Dehydrative Glycosylation in Water Using a Brønsted Acid–Surfactant-Combined Catalyst

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Brønsted acid–surfactant-combined catalyst, dodecylbenzenesulfonic acid (DBSA), was used in catalytic dehydrative glycosylation reactions in water. 1-Hydroxy sugars, such as *O*-benzyl-protected furanose and pyranose, reacted with alcohols and a nitrogen nucleophile in the presence of a catalytic amount of DBSA to afford the desired adducts in good yields. Detailed study of the glycosylation of 2-deoxy-D-ribofuranose showed that hydrophobicity of the substrates was important to attain higher yields. Regarding the α/β selectivities, D-ribose and D-mannose derivatives gave the products in high β- and α-selectivities, respectively.

Recently, organic reactions in water have attracted much attention in synthetic organic chemistry.[1] Water is a cheap, safe, and environmentally benign solvent. In addition, water has unique physical and chemical properties (high polarity, high boiling point, and tight hydrogen-bonding network), which sometimes induce reactivities and selectivities that can not be attained in organic solvents.

Although various efficient catalytic systems in water have been developed so far, dehydration reactions in water are among the most challenging research topics. In the course of our investigations on dehydration reactions in water, we have recently reported DBSA (dodecylbenzenesulfonic acid)-catalyzed dehydration reactions (esterification, etherification, thioetherification, and dithioacetalization) in water.[2] In these reactions, DBSA and substrates form emulsion droplets whose interior is hydrophobic enough to exclude water molecules generated during the reactions. To expand the utility and applicability of this work, we next focused on dehydrative glycosylation in water. Brønsted acid-catalyzed dehydrative glycosylation of 1-hydroxy sugars with alcohols is among the most important and efficient reactions to prepare glycosides.[3] Although the reaction is known as Fischer glycosylation, excess amounts of Brønsted acids or alcohols are necessary in many cases.[4] Therefore, further exploration of a more efficient process is desired. Here, we report DBSA-catalyzed dehydrative glycosylation in water. Under the reaction conditions, *O*-protected furanoses and pyranoses reacted with hydrophobic alcohols in water to afford the desired products in good yields.

First, we carried out the reactions using 1-dodecanol **2a** as a glycosyl acceptor (Table 1). In the presence of 10 mol % of DBSA,[5] the reaction with *O*-benzyl-protected 2-deoxy-D-ribofuranose **1a** proceeded smoothly albeit with low α/β selectivity (Entry 1). While *O*-benzyl-protected D-ribofuranose **1b** also reacted with **2a** to afford the desired product in high β-selectivity (Entry 2), a longer reaction time was needed due to its low reactivity. It is noteworthy that not only D-ribofuranose but also methyl D-ribofuranoside reacted with **2a**; in the latter case the reaction proceeded by releasing methanol (Entries 3 and 4). In general, D-ribofuranose was prepared from the corresponding methyl D-ribofuranoside via hydrolysis under acidic conditions.[6] Although the reactivities of **1c** and **1d** were lower than those of **1a** and **1b** respectively, direct use of methyl furanosides allowed the omission of the tedious hydrolysis steps.

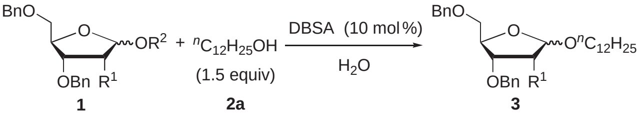
N-Protected ribofuranosylamines are important scaffolds for the synthesis of 2-deoxy-D-ribonucleotides, a unit of DNA or RNA. The present reaction system could be applied to *N*-glycosylation of ribofuranose as well (Table 2). A nitrogen nucleophile such as benzyl carbamate reacted with **1a** or **1b** to give the corresponding product in good yield.

