ORGANIC LETTERS

2007
Vol. 9, No. 2
311−314

Surfactant-Type Brønsted Acid Catalyzed Dehydrative Nucleophilic Substitutions of Alcohols in Water

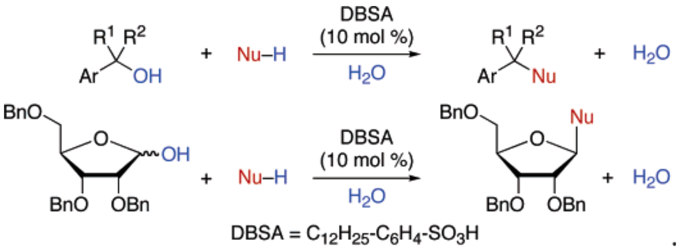
Seiji Shirakawa and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo,
The HFRE Division, ERATO, Japan Science and Technology Agency (JST),
Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

skobayas@mol.f.u-tokyo.ac.jp

Received November 19, 2006

ABSTRACT



A protocol for the dehydrative nucleophilic substitution of benzyl alcohols with a variety of carbon- and heteroatom-centered nucleophiles using dodecylbenzenesulfonic acid (DBSA) as a surfactant-type Brønsted acid catalyst in water has been developed. The reaction system can be applied to the stereoselective C-glycosylation of 1-hydroxy sugars in water.

Coupling reactions of alkyl halides with nucleophiles are among the most useful protocols for carbon−carbon bond formation in organic synthesis. The reaction may be further enhanced from the viewpoint of atom efficiency, when alcohols are used as substrates instead of alkyl halides, as in this case where water is generated as the sole byproduct for the reactions. However, the catalytic activation of alcohols is difficult due to the poor leaving ability of the hydroxyl group, and as a result, an excess amount of a Brønsted acid or a stoichiometric amount of a Lewis acid is often required to promote the reactions.[1] Therefore, the development of a procedure for the nucleophilic substitutions of alcohols using catalytic amounts of Brønsted or Lewis acids is highly desirable and, accordingly, a number of catalytic methods for the promotion of this process in organic solvent systems have recently been reported.[2]

The use of water as a reaction medium has received considerable attention in organic synthesis due to its many advantages from economical, environmental, and safety standpoints.[3] In addition, it has been found that reactions in water can facilitate access to different reactivity and selectivity patterns compared with those observed in common organic solvents due to its unique physical and chemical properties.[4] Although various efficient catalytic systems in water have been developed to date, execution of dehydration reactions in water is one of the most challenging research

---

[1] For example: (a) Gullickson, G. C.; Lewis, D. E. *Aust. J. Chem.* **2003**, *56*, 385. (b) Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823. (c) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *Tetrahedron Lett.* **1989**, *30*, 3581. (d) Khalaf, A. A.; Roberts, R. M. *J. Org. Chem.* **1972**, *37*, 4227.

[2] For a recent example, see: (a) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2605. (b) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793. (c) Zhan, Z.-P.; Yang, W.-Z.; Yang, R.-F.; Yu, J.-L.; Li, J.-P.; Liu, H.-J. *Chem. Commun.* **2006**, 3352. (d) Sanz, R.; Martínez, A.; Miguel, D.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Adv. Synth. Catal.* **2006**, *348*, 1841. (e) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033. (f) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913. (g) Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. *J. Org. Chem.* **2003**, *68*, 9340.

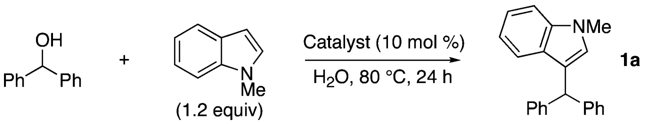
[3] (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (b) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998. (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095.

