A Novel Activating Agents of 'Disarmed' Thioglycosides, Combination of Trityl Tetrakis(pentafluorophenyl)borate, Iodine and 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)

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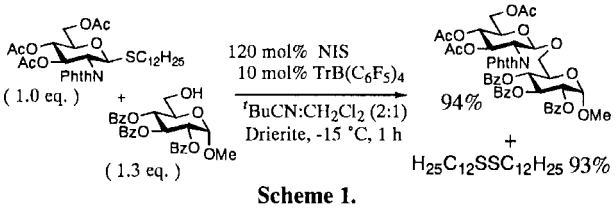
A combined use of trityl tetrakis(pentafluorophenyl) borate [$TrB(C_6F_5)_4$], iodine (I_2) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) effectively activates "disarmed" thioglycosides to afford the corresponding disaccharides in high yields on treatment with several glycosyl acceptors.

Thioglycosides are frequently employed in the synthesis of complex carbohydrates[1] since they are stable under most reaction conditions and are activated by such reagents in combination with TfOH-NIS[2] or Lewis acids and NIS or NBS, or reagents as MeOTf,[3] DMTST,[4] IDCP,[5] and $TrB(C_6F_5)_4$-$NaIO_4$[6] and some other promoters.[7] Among these activating agents, the combination of NIS-TfOH effectively activates glycosyl donors to generate highly reactive key intermediate, an iodonium ion. Recently, it was reported from our laboratery that the respective combinations of catalytic amount of $TrB(C_6F_5)_4$ and stoichiometric amount of NIS or NBS were useful for activating "disarmed" thioglycosides.[8] A study on the above glycosylation was further continued to confirm the co-product resulted from alkylthio moiety left during the present reaction. As shown in Scheme 1, dodecyl thioglycoside smoothly reacted with an acceptor in the presence of NIS-$TrB(C_6F_5)_4$ to afford the corresponding disaccharide and didodesyldisulfide in high yields. This result indicated that dodesylsulfenyl iodide, formed by iodonium ion acivation, was rapidly converted to iodine and the corresponding disulfide. Based on this observation, generation of active iodonium ion from iodine was then examined in order to establish the catalytic cycle of the glycosylation using thioglycoside.



Scheme 1.

The iodine-based novel activating agents of thioglycosides were studied by taking the reaction of ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimide-1-thio-β-D-glucopyranoside (**1**) with methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**2**) as a model (Table 1). Firstly, a combination of $TrB(C_6F_5)_4$ and I_2 was employed as an activating agent and the desired disaccharide was obtained in moderate yield (Entry 1). Concerning this type of iodine-based agent, R. A. Field reported the glycosylation of simple alcohols using several glycosyl halides as donors by using equimolar amounts of I_2 / DDQ.[9] Although the precise mechanism of the I_2 / DDQ-promoted glycosylation reaction was not cleary described in the above paper, we assumed that

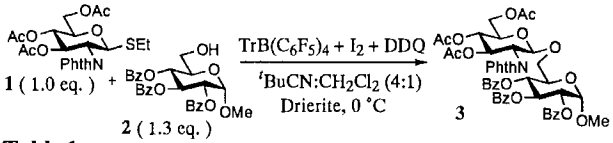


Table 1.

Entry	Tr[a] /mol%	I_2 /mol%	DDQ /mol%	Time /h	Yield /%
1	30	100	——	22	45
2	——	100	100	12	54
3	30	——	100	17	54
4	30	100	100	1.5	93
5[b]	30	100	100	6	89
6[c]	5	100	100	2.5	93
7[c]	5	100	55	4	96
8[c]	**5**	**10**	**55**	**8**	**94**

[a] Tr = $TrB(C_6F_5)_4$. [b] Solvent = CH_2Cl_2. [c] Solvent = $^tBuCN:CH_2Cl_2$ (2:1).

the active species should be an iodonium ion generated in situ from I_2 / DDQ. Interestingly enough, the addition of DDQ to the above combination of $TrB(C_6F_5)_4$ / I_2 dramatically accelerated the glycosylation reaction to afford the corresponding disaccharide in high yield (Entry 4). These observations promted us to screen reaction conditions in detail and the results are shown in Table 1. It was made thus clear that the coexistence of the above three reagents was essential to the promotion of the reaction while each combination such as I_2 / DDQ, $TrB(C_6F_5)_4$ / DDQ, was not so effective (Entry 2, 3). Further, it was observed that the effect of solvents was influential to the present glycosylation and that use of pivalonitrile enhanced the rate of the reaction (Entry 4, 5).

Next, the effects of the amount of activating agents were examined for the optimization of reaction conditions. In the presence of 1 equiv each of I_2 and DDQ, 5 mol% of $TrB(C_6F_5)_4$ was shown to be sufficient (Entry 6). It was further demonstrated that the minimum requirement of DDQ was 55 mol% in the coexistence of 5 mol% of $TrB(C_6F_5)_4$ and 1 equiv. of I_2 (Entry 7). The amount of I_2 was further examined in the coexistence of 5 mol% of $TrB(C_6F_5)_4$ and 55 mol% of DDQ, and it was shown that the only 10 mol% of I_2 was enough to promote the present glycosylation reaction (Entry 8). It is well-known that the rate of oxidation reaction of using quinones increased when a catalytic amount of protic acid was added. The conjugated acid, protonated DDQ, was counted to be a stronger anion or electron acceptor compared with DDQ. Consequently, it was considered that the reactivity of the present glycosylation reaction was essentially determined by both the reduction potential of quinones and the acidity of Lewis acids. In order to prove the above hypothesis, combinations of various quinones and Lewis acids were applied to the present

reaction. As shown in Table 2, the rate of reaction revealed to be dependent on the reduction potential of quinones[10] in the presence of 5 mol% of $TrB(C_6F_5)_4$, 10 mol% of I_2, 55 mol% of several quinones.

