Lipase-catalyzed Enantioselective Acylation in a Halogen Free Ionic Liquid Solvent System

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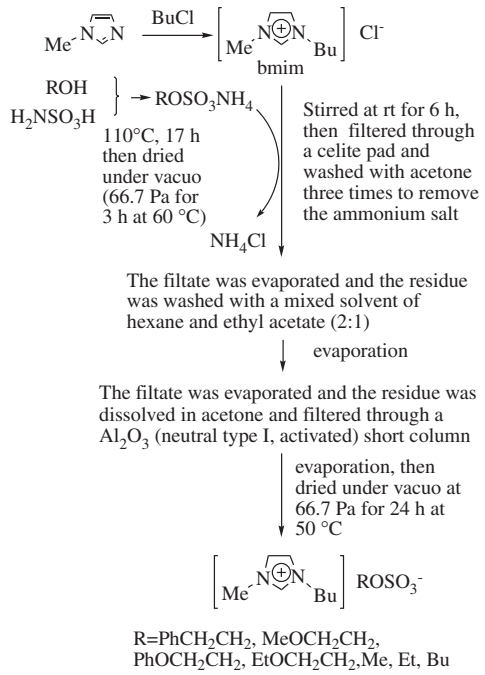
Lipase-catalyzed enantioselective transesterification was demonstrated using several types of imidazolium alkyl sulfate as a reaction medium. The desired optically pure acetate was successfully obtained under the conditions used, although reaction rate was inferior to that in imidazolium tetrafluoroborate.

Ionic liquids have very good properties as a reaction medium in chemical reactions: they are non-volatile, non-flammable, have low toxicity, and good solubility for many organic and inorganic materials.[1] We recently reported the lipase-catalyzed enantioselective transesterification of the secondary alcohols in an ionic liquid solvent system, butylmethylimidazolium([bmim]) hexafluorophosphate (PF_6) and tetrafuloroborate (BF_4), and showed that it was possible to use the enzyme repeatedly in the solvent system.[2–4] From the standpoint of green chemistry and practical aspects, we should reduce the use of halogenated compounds and develop cheaper ionic liquids. Imidazolium sulfonates might be seen as good candidates, because we are able to prepare various types of alkyl sulfate very easily. However, there has been no successful result of the enzymatic reaction in an imidazolium alkyl sulfate solvent system; Kragl and his co-workers reported that lipase-catalyzed reaction in imidazolium methyl sulfate was unsuccessful.[5] Since it is well known that physical properties of imidazolium salts are drastically changed by modification of their structure, even in the counter ion portion,[1] we decided to more carefully investigate the possibility of using imidazolium alkyl sulfates. We report here the first successful example of lipase-catalyzed reaction in a halogen-free ionic liquid solvent system of imidazolium alkyl sulfate.

The imidazoium alkyl sulfate was prepared starting from the corresponding ammonium alkyl sulfate following Scheme 1. Ammonium alkyl sulfate are easily prepared by the reaction of an alcohol with ammonium sulfate; 2-ethoxyethanol was treated with sulfamic acid to give ammonium 2-ethoxyethyl sulfate, and subsequent anion exchange reaction with [bmim] chloride gave the corresponding [bmim] alkyl sulfate.[6] Two interesting physical properties were found in the color and viscosity of these salts. [Bmim] alkyl sulfate was light to dark brown in color, while [bmim]PF_6 or [bmim]BF_4 were colorless. The second was recognized in their viscosity. The viscosity of [bmim] alkyl sulfate was independent of the alkyl chain of the sulfate ion portion; [bmim]2-ethoxyethyl sulfate showed a low viscose oily form, but high viscosity was found for [bmim]butyl sulfate, although it has been generally supposed that an ethoxyethyl-substituted molecule is more viscous than a butyl-substituted molecule. We failed to obtain pure [bmim] octyl sulfate because this salt was completely miscible with both the organic solvent tested and water.[7] Preparation of pure [bmim]*i*-propyl sulfate and [bmim]*t*-butyl sulfate was also failed because the anion exchange reaction of *i*-propyl sulfate or t-butyl sulfate with [bmim]Cl was incompleted.



