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Synthesis of Chiral Ionic Liquids from Natural Amino Acids

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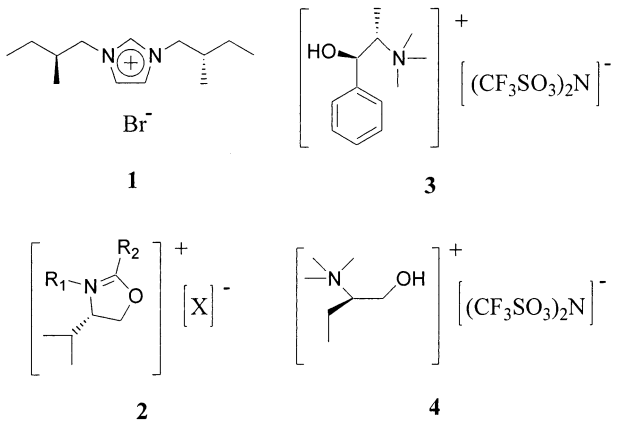
Abstract: For the first time, chiral imidazolium ionic liquids containing one chiral carbon (**10a**−**c**) were synthesized from the natural amino acids by a simple and straightforward procedure. The characteristics of the chiral ILs are very similar to the popular ionic liquids.

One of the prime concerns of industry and academia is the search for replacements to the environmentally damaging solvents used on a large scale, especially those that are volatile and difficult to contain. In the recent years, considerable attention has been focused on the use of the room-temperature ionic liquids (RTIL) as new clean media. These solvents possess a number of interesting properties, such as lack of significant vapor pressure, ease of reuse, absence of flammability, and tolerance for large temperature variations. One of the main expected applications of ionic liquids is to replace volatile organic solvents traditionally used in industry. There are many reports concerning the applications of ionic liquids in organic reactions, such as Friedel−Crafts reactions,[1,2] Diels−Alder reactions,[3−5] Heck Reactions,[6,7] Pechmann condensations,[8] Biginelli reactions,[9] and Beckmann rearrangements.[10−11] There has been also a great deal of interest in the application of the ionic liquids as novel biphasic catalysts,[12] extraction solvents,[13] and stationary phase for chromatography.[14]

Asymmetric synthesis is one of the most important areas in organic chemistry, biochemistry, and pharmacology. Usually, asymmetric induction is achieved by use of optically active substrates and/or reagents, chiral catalysts, enzymes or chiral solvents.[15] Now that the room-temperature ionic liquids have gained more and more popularity, synthesis and characterization of chiral IL are underway. Some of the chiral anions as sodium salts are readily available. For example, Seddon et al. investigated Diels−Alder reactions in lactate ILs.[16] Howarth and co-workers described the use of chiral imidazolium cations (**1**) in Diels−Alder reactions (Scheme 1).[17] However, the synthesis of these systems required an expensive chiral alkylating agent; furthermore, two symmetrical chiral centers may not be favorable to chiral inducement. Wasserscheid and co-workers synthesized three different groups of chiral ionic liquids (**2**−**4**).[18] However, under acidic conditions, the oxazoline ring of **2** has lower stability than the imidazole ring, and **3** and **4** are not very similar to the popular ionic liquids encompassing imidazolium cations, which are favorable species for investigation because of their facile and inexpensive preparation, their air and water stability, their wide liquids range, and their relatively favorable viscosity and density characteristics.[19,20] Chiral imidazolium ionic liquids with one chiral center have not been reported until now.

SCHEME 1



1 **3** **2** **4**

Herein, we report for the first time the synthesis of chiral imidazolium ionic liquids (**10a**−**c**) derived from natural amino acids. First, we used the chiral amine as the starting material. Because the aromatic chiral amine is easilier resoluted than the aliphatic chiral amine, we chose the α-phenylethylamine as the starting substrate. We synthesized D-1-ethyl-2-(α-phenylethyl)-imidazolium tetrafluoroborate, **5**, according to the route

