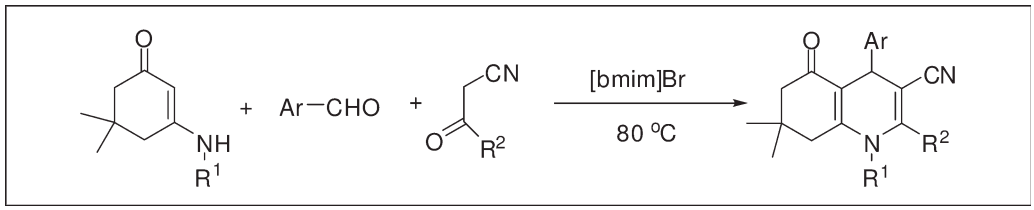
An Efficient Three-Component Synthesis of Hexahydroquinoline Derivatives in Ionic Liquid

Ju-Xian Wang,[a] Gao-Ling Shen,[b] and Da-Qing Shi[b]*

[a]Institute of Medical Biotechnology, Chinese Academy of Medical Sciences and Perking Union Medical College, Beijing 100050, People's Republic of China
[b]Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, People's Republic of China
*E-mail: dqshi@suda.edu.cn

Received July 15, 2010
DOI 10.1002/jhet.703
Published online 8 June 2011 in Wiley Online Library (wileyonlinelibrary.com).



A series of hexahydroquinoline derivatives were synthesized by the three-component reaction of 5,5-dimethyl-3-aminocyclohex-2-enone, aromatic aldehyde, and acyl acetonitrile in ionic liquid without using any catalyst. This protocol has the advantages of easier work-up, milder reaction conditions, high yields, and environmentally benign procedure.

J. Heterocyclic Chem., **48**, 1145 (2011).

INTRODUCTION

Quinolines are important as the scaffolds of bioactive substances. The ring structure is one of the most popular N-heteroaromatic moieties incorporated into the structures of pharmaceuticals. Many quinoline-containing compounds exhibit a wide range of pharmacological activities, such as antiplasmodial [1], intrinsic [2], cytotoxic [3], functional [4], antibacterial [5], antiproliferative [6], antimalarial [7], and anticancer activities [8]. Therefore, the synthesis of quinolines has become an attractive research field.

Multicomponent reactions (MCRs) [9] are special types of synthetically useful organic reactions in which three or more different starting materials react to give a final product in a one-pot procedure. Such reactions are one of the best tools in modern organic synthesis to generate compound libraries for screening purposes because of their productivity, simple procedures, convergence, and facile execution [10]. This methodology allows molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation quite closely approaching the concept of an ideal synthesis and is particularly well adapted for combinatorial synthesis [11].

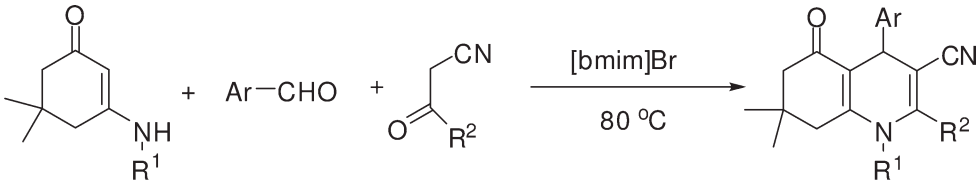
The ionic liquids have been the subject of considerable current interest as environmentally benign reaction media in organic synthesis because of their unique properties of nonvolatility, nonflammability, and recyclability, among others [12]. Numerous chemical reaction, such as polymerization [13], hydrogenation [14], regioselective alkylation [15], Friedel-Crafts reactions [16], dimerization of alkenes [17], Diels-Alder reactions [18], Michael reactions [19], Cross-coupling reactions [20], and some enzymic reactions [21] can be carried out in ionic liquid. As part of our current studies on the development of new routes to heterocyclic systems [22], we herein describe a facile synthesis of hexahydroquinoline derivatives by the three-component reaction of 5,5-dimethyl-3-aminocyclohex-2-enone, aromatic aldehyde, and acyl acetonitrile in ionic liquid without using any catalyst.

RESULTS AND DISCUSSION

The one-pot, three-component reaction of 5,5-dimethyl-3-aminocyclohex-2-enone **1**, aromatic aldehyde **2,** and acyl acetonitrile **3** proceeded rapidly at 80°C in ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br) without using any catalyst and were complete after 4–8 h to afford 1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile derivatives **4** in good yields (Scheme 1). The results are summarized in Table 1.

