Dehydration Reactions in Water. Surfactant-type Brønsted Acid-catalyzed Dehydrative Etherification, Thioetherification, and Dithioacetalization in Water

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Dehydration reactions such as etherification, thioetherification, and dithioacetalization are efficiently catalyzed by a surfactant-type Brønsted acid in water.

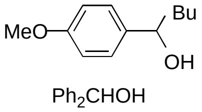
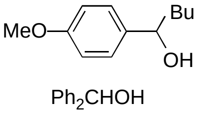
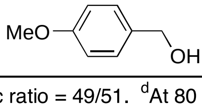
Organic reactions in water without use of harmful organic solvents are of great current interest, because water is an easily available, economical, and environmentally benign solvent.[1] We have revealed that surfactant-type Lewis or Brønsted acids effectively worked as catalysts in carbon–carbon bond-forming reactions such as Mukaiyama aldol reactions,[2] Mannich-type reactions,[3] etc.[4] in water. Under the reaction conditions, hydrophobic emulsion droplets, which are essential for efficient catalysis, were formed from catalytic amounts of these catalysts and hydrophobic reaction substrates. Quite recently, we have achieved dehydrative esterification of carboxylic acids with alcohols in water using this hydrophobic emulsion system created by dodecylbenzenesulfonic acid (DBSA) as a surfactant-type Brønsted acid.[5] In this paper, we report that other dehydration reactions such as etherification, thioetherification, and dithioacetalization in water are successfully carried out using this reaction medium.

Although the Williamson ether synthesis is probably one of the most common methods for preparation of ethers, the method was required initial conversion of alcohols to halides or tosylates.[6] Acid-promoted dehydration of alcohols provides an alternative important method of preparing ethers.[7]

First, we carried out symmetric etherification of alcohols (0.5 mmol) in water (3 ml) using 10 mol% of DBSA[8] as a surfactant-type Brønsted acid (Table 1, entries 1 and 2). The reactions proceeded in water to afford the corresponding symmetric ethers in high yields. Unsymmetrical etherification of alcohols in water also proceeded smoothly to give the desired ethers in high yields (entries 3, 4, and 5).[9] It should be noted that the etherification of the substrate shown in entry 1 in the presence of *p*-toluenesulfonic acid (TsOH) instead of DBSA gave only a trace amount of the product. This result indicates that the long alkyl chain of DBSA, which leads to the formation of hydrophobic emulsion droplets, is essential for the efficient catalysis.

Table 1. DBSA-catalyzed synthesis of ethers in water

$$R^1OH \ + \ R^2OH \ \xrightarrow[H_2O,\ 24\ h]{DBSA\ (10\ mol\%)} \ R^1OR^2$$

Entry	R^1OH	R^2OH (equiv.)	Yield/%
$1^{a,b}$			90^c
2^d	Ph_2CHOH	Ph_2CHOH	91
3^d	$CH_3(CH_2)_{11}OH$	Ph_2CHOH (2.0)	89
4^e	$CH_3(CH_2)_{11}OH$	$PhMe_2COH$ (2.0)	83
5^d	$CH_3(CH_2)_{11}OH$	 (2.0)	77

[a]At 30 °C. [b]7 h. [c]Diastereomeric ratio = 49/51. [d]At 80 °C. [e]At 50 °C.

We then investigated selective etherification in the present reaction system using alcohols of different hydrophobicity (eq 1).[10] When an equimolar mixture of dodecanol and propanol was etherified with benzhydrol in the presence of DBSA in water, benzhydryl dodecyl ether was selectively obtained. This result of the selective reaction based on the difference in hydrophobicity is one of the characteristics of this system.

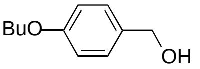
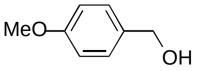
$$\underset{(1.0\ equiv.)}{CH_3(CH_2)_{11}OH} + \underset{(1.0\ equiv.)}{CH_3(CH_2)_2OH} + \underset{(1.0\ equiv.)}{Ph_2CHOH} \xrightarrow[H_2O,\ 80\ ^\circ C,\ 24\ h]{DBSA\ (10\ mol\%)} \begin{array}{lr} CH_3(CH_2)_{11}OCHPh_2 & 65\% \\ + & \\ CH_3(CH_2)_2OCHPh_2 & 8\% \end{array} \quad (eq\ 1)$$

