

Generation of Alkoxycarbenium Ion Pools from Thioacetals and Applications to Glycosylation Chemistry

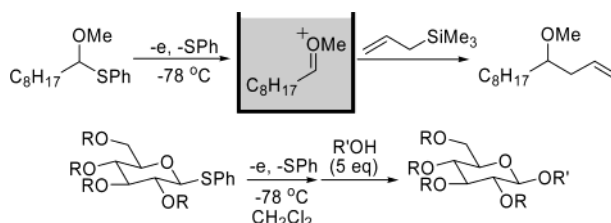
Shinkiti Suzuki, Kouichi Matsumoto, Kohsuke Kawamura, Seiji Suga,* and Jun-ichi Yoshida*

Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan

yoshida@sbchem.kyoto-u.ac.jp

Received July 28, 2004

ABSTRACT



Alkoxycarbenium ions have been generated and accumulated as “cation pools” by the low-temperature electrochemical oxidation of α -phenylthioethers. Although an unsuccessful attempt to accumulate glycosyl cations was made, a one-pot method for electrochemical glycosylation, which involves anodic oxidation of thioglycosides to generate glycosyl cation equivalents followed by their reactions with glycosyl acceptors, has been developed.

Glycosyl cations have received significant research attention both from mechanistic chemists and those involved in the synthesis of oligosaccharides.¹ Studies on glycosyl cations have been important for helping the design of inhibitors of glycosidases by providing information on the transient species present in the active site of the enzyme.² After the pioneering work by Crich³ on the characterization of glycosyl triflate intermediates, glycosyl cation equivalents were recognized as discrete intermediates with reasonable stability.

(1) (a) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997. (b) Sears, P.; Wong, C.-H. *Science* **2001**, 291, 2344. (c) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, 40, 1576. (d) Seeberger, P. H.; Haase, W.-C. *Chem. Rev.* **2000**, 100, 4349. (e) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, 100, 4465. (f) Herzner, H.; Reipen, T.; Schlitz, M.; Kunz, H. *Chem. Rev.* **2000**, 100, 4495.

(2) For example: (a) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, 26, 182. (b) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, 3, 199. (c) Bernotas, R. C.; Pezzone, M. A.; Ganem, B. *Carbohydr. Res.* **1987**, 167, 305. (d) Papandreou, G.; Tong, M. K.; Ganem, B. *J. Am. Chem. Soc.* **1993**, 115, 11682. (d) Fotsch, C. H.; Wong, C.-H. *Tetrahedron Lett.* **1994**, 35, 3481. (e) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, 102, 515.

(3) (a) Crich, D.; Sanxing, S. *J. Am. Chem. Soc.* **1997**, 119, 11217. (b) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, 120, 435. (c) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, 64, 4926.

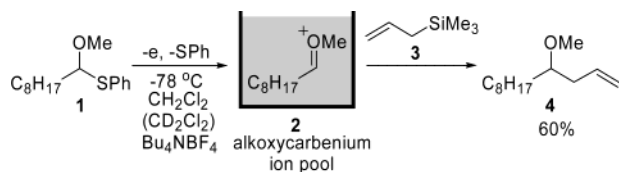
Although they are quite effective for glycosylation, they are covalent rather than ionic species. Despite extensive effort to observe ionic glycosyl cation intermediates, they have not been detected spectroscopically.

Recently, we developed the “cation pool” method for carbocation generation, in which carbocations are accumulated in solution by low-temperature electrolysis.⁴ In the next step, the carbocations are allowed to react with nucleophiles. This one-pot method serves as a powerful method for combinatorial synthesis. The method has since been successfully applied to *N*-acyliminium ions⁵ and alkoxycarbenium ions.⁶ Thus, we initiated the present project in which glycosyl cations would be generated and accumulated by the “cation pool” method with great anticipation.

(4) Yoshida, J.; Suga, S. *Chem. Eur. J.* **2002**, 8, 2650. For cation flow method, see: Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, 123, 7941.

(5) (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, 121, 9546. (b) Suga, S.; Okajima, M.; Yoshida, J. *Tetrahedron Lett.* **2001**, 42, 2173. (c) Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, 124, 30. (d) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, 124, 14824. (e) Suga, S.; Nagaki, A.; Yoshida, J. *Chem. Commun.* **2003**, 354. (f) Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J. *Org. Lett.* **2003**, 5, 945.

