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Synthesis and properties of thiazoline based ionic liquids derived from the chiral pool

Jocelyne Levillain, Guillaume Dubant, Isabelle Abrunhosa, Mihaela Gulea and Annie-Claude Gaumont*

Laboratoire de Chimie Moléculaire et Thioorganique UMR-CNRS 6507, ENSI-CAEN, ISMRA, Université de Caen, 6 Bd du Maréchal Juin, F-14050 Caen, France. E-mail: gaumont@ismra.fr; Fax: 33 2 31 45 28 77; Tel: 33 2 31 45 28 73

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A novel class of chiral ionic liquids derived from amino alcohols is prepared in multi-gram scale. Their potential in chiral recognition is shown in a preliminary example with racemic Mosher's acid salt.

Ionic liquids (ILs) are low melting point salts (< 100 °C) that have attracted considerable attention recently as greener alternatives to classical environmentally damaging solvents.[1] This is mainly due to their peculiar properties such as the absence of flammability, the lack of measurable vapour pressure and their ability to dissolve a wide range of organic, organometallic and even some inorganic compounds. In addition, reactions carried out in these new media frequently have different thermodynamic and kinetic behaviours with respect to those in traditional solvents. Several excellent reports concerning their applications in organic synthesis (Diels–Alder, Friedel–Crafts, Wittig reactions…) and in catalysis (cyclopropanation, Heck, Suzuki reactions…) can be found in the recent literature.[2] The most widely used ionic liquids are the quite expensive *N*,*N*-dialkylimidazolium salts. Recently, new families of ILs derived from ammonium, pyrrolidinium or phosphonium cations have been synthesized and studied.[3] Nevertheless, chiral derivatives remain limited so far[4] although they could provide a simple entry into the area of chiral solvents with potential applications in resolution chemistry, chromatography and even synthesis. Four types of chiral ionic liquids have been reported until now: imidazolium with chirality brought either by the anion[5] or the cation,[6,7] ammonium derived from chiral amino alcohol[8] and oxazolinium derived from valinol.[8] Finally, a novel imidazolium based ionic liquid with cyclophane type planar chirality was proposed.[9] This compound is obtained in a racemic form and must be resolved before being used. Among these various examples, the chiral ammonium based ionic liquid derived from ephedrine was shown to be successful in chiral discrimination.[8]

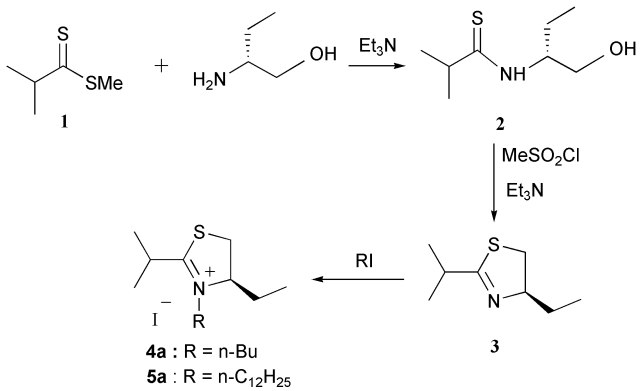
Herein, we report the synthesis and properties of a novel class of chiral ionic liquids based on a thiazolinium cation. Chiral thiazolinium salts are poorly studied derivatives. We found only one report dealing with such compounds in the literature,[10] due probably to the low availability of chiral aminothiol precursors. Some of us recently published a general and convenient synthesis of chiral thiazolines starting from commercial low cost enantiopure 2-amino alcohols and easily accessible dithioesters as sulfur source.[11] The new chiral ILs can then be prepared by alkylation of the corresponding chiral thiazolines with an alkyl halide followed by an anion exchange.

