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Synthesis of alkyl and arylthioglycosides and thiodisaccharides via thioiminium salts in a two-phase system

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Abstract

A novel method was developed for the synthesis of alkyl- and arylthioglycosides and thiodisaccharides via glycosylthioiminium salt in a two-phase system using a phase transfer catalyst (PTC). Tetrabutylammonium thiocyanate and tetrabutylphosphonium bromide show a highest efficiency as a PTC for this method. In general, the phosphonium salt is more effective than the ammonium salt as a PTC, and the effect of counter anions of PTC of tetrabutylammonium type is in the order, $SCN^- > Br^- > HSO_4^- > Cl^-$. The reactivity of alkyl halide RX is in the order RI > RBr > RCl, independently of the kind of PTC. Using this method, various thioglycosides were prepared in fairly good yields higher than 80%. The reactions proceed easily under mild conditions without a sulfur reagent giving an unpleasant smell.

Keywords: Thioglycoside; Iminium salt; Phase transfer catalyst (PTC)

1. Introduction

Thioglycosides, in which an oxygen atom at 1-position of glycosides is substituted with a soft sulfur atom, are used as an enzyme inhibitor of sugars [1–3] and surface-active agents [4], and especially glycosyl donors for synthesizing intricate oligosaccharides [5–11]. Applications of thioglycosides as a glycosyl donor have some merits; that is, they are not influenced by the acid or basic conditions of introduction of protecting groups and deprotection and also by the general conditions of glycosylation reactions (see, e.g., Ref. [12]). Regards to the reactions of sugars in a two-phase system using a phase-transfer catalyst (PTC), the introduction of protecting groups [13], the ester interchange [14], the synthesis of *O*-glycosides [15–18] and also the isomerization of sugar [19] were reported, but there are only few reports on the synthesis of thioglycosides. These reports deal with the method of reaction of thiol with alkyl halides under alkaline conditions [20,21] and the method using the strong anion-exchange resin [22]. These methods afford symmetric and asymmetric thioglycosides and the reaction with sodium sulfide gives only symmetric thioglycoside [21,23]. The synthetic method of thioglyco-

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sides using a Lewis acid catalyst instead of PTC was also examined [24–28].

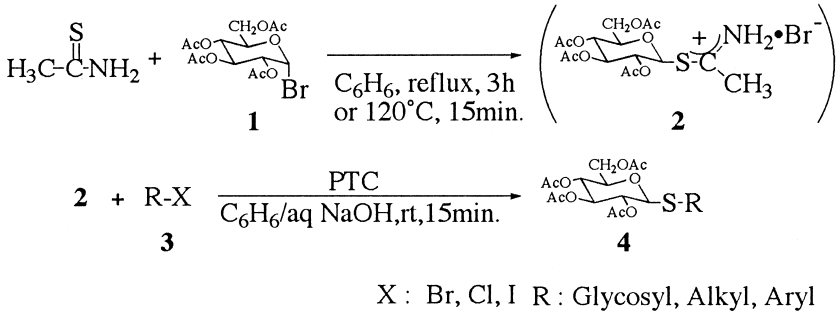
In preceding papers [29,30], we reported a novel method using a PTC system, which utilizes reactions of alkyl or aryl halide with thiolate anions formed by the decomposition of 1-alkylethaniminium halide under alkaline conditions. The iminium halide was prepared in situ from alkyl halide with thioacetamide. In addition, we discussed preliminarily the method of synthesis of thiodisaccharides by the similar procedure [31]. This paper describes fully a facile and efficient method of synthesis of alkyl and arylthioglycoside and thiodisaccharide utilizing the reaction of thioiminium salt in a two-phase system with PTC.

