HETEROCYCLES, Vol. 63, No. 9, 2004, pp. 2033 - 2041
Received, 27th May, 2004, Accepted, 22nd July, 2004, Published online, 23rd August, 2004

NEW PYRIDINIUM CHIRAL IONIC LIQUIDS

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Abstract – New pyridinium chiral ionic liquids have been synthesised from the corresponding pyridine and chiral primary amines. The physical properties of these salts were determined; one of the salts is a room-temperature ionic liquid thermally stable up to 215 °C and suitable for organic synthesis.

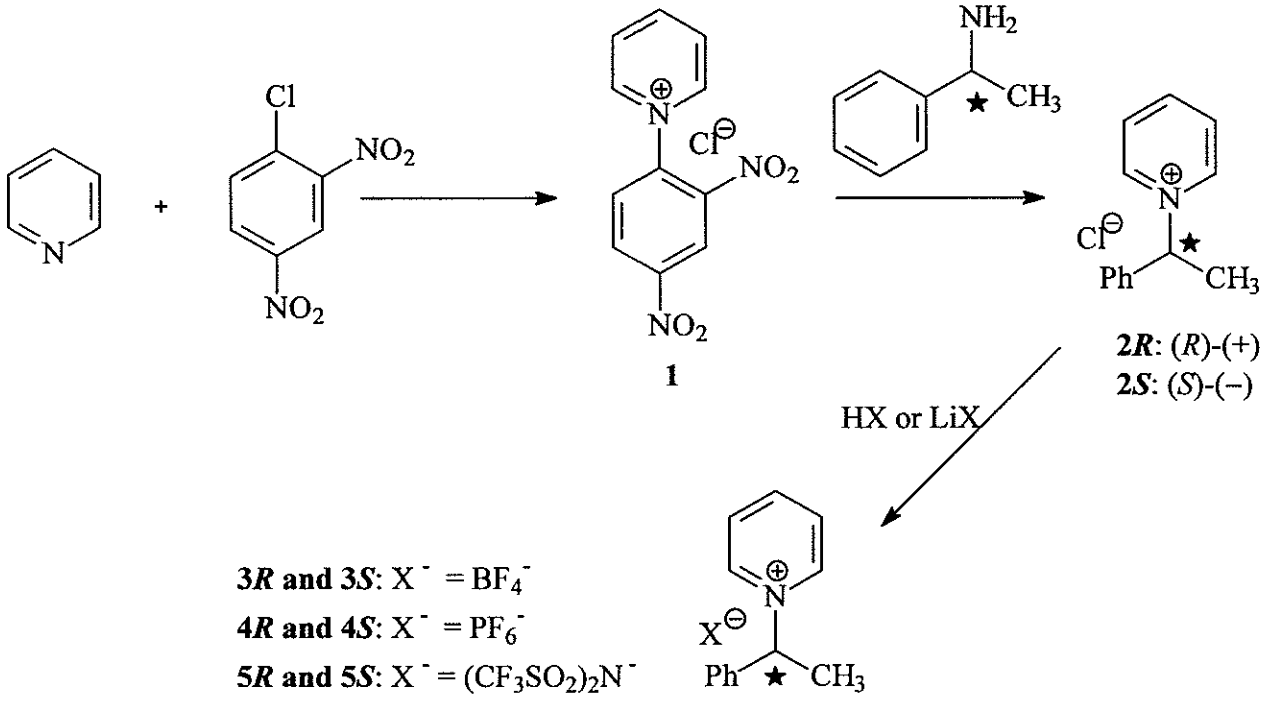
INTRODUCTION

Room temperature ionic liquids (RTILs) are widely accepted as an alternative to conventional organic solvents in many areas of organic,[1] organometallic[2] and enzymatic[3] synthesis as well as in separation chemistry.[4] Among them, chiral ionic liquids are attractive for their potential application to chiral discrimination, including asymmetric synthesis and optical resolution of racemates. A significant transfer of chirality in these solvents should be expected.[5] However, only few chiral ionic liquids (ILs) have been reported to date: in these examples the chirality is either brought by the anion[6] or the cation.[7]

In the present paper, we report the preparation and the physical properties of new ILs incorporating *N*-alkylpyridinium chiral cations associated with different anions: tetrafluoroborate (BF_4^-), hexafluorophosphate (PF_6^-) and bis(trifluoromethanesulfonyl) imide (NTf_2^-).

