Available online at www.sciencedirect.com
SCIENCE DIRECT®

ELSEVIER

Tetrahedron Letters 45 (2004) 2013–2015

Tetrahedron Letters

An ionic liquid based on a cyclic guanidinium cation is an efficient medium for the selective oxidation of benzyl alcohols

Haibo Xie, Suobo Zhang* and Haifeng Duan

State Key Laboratory of Polymer Physics and Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, China

Received 17 March 2003; revised 30 November 2003; accepted 12 December 2003

Abstract—A novel room temperature ionic liquid (RTIL) has been prepared containing a cyclic hexaalkylguanidinium cation. The selective oxidation of a series of substituted benzyl alcohols has been carried out in it, with sodium hypochlorite as the oxidant. The RTIL acts as both phase transfer catalyst (PTC) and solvent. The ionic liquid could be recycled after extraction of the benzaldehyde product with ether.

Ionic liquids are defined as compounds that are comprised entirely of ions and are liquids below 100 °C.[1] They exhibit a number of notable physical properties that may be exploited in synthetic processes. For instance, ionic liquids have negligible vapor pressure, which makes them optimal replacements for the volatile organic solvents and for use in high vacuum systems. A nice feature of ionic liquids is that changing the anion or properties of the cation can optimize yield and selectivity of reactions. In addition, ionic solvents can be recovered and reused. The synthetic utility of ionic liquids is reflected in the rapidly increasing volume of literature available. Reaction types successfully performed in ionic liquids include Friedel–Crafts,[2] olefin hydrogenation,[3] hydroformylation[4,5] and Suzuki coupling reactions.[6]

Oxidation of alcohols to the corresponding aldehydes and ketones is one of the most important functional group transformations in organic synthesis. Nowadays, more and more example involving oxidations of non-activated alcohols with dioxygen are being reported. Many examples of homogeneous systems make use of palladium,[7–9] copper,[10] cobalt[11] or ruthenium compounds,[12] usually in aromatic or halogenated hydrocarbon solvents. However, most of these catalysts are not very active (TOF < 10 h^{-1}) and therefore require fairly large amounts of catalyst (5 mol %) and sometimes co-catalysts (10–20 mol %) are used. Furthermore, most systems operate under anhydrous conditions. Recently, Seddon co-workers demonstrated that benzyl alcohols can be oxidized selectively to benzaldehydes in dry ionic liquids using $Pd(OAc)_2$ as catalyst and O_2 as oxidant. The reaction time ranged 15–23 h and the reaction temperature was 353 K.[13] The aerobic oxidation of aromatic and aliphatic alcohols with TPAP/CuCl and CuCl/TEMPO in RTILs has also been published.[14,15] Large amounts of catalyst (5–10%), the need for additives, the high reaction temperatures, and long reaction times make these reactions unattractive. Other examples of oxidation of alcohols with TPAP/*N*-methylmorpholine-*N*-oxide and Ru catalyst have also been demonstrated.[16,17] It is preferable that these transformations be based on the principles of green chemistry and avoid heavy metal reagents, toxic solvents and the generation of large volumes of hazardous waste. Sodium hypochloride is an effective, inexpensive and non-toxic oxidant, which has been reported to be transferred into the organic phase in the presence of a quaternary ammonium salt and is capable of oxidizing alcohols, including benzyl alcohol, although it can be difficult to control selectivity.[18–23] However, organic solvents used in this phase transfer catalytic reaction are environmentally undesirable, and catalyst separation and recovery are significant challenges.

As part of our research aimed at developing green chemistry methods, we have prepared a novel ionic

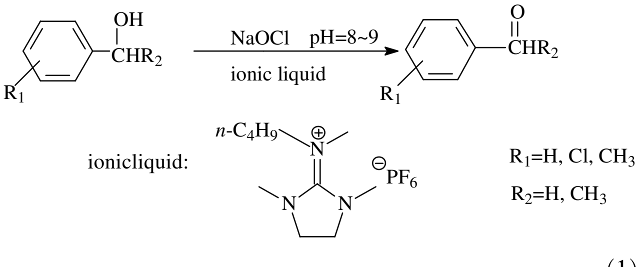
---

Keywords: Ionic liquids; Oxidation of benzyl alcohols; Phase transfer catalyst.