2. Results and discussion

2.1. Method of synthesis

The method of synthesis of thioglycoside is designed as shown in Scheme 1. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide(abbreviated as acetobromglucose) **1** is prepared by the reaction of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose with PBr5, which is prepared in situ from red phosphorus and bromine [32]. It was shown from HPLC analysis that, when acetobromglucose **1** was reacted with thioacetamide (TA) in dry benzene at refluxing temperature, it disappears almost completely in 2.5 h. The product is predicted to be thioiminium salt. Since the iminium salt is unstable in moist air, the product was analyzed with IR without isolation. The absorption peak assigned to the iminium double bond was observed at 1650 cm^{-1} and, therefore, the product is confirmed to be 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thioethaniminium bromide **2**, although the absorption to the sulfide bond at about 760 cm^{-1} could not be confirmed owing to overlapping with the absorption of symmetric ring breathing vibration of pyranosyl ring [33]. It was shown by a separate experiment that this reaction proceeds almost completely. The reaction of acetobromglucose **1** with TA without solvent at 120°C under dry nitrogen atmosphere was carried out. After 15 min, the viscous reaction mixture was cooled to room temperature to give amorphous solid. This solid was so hygroscopicity. In order to confirm it to be the thioiminium salt **2**, this product was rapidly analyzed by FAB-MS (positive ion) (see Fig. 1). The fragmental ion peak of m/z 406 ($[M - Br^-]^+$) was observed and it indicates the existence of thioiminium salt **2**. As shown later, the preparation of thioiminium salt without solvent gives a better result than that in solution (benzene).

The next step of synthesis is the reaction of thioiminium salt **2** with alkyl halide **3** in a two-phase system using PTC. Into the reaction



Scheme 1. Synthesis of thioglycoside from thioiminium salt using PTC.

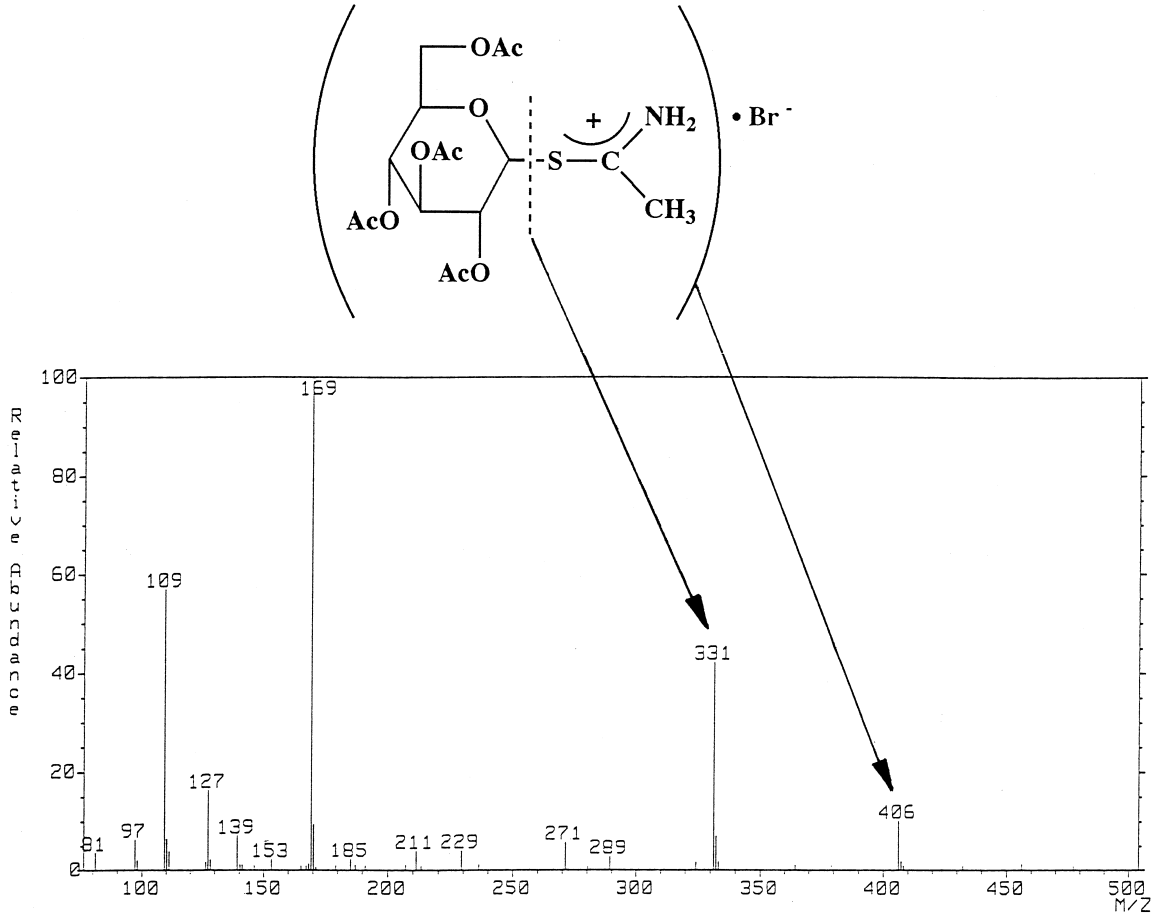


Fig. 1. FAB spectrum of thioiminium salt from acetobromglucose with thioacetamide.