RESULTS AND DISCUSSION

The use of Marazano's route,[8] based on the original work of Zincke,[9] allowed access to unique chiral pyridinium salts. Reaction of Zincke's salt (**1**), readily obtained from pyridine and 1-chloro-2,4-dinitrobenzene, with chiral primary amines gave the corresponding enantiopure alkyl-pyridinium chlorides (Scheme 1).



Scheme 1: Synthesis of pyridinium salts

The use of (*R*)-(+)-1-phenylethylamine and (*S*)-(–)-1-phenylethylamine allowed preparation of the pyridinium chlorides (**2*R***) and (**2*S***) respectively. Starting from **2*R***, pyridinium salts (**3*R***, **4*R*** and **5*R***) were obtained in quantitative yields upon anion exchange with tetrafluoroboric acid (HBF_4), hexafluorophosphoric (HPF_6) and lithium bis(trifluoromethanesulfonyl)imide[10] ($LiNTf_2$) respectively. In a similar way compounds (**3*S***, **4*S*** and **5*S***) were obtained from **2*S***. The absence of epimerization throughout this process was checked by ^1H NMR spectroscopy in the presence of non-racemic europium salts (Figure 1) and confirmed by the coherence of the optical rotations of both enantiomers (Table 1). All the corresponding racemates were synthesized and their properties were compared with the enantiopure samples. All the chiral salts synthesized were miscible with methanol, acetone, dichloromethane and immiscible with hexane and more interestingly with 1,1,1-trichloroethane. Hexafluorophosphate salts (**4*R*** and **4*S***) and bis(trifluromethanesulfonyl)imide salts (**5*R*** and **5*S***) are immiscible with water.