1 (1.0 eq.) + **2** (1.3 eq.) → **3**
5 mol% $TrB(C_6F_5)_4$, 10 mol% I_2 + 55 mol% Quinone, $^tBuCN:CH_2Cl_2$ (2:1), Drierite, 0 °C, 8 h

Table 2.

Entry	Quinone	Yield /%
1	DDQ	94
2	*o* - Chloranil	77
3	Chloranil	23
4	*p* - Benzoquinone	11

Effects of various Lewis acid catalysts were further screened in the glycosylation reaction by using 10 mol% of I_2 and 55 mol% of DDQ. Significant difference of reactivity was observed among various trityl salts screened (see Table 3): that is, the corresponding disaccharide was obtained in poor yield in the case of using 4-methoxytrityl tetrakis(pentafluorophenyl)-boate, a less reactive Lewis acid catalyst, while $TrB(C_6F_5)_4$ and 4,4',4"-trifluorotrityl tetrakis(pentafluorophenyl)borate gave good results. It also became apparent that $TrB(C_6F_5)_4$ gave even better results than trityl tetrafluoroboarte because the former had a highly stabilized counter anion, tetrakis(pentafluoro-phenyl)borate. Of other Lewis acids and protic acids employed in place of the trityl salts, trifluoromethanesulfonic acid behaved relatively effective .

1 (1.0 eq.) + **2** (1.3 eq.) → **3**
5-10 mol% Catalyst, 10 mol% I_2 + 55 mol% Quinone, $^tBuCN:CH_2Cl_2$ (2:1), Drierite, 0 °C, 8 h

Table 3.

Entry	Catalyst /mol%	Yield /%
1	$TFTrB(C_6F_5)_4$ / 5	93
2	$TrB(C_6F_5)_4$ / 5	94
3	$MMTrB(C_6F_5)_4$ / 5	11
4	$TrBF_4$ / 5	16
5	TfOH / 10	77
6	TMSOTf / 10	18
7	$BF_3 \cdot OEt_2$ / 10	18

Finally, the present glycosylation reaction of using several glycosyl donors and acceptors was tried and the optimized reaction conditions were summarized in Table 4. In each case, the "disarmed" thioglycosides reacted with glycosyl acceptors, methyl glucosides, to afford the corresponding β-glycosides in good to high yields.

The typical experimental procedure is as follows: to a stirred suspension of trityl tetrakis(pentafluorophenyl)borate (2.3 mg, 2.5 μmol), DDQ (6.2 mg, 27.5 μmol) and Drierite (100 mg) in a mixed solvent (pivalonitrile:dichloromethane = 2:1, 0.45 mL) was successively added a solution (pivalonitrile:dichloromethane = 2:1, 0.8 ml) of **1** (24.0 mg, 0.05 mmol) and **2** (32.9 mg, 0.065 mmol) at 0 °C, followed by addition of iodine (1.3 mg, 5.0

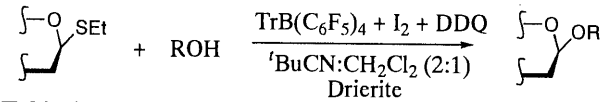
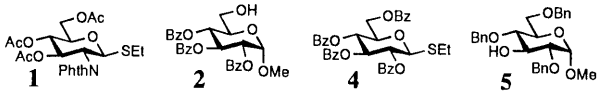


Table 4.

Entry	Donor	Acceptor	Reagents /mol% Tr	I_2	DDQ	Yield /%
1[a]	**1** (1.0 eq.)	**2** (1.3 eq.)	5	10	55	94
2[b]	**1** (1.3 eq.)	**5** (1.0 eq.)	20	30	65	93
3[a]	**4** (1.0 eq.)	**2** (1.3 eq.)	5	10	55	83
4[b]	**4** (1.3 eq.)	**5** (1.0 eq.)	20	30	65	65

Reaction temp. and time; [a] 0 °C, 8 h, [b] -15 °C, 27 h.

Glycosyl Donors and Acceptors



μmol). After the reaction mixture was stirred for 8 h at 0 °C, it was quenched by adding saturated aqueous $NaHCO_3$ (10 mL). The mixture was filtered through Celite and extracted with dichloromethane (3 times, each of 20 mL). The combined organic layer was washed with brine (5 mL) and the resulted organic layer was dried over Na_2SO_4. After filtration and evaporation, the resulted residue was purified by preparative TLC (silica gel) to give the desired product (43.3 mg, 94%).

Thus, a novel activator composed of $TrB(C_6F_5)_4$ / I_2 / DDQ, was effectively employed for the glycosylation of "disarmed" thioglycoside. It is noted that the experimental procedure of the present glycosylation is quite simple and all reagents are easily-available, stable, and nonhygroscopic.

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