10.1021/ol062813j CCC: $37.00

topics. In the course of our investigation of organic reactions in water,[5] we recently reported that dodecylbenzenesulfonic acid (DBSA) efficiently catalyzes dehydrative esterifications of carboxylic acids with alcohols and etherification of alcohols in water.[6] In this context, we have been interested in the DBSA-catalyzed dehydrative carbon−carbon bond-forming reactions in water.[7] We herein report the catalytic nucleophilic substitution of benzyl alcohols with various carbon nucleophiles in water and describe its application to the dehydrative C-glycosylation of 1-hydroxy sugars.[8]

Initially, we examined various Brønsted acids as catalysts in the Friedel−Crafts-type substitution reaction of benzhydrol with 1-methylindole as model substrates in water (Table 1).

Table 1. Effect of Catalysts



entry	catalyst	yield (%)[a]
1	none	0
2	AcOH	0
3	TFA	3
4	TfOH	8
5	TsOH ($4\text{-}CH_3\text{-}C_6H_4\text{-}SO_3H$)	3
6	DBSA ($C_{12}H_{25}\text{-}C_6H_4\text{-}SO_3H$)	85
7	$C_9H_{19}COOH$	0

[a] Isolated yield.

Common Brønsted acids such as AcOH, TFA, TfOH, and TsOH were not effective for this reaction (entries 2−5). Gratifyingly, however, a surfactant-type Brønsted acid such as DBSA was found to catalyze the reaction efficiently to give the product **1a** in good yield (entry 6). It is interesting that use of a long-chain carboxylic acid, which is known to be an effective catalyst for the three-component aza-Friedel−Crafts reaction in water,[9] was not effective for the reaction (entry 7), suggesting that both the surfactant property and the strong Brønsted acidity of DBSA are essential to promote the reaction efficiently.

With this information in hand, we investigated the substrate generality of DBSA-catalyzed nucleophilic substitutions of alcohols using a variety of nucleophiles. Initially, we selected benzhydrol derivatives as the alcohol component because the resulting products **1** obtained from the reaction contain a diarylmethane motif that is an integral part of a number of biologically active and pharmaceutical compounds (Figure 1). Friedel−Crafts-type substitution reactions of benzhydrols containing electron-donating or -withdrawing groups occurred cleanly on treatment with electron-rich heteroaromatic or aromatic compounds to afford the desired triarylmethanes **1a**−**e** (entries 1−5 in Table 2). Substitution reactions using active methylene compounds also proceeded smoothly to give the products **1f**−**h** in high yields (entries 6−8). Furthermore, it was shown that even a simple enolizable ketone could be used as the nucleophile giving the corresponding product **1i** in good yield (entry 9). The present reaction system could also be applied to carbon−nitrogen[10] and carbon−sulfur[11] bond formations, and the desired compounds **1j**−**l** were obtained in good yields (entries 10−12).

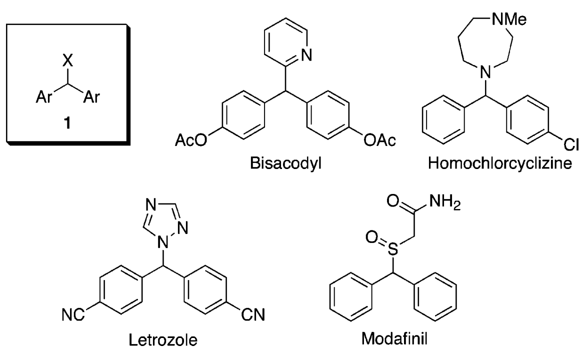


Figure 1. Biologically active compounds.

Next, we examined the substrate generality with respect to the alcohol substrate, and a variety of benzyl alcohols were subjected to Friedel−Crafts-type substitutions with 1-methylindole (Table 3). Pleasingly, it was found that primary, secondary, and tertiary alcohols could be applied to this reaction and that the desired 3-substituted indoles **2a**−**g** were obtained in moderate to good yields.[12] Substrates containing heteroaromatic and allylic alcohols also worked well in this reaction (entries 4 and 5).

