# An Efficient Method for Catalytic and Stereoselective Glycosylation with Thioglycosides Promoted by Trityl Tetrakis(pentafluorophenyl)borate and Sodium Periodate

Hiromi Uchiro and Teruaki Mukaiyama
*Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162*

(Received October 14, 1996)

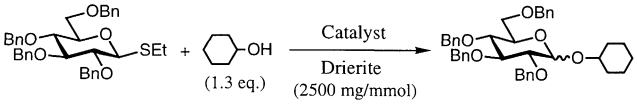
A new and efficient method for catalytic stereoselective synthesis of several glycosides from thioglycosides is successfully performed by the combined use of trityl salt and sodium periodate. Several β-D-gluco- and galactopyranosides are prepared in good yields with high stereoselectivities.

Stereoselective synthesis of oligosaccharides is one of the most important topics in carbohydrate chemistry and numerous methods using various glycosyl donors have been developed in order to achieve this purpose. Thioglycosides have especially attracted much attention as versatile glycosyl donors[1] since they are easily available and are stable under various conditions such as in protection and deprotection steps of hydroxy group in carbohydrates. In addition, the thioglycosides were reported to be selectively activated by "thiophillic" reagent such as DMTST,[2] MeOTf,[3] PhSeOTf,[4] IDCP,[5] NIS-TfOH,[6] PhIO-$Tf_2O$,[7] etc. However, all of these reagents require stoichiometric use and have several disadvantageous properties such as moisture or light sensitive, corrosive, carcinogenic, explosive or expensive. Thus, development of an efficient method to activate thioglycosides by using a catalytic amount of easy-to-handle and cheap reagent is strongly desired. In this communication, we would like to report a new method for catalytic activation of thioglycosides by combined use of trityl salt, an easy-to-handle catalyst, and sodium periodate, a cheap co-oxidant, affording several β-D-gluco- and galactopyranosides in good yields with high stereoselectivities.

In general, thioglycosides cannot be efficiently activated by Lewis acid catalyst since an equiliblium is not shifted to oxocarbenium ion intermediate, an active species. It is because the formed metal thiolate, a strong nucleophile, easily recombines to regenerate the original thioglycoside. Therefore, it is expected that the activation of thioglycosides would proceed smoothly when the thiolate is oxidized to non-nucleophilic disulfide by use of co-oxidant.

Firstly, the effect of co-oxidant was examined taking the reaction of ethyl 1-thio-2,3,4,6-tetra-*O*-benzyl-β-D-gluco pyranoside **1a** with cyclohexanol **3a** in dichloromethane as a model. The reaction was carried out in the presence of 20 mol% of trityl tetrakis(pentafluorophenyl)borate[8] as a catalyst, 105 mol% of sodium periodate,[9] a co-oxidant, and Drierite, a dehydrating agent (Table 1). As a result, a remarkable effect of co-oxidant was observed and desired glycoside was obtained in good yield.[10] It is noteworthy that this trityl salt has high potential as a glycosylation catalyst.[11] Besides, this salt is moisture insensitive different from the conventional one such as trityl perchlorate and trityl tetrafluoroborate, and easily available by one pot procedure starting from bromopentafluorobenzene.[12] Then, several solvents and temperature were examined in order to improve the stereoselectivity (Table 2). A great improvement of β-selectivity was observed when nitrile solvents were used and it was enhanced with steric hindrance of nitrile. Especially, as the best result, a compatibility of high yield and β-selectivity were

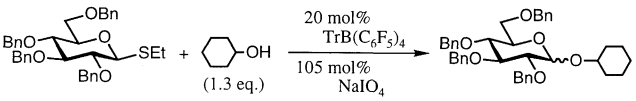
**Table 1.** Effect of co-oxidants




**1a** **3a** **4a**

| Catalyst / mol% | Co-oxidant / mol% | Yield / % | α / β |
|---|---|---|---|
| $TrB(C_6F_5)_4$ (20) | None | Trace | - |
| None | $NaIO_4$ (105) | No reaction | - |
| $TrB(C_6F_5)_4$ (20) | $NaIO_4$ (105) | **88** | **57 / 43** |

