Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 47 (2006) 1801–1804

Tetrahedron Letters

Preparation of novel hydrophobic fluorine-substituted-alkyl sulfate ionic liquids and application as an efficient reaction medium for lipase-catalyzed reaction

Yasuhiro Tsukada,[b] Kazuhisa Iwamoto,[a] Hiroyuki Furutani,[b] Yuichi Matsushita,[a] Yoshikazu Abe,[a] Kei Matsumoto,[a] Keishi Monda,[a] Shuichi Hayase,[a] Motoi Kawatsura[a] and Toshiyuki Itoh[a,]*

[a]*Department of Materials Science, Faculty of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan*
[b]*KANEKA CORPORATION, 5-1-1 Torikai-nishi, Settsu, Osaka 566-0072, Japan*

Received 21 November 2005; revised 5 January 2006; accepted 6 January 2006

Abstract—Various types of differently fluorinated-alkyl sulfate ionic liquids have been prepared; the hydrophobicity was dependent on the content ratio of the fluorine on the alkyl sulfate anion and 2,2,3,3,4,4,5,5-octafluoropentyl sulfate salts showed hydrophobic properties. Melting point and viscosity were also dependent on the fluorine contents of the anionic part, while conductivity was determined by the cationic part and not influenced by the fluorine contents. Efficient lipase-catalyzed transesterification was demonstrated using hydrophobic 1-butyl-3-methylimidazolim 2,2,3,3,4,4,5,5-octafluoropentyl sulfate ([bmim][C5F8]) as solvent.

Room temperature ionic liquids (ILs) are a new class of solvents and have attracted growing interest recently because of their unique physical and chemical properties; they are non-volatile, non-flammable, have low toxicity, and good solubility for many organic and inorganic materials.[1] We have been investigating enzymatic[2] or chemical[3] reactions in an ionic liquid solvent system. It is acknowledged that the key point for realizing successful reactions is finding an appropriate combination of the cationic and anionic parts of this solvent.[1] Although there are many reports concerning enhanced enantioselectivity or regioselectivity of lipase-catalyzed reaction in an ionic liquid solvent system,[1,4] it has also been reported that some ionic liquids significantly inhibited the lipase-catalyzed reaction.[1,2a,5–7] It is known that the anionic part of the ionic liquids has a strong impact on the activity of lipases.[1c,2a,4–7] Among the ionic liquids solvent for lipase-catalyzed reactions, the results of reactions in imidazolium alkyl sulfates are interesting.[2d,5,6] We established that a lipase worked well as catalyst for transesterification of secondary alcohols in 1-butyl-3-methylimidazolium ([bmim]) methoxyethoxymethyl sulfate or phenoxyethoxymethyl sulfate, while a very poor reaction rate was obtained for the reactions in a [bmim][$MeSO_4$] or [bmim][$BuSO_4$] solvent system.[2d,5] Sheldon and co-workers suggested that ethyl sulfate anion interacted with the lipase protein and caused deactivation of the lipase based on the results of a FT-IR experiment of the lipase protein.[6] Hydrophobic ionic liquids generally work as a good solvent for lipase-catalyzed reaction,[1–7] and imidazolium alkyl sulfates are very hydrophilic with strong hygroscopic property.[2d] Therefore, we expected that improved reaction might be obtained if we conducted the lipase-catalyzed transesterification in more highly hydrophobic imidazolium alkyl sulfate ionic liquids. In this letter, we report that modification of the alkyl part of the sulfate by fluorine atom made it possible to prepare hydrophobic alkyl sulfate ionic liquids. Efficient lipase-catalyzed transesterification was accomplished using a fluorinated-alkyl sulfate imidazolium as solvent.

First, we prepared [bmim] salts with three types of alkyl sulfates: pentyl sulfate ([C5F0]), 4,4,5,5,5-pentafluoropentyl sulfate ([C5F5]), or 2,2,3,3,4,4,5,5-octafluoropentyl sulfate ([C5F8]) following the method that we

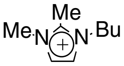
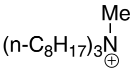
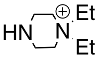
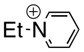
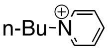
---

Keywords: Novel ionic liquid; Lipase; Fluorine; Enantioselective transesterification.