Next, we examined the effects of varying the hydrophobicity of alcohols (Table 3). When alcohols having various length of alkyl chains were used, the alcohols with longer alkyl chains afforded the corresponding glycosides in higher yields. A similar tendency was observed in the DBSA-catalyzed dehydrative esterifications in water.[7]

The origin of the α/β ratio in dehydrative glycosylation in water was investigated in a model reaction of **1a** with **2a** (Table 4). The α/β ratio was found to be almost unchanged during the reaction course. This result may suggest that the glycosylation reactions proceed under kinetic control.[8]

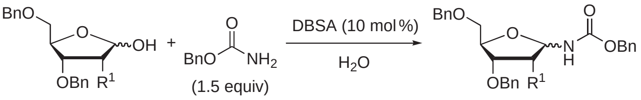
Finally, several examples of dehydrative glycosylation of pyranose in water were examined (Table 5). As for *O*-benzyl-protected glucopyranose **4a**, the reaction mixture did not form

Table 1. DBSA-catalyzed dehydrative glycosylation of D-ribofuranose



Entry	Glycosyl donor R^1	R^2		Condition	Product	Yield/%	α/β
1	H	H	**1a**	40 °C, 3 h	**3a**	88	36/64
2	OBn	H	**1b**	40 °C, 12 h	**3b**	83	9/91
3	H	Me	**1c**	40 °C, 12 h	**3c**	73	39/61
4	OBn	Me	**1d**	80 °C, 12 h	**3d**	82	6/94

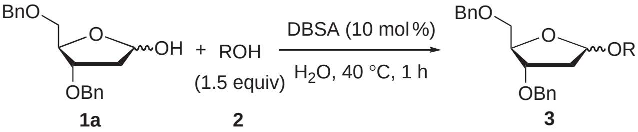
Table 2. Reaction with benzyl carbamate



Entry	R^1		Condition	Yield/%
1	H	**1a**	40 °C, 3 h	75[a]
2	OBn	**1b**	60 °C, 18 h	70[a]

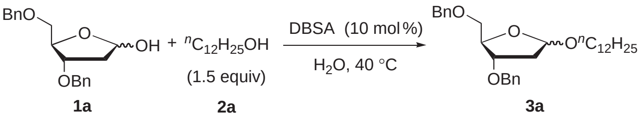
[a] α/β Selectivity was not determined.

Table 3. Effect of the hydrophobicity of glycosyl acceptors



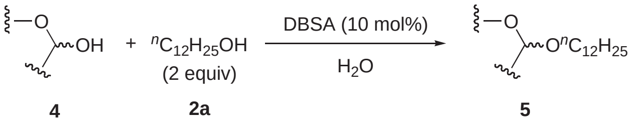
Entry	ROH	Yield/%	α/β
1	C_2H_5OH	15	42/58
2	n-C_3H_7OH	28	39/61
3	n-C_4H_9OH	50	40/60
4	n-$C_5H_{11}OH$	63	38/62
5	n-$C_{12}H_{25}OH$	85	35/65

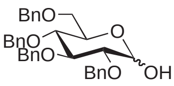
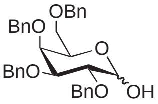
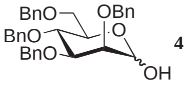
Table 4. Reaction profile



Entry	Time/h	Yield/%	α/β
1	0.33	44	39/61
2	1	85	35/65
3	3	88	36/64
4	12	91	38/62

Table 5. DBSA-catalyzed glycosylation of pyranose



Pyranose		Temperature/°C	Time/h	Yield/%	α/β
	4a	reflux	6	10	60/40
		150[a]	6	55	61/39
		150[a]	12	66	61/39
	4b	reflux	12	70	55/45
		reflux	48	67	61/39
	4c	reflux	12	51	87/13
		reflux	48	64	94/6

[a] The reaction was carried out in a sealed tube.

