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Design and Synthesis of Novel Chiral Spiro Ionic Liquids

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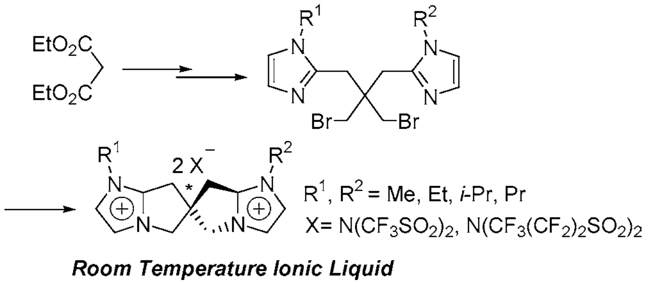
ABSTRACT



Novel chiral imidazolium salts have been synthesized as examples of chiral ionic liquids with a spiro skeleton. Effects of N-substituents and counteranions on the melting point of spiro imidazolium salts and their chiral discrimination abilities are described.

In the past decade, ionic liquids have attracted considerable attention as a new type of media in electrochemistry, materials science, and green chemistry.[1] Ionic liquids serve as an excellent alternative to classical organic solvents,[2] and the chiral version of ionic liquids is of importance in the domain of chiral solvents as a result of their potential applications in asymmetric synthetic and analytical chemistry. However, studies on chiral ionic liquids are still in a preliminary stage, and their synthesis and applications have only recently been focused upon.[2d−e,3,4] The known chiral ionic liquids are mainly derived from chiral pools and provide a very limited scope for structural modifications. Structural diversity often plays an important role in ionic liquid catalyzed reactions. Therefore, the design and synthesis of novel chiral ionic liquids with the possibility of easy structural refinement is a major challenge. Recently, we have

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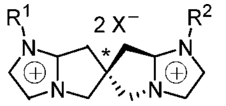
developed highly efficient spiro chiral ligands[5] for asymmetric reactions and spiro heteroaromatic salts[6] as potential chiral phase transfer catalysts.

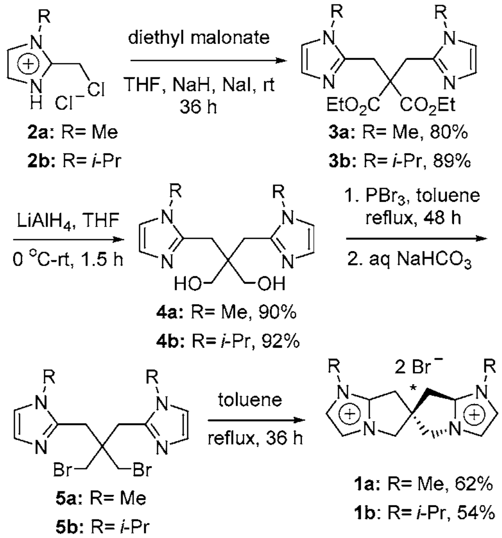
We envisaged that the introduction of a rigid spiro skeleton into imidazolium salts would produce novel chiral spiro ionic liquids. Herein, we describe the synthesis and properties of chiral spiro imidazolium salts as potential ionic liquids. A flexible, common synthetic approach has been developed for the synthesis of symmetrical and unsymmetrical spiro imidazolium salts **1a**−**d**.



1a: R1= Me, R2= Me, X= Br
1b: R1= *i*-Pr, R2= *i*-Pr, X= Br
1c: R1= Me, R2= Et, X= Br
1d: R1= *i*-Pr, R2= Pr, X= Br

The syntheses of symmetrical spiro imidazolium salts **1a** and **1b** commenced from **2a**[7] and **2b**[8] (Scheme 1). The alkylation of diethyl malonate with imidazolium salt **2a**, followed by reduction with LAH, produced diol **4a** in good yield. The conversion of diol **4a** to its corresponding dibromide **5a**, where substitution occurs at the neopentyl position, represents a significant challenge, as neopentyl displacement reactions often result in rearranged products. Nevertheless, the treatment of diol **4a** with PBr_3 produced dibromide **5a**,[9] which underwent smooth N-alkylation in refluxing toluene to yield spiro imidazolium salt **1a**. Similarly, spiro imidazolium salt **1b** was synthesized starting from imidazolium salt **2b**.