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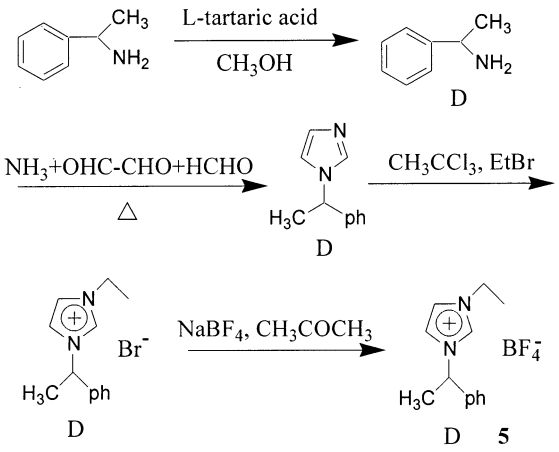
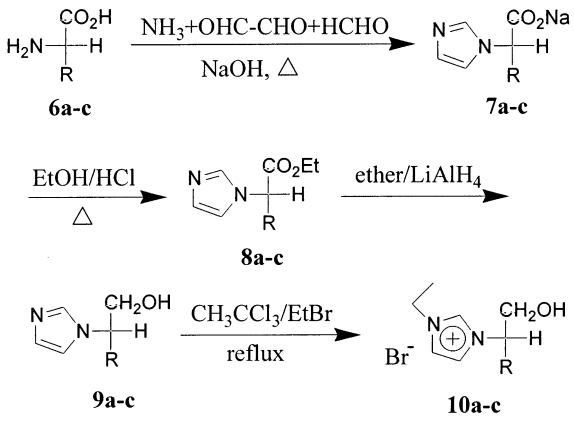
SCHEME 2



of Scheme 2.[21−23] Unfortunately, its melting point is about 90 °C, and this is not ideal for the chiral inducement, for chiral inducement in many asymmetric reactions at lower reaction temperatures is better than at higher ones. In addition, optical purity of α-phenylethylamine is not ideal by resolution(ee 95%). Thus, our studies have focused on the natural amino acids, which are optically pure and commercially available. We used L-alanine, L-valine, and L-leucine as the starting materials, which are not very expensive.

There are two ways to obtain imidazolium rings from amino acids. Amino acids can be first reduced to amino alcohols and the amino alcohols then condensed with aldehydes to form imidazoline rings. However, the hydroxy group may interfere with the condensation of amino group with aldehydes. So we chose the second route, that is, to allow the amino acids to condense with aldehydes to form imidazole rings under basic conditions. We put amino acids, formaldehyde, glyoxal, and aqueous ammonia together and regulated the pH with NaOH solution, and the crude products, sodium L-2-(1-imidazolyl)alkanoic acids (**7**), were obtained.[21] The ethyl acetic esters (**8**) were prepared by refluxing **7** in anhydrous ethyl alcohol saturated with dry hydrogen chloride according to known procedures.[24] The yields of the above two steps were 65−79%. The alcohols (**9**) was prepared by the reduction of **8** using $LiAlH_4$ in anhydrous Et_2O under reflux (yield 57−60%).[25] Finally, the objective products (**10**) were obtained by the substitution reaction of **9** and bromoethane in CH_3CCl_3.[22] The yields of the reaction were good (80−82%). Thus, the chiral ionic liquids (**10**) were prepared in four steps from optically pure amino acids (**6**) in 30−33% overall yields (Scheme 3). The chiral ionic liquids are miscible with water, methanol, acetone, and other strong polar organic solvents and immiscible with ether, 1,1,1-trichloroethane, and other weakly polar organic solvents.

SCHEME 3



a: R=CH_3; **b**: R=$CH(CH_3)_2$; **c**: R=$CH_2CH(CH_3)_2$

In conclusion, we could demonstrate that chiral imidazolium ILs with one chiral center can readily be prepared from the natural amino acids. Comparing with the criteria proposed by Wasserscheid[18] (easy preparation by direct synthesis in enantiopure form; melting point <80 °C; thermal stability up to 100 °C; good chemical stability vs water and common organic substrates and relatively low viscosity), our chiral ILs are more satisfactorily meet it. Furthermore, there are other merits in this synthesis: (a) the characterization of the chiral ILs (mp 5−16 °C) are very similar to the popular ionic liquids encompassing imidazolium cations; (b) good thermal stability (do not decompose up to 180 °C); (c) the starting materials are commercially available and synthetic procedures are simple and straightforward.