Next, we turned our attention to thioether synthesis. Thioethers are, in general, synthesized from halides and thiolates.[11] However, a problem of this method is that oxidation to disulfides is prone to occur. On the other hand, a DBSA-catalyzed system would be applicable to the thioetherification, if one of the alcohols displaces the thiol. We thus tested the reaction of dodecanethiol with several alcohols which were used for the protective groups of thiols in the presence of 10 mol% of DBSA in water (Table 2). As we expected, the reactions accompanying the dehydration in water proceeded to afford the corresponding thioethers in high yields (entries 1-4). Tritylation of other thiols such as an aromatic thiol in water also gave good yields of the desired thioethers (entries 5 and 6). These results demonstrate that this direct thioetherification in water provides a general method to protect thiols.[12]

Finally, we investigated dithioacetalization in water. Dithioacetals are useful in organic synthesis as protective groups for carbonyl compounds or as precursors of acyl carbanion equivalents.[11] Although dithioacetalization in water from carbonyl compounds and thiols has recently been reported,[13] the method still lacks substrate generality. Therefore, we tested DBSA-catalyzed dithioacetalization in water (Table 3). The reactions proceeded smoothly not only for aromatic and aliphatic but also for α,β-unsaturated aldehydes under mild conditions

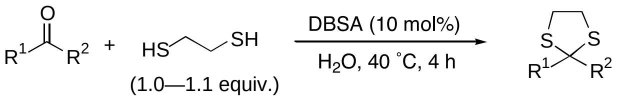
Table 2. DBSA-catalyzed synthesis of thioethers in water

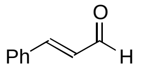
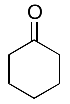
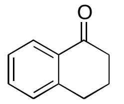
$$R^1SH + R^2OH \xrightarrow[H_2O,\ 80\ ^\circ C,\ 24\ h]{DBSA\ (10\ mol\%)} R^1SR^2$$

Entry	R^1SH	R^2OH (equiv.)	Yield/%
1	$CH_3(CH_2)_{11}SH$	Ph_3COH (1.0)	97
2	$CH_3(CH_2)_{11}SH$	Ph_2CHOH (2.0)	93
3[a]	$CH_3(CH_2)_{11}SH$	 (2.0)	87
4	$CH_3(CH_2)_{11}SH$	 (1.0)	82
5[b]	PhSH	Ph_3COH (1.0)	76
6[c]	$PhCH_2SH$	Ph_3COH (1.0)	96

[a]At 50 °C. [b]16 h. [c]12 h.

Table 3. DBSA-catalyzed dithioacetalization in water[a]

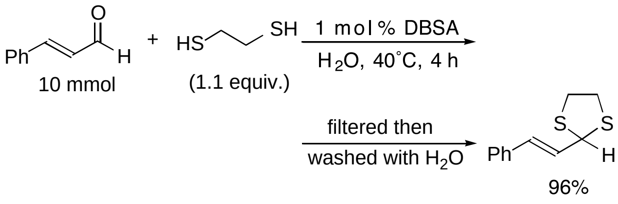


Entry	Substrate	Yield/%
1	PhCHO	94
2[b]	PhCHO	88
3	$CH_3(CH_2)_4CHO$	92
4		94 (95)[c]
5[d]		82
6[d,e]		74

[a]0.5 mmol scale. [b]1,3-Propanedithiol was used as a dithiol. [c]DBSA (1 mol%) was used. [d]24 h. [e]At 80 °C.

(entries 1-4). Furthermore, aliphatic or aromatic ketones also reacted well to give the corresponding adducts in good yields (entries 5 and 6). It is noteworthy that only 1 mol% of DBSA was sufficient to catalyze the reaction without any difficulty in the case of the substrate shown in entry 4.

In addition, easy work-up has been realized without use of organic solvents when the products are solid and insoluble in water. In fact, the dithioacetalization of cinnamaldehyde on 10 mmol-scale with 1 mol% of DBSA proceeded smoothly to deposit crystals. Pure product was obtained in excellent yield after the crystals were filtered and washed with water (eq 2). This simple procedure is one of the advantages of the present reaction system.