Scheme 1. Generation of Alkoxy-carbenium Ion Pool from α -Phenylthio Ether and Its Reaction with Allylsilane



In our previous study, alkoxy-carbenium ions were generated by the oxidation of α -silyl ethers⁷ since silyl groups are effective electroauxiliaries⁸ for activating ethers to oxidation. They can also play a useful role in helping to determine the regiochemistry of subsequent reactions. In our project aimed at creating glycosyl cation pools, we did, however, choose to study thioglycosides as precursors, because thioglycosides have been widely used in oligosaccharide synthesis due to their ease of preparation and high stability.⁹

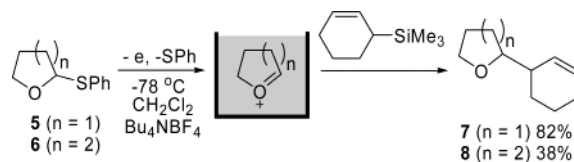
We have already demonstrated that arylthio groups can serve as effective electroauxiliaries for the oxidation of ethers.¹⁰ Thus, at outset of our work, we focused on the generation of alkoxy-carbenium ion pools from arylthio-substituted ethers.

α -Phenylthioether **1** was oxidized in a conventional H-type divided cell equipped with a carbon felt anode and a platinum plate cathode in deuterated dichloromethane in the presence of tetrabutylammonium tetrafluoroborate (Bu_4NBF_4) as the supporting electrolyte at -78°C (Scheme 1).

^1H and ^{13}C NMR spectra (-80°C) of the solution so obtained indicated the formation of alkoxy-carbenium ion **2** as an ionic species. The 500 MHz ^1H NMR spectrum exhibited a signal at δ 9.55 ppm due to the methine proton. The 125 MHz ^{13}C NMR exhibited a signal at δ 230.9 ppm due to the methine carbon.^{11, 12} The reaction of **2** with allyltrimethylsilane (**3**) gave the allylated product **4**.

Cyclic α -phenylthioethers **5** and **6** were also successfully oxidized under the same conditions, and the resulting solutions were allowed to react with an allylsilane to give the corresponding C–C bond formation products **7** and **8**

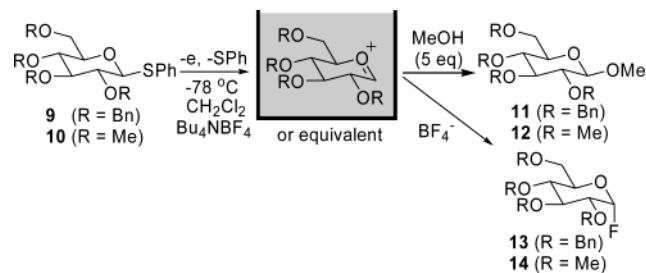
Scheme 2. Generation of Cyclic Alkoxy-carbenium Ion Pools and Their Reactions with Allylsilane



(Scheme 2). The reason the yield of the product for the six-membered ring case was moderate is not clear at present. Significant amounts of unidentified products were also formed.

Following on from this we next attempted to generate a glycosyl cation by the “cation pool” method. β -Tetra-*O*-benzyl-1-phenylthioglycoside (**9**) and β -tetra-*O*-methyl-1-phenylthioglycoside (**10**) were selected as precursors in order to avoid neighboring group participation. The electrochemical oxidation reactions **9** and **10** were carried out in $\text{Bu}_4\text{NBF}_4/\text{CH}_2\text{Cl}_2$ at -78°C in the absence of an alcohol (Scheme 3).

Scheme 3. Electrochemical Glycosylation Reaction



However, when methanol was added after the electrolysis, methoxylated compounds **11** and **12** were not obtained, but the corresponding glycosyl fluorides **13** (77%) and **14** (91%)

(6) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244.

(7) (a) Yoshida, J.; Murata, T.; Ise, S. *J. Organomet. Chem.* **1988**, *345*, C23. (b) Yoshida, J.; Matsunaga, S.; Murata, T.; Ise, S. *Tetrahedron* **1991**, *47*, 615.

