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Palladium(II) Promoted *O*-Glycosylation Involving 1-Thio-2-enosides and 3-Thio-1-enoses

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Abstract: *O*-glycosylation of thioglycosyl donors, 2,3-dideoxy-hex-1-thio-2-enopyranosides,1,2-dideoxy-hex-3-thio-1-nopyranoses and 2-pyridyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside was achieved by use of a Pd(II) activator which was prepared from bis(acetonitrile)dichloropalladium(II)($Pd(CH_3CN)_2Cl_2$) and silver triflate (AgOTf).

The structure of the repeating unit of the capsular polysaccharide of *Streptococcus pneumoniae* type 19F bacteria has been elucidated[1-3] as *N*-acetyl-β-D-mannosamine-containing trisaccharide:

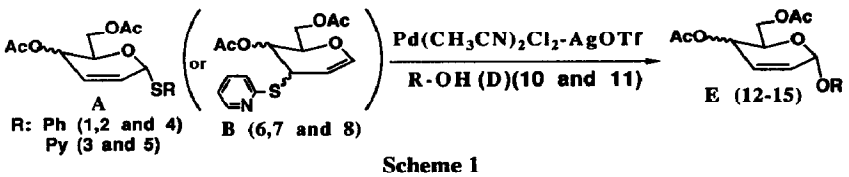
→4)-β-D-Man*p*NAc-(1→4)-α-D-Glc*p*-(1→2)-α-L-Rha*p*-(1-PO_4→

while the group-specifc antigens of *Neisseria meningitidis* serogroups A and X polysaccharides have been characterized as *N*-acetyl-α-D-mannosamine-containing homopolymer[4]:

→4)-α-D-Man*p*NAc-(1-PO_4→

We have been interested in the chemical construction of oligosaccharides containing *N*-acetyl-D-mannosamine as potential group-specific antigens. Recently, we reported the regio- and stereoselective synthesis of D-mannosamine employing a [3,3]-sigmatropic rearrangement as a key reaction from 2-enopyranoside having a 4-trichloroacetimidate group[5]. Our interest in this work stemmed from the synthesis of 2-enopyranoside-containing α-linked disaccharides which can be converted to mannosamine-containing disaccharides by use of [3,3]-sigmatropic rearrangement[6]. For this purpose, we examined a new glycosylation involving 1-thio-2-enosides **A** and 3-thio-1-enoses **B**, prepared from 3,4,6-tri-*O*-acetyl-D-glucal or 3,4,6-tri-*O*-acetyl-D-galactal and mercapto compounds, respectively. Modification of reactivity of stable 1-thioglycosides to afford reactive glycosyl donors has been achieved by use of many methods[7]. We have already reported the intramolecular glycosylation reaction employing a novel activation of 2-mercaptotetrazolyl-*N*-acetylneuraminic acid, i.e., a combination of $Pd(CH_3CN)_2Cl_2$ (II) and AgOTf, whose efficiency was shown in the case of the formation of 1,7-anhydro *N*- acetylneuraminic acid in cerumen of the wet type[8].

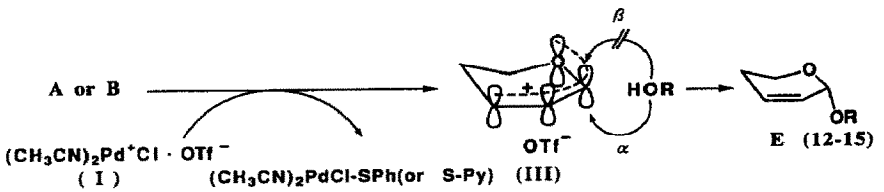
In this communication, we wish to describe a new and efficient system for the activation of 1-thio-2-enosides (**A**=**1**,**2**,**3**,**4** and **5**) or 3-thio-1-enoses (**B**=**6**,**7** and **8**), $Pd(CH_3CN)_2Cl_2$ - AgOTf, which gives 2-enosides (**E**= **12**,**13**,**14** and **15**), showing that this glycosylation is highly α-selective (Scheme 1). The reaction of 1-thio-2-enosides **1**[9],**2**[9],**3**[10],**4**[11] and **5**[12], 3-thio-1-enoses **6**[10],**7**[10] and **8**[12] and 1-thioglucoside **9** as glycosyl donor and alcohols **10** and **11** as glycosyl acceptors was examined. As summarized in Table 1, all reactions proceeded at -20 ℃ ~ room temperature by the combination of $Pd(CH_3CN)_2Cl_2$ and AgOTf (1:1~1:2 ratios) and 4Å molecular



Scheme 1

