Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5143–5146

Ionic liquid supported synthesis of β-lactam library in ionic liquid batch

Xiao-Le Tao, Ming Lei* and Yan-Guang Wang

Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China

Received 30 January 2007; revised 9 May 2007; accepted 11 May 2007
Available online 17 May 2007

Abstract—An efficient and general ionic liquid supported synthesis of *cis*-β-lactam library via multistep reactions have been successfully carried out in a single ionic liquid batch. The method exhibited the advantages over soluble and insoluble polymeric support strategies, such as high loading capacity, avoiding of large excesses of reagents and easy purification. Also, the products were obtained in good yields and purities.

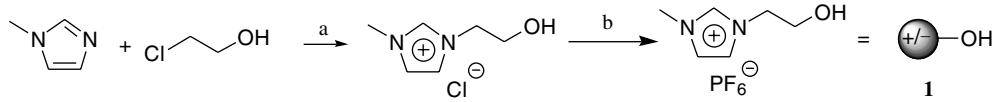
Since the discovery of penicillins, tremendous and continuous efforts have been made for the synthesis and derivation of β-lactams to increase their antimicrobial activity and clinical performance.[1,2] Although much progress has been made in the past few decades, the rapid increase of bacterial resistance against standard therapy has stimulated development of novel β-lactam agents that are stable to β-lactamase and possess high potency and broad spectrum activity. Apart from the clinical treatment of bacterial infection, β-lactams have also been clinically used as therapeutic agents for lowering the cholesterol level in plasma,[3,4] as anti-cancer agents,[5,6] and as enzyme inhibitors.[7,8]

In recent years, supported synthesis has become an effective strategy to access β-lactams libraries. The solid-phase approach is attractive due to the facile purification process of removing the excess reagents and side products allow for the ease of product isolation and makes automation possible.[9] Additionally, the liquid-phase approach using soluble polymers such as polyethylene glycol (PEG), polyethylene glycol monomethylether (MeOPEG) and other ingenious variant polymers as supports have also received considerable attention because of their homogeneous phase chemistry strategies, which have been employed successfully in the synthesis of β-lactams.[10] However, there were some limitations such as low loading capacity, limited solubility during the reaction processes, aqueous solubility, and insolubility in ether solvents.[11] Recently, ionic liquids (ILs) have attracted considerable interest as environmentally benign reaction media in synthetic chemistry.[12] Numerous chemical reactions, including some enzymatic reactions, can be carried out in ILs. An attractive feature of ILs is that their solubility can be turned readily. Therefore, phase separation from organic solvent or aqueous phase is allowed depending on the choice of cations and anions. This suggests the possibility of using the functionalized ILs (so-called task-specific ILs) as soluble supports for organic synthesis. Substrates anchored on ILs are expected to retain their reactivities, as in solution reactions, and allowed the use of conventional spectroscopic analysis during the synthetic process. We and several other groups have demonstrated the feasibility of ILs supported organic synthesis of small molecules,[13] oligosaccharides[14] and peptides,[15] in which the excess reagents and byproducts in the multistep reactions can be removed easily by simple solvent washing. More conveniently, as the IL-supported reagents with high affinity for the ionic liquid phase, the multistep reactions could perform in a single IL batch, which combine the advantage of performing homogeneous chemistry on a relatively large scale, while avoiding of large excesses of reagents and the strategy have been demonstrated by the synthesis of tirofiban analogue.[16] As a part of our work on combinatorial chemistry[14,17] and β-lactam chemistry,[18] we herein described a novel and facile method for the IL-supported synthesis of β-lactams library in IL batch.