Experimental Section

General Methods. All reagents and solvents were pure analytical grade materials purchased from commercial sources and were used without further purification, if not stated otherwise. Et_2O was distilled from sodium benzophenone ketyl prior to used. Ethyl alcohol was purified by standard procedure. All melting points are uncorrected. The NMR spectra were recorded in $CDCl_3$ on a 400 MHz instrument with TMS as internal standard. IR spectra were taken as KBr plates. TLC was carried out with 0.2 mm thick silica gel plates (GF_{254}). Visualization was accomplished by UV light or I_2 staining. The columns were handpacked with silica gel 60 (200−300). All reactions were carried out under atmosphere, if not stated otherwise. The products were further purified by column chromatography.

L-Ethyl 2-(1-Imidazolyl) propanoate (8a).[26] Formaldehyde water solution (36%, 16.7 g) and glyoxal water solution (32%, 36.2 g) were added to a 250 mL, three-necked flask provided with a stirrer and reflux condenser. While the mixture was heated at 50 °C with stirring, a mixture of alanine (**6a**) (17.8 g, 0.2 mol), ammonia solution (28%, 12.1 g), and sodium hydroxide solution (10%, 80 g) was added in small portions during 0.5 h. After the mixture was stirred for an additional 4 h at 50 °C, the water was removed under reduced pressure. The residue was absolutely dried in a vacuum desiccator with P_2O_5. The crude product, sodium l-2-(1-imidazolyl)propanoic acid (**7a**), was obtained.[21] L-Ethyl 2-(1-imidazolyl)propanoate (**8a**) was prepared by refluxing **7a** in anhydrous ethyl alcohol saturated with dry hydrogen chloride. After the reaction was complete, excess hydrogen chloride and alcohol were removed under reduced pressure.[24] Saturated Na_2CO_3 solution was added to the residue until pH 8−9. The resultant product was extracted with ethyl acetate and dried with Na_2SO_4. The product was further purified

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by column chromatography (1:4 petroleum ether/ethyl acetate): yield 24 g; 70% (two steps overall); oil (bp 122−123/7 mmHg); $[\alpha]^{25}_D = +8.8$ (*c* 2.0, CH_3OH); ^1H NMR δ 1.24−1.28 (t, $J = 7.14$ Hz, 3H), 1.73−1.75 (d, $J = 7.30$ Hz, 3H), 4.17−4.23 (q, $J = 7.12$ Hz, 2H), 4.85−4.90 (q, 7.29 Hz, 1H), 7.03 (s, 1H), 7.07 (s, 1H), 7.59 (s, 1H); ^{13}C NMR δ 13.41, 17.88, 54.48, 61.42, 117.33, 128.76, 135.87, 169.55; IR 3386, 3114, 2986, 1742 cm^{-1}. Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66; Found: C, 57.36; H, 7.31; N,16.46.

L-2-(1-Imidazolyl)propanol (9a).[26] Lithium aluminum hydride (11.4 g) was added to 300 mL of anhydrous ether in a 500 mL three-necked flask with a stirrer and reflux condenser. With stirring, 33.6 g of **8a** was added in small portions during 1 h.[25] After the mixture was stirred for 1 h at room temperature, more lithium aluminum hydride (11.4 g) was added. The mixture was stirred for an additional 2 h, and then 70 mL of water was very carefully added dropwise. The resulting suspension of white granular solid in ether was filtered. The solid was suspended in methanol, and the mixture was saturated with carbon dioxide under reflux for 1 h and then filtered. The combined ether and methanol filtrates were evaporated to dryness, and the resultant product was further purified by column chromatography (1:4, methanol/ethyl acetate): yield 17 g, 59%; mp 114−115 °C; $[\alpha]^{25}_D = +8.4$ (*c* 2.0, CH_3OH); ^1H NMR 1.37−1.39 (d, $J = 6.80$ Hz, 3H), 3.59−3.69 (m, 2H), 4.14−4.18 (m, 1H), 5.84 (br, OH), 6.82 (s, 1H), 6.90 (s, 1H), 7.37 (s, 1H); ^{13}C NMR δ 17.30, 55.77, 65.81, 117.29, 127.79, 135.93; IR 3116, 2980, 2938, 1578 cm^{-1}; Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.20. Found: C, 56.99; H, 7.85; N, 22.02.