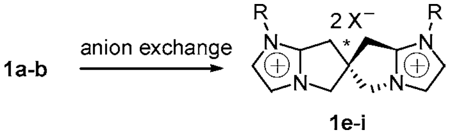
Scheme 1. Symmetrical Spiro Bis(imidazolium) Salts



Next, we investigated the exchange of counteranions. Spiro bis(imidazolium) bis(tetrafluoroborate) **1e** and the corresponding bis(triflate) **1f** were obtained in almost quantitative yields upon the anion exchange of spiro imidazolium salt **1a** with $AgBF_4$ or AgOTf. Similarly the anion exchange of **1a** with $LiNTf_2$ produced spiro bis(imidazolium) bis(trifluoromethanesulfonyl)imidate **1g** in excellent yield.[10]

Results of the counteranion exchange are summarized in Table 1. Unfortunately, the melting points of dibromides **1a**−**b**, bis(tetrafluoroborate) **1e**, and bis(triflate) **1f** were high (entries 1−3 and 5).

Table 1. Effect of Counteranions



entry	method[a]	imidazolium salt	product (X−)	mp or T_g (°C)
1		**1a**	Br	>300[b]
2	A	**1a**	BF_4 (**1e**)	272[b]
3	A	**1a**	CF_3SO_3 (**1f**)	166[b]
4	B	**1a**	$N(CF_3SO_2)_2$ (**1g**)	112[b]
5		**1b**	Br	>300[b]
6	B	**1b**	$N(CF_3SO_2)_2$ (**1h**)	68[b]
7	B	**1b**	$N(CF_3CF_2CF_2SO_2)_2$ (**1i**)	−10[c]

[a] Method A: AgX, MeOH, rt, 16 h. Method B: $LiN(CF_3(CF_2)_nSO_2)_2$, water, rt, 16 h. [b] Melting point (mp). [c] Glass transition temperature (T_g).

It is noteworthy that the melting point of bis(trifluoromethanesulfonyl)imide derivative **1g** decreased (entry 4), while that of bis(trifluoromethanesulfonyl)imide derivative **1h** decreased dramatically (entry 6). Furthermore, by increasing the fluoroalkyl chain of sulfonylimide counteranion to bis(heptafluoropropanesulfonyl)imide, room temperature ionic liquid **1i** with a glass transition temperature (T_g) at −10 °C was produced (entry 7).

To obtain ionic liquids with low melting points, we then investigated unsymmetrical imidazolium salts **1j** and **1k** (Scheme 2). It is known that the unsymmetrical N-alkylation pattern of *N*,*N′*-dialkylimidazolium salts causes crystallographic disorder and is the main cause of the low melting points of ionic liquids with unsymmetrical cations.[2f,11]

Spiro bis(imidazolium) salt **1j** was prepared by the monoalkylation of diethyl malonate with **2a** to produce compound **6a**. The second alkylation of ester **6a** with imidazolium salt **2c** yielded unsymmetrical ester **3c**. Reduction of ester **3c** with LAH followed by treatment with PBr_3 and N-alkylation produced the desired unsymmetrical spiro

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[8] Prepared by a method similar to that for **2a**.

[9] During the bromination by PBr_3, the HBr salt of **5a** was generated, which did not cyclized to give **1a** under the reaction conditions.

[10] See Supporting Information.