As shown in Scheme 1, ion support **1** equipped with hydroxyl group linker, 1-(2-hydroxyethyl)-3-methylimidazolium hexafluorophosphate ([hydemim][PF_6]) was

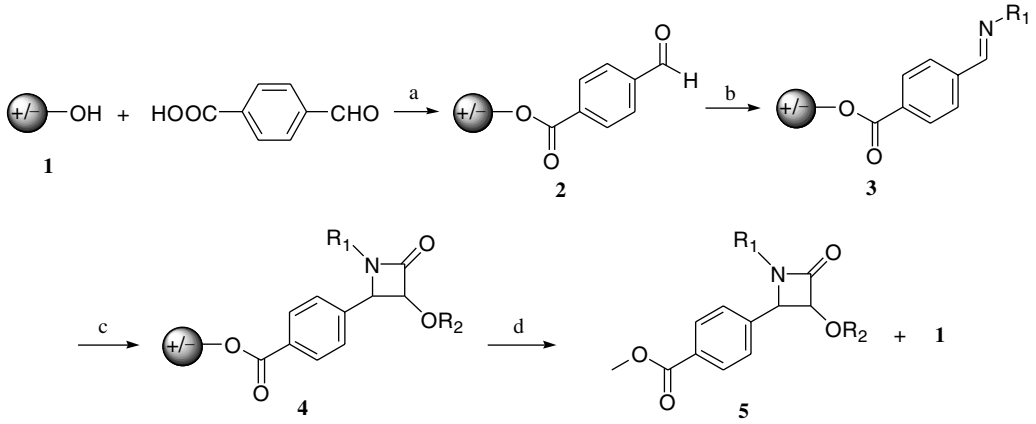
* Corresponding author. Tel./fax: +86 571 87951512; e-mail: leiming@zju.edu.cn

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.053



Scheme 1. Synthesis of ion support **1**. Reagents and conditions: (a) chloroethanol (1 equiv), MeCN, 80 °C, N_2, 96 h; (b) K_6PF_4 (1.5 equiv), MeCN, 60 °C, 20 h.

easily prepared in two steps using standard procedures.[13b] The subsequent multistep transformations were carried out in a single batch of IL (Scheme 2). The esterification of 4-formylbenzoic acid with **1** in IL medium [bmim][PF_6] in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) afforded the IL-supported aldehyde **2** as a pale yellow oil. The resulting solution of **2** in [bmim][PF_6] was treated with primary amines in the presence of molecular sieves at 50 °C to give IL-supported imines **3**. After filtration and washing with diethyl ether/ethyl acetate imines **3** underwent Staudinger cycloaddition reaction with the in situ generated ketene from the corresponding acid chlorides in the presence of triethylamine to give the IL-supported β-lactams **4**. Finally, cleavage of the ester linkage using Et_3N/MeOH (1:4) and extraction with



Scheme 2. IL-supported synthesis of β-lactams. All reactions were carried out in [bmim][PF_6]. Reagents and conditions: (a) DCC (1 equiv), DMAP (0.05 equiv), rt, 24 h; (b) 4 Å MS, R_1NH_2 (1.5 equiv), 50 °C, 24 h; (c) R_2CH_2COCl (1.5 equiv), TEA (1.5 equiv), 0 °C, 2 h and then rt, 24 h; (d) Et_3N/MeOH (1:4), rt, 24 h.

Table 1. IL-supported synthesis of β-lactams in ionic liquid batch

Entry	Product	R_1	R_2	Purity[a] (%)	Yield[b] (%)	Cis:trans[c]
1	**5a**	Ph	Ph	97	82	>99:1
2	**5b**	4-$MeOC_6H_4$	Ph	93	81	>99:1
3	**5c**	2-$MeOC_6H_4$	Ph	98	82	>99:1
4	**5d**	2-MeC_6H_4	Ph	90	83	95:5
5	**5e**	2,4-$Me_2C_6H_3$	Ph	98	80	98:2
6	**5f**	$PhCH_2$	Ph	96	78	>99:1
7	**5g**	4-ClC_6H_4	Ph	88	82	81:19
8	**5h**	2-ClC_6H_4	Ph	87	82	88:12
9	**5i**	4-FC_6H_4	Ph	91	79	94:6
10	**5j**	*t*-Bu	Ph	97	80	98:2
11	**5k**	Cyclohexanyl	Ph	98	82	90:10
12	**5l**	$CH_3(CH_2)_{10}CH_2$	Ph	97	82	92:8
13	**5m**	Ph	4-Cl–Ph	93	80	>99:1
14	**5n**	4-$MeOC_6H_4$	4-Cl–Ph	95	82	98:2
15	**5o**	2-$MeOC_6H_4$	4-Cl–Ph	95	83	>99:1
16	**5p**	2-MeC_6H_4	4-Cl–Ph	93	81	96:4
17	**5q**	4-ClC_6H_4	4-Cl–Ph	90	82	85:15
18	**5r**	2-ClC_6H_4	4-Cl–Ph	92	80	87:13
19	**5s**	4-FC_6H_4	4-Cl–Ph	95	82	92:8
20	**5t**	Cyclohexanyl	4-Cl–Ph	93	83	90:10
21	**5u**	$CH_3(CH_2)_{10}CH_2$	4-Cl–Ph	93	82	93:7