L-1-Ethyl-3-(1′-hydroxy-2′-propanyl)imidazolium Bromide (10a). Under vigorously stirring, 76.3 g of bromoethane was added dropwise to a solution of 25.2 g of **9a** in 200 mL of 1,1,1-trichloroethane over 0.5 h.[22] The mixture was stirred for an additional 5 h under reflux and then evaporated to dryness. The resultant product was further purified by column chromatography (1:2, methanol/ethyl acetate): yield 43 g, 80%; mp 5−6 °C; $[\alpha]^{25}_D = +3.7$ (*c* 2.0%, CH_3OH); ^1H NMR 1.56−1.71 (m, 6H), 1.92 (br, OH), 3.43−3.48 (m, 2H), 3.73−3.78 (m, 1H), 4.36−4.38 (m, 2H), 4.87 (br, 1H), 7.35 (s, 1H), 7.45 (s, 1H), 9.86 (s, 1H); ^{13}C NMR 15.21, 16.63, 45.37, 58.92, 64.54, 120.60, 121.05, 136.09. IR 3444, 2078, 1634 cm^{-1}; Anal. Calcd for $C_8H_{15}BrN_2O$: C, 40.87; H, 6.43; N, 11.91. Found: C, 40.62; H, 6.56; N, 11.79.

L-Ethyl 2-(1-Imidazolyl)-3-methylbutanoate (8b). This compound was prepared by a procedure similar to that for the preparation of **8a** and was further purified by column chromatography (1:4 petroleum ether/ethyl acetate): yield 27 g, 68% (two steps overall); oil (bp 137−138 °C/7 mmHg); $[\alpha]^{25}_D = +9.9$ (*c* 2.0%, CH_3OH); ^1H NMR δ 0.79−0.80 (d, $J = 6.71$ Hz, 3H), 1.00−1.02 (d, $J = 6.69$ Hz, 3H), 1.26−1.30 (t, $J = 7.14$ Hz, 3H), 2.39−2.44 (m, 1H), 4.17−4.25 (m, 2H), 4.31−4.33 (d, $J = 9.58$ Hz, 1H), 7.06 (s, 1H), 7.11 (s, 1H), 7.59 (s, 1H); ^{13}C NMR 13.91, 18.38, 19.12, 31.98, 61.59, 66.45, 118.38, 129.16, 137.02, 169.30; IR 3386, 3114, 2971, 2878, 1742 cm^{-1}. Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.45; H, 8.31; N, 14.06.

L-2-(1-Imidazolyl)-3-methylbutanol (9b). This compound was prepared by a procedure similar to that for the preparation of **9a** and was further purified by column chromatogramphy (1: 10 methanol/ethyl acetate): yield 22 g, 60%; mp 95−97 °C; $[\alpha]^{25}_D = -20.5$ (*c* 2.0, CH_3OH); ^1H NMR 0.73−0.74 (d, $J = 6.70$ Hz, 3H), 1.02−1.03 (d, $J = 6.66$ Hz, 3H), 2.08−2.13 (m, 1H), 3.66−3.71 (m, 1H), 3.88−3.90 (m, 1H), 4.46 (br, OH), 6.92 (m, 2H), 7.37 (s, 1H); ^{13}C NMR δ 19.22, 19.88, 29.96, 62.76, 67.04, 118.05, 128.13, 136.73; IR 3113, 2965, 2876, 1598 cm^{-1}. Anal. Calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.12; H, 9.36; N, 18.31.

L-1-Ethyl-3-(1′-hydroxy-3′-methyl-2′-butanyl)imidazolium Bromide (10b). This compound was prepared by a procedure similar to that for the preparation of **10a** and was further purified by column chromatography (1:5 CH_3OH/ethyl acetate): yield 48 g, y82%; mp 11−12 °C; $[\alpha]^{25}_D = -10.0$ (*c* 2.0%, CH_3OH); ^1H NMR δ 0.82−0.84 (d, $J = 6.68$ Hz, 3H), 1.06−1.08 (d, $J = 6.65$ Hz, 3H), 1.58−1.62 (t, $J = 7.35$ Hz, 3H), 2.21−2.28 (m, 1H), 3.75 (br, OH), 3.95−4.02 (m, 2H), 4.29−4.34 (m, 1H), 4.34−4.42 (m, 2H), 7.54 (m, 2H), 9.72 (s, 1H); ^{13}C NMR δ 15.42, 19.35, 19.37, 29.68, 45.28, 61.08, 69.47, 121.37, 122.01, 135.88; IR 3356, 3134, 3080, 2968, 2878, 1637, 1560 cm^{-1}. Anal. Calcd for $C_{10}H_{19}BrN_2O$: C, 45.64; H, 7.28; N, 10.64. Found: C, 45.55; H, 7.43; N, 10.44.