mixture containing thioiminium salt **2** in benzene, PTC and halide **3** together with an aqueous NaOH solution were added, and the two-phase mixture was stirred vigorously at room temperature. After the reaction, the benzene phase was separated from the reaction system, washed with water and dehydrated with anhydrous $MgSO_4$. The crude product was obtained by removing benzene by distillation at reduced pressure at temperature lower than 40°C. Purified thioglycoside **4** was obtained by the recrystallization from methanol or ethanol.

2.2. Examinations of reaction conditions

At first, the effect of NaOH concentration on the yield of thiodisaccharide in the designed reaction process (using solvent) was examined. In the following experiments, tetrabutylammonium bromide (TBAB) or tetrabutylphosphonium bromide (TBPB) is used as a PTC by a molar ratio 6:5 against acetobromglucose **1**. The reaction of **2** with acetobromglucose **3** in a two-phase system consisting of benzene and water containing no NaOH for 15 min at room temperature did not proceed and almost all the starting materials were recovered. When 10 and 20 wt.% NaOH solutions were used, the reaction did not also occur. The reactions using an aqueous 30 wt.% NaOH phase afford the desired product in the yields of 25% and 1%, respectively, in the cases using TBAB and TBPB. These results are shown in Fig. 2. The reaction proceeds effectively in a two-phase

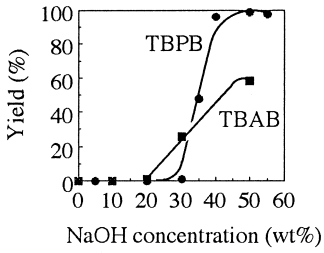


Fig. 2. Effect of NaOH concentration on yield of bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)sulfide.

system using an aqueous NaOH solution higher than 30 wt.% and the yield of bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) sulfide (β,β-thiotrehalose) becomes about 59% in the case using TBAB when a 50 wt.% NaOH solution, which is nearly saturated, is used, while the yield becomes nearly quantitative in the case using TBPB.

Next, the effects of the amount of PTC and the reaction temperature were examined. When the reactions in the presence of various amounts of TBAB in a benzene–aqueous 50 wt.% NaOH solution system were carried out at 5°C, 23°C (room temperature) and 60°C, the results shown in Table 1 were obtained. The reaction using TBAB of the molar ratio of 1 against acetobromglucose **1** at room temperature (23°C) gave the yield of β,β-thiotrehalose of 59% for 15 min, and the prolonged reaction time of 30 min did not result in an increase of yield. On the other hand, the amount of TBAB affects the yield of β,β-thiotrehalose; the use of TBAB of the molar ratio of 3 against acetobromglucose **1** increased the yield from 59% to 77%. To the contrary, when TBAB of molar ratio 0.5 was used, the yield decreased to 39%. This result shows that the presence of PTC is essential in this method of 1-thioglycoside.

In the reactions of the molar ratio of PTC of 3, the yield of β,β-thiotrehalose increased from 77% to 83%, when the reaction temperature was lowered from 23°C to 5°C. On the other hand, the yield of β,β-thiotrehalose at elevated temperature of 60°C decreased very remarkably, and the product β,β-thiotrehalose was scarcely obtained from the benzene phase and instead some amount of deacetylated product was isolated from the aqueous phase. This result indicates that the product β,β-thiotrehalose is partly deacetylated in the benzene phase under alkaline conditions and the deacetylated product is transferred to the aqueous phase.