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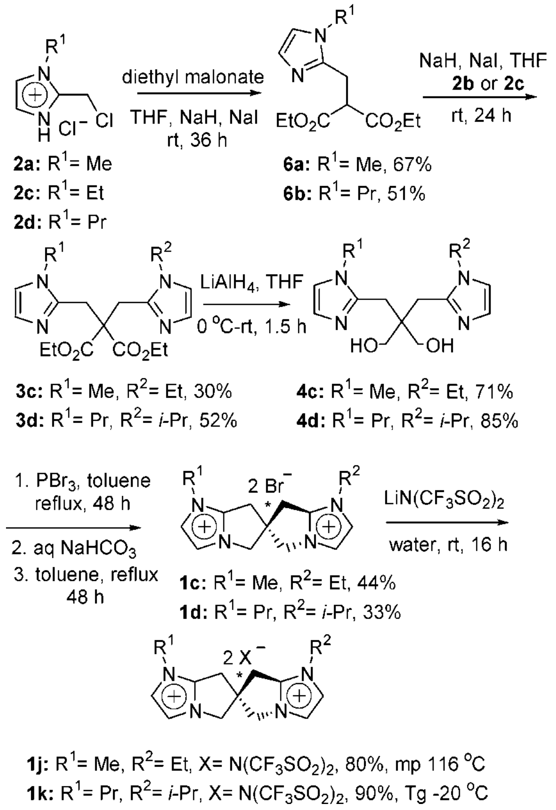
Scheme 2. Unsymmetrical Spiro Bis(imidazolium) Salts



bis(imidazolium) salt **1c**. Similarly, unsymmetrical spiro bis(imidazolium) salt **1d** was prepared based on the synthetic protocol for **1c**. The counteranion exchange of these spiro imidazolium salts gave bis(trifluoromethanesulfonyl)imide derivatives **1j** and **1k**.

Using these imidazolium salts we investigated the effect of the N-substituent on the melting point. To gain insight into the effect of N-substituent, we compared the melting points of the symmetrical and unsymmetrical imidazolium salts. The melting point of *N*-methyl-substituted imidazolium salt **1g** (Table 1, entry 4) was above 100 °C, whereas that of its unsymmetrical analogue **1j**, with an *N*-methyl-*N′*-ethyl substitutent, was in a similar range (116 °C). Interestingly, the melting point of *N*-isopropyl-substituted spiro imidazolium salt **1h** (Table 1, entry 6) was below 100 °C and its unsymmetrical analogue **1k**, with an *N*-propyl-*N′*-isopropyl substituent was liquid at room temperature ($T_g = -20$ °C). The unsymmetrical substituents in imidazolium salt **1k** contribute to inefficient crystal packing and result in low melting ionic liquids.

All spiro imidazolium salts were characterized by spectroscopic analysis.[10] Furthermore, the structure of **1g** was determined unequivocally by X-ray crystallographic analysis (Figure 1).

As a preliminary study on the chiral discrimination ability of the novel spiro imidazolium salts, the diastereomeric interaction between **1b** and the potassium salt of (*S*)-Mosher's acid[12] was examined. The ^{1}H NMR spectrum of racemic spiro imidazolium salt **1b** exhibited two pairs of doublets. The pair of doublets that appeared at δ 4.08 (H_a) and 4.41 (H_b) corresponds to -CH_2 protons of the spiro skeleton fused to the imidazole ring, whereas that at δ 4.89 (H_c) and 5.03 (H_d) represents N-CH_2 protons. Excellent diastereomeric interactions were observed by changing the

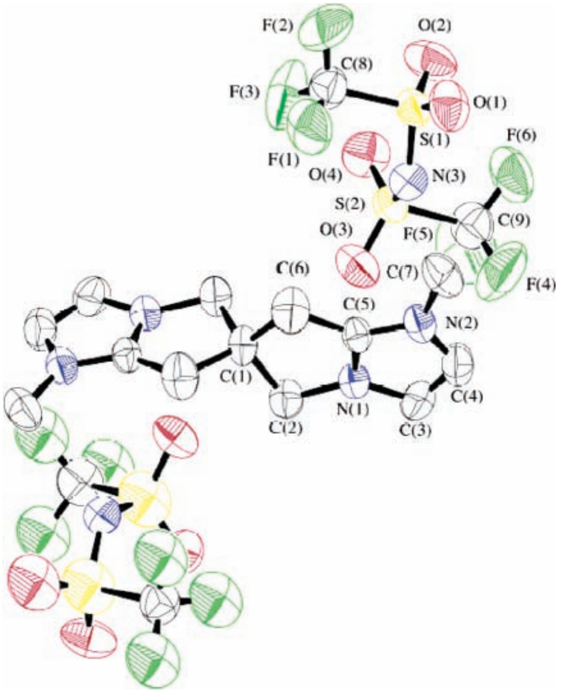


Figure 1. X-ray crystal structure of **1g**.