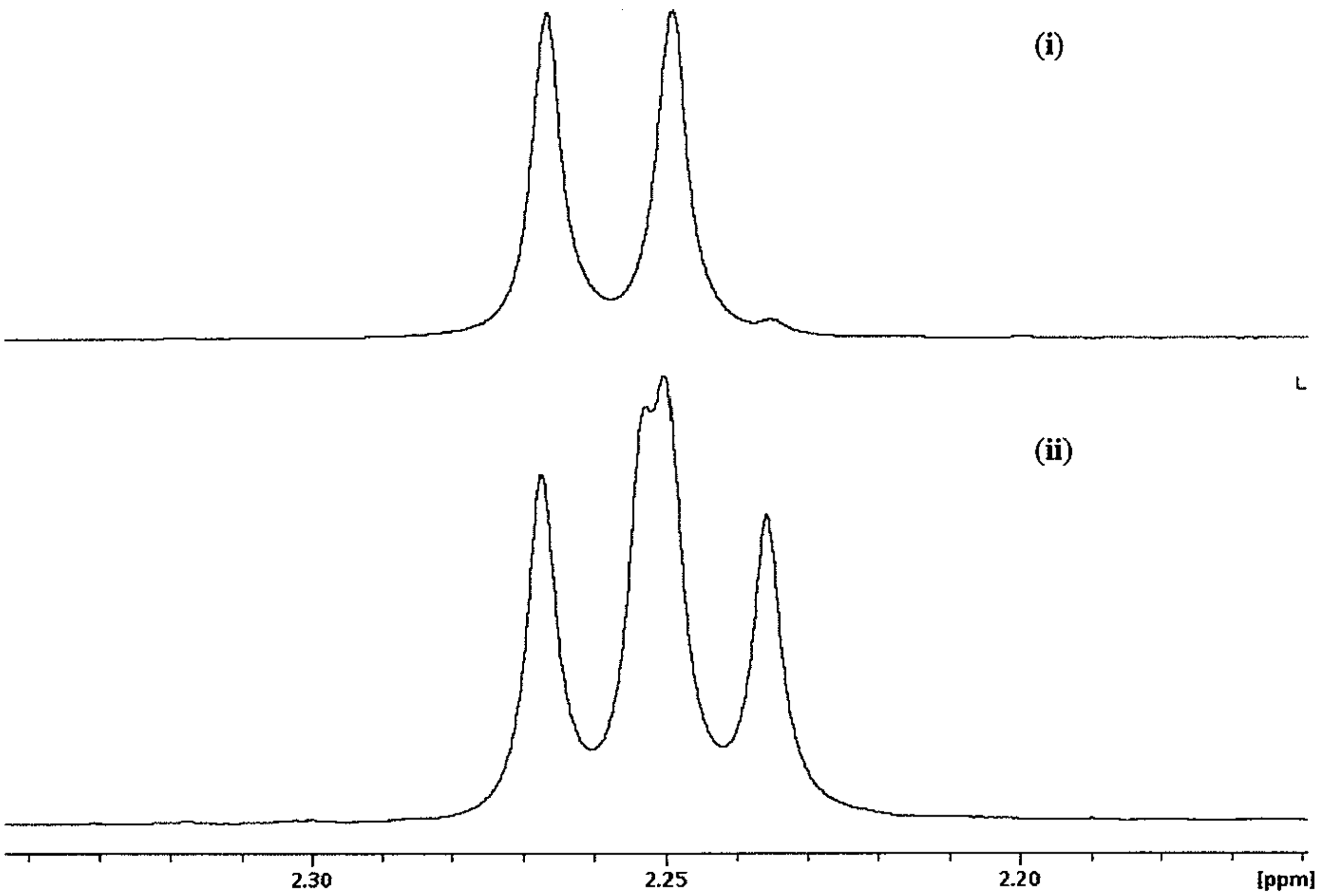


Figure 1 Characteristic signal of the methyl group on the ^{1}H NMR (400 MHz) spectra of compound **5S** (i) and **5*rac*** (ii) upon addition of europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] in CD_3OD

The thermal behaviour (glass transition temperatures T_g) of all compounds was determined by differential scanning calorimetry and, as expected, is dependent on the nature of the counteranion (from 125 °C to –30 °C). The upper limit of the liquidus range of these salts which is bounded by the thermal decomposition was also determined: it is 200 °C for compounds (**2** and **3**), 188 °C for compound (**4**) and 215 °C for compound (**5**). For the RTILS (**5*R***, **5*S*** and **5*rac***) viscosity, density and surface tension were determined and reported in Table 2. The liquid state of the two enantiomers of compound (**5**) (above –30 °C) and its relatively low viscosity allow their use as chiral solvents.

Table 1 Physical properties of compounds (**2**, **3** and **4**)

Anion (compound)	Cation configuration	T_g (°C)	$[\alpha]_D^{20}$ (*c* 1%, MeOH)
Cl^- (**2**)	*S*-	+ 125	-45.2
	R-	+ 125	+44.9
	rac -	+ 125	0.0
BF_4^- (**3**)	*S*-	+ 65[a]	-11.5
	R-	+ 65[a]	+11.5
	rac -	+ 65[a]	0.0
PF_6^- (**4**)	*S*-	+ 110	- 9.4
	R-	+ 107	+ 8.9
	rac -	+ 110	0.0

[a] This value was measured in a capillary on a Büchi-Tottoli apparatus due to highly hygrocopic character of compounds (**3**)

Table 2 Physical properties of RTILs (compounds **5**)

Cation configuration	T_g (°C)	$[\alpha]_D^{20}$ (*c* 1%, MeOH)	Density (g/cm^3) 25 °C	Viscosity (cP) 20 °C	Viscosity (cP) 25 °C	Surface tension (mN/m) 25 °C
S-	- 30	-22.3	1.33 ± 0.02	428	288	37.9± 0.1
R-	- 30	+21.5	1.31 ± 0.04	411	279	37.9± 0.1
rac -	- 37	0.0	1.32 ± 0.01	426	275	38.2± 0.3

Diels-Alder cycloaddition[11] between 3-(2-propenoyl)-2-oxazolidinone and excess cyclopentadiene was chosen as a model reaction. Clean conversion was observed after 5 h at 0 °C (at a concentration of 0.7M in dienophile) and in the absence of any catalyst. A reproducible 85% yield of the expected cycloadduct was isolated after extraction with 1,1,1-trichloroethane and standard purification. (This process was repeated several times without affecting the efficiency of the transformation). Thus, use of **5** as solvent in this Diels-Alder reaction led to an appreciable acceleration in comparison to dichloromethane (< 60% yield under identical conditions), and compares well with related examples using imidazolium type RTILs.[12] No influence on the stereochemical outcome of the reaction was noted in this preliminary study (a 89:11 endo-exo ratio was measured by ^{1}H NMR spectrum, similar to what is observed in dichloromethane, and no asymmetric induction could be detected by chiral HPLC).

Finally, the flexibility of the synthetic route employed, in regard with the substituent on the heterocyclic ring and/or the nature of the amines should, in principle, allow the "fine tuning" of the physical properties of these new chiral RTILs. Moreover, this approach gives access to both optical series, each enantiomer of the starting amine being equally available. This represents an advantage over chiral pool derived RTILs.
In conclusion, this work describes the first of a new class of pyridinium-based chiral RTILs, readily accessible in three steps from commercially available material, in which a stereogenic centre is directly attached to the cationic heterocyclic moiety.