* Corresponding author. Tel./fax: +86-0431-5262347; e-mail: sbzhang@ciac.jl.cn

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.141

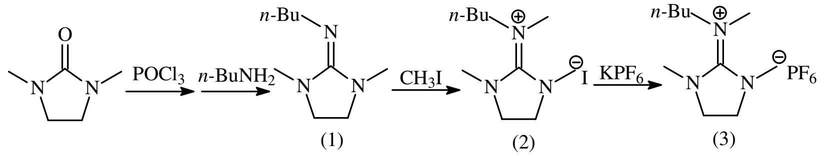
liquid **3** and applied it in the biphasic oxidation of substituted benzyl alcohols using sodium hypochloride as an oxidant (Eq. 1). Furthermore, we demonstrate the possibility of recycling and reusing the ionic solvent. Our work is based on the principles of green chemistry, and avoids heavy metal reagents, toxic solvents, and does not generate large volumes of hazardous waste.



(1)

Taking into account the conditions of benzyl alcohol oxidation (involving the use aqueous NaOCl), 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]), which was prepared by literature methods,[24] was initially selected as a solvent for our experiments among the many other ionic liquids (cf. the BF_4^- or halides salts, which are soluble in water). The reaction was carried out by stirring at room temperature with an excess of 10% aqueous NaOCl and a [bmim][PF_6] solution of substrate. The products were isolated by simple extraction with ether. Reactions were monitored by GC with an internal standard. The yield of 65% obtained using the ionic liquid as the solvent for the reaction is close to the yield obtained by the biphasic PTC method.[18] To compare the effect of the cation of the ionic liquids on both reactivity and selectivity, a new ionic liquid **3** was prepared (Eq. 2) and used in the same reaction as solvent. There are several advantages and reasons for synthesizing hexaalkylguanidinium-based ionic liquids: 1. The hexaalkylguanidinium salts are widely used as phase transfer catalyst.[25] Due to their exceptional stability at high temperature. 2. The positive charge in the guanidinium salts is delocalized over one carbon and three nitrogen atoms, which gives them a high degree of thermal stability compared to tetraalkylammonium salts.

Cyclic pentaalkylguanidine **1** was prepared by the reaction of the corresponding urea with phosphorus oxychloride, to yield a chloroformamidinium salt, frequently referred to as a 'Vilsmeier salt', followed by reaction of said salt with a *n*-butylamine. The reaction of **1** with CH_3I in acetonitrile gave high yield (95%) of **2**. Salt **3** was synthesized by metathesis of the guanidinium iodine salt **2** with potassium hexafluorophosphate in water. NMR and FAB-MS verified the structure and composition of the new IL.[26]



(2)

When the oxidation reaction was carried out under identical conditions using ionic liquid **3** as a solvent, we found that the yield of 95% was higher than was obtained in [bmim][PF_6]. The selectivity towards the aldehydes was higher than 98%. Using a catalytic amount of **3** (5 mol%) in the aqueous/dichloromethane biphasic system, the oxidized product was obtained in 48% yield. This data points out an accelerating effect of the ionic liquid solvent **3**. The influence of several parameters has been investigated so as to optimize the performance of the ionic liquid **3** system (Table 1). The effect of amount of ionic liquid **3** on the reaction was first investigated. The conversion of benzyl alcohol increased with increasing amount of **3** under the same reaction conditions, entries 1–4.