As shown in Table 1, this protocol can be applied not only to the aromatic aldehyde with electron-withdrawing groups (such as nitro and halide groups) and with electron-donating groups (such as methyl group) but also to the heterocyclic aromatic aldehyde. Therefore, we concluded that the electronic nature of the substituents of aldehydes has no significant effect on this reaction.

Scheme 1



1 **2** **3** **4**

In this study, all the structures of products **4** were characterized by mp, IR, and ^{1}H-NMR spectral data as well as HRMS analysis. The IR spectrum of **4** showed bands at 3261–3485 cm^{-1} due to NH, and strong absorption at 2195–2205 and 1637–1657 cm^{-1} due to cyano and carbonyl group, respectively. The ^{1}H-NMR specrtum of compound **4** showed signals at 4.53–5.66 due to C_4-H.

A possible mechanism for the formation of **4** is proposed in Scheme 2. It is reasonable to assume that **4** results from initial formation of intermediate arylidene acyl acetonitrile **5** by standard Knoevenagel condensation of the aldehyde **2** and acyl acetonitrile **3**. Then, the subsequent Michael-type addition of the 5,5-dimethyl-3-aminocyclohex-2-enone **1** to the intermediate **5**, followed by tautomerization, cyclization, and dehydration, affords the corresponding products **4** (Scheme 2).

In conclusion, we have developed an efficient, clean, one-pot and three-component synthesis of new hexahydroquinoline derivatives in ionic liquid without any catalyst. This protocol has the advantages of easier work-up, milder reaction conditions, high yields, and environmentally benign procedure.

EXPERIMENTAL

Commercial solvents and reagents were used as received. Melting points were uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H-NMR was determined on Varian-400 MHz or Varian-300 MHz spectrometer in DMSO-d_6 solution. J values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS data were obtained using TOF-MS instrument.

General procedure for the synthesis of 1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile derivatives 4. A dry 50 mL flask was charged with 5,5-dimethyl-3-aminocyclohex-2-enone **1** (1 mmol), aldehyde **2** (1 mmol), acyl acetonitrile **3** (1 mmol), and ionic liquid [bmim]Br (2 mL). The mixture was stirred at 80°C for 4–8 h to complete the reaction (monitored by TLC), then 50 mL H_2O was added. The solid was filtered off and washed with water. The crude product was purified by recrystallization from ethanol to give **4**.

2-(4-Chlorophenyl)-7,7-dimethyl-5-oxo-1,4-di(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4a). Mp: 212–213°C; IR (potassium bromide): 3035, 2953, 2886, 2198, 1641, 1580, 1512, 1373, 1245 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.74 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 1.79 (d, J = 17.4 Hz, 1H, CH), 2.02 (d, J = 16.2 Hz, 1H, CH), 2.20 (s, 3H, CH_3), 2.26–2.32 (m, 5H, CH_3+CH_2), 4.64 (s, 1H, CH), 7.08–7.15 (m, 5H, ArH), 7.18–7.21 (m, 2H, ArH), 7.26–7.33 (m, 5H, ArH). HRMS [Found: m/z: 492.1968 (M^+); Calcd for $C_{32}H_{29}{}^{35}ClN_2O$: M 492.1968].

2,4-Di(4-chlorophenyl)-7,7-dimethyl-5-oxo-1-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4b). Mp: 239–241°C; IR (potassium bromide): 3035, 2953, 2885, 2199, 1640, 1579, 1512, 1371, 1247 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.75 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.82 (d, J = 17.7 Hz, 1H, CH), 2.05 (d, J = 16.2 Hz, 1H, CH), 2.23 (s, 3H, CH_3), 2.26–2.33 (m, 2H, CH_2), 4.74 (s, 1H, CH), 7.10–7.19 (m, 5H, ArH), 7.29–7.32 (m, 3H, ArH), 7.46–7.51 (m, 4H, ArH). HRMS [Found: m/z: 512.1426 (M^+); Calcd for $C_{31}H_{26}{}^{35}Cl_2N_2O$: M 512.1422].