* Corresponding author. Tel./fax: +81 857 31 5259; e-mail: titoh@chem.tottori-u.ac.jp

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.01.017

Table 1. Physical properties of ionic liquids containing fluorinated-alkyl sulfate

IL	Cation	Anion	Hydrophobic property[a]	Mp/°C	Viscosity/P	Conductivity/S cm^{-1}
[bmim][C5F0]		$n\text{-}C_5H_{11}OSO_3^{\ominus}$	■	−17.0	2.4	8.3×10^{-4}
[bmim][C5F5]		$CF_3CF_2(CH_2)_3OSO_3^{\ominus}$	□	−15.1	2.5	6.3×10^{-4}
[bmim][C5F8]		$CHF_2(CF_2)_3CH_2OSO_3^{\ominus}$	○	−61.2	1.7	8.5×10^{-4}
[emim][C5F5]		$CF_3CF_2(CH_2)_3OSO_3^{\ominus}$	□	—	—	—
[emim][C5F8]		$CHF_2(CF_2)_3CH_2OSO_3^{\ominus}$	○	−16.1	0.54	2.4×10^{-3}
[bdmim][C5F5]		$CF_3CF_2(CH_2)_3OSO_3^{\ominus}$	□	12.6	32	1.0×10^{-4}
[bdmim][C5F8]		$CHF_2(CF_2)_3CH_2OSO_3^{\ominus}$	○	−14.2	8.4	2.7×10^{-4}
[tea][C2F3]	$Et_4N^{\oplus}$	$CF_3CH_2OSO_3^{\ominus}$	■	5.0	13	3.5×10^{-4}
[tea][C3F4]		$CHF_2CF_2CH_2OSO_3^{\ominus}$	□	−9.0	8.2	2.8×10^{-4}
[tea][C5F8]		$CHF_2(CF_2)_3CH_2OSO_3^{\ominus}$	○	−13.0	9.1	2.6×10^{-4}
[tba][C2F3]	$n\text{-}Bu_4N^{\oplus}$	$CF_3CH_2OSO_3^{\ominus}$	■	76–83	—	—
[tba][C3F4]		$CHF_2CF_2CH_2OSO_3^{\ominus}$	□	−4.0	5.8	4.6×10^{-5}
[tba][C5F8]		$CHF_2(CF_2)_3CH_2OSO_3^{\ominus}$	○	−8.0	1.8	3.6×10^{-5}
[oma][C2F3]	 $(n\text{-}C_8H_{17})_3\overset{Me}{N}^{\oplus}$	$CF_3CH_2OSO_3^{\ominus}$	■	4.0	14.2	4.4×10^{-6}
[oma][C3F4]		$CHF_2CF_2CH_2OSO_3^{\ominus}$	□	−5.0	6.9	2.8×10^{-5}
[oma][C5F8]		$CHF_2(CF_2)_3CH_2OSO_3^{\ominus}$	○	−2.0	6.5	2.2×10^{-5}
[dep][C5F8]		$CHF_2(CF_2)_3CH_2OSO_3^{\ominus}$	○	−7.0	6.8	2.8×10^{-5}
[epy][C5F8]		$CHF_2(CF_2)_3CH_2OSO_3^{\ominus}$	○	−11.0	2.5	2.8×10^{-4}
[bpy][C5F8]		$CHF_2(CF_2)_3CH_2OSO_3^{\ominus}$	○	3.1	19	2.2×10^{-4}

○: Hydrophobic, □: half hydrophobic, ■: hydrophilic.

[a] Hydrophobic property was estimated by a simple test: a 1:1 (v/v) mixture of IL with water was vigorously shaken and allowed to stand for 5 min. Hydrophobic IL: a 1 to 1 (v/v) biphasic layer was formed. Hydrophilic IL: it was completely dissolved in water and no biphasic layer was obtained. Half hydrophobic IL: a biphasic layer was obtained but IL:water = <1:>1 (v/v).

reported earlier.[2d] As can be seen in Table 1, [bmim][C5F8] showed the lowest melting point and very hydrophobic property. We evaluated the hydrophobicity of the salts by a simple test: 1:1 (v/v) mixture of the alkyl sulfate salt and water was vigorously shaken and allowed to stand for 5 min. Hydrophobic ionic liquid formed a biphasic layer, while a hydrophilic liquid dissolved in water: a 1:1 biphasic layer was obtained for [bmim][C5F8] (Fig. 1, left), while [bmim][C5F0] was completely dissolved in the water (Fig. 1, right), and [bmim][C5F5] showed a half hydrophobic property (Fig. 1, center). Highly fluorinated-alkyl sulfate salts had low viscous property. On the other hand, the conductivity was independent of the fluorine contents on the alkyl part of the sulfate anion. Some typical physical properties of 19 types of alkyl sulfates ionic liquids are summarized in Table 1.