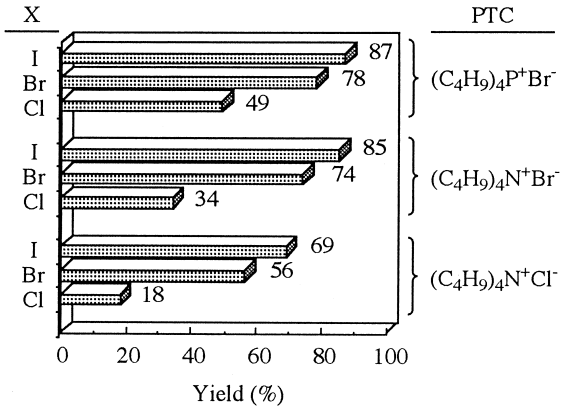
2.3. Reactivities of various alkyl halides

In the synthesis of alkyl thioglycoside, the reactivity of alkyl halides **3**, e.g., propyl chloride, bromide and iodide, toward glucosylthioiminium salt **2** was investigated. As PTC, TBPB,

Table 1
Effects of temperature and amount of PTC in the synthesis of bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) sulfide

Reaction conditions			Yield (%)
Temperature (°C)	Time (min)	Molar ratio of PTC/AcGlcBr	
5	15	5	90
5	15	3	83
r.t. (23°C)	15	5	74
r.t. (23°C)	15	3	77
r.t. (23°C)	15	1	59
r.t. (23°C)	15	0.5	39
r.t. (23°C)	30	1	52
60	15	1	1

PTC: $(C_4H_9)_4N^+Br^-$, solvent: benzene–50 wt.% NaOH(aq).
AcGlcBr: 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **1**.



Solvent: benzene-50wt% NaOH aq.
Reaction conditions: 20°C, 15min.
Molar ratio PTC : acetobromglucose = 6 : 5

Fig. 3. Reactivity of propyl halides C_3H_7X.

TBAB and TBAC (tetrabutylammonium chloride) were used. The result is shown in Fig. 3. The reactivity of propyl halide is in the order RI > RBr > RCl, independently of the kind of PTC. As described later, alkyl halide reacts with glucosylthiolate anion transferred to the organic phase with PTC. This order would reflect that of the bond energy of these alkyl halides.

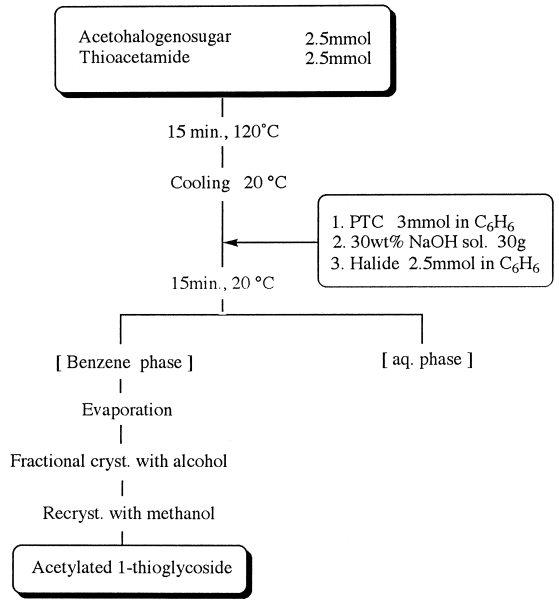
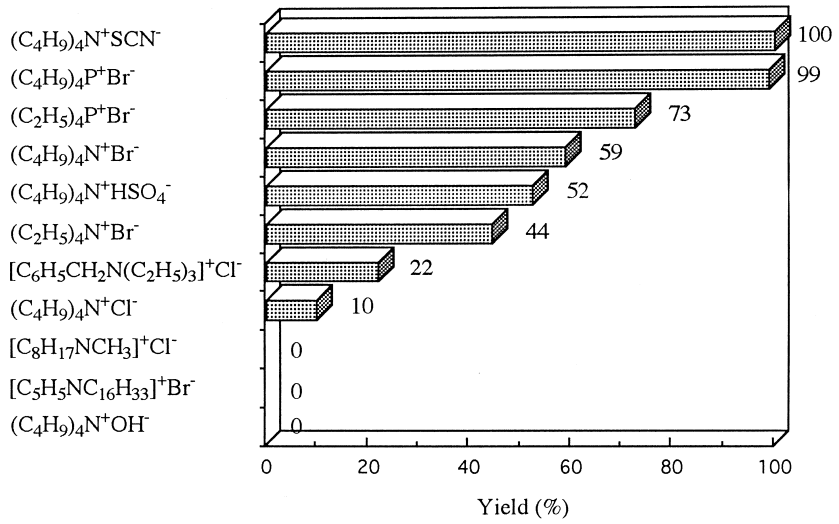


Fig. 5. Optimum synthetic procedure of 1-thioglycoside.