As a preliminary study, we synthesized chiral salt **4a**.† Thioamide **2** was readily prepared by thioacylation of the commercially available (*R*)-2-aminobutanol with the appropriate dithioester **1**. Upon treatment of thioamide **2** with mesyl chloride and Et_3N in CH_2Cl_2, **3** was obtained in 90% yield. Thiazoline **3** was then refluxed for 48 hours with butyl iodide (1 eq) in acetonitrile leading to salt **4a** (Scheme 1). After crystallization (acetonitrile/Et_2O), **4a** was obtained in 69% overall yield.

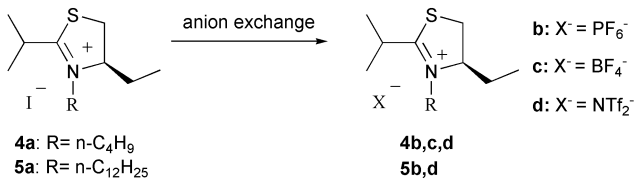
Starting from **4a**, thiazolinium salts **4b–d** were obtained in quantitative yields upon ion exchange with hexafluorophosphoric acid (HPF_6), tetrafluoroboric acid (HBF_4) or lithium bis(trifluoromethanesulfonyl)imide ($LiNTf_2$) (Scheme 2). They were purified by washing with aqueous sodium bicarbonate or water until neutrality was reached, then with sodium thiosulfate to remove iodine traces, followed by filtration over black charcoal. Compounds **4b–d** can be prepared in multi-gram scale with correct overall yields (68% in pure form).

The chiral salts **4b–d** are soluble in dichloromethane, chloroform, acetonitrile and strongly polar solvents, slightly soluble in ether, toluene and other weakly polar solvents and soluble in water. All the salts show good chemical stability under aqueous basic and acidic conditions. Hydrolysis to the amino alcohol was not observed even under acidic conditions, in contrast to oxazolinium derivatives.[8] Thiazolinium salts also exhibit good thermal stability up to at least 170 °C as shown by TGA measurements. The effect of the thiazolinium counter ions on the melting point of salts **4** was examined by DSC. Salts **4a–c** having respectively iodide, hexafluorophosphate or tetrafluoroborate as counter ion display high melting points (respectively of 137, 136 and 111 °C). Only the bis(trifluoromethanesulfonyl)imide derivative **4d** is liquid at room temperature (glass transition temperature = −68 °C). Thus, except for **4d**, the high melting points of salts **4** prohibit their use as chiral solvents.

To lower the melting point, we then changed the alkylating agent chain length. Using the same methodology but replacing the butyl chain by a dodecyl one when performing the N-alkylation led to compound **5a** in 31% yield after purification. Upon ion exchange with either hexafluorophosphoric acid (HPF_6) or lithium bis(trifluoromethanesulfonyl)imide ($LiNTf_2$), salts **5b,d** were obtained. Whatever the nature of the



Scheme 1 Synthesis of iodide thiazolinium salts **4a** and **5a**.



Scheme 2 Thiazolinium anion exchange.

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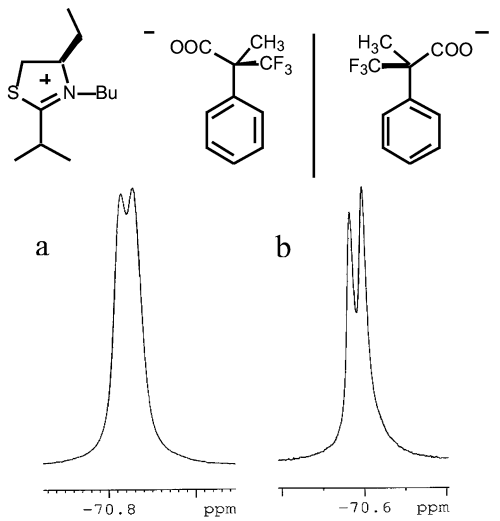

Fig. 1 ^{19}F NMR spectrum of water saturated racemic Mosher's acid thiazolinium salt in C_6D_6.

anion, compounds **5** have a melting point below 50 °C (42 °C for **5b** and < 0 °C for **5d**) indicating that the length of the N-alkyl chain can regulate the melting point of the salt.