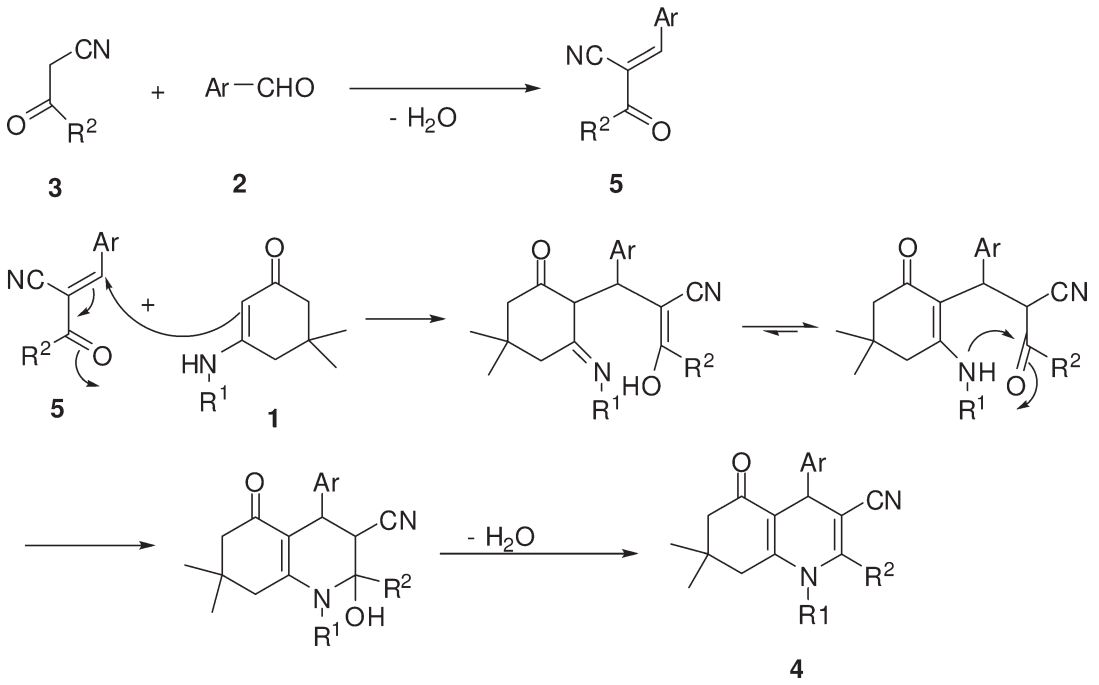
4-(2-Chlorophenyl)-2-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4c). Mp: 218–219°C; IR (potassium bromide): 3056, 2953, 2870, 2201, 1641, 1576, 1513, 1373, 1250 cm^{-1}; ^{1}H-

Table 1

Synthesis of hexahydroquinoline derivatives **4** in ionic liquid.

Entry	R^1	Ar	R^2	Time (h)	Isolated yield (%)
4a	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	4-ClC_6H_4	8	92
4b	4-$CH_3C_6H_4$	4-ClC_6H_4	4-ClC_6H_4	4	95
4c	4-$CH_3C_6H_4$	2-ClC_6H_4	4-ClC_6H_4	5	96
4d	4-$CH_3C_6H_4$	3-ClC_6H_4	4-ClC_6H_4	4	95
4e	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	C_6H_5	7	90
4f	4-$CH_3C_6H_4$	2-$NO_2C_6H_4$	C_6H_5	5	95
4g	n-But	3-ClC_6H_4	4-ClC_6H_4	5	95
4h	H	4-$CH_3C_6H_4$	4-ClC_6H_4	5	96
4i	H	Pyridin-3-yl	4-ClC_6H_4	7	91

Scheme 2



NMR (DMSO-d_6) δ: 0.90 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.91 (d, J = 17.4 Hz, 1H, CH), 2.12 (d, J = 17.7 Hz, 1H, CH), 2.13 (d, J = 16.5 Hz, 1H, CH), 2.23 (d, J = 16.5 Hz, 1H, CH), 2.29 (s, 3H, CH_3), 5.31 (s, 1H, CH), 6.87 (d, J = 8.1Hz, 2H, ArH), 6.99–7.15 (m, 6H, ArH), 7.18–7.23 (m, 1H, ArH), 7.26–7.32 (m, 1H, ArH), 7.40 (d, J = 7.8 Hz, 1H, ArH), 7.50–7.53 (m, 1H, ArH). HRMS [Found: m/z: 512.1424 (M^+); Calcd for $C_{31}H_{26}{}^{35}Cl_2N_2O$: M 512.1422].