(8) (a) Yoshida, J.; Maekawa, T.; Murata, T.; Matsunaga, S.; Ise, S. *J. Am. Chem. Soc.* **1990**, *112*, 1962. (b) Yoshida, J.; Nishiwaki, K. *J. Chem. Soc., Dalton Trans.* **1998**, 2589.

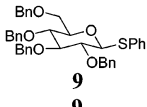
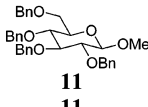
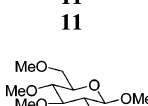
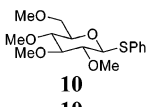
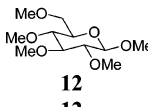
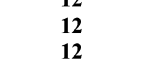
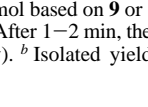
(9) For example: (a) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015. (b) Yamago, S.; Yamada, T.; Maruyama, T.; Yoshida, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2145 and references therein.

(10) (a) Yoshida, J.; Sugawara, M.; Kise, N. *Tetrahedron Lett.* **1996**, *37*, 3157. (b) Yoshida, J.; Sugawara, M.; Tatsumi, M.; Kise, N. *J. Org. Chem.* **1998**, *63*, 5950. See also: Chiba, K.; Uchiyama, R.; Kim, S.; Kitano, Y.; Tada, M. *Org. Lett.* **2001**, *3*, 1245.

(11) Alkoxy-carbenium ions in superacids: (a) Olah, G. A.; Bollinger, J. M. *J. Am. Chem. Soc.* **1967**, *89*, 2993. (b) Olah, G. A.; Sommer, J. *J. Am. Chem. Soc.* **1968**, *90*, 4323. (c) Forsyth, D. A.; Osterman, V. M.; DeMember, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 818.

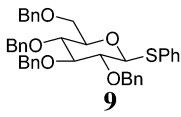
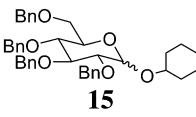
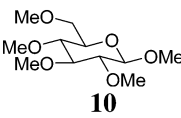
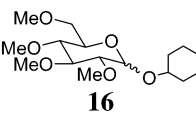
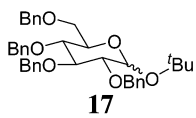
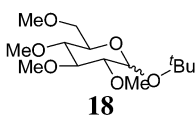
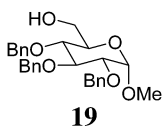
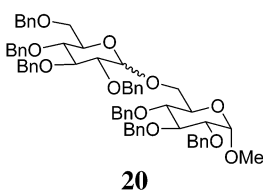
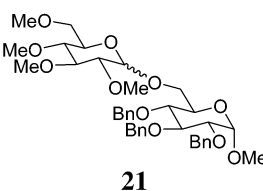
(12) Signals that could be assigned to the species having a C–F covalent bond were not observed, although tetrafluoroborate is well-known as a fluorination reagent. NMR spectra of compounds having O–C–F units are reported; see: Rozov, L. A.; Rafalko, P. W.; Evans, S. M.; Brockunier, L.; Ramig, K. *J. Org. Chem.* **1995**, *60*, 1319.

Table 1. Effect of Supporting Electrolyte on Electrochemical Glycosylation (One-Pot Procedure)^a

| Thioglycoside | Electrolyte | Product | Yield (%) ^b | α/β |
|--|----------------------------|--|------------------------|--------------------|
|  9 | Bu_4NClO_4 |  11 | 77 | 5:95 |
| | Bu_4NOTf |  11 | 39 | 5:95 |
|  10 | Bu_4NClO_4 |  12 | 67 | 15:85 |
| | Bu_4NSbF_6 |  12 | 61 ^c | 20:80 ^c |
| | Bu_4NTEPB |  12 | 36 | 0:100 |

^a After the electrolysis (1.25 F/mol based on **9** or **10**), methanol (5 equiv) was added to the anodic chamber. After 1–2 min, the reaction was quenched by the addition of Et_3N (5 equiv). ^b Isolated yield. ^c Determined by GC analysis.