As a first study on the chiral recognition ability of the thiazolinium salts, we attempted to detect diastereomeric interactions between **4a** and racemic Mosher's acid silver salt. The formation of diastereomeric complexes was probed by ^{19}F NMR (Fig. 1). Interaction between thiazolinium cation and Mosher's acid anion induces a downfield shift of the fluorine atom signal in the ^{19}F NMR spectrum (1 ppm). Moreover the interaction causes a splitting of the Mosher's acid salt fluorine signals, clearly illustrating the formation of diastereomeric complexes. The chemical shift distance between the two CF_3 groups depends on the concentration of the ionic liquid in the solvent (1 eq: spectrum a) and amounts to 11 Hz with 5 eq of wet thiazolinium salts[12] (spectrum b). As already reported for ammonium salts,[8] water added to the chiral thiazolinium salt has a major influence on the extent of signal splitting.

In summary, we have designed a new family of chiral ionic liquids based on amino alcohols derived from the chiral pool. These enantiopure ILs were easily prepared in multi-gram scale. They are water tolerant and stable under acidic or basic conditions. By a judicious choice of the anion and the cation, salts with low melting points are obtained. This property makes them potential candidates for new chiral solvents. Diastereomeric interactions between thiazolinium **4a** and a racemic substrate were probed by NMR, clearly demonstrating that the racemic substrate is dissolved in a chiral environment. Use of these chiral salts in the resolution of racemates or in asymmetric catalysis is currently under investigation.