**Table 2.** Effects of solvent and temperature




**1a** **3a** **4a**

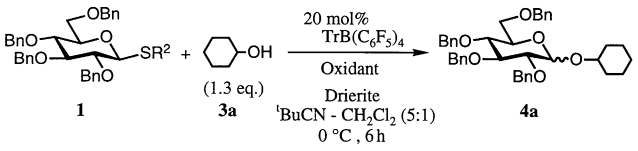
| Solvent | Temp | Time / h | Yield / % | α / β |
|---|---|---|---|---|
| $CH_2Cl_2$ | r.t. | 3 | 88 | 57 / 43 |
| Benzene | r.t. | 5 | 81 | 60 / 40 |
| MeCN | 0 °C | 6 | 27 | 15 / 82 |
| EtCN | 0 °C | 6 | 72 | 13 / 87 |
| $^{i}$PrCN | 0 °C | 6 | 75 | 12 / 88 |
| $^{t}$BuCN | r.t. | 3 | 82 | 15 / 85 |
| $^{t}$BuCN - $CH_2Cl_2$ (5:1) | 0 °C | 6 | 89 | 8 / 92 |
| $^{t}$BuCN - $CH_2Cl_2$ (4:1) | **0 °C** | **6** | **93** | **8 / 92** |

achieved when the reaction was carried out in pivalonitrile ($^{t}$BuCN) - dichloromethane (4 : 1)[13] at 0 °C. Such effect of nitrile solvent has already been reported in some papers;[14] however, the relationship between steric hindrance of nitrile solvent and the stereoselectivity of glycosylation was hardly discussed. This result strongly suggested the existence of non-conjugate type nitrilium ion intermediate during glycosylation. Next, the amount of dehydrating agent and sevral kinds of co-oxidants and of thioglycosides were examined (Table 3). In the absence of Drierite, the yield was significantly lowered and a large quantity of 1-hydroxy sugar was obtained as a by-product. Therefore, it was assumed that the appropriate amount of water was formed during this oxidative catalytic cycle. Sodium iodate and bromate[15] which have lower oxidation number than sodium periodate were slightly less effective. A use of more reactive methylthioglycoside **1b** led to higher yield. The amount of sodium periodate could be reduced down to 40 mol% when this donor was used.

Several examples of the present glycosylation reaction are demonstrated in Table 4. In every case, the desired β-D-gluco- and galactopyranosides were obtained in high yields with high stereoselectivities.

The typical experimental procedure is as follows: to a stirred suspension of trityl tetrakis(pentafluorophenyl)borate (22.1 mg,

**Table 3.** Effects of Drierite and the kind of donors and oxidants

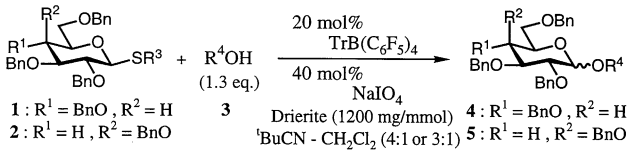



1 3a 4a

| Donor | $SR^2$ | Oxidant (mol%) | Drierite (mg / mmol) | Yield / % | α / β |
|---|---|---|---|---|---|
| **1a** | SEt | $NaIO_4$ (105) | 2500 | 89 | 8 / 92 |
| **1a** | SEt | $NaIO_4$ (105) | 1000 | 90 | 8 / 92 |
| **1a** | SEt | $NaIO_4$ (105) | 500 | 83 | 8 / 92 |
| **1a** | SEt | $NaIO_4$ (105) | None | 41 | 8 / 92 |
| **1a** | SEt | $NaIO_3$ (105) | 2500 | 87 | 7 / 93 |
| **1a** | SEt | $NaBrO_3$ (105) | 2500 | 84 | 7 / 93 |
| **1a** | SEt | CAN (105) | 2500 | 16 | 2 / 98 |
| **1a** | SEt | Oxone® (105) | 2500 | No reaction | - |
| **1b** | SMe | $NaIO_4$ (105) | 2500 | 97 | 8 / 92 |
| **1b** | SMe | $NaIO_4$ (50) | 2500 | 97 | 7 / 93 |
| **1b** | **SMe** | **$NaIO_4$ (40)** | **2500** | **97** | **7 / 93** |
| **1b** | SMe | $NaIO_4$ (30) | 2500 | 91 | 6 / 94 |
| **1c**[a] | SPh | $NaIO_4$ (105) | 2500 | 78 | 13 / 87 |

[a] The reaction was carried out in $^t$BuCN under room temp for 20h.

