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Amphiphilic Organocatalyst for Schotten-Baumann-Type Tosylation of Alcohols under Organic Solvent Free Condition

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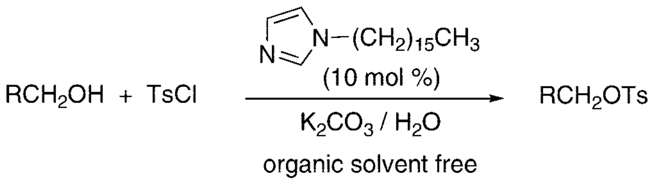
ABSTRACT



A Tosylation of primary alcohol with tosyl chloride was performed effectively with an *N*-hexadecylimidazole catalyst in water containing K$_2$CO$_3$. aggregation of the catalyst carrying a hydrophobic methylene chain worked as a substitute for organic solvent.

Tosylation has long been recognized as a method for converting alcohols into reactive electrophiles.[1] While treatment of alcohols with tosyl chloride and amine in an organic solvent is a conventional method to prepare the tosylates, the Schotten-Baumann method,[2] which is performed with tosyl chloride and an inorganic base such as potassium carbonate in an organic solvent[3] or in a biphase system consisting of water and organic solvent,[4] has also been developed. As the Schotten-Baumann reaction can avoid the use of a stoichiometric amount of amine, the procedures have been evaluated from the economical and environmental superiority. Even though the method was well planned, it still requires an organic solvent. Tanabe reported an organic solvent-free Schotten-Baumann-type tosylation in water, but it requires control of the pH of water and slow addition of tosyl chloride to prevent hydrolysis of the chloride.[5] The procedure reported by Kazemi without water and organic solvent seems to be attractive, but it should be performed under harsh conditions to use inorganic bases without water.[6] We supposed that use of *N*-alkylimidazole as a nucleophilic catalyst with a hydrophobic group[7] for Schotten-Baumann-

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(1) (a) Larock, R. C. In *Comprehensive of Organic Transformation*; VCH: Weinheim, 1989. (b) Kabalka, G. W.; Varma, M.; Varma, R. S. *J. Org. Chem.* **1986**, *51*, 2386–2388.

(2) (a) Schotten, C. *Chem. Ber.* **1884**, *19*, 2544–2547. (b) Baumann, E. *Chem. Ber.* **1886**, *21*, 3218–3222.

(3) (a) Tanabe, Y.; Yamamoto, H.; Yoshida, Y.; Miyawaki, T.; Utsumi, N. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 297–300. (b) Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, *55*, 2183–2192.

(4) Ouchi, M.; Inoue, Y.; Liu, Y.; Nagamune, S.; Nakamura, S.; Wada, K.; Hakushi, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1260–1262.

(5) (a) Morita, J.; Nakatsuji, H.; Misaki, T.; Tanabe, Y. *Green Chem.* **2005**, *7*, 711–715. (b) Nakatsuji, H.; Morita, J.; Misaki, T.; Tanabe, Y. *Adv. Synth. Catal* **2006**, *348*, 2057–2062.

(6) (a) Kazemi, F.; Massah, A. R.; Javaherian, M. *Tetrahedron* **2007**, *63*, 5083–5087. (b) Fazaeli, R.; Tangestaninejad, S.; Aliyan, H. *Can. J. Chem.* **2006**, *86*, 812–818.

(7) (a) Asano, K.; Matsubara, S. *Synlett* **2009**, 35–38. (b) Nakatsuji, H.; Ueno, K.; Misaki, T.; Tanabe, Y. *Org. Lett.* **2008**, *10*, 2131–2134.

(8) (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817. (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164. (c) Lubineau, A. *Chem. Ind.* **1996**, 123–126. (d) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751–2772. (e) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741–760. (f) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3166. (g) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768–1769. (h) Loncaric, C.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 574–575. (i) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170–1186. (j) Inoue, Y.; Araki, K.; Shiraishi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3079–3083. (k) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267–9331. (l) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. (m) Pan, C.; Wang, Z. *Coord. Chem. Rev.* **2008**, *252*, 736–750.