EXPERIMENTAL

Synthesis

Zincke salt (1)

Freshly distilled pyridine (7.81 g, 98.74 mmol) was added to a solution of 1-chloro-2,4-dinitrobenzene (20 g, 98.74 mmol) in acetone (300 mL). This mixture was heated under reflux for 24 h. After cooling (ice bath), the salt (**1**) was then precipitated in acetone and filtered. After purification by recrystallization from acetone, pale yellow crystals were collected in 81 % yield.
mp 200 °C ; ^{1}H-NMR (250 MHz), CD_3OD: δ =8.30 (d, J= 8.6 Hz, 1H), 8.40 (t, J= 8 Hz, 2H), 8.94 (m, 2H), 9.29 (m, 3H) ppm ; ^{13}C NMR (100 MHz, CD_3OD): δ = 120.98, 127.36, 128.99, 130.50, 137.95, 142.40, 145.10, 148.02, 148.99 ppm. Anal. Calcd for $C_{11}H_8N_3O_4Cl$, H_2O: C, 44.09; H, 3.36; N, 14.42; Found: C, 44.07; H, 3.29; N, 14.59.

Synthesis of 2*R*, 2*S* and 2*rac*

To a solution of Zincke salt (**1**) (15.38 g, 70 mmol) in *n*-BuOH (200 mL) was added (+)-(*R*) or (–)-(*S*) or *rac*-1-phenylethylamine (9.38 g, 77 mmol). The mixture was boiled under reflux for 24 h. The solvent was removed under vacuum. To the residue was added distilled water. The precipitates were filtered off, and the filtrate was washed with dichloromethane three times. The aqueous solution was concentrated under reduced pressure. The residue was purified by HPLC (Waters Alliance 2695, column C18 Delta Park 300Å (19x300mm), isocratic mode water:acetonitrile 80:20, flow rate 5mL/min). Compounds (**2*R***) or (**2*S***) or (**2*rac***) were obtained as colourless and very hygroscopic salts (**2*R***: 91.6 %; **2*S***: 93, 51 %; **2*rac***: 92 %). ^{1}H-NMR (250 MHz), CD$_3$OD: δ =2.12 (d, J= 7.0 Hz, 3H), 6.22 (q, J= 7.0 Hz, 1H), 7.46 (m, 5H), 8.13 (t, J = 6.87 Hz, 2H), 8.58 (t, J = 7.94 Hz, 1H), 9.11 (d, J=5.62 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD$_3$OD): δ = 20.84, 71.77, 121.65, 127.76, 129.08, 130.11, 130.62, 143.26, 145.99. **2*R***: Anal. Calcd for $C_{13}H_{14}NCl$, 0.4H_2O: C, 68.74; H, 6.52; N, 6.17; Found: C, 68.65; H, 6.74; N, 6.26; **2*S***: Anal. Calcd for $C_{13}H_{14}NCl$, 0.5: C, 68.27; H, 6.61; N, 6.12; Found: C, 68.35; H, 6.64; N, 6.16; **2*rac*** : Anal. Calcd for $C_{13}H_{14}NCl$, 0.5: C, 68.27; H, 6.61; N, 6.12; Found: C, 68.45; H, 6.74; N, 6.26.

Compounds (3*R*, 3*S* and 3*rac*)

To a solution of **2*R***, **2*S***, **2*rac*** (1.52g, 6.93 mmol) in 20 mL of water was added 0.61g (6.93 mmol) of aqueous HBF_4 (50% in water). The mixture was kept at 0°C for 2 h and then stirred for 16 h at rt. The solution was neutralised with basic aluminium oxide, pH 9.5. The neutralised solution was filtered and concentrated under reduced pressure. Compounds (**3**) were obtained as white hygroscopic crystals.
3*S*: Anal. Calcd for $C_{13}H_{14}NBF_4$: C, 57.60; H, 5.21; N, 5.17. Found: C, 56.68; H, 5.26; N, 5.26; **3*R***: Found: C, 57.68; H, 5.26; N, 5.16; **3*rac***: Anal. Calcd for $C_{13}H_{14}NBF_4$,H_2O: C, 54.01; H, 5.58; N, 4.85; Found: C, 54.29; H, 5.24; N, 4.94; MS-ES, + mode, - mode: m/z=+184(100%) ; m/z=87(100%)

Compounds (4*R*, 4*S* and 4*rac*)