[a] Purities were determined by HPLC of crude diastereomeric products.
[b] Yields were determined based on ion support **1**.
[c] Determined by HPLC analysis.

EtOAc afforded β-lactams **5** with the recovery of ion support **1**.[19]

As shown in Table 1, we obtained *cis*-β-lactams[20] as major products in high yields (78–83%, based on the ion support **1**) with excellent purities (87–98%). The residue solution of [hydemim][PF_6] in [bmim][PF_6] could be reused for another cycle of synthesis after washing and drying. Compared with previously reported supported synthesis of β-lactams, our IL-supported version in IL batch performed more efficiently and is a cleaner process.

In summary, we have developed a novel, general and facile ionic liquid supported synthesis of *cis*-β-lactam in a single IL batch. Our method represents an attractive alternative to classical solid- and liquid-phase synthesis strategies and combines the advantage of performing homogeneous chemistry on a relatively large scale while avoiding of large excesses of reagents. The applications of our method for the synthesis and biological evaluation of β-lactam libraries are currently in progress.

Acknowledgments

Authors thank the National Natural Science Foundation of China (No. 20272051) as well as the Research Program of Educational Bureau of Zhejiang Province of China (No. 20061311).

References and notes

1. For recent reviews see: Bose, A. K.; Manhas, M. S.; Banik, B. K.; Srirajan, V. In *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry and Material Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley-Interscience: New York, 2000; Chapter 7; p 157.
2. Singh, G. S. *Mini Rev. Med. Chem.* **2004**, *4*, 69.
3. For review on pharmacological approaches to the treatment of atherosclerosis, see: Krause, B. R.; Sliskovic, D. R.; Bocan, T. M. A. *Expert Opin. Inv. Drug.* **1995**, *4*, 353.
4. Clader, J. W.; Burnett, D. A.; Caplen, M. A.; Dolmalski, M. S.; Dugar, S.; Vaccaro, W.; Sher, R.; Browne, M. E.; Zhao, H.; Burrier, R. E.; Salisbury, B.; Davis, H. R. *J. Med. Chem.* **1996**, *39*, 3684.
5. Banik, F.; Beker, F.; Banik, B. K. *J. Med. Chem.* **2003**, *46*, 12.
6. Veinberg, G.; Vorona, M.; Shestakova, I.; Kanepe, I.; Zharkova, O.; Mezapuke, R.; Turovskis, I.; Kalvinsh, I.; Lukevics, E. *Bioorg. Med. Chem.* **2000**, *8*, 1033.
7. Doherty, J. B.; Ashe, B. M.; Barker, P. L.; Blacklock, T. J.; Butcher, J. W.; Chandler, G. O.; Dahlgren, M. E.; Davies, P.; Dorn, C. P.; Finke, P. E.; Firestone, R. A.; Hagmann, W. K.; Halgren, T.; Knight, W. B.; Maycock, A. L.; Navia, M. A.; O'Grady, L.; Pisano, J. M.; Shah, S. K.; Thompson, K. R.; Weston, H.; Zimmerman, M. *J. Med. Chem.* **1990**, *33*, 2513.
8. Zhou, N. E.; Guo, D.; Thomas, G.; Reddy, A. V. N.; Kaleta, J.; Purisima, E.; Menard, R.; Micetich, R. G.; Singh, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 139.
9. For the examples of solid-phase synthesis of β-lactams see: (a) Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253; (b) Pei, Y. Z.; Houghten, R. A.; Kiely, J. S. *Tetrahedron Lett.* **1997**, *38*, 3349; (c) Singh, R.; Nuss, J. M. *Tetrahedron Lett.* **1997**, *38*, 1249; (d) Gordon, K.; Bolger, M.; Khan, N.; Balasubramanian, S. *Tetrahedron Lett.* **2000**, *41*, 8621; (e) Schunk, S.; Enders, D. *Org. Lett.* **2000**, *2*, 907; (f) Ruhland, B.; Bombrun, A.; Gallop, M. A. *J. Org. Chem.* **1997**, *62*, 7820; (g) Furman, B.; Thürmer, R.; Kaluża, Z.; Łysek, R.; Voelter, W.; Chmielewski, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1121; (h) Furman, B.; Thürmer, R.; Kaluża, Z.; Łysek, R.; Voelter, W.; Chmielewski, M. *Tetrahedron Lett.* **1999**, *40*, 5909; (i) Gordon, K. H.; Balasubramanian, S. *Org. Lett.* **2001**, *3*, 53.