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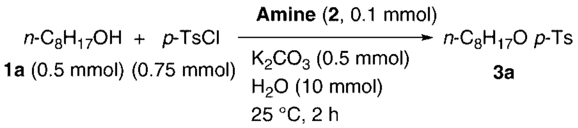
type tosylation might realize an organic solvent-free condition, because aggregation of the amphiphilic compound in water will form a hydrophobic phase, which may work as a substitute for an organic solvent.[8,9] It will prevent tosyl chloride and the product from undergoing hydrolysis.

As shown in Scheme 1, *n*-octanol (0.5 mmol) was treated with tosyl chloride (0.75 mmol) and potassium carbonate (0.5 mmol) in the presence of *N*-alkylimidazole (0.1 mmol) and water (10 mmol) at 25 °C for 2 h. The length of the alkyl chain on imidazole determined the efficiency of the reaction. While *N*-methyl or -butylimidazole afforded the corresponding tosylate in poor yield, *N*-hexadecylimidazole gave the product in 82% yield. When the reaction was examined with 5.0 mmol of water in the *N*-hexadecylimidazole case, the yield of tosylate was improved from 82% to 95%. In the absence of water, the yield of the tosyate was decreased to 43%.

Scheme 1. Organic Solvent Free Schotten-Baumann-Type Tosylation of 1-Octanol with Amines as a Catalyst

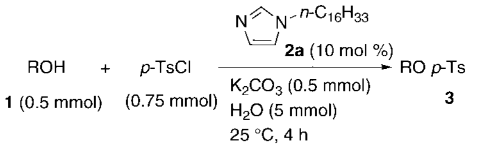


$$\underset{\mathbf{1a}\ (0.5\ \text{mmol})}{n\text{-}C_8H_{17}OH} + \underset{(0.75\ \text{mmol})}{p\text{-}TsCl} \xrightarrow[\substack{K_2CO_3\ (0.5\ \text{mmol})\\ H_2O\ (10\ \text{mmol})\\ 25\ °C,\ 2\ h}]{\textbf{Amine}\ (\mathbf{2},\ 0.1\ \text{mmol})} \underset{\mathbf{3a}}{n\text{-}C_8H_{17}O\ p\text{-}Ts}$$

Et_3N	17%
DMAP	18%
N-Methylimidazole	29%
N-Butylimidazole	36%
N-Decylimidazole	78%
N-Hexadecylimidazole	82%

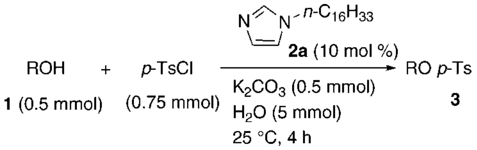
Under this organic solvent-free condition, various *n*-alkanols were converted into the corresponding tosylates. As shown in Scheme 2, *n*-alkanols from C1 to C10 were examined. Among them, methanol, ethanol, and propanol gave unsatisfactory results, as they are too soluble in water to be tosylated.

Scheme 2. Organic Solvent Free Schotten-Baumann-Type Tosylation of 1-Alkanols with *N*-Hexadecylimidazole as a Catalyst



R	**3** / %	**R**	**3** / %
CH_3	35	$n\text{-}C_6H_{13}$	88
C_2H_5	35	$n\text{-}C_7H_{15}$	90
$n\text{-}C_3H_7$	52	$n\text{-}C_8H_{17}$	95
$n\text{-}C_4H_9$	71	$n\text{-}C_9H_{19}$	89
$n\text{-}C_5H_{11}$	82	$n\text{-}C_{10}H_{21}$	96

Table 1. Organic Solvent Free Schotten-Baumann-Type Tosylation of Various Alcohols with *N*-Hexadecylimidazole as a Catalyst



entry	alkanols (ROH)	tosylates/%[a]
1	$HC{\equiv}C(CH_2)_9OH$	90
2	$C_3H_7C{\equiv}CCH_2OH$	79
3	$HC{\equiv}CCH_2OH$	70
4	$CH_2{=}CHCH_2OH$	44
5	$CH_2{=}CH(CH_2)_4OH$	83
6	$E\text{-}C_2H_5CH{=}CH(CH_2)_2OH$	56
7	$Z\text{-}C_2H_5CH{=}CH(CH_2)_2OH$	56
8	$CH_3O(CH_2)_6OH$	61
9	$C_2H_5O(CH_2)_5OH$	66
10	$C_3H_7O(CH_2)_4OH$	54
11	$CH_3(Ph)CHCH_2OH$	73
12	Benzylalcohol	34
13	PhOH	80
14	3,5-Dimethylphenol	50
15	2,2,2-Trifluoroethanol	75
16	$C_6H_{13}CH(OH)CH_3$	21[b]
17	$C_5H_{11}CH(OH)C_2H_5$	24[c]

[a] Isolated Yields. [b] Starting material recovered in 64%. [c] Starting material recovered in 66%.