The optimized system was successfully used for the selective oxidation of a series of substituted benzyl

Table 1. The oxidation of substituted benzyl alcohols to aldehydes and ketone under different conditions[a]

Entry	Substrates	Ionic liquids (mL)	Products	Unreacted alcohols (%)[b]	Aldehydes or ketone (%)[b]
1	$C_6H_5CH_2OH$	5	C_6H_5CHO	13	83
2		8		5	94
3		10		3	95
4		15		4	94
5		10		32	65[c]
6	*o*-$ClC_6H_4CH_2OH$	10	*o*-$ClC_6H_4CH_2O$	6	94
7	*p*-$ClC_6H_4CH_2OH$	10	*p*-$ClC_6H_4CH_2O$	8	92
8	*o*-$CH_3C_6H_4CH_2OH$	10	*o*-$CH_3C_6H_4CH_2O$	2	95
9	*p*-$CH_3C_6H_4CH_2OH$	10	*o*-$CH_3C_6H_4CH_2O$	5	95
10	*p*-$CH_3C_6H_4CH(OH)CH_3$	10	*p*-$CH_3C_6H_4COCH_3$	1	99

[a] Reaction conditions: substrate (10 mmol), aqueous solution of NaOCl 10% (25.0 g) at pH = 8–9, reaction time is 60 min.

[b] Determined by gas chromatography with an internal standard.

[c] [bmim][PF_6] as reaction medium.

alcohols.[27] As shown in Table 1, we can see that the RTIL is a good alternative to the traditional toxic solvents and catalysts in the selective oxidation of benzylic alcohols to benzaldehydes and ketones. The result shows good selectivity (no benzoic acid was observed) and high yield compared with the traditional PTCs procedure.[18]

Next the stability and the recovery of the ionic liquid was studied. An IL solution after extraction of the benzaldehyde product with ether was washed by water to remove inorganic salts and dried under vacuum at 70 °C for more than 10 h. The H^1 NMR spectra of the recovered IL indicated no evidence of degradation during the course of the reactions and the recovered solvent has been recycled five times with no appreciable decrease in yield. The only observed limitation to this recycling procedure is the overall reduction of the ionic liquid phase to 85% of the initial volume after five cycles, which arises from solubility of ionic liquid in water and in diethyl ether, and mechanical lose. This problem could be minimized by a direct distillation of the carbonyl compounds from the reaction mixture.[15]

In conclusion, a new room temperature ionic liquid based on a cyclic hexaalkylguanidinium salt has been prepared. We have demonstrated the use of this RTIL as a catalytic, environmentally benign solvent for the selective oxidation of benzyl alcohol to benzaldehyde, replacing phase-transfer catalyzed biphasic systems and thus eliminating the need for a volatile organic solvent and hazardous catalyst disposal. The ability to recycle and reuse the ionic liquid for oxidation also has been demonstrated.