2.4. Effect of PTC

The effect of the kind of PTC in the present reaction system (using solvent) was examined by using various ammonium and phosphonium



Solvent: benzene-50wt% NaOH aq., Reaction conditions: 23°C,15min., Molar ratio PTC : acetobromglucose = 6 : 5

Fig. 4. Effect of PTC on yield acetylated β,β-thiotrehalose.

Table 2
Yields of thioglycosides **4**

Product **4**	R **1**	R′ **3**	X in R′X **3**	Yield (%)
				TBPB (TBAB)
a	AcGlc	AcGlc	Br	99(58)
b	AcGlc	AcGal	Br	86
c	AcGlc	$C_6H_5CH_2$	Br	88
d	AcGlc	CH_3	I	90
e	AcGlc	C_2H_5	I	94
f	AcGlc	C_3H_7	I	87
g	AcGlc	C_3H_7	Br	78
h	AcGlc	C_3H_7	Cl	49
i	AcGlc	C_4H_9	Br	84
j	AcGlc	C_6H_{13}	Br	77
k	AcGlc	C_8H_{17}	Br	89
l	AcGlc	$C_{10}H_{23}$	Br	85
m	AcGal	AcGlc	Br	82
n	AcGal	AcGal	Br	93
o	$C_6H_5CH_2$	AcGlc	Br	88 (22[a])

AcGlc: 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl.
AcGal: 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl.
[a] Dibenzyl disulfide was obtained in yield of 58%.

salts. The concentration of aqueous NaOH solution was set to be 50 wt.%, and 3 mol of PTC was used against 2.5 mol of acetobromglucose **3**. The results are shown in Fig. 4. The yield of β,β-thiotrehalose is almost quantitative, when tetrabutylammonium thiocyanate or TBPB was used as PTC. The effect of counter anions of PTC of tetrabutylammonium type on the yield of β,β-thiotrehalose is in the order, $SCN^- > Br^- > HSO_4^- > Cl^-$. By the comparison between the tetraalkylammonium type and the tetraalkylphosphonium type, the following order is confirmed; TBPB > TBAB and TEPB (tetraethylphosphonium bromide) > TEAB (tetraethylammonium bromide). Clearly, the phosphonium salt is more effective than the ammonium salt as PTC in this synthetic method.

PTC carries a thiolate anion from the aqueous phase to the organic phase. Phosphonium ions and thiolate anions are soft bases and, therefore, it is well explained according to Pearson's HSAB theory that a phosphonium cation combines a thiolate anion and transfers it to the organic phase more effectively than an ammonium cation. Among the phosphonium cations, $(C_4H_9)_4P^+Br^-$ is more effective than $(C_2H_5)_4P^+Br^-$. In general, a more oleophilic cation is more effective, but hexadecylpyridinium bromide does not exert the catalytic activity under similar conditions. This suggests that a more symmetrically shaped anion is more effective. The role of counter anion is also important. Softer and more oleophilic anions, SCN^- and Br^-, are more effective than harder and less oleophilic anions, HSO_4^- and Cl^-. Thus, $(C_4H_9)_4N^+SCN^-$ and $(C_4H_9)_4P^+Br^-$ are the most effective PTC.

Since the hydrolysis of acyl groups of acylated sugar slowly occurs in an alkaline solution

Table 3
Physical properties of thioglycosides **4**

Product **4**	m.p. (°C)		Optical rotation $[\alpha]_D^{20}$ (*c*, $CHCl_3$)	
	Observed	Literature	Observed	Literature
a	174–175	175–176 [36]	−40.7° (0.08)	−40.5° (0.7) [36]
b and **m**	167–168	169–171 [21]	−27.6° (0.20)	
c and **o**	102–103	102–103 [37]	−94.4° (1.01)	−92° (0.48) [37]
d	96	96 [38]	−17.9° (1.04)	−18.6° (2.6)[a] [39]
e	84–85	82.5–83 [40]	−27.2° (2.90)	−28° (0.9) [40]
f, **g** and **h**	82–83	79–82 [38]	−22.2° (0.97)	−22.2° (1.06) [38]
i	65–66	67–68 [38]	−30.8° (1.39)	−25.0° (1.11) [38]
j	64–65	64–65 [4]	−32.3° (0.85)	−34.4° (1.11) [41]
k	68–69	71–72 [4]	−25.2° (0.21)	−25.2° (1.16) [41]
l	74–75	76–77 [4]	−39.7° (0.37)	
n	201.5–202.5	196–197 [23]	−15.1° (0.13)	−14° (0.65) [23]

[a] Tetrachlorethane.