(eq 2)

In summary, dehydration reactions such as etherification, thioetherification, and dithioacetalization are efficiently catalyzed by DBSA in water. The present system has advantages such as selectivity based on the difference in hydrophobicity and easy work-up, and would lead to environmentally benign chemical processes.

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday and also in recognition of his outstanding contributions to synthetic organic chemistry.

References and Notes

1 P. A. Grieco, "Organic Synthesis in Water," Blacky Academic and Professional, London (1998); C.-J. Li and T.-H. Chan, "Organic Reactions in Aqueous Media," John Wiley & Sons, New York (1997).

2 S. Kobayashi and T. Wakabayashi, *Tetrahedron Lett.*, **39**, 5389 (1998); K. Manabe and S. Kobayashi, *Synlett*, **1999**, 547; K. Manabe and S. Kobayashi, *Tetrahedron Lett.*, **40**, 3773 (1999); S. Kobayashi, Y. Mori, S. Nagayama, and K. Manabe, *Green Chem.*, **1999**, 175; K. Manabe, Y. Mori, S. Nagayama, K. Odashima, and S. Kobayashi, *Inorg. Chim. Acta* **296**, 158 (1999); K. Manabe, Y. Mori, and S. Kobayashi, *Tetrahedron*, **55**, 11203 (1999); K. Manabe, Y. Mori, T. Wakabayashi, S. Nagayama, and S. Kobayashi, *J. Am. Chem. Soc.*, **122**, 7202 (2000).

3 S. Kobayashi, T. Busujima, and S. Nagayama, *Synlett*, **1999**, 545; K. Manabe, Y. Mori, and S. Kobayashi, *Synlett*, **1999**, 1401; K. Manabe and S. Kobayashi, *Org. Lett.*, **1**, 1965 (1999); K. Manabe, Y. Mori, and S. Kobayashi, *Tetrahedron*, **57**, 2537 (2001).

4 S. Kobayashi, T. Busujima, and S. Nagayama, *J. Chem. Soc., Chem. Commun.*, **1998**, 19; K. Manabe and S. Kobayashi, *Chem. Commun.*, **2000**, 669; Y. Mori, K. Kakumoto, K. Manabe, and S. Kobayashi, *Tetrahedron Lett.*, **41**, 3107 (2000); S. Kobayashi, W. W.-L. Lam, and K. Manabe, *Tetrahedron Lett.*, **41**, 6115 (2000); K. Manabe, N. Aoyama, and S. Kobayashi, *Adv. Synth. Catal.*, **343**, 174 (2001); Y. Mori, K. Manabe, and S. Kobayashi, *Angew. Chem., Int. Ed.*, **40**, 2815 (2001).

5 K. Manabe, X.-M. Sun, and S. Kobayashi, *J. Am. Chem. Soc.*, **123**, 10101 (2001).

6 A. W. Williamson, *J. Chem. Soc.*, **4**, 229 (1852); N. Baggett, "Comprehensive Organic Synthesis," ed. by D. Barton and W. D. Ollins, Pergaman, Oxford (1979), Vol. 1, p 77.

7 For recent examples of acid-catalyzed etherification: G. V. M. Sharma and A. K. Mahalingam, *J. Org. Chem.*, **64**, 8943 (1999); T. Ooi, H. Ichikawa, Y. Itagaki, and K. Maruoka, *Heterocycles*, **52**, 575 (2000); G. V. M. Sharma, T. R. Prasad, and A. K. Mahalingam, *Tetrahedron Lett.*, **42**, 759 (2001).

8 Dodecylbenzenesulfonic acid (soft type) was purchased from Tokyo Kasei Kogyo Co., Ltd.

9 Symmetric ethers derived from benzyl alcohols were also obtained as by-products.

10 The log P_{oct} value: dodecanol (5.13), propanol (0.25). M. H. Abraham, H. S. Chadha, G. S. Whiting, and R. C. Mitchell, *J. Pharm. Sci.*, **83**, 1085 (1994).

11 T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., Wiley, New York (1999).

12 For examples of acid-catalyzed thioetherification: J. J. Pastuszak and A. Chimiak, *J. Org. Chem.*, **46**, 1868 (1981); R. Breitschuh and D. Seebach, *Synthesis*, **1992**, 83.

13 M. A. Ceschi, L. A. Felix, and C. Peppe, *Tetrahedron Lett.*, **41**, 9695 (2000).