L-Ethyl 2-(1-Imidazolyl)-4-methylpentanoate (8c). This compound was prepared by a procedure similar to that for the preparation of **8a** and was further purified by column chromatography (1:1 petroleum ether/ethyl acetate): yield 28 g, 65% (two steps overall); oil (bp 144−145 °C/7 mmHg); $[\alpha]^{25}_D = +4.4$ (*c* 2.0%, CH_3OH); ^1H NMR δ 0.92−0.93 (d, $J = 6.73$ Hz, 3H), 0.94−0.95 (d, $J = 6.66$ Hz, 3H), 1.25−1.29 (t, $J = 7.10$ Hz, 3H), 1.35−1.45 (m, 1H), 1.94−1.97 (t, $J = 7.51$ Hz, 2H), 4.18−4.23 (q, $J = 7.12$ Hz, 2H), 4.76−4.80 (t, $J = 7.86$ Hz, 1H), 7.06 (s, 1H), 7.11 (s, 1H), 7.68 (s, 1H); ^{13}C NMR 14.03, 21.46, 22.63, 24.54, 41.53, 58.45, 62.06, 118.06, 128.59, 136.73, 170.08; IR 3385, 3133, 2959, 1735 cm^{-1}. Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.59; H, 8.51; N, 13.48.

L-2-(1-Imidazolyl)-4-methylpentanol (9c). This compound was prepared by a procedure similar to that for the preparation of **9a** and was further purified by column chromatography (1:5 petroleum ether/ethyl acetate): yield 22 g, 57%; mp 53 °C; $[\alpha]^{25}_D = -10.8$ (*c* 2.0%, CH_3OH); ^1H NMR δ 0.85−0.87 (d, $J = 6.40$ Hz, 3H), 0.88−0.89 (d, $J = 6.80$ Hz, 3H), 1.28−1.40 (m, 1H), 1.50−1.57 (m, 1H), 1.67−1.75 (m, 1H), 3.71−3.77 (m, 2H), 4.11−4.16 (m, 1H), 4.33 (br, OH), 6.90 (m, 2H), 7.37 (s, 1H); ^{13}C NMR δ 21.73, 22.97, 24.46, 40.11, 59.03, 65.67, 117.24, 128.38, 136.43; IR 3115, 2958, 2871, 1659 cm^{-1}. Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.66. Found: C, 64.45; H, 9.40; N, 16.39.

L-1-Ethyl-3-(1′-hydroxy-4′-methyl-2′-pentanyl)imidazolium Bromide (10c). This compound was prepared by a procedure similar to that for the preparation of **10a** and was further purified by column chromatography (1:10 methanol/ethyl acetate): yield 50 g, 81%; mp 15−16 °C; $[\alpha]^{25}_D = +9.2$ (*c* 2.0%, CH_3OH); ^1HNMR δ 0.92−0.93 (d, $J = 6.40$ Hz, 3H), 0.94−0.96 (d, $J = 6.40$ Hz, 3H), 1.42−1.50 (m, 1H), 1.57−1.61 (t, $J = 7.00$ Hz, 3H), 1.64−1.72 (m, 1H), 1.75−1.83 (m, 1H), 2.93 (br, OH), 3.74−3.77 (m, 1H), 3.90−3.93 (m, 1H), 4.33−4.39 (q, $J = 7.20$ Hz, 2H), 4.70 (br, 1H), 7.40 (s, 1H), 7.42 (s, 1H), 9.67 (s, 1H); ^{13}C NMR δ 15.10, 22.07, 22.67, 24.76, 39.32, 45.32, 62.00, 63.77, 120.94, 121.36, 136.36; IR 3385, 2959, 2873, 1636 cm^{-1}. Anal. Calcd for $C_{11}H_{21}BrN_2O$: C, 47.66; H, 7.64; N, 10.11. Found: C, 47.70; H, 7.84; N, 10.00.

Supporting Information Available: ^1H NMR, ^{13}CNMR, and IR spectra of compounds **8a**−**c**, **9a**−**c**, and **10a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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