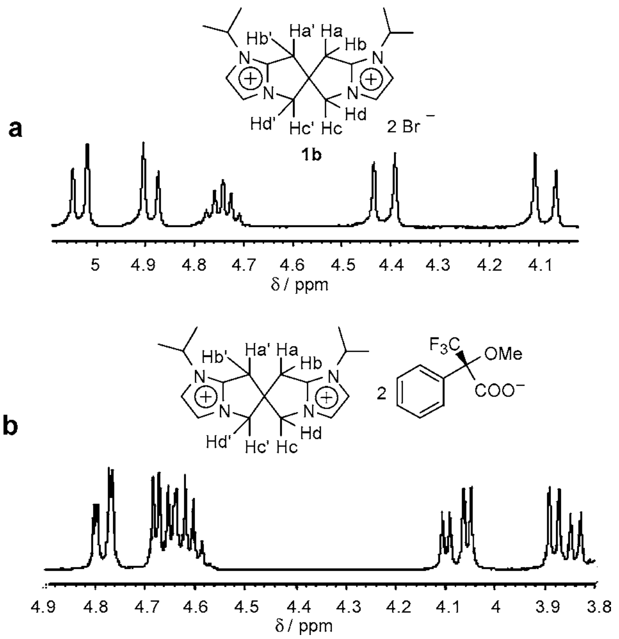


Figure 2. (a) ^{1}H NMR spectrum of **1b** in 20% DMSO-d_6−$CDCl_3$. (b) ^{1}H NMR spectrum of **1b** and potassium salt of (*S*)-Mosher's acid in 20% DMSO-d_6−$CDCl_3$ in the presence of 18-crown-6.

counteranion from bromide to a chiral anion. The counteranion was changed in situ by treating racemic **1b** with the potassium salt of (*S*)-2-methoxy-2-(trifluoromethyl)phenylacetate in the presence of 18-crown-6. The ^{1}H NMR spectrum exhibited excellent splitting in each pair of doublets. These results demonstrate the potential of spiro imidazolium salts in molecular recognition studies (Figure 2).

Further, we attempted the optical resolution of these novel spiro bis(imidazolium) salts to obtain chiral ionic liquids. However, the method of resolution in which a diastereomeric salt is formed with (1*S*)-(+)-10-camphorsulfonic acid followed by recrystallization was unsuccessful. After screening several conditions, the optical resolution of **1b** was achieved by HPLC using a chiral stationary phase column Sumichiral OA-4500.[10] Each enantiomer of **1b** separated by preparative HPLC exhibited opposite optical rotations; $[\alpha]_D^{19}$ −1.86 (*c* 0.27, MeOH) and $[\alpha]_D^{19}$ +1.79 (*c* 0.28, MeOH). The counteranion of enantiomer **1b** was exchanged with lithium bis(heptafluoropropanesulfonyl)imide to produce the enantiomer of chiral ionic liquid **1i** with the rotations; $[\alpha]_D^{28}$ −1.74 (*c* 0.24, MeOH) and $[\alpha]_D^{28}$ +1.75 (*c* 0.27, MeOH).

In conclusion, novel spiro chiral ionic liquids were synthesized and their optical resolution was achieved. Room temperature ionic liquids were produced by appropriately selecting N-substituents and counteranions. As a preliminary study we have also demonstrated their chiral discrimination abilities. Applications of these novel spiro chiral imidazolium salts in asymmetric reactions are in progress.

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Supporting Information Available: Experimental procedures, full characterization, and X-ray crystallography in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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