To a solution of **2R**, **2S**, **2*rac*** (2.01 g, 9.16 mmol) in 20 mL of water was added 1.47 g (11.08 mmol) of aqueous HPF_6 (60% in H_2O). The mixture was kept at 0°C for 2 h and stirred for 16 h at rt. Compound (**4**) precipitated in water. The mixture was filtered and washed with water until neutral. The white crystals were recrystallized in ethanol. ^{19}F NMR (376MHz, CD$_3$OD): δ=1.6 ppm (d, J=706.7 Hz)
Anal. Calcd for $C_{13}H_{14}N F_6P$: C, 47.43; H, 4.29; N, 4.25; **4*R***: Found: C 47.07; H, 3.88; N, 4.17; **4*S***: Found: C, 46.99; H, 3.93; N, 4.18; **4*rac***: Found: C, 47.16; H, 3.82; N, 4.18; MS-ESI+: m/z = +184; ESI-: m/z =145.

Compounds (5*R*, 5*S* and 5*rac*)

5*R*, **5*S*** and **5*rac*** were prepared from **2*R***, **2*S*** and **2*rac*** respectively and $LiNTf_2$ following the anion exchange method described in the literature.[10]

As a representative example NMR spectral data for compound (**5**) are given: ^{1}H-NMR (400 MHz, CD_3OD): δ (ppm) 2.11 (d, *J* = 7.0 Hz, 3H), 6.13 (q, *J* = 7.0 Hz, 1H), 7.43-7.48 (m, 5H), 8.04-8.07 (m, 2H), 8.46 (t, J = 7.94 Hz, 1H), 8.92 (d, *J* =5.62 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) : δ (ppm) 20.8, 71.8, 121.7, 127.8, 129.1, 130.1, 130.6, 136.0, 143.3, 146.0; ^{19}F-NMR (376 MHz, CD_3OD): δ = -2.4 ppm.

Anal. Calcd for $C_{15}H_{14}N_2O_4F_6S_2$: C, 38.80; H, 3.04; N, 6.03; S, 13.81; ***5R***: Found: C, 38.79; H, 3.18; N, 6.08; S, 13.79; ***5S***: Found: C, 38.90; H, 3.24; N, 6.20; S, 13.75; ***5rac***: Found: C, 38.89 ; H, 3.02; N, 6.11; S, 13.56; MS-ESI+: m/z = 184; ESI- : m/z = 280.

It might happen that upon standing at rt compound (**5**) crystallizes to give a hydrated form having a melting point of 47.5 °C. Gentle heating under high vacuum on P_2O_5 allows return to the liquid phase.

Analysis of physical properties

^{1}H-NMR spectrum

The ^{1}H-NMR spectra (400 MHz) were obtained from a molar mixture of the synthesized salt and europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] in CD_3OD at 20 °C.

Optical rotations

The measurements were performed at 20 °C in a Perkin Elmer 241 polarimeter (Na lamp, λ = 589 nm) using 1% solutions in MeOH.

DSC analysis

The thermograms of the various products were recorded on a Differential Scanning Calorimeter (model PYRIS 1DSC Perkin Elmer). About 15 mg of sample was placed in a pin-holed aluminium sample pan (50μL, Perkin Elmer B 0143017 model), and heated for 4 cycles at various rates (5, 10, 15, 20 °C/min) in the range of -50 °C to 200 °C under a stream of nitrogen. The temperature values were extrapolated to 0 °C/min.

Viscosity

The viscosity of the RTIL was determined with a Brookfield, model DV III viscosimeter. For each analysis a 0.5 mL sample was used and the measurements were repeated three times. The temperature of the samples was maintained at 0.1 °C by means of an external temperature controller (at 20 °C and 25 °C).

Density

The density of each RTIL was determined by weighing using a Mettler AE 240. : the density of each ionic liquid (***5R***, **5*S***, ***5rac***). was determined on a Mettler AE 240 balance and a Nichiryo 5000 pipetman. For each analysis a 1 mL sample was used and the mass of the volume of liquid was determined using 50 μL portions. The measurements were repeated three times and the average value is reported. All measurements were made at room temperature (25±1 °C). The pipetman was calibrated on a 2 mL sample of water using 50 μL portions.

It is worth noting that compound (**5**) displayed physical properties (viscosity, density) identical to that of the known 1-methyl-3-(5-hydroxypent-1-yl)imidazolium hexafluorophosphate.

Surface tensions

The measurements were made at 25°C with a pendant drop tensiometer (KRUSS GmbH) model DSA 10-Mk2. The density of the drops was taken to be 1.32.

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