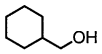
**Table 4.** Syntheses of β-D-Gluco- and galactopyranosides

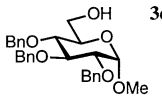
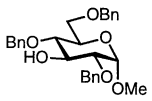
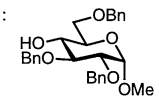



1 : $R^1$ = BnO , $R^2$ = H
2 : $R^1$ = H , $R^2$ = BnO
3
4 : $R^1$ = BnO , $R^2$ = H
5 : $R^1$ = H , $R^2$ = BnO

| Donor | $SR^3$ | $R^4OH$ | Product | Solv. | Temp | Time | Yield / % | α / β |
|---|---|---|---|---|---|---|---|---|
| **1b** | SMe | **3a** | **4a** | 4:1 | 0°C | 3h | 97 | 7 / 93 |
| **1b** | SMe | **3b** | **4b** | 4:1 | 0°C | 12h | 90 | 7 / 93 |
| **1b** | SMe | **3c** | **4c** | 4:1 | 0°C | 8h | 91 | 7 / 93 |
| **1b** | SMe | **3d** | **4d** | 4:1 | 0°C | 3h | 93 | 7 / 93 |
| **1b** | SMe | **3d** | **4d** | 3:1 | -15°C | 9h | 93 | 4 / 96 |
| **1b** | SMe | **3e**[a] | **4e** | 3:1 | -15°C | 15h | 92 | 8 / 92 |
| **1b** | SMe | **3f**[a] | **4f** | 3:1 | -15°C | 15h | 85 | 9 / 91 |
| **2a** | SEt | **3a** | **5a** | 3:1 | -15°C | 8h | 95 | 9 / 91 |
| **2a** | SEt | **3d** | **5d** | 3:1 | -15°C | 6h | 93 | 10 / 90 |

[a] 1.5 eq. of acceptor was used.

$R^4OH$ : **3a** :  **3b** : $CH_3(CH_2)_7OH$ **3c** : 

**3d** :  **3e** :  **3f** : 

0.024 mmol), sodium periodate (10.3 mg, 0.060 mmol) and Drierite (150 mg) in mixed solvent (pivalonitrile/dichloromethane =4/1, 2 ml) was successively added a mixed solvent (2 ml) solution of cyclohexanol **3a** (15.6 mg, 0.156 mmol) and methyl 1-thio-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside **1b** (68.5 mg, 0.12 mmol) at 0 °C. The reaction mixture was stirred for 3 hours at 0 °C, then it was quenched by adding saturated aqueous sodium hydrogen carbonate (20 ml). The mixture was diluted with dichloromethane (30 ml) and filtered through Celite. The organic layer was separated and washed with 10% aqueous sodium thiosulfate, water and brine (each of 20 ml), respectively. After dryness and evaporation, resulting residue was purified by preparative TLC (silica gel), cyclohexyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside **4a** (72.2 mg, 97% yield) was isolated. The ratio of the anomers was determined by HPLC analysis.

Thus, a new and efficient catalytic glycosylation was successfully developed using thioglycosides with several alcohols to afford several β-D-gluco- and galactopyranosides in high yields with high stereoselectivities. It is noted that this catalyst system has great advantages over the conventional glycosylation method in its efficiency such as of easy operation and low cost.

Further investigation on applications of this novel glycosylation method to other valuable glycosides and on precise reaction mechanism is now in progress.

The present research is partially supported by Grant-in-Aids for Scientific Research from Ministry of Education, Science and Culture.

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