Scheme 1. Preparation of [bmim]alkyl sulfate.

The enantioselective transesterification of 5-phenyl-1-penten-3-ol ((±)-**1**) was carried out in [bmim] alkyl sulfate solvents and the results are shown in Table 1. To a mixture of Novozym 435[8] (50 wt% based on the substrate) in the ionic liquid (0.2 M) were added (±)-**1a** and vinyl acetate. The resulting mixture was stirred at 35 °C for 24 h. The reaction course was monitored by GC analysis and the product (*S*)-**2a**[9] and unreacted

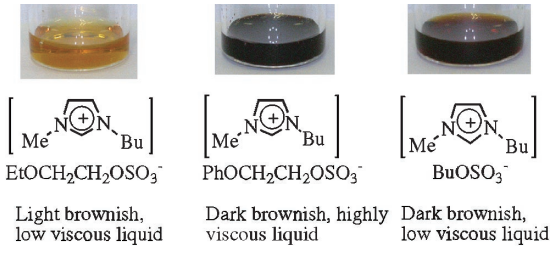


Figure 1. Property of several imidazolium alkyl sulfates.

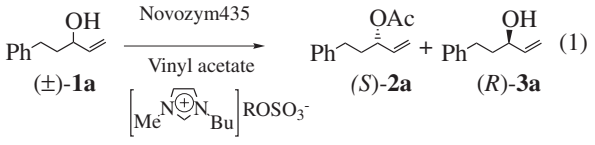
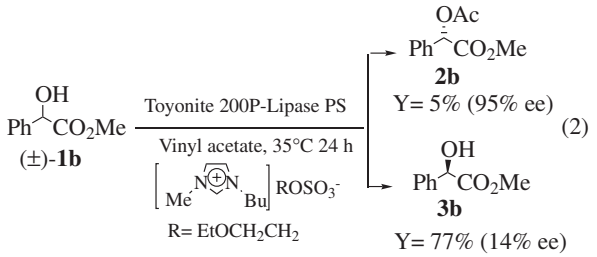


Table 1. Lipase-catalyzed transesterification in a halogen-free ionic liquid solvent system[a]

Entry	R [bmim]$ROSO_3^-$	Time /h	%ee of **2a** (%Yield)[b]	conv. /c	*E* value[c]
1	Me	24	>99 (8)	0.10	>200
2	Et	24	>99 (8)	0.11	>200
3	Bu	24	>99 (15)	0.15	>200
4	$MeOCH_2CH_2$	24	>99 (8)	0.12	>200
5	$EtOCH_2CH_2$	24 (1st run)	>99 (23)	0.23	>200
6	$PhOCH_2CH_2$	24	>99 (24)	0.29	>200
7	$EtOCH_2CH_2$	24 (2 nd run)	>99 (16)	0.17	>200
8	$EtOCH_2CH_2$	24 (3 rd run)	>99 (2)	0.04	>200
9	$[bmim]PF_6$	5	>99 (45)	0.47	>200

[a]The reaction was carried out at 35 °C using $[bmim]ROSO_3^-$ (0.2 M) in the presence of 1.5 equiv. of vinyl acetate as an acyl donor. [b]Isolated yield. Enantiomeric excess was determined by capillary GC analysis using a chiral column (Chiraldex G-TA); >99% ee means that no isomer was detected under the analysis conditions. [c]$E = \ln[(1-c)(1+ee\mathbf{2a})]/\ln[(1-c)(1-ee\mathbf{2a})]$, here c means conv. which was calculated by the following formula: c=ee**3a**/(ee**2a**+ee**3a**), ref. 10.

