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Room Temperature Ionic Liquids – New Choline Derivatives

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New room temperature ionic liquids – choline derivatives were prepared by Menschutkin reaction with alkyl chloromethyl ethers and anion changed to bis(trifluoromethylsulfonyl)amide ion. The newly obtained butoxymethyl(2-hydroxyethyl)dimethylammonium bis(trifluoromethanesulfonyl)amide was successfully tested as a solvent for *O*-acylation in two-phase reaction system. The ionic liquid-catalyst system was recycled and reused.

Key words: room temperature ionic liquid, choline derivatives, phase-transfer catalysis

In the last few years an acceleration of synthesis and application of ionic liquids (ILs) has been observed. Their main advantages include a negligible vapor pressure and the availability of a wide range of liquids with melting points below the temperature of boiling water. They seem to provide "green" alternatives to classical organic solvents in synthesis, catalysis and separation techniques (*e.g.* extraction, chromatography). Among the multitude of possible ILs, the main area of research has involved the synthesis and application of imidazolium and pyridinium salts. In literature there are many excellent reviews of these ILs, summarizing their preparation, use and advantages compared to traditional solvents [1–6].

Wasserscheid and co-workers have presented chiral ILs, derived from aminalcohols, which can be used in new chiral systems with synthetic and analytical applications [7]. Abbott and co-workers have applied choline ILs with a zinc and tin chloride complex as moisture-stable Lewis-acidic catalyst and solvent [8]. The synthetic precursors of ILs represent, in many cases, quaternary ammonium compounds (QACs), which are popular as a phase-transfer (PT) catalyst. QACs of natural origin, *e.g.*, *Cinchona*-derived ammonium salts [9–12] have also started to be used as PT catalyst.

RESULTS AND DISCUSSION

Two homologous series of the new choline ionic liquid derivatives were prepared in a two-step synthesis (Scheme 1). In the first step deanol – 2-(dimethylamino)ethanol or 2-(dimethylamino)ethyl acetate was reacted with alkyl chloromethyl ethers with

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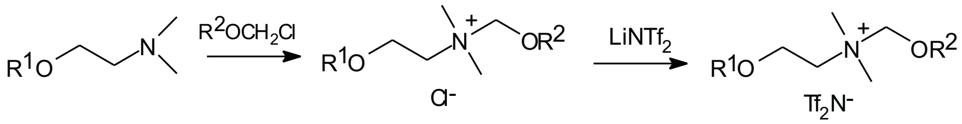
Scheme 1



(**1a**–**k** and **2a**–**k**) (**3a**–**k** and **4a**–**k**)

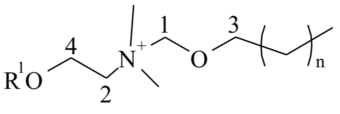
2–12 carbons in an alkyl chain. This was Menschutkin reaction type S_N1, in which the formation of the cation $ROCH_2^+$ by ionization involved the slowest step. The alkoxymethyl(2-hydroxyethyl)dimethylammonium chlorides **1a–k** were obtained with 83–90% yields as colorless oils for **1a–f**, grease for **1g–h** and white precipitate for **1i–k**. The (2-acetoxyethyl)alkoxymethyldimethylammonium chlorides **2a–k** gave higher yields (87–99%) and formed very hygroscopic precipitates. The chlorides were employed as synthetic precursors of ILs. The subsequent reaction was ion exchange chloride on bis(trifluoromethylsulfonyl)amide ion – $[Tf_2N]^-$ in aqueous solutions. The reactions provided a range of 22 new room temperature ionic liquids (RTILs): alkoxymethyl(2-hydroxyethyl)dimethylammonium $[Tf_2N]$ **3a–k** and (2-acetoxyethyl)alkoxymethyldimethylammonium $[Tf_2N]$ **4a–k**. (Table 1). The anhydrous salts were obtained by heating of the samples at 60°C in vacuum (10 mmHg) for 12 h. Karl-Fisher measurements showed water content of dried salts to be < 500 ppm.

Table 1. Ammonium chlorides (**1a**–**k** and **2a**–**k**) and RTILs (**3a**–**k** and **4a**–**k**) prepared.