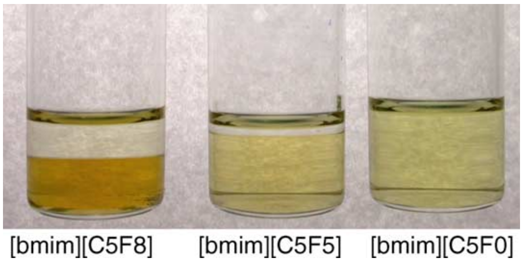
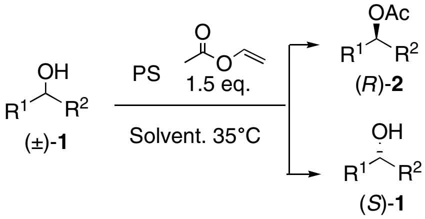


Figure 1. Hydrophobicity test of three types of ionic liquids.

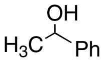
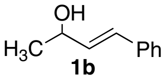
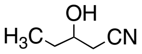
Among imidazolium salts, [emim][C5F8] showed the least viscosity and the highest was recorded for [bdmim][C5F5]. Presence of the methyl group on the 2-position of the imidazolium ring caused an elevated melting point and increased viscosity. Combination of [C5F8] anion with three types of alkylammonium cations, triethylammonium (tea), tributylammonium (tba), and tris-*n*-octyl-methylammonium (oma), gave hydrophobic salts. [C5F8] salts with *N*,*N*′-diethylpyperizinium (dep), *N*-ethyl (epy)-, and *N*-butylpyridinium (bpy) cations again showed a highly hydrophobic property. It was thus found that the hydrophobic property of these solvents was dependent on the content ratio of the fluorine atom on the alkyl sulfate part.

We next focused our attention on the application of alkyl sulfate imidazolium salts as solvent for lipase-catalyzed reaction (Eq. 1). Lipase PS-catalyzed transesterification for three different substrates, 1-phenylethanol (**1a**), 4-phenyl-3-buten-2-ol (**1b**), and 3-hydroxypentanenitrile (**1c**), using vinyl acetate as acyl donor was demonstrated and the results are shown in

Table 2. Lipase PS-catalyzed transesterification in different types of alkyl sulfate IL



(1)

Entry	Substrate	Solvent	Time (h)	% ee of (*R*)-**2**[a] (% yield)[b]	% ee of (*S*)-**1**[a] (% yield)[b]	% conv.[c]	*E*[c]
1	 **1a**	Toluene	27	99 (31)	76 (40)	43	>200
2		*i*-Pr$_2$O	24	73 (37)	42 (62)	37	10
3		[bmim][PF$_4$]	168	99 (16)	24 (77)	19	>200
4		[bmim][BF$_4$]	120	99 (18)	27 (69)	21	>200
5		[bmim][EtSO$_4$]	24	— (0)	0 (91)	0	—
6		[bmim][C5F0]	49	90 (7)	18 (68)	16	23
7		[bmim][C5F8]	26	98 (25)	31 (68)	24	150
8	 **1b**	[bmim][C5F0]	24	99 (3)	7 (82)	7	>200
9		[bmim][C5F8]	48	>99 (31)	69 (33)	25	>200
10	 **1c**	[bmim][C5F0]	16	72 (12)	72 (10)	13	7
11		[bmim][C5F8]	11	92 (30)	17 (50)	16	28

[a] Determined by HPLC (Chiralcel OJ-H, hexane–*i*-PrOH = 9:1).

[b] Isolated yield.

[c] Calculated by % ee of **2** (ee$_p$) and % ee of **3** (ee$_s$). $E = \ln[(1-c)(1+ee_p)]/\ln[(1-c)(1-ee_p)]$, here *c* means conv. which was calculated by the following formula: $c = ee_p/(ee_p+ee_s)$. See Ref. 8.

Table 2. We initially tested the solvent effect using 1-phenylethanol (**1a**) as substrate; toluene gave the best results (entry 1) and [bmim][C5F8] was next among the five solvents tested; the desired (*R*)-**2a** was obtained in 25% yield with 98% ee when the reaction was carried out using [bmim][C5F8] solvent (entry 7). On the contrary, the reaction proceeded very slowly in a conventional ionic liquid [bmim][PF$_6$] (entry 3) or [bmim][BF$_4$] (entry 4), and no reaction took place if the reaction was carried out in [bmim][EtSO$_4$] (entry 5). Further, only 7% of (*R*)-**2a** with 90% ee was obtained by the reaction using [bmim][C5F0] solvent (entry 6). It was thus found that [bmim][C5F8] was the best solvent among the tested five ionic liquids (entries 3–7). It should be emphasized that [bmim][C5F8] is non-volatile and non-flammable solvent. Use of [bmim][C5F8] as solvent makes it possible to realize a very safety reaction process instead of traditional flammable organic solvent such as toluene.

