Green Chemistry

Cite this: *Green Chem.*, 2011, **13**, 2459

www.rsc.org/greenchem

PAPER

Functional ionic liquid mediated synthesis (FILMS) of dihydrothiophenes and tacrine derivatives†

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Received 14th April 2011, Accepted 15th June 2011
DOI: 10.1039/c1gc15410a

Natural amino acid-based functional ionic liquid [Bz-His(n-propyl)$_2$-OMe$^+$Br$^-$] promoted diastereoselective synthesis of dihydrothiophenes is described. Further this functional ionic liquid was efficiently utilized to form tacrine derivatives from dihydrothiophenes using microwave irradiation. The functional ionic liquid exhibits organocatalytic as well as medium engineering capability, thus we named this synthetic protocol functional ionic liquid mediated synthesis (FILMS).

Introduction

Ionic liquids (ILs) have captured the attention of the chemical community across the globe as green alternatives to classical environmentally destructive media for synthesis, catalysis, separation and other various chemical tasks.[1] Ionic liquids encompass many unique properties, such as non-volatility, wide liquid range, high thermal stability, low toxicity, good solubility, incombustibility and reusability.[2] These properties make ionic liquids a modern material of immense importance with wide variety of applications. Introduction of functional groups to the cation or anion part *via* covalent tethering further revolutionized the field of ionic liquids in terms of application as modern materials. These ionic liquids are filling the imagination of chemists to use these for different applications. Several different functional groups have been already introduced in the cationic part of ionic liquids such as amines,[3] amides,[4] and acids[5] as well as in the anionic part, for example bis(trifluoromethylsulfonyl)amide[6] and nitrile.[7] A general term functional ionic liquids (FILs)[8] has been introduced which deals with ionic liquids having functional groups on cationic or anionic parts. We wish to introduce here functional ionic liquid mediated synthesis (FILMS), a specific term for the organic synthesis involving functional ionic liquids. In order to obtain "green" functional ionic liquids, the starting material must be non-toxic, renewable, cost effective and should have organocatalytic properties. Biorenewable natural compounds are ideal resources from both environmental and economical viewpoints.[8c,9] Thus we look forward to the development of second generation of biodegradable, environmentally compatible or natural functional ionic liquids (FILs) with reduced toxicity and high biocompatibility.

Thiophenes, dihydrothiophenes and tetrahydrothiophenes are valuable heterocycles which are essential constituents of a range of products, varying from pharmacologically active substances to materials (Fig. 1).[10] While synthesis of thiophenes and tetrahydrothiophenes has been an important area of research, dihydrothiophenes have received much less attention even though they are more amenable to further functionalize dihydrothiophenes.[11] However most of the methods described for the synthesis of dihydrothiophenes suffer from several drawbacks such as low yields, long reaction time, use of large quantity of volatile organic solvents, and harsh reaction conditions.[12] Therefore, it is challenging to develop an efficient and versatile methodology for the synthesis of dihydrothiophenes.

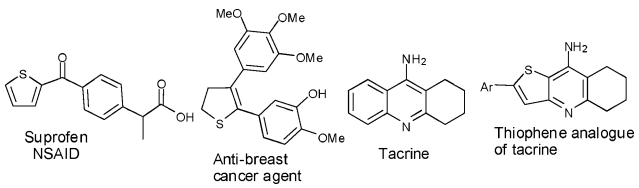

Fig. 1 Biologically important thiophene, dihydrothiophene, tacrine and tacrine analogue.

Tacrine (9-amino-1,2,3,4-tetrahydroacridine) was the first drug that proved to have beneficial effect in patients with Alzheimer's disease.[13] In recent decades tacrine has been one of the most used and well-known acetylcholinesterase (AChE) inhibitors for Alzheimer's therapy, but not without side effects. This has prompted great synthetic and pharmacological attempts in order to design more potent and less aggressive tacrine analogues. Several tacrine-based compounds were also developed but by use of toxic reagents and/or volatile solvents (Fig. 1).[14] In this context, in a current project under progress

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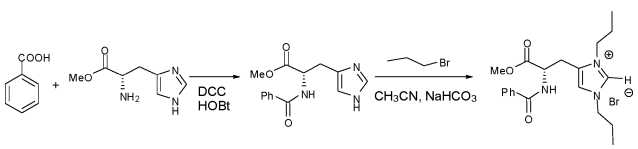
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1gc15410a

in our laboratory we have been very recently involved in the synthesis of biologically important heterocycles through environmentally friendly green protocols. Recently our efforts toward development of ecologically friendly procedures has led to an efficient and green methodology for the synthesis of tryptanthrin.[15]