4-(3-Chlorophenyl)-2-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4d). Mp: 194–196°C; IR (potassium bromide): 3039, 2960, 2888, 2198, 1639, 1577, 1512, 1371, 1248 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.87 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.95 (d, J = 17.7 Hz, 1H, CH), 2.15–2.26 (m, 3H, CH_2+CH), 2.30 (s, 3H, CH_3), 4.90 (s, 1H, CH), 6.86 (d, J = 8.1 Hz, 2H, ArH), 7.05–7.08 (m, 3H, ArH), 7.14–7.17 (m, 2H, ArH), 7.23–7.27 (m, 1H, ArH), 7.29–7.44 (m, 4H, ArH). HRMS [Found: m/z: 512.1425 (M^+); Calcd for $C_{31}H_{26}{}^{35}Cl_2N_2O$: M 512.1422].

7,7-Dimethyl-5-oxo-2-phenyl-1,4-di(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4e). Mp: 189–191°C; IR (potassium bromide): 3057, 2961, 2870, 2197, 1642, 1584, 1512, 1373, 1248 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.80 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.87 (d, J = 17.2 Hz, 1H, CH), 2.08 (d, J = 16.4 Hz, 1H, CH), 2.24 (s, 3H, CH_3), 2.30 (d, J = 16.4 Hz, 1H, CH), 2.35 (s, 3H, CH_3), 2.36 (d, J = 17.2 Hz, 1H, CH), 4.71 (s, 1H, CH), 7.10–7.17 (m, 5H, ArH), 7.23–7.30 (m, 6H, ArH), 7.36–7.41 (m, 2H, ArH). HRMS [Found: m/z: 458.2380 (M^+); Calcd for $C_{32}H_{30}N_2O$: M 458.2358].

7,7-Dimethyl-4-(2-nitrophenyl)-5-oxo-2-phenyl-1-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4f). Mp: 246–248°C; IR (potassium bromide): 3061, 2962, 2870, 2205, 1639, 1603, 1528, 1375, 1251 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.84 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.93 (d, J = 18.0 Hz, 1H, CH), 2.04 (d, J = 18.3 Hz, 1H, CH), 2.10–2.22 (m, 2H, CH_2), 2.27 (s, 3H, CH_3), 5.66 (s, 1H, CH), 6.94–7.08 (m, 5H, ArH), 7.13–7.20 (m, 4H, ArH), 7.36–7.41 (m, 1H, ArH), 7.59–7.65 (m, 1H, ArH), 7.72–7.78 (m, 2H, ArH). HRMS [Found: m/z: 489.2059 (M^+); Calcd for $C_{31}H_{27}N_3O_3$: M 489.2052].

1-Butyl-4-(3-chlorophenyl)-2-(4-chlororphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4g). Mp: 152–154°C; IR (potassium bromide): 3035, 2956, 2872, 2196, 1657, 1570, 1379, 1294 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.62 (t, J = 7.2 Hz, 3H, CH_3), 0.88–1.01 (m, 5H, CH_3+CH_2), 1.07 (s, 3H, CH_3), 1.24–1.39 (m, 2H, CH_2), 2.20 (d, J = 16.2 Hz, 1H, CH), 2.27 (d, J = 16.2 Hz, 1H, CH), 2.59 (d, J = 17.4 Hz, 1H, CH), 2.72 (d, J = 17.1 Hz, 1H, CH), 3.07–3.17 (m, 1H, CH), 3.56–3.65 (m,1H, CH), 4.68 (s, 1H, CH), 7.20–7.32 (m, 3H, ArH), 7.36–7.48 (m, 3H, ArH), 7.56–7.64 (m, 2H, ArH). HRMS [Found: m/z: 478.1570 (M^+); Calcd for $C_{28}H_{28}{}^{35}Cl_2N_2O$: M 478.1579].