To expand the utility and applicability of the present system, we next focused on its application to the stereoselective dehydrative C-glycosylations of 1-hydroxy sugars[13] in water. Because of the biological and synthetic importance of *C*-glycosides and *C*-nucleosides, the development of

---

(4) (a) Lindström, U. M.; Andersson, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 548. (b) Pirrung, M. C. *Chem.−Eur. J.* **2006**, *12*, 1312. (c) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68. (d) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809. (e) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159.

(5) (a) Kobayashi, S.; Ogawa, C. *Chem.−Eur. J.* **2006**, *12*, 5954. (b) Manabe, K.; Kobayashi, S. *Chem.−Eur. J.* **2002**, *8*, 4095. (c) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209.

(6) (a) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971. (b) Kobayashi, S.; Iimura, S.; Manabe, K. *Chem. Lett.* **2002**, 10. (c) Manabe, K.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10101.

(7) For DBSA-catalyzed three-component Mannich-type reactions in water, see: Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537.

(8) For DBSA-catalyzed O-glycosylation in water, see: Aoyama, N.; Kobayashi, S. *Chem. Lett.* **2006**, *35*, 238.

(9) Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 4939.

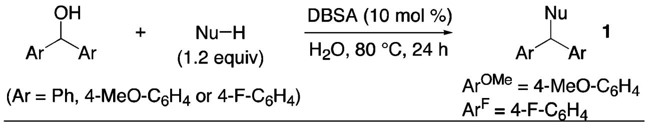
(10) For C−N bond formation with alcohols in organic slovent, see: (a) Motokura, K.; Nakagiri, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Org. Lett.* **2006**, *8*, 4617. (b) Terrasson, V.; Marque, S.; Georgy, M.; Campagne, J.-M.; Prim, D. *Adv. Synth. Catal.* **2006**, *348*, 2063.

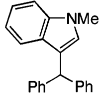
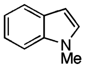
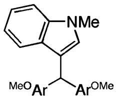
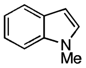
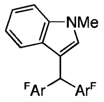
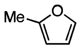
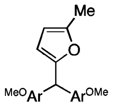
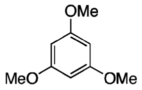
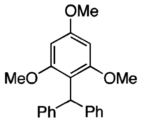
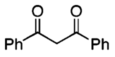
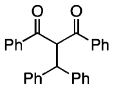
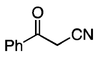
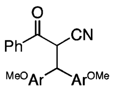
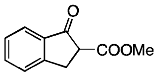
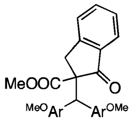
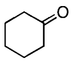
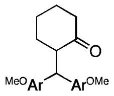
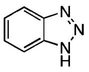
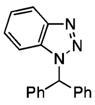
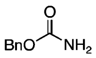
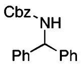
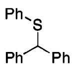
(11) C−S bond formation of alcohols was also described in ref 6.

(12) For reviews for the synthesis of 3-substituted indoles, see: (a) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.

(13) For a review, see: Gin, D. *J. Carbohydr. Chem.* **2002**, *21*, 645.

Table 2. Nucleophilic Substitution Reactions of Benzhydrols in Water



entry	Nu–H	product	yield (%)[a]
1			85 (**1a**)
2			92 (**1b**)
3			92 (**1c**)
4[b]			94 (**1d**)
5			89 (**1e**)
6[c]			82 (**1f**)
7[c]			93 (**1g**)
8[b]			92 (**1h**)
9[b]			76 (**1i**)
10			62 (**1j**) [+24 (**1j’**)[e]]
11[d]			84 (**1k**)
12[b]	Ph-SH		83 (**1l**)

[a] Isolated yield. [b] Nu–H (2 equiv). [c] Nu–H (3 equiv). [d] Nu–H (5 equiv). [e] Isomerization product **1j’** was obtained in 24% yield.