Thus we developed a environmentally benign methodology for the synthesis of diastereoselective dihydrothiophenes and tacrine derivatives through Friedlander reaction. Recently Lu and coworkers reported synthesis of dihydrothiophenes using PEG/H_2O system, however they did not report any diastereoselectivity in the reaction.[16] Earlier ionic liquids like [Hbim][Br], [Hbim][BF_4] and [bmim][BF_4] were used as media as well as catalyst in the Friedlander reaction for the synthesis of quinolines.[17] We wish to report here histidine-derived functional ionic liquid mediated synthesis (FILMS) of dihydrothiophenes and tacrine derivatives. The functional ionic liquid has both organocatalytic as well as medium engineering capability in these protocols.

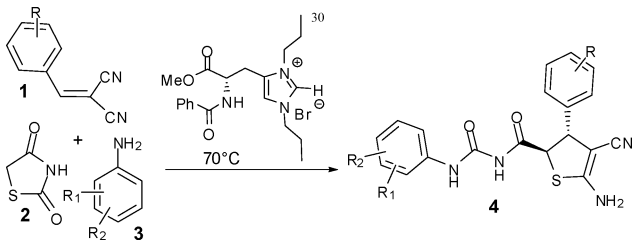
Results and discussion

The most commonly used ionic liquids are *N*,*N*-dialkylimidazolium salts. Keeping this in mind we have selected histidine, the only natural amino acid having imidazole moiety. We transformed histidine into functional ionic liquid [Bz-His(n-propyl)$_2$-OMe$^+$Br$^-$] or [BHP-OMe][Br] containing imidazole scaffold, amide and ester functionalities (Scheme 1). Functional ionic liquid [BHP-OMe][Br] was found to catalyse synthesis of diastereoselective dihydrothiophenes and also tacrine derivatives.



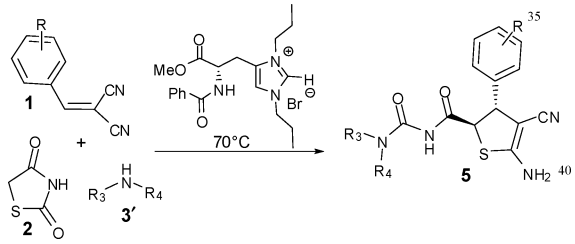
Scheme 1 Synthesis of histidine based ionic liquid [Bz-His(n-propyl)$_2$-OMe$^+$Br$^-$].

A three-component one-pot methodology has been developed in which 2-arylidenemalononitrile, 1,3-thiazolidinedione, aliphatic/aromatic amines were added with ionic liquid [BHP-OMe][Br] and water to form dihydrothiophenes (Scheme 2, 3). The results indicated formation of dihydrothiophenes in good yield (Table 2).



Scheme 2 Synthesis of dihydrothiophenes by aromatic amines.

For the optimisation of the reaction conditions, 2-(4-fluorobenzylidene)malononitrile, 1,3-thiazolidinedione, and aniline were reacted *via* three component methodology at different reaction conditions to synthesize dihydrothiophenes. We started our exploration by synthesizing different conventional ionic liquids as medium as well as promoter such as [bmim][Br], [bmim][OH], [bmim][BF_4] and [bmim][SCN]. Unfortunately only [bmim][Br], [bmim][OH] facilitates reaction in low yields 10 and 30% respectively. All other media remained inactive for the reaction. To further substantiate this finding we have used natural amino acids such as proline, alanine and histidine as catalyst along with ionic liquid [bmim][OH] as reaction medium. Histidine with [bmim][OH] catalyses the reaction in moderate yield (40%) at 40 °C, whereas other amino acids did not show any further improvement in reaction yield. Encouraged by these results we used histidine with [bmim][Br] and got 50% reaction yield at 40 °C. In order to investigate whether ionic liquid or histidine is driving the reaction we performed the reaction with histidine alone in water as solvent. The reaction afforded dihydrothiophene in 30% yield at 40 °C (Table 1). These results prompted us to convert histidine into ionic liquid [BHP-OMe][Br].



Scheme 3 Synthesis of dihydrothiophenes by aliphatic amines.