10. For the examples of soluble polymer (PEG) sopported synthesis of β-lactams: (a) Molteni, V.; Annunziata, R.; Cinquini, M.; Cozzi, F.; Benaglia, M. *Tetrahedron Lett.* **1998**, *39*, 1257; (b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Chem. Eur. J.* **2000**, *6*, 133; (c) Shou, W. G.; Yang, Y. Y.; Wang, Y. G. *Synthesis* **2005**, 530.
11. For reviews, see: (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489; (b) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546.
12. For recent reviews, see: (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772; (c) Wilkes, J. S. *Green Chem.* **2002**, *4*, 73; (d) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, Germany, 2003.
13. (a) *Task-Specific Ionic Liquids: Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH: Weinheim, 2003; p 33; (b) Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron Lett.* **2001**, *42*, 6097; (c) Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron* **2003**, *59*, 6121; (d) Handy, S. T.; Okello, M. *Tetrahedron Lett.* **2003**, *44*, 8399; (e) Miao, W.; Chan, T. H. *Org. Lett.* **2003**, *5*, 5003; (f) Hakkou, H.; Vanden Eynde, J. J.; Bazureau, J. P.; Hamelin, J. *Tetrahedron* **2004**, *60*, 3745; (g) Anjaiah, S.; Chandrasekhar, S.; Gree, R. *Tetrahedron Lett.* **2004**, *45*, 569; (h) Legeay, J.-C.; Vanden Eynde, J. J.; Bazureau, J. P. *Tetrahedron* **2005**, *61*, 12386.
14. Huang, J. Y.; Lei, M.; Wang, Y. G. *Tetrahedron Lett.* **2006**, *47*, 3047.
15. Miao, W. S.; Chan, T. H. *J. Org. Chem.* **2005**, *70*, 3251.
16. de Kort, M.; Tuin, A. W.; Kuiper, S.; Overkleeft, H. S.; van der Marel, G. A.; Buijsman, R. C. *Tetrahedron Lett.* **2004**, *45*, 2171.
17. (a) Cui, S. L.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2005**, *70*, 2866; (b) Shou, W. G.; Yang, Y. Y.; Wang, Y. G. *Synthesis* **2005**, 530; (c) Shou, W. G.; Yang, Y. Y.; Wang, Y. G. *Synthesis* **2005**, 3535; (d) Du, L. H.; Zhang, S. J.; Wang, Y. G. *Tetrahedron Lett.* **2005**, *46*, 3399; (e) Wang, Y. G.; Lin, X. F.; Cui, S. J. *Synlett* **2004**, 1175; (f) Wang, Y. G.; Zhang, J.; Lin, X. F.; Ding, H. F. *Synlett* **2003**, 1467; (g) Lin, X. F.; Zhang, J.; Cui, S. L.; Wang, Y. G. *Synthesis* **2003**, 1569; (h) Shang, Y. J.; Shou, W. G.; Wang, Y. G. *Synlett* **2003**, 1064; (i) Lin, X. F.; Zhang, J.; Wang, Y. G. *Tetrahedron Lett.* **2003**, *44*, 4113; (j) Shang, Y. J.; Wang, Y. G. *Tetrahedron Lett.* **2002**, *43*, 2247; (k) Xia, M.; Wang, Y. G. *Tetrahedron Lett.* **2002**, *43*, 7703; (l) Lei, M.; Tao, X. L.; Wang, Y. G. *Helv. Chim. Acta* **2006**, *89*, 532.
18. (a) Jian, S. Z.; Yuan, Q.; Wang, Y. G. *Synthesis* **2006**, 1829; (b) Yuan, Q.; Jian, S. Z.; Wang, Y. G. *Synlett* **2006**, 1113; (c) Jia, S. Z.; Ma, C.; Wang, Y. G. *Synthesis* **2005**, 725.
19. *Typical procedure for the synthesis of compound* **5a**: To a mixture of DCC (2.06 g, 10 mmol) and DMAP (63 mg, 0.5 mmol) in [bmim][PF_6] (20 mL) was added successively [hydemim][PF_6] (**1**) (2.72 g, 10 mmol) and then 4-formylbenzoic acid (1.50 g, 10 mmol). After vigorous stirring at