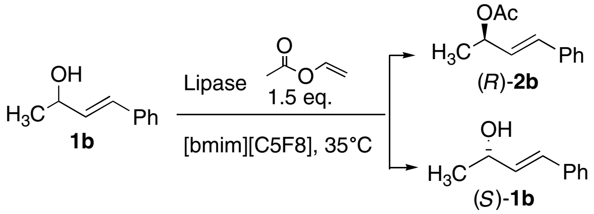
Better results were again recorded for the reactions of **1b** and **1c** using [bmim][C5F8] solvent (entries 7 and 9) compared to those in the [bmim][C5F0] solvent system (entries 6 and 8). It should be noted that a remarkable enhancement of enantioselectivity was obtained when **1c** was subjected to the lipase-catalyzed reaction switching the solvent from [bmim][C5F0] (entry 8) to [bmim][C5F8] (entry 9). It has thus been confirmed that 1-butyl-3-methylimidazolium 2,2,3,3,4,4,5,5-octafluoropentyl sulfate is an appropriate solvent to achieve lipase-catalyzed transesterification.

We next demonstrated the recycling use of enzyme in the [bmim][C5F8] solvent system using **1b** as substrate (Eq. 2 and Table 3). As shown in Table 3, recycling of the enzyme was indeed possible in our novel ionic liquid solvent system, though both the reaction rate and enantioselectivity gradually dropped with repetition of the reaction process in the system when lipase PS was used as catalyst (entries 1–5).[2]

For the recycling of lipase, 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim][BF$_4$]) solvent gave better results than did [bmim][BF$_4$].[2e] However, it was found that the transesterification of **1b** using [bdmim][C5F8] solvent proceeded very slowly due to the highly viscous nature of the solvent. We recently reported that 1-butyl-2,3-dimethylimidazolium cetyl-PEG10-sulfate (IL1) coated lipase PS (IL1-PS) showed excellent reactivity.[2g] IL1-PS worked very efficiently in the [bmim][C5F8] solvent system. To our delight, (*R*)-**2b** was obtained with excellent enantioselectivity using IL-1-PS and, five repetitions of this process showed no significant drop of the reaction rate (entries 6–10). We thus succeeded to demonstrate the recycling use of lipase in [bmim][C5F8] using IL-1-PS as catalyst.

In conclusion, we demonstrated a successful example of lipase-catalyzed enantioselective transesterification in a novel alkyl sulfate imidazolium solvent system. It was possible to use the enzyme repeatedly in this system, particularly, when IL-1-PS was used as catalyst. Since the starting material of 2,2,3,3,4,4,5,5-octafluoropentanol

Table 3. Lipase PS-catalyzed transesterification in different types of alkyl sulfate IL



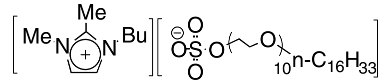
(2)

Entry	Run	Lipase	Time (h)	% ee of (*R*)-**2b**[a] (% yield)[b]	% ee of (*S*)-**1b**[a] (% yield)[b]	% conv.[c]	*E*[c]
1	1st	PS	24	98 (13)	25 (87)	20	148
2	2nd	PS	24	96 (22)	16 (77)	14	62
3	3rd	PS	24	93 (10)	10 (67)	10	31
4	4th	PS	24	93 (6)	9 (75)	9	31
5	5th	PS	24	88 (5)	5 (60)	5	16
6	1st	IL1-PS	2.5	98 (32)	51 (62)	34	165
7	2nd	IL1-PS	4.5	96 (22)	29 (66)	23	65
8	3rd	IL1-PS	6.0	96 (30)	39 (61)	29	72
9	4th	IL1-PS	8.0	97 (20)	29 (77)	23	87
10	5th	IL1-PS	13	97 (18)	23 (78)	19	54

[a] Isolated yield.

[b] The enantiomeric excess was determined by HPLC analysis using OJ-H (ϕ 4.6 mm × 250 mm, hexane–*i*-PrOH = 9:1, 35 °C).

[c] See Ref. 8.



IL1

is not expensive, we believe this ionic liquid might become a useful solvent for various types of reactions. Further investigation of the optimization of the combination of imidazolium cation and alkyl sulfate anion will make it even more beneficial.