Reactions starting from alcohols other than *n*-alkanols were also examined, as shown in Table 1. The existence of a C−C triple bond in the substrate did not disturb the reaction (Table 1, entries 1−3). In the case of hexenols, the position of C−C double bond was significant for the reaction to proceed efficiently (Table 1, entries 5−7). Phenols were also converted into the corresponding tosylates (Table 1, entries 13, 14). Conversions of secondary alcohols were not high (entries 16, 17). The low conversion of 3-hexenols (Table 1, entries 6,7) into the corresponding tosylates compared to 5-hexenol (Table 1, entry 5) may be explained as follows: We suppose that *N*-alkylimidazole molecules align along the interface between water and organic compounds (Figure 1).[7a,9,10] The imidazo-

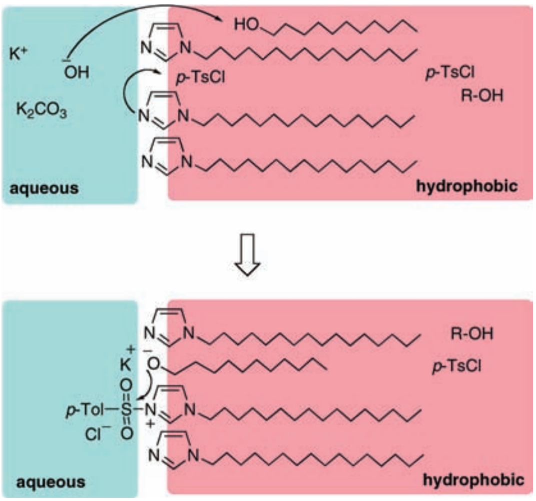
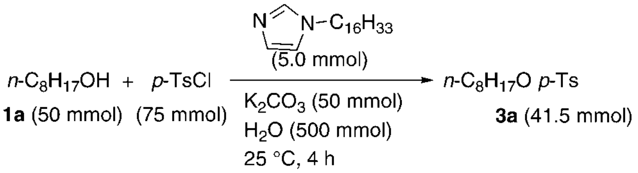


Figure 1. Role of alkyl chain in the catalyst.

lium species, which are formed from *p*-tosyl chloride and *N*-alkylimidazole, may also work as an efficient surfactant. Alkoxide, which is also formed by inorganic base in water, can also work as a surfactant. The *N*-alkylimidazole, imidazolium, and alkoxide are aligned in close proximity and react to give the tosylate efficiently. Thus the alignment of alkoxide, which keeps the right orientation in the *N*-alkylimidazolium phase, will lead to high conversion; the bent carbon chain skeleton such as 3-hexenol was unfavorable for the reaction.

This organic solvent-free method was also perfomed on preparative scale, as shown in Scheme 3: to a 100 mL glassvessel, 1-octanol (50 mmol, 6.5 g), *N*-hexadecylimidazole (5.0 mmol, 1.5 g), *p*-toluenesulfonyl chloride (75 mmol, 14 g), potassium carbonate (50 mmol, 6.9 g) and water (500 mmol, 9 mL) were added one by one. The mixture was stirred for 4 h in an oil bath kept at 25 °C. The mixture was then diluted with ethyl acetate and dried over anhydrous magnesium sulfate. The organic solution was concentrated in vacuo. After purification with silica gel column chromatography using hexane/ethyl acetate (v/v = 30/1) as an eluent, 12 g of **3a** was isolated in 83% yield.

Scheme 3. Tosylation of 1-Octanol in Water with Semi-Large Scale



Thus, we showed a novel organic solvent-free Schotten-Baumann-type tosylation of primary alcohols. In this method, the reaction proceeds efficiently by using a combination of *N*-alkylimidazole and water without any organic solvent. The affinity of the substrate to the hydrophobic part of the catalyst plays an important role, and the method could be extended to a tosylation that accompanies a molecular recognition.

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Supporting Information Available: Experimental details and spectral data of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527–5529. (b) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takebe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734–735.

(10) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279.