emulsion droplets under reflux conditions, presumably because of its high melting point. The reaction proceeded by increasing the reaction temperature to 150 °C in a sealed tube. On the other hand, *O*-benzyl-protected galactopyranose **4b** and mannose **4c** are colorless oils at room temperature, and the reaction with **2a** gave the corresponding products in moderate yields under reflux conditions. It should be noted that high α-selectivity was attained in the reaction of **4c**.[9]

In conclusion, *O*-benzyl-protected furanoses and pyranoses reacted with hydrophobic alcohols in water to afford the desired products in good to high yields. It is note that dehydrative glycosylation proceeded smoothly in water. Detailed study of the glycosylation of 2-deoxy-D-ribofuranose showed that hydrophobicity of substrates was important to attain higher yields. Regarding the α/β selectivities, D-ribose and D-mannose derivatives were found to give the corresponding products in high β- and α-selectivities, respectively. Further investigations on stereoselective dehydrative glycosylation in water are in progress.

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References and Notes

1 For a review, see: C.-J. Li, T.-H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, **1997**; P. A. Grieco, *Organic Synthesis in Water*, Blackie Academic and Professional, London, **1998**.

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

3 For recent examples of catalytic glycosylations of 1-hydroxy sugars, see: a) T. Mukaiyama, K. Matsubara, M. Hora, *Synthesis* **1994**, 1368. b) H. Uchiro, K. Miyazaki, T. Mukaiyama, *Chem. Lett.* **1997**, 403. c) H. Uchiro, T. Mukaiyama, *Chem. Lett.* **1996**, 79. d) H. Uchiro, T. Mukaiyama, *Chem. Lett.* **1996**, 271. e) K. Toshima, H. Nagai, S. Matsumura, *Synlett* **1999**, 1420. f) J. Inanaga, Y. Yokoyama, T. Hashimoto, *J. Chem. Soc., Chem. Commun.* **1993**, 1090. g) B. Wagner, M. Heneghan, G. Schnabel, B. Ernst, *Synlett* **2003**, 1303. h) T. Suzuki, S. Watanabe, T. Yamada, K. Hiroi, *Tetrahedron Lett.* **2003**, *44*, 2561. i) H. Jona, H. Mandai, T. Mukaiyama, *Chem. Lett.* **2001**, 426. j) D. Gin, *J. Carbohydr. Chem.* **2002**, *21*, 645.

4 E. Fischer, *Chem. Ber.* **1893**, 2400.

5 For DBSA-catalyzed carbon-carbon bond-forming reactions, see: a) K. Manabe, S. Kobayashi, *Org. Lett.* **1999**, *1*, 1965. b) K. Manabe, Y. Mori, S. Kobayashi, *Synlett* **1999**, 1401. c) K. Manabe, Y. Mori, S. Kobayashi, *Tetrahedron* **2001**, *57*, 2537.

6 a) S. Tejima, H. G. Fletcher, Jr., *J. Org. Chem.* **1963**, *28*, 2999. b) K. Jansson, G. Noori, G. Magnusson, *J. Org. Chem.* **1990**, *55*, 3181. c) O. R. Martin, C. A. V. Hendricks, P. P. Deshpande, A. B. Cutler, S. A. Kane, S. P. Rao, *Carbohydr. Res.* **1990**, *196*, 41. d) N. Hossain, H. van Halbeek, E. D. Clercq, P. Herdewijin, *Tetrahedron* **1998**, *54*, 2209.

7 For example, lauric acid and 3-phenyl-1-propanol gave the ester in 84% yield, whereas lauric acid and ethanol gave the ester in 15% yield (10 mol % of DBSA in water at 40 °C). For details, see Ref. 2b.

8 When each isolated anomeric product was treated under the reaction conditions, anomeric isomerization occurred. While the α anomer gave an anomeric mixture with the ratio of $\alpha/\beta = 49/51$, the β anomer provided the ratio of $\alpha/\beta = 29/71$ during 12 h.

9 **4c** reacted with cyclohexanol (reflux, 48 h) to afford the desired glycoside in 26% yield ($\alpha/\beta = 92/8$).

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