Acknowledgments

This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

1. (a) For recent reviews of reactions in an ionic liquid solvent system see: *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH, 2003; (b) *Ionic Liquids as Green Solvents*; Rogers, R. D., Seddon, K. R., Eds.; ACS Symposium Series 856; American Chemical Society, 2002; (c) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *61*, 1015–1060.
2. (a) Itoh, T.; Akasaki, E.; Kudo, K.; Shirakami, S. *Chem. Lett.* **2001**, 262–263; (b) Itoh, T.; Akasaki, E.; Nishimura, Y. *Chem. Lett.* **2002**, 154–155; (c) Itoh, T.; Nishimura, Y.; Kashiwagi, M.; Onaka, M. In *Ionic Liquids as Green Solvents: Progress and Prospects*; Rogers, R. D., Seddon, K. R., Eds.; ACS Symposium Series 856; American Chemical Society: Washigton, DC, 2003; pp 251–261, Chapter 21; (d) Itoh, T.; Ouchi, N.; Hayase, S.; Nishimura, Y. *Chem. Lett.* **2003**, *32*, 654–655; (e) Itoh, T.; Nishimura, Y.; Ouchi, N.; Hayase, S. *J. Mol. Catal. B: Enzym.* **2003**, *26*, 41–45; (f) Itoh, T.; Ouchi, N.; Nishimura, Y.; Han, S.-H.; Katada, N.; Niwa, M.; Onaka, M. *Green Chem.* **2003**, *5*, 494–496; (g) Itoh, T.; Han, S.; Matsushita, Y.; Hayase, S. *Green Chem.* **2004**, *6*, 437–439.
3. (a) Ohara, H.; Kiyokane, H.; Itoh, T. *Tetrahedron. Lett.* **2002**, *43*, 3041–3044; (b) Itoh, T.; Kawai, K.; Hayase, S.; Ohara, H. *Tetrahedron Lett.* **2003**, *44*, 4081–4084; (c) Itoh, T.; Uehara, H.; Kawai, K.; Hayase, S.; Ohara, H.; Oyama, M. In *Analytical Mechanistic and Synthetic Organic Electrochemistry—6th International M. Baizer Award Symposium in Honor of Dennis H. Evans and Masao Tokuda*; Lessard, J., Hapiot, P., Nishiguchi, I., Eds.; The Electrochemical Society: USA, 2004; pp 9–12.
4. For several recent examples, see: (a) Xin, J.-Y.; Zhao, Y.-J.; Shi, Y.-G.; Xia, C.-G.; Li, S.-B. *World J. Microbiol. Biotechnol.* **2005**, *21*, 193–199; (b) Malhotra, S. V.; Zhao, H. *Chirality* **2005**, *17*, S240–S242; (c) Yu, H.; Wu, J.; Bun, C. C. *Chirality* **2004**, *17*, 16–21; (d) Noel, M.; Lozano, P.; Vaultier, M.; Iborra, J. L. *Biotechnol. Lett.* **2004**, *26*, 301–306; (e) Irimescu, R.; Kato, K. *Tetrahedron Lett.* **2004**, *45*, 523–525; (f) Rasalkar, M. S.; Potdar, M. K.; Salunkhe, M. M. *J. Mol. Catal. B: Enzym.* **2004**, *27*, 267–270; (g) Mohile, S. S.; Potdar, M. K.; Harjani, J. R.; Nara, S. J.; Salunkhe, M. M. *J. Mol. Catal. B: Enzym.* **2004**, *30*, 185–188; (h) Ulbert, O.; Frater, T.; Belafi-Bako, K.; Gubicza, L. *J. Mol. Catal. B: Enzym.* **2004**, *31*, 39–45; (i) Kamal, A.; Chouhan, G. *Tetrahedron Lett.* **2004**, *45*, 8801–8805.
5. First attempt of alkyl sulfate ionic salt as reaction medium for lipase-catalyzed reaction: Schöfer, S. H.; Kaftzik, N.; Wasserscheid, P.; Kragl, U. *Chem. Commun.* **2001**, 425–426.
6. Madeira, L. R.; Sorgedrager, M. J.; Carrea, G.; Van Rantwijk, F.; Secundo, F.; Sheldon, R. A. *Green Chem.* **2004**, *6*, 483–487.
7. Kaar, J. L.; Jesionowski, A. M.; Berberich, J. A.; Moulton, R.; Russell, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 4125–4131.
8. Chen, C.-S.; Fujimoto, Y.; Girdauskas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *102*, 7294–7298.