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Notes and references

† The thiazolines **3** were prepared from (*R*)-(−)2-aminobutanol in 90% yield according to prior work.[11] Synthesis of **4a** and **5a**: Thiazoline **3** (2.33 g, 12 mmol) was mixed with alkyl iodide (23.6 mmol) in acetonitrile and refluxed for 2 days. The remaining alkyl iodide was removed under vacuum or by washing with heptanes. The crude products were purified by crystallization in acetonitrile/Et_2O for **4a** and ethyl acetate for **5a**. (*R*)-3-Butyl-4-ethyl-2-isopropyl-2-thiazolinium iodide **4a** (2.82 g, 69% yield, mp = 137 °C). ^{1}H-NMR (250 MHz), $CDCl_3$–TMS: δ = 1.01 (3H, t, J = 7.3 Hz), 1.08 (3H, t, J = 7.4 Hz), 1.41 (3H, d, J = 6.8 Hz), 1.48 (3H, d, J = 6.7 Hz), 1.46–1.51 (2H, m), 1.7–2.1 (4H, m), 3.3–3.5 (2H, m), 3.8–3.88 (1H, m), 3.95–4.02 (1H, m), 4.28 (1H, dd, J = 11.8 Hz, J = 9.9 Hz), 5.2–5.31 (1H, m); ^{13}C-NMR (62.89 MHz), $CDCl_3$–TMS: δ = 8.6, 13.2, 19.6, 21.6, 21.7, 23.6, 30.1, 31.6, 33.0, 50.4, 73.1, 199.3. $[\alpha]_D^{20}$ −40.7 (*c* 1, acetone). Anal. Calc. for $C_{12}H_{24}INS$: C, 42.23; H, 7.09; Found: C, 42.02; H, 7.16%. (*R*)-3-Dodecyl-4-ethyl-2-isopropyl-2-thiazolinium iodide **5a** (1.96 g, 31% yield, mp = 38 °C). ^{1}H-NMR (250 MHz), CD_3CN–TMS: δ = 0.58–0.64 (3H, m), 0.7–0.8 (3H, m), 1–1.1 (23H, m), 1.25–1.75 (5H, m), 3.2–3.5 (3H, m), 3.6–3.8 (2H, m), 4.6–4.7 (1H, m); ^{13}C-NMR (62.89 MHz), CD_3CN–TMS: δ = 9.4, 14.6, 22.2, 22.3, 23.4, 24.3, 27.2, 29.8, 30.1, 30.2, 30.3, 30.4, 32.5, 32.6, 34.2, 51.0, 73.8, 200.3. Anal. Calc. for $C_{20}H_{40}INS$: C, 52.97; H, 8.89; Found: C, 53.04; H, 9.29%. $[\alpha]_D^{20}$ −38.8 (*c* 1, acetone). (*R*)-3-Butyl-4-ethyl-2-isopropyl-2-thiazoliniumbis(trifluoromethylsulfonyl)imide **4d** was prepared from **4a** and $LiNTf_2$ following the anion exchange method for [Bmpy][NTf_2].[13] (T_g = −68 °C). ^{1}H-NMR (250 MHz), CD_3CN–TMS: δ = 0.8–0.91 (6H, m), 1.32 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 7.0 Hz), 1.3–1.5 (2H, m), 1.6–1.9 (4H, m), 3.1–3.8 (5H, m), 4.5–4.7 (1H, m); ^{13}C-NMR (62.89 MHz), CD_3CN–TMS: δ = 8.9, 13.8, 20.4, 21.7, 21.8, 24.1, 30.7, 32.4, 32.9, 50.4, 74.0, 120.9 (q, J = 321 Hz), 201.0; ^{19}F-NMR (376.50 MHz), $CDCl_3$–TMS: δ = −80.48. $[\alpha]_D^{20}$ −29.5 (*c* 1, acetone). HRMS calcd, 214.1630; found 214.1619. (*R*)-3-Dodecyl-4-ethyl-2-isopropyl-2-thiazolinium hexafluorophosphate **5b** was prepared in 84% from **5a** and HPF_6 following the anion exchange method described by Carlin *et al.* for [Emim][PF_6].[14] (mp = 42 °C). ^{1}H-NMR (400.13 MHz), CD_3CN–TMS: δ = 0.91 (3H, t, J = 7 Hz), 0.99 (3H, t, J = 7.4 Hz), 1.3–1.4 (24H, m), 1.6–1.65 (1H, m), 1.7–2.0 (3H,m), 3.31 (1H, sept, J = 6.75 Hz), 3.42 (1H, dd, J = 12.1 Hz, J = 4.3 Hz,), 3.5–3.65 (1H, m), 3.76 (1H, dd, J = 12.1 Hz, J = 9.6 Hz), 3.8–3.9 (1H, m), 4.7–4.75 (1H, m); ^{13}C-NMR (62.89 MHz), CD_3CN–TMS: δ = 8.9, 14.4, 21.6, 21.8, 23.4, 24.0, 27.0, 28.7, 29.7, 30.0, 30.2, 30.3, 32.4, 32.6, 32.9, 50.5, 73.9, 200.9; ^{31}P-NMR (101.25 MHz), CD_3CN–TMS: δ = −143.3 (sept., J = 699 Hz); $[\alpha]_D^{20}$ −36.7 (*c* 1, acetone). HRMS calcd, 326.2882; found, 326.2879. NMR experiment: to an acetonitrile solution (1 mL) of thiazolinium salt **4a** (0.05 mmol, 18 mg), was added Mosher's acid silver(I) salt (0.05 mmol, 18 mg). The mixture was shaken at room temp. for 1 h. After removal of AgI by filtration, CH_3CN was evaporated. The new salt (Mosher's acid thiazolinium salt) was transferred in an NMR tube containing a solution of C_6D_6 and a drop of water. The sample was shaken and the spectrum recorded (a). Then, 4 equiv. of thiazolinium salts were added to the sample and a new spectrum was recorded (b).

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12 Under similar conditions but in the absence of a co-solvent (water), diastereomer discrimination between **5b** and the Mosher's acid sodium salt cannot be observed by NMR indicating that the differences in the binding energies for the 2 diastereomeric complexes must be too small under the used conditions. Nevertheless, the chemical shift difference for the methoxy group ($\Delta\delta$ 1.3) in ^{1}H NMR and the CF_3 group in ^{19}F NMR ($\Delta\delta$ 0.1) as well as the important broadening of the signals account for diastereomeric interactions.
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