Table 4
^{1}H-NMR chemical shift and coupling constants for product **4**

4	Chemical shift (δ, ppm) and signal multiplicities													
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	H-1′	H-2′	H-3′	H-4′	H-5′	H-6a′	H-6b′
a	4.83	5.05	5.22	5.10	3.69	4.16	4.27							
	2H,d	2H,dd	2H,dd	2H,dd	2H,ddd	2H,dd	2H,dd							
	4.84[a]	5.07[a]	5.24[a]	5.12[a]	3.70[a]	4.18[a]	4.28[a]							
b, **m**	4.81	5.03	5.22	5.09	3.69	4.16	4.26	4.81	5.03	5.22	5.09	3.69	4.16	4.26
	1H,d	1H,dd	1H,dd	1H,dd	1H,ddd	1H,dd	1H,dd	1H,d	1H,dd	1H,dd	1H,dd	1H,ddd	1H,dd	1H,dd
n	4.81	5.23	5.06	5.44	3.91	4.12	4.18							
	2H,d	2H,dd	2H,dd	2H,dd	2H,ddd	2H,dd	2H,dd							
	Coupling constants (Hz)													
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
a	10.2	9.6	9.6	9.6	4.9	2.5	12.5							
	10.2[a]	9.6[a]	9.6[a]	9.6[a]	4.9[a]	2.5[a]	12.5[a]							
b, **m**	10.2	9.9	9.9	9.9	5.2	3.0	12.5	10.2	10.2	3.3	0.9	6.9	6.6	11.3
n	10.2	9.9	3.3	0.8	6.6	6.6	11.5							

4	Chemical shift (δ, ppm) and signal multiplicities										
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	Acetyl–	S-CH_2–	S-CH_3	–CH_2–	–CH_3
d	4.40	5.06	5.24	5.10	3.74	4.26	4.15	2.01, 2.03, 2.07, 2.09		2.68		
	1H,d	1H,dd	1H,dd	1H,dd	1H,ddd	1H,dd	1H,dd			3H,s		
e	4.50	5.04	5.23	5.08	3.71	4.25	4.14	2.01, 2.03, 2.06, 2.08	2.71			1.27
	1H,d	1H,dd	1H,dd	1H,dd	1H,ddd	1H,dd	1H,dd		2H,m			3H,t
f,g,h	4.50	5.03	5.22	5.08	3.72	4.25	4.14	2.01, 2.03, 2.06, 2.08	2.66		1.59	0.99
	1H,d	1H,dd	1H,dd	1H,dd	1H,ddd	1H,dd	1H,dd		2H,m		2H,m	3H,t
	Coupling constants (Hz)											
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	J_{-CH3}				
d	9.83	9.40	9.40	9.62	4.70	2.57	12.40					
e	9.83	9.83	9.41	9.41	5.12	2.56	12.40	7.26				
f, **g**, **h**	10.26	9.41	9.41	9.83	4.71	2.14	12.40	7.26				

4	Chemical shift (δ, ppm) and signal multiplicities												
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	Acetyl–	S-CH_2–		–CH_2–	–CH_3	–Ph
i	4.50	5.03	5.23	5.08	3.73	4.25	4.14	2.01, 2.03, 2.06, 2.08	2.68	1.41	1.59	0.92	
	1H,d	1H,dd	1H,dd	1H,dd	1H,ddd	1H,dd	1H,dd		2H,m	2H,m	2H,m	3H,t	
j	4.50	5.03	5.22	5.08	3.72	4.25	4.14	2.01, 2.03, 2.06, 2.08	2.67	1.60	1.38	1.29	0.89
	1H,d	1H,dd	1H,dd	1H,dd	1H,ddd	1H,dd	1H,dd		2H,m	2H,m	2H,m	4H,m	3H,t
k	4.48	5.03	5.22	5.08	3.70	4.24	4.14	2.01, 2.03, 2.06, 2.08	2.67	1.59	1.36	1.27	0.88
	1H,d	1H,dd	1H,dd	1H,dd	1H,ddd	1H,dd	1H,dd		2H,m	2H,m	2H,m	8H,m	3H,t
l	4.48	5.03	5.22	5.08	3.71	4.25	4.14	2.01, 2.03, 2.06, 2.08	2.67	1.59	1.37	1.26	0.88
	1H,d	1H,dd	1H,dd	1H,dd	1H,ddd	1H,dd	1H,dd		2H,m	2H,m	2H,m	12H,m	3H,t
c,o	4.29	5.07	5.14	5.12	3.59	4.24	4.13	1.99, 2.01, 2.11	3.83, 3.94				7.29
	1H,d	1H,dd	1H,dd	1H,dd	1H,ddd	1H,dd	1H,dd		1H,d, 1H,d				5H

