room temperature for 90 minutes at 70˚C followed by the addition of $NaBH_4$. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The extract was dried over anhydrous Na_2SO_4 and evaporated to afford the product 0.68 g (75.6%). ^{1}H NMR (400 MHz, DMSO-d_6, 25˚C, ppm): δ 7.00-7.72 (m, 9H, Ar-H), 6.21 (S,1H), 7.75 (merged, m, 1H, NH), 4.57 (t,1H, *CH), 0.88 (t, 3H), 1.77(m, 2H, 2'H).

4. Conclusion

In conclusion, we have synthesized novel aliphatic quarternary ammonium based chiral ionic liquids for catalysis of asymmetric reductive amination. The present investigation reports a novel procedure to synthesize chiral amines using novel chiral ionic liquids which are considerably faster with cleaner technology under neutral conditions. As a testimony to the ILs efficiency, these chiral ionic liquids could be easily recycled and reused for three times. Our current study proved that the newly synthesized chiral ionic liquids could be used as solvent, highly efficient and reusable organocatalyst. The results and observations in this study could also be useful in designing of a new type of aliphatic quarternary ammonium based IL with improved stereoselectivity. These preliminary results are encouraging, however, the catalytic efficiency of these new ILs needs to be performed for various reductive amination reactions.

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