Interestingly, histidine-based ionic liquid gave encouraging results. [BHP-OMe][Br] catalyses reaction in 14 h and 80%

Table 1 Optimization of reaction conditions

Entry	*T*/°C	Ionic liquid	Catalyst	Time (h)	Yield %[f]
1[a]	40	[bmim][Br]	—	24	10
2[a]	40	[bmim][OH]	—	24	30
3[a]	40	[bmim][BF_4]	—	24	0
4[a]	40	[bmim] [SCN]	—	24	0
5[a]	40	[bmim][OH]	L-Proline	24	32
6[a]	40	[bmim][OH]	L-Alanine	24	30
7[a]	40	[bmim][OH]	L-Histidine	24	40
8[a]	40	[bmim][Br]	L-Histidine	24	50
9[b]	40	—	L-Histidine	24	30
10[c]	39[e]	[BHP-OMe][Br]	—	24	60
11[c]	70	[BHP-OMe][Br]	—	14	80
12[c]	100	[BHP-OMe] [Br]	—	12	20
13[d]	39[e]	[BHP-OMe][Br]	—	28	55
14[d]	70	[BHP-OMe][Br]	—	15	70
15[d]	100	[BHP-OMe] [Br]	—	14	10

[a] Ionic liquid (2.5 mL), catalyst (30 mol%), 2-(4-fluorobenzylidene)-malononitrile (2.0 mmol), 1,3-thiazolidinedione (2.0 mmol), aniline (2.0 mmol). [b] L-Histidine (30 mol%), 2-(4-fluorobenzylidene)-malononitrile (2.0 mmol), 1,3-thiazolidinedione (2.0 mmol), aniline (2.0 mmol), water (2 mL). [c] [BHP-OMe][Br] (2.0 mmol), 2-(4-fluorobenzylidene)malononitrile (2.0 mmol), 1,3-thiazolidinedione (2.0 mmol), aniline (2.0 mmol), water (2 mL). [d] [BHP-OMe][Br] (2.0 mmol), 2-(4-fluorobenzylidene)malononitrile (2.0 mmol), 1,3-thiazolidinedione (2.0 mmol), piperidine (2.0 mmol), water (2 mL). [e] T_m (solid-liquid phase transition temperature for [BHP-OMe][Br]) = 39 °C. [f] Yield of isolated products.

yield was obtained at 70 °C. Further optimization of reaction was done and effect of temperature on the reaction has been studied. We have performed reaction at T_m (solid-liquid phase transition temperature for [BHP-OMe][Br]) = 39 °C, 70 °C and at 100 °C. The best result was obtained at 70 °C in 14 h with [BHP-OMe][Br] as reaction media which gave dihydrothiophene derivative in 80% yield. At T_m for 24 h only 60% yield was obtained while most of the starting material remained unreacted, whereas at 100 °C a complex mixture of products was obtained that was mostly dominated by unreacted starting materials and some byproducts. Only 20% desired product was obtained. To confirm effectivity of [BHP-OMe][Br]-catalysed reaction we reacted 2-(4-fluorobenzylidene)malononitrile, 1,3-thiazolidinedione and piperidine at temperatures 39 °C, 70 °C and 100 °C, we obtained maximum yield in 28 h, 15 h and 14 h respectively. These results are summarised in Table 1.

All the 2-arylidenemalononitrile, aromatic and aliphatic amines reacted smoothly to give dihydrothiophene independent of the nature of either electron-withdrawing or electron-donating substituents (Table 2). The structures of dihydrothiophenes were confirmed by elemental analysis, ^{1}H, ^{13}C and mass spectroscopy. The comparison of ^{1}H NMR spectra of these synthesized compounds with known dihydrothiophene library confirmed the formation of *trans* dihydrothiophenes.[12]

A plausible mechanism for the formation of dihydrothiophenes is given in Fig. 2. [BHP-OMe][Br] causes deprotonation of 1,3-thiazolidinedione to form carbanion which reacts with 2-arylidenemalononitrile *via* Michael addition to form intermediate A. Further ring of 1,3-thiazolidinedione in intermediate A opens by various amines which further cyclizes to form dihydrothiophene derivatives.