Table 4 (continued)

	Coupling constants (Hz)								
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	J_{-CH3}	$J_{Ph-CH2-}$
i	10.17	9.61	9.61	10.17	4.94	2.47	12.23	7.14	
j	9.89	9.62	9.62	9.62	4.95	2.47	12.36	6.59	
k	9.89	9.61	9.61	10.03	4.94	2.20	12.36	6.87	
l	9.89	9.62	9.62	10.23	4.94	2.47	12.36	6.59	
c, **o**	9.89	9.61	9.61	9.61	5.22	2.47	12.36		12.92

Solvent: $CDCl_3$, TMS standard.
[a]Taken from Ref. [36].

and the product redissolves into the aqueous phase, the use of PTC of adequate amount gives a good yield to raise the reaction efficiency, and shorten the reaction time. For the same reason, lower reaction temperature in the reaction using acylated sugar gives a better result.

2.5. Reaction mechanism

Thioiminium salt tends to disrupt at the C–N bond under acidic conditions and at the C–S bond under neutral and basic conditions. In this reaction system, hydroxide ions make nucleophilic attack on imino carbon of glycosylthioiminium salt to cleave the thioamide C–S bond and glycosylthiolate anions are formed in the aqueous alkaline solution. The thiolate anion in the aqueous phase does not react with alkyl halide in the organic phase. Q^+X^- exerts its catalytic activity of PTC in such a situation. Q^+ of PTC combines with a thiolate anion RS^- in the phase boundary and the resultant oleophilic salt Q^+RS^- is transferred to the organic phase, where Q^+RS^- reacts with alkyl halide $R'X$ to produce thioglycoside RSR'.

Thioglycoside RSR' obtained is always of the β-form. Because glycosyl bromide of starting material is of α-form, this result shows that the reaction of **1** with TA is the second-order nucleophilic substitution SN2, which is similar to the Königs–Knorr reaction [34] and the Michael reaction [35]. And the reaction of Q^+RS^- with $R'X$ such as acetohalogenosugar proceeds in the same way. Since more oleophilic PTC exerts more efficiently as described before, it would be supposed that this reaction step occurs mainly in the organic phase.

Some amount of acetonitrile was detected in the organic phase after the reaction. It would be formed with thiolate anion from the alkali-decomposition of thioiminium salt.

$$RSC(CH_3)=NH_2^+X^- + NaOH \rightarrow RS^-Na^+ + CH_3CN + HX + H_2O$$

In the case of thioiminium salt prepared from acetobromglucose with thiobenzamide instead of TA, benzonitrile was also isolated by the same procedure. In the presence of an adequate amount of NaOH, thioiminium salt is completely decomposed to yield thiolate anion, which is consumed by the subsequent reaction step, and after the reaction the organic phase of the reaction mixture contains only acetonitrile except the desired product. On this account, the final treatment of the reaction mixture is very easy; this is one of the merits of this synthetic method.

2.6. Optimum conditions of synthesis

In order to confirm the optimum conditions for the preparation of thioglycoside, the conditions of formation of thioiminium salt were examined. In the experiments described above, thioiminium salt was prepared from the reaction of TA with acetobromglucose in benzene, and then into the reaction mixture was added alkyl- or glycosylhalide and aqueous NaOH solution.