Chloride No	R^1	R^2	Yield (%)	RTIL No	R^1	R^2	Yield (%)
1a	H	C_2H_5	88	**3a**	H	C_2H_5	93
1b	H	C_3H_7	83	**3b**	H	C_3H_7	90
1c	H	C_4H_9	85	**3c**	H	C_4H_9	89
1d	H	C_5H_{11}	83	**3d**	H	C_5H_{11}	90
1e	H	C_6H_{13}	83	**3e**	H	C_6H_{13}	90.5
1f	H	C_7H_{15}	88	**3f**	H	C_7H_{15}	89
1g	H	C_8H_{17}	90	**3g**	H	C_8H_{17}	94
1h	H	C_9H_{19}	84	**3h**	H	C_9H_{19}	86
1i	H	$C_{10}H_{21}$	89	**3i**	H	$C_{10}H_{21}$	88
1j	H	$C_{11}H_{23}$	84	**3j**	H	$C_{11}H_{23}$	87.5
1k	H	$C_{12}H_{25}$	85	**3k**	H	$C_{12}H_{25}$	88
2a	Ac	C_2H_5	99	**4a**	Ac	C_2H_5	75
2b	Ac	C_3H_7	99	**4b**	Ac	C_3H_7	78
2c	Ac	C_4H_9	98	**4c**	Ac	C_4H_9	83
2d	Ac	C_5H_{11}	99	**4d**	Ac	C_5H_{11}	80
2e	Ac	C_6H_{13}	92	**4e**	Ac	C_6H_{13}	99
2f	Ac	C_7H_{15}	95	**4f**	Ac	C_7H_{15}	98
2g	Ac	C_8H_{17}	93	**4g**	Ac	C_8H_{17}	81
3h	Ac	C_9H_{19}	94	**4h**	Ac	C_9H_{19}	85
3i	Ac	$C_{10}H_{21}$	96	**4i**	Ac	$C_{10}H_{21}$	87
3j	Ac	$C_{11}H_{23}$	98	**4j**	Ac	$C_{11}H_{23}$	90
3k	Ac	$C_{12}H_{25}$	87	**4k**	Ac	$C_{12}H_{25}$	90

The prepared new RTILs were characterized by ^{1}H and ^{13}C NMR spectra and elemental analyses CHN. Comparison of ^{1}H NMR spectra of chlorides **1**, **2** with those of salts **3**, **4** demonstrated shifts in proton signals in five groups, as listed in Table 2. The shifts were observed of 10 protons localized adjacent to the quaternary nitrogen atom and of 4 protons of two CH_2 groups $\underline{CH_2}CH_2NCH_2O\underline{CH_2}$. The substitution of a small anion $[Cl]^-$ for a large one $[Tf_2N]^-$ resulted in proton signal shifts to as much as 0.53 ppm. Similar observation was made by Fannin and co-workers [13] for chloroaluminate 1,3-dialkylimidazolium. In this case only 3 protons of the imidazole ring altered their position depending upon the type of the anion. In ^{13}C NMR spectrum for salts **1**–**4** no alterations in the carbon signal shifts were seen.

Table 2. The shifts in proton signals.



Group	Chlorides (**1a**–**k**)	Tf_2N (**3a**–**k**)	Chlorides (**2a**–**k**)	Tf_2N (**4a**–**k**)
$N(CH_3)_2$	3.32 (s)	3.12 (s)	3.44 (s)	3.11 (s)
CH_2 (1)	4.98 (s)	4.64 (s)	5.16 (s)	4.63 (s)
CH_2 (2)	3.67 (t, J = 4.9)	3.47 (t, J = 4.7)	4.04 (t, J = 4.9)	3.64 (t, J = 4.8)
CH_2 (3)	3.86 (t, J = 6.6)	3.79 (t, J = 6.6)	3.40 (t, J = 6.6)	3.80 (t, J = 6.6)
CH_2 (4)	4.07 (t, J = 4.3)	4.05 (t, J = 4.3)	4.57 (t, J = 4.8)	4.46 (t, J = 4.7)

s – singlet, t – triplet, J in Hz.

The obtained RTILs have no distinguishable vapor pressure and the first thermal event on heating is thermal decomposition. The established temperature onsets for decomposition are presented in Table 3. The measurements were performed using Bűchi melting point apparatus (B-540 for the visual determination of melting and boiling points) and their results overlapped with those of TGA. The thermal stability depends on the number of oxygen atoms in the molecule. $[Tf_2N]$ salts with two oxygen atoms (**3**) are stable up to a temperature of 210–250°C and those with three oxygen atoms (**4**) only up to 170°C. The obtained RTILs should be classified as "high-flying" ionic liquids as compared to the well known "low-flying" 1-alkyl-3-methylimidazolium $[Tf_2N]$, which was stable up to 400°C [14].