alcohol (*R*)-**1a**[9] were extracted with diethyl ether and purified by silica-gel thin layer chromatography (TLC). The lipase-catalyzed transesterification proceeded in these solvent systems and optically pure acetate (*S*)-**2a** was obtained with excellent enantioselectivity (Entries 1-8), though the reaction rate was inferior to the reaction in $[bmim]PF_6$ (Entry 9). In addition, we succeeded to obtain the product with perfect enantioselectivity even in $[bmim]CH_3OSO_3$ (Entry 1), while it was reported that no reaction took place in this solvent;[5] the differences in the results might be due to the quality of the ionic liquid employed.[6] Ethoxyethyl sulfate and 2-phenoxyethyl sulfate gave good results and (*S*)-**2a** was obtained in 23% and 24% yield with >99% ee, respectively (Entries 5 and 6). We previously showed that the repeated use of enzyme was possible in $[bmim]PF_6$ solvent system and it was again realized in this solvent system; three repetitions of the reaction gave (*S*)-**2a** with >99% ee in the $[bmim]EtOCH_2CH_2OSO_3$ solvent system (Entries 5,7, and 8). Interestingly, no reaction took place when transesterification of (±)-**1a** was carried out using methyl phenylthioacetate as acyl donor under reduced conditions.[3,4] We assume that the exchange reaction of **1a** with the ethoxyethyl group in the solvent took place under the reduced conditions because only a trace amount of the starting **1a** was recovered after the reaction.[11] Although the reaction rate was still insufficient, immobilized lipase PS by Toyonite 200P[4,12] was active in the $[bmim]EtOCH_2CH_2OSO_3$ solvent system and acetate (*S*)-**2b**[4] was obtained with 95% ee (Eq. 2). It was thus obvious that imidazolium alkyl sulfates can be used as solvent for lipase-catalyzed transesterification.



In conclusion, we demonstrated the first successful example of lipase-catalyzed enantioselective transesterification in the imidazolium alkyl sulfate solvent system. It was possible to use the enzyme repeatedly in this system, though the reaction rate was not satisfactory. We do believe, however, that further investigation of the scope and limitations of this reaction, especially optimization of the combination of imizadolium cation and alkyl sulfate anion, will make it even more beneficial.

References and Notes

1 Reviews, see: a) "Ionic Liquids Industrial Applications to Green Chemistry," ed. by R. D. Rogers and K. R. Seddon, American Chemical Society, ACS Symposium Series 818, Oxford University Press (2002). b) "Ionic Liquids in Synthesis," ed. by P. Wassersceid and T. Welton, Wiley-VCH (2003), and references cited there.
2 T. Itoh, E. Akasaki, K. Kudo, and S. Shirakami, *Chem. Lett.*, **2001**, 262.
3 T. Itoh, E. Akasaki, and Y. Nishimura, *Chem. Lett.*, **2002**, 154 .
4 T. Itoh, Y. Nishimura, M. Kashiwagi, and M. Onaka, "Ionic Liquids as Green Solvents: Progress and Prospects," ACS Symposium Series, ed. by R. D. Rogers and K. R. Seddon, American Chemical Society, Oxford University Press, in press.
5 S. H. Schöfer, N. Kaftzik, P. Wasserscheid, and U. Kragl, *Chem. Commun.*, **2001**, 425.
6 It was essential to rinse out the impurities from the salt using a mixed organic solvent of hexane and ethyl acetate prior to evaporation. We usually used at least ten washings and confirmed that no more free imidazole or alcohols could be detected in the rinsed solvent by GC analysis.
7 This salt was completely miscible in toluene, ether, hexane, benzene, ethyl acetate, methanol, chloroform, dichloromethane, acetonitrile, acetone, and water.
8 Novozym435 (*Candida Antarctica*) is now commercially available as CHIRAZYME L-2,c.-f.,C2,Iyo from Roche Molecular Biochemicals.
9 a) Y. Takagi, R. Ino, H. Kihara, T. Itoh, and H. Tsukube, *Chem. Lett.*, **1997**, 1247. b) Y. Takagi, T. Nakatani, T. Itoh, and T. Oshiki, *Tetrahedron Lett.*, **41**, 7889 (2000).
10 C.-S. Chen, Y. Fujimoto, G. Girdauskas, and C. J. Sih, *J. Am. Chem. Soc.*, **102**, 7294 (1982).
11 In addition, ^1H NMR analysis of the used $[bmim]EtOCH_2CH_2OSO_3$ showed that ethoxyethyl group was partly replaced by 5-phenyl-1-penten-3-ol after the reaction was carried out under reduced pressure conditions.
12 The authors are grateful to Mr. Masanobu Kamori of Toyodenka Co., Ltd. for providing Toyonite.

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