Table 5
^{13}C-NMR chemical shift data for products **4**

Product **4**	Chemical shift (δ, ppm)											
	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
a	80.5	70.1	73.7	68.1	76.0	62.0						
b, **m**	80.7 (Glucopyranosyl)	70.1	73.8	68.2	76.7	62.1	81.2	67.3	71.8 (Galactopyranosyl)	67.1	74.7	61.3
n	81.3	67.3	71.7	67.1	74.6	61.3						

	Chemical shift (δ, ppm)							
	C-1	C-2	C-3	C-4	C-5	C-6	alkyl	acetyl
d	82.8	69.0	73.8	68.3	75.9	62.1	11.2	20.5×2, 20.6, 20.7, 169.4, 170.1, 170.6
e	83.4	69.8	73.8	68.3	75.8	62.1	14.7, 24.1	20.5, 20.6, 169.3, 170.1, 170.5
f, **g**, **h**	83.5	69.8	73.8	68.3	75.7	62.1	13.2, 22.9, 31.9	20.4, 20.5, 169.2×2, 170.0, 170.4
i	83.4	69.7	73.7	68.2	75.7	62.0	13.4, 21.6, 29.4, 31.5	20.4, 20.5, 169.1, 169.2, 169.9, 170.4
j	83.4	69.8	73.8	68.2	75.7	62.0	13.4, 22.3, 28.2, 29.4, 29.7, 31.1	20.4, 20.5, 169.2×2, 170.0, 170.4
k	83.6	69.9	73.9	68.4	75.9	62.2	14.0, 22.6, 28.8, 29.1×2, 29.6, 30.0, 31.8	20.5, 20.6, 20.7, 169.4×2, 170.2, 170.6
l	83.6	69.9	73.9	68.3	75.8	62.2	14.0, 22.6, 28.7, 29.1, 29.2, 29.5×2, 29.6, 30.0, 31.8	20.5, 20.7, 169.3, 169.4, 170.1, 170.6
c, **o**	81.9	69.8	73.8	68.4	75.8	62.2	(benzyl) 127.4, 128.6, 129.0, 136.8	20.5, 20.6×2, 20.7, 169.4, 170.1, 170.6

Solvent: $CDCl_3$, TMS standard.

Instead, when thioiminium salt was prepared in the melt conditions at 120°C, and subsequently the product was added into benzene containing alkylhalide, the yield was increased. For an example, the yield is 90% when the NaOH concentration is 30 wt.% and PTC is TBPB. Therefore, the method of preparation of iminium salt under the melt conditions is recommended.

The optimum synthetic procedure could be set up as illustrated in Fig. 5 from the results of the above-described examinations of reaction conditions. The results of synthesis of various alkyl- and arylthioglycosides and thiodisaccharides are shown in Table 2. These thioglycosides were prepared in fairly good yields higher than 80%. As described before, the reaction with propyl chloride gave a lower yield (45%). The physical properties of the products are shown in Tables 3–5.

There are two routes for preparing alkyl or arylthioglycosides by this method. One is the reaction of glycosylthioiminium salt with alkyl or aryl halide and another is to react alkyl or arylthioiminium salt with acetylated glycosyl halide. In general, the former affords a better yield than the latter. In the latter route some amount of dialkyl disulfide is formed as a by-product. It was reported that dialkyl disulfide is formed, when the amount of PTC is small or PTC is less functional [42]. In such a ease, alkylthioiminium salt is not transferred to the organic phase, but reacts in the aqueous phase. These results suggest that alkylthiolate anion is hard to transfer to the organic phase than glycosylthiolate anion. Moreover, glycosylthioiminium salt is more reactive than alkylthioiminium salt. As shown in Table 2, thiodisaccharides such as bis(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)sulfide and (2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-galactopyranoside are synthesized in good yields.

This method for preparing thioglycosides has many advantages; that is, this method is carried out as one-pot reaction for a short time and under mild conditions, and the reaction procedure is easily handled, for the product can be obtained by extraction from the organic phase. Moreover, this method is prevented from having the unpleasant smell of thiol, since thiolate anion which is formed in the reaction medium is consumed in situ immediately.

3. Experimental

^{1}H and ^{13}C-NMR spectra were recorded with a JEOL GX-400 instrument using tetramethylsilane as a standard. Optical rotation was determined with a Horiba SEPA-200 polarimeter at 20°C in chloroform. FAB-MS was recorded with a JMS-AX500 instrument using PEG-400 as a matrix.

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