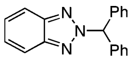
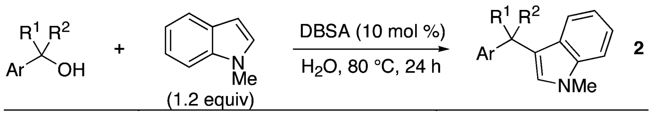
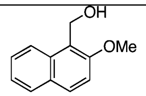
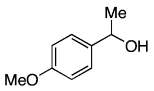
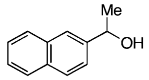
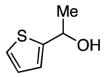
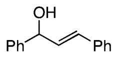
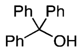
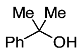

1j'

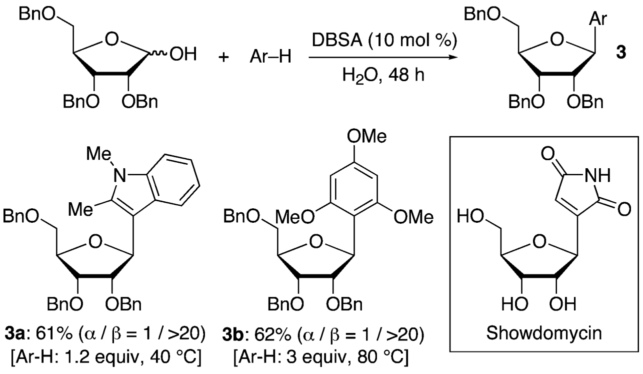
Table 3. Nucleophilic Substitution Reactions of Benzyl Alcohols in Water



entry	alcohol	yield (%)[a]
1		75 (**2a**)
2		73 (**2b**)
3		63 (**2c**)
4		85 (**2d**)
5		86 (**2e**)
6		96 (**2f**)
7		95 (**2g**)

[a] Isolated yield.

Scheme 1. C-Glycosylations of 1-Hydroxy Sugar in Water



methods for their stereoselective generation has been extensively studied.[14] However, methods for the synthesis of *C*-glycosides via the conversion of 1-hydroxy sugars using a catalytic amount of an activator are still limited.[15] To test the viability of our methodology, we selected the reaction of 1-hydroxy-D-ribofuranose with electron-rich heteroaromatic or aromatic compounds as a model of C-glycosylation and were delighted to discover that the reactions proceeded smoothly to afford the corresponding *C*-nucleosides **3a**[16] and **3b**[17] in good yields with excellent β-selectivity

---

(14) For reviews, see: (a) Wu, Q.; Simons, C. *Synthesis* **2004**, 1533. (b) Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913.

(15) (a) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516. (b) Mukaiyama, T.; Matsubara, K.; Hora, M. *Synthesis* **1994**, 1368.

(16) Yokoyama, M.; Nomura, M.; Togo, H.; Seki, H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2145.

(Scheme 1). The synthesis of *C*-nucleoside **3b** is of particular note as it is a key intermediate in the total synthesis of showdomycin.[18]

In summary, we have developed a method for surfactant-type Brønsted acid catalyzed dehydrative nucleophilic substitutions of benzyl alcohols in water. It is noteworthy that the present reaction proceeded under nonmetallic conditions in water and that a variety of diarylmethanes and 3-substituted indoles bearing a biologically interesting structure could be prepared using the procedure. Furthermore, this reaction system could be applied to stereoselective C-glycosylations of 1-hydroxy sugars. This simple system offers an efficient method for the synthesis of various biologically interesting compounds.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Science (JSPS). S.S. thanks JSPS for a postdoctoral research fellowship.

Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062813J

---

(17) He, W.; Togo, H.; Waki, Y.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2425.

(18) (a) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289. (b) Kalvoda, L.; Farkas, J.; Sorm, F. *Tetrahedron Lett.* **1970**, 2297.