Table 2. Electrochemical Glycosylation Reactions^a

| Thioglycoside | Glycosyl Acceptor | Method | Product | Yield (%) ^b | α/β |
|---|---|----------------|---|------------------------|--------------------|
|  9 | <i>c</i> -C ₆ H ₁₁ OH | one-pot |  15 | 67 | 6:94 ^c |
|  10 | <i>c</i> -C ₆ H ₁₁ OH | one-pot |  16 | 74 | 13:87 |
| 10 | <i>c</i> -C ₆ H ₁₁ OH | <i>in-situ</i> | 16 | 64 | 63:37 |
| 9 | <i>t</i> -C ₄ H ₉ OH | one-pot |  17 | 62 | 10:90 ^c |
| 10 | <i>t</i> -C ₄ H ₉ OH | one-pot |  18 | 68 | 5:95 |
| 10 | <i>t</i> -C ₄ H ₉ OH | <i>in-situ</i> | 18 | 91 | 56:44 |
| 10 | CH ₃ OH | <i>in-situ</i> | 12 | 90 | 63:37 |
|  19 | | one-pot |  20 | 62 | 18:82 ^c |
| 9 | 19 | <i>in-situ</i> | 20 | 94 | 60:40 ^c |
| 10 | 19 | one-pot |  21 | 47 | 0:100 |
| 10 | 19 | <i>in-situ</i> | 21 | 82 | 67:33 |

^a **One-Pot Procedure.** After the electrolysis (1.25 F/mol based on **9** or **10**), a glycosyl acceptor (5 equiv) was added to the anodic chamber. After 1–2 min, the reaction was quenched by the addition of Et₃N (5 equiv). Bu₄ClO₄ was used as the supporting electrolyte. **In Situ Method.** Electrolysis (1.25 F/mol of electricity based on **9** or **10**) was carried out in the presence of a glycosyl acceptor (10 equiv) using Bu₄NTEBP as the supporting electrolyte. ^b Isolated yield. ^c Determined by ¹H NMR.

were obtained, respectively. The glycosyl cation was apparently trapped by fluoride derived from BF₄[−].¹³ The present observations suggested that glycosyl cations are more reactive toward BF₄[−] than simple alkoxy-carbenium ions.

To avoid the attack of the fluoride, we examined tetrabutylammonium perchlorate (Bu₄NClO₄) as a supporting electrolyte. The electrochemical oxidation using Bu₄NClO₄ followed by the addition of methanol gave rise to the formation of the glycosylation products **11** and **12** (one-pot

procedure) (Table 1). However, our efforts to detect the glycosyl cation by NMR spectroscopy¹⁴ were in vain. The signal due to the proton adjacent to the cationic carbon and the signal due to the cationic carbon were absent. The formation of glycosyl perchlorates¹⁵ is most likely, but the

(14) Spectroscopic characterization of glycosyl perchlorate: Igarashi, K.; Honma, T.; Irisawa, J. *Carbohydr. Res.* **1970**, *15*, 329. For glycosyl triflate, see ref 3.

(15) (a) Böhn, G.; Waldmann, H. *Liebigs Ann.* **1996**, 613. (b) Schene, H.; Waldmann, H. *Eur. J. Org. Chem.* **1998**, 1227. (c) Hirooka, M.; Koto, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2893. (d) Wakao, M.; Nakai, Y.; Fukase, K.; Kusumoto, S. *Chem. Lett.* **1999**, 27.

(13) Formation of glycosyl fluorides: Mallet, J.-M.; Meyer, G.; Yvelin, F.; Jutand, A.; Amatore, C.; Sinay, P. *Carbohydr. Res.* **1993**, *244*, 237.

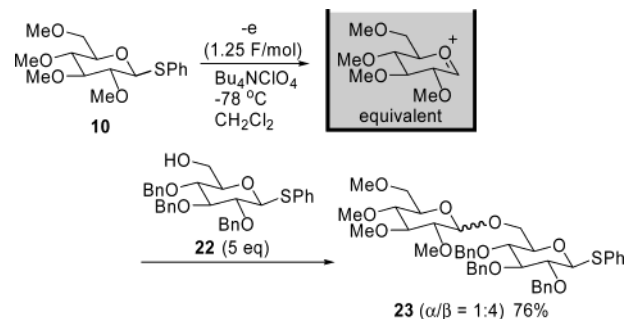
spectrum was not simple presumably because of the byproducts based on the cleaved phenylthio group. As shown in Table 1, the electrochemical oxidation using other supporting electrolytes such as triflate (Bu_4NOTf), hexafluoroantimonate (Bu_4NSbF_6), and tetrakis(pentafluorophenyl)borate (Bu_4NTEPB) followed by the addition of methanol also gave **11** and **12**, though Bu_4NClO_4 gave the best results among the examined. With these supporting electrolytes, our efforts to detect the glycosyl cation were also not successful.