2-(4-Chlorophenyl)-7,7-dimethyl-5-oxo-4-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4h). Mp: 248–250°C; IR (potassium bromide): 3485, 3364, 3090, 2958, 2870, 2195, 1637, 1605, 1539, 1382, 1251 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.92 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.05 (d, J = 16.4 Hz, 1H, CH), 2.24 (d, J = 16.4 Hz, 1H, CH), 2.41 (d, J = 17.2 Hz, 1H, CH), 2.52 (d, J = 17.2 Hz, 1H, CH), 4.53 (s, 1H, CH), 7.13 (d, J = 8.0 Hz, 2H, ArH), 7.17 (d, J = 8.4 Hz, 2H, ArH), 7.56 (d, J = 8.8 Hz, 2H, ArH), 7.60 (d, J = 8.8 Hz, 2H, ArH), 9.64 (s, 1H, NH). HRMS [Found: m/z: 402.1502 (M^+); Calcd for $C_{25}H_{23}{}^{35}ClN_2O$: M 402.1499].

2-(4-Chlorophenyl)-7,7-dimethyl-5-oxo-4-(pyridin-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4i) Mp: 290–292°C; IR (potassium bromide): 3485, 3261, 3015, 2952, 2873, 2200, 1637, 1605, 1592, 1380, 1260 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.88 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.03 (d, J = 16.2 Hz,

1H, CH), 2.23 (d, J = 15.9 Hz, 1H, CH), 2.01 (d, J = 17.4 Hz, 1H, CH), 2.52 (d, J = 17.4 Hz, 1H, CH), 4.63 (s, 1H, CH), 7.34–7.38 (m, 1H, ArH), 7.57–7.62 (m, 4H, ArH), 7.65–7.68 (m, 1H, ArH), 8.41–8.43 (m, 1H, ArH), 8.50 (s, 1H, ArH), 9.81 (s, 1H, NH). HRMS [Found: m/z: 389.1295 (M^+); Calcd for $C_{23}H_{20}{}^{35}ClN_3O$: M 389.1281].

REFERENCES AND NOTES

[1] Beagley, P.; Blackie, M. A. L.; Chibale, K.; Clarkson, C.; Meijboom, R.; Moss, J. R.; Smith, P.; Su, H. J Chem Soc Dalton Trans 2003, 3046.

[2] Sawada, Y.; Kayakiri, H.; Abe, Y.; Mizutani, T.; Inamura, N.; Asano, M.; Hatori, C.; Aramori, I.; Oku, T.; Tanaka, H. J Med Chem 2004, 47, 2853.

[3] Ma, Z.; Hano, Y.; Nomura, T.; Chen, Y. Bioorg Med Chem Lett 2004, 14, 1193.

[4] Denton, T. T.; Zhang, X.; Cashman, J. R. J Med Chem 2005, 48, 224.

[5] Fokialakis, N.; Magiatis, P.; Chinou, L.; Mitaku, S.; Tillequin, F. Chem Pharm Bull 2002, 50, 413.

[6] Fossa, P.; Mosti, L.; Menozzi, G.; Marzano, C.; Baccichetti, F.; Bordin, F. Bioorg Med Chem 2002, 10, 743.

[7] Ryckebusch, A.; Derprez-Poulain, R.; Mase, L.; Debreu-Fontaine, M. A.; Mouray, E.; Grellier, P.; Sergheraert, C. J Med Chem 2003, 46, 542.

[8] Morgan, L. R.; Jursic, B. S.; Hooper, C. L.; Neumann, D. M.; Thangaraj, K.; Leblane, B. Bioorg Med Chem Lett 2002, 12, 3407.

[9] (a) Dömling, A.; Ugi, I. Angew Chem Int Ed 2000, 39, 3168; (b) Dömling, A. Chem Rev 2006, 106, 17.

[10] Zhu, J.; Bienayme, H. Multicomponent Reactions; Wiley-VCH: Weinheim, Germany, 2005.

[11] de Meijere, A.; Nüske, H.; Es-Sayed, M.; Labahn, T.; Schroen, M.; Bräse, S. Angew Chem Int Ed 1999, 38, 3669.

[12] (a) Welton, T. Chem Rev 1999, 99, 2071; (b) Wasserscheid, P.; Keim, W. Angew Chem Int Ed 2000, 39, 3773; (c) Sheldon, R. Chem Commun 2001, 2399; (d) Wilkes, J. S. Green Chem 2002, 4, 73; (e) Yao, Q. Org Lett 2002, 4, 2197; (f) Zerth, H. M.; Leonard, N. M.; Mohan, R. S. Org Lett 2003, 5, 55; (g) Su, C.; Chen, Z. C.; Zheng, Q. G. Synthesis 2003, 555; (h) Rajagopal, R.; Jarikote, D. V.; Lahoti, R. J.; Daniel, T.; Srinivasan, K. V. Tetrahedron Lett 2003, 44, 1815; (i) Kumar, A.; Pawar, S. S. J Org Chem 2004, 69, 1419.