Table 3. Temperature onset for decomposition, density, viscosity and conductivity for prepared RTILs **3a**–**k** and **4a**–**k**.

RTIL No	Tc (°C)	ρ ($g \cdot mL^{-1}$)	η (cP)	κ ($mS \cdot cm^{-1}$)
3a	208.9	1.453	73	1.79
3b	213.4	1.420	84	1.69
3c	218.3	1.386	90	1.60
3d	222.1	1.378	100	1.42
3e	227.5	1.343	114	1.27
3f	233.8	1.309	134	1.18
3g	242.8	1.284	149	0.88
3h	247.3	1.268	166	0.77
3i	251 (dec.)	1.259	187	0.55
3j	251 (dec.)	1.230	200	0.53
3k	251 (dec.)	1.194	232	0.38
4a	170 (dec.)	1.426	170	1.34
4b	170 (dec.)	1.393	179	1.21
4c	170 (dec.)	1.359	183	0.92
4d	170 (dec.)	1.342	187	0.88
4e	170 (dec.)	1.315	193	0.70
4f	170 (dec.)	1.297	200	0.60
4g	170 (dec.)	1.254	214	0.49
4h	170 (dec.)	1.244	232	0.42
4i	170 (dec.)	1.220	251	0.37
4j	170 (dec.)	1.210	270	0.31
4k	170 (dec.)	1.200	293	0.27

Tc – temperature onset for decomposition; ρ – density at 25°C;
η – viscosity 25°C; κ – electrical conductivity.

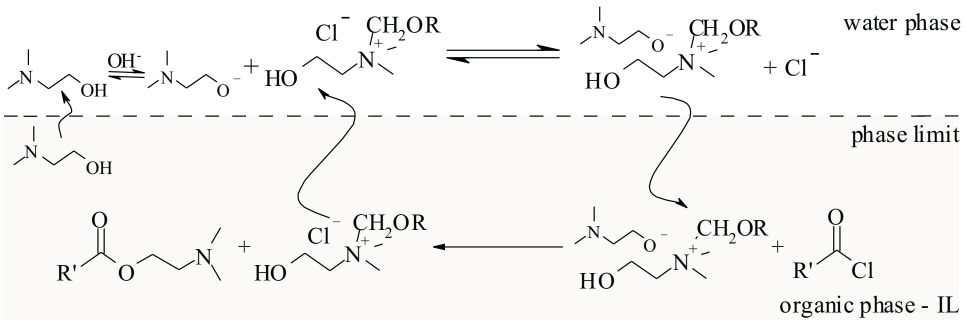
With increasing alkoxy chain length, the RTILs become less dense. The relationships between density and the number of atoms in the alkoxy group were close to linear, similar to that observed for asymmetric RTILs [15,16] and protonated RTILs [17] with 3-alkoxymethylimidazolium cation. Comparing density of the salts with the same alkoxymethyl substituent in the **3a**–**k** series homologous with **4a**–**k** series no significant changes could be noted even if the molecular weights of the compounds differed. In the range of 15 to 30°C only insignificantly affected results of density measurement were noted.

Viscosities of RTILs **3a**–**k** were definitely lower than those of **4a**–**k**. In this case, molecular weight played a significant role: increase in its value was accompanied by an increase in viscosity. Effects of temperature on results of viscosity measurements were quite evident: a decrease in temperature from 25°C to 20°C resulted in viscosity increased by 20%. The lowest viscosity was demonstrated in ethoxymethyl(2-hydroxyethyl)dimethylammonium [Tf_2N] **3a**: it amounted to 73.07 mPa·s at 25°C, which was comparable to viscosity of 3-butyl-1-methylimidazolium [Tf_2N] [14,18] and trifluoroacetate [14]. The RTILs exhibited conductivity values between 3.8 and 17.9×10^{-4} S/cm for alkoxymethyl(2-hydroxyethyl)dimethylammonium [Tf_2N] **3a**–**k** and between 2.7 and 13.4×10^{-4} S/cm for (2-acetoxyethyl)alkoxymethyldimethylammonium [Tf_2N] **4a**–**k**. (Table 3). The highest conductivity was shown for ethoxymethyl(2-hydroxyethyl)dimethylammonium [Tf_2N] **3a** and was similar to that found in 1-butyl-3-methylimidazolium tetrafluoroborate [14] and sufficient to represent suitable media for electrochemical applications, such as in batteries and for metal deposition. For each RTIL we have observed lack of miscibility with hexane and water. The water-RTIL mixture consisted of a lower organic layer with evident opalescence, containing around 1% of water. In contrast to 1-alkyl-3-methylimidazolium tetrafluorobarates [19] all the synthesized RTILs were practically insoluble in water (although to a variable degree) independently of the length of the alkoxy chain. At room temperature, the obtained RTIL dissolved in acetone, ethyl acetate, CH_3OH, CH_2Cl_2 and DMF. They also dissolved in $CHCl_3$, except **3a**–**f**, **4a**–**b** and toluene, excep **3a**–**h** and **4a**–**h**.

The physical properties seemed to be optimal for application of the compounds in chemical processes. Low viscosity facilitated mixing and the density, high as compared to that of water and hexane, accelerated phase separation. Therefore, we decided to investigate the two-phase transfer catalyzed reaction of *O*-acylation of deanol with acid chloride. Deanol esters are very widely applied pharmaceuticals. The convenient method of synthesis is acid chloride alcoholysis. The reaction can be catalyzed by the addition of QAC into a two-phase water–organic system. The addition of a base to the aqueous phase neutralizes the produced hydrochlorides. A series of QACs was tested as PT catalysts to promote reactions between phenols and alkyl halides in an aqueous solution of sodium hydroxide in the absence of an organic solvent. Methyltrioctylammonium chloride emerges as the most effective catalyst [20]. Esterification of alcohols with carboxylic acids in 1-butylpyridinium chloroaluminate (at the molar ratio of $AlCl_3$/butylpyridinium chloride lower than 0.1 – Lewis basic) was reported by Deng *et al.* [21]. Most of the resultant products were easily recovered due to their immiscibility with IL. In this case, IL played the role of a catalyst and a solvent. The investigated reactions also included catalyzed esterifications in ILs with acidic counteranions as recyclable reaction media. Good yields and high selectivities were obtained [22]. Recently, ILs have been used as effective reaction media in the esterification of carboxylate sodium salts with alkyl halides [23].

In this report deanol ester synthesis is presented in new RTIL, *via* PT catalyst. Chlorate solvents such as $CHCl_3$ and CH_2Cl_2 were replaced by the newly obtained RTIL – butoxymethyl(2-hydroxyethyl)dimethylammonium [Tf_2N] **3c** and alkoxymethyl(2-hydroxyethyl)dimethylammonium chloride **1** was used as a catalyst. In relation to forming emulsion and the time of duration of two phase butoxymethyl-(2-hydroxyethyl)dimethylammonium chloride **1c** was found to be the optimum catalyst.

The reaction system was constructed on the reaction procedure described by Szeja [24]and adapted to aminoalcohol reaction. The reaction was carried out in a two phase system, where the water phase of 10% aq NaOH was accompanied by an organic phase. NaOH reacted with deanol to give reactive alcoholate anions and also protected against the formation of hydrochlorides during the reaction. Transport of alcoholate anion to RTIL played a key role in the reaction (Scheme 2). The ester was



Scheme 2. Base-initiated reaction mechanism *O*-acylation of deanol.

isolated by washing with a non-polar solvent; in this case with hexane. This permitted the removal of the ester and remaining reactants from RTIL. The extract, ester and RTIL-catalyst system was controlled by TLC and ^{1}H NMR.

CH_3COCl, $C_7H_{15}COCl$, $C_9H_{19}COCl$ and PhCOCl were used as the acid chloride, which resulted in the 83, 90.5, 93 and 91% yield of *O*-acylation of deanol, respectively, after 35 min.

The RTIL-catalyst system was reused without additional purification. This system was examined for 6 cycles with no significant loss in purity and efficiency. The reaction efficiency averaged at 89% after 35 minutes and the solvent loss was below 1.5% (Table 4). After the reaction cycles, the RTIL was recovered by washing with water, which removed the used catalyst, and by drying in vacuum.

Table 4. Reaction yield and solvent loss in successive *O*-acylation in two-phase reaction system.

Cycle	I	II	III	IV	V	VI
Yield (%)	90.5	88	89	89	87	88
Solvent loss (%)	1.0	1.3	1.2	1.0	1.0	1.0

CONCLUSIONS

We have presented a rapid and easy method for the synthesis of new RTILs, alkoxymethyl(2-hydroxyethyl)dimethylammonium and (2-acetoxyethyl)alkoxymethyldimethylammonium [Tf$_2$N]. These low viscosity liquids could be used as solvents for *O*-acylation. Butoxymethyl(2-hydroxyethyl)dimethylammonium chloride as a new PT catalyst and butoxymethyl(2-hydroxyethyl)dimethylammonium [Tf$_2$N] as a solvent have been found in *O*-acylation reaction. The applied RTIL has been surprisingly inert in conditions of the reaction and could be easily separated from water, due to a miscibility gap with water. The product could have been completely extracted with hexane. This new RTIL seems to provide an alternative to volatile organic solvents.

EXPERIMENTAL

NMR spectra were recorded on a Varian model XL 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, with TMS as standard. Elemental analyses CHN were done at the A. Mickiewicz University, Poznań. Satisfactory microanalysis was obtained C ± 0.34; H ± 0.38 and N ± 0.29. A Mettler Toledo DA 110M scale was used for the mass/density measurements.

General procedure for alkoxymethylation of 1a–k and 2a–k: To a stirred solution of 2-(dimethylamino)ethanol or 2-(dimethylamino)ethyl acetate (0.05 mol) in anhydrous hexane (20 ml) the corresponding chloromethyl alkyl ether (0.055 mol) in anhydrous hexane (10 ml) was added dropwise at r.t. After 10 minutes the precipitate or oil was washed with 3×10 ml dry hexane. The solid products were filtered and, then recrystallized from acetone.

Procedure for ion exchange: A saturated aqueous solution of $(CF_3SO_2)_2NLi$ was added to stechiometric amounts of saturated hot water solution of prepared quaternary ammonium chloride. After phase separation the water phase was decanted and obtained salt was washed with 3×50 ml water. The prepared RTIL was dried for 6 h at 50°C in vacuum.

Spectroscopic data of chloride **1c**: ^{1}H NMR ($CDCl_3$) δ ppm = 4.98 (s, 2H), 4.07 (t, J = 4.3 Hz, 2H), 3.86 (t, J = 6.6 Hz, 2H), 3.67 (t, J = 4.9 Hz, 2H), 3.32 (s, 6H), 1.62 (q, J = 7.1 Hz, 2H), 1.40 (m, J = 7.1 Hz, 2H), 0.93 (t, J = 7.1 Hz, 3H), ^{13}C NMR ($CDCl_3$) δ ppm = 90.9, 72.9, 62.4, 55.2, 48.0, 31.2, 18.6, 13.4; salt [Tf_2N] **3c**: ^{1}H NMR ($CDCl_3$) δ ppm = 4.64 (s, 2H), 4.05 (t, J = 4.3 Hz, 2H), 3.79 (t, J = 6.6 Hz, 2H), 3.47 (t, J = 4.7 Hz, 2H), 3.12 (s, 6H), 1.63 (q, J = 7.0 Hz, 2H), 1.28 (m, J = 7.1 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H), ^{13}C NMR ($CDCl_3$) δ ppm = 121.9, 117.6, 91.6, 73.4, 62.6, 56.1, 48.4, 31.3, 18.8, 13.5.

Spectroscopic data of chloride **2f**: ^{1}H NMR ($CDCl_3$) δ ppm = 5.16 (s, 2H), 4.57 (t, J = 4.8 Hz, 2H), 3.40 (t, J = 6.6 Hz, 2H), 4.04 (t, J = 4.9 Hz, 2H), 3.44 (s, 6H) 2.12 (s, 3H), 1.64 (q, J = 7.1 Hz, 2H), 1.30 (m, 8H), 0.89 (t, J = 6.7 Hz, 3H), ^{13}C NMR ($CDCl_3$) δ ppm = 169.7, 90.9, 73.6, 59.3, 57.4, 47.8, 31.4, 29.4, 28.7, 25.5, 22.3, 20.6, 13.8; salt [Tf_2N] **4f**: ^{1}H NMR ($CDCl_3$) δ ppm = 4.63 (s, 2H), 4.46 (t, J = 4.7 Hz, 2H), 3.80 (t, J = 6.6 Hz, 2H), 3.64 (t, J = 4.8 Hz, 2H), 3.11 (s, 6H) 2.10 (s, 3H), 1.64 (q, J = 7.0 Hz, 2H), 1.30 (m, 8H), 0.89 (t, J = 6.7 Hz, 3H), ^{13}C NMR ($CDCl_3$) δ ppm = 169.9, 126.1, 121.9, 117.6, 113.4, 91.4, 73.8, 59.8, 57.0, 48.2, 31.5, 29.3, 28.8, 25.5, 22.4, 20.4, 13.9.

Procedure for two phase catalysis in RTIL: Deanol (25 mmol) in RTIL **3c** (12 ml) and chloride **1c** as a catalyst (2.5 mmol) was stirred (>500 mph) with 10% aq NaOH (15 ml) at 0–5°C for 5 min before the addition of acid chloride (30 mmol). The mixture was stirred vigorously (>750 mph) and the organic phase was then separated and extracted by hexane (2×2 ml, 3×5 ml, 5×10 ml). The hexane was removed and the residue was fractionally distilled to yield the ester.

Acknowledgments

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REFERENCES

1. Welton T., *Chem. Rev.*, **99**, 2071 (1999).
2. Wasserscheid P. and Keim W., *Angew. Chem. Int. Ed. Engl.,* **39**, 3772 (2000).
3. Sheldon R., *Chem. Commun.*, 2399 (2001).
4. Olivier-Bourbigou H. and Magna L., *J. Mol. Catal. A: Chem.,* **182**–**183**, 419 (2002).
5. Dupont J., de Souza R.F. and Suarez P.A.Z., *Chem. Rev.,* **102**, 3667 (2002).
6. Wasserscheid P. and Welton T., *Ionic Liquids in Synthesis.* John Wiley & Sons, NY **2002**.
7. Wasserscheid P., Bösmann A. and Bolm C., *Chem. Comm.*, 200 (2002).
8. Abbott A.P., Capper G., Davies D.L., Munro H.L. and Tambyrajah V., *Chem. Comm.*, 2010 (2001).
9. Lygo B., Crosby J. and Peterson J.A., *Tetrahedron Lett.,* **40**, 1385 (1999).

10. Ooi T., Kameda M. and Maruoka K., *J. Am. Chem. Soc.,* **121**, 6519 (1999).
11. Kim D.Y., Huh S.C. and Kim S.M., *Tetrahedron Lett.,* **42**, 6299 (2001).
12. Chinchilla R., Mazon P. and Najera C., *Tetrahedron Asymmetry,* **13**, 927 (2002).
13. Fannin Jr. A.A., King L.A., Levisky J.A. and Wilkes J.S., *J. Phys. Chem.,* **88**, 2609 (1984).
14. Huddleston J.G., Visser A.E., Reichert M., Willauer H.D., Broker G.A. and Rogers R.D., *Green Chemistry,* **3**, 156 (2001).
15. Pernak J., Czepukowicz A. and Poźniak R., *Ind. Eng. Chem. Res.,* **40**, 2379 (2001).
16. Pernak J., Olszówka A. and Olszewski R., *Polish J. Chem.,* **77**, 179 (2003).
17. Pernak J. and Goc I., *Polish J. Chem.,* **77**, 975 (2003).
18. Aggarwal A., Lancaster N.L., Sethi A.R. and Welton T., *Green Chemistry,* **4**, 517 (2002).
19. Holbrey J.D. and Seddon K.R., *J. Chem. Soc., Dalton Trans.*, 2133 (1999).
20. Eynde J.J.V. and Mailleux I., *Synthetic Commun.,* **31**, 1 (2001).
21. Deng Y., Shi F., Beng J. and Qiao K., *J. Mol. Catal. A-Chem.,* **165**, 33 (2001).
22. Fraga-Dubreuil J., Bourahla K., Rahmouni M., Bazureau J. P. and Hamelin J., *Catalysis Commun.,* **3**, 185 (2002).
23. Brinchi L., Germani R. and Savelli G., *Tetrahedron Lett*., **44**, 2027 (2003).
24. Szeja W., *Synthesis*, 402 (1980).