room temperature for 24 h, the insoluble *N*,*N*-dicyclohexylurea was eliminated by filtration. The filtrate containing **2** was washed with benzene and then filtrated through a short pad of silica gel. To the IL solution of **2** was then added aniline (1.4 g, 15 mmol) and 4 Å molecular sieve (6.0 g), and stirred at 50 °C for 24 h. After filtration, the mixture was washed with diethyl ether/ethyl acetate (3:1, 3 × 50 mL) and dried in vacuo (10 mmHg) at 50 °C for 3 h to give imine **3** in [bmim][PF_6]. Staudinger cycloaddition reaction was initiated by the slow addition of phenoxyacetyl chloride (2.55 g, 15 mmol) to the [bmim][PF_6] solution of **3** in the presence of Et_3N (1.52 g, 15 mmol) at 0 °C, after 2 h at 0 °C, the reaction mixture was allowed to warm to room temperature. After 24 h, the by-product and excesses of reagents were removed by extraction with H_2O (2 × 30 mL) and diethyl ether/ethyl acetate (3:1, 3 × 50 mL), respectively and dried in vacuo (10 mmHg) at room temperature for 3 h. Then to the solution of ion supported β-lactam **4a** was added Et_3N/MeOH (1:4, 20 mL). The mixture was stirred at room temperature for 24 h. After evaporated in vacuo, the residue was extracted with EtOAc (5 × 50 mL) and the extraction was filtered through a short pad of silica gel. The filtration was dried over anhydrous Na_2SO_4 and then removal of the solvent afforded **5a** as a white solid (3.06 g, 82% yield). All products gave satisfactory ^1H NMR, ^{13}C NMR, FT-IR and MS. Spectral data for **5a**: ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.96 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.27–7.35 (m, 6H), 7.10–7.12 (m, 1H), 6.90–6.94 (m, 1H), 6.78 (d, J = 8.4 Hz, 2H), 5.61 (d, J = 4.8 Hz, 1H, H-4), 5.45 (d, J = 4.8 Hz, 1H, H-3), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 166.8, 162.9, 156.9, 138.0, 136.8, 130.7, 129.8, 129.6, 129.5, 128.3, 125.0, 122.6, 117.6, 115.7, 81.3, 61.8, 52.4; FT-IR (KBr): 1758, 1726, 1508, 1495, 1278 cm^{-1}. MS (ESI): m/z = 396 $[M+Na]^+$.

20. The value of coupling constants of the H3 and H4 (ca. 4.8 Hz) is in agreement with that of the *cis*-β-lactam ring.