[13] Abdul-Sada, A. A. K.; Ambler, P. W.; Hodgson, P. K. G.; Seddon, K. R.; Stewark, N. J. Word Pat.WO9521871, 1995.

[14] (a) Chauvin, Y.; mussman, L.; Olivier, H. Angew Chem Int Ed Engl 1995, 38, 3097; (b) Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; de Souza, R. F.; Dupont, J. Polyhedron 1996, 15, 1217; (c) Monteiro, A. L.; Zimn, F. K.; de Souza, R. F.; Dupont, J. Tetrahedron: Asymmetry 1997, 8, 177; (d) Fisher, T.; Sethi, A.; Wellton, T.; Woolf, J. Tetrahedron Lett 1999, 40, 293; (e) Asams, C. J.; Earle, M. J.; Seddon, K. R. Chem Commun 1999, 25; (f) Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. Chem Commun 1999, 1043.

[15] (a) Badri, M.; Brunet, J. J.; Perron, R. Tetrahedron Lett 1992, 33, 4435; (b) Earle, M. J.; McMormac, P. B.; Seddon, K. R. Chem Commun 1998, 2245.

[16] (a) Luer, G. D.; Bartalk, D. E. J Org Chem 1982, 47, 1238; (b) Boon, J. A.; Levisky, J. A.; Pflug, J. L.; Wilkes, J. S. J Org Chem 1986, 54, 480; (c) Adams, C. J.; Earle, M. J.; Roberts, G.; Seddon, K. R. Chem Commun 1998, 2097.

[17] Ellis, B.; Keim, W.; Wasserscheid, P Chem Commun 1999, 337.

[18] Earle, M. J.; McMormac, P. B.; Seddon, K. R. Green Chem 1999, 1, 23.

[19] Corey, E. J.; Zhang, F. Y. Org Lett 2000, 2, 1097.

[20] (a) Kaufmann, D. E.; Nouroozian, M.; Henze, H. Synlett 1996, 1091; (b) Zim, D.; de Souza, R. F.; Dupont, J.; Monteiro, A. L. Tetrahedron Lett 1998, 39, 7071; (c) Carmichael, A. J.; Earle, M. J.; Holberey, J. D.; McMormac, P. B.; Seddon, K. R. Org Lett 1999, 1, 997; (d) Bohm, V. P. W.; Herrmann, W. A. Chem Eur J 2000, 6, 1017; (e) Song, L. E.; Roh, E. J. Chem Commun 2000, 837.

[21] Schoeffer, S. H.; Kaftzik, N.; Wasserscheid, P.; Kragl, U. Chem Commun 2001, 425.

[22] (a) Shi, D. Q.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Wang, X. S. J Heterocycl Chem 2008, 45, 653; (b) Shi, D. Q.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Wang, X. S.; Ji, S. J. J Heterocycl Chem 2008, 45, 693; (c) Shi, D. Q.; Yang, F.; Ni, S. N. J Heterocycl Chem 2009, 46, 469; (d) Dou, G. L.; Wang, M. M.; Huang, Z. B.; Shi, D. Q. J Heterocycl Chem 2009, 46, 645; (e) Shi, D. Q.; Niu,. L. H.; Yao, H.; Jiang, H. J Heterocycl Chem 2009, 46, 237; (f) Dou, G. L.; Shi, C. L.; Shi, D. Q. J Comb Chem 2008, 10, 810; (g) Dou, G. L.; Wang, M. M.; Shi, D. Q. J Comb Chem 2009, 11, 151; (h) Dou, G. L.; Shi, D. Q. J Comb Chem 2009, 11, 1073; (i) Shi, D. Q.; Rong, S. F.; Dou, G. L.; Wang, M. M. J Comb Chem 2010, 12, 25; (j) Dou, G. L.; Shi, D. Q.; Li, Y. H. J Comb Chem 2010, 12, 195; (k) Li, Y. L.; Chen, H.; Shi, C. L.; Shi, D. Q.; Ji, S. J. J Comb Chem 2010, 12, 231; (l) Liu, H.; Dou, G. L.; Shi, D. Q. J Comb Chem 2010, 2, 292.