Although glycosyl cations were not detected by NMR spectroscopy, this one-pot procedure serves as a new type of electrochemical glycosylation¹⁶ in which the oxidation is carried out in the absence of a glycosyl acceptor.¹⁷ The present one-pot method has been successfully applied to several glycosyl acceptors as shown in Table 2.

It is noteworthy that high β -selectivity was observed for the one-pot method using Bu_4NClO_4 , whereas the corresponding in situ method (the electrochemical reaction in the presence of a glycosyl acceptor using Bu_4NTEPB) exhibited α preference. In the case of the one-pot method, ClO_4^- may interact strongly with the α side so that the glycosyl acceptor attacks preferentially from the β side, although the detailed mechanism has not yet been determined.

The advantage of the present one-pot method is obvious. One can use glycosyl acceptors that are easily oxidized during the in situ method.¹⁶ For example, thioglycosides can be used as glycosyl acceptors. Thus, the electrochemical oxidation of **10** followed by the addition of thioglycoside

Scheme 4. One-Pot Electrochemical Glycosylation Using a Thioglycoside as an Acceptor



22 was examined, and the reaction took place smoothly to afford **23** in 76% yield (Scheme 4).

In summary, alkoxy-carbenium ion pools can be generated by low-temperature electrochemical oxidation of α -phenylthioethers. Although glycosyl cation pools have not been detected under these conditions, a one-pot electrochemical glycosylation method, in which a glycosyl acceptor is added after the electrolysis, has been developed. It is also noteworthy that high β selectivity was observed in the one-pot method in the absence of the neighboring group participation. The present method opens new possibilities for electrochemical glycosylation reactions. Further work aimed at generating glycosyl cation pools is currently in progress.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research. We are also grateful to Nippon Shokubai Co. for providing sodium tetrakis(pentafluorophenyl)borate as a precursor of Bu_4NTEPB .

Supporting Information Available: Experimental procedures and analytical and spectroscopic data of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL048524H

(16) (a) Noyori, R.; Kurimoto, I. *J. Org. Chem.* **1986**, *51*, 4322. (b) Amatore, C.; Jutand, A.; Mallet, J.-M.; Meyer, G.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1990**, 718. (c) Amatore, C.; Jutand, A.; Meyer, G.; Bourhis, P.; Machetto, F.; Mallet, J.-M.; Sinay, P.; Tabeur, C.; Zhang, Y.-M. *J. Appl. Electrochem.* **1994**, *24*, 725. (d) Balavoine, G.; Gref, A.; Fischer, J.-C.; Jubineau, A. *Tetrahedron. Lett.* **1990**, *31*, 5761. (e) Balavoine, G.; Berteina, S.; Gref, A.; Fischer, J.-C.; Lubineau, A. *J. Carbohydr. Chem.* **1995**, *14*, 1217. (f) Balavoine, G.; Berteina, S.; Gref, A.; Fischer, J.-C.; Lubineau, A. *J. Carbohydr. Chem.* **1995**, *14*, 1237. (g) Nokami, J.; Osafune, M.; Ito, Y.; Miyake, F.; Sumida, S.; Torii, S. *Chem. Lett.* **1999**, 1053. (h) Yamago, S.; Kokubo, K.; Yoshida, J. *Chem. Lett.* **1997**, 111. (i) Yamago, S.; Kokubo, K.; Hara, O.; Masuda, S.; Yoshida, J. *J. Org. Chem.* **2002**, *67*, 8584. See also ref 13.

(17) (a) Yamago, S.; Yamada, T.; Hara, O.; Ito, H.; Mino, Y.; Yoshida, J. *Org. Lett.* **2001**, *3*, 3867.