References and notes

1. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772–3789; (c) Seldon, R. A. *Chem. Commun.* **2001**, 2399–2407; (d) Dupont, J.; De Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3692.
2. Boon, J. A.; Levisky, J. A.; Pflug, J. L.; Wilkes, J. S. *J. Org. Chem.* **1986**, *51*, 480–483.
3. Brown, R. A.; Pollet, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1254–1255.
4. Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2698–2700.
5. Favre, F.; Olivier-Bourbigou, H.; Commereuc, D.; Saussine, L. *Chem. Commun.* **2001**, 1360–1361.
6. Mattews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun.* **2000**, 1249–1250.
7. Nishimura, T.; Ohe, K.; Onoue, T.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755; Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645–2646.
8. Hallman, K.; Moberg, C. *Adv. Synth. Catal.* **2001**, *343*, 260–263.
9. Bortolo, R.; Bianchi, D.; D' Aloisio, R.; Querci, C.; Ricci, M. *J. Mol. Catal. A. Chem.* **2000**, *153*, 25–29.
10. Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044–2046.
11. Iwahama, T.; Yoshino, Y.; Keitoku, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2000**, *65*, 6502–6507.
12. Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chellé-Regnaut, I.; Urch, C. J.; Brown, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 12661–12662; Dijksman, A.; Marino-Gonzalez, A.; Mairata I Payeras, A.; Arends, I. W. C. E.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826–6833.
13. Seddon, K. R.; Stark, A. *Green Chem.* **2002**, *4*, 119–123.
14. Farmer, V.; Welton, T. *Green Chem.* **2002**, *4*, 97–102.
15. Ansai, I. A.; Gree, R. *Org. Lett.* **2002**, *4*, 1507–1509.
16. Ley, S. V.; Ramarao, C.; Smith, M. D. *Chem. Commun.* **2001**, 2278–2279.
17. Wolfson, A.; Wuyts, S.; De Vos, D. E.; Vankelecom, I. F. J.; Jacobs, P. A. *Tetrahedron Lett.* **2002**, *43*, 8107–8110.
18. Lee, G. A.; Freedman, H. H. *Tetrahedron Lett.* **1976**, *20*, 1641–1644.
19. Abramovici, S.; Neumann, R.; Sasson, Y. *J. Mol. Catal.* **1985**, *29*, 291–297.
20. Reddy, Ch. V.; Mashsh, M.; Raju, P. V. K.; Reddy, V. V. N. *Syn. Commun.* **2002**, 2797–2802.
21. Abramovici, S.; Neumann, R.; Sasson, Y. *J. Mol. Catal.* **1985**, *29*, 299–303.
22. Do, J. S.; Chou, T. C. *Ind. Eng. Chem. Res.* **1990**, *29*, 1095–1103.
23. Grigoropoulou, G.; Clark, J. H.; Hall, D. W.; Scott, K. *Chem. Commun.* **2001**, 547–548.
24. Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; de Souza, R. F.; Dupont *J. Polyhedron* **1996**, *15*, 1217–1219.
25. US Patent 5,132,423.
26. Compound **1**: ^{1}H NMR (300.1 MHz, $CDCl_3$) δ: 3.34 (t, $J = 7$ Hz, 2H, $-CH_2-N=$), 3.14 (s, 4H, $N-CH_2-CH_2-N$), 2.79 (s, 6H, $2CH_3N$), 1.48–1.58 (m, 2H, $-CH_2-$), 1.31–1.43 (m, 2H, $-CH_2-$), 0.91 (t, $J = 7.2$ Hz, 3H, CH_3-C). Compound **2**: mp: 46 °C, ^{1}H NMR (300.1 MHz, $CDCl_3$) δ: 3.87 (s, 4H, $N-CH_2-CH_2-N$), 3.28 (t, $J = 7.4$ Hz, 2H, $-CH_2-N=$), 3.03(s, 9H, $CH_3-N{=}C(NCH_3)_2$), 1.55–1.65 (m, 2H, $-CH_2-$) 1.25–1.35 (m, 2H, $-CH_2-$),0.90 (t, $J = 7.3$ Hz, 3H, CH_3-C); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 164.5, 53.2, 50.4, 38.9, 37.7, 30.1, 20.0, 14.1; MS m/z 184.2 (A^+, 100%), ($A^+{=}[BuMeN^+{=}C(CH_3NCH_2)_2]$). Compound **3**: mp: −15.3 °C; $d = 1.301$ g/mL; ^{1}H NMR(300.1 MHz, $CDCl_3$) δ: 3.77 (s, 4H, $N-CH_2-CH_2-N$), 3.28 (t, $J = 7.5$ Hz, 2H, $-CH_2-N=$), 3.03 (s, 9H, $CH_3-N{=}C(NCH_3)_2$), 1.59–1.69 (m, 2H, $-CH_2-$), 1.28–1.38 (m, 2H, $-CH_2-$), 0.96 (t, $J = 7.3$ Hz, 3H, CH_3-C); MS m/z 184.2 (A^+, 100%), ($A^+{=}[BuMeN^+{=}C(CH_3NCH_2)_2]$); IR ν 1619(N=C), 2961(CH_3-N).
27. Typical procedure for oxidation: RTIL(10 mL) was added to a 250 mL three-necked, round-bottomed flask containing benzyl alcohol (1.08 g 10 mmol), then 25 g 10% aqueous sodium hypochlorite (pH = 8–9) was added dropwise under vigorous mechanical stirring. The biphasic mixture was stirred for one hour under ambient conditions ($T \sim 25$ °C, atmospheric pressure) and then the mixture was extracted with diethyl ether (3 × 20 mL), after which the diethyl ether was evaporated and the yield was checked by gas chromatography with an internal standard.