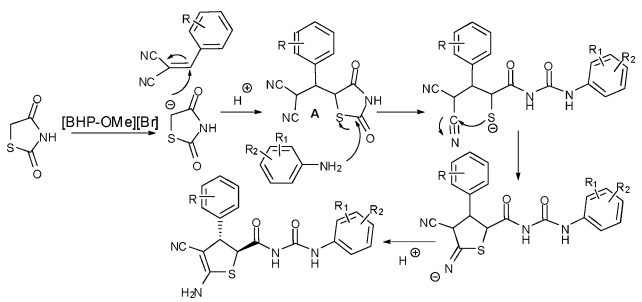
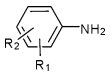
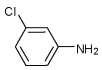
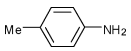
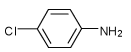
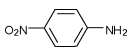
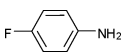
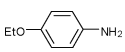
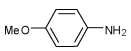
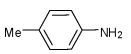


Fig. 2 Plausible mechanism for formation of dihydrothiophenes.

Further, we were concerned with the cyclization of dihydrothiophenes to corresponding tacrine derivatives (hexahydrothieno[2,3-b]quinoline-2-carboxamide). Different ionic liquids such as [bmim][Br], [bmim][OH], [bmim][SCN] and [bmim][BF_4] were used as medium and promoter for the cyclization of dihydrothiophene (**4k**) to hexahydrothieno[2,3-b]quinoline-2-carboxamide (tacrine derivatives). Only [bmim][Br] and [bmim][BF_4] catalyzed reaction in low yield (20–30%) at 100 °C. In order to demonstrate the versatility of FILMS dihydrothiophene (**4k**) and cyclohexanone were stirred at 100 °C in [BHP-OMe][Br] and water, we got cyclized product in 50% yield in 15 h. In order to improve reaction yield, we tried microwave radiation to catalyse cyclization of dihydrothiophenes to corresponding tacrine derivatives. Our

Table 2 Synthesis of dihydrothiophenes by aromatic/aliphatic amines[a]

Entry	Product	R			Time (h)	Yield %[b]
1	**4a**	4-MeO		—	14	75
2	**4b**	4-MeO		—	14	70
3	**4c**	4-MeO		—	14	80
4	**4d**	4-MeO		—	18	65
5	**4e**	4-MeO		—	18	65
6	**4f**	4-MeO		—	16	80
7	**4g**	4-MeO		—	16	75
8	**4h**	4-MeO		—	15	80
9	**4i**	4-MeO		—	14	75
10	**4j**	4-Cl		—	14	80
11	**4k**	4-F		—	14	80
12	**4l**	4-F		—	14	70
13	**4m**	4-F		—	17	75
14	**5a**	4-MeO	—		14	80
15	**5b**	4-Cl	—		15	75
16	**5c**	4-F	—		15	70
17	**5d**	4-$(Me)_2$N	—		14	70
18	**5e**	3-Br	—		14	75
19	**5f**	4-Cl	—		14	80
20	**5g**	4-MeO	—		14	65

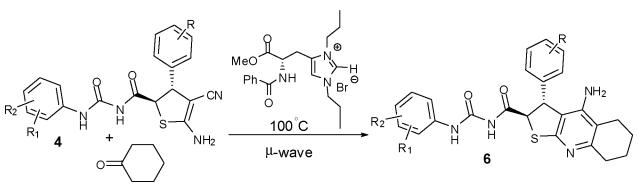
[a] Reaction conditions: [BHP-OMe][Br] (2.0 mmol), **1** (2.0 mmol), **2** (2.0 mmol), **3** or **3′** (2.0 mmol), water (2.0 mL), 70 °C, 14–18 h. [b] Yield of isolated products.

Table 3 Synthesis of tacrine derivatives from dihydrothiophenes[a]

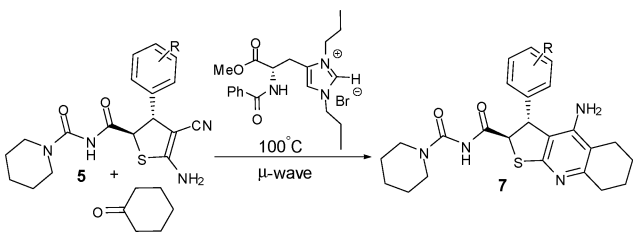
Entry	Product	R	R_1	R_2	Time (h)	Yield %[b]
1	**6a**	4-Cl	4-Me	H	30	54
2	**6b**	4-MeO	4-MeO	H	30	66
3	**6c**	4-MeO	2-Cl	5-Cl	35	70
4	**6d**	4-F	H	H	30	65
5	**6e**	4-F	2-MeO	H	35	60
6	**6f**	4-MeO	4-NO_2	H	30	65
7	**6g**	4-MeO	4-MeO	H	30	70
8	**7a**	4-MeO	—	—	30	72
9	**7b**	3-Br	—	—	35	65
10	**7c**	4-F	—	—	35	55
11	**7d**	4-Cl	—	—	30	60

[a] Reaction conditions: [BHP-OMe][Br] (1.0 mmol), dihydrothiophenes (1.0 mmol), cyclohexanone (3.0 mmol), water (1.0 mL), 100 °C, microwaves, 30–35 min. [b] Yield of isolated products.

initial efforts gave positive results to us. Dihydrothiophene (**4k**) and cyclohexanone in ionic liquid [BHP-OMe][Br] and water were treated with microwave radiation for 10 min; we got cyclized product although in low yield (30%) along with unreacted starting materials. Encouraged by these results we continued exposing the reaction for some more time in microwave radiation and got maximum yield (65%) in 30 min. In order to demonstrate the efficiency and the applicability of the green method, we performed the reaction of a variety of dihydrothiophenes with cyclohexanone under standard reaction conditions (Scheme 4, 5). No obvious electronic effects were observed in the organic synthesis and products were obtained in moderate yields (Table 3). The structures were confirmed by elemental analysis ^1H, ^{13}C and mass spectroscopy.



Scheme 4 Synthesis of tacrine derivatives from aromatic amine-derived dihydrothiophenes.



Scheme 5 Synthesis of tacrine derivatives from aliphatic amine-derived dihydrothiophenes.

One of the advantages of the ionic liquid catalysed reaction is their reusability. Reusability of catalyst was checked under standard reaction conditions. 2-(4-Fluorobenzylidene)malononitrile, 1,3-thiazolidinedione, and aniline were stirred in ionic liquid [BHP-OMe][Br] and water at 70 °C for 14 h. After each run, the product was filtered. Filtrate containing ionic liquid was diluted with 15 mL water and extracted with CH_2Cl_2 (3 × 10 ml) to remove non-ionic organic impurities. Then water was evaporated and the catalyst was dried at 90 °C under reduced pressure for 2 h and reused under the same reaction conditions. It was observed that the catalyst displayed good reusability at least in four subsequent reactions under the same reaction conditions without any considerable loss in reaction yield (Fig. 3).

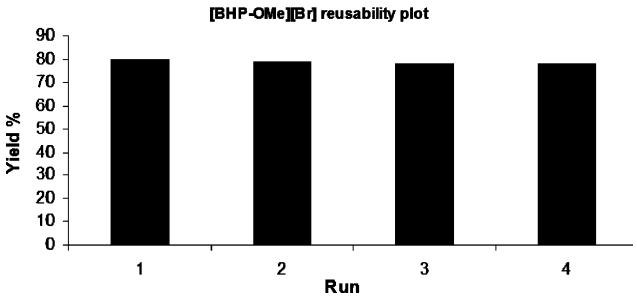


Fig. 3 Ionic liquid reusability plot.

Conclusions

In conclusion, we have developed natural amino acid-based functional ionic liquid mediated synthesis of diastereoselective dihydrothiophenes and tacrine derivatives. The advantages of this procedure are good yield, short reaction time, reusable medium and environmentally friendly procedure.

It is interesting to report a new approach of organic synthesis for functional ionic liquid promoted reactions named as functional ionic liquid mediated synthesis (FILMS).

Experimental

General procedure for synthesis of 1-butyl-3-methylimidazolium hydroxide [bmim][OH][18]

To a solution of [bmim]Br (20.0 mmol) in dry methylene chloride (10.0 mL) solid potassium hydroxide (20.0 mmol) was added, and the mixture was stirred at room temperature for 12 h. The precipitated KBr was filtered off, and the filtrate was evaporated *in vacuo* to obtain crude [bmim][OH] as a viscous liquid that was washed with ether (2 × 20 mL) and dried at 80 °C for 14 h to prepare the pure ionic liquid for use. This was characterized by spectroscopic analysis of product.

General procedure for synthesis of [Bz-His(n-propyl)$_2$-OMe$^+$Br$^-$] ([BHP-OMe][Br])[19]

To a stirred suspension of benzoic acid (1.0 mmol) in DCM (10 mL), DCC (1.5 mmol) and HOBt (1.0 mmol) were added. This mixture was stirred for 15 min followed by addition of L-histidine methyl ester dihydrochloride (1.1 mmol) and NEt_3 (1.5 mmol). Again it was allowed to stir for 12 h under nitrogen atmosphere at room temperature. After completion of reaction as evidenced by TLC, precipitate obtained was filtered and filtrate was concentrated using rotary evaporator. The residue obtained was dissolved in $CHCl_3$ and extracted with saturated solution of $NaHCO_3$ followed by water. The aqueous layer was

further extracted with $CHCl_3$. Combined organic layers were dried with Na_2SO_4, filtered and solvent was removed *in vacuo*. This was purified *via* column chromatography to afford [Bz-His-OMe] as pure product.

To a stirred suspension of [Bz-His-OMe] (0.25 mol) in 150 mL acetonitrile 1.00 mol of $NaHCO_3$ was added. Again 1-bromopropane (300 mL, 6.25 mol) was slowly added to it and the suspension was stirred under nitrogen for 70 h at 65 °C. The mixture was allowed to cool at room temperature, filtered and the solvent removed *in vacuo*. The residue obtained was dissolved in water (250 mL) and extracted with 200 mL of $CHCl_3$. The water was removed *in vacuo* and the product dried to obtain pure [BHP-OMe][Br]. The structure of ionic liquid was confirmed by spectroscopic analysis. It was also observed that ionic liquid does not lose its properties even if heated for 12 h at 100 °C in a biphasic system with toluene.

General procedure for synthesis of dihydrothiophenes

To a mixture of 2-arylidenemalononitrile (2.0 mmol), 1,3-thiazolidinedione (2.0 mmol), and amine (aromatic or aliphatic) (2.0 mmol), ionic liquid [BHP-OMe][Br] (2.0 mmol) and water (2.0 mL) were added and mixture was stirred at 70 °C for 14–18 h until completion of reaction as evidenced by TLC. The resulting precipitate was collected by filtration and washed with ethanol. The crude precipitate was recrystallized by ethanol to give pure products (**4a–m**, **5a–g**) (Table 2).

General procedure for synthesis of tacrine derivatives (hexahydrothieno[2,3-b]quinoline-2-carboxamide)

An oven-dried microwave vial charged with dihydrothiopene (1.0 mmol) and cyclohexanone (3.0 mmol), in 1.0 mmol of [BHP-OMe][Br] and water (1.0 mL) was stirred at 100 °C (power input 140 W) under microwave radiation for 30–35 min. After completion of reaction as evidenced by TLC, it was diluted with 50 mL of ethyl acetate and washed with water. The aqueous part was further extracted with ethyl acetate. The combined organic part was washed with brine and dried over Na_2SO_4. The solvent was evaporated to yield a crude residue, which upon purification *via* silica gel column chromatography using EtOAc/hexane gave pure products (**6a–g**, **7a–d**) (Table 3).

Acknowledgements

Authors G. G. and S. S. are thankful to CSIR-UGC New Delhi for the award of senior research fellowship. Authors also acknowledge to SAIF-CDRI for providing the spectral and analytical data. CDRI communication no. 8095.

References

1 (*a*) T. Welton, *Green Chem.*, 2011, **13**, 225; (*b*) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; (*c*) C. Wang, L. Guo, H. Li, Y. Wang, J. Weng and L. Wu, *Green Chem.*, 2006, **8**, 603; (*d*) C. Wang, W. Zhao, H. Li and L. Guo, *Green Chem.*, 2009, **11**, 843; (*e*) J. Weng, C. Wang, H. Li and Y. Wang, *Green Chem.*, 2006, **8**, 96; (*f*) R. Sheldon, *Chem. Commun.*, 2001, 2399; (*g*) J. Dupont, R. F. de Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667.
2 (*a*) P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772; (*b*) M. J. Earle and K. R. Seddon, *Pure Appl. Chem.*, 2000, **72**, 1391; (*c*) C. M. Gordon, *Appl. Catal., A*, 2001, **222**, 101.
3 W. A. Herrmann, C. Köcher, L. J. Goossen and G. R. J. Artus, *Chem.–Eur. J.*, 1996, **2**, 1627.
4 K.-M. Lee, Y.-T. Lee and I. J. B. Lin, *J. Mater. Chem.*, 2003, **13**, 1079.
5 (*a*) A. C. Cole, J. L. Jensen, I. Ntai, K. L. T. Tran, K. J. Weaver, D. C. Forbes and J. H. Davis Jr., *J. Am. Chem. Soc.*, 2002, **124**, 5962; (*b*) J. D. Holbrey, W. M. Reichert, I. Tkatchenko, E. Bouajila, O. Walter, I. Tommasi and R. D. Rogers, *Chem. Commun.*, 2003, 28.
6 P. Wasserscheid, A. Bösmann and C. Bolm, *Chem. Commun.*, 2002, 200.
7 D. Zhao, Z. Fei, C. A. Ohlin, G. Laurenczy and P. J. Dyson, *Chem. Commun.*, 2004, 2500.
8 (*a*) T. Jiang, X. Ma, Y. Zhou, S. Liang, J. Zhang and B. Han, *Green Chem.*, 2008, **10**, 465; (*b*) D. Li, F. Shi, J. Peng, S. Guo and Y. Deng, *J. Org. Chem.*, 2004, **69**, 3582; (*c*) G. Tao, L. He, W. Liu, L. Xu, W. Xiong, T. Wang and Y. Kou, *Green Chem.*, 2006, **8**, 639; (*d*) S. A. Forsyth, U. Frhlich, P. Goodrich, H. Q. N. Gunaratne, C. Hardacre, A. McKeown and K. R. Seddon, *New J. Chem.*, 2010, **34**, 723.
9 S. T. Handy, *Chem.–Eur. J.*, 2003, **9**, 2938.
10 (*a*) M. J. de Groot, A. A. Alex and B. C. Jones, *J. Med. Chem.*, 2002, **45**, 1983; (*b*) M. Lee, D. Hesek and S. Mobashery, *J. Org. Chem.*, 2005, **70**, 367; (*c*) B. L. Flynn, G. P. Flynn, E. Hamel and M. K. Jung, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2341.
11 (*a*) M.-G. A. Shvekhgeimer, *Chem. Heterocycl. Compd.*, 1998, **34**, 1101; (*b*) J. M. McIntosh, H. B. Goodbrand and G. M. Masse, *J. Org. Chem.*, 1974, **39**, 202; (*c*) A. M. Leusen and K. J. Berg, *Tetrahedron Lett.*, 1988, **29**, 2689.
12 (*a*) J. Sun, E. Y. Xia, L. Zhang and C. G. Yan, *J. Org. Chem.*, 2009, **74**, 3398; (*b*) J. Sun, E. Y. Xia, L. Zhang and C. G. Yan, *Eur. J. Org. Chem.*, 2009, 5247.
13 (*a*) W. K Summers, L. V. Majovski, G. M. Marsh, K. Tachiki and A. N. Kling, *N. Engl. J. Med.*, 1986, **315**, 1241; (*b*) B. J. Sahakian, A. M. Owen, N. J. Morant, S. A. Eagger, S. Boddington, L. Crayton, H. A. Crockford, M. Crooks, K. Hill and R. Levy, *Psychopharmacology*, 1993, **110**, 395.
14 (*a*) D. Thomae, G. Kirsch and P. Seck, *Synthesis*, 2007, **7**, 1027; (*b*) M. Ouberai, K. Brannstrom, M. Vestling, A. Olofsson, P. Dumy, S. Chierici and J. Garcia, *Org. Biomol. Chem.*, 2011, **9**, 1140; (*c*) H. Chaki, H. Yamabe, M. Sugano, S. Morita, T. Bessho, R. Tabata, K. I. Saito, M. Egawa, A. Tobe and Y. Morinaka, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1495; (*d*) J. C. Jaén, V. E. Gregor, C. Lee, R. Davis and M. Emmerling, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 737.
15 A. Kumar, V. D. Tripathi and P. Kumar, *Green Chem.*, 2011, **13**, 51.
16 G.-P. Lu, L.-Y. Zeng and C. Cai, *Green Chem.*, 2006, **8**, 603.
17 (*a*) S. S. Palimkar, S. A. Siddiqui, T. Daniel, R. J. Lahoti and K. V. Srinivasan, *J. Org. Chem.*, 2003, **68**, 9371; (*b*) J. Akbari, A. Heydari, H. R. Kalhor and S. A. Kohan, *J. Comb. Chem.*, 2010, **12**, 137.
18 B. C. Ranu and S. Banerjee, *Org. Lett.*, 2005, **7**, 3049.
19 F. Hannig, G. Kehr, R. Fröhlich and G. Erker, *J. Organomet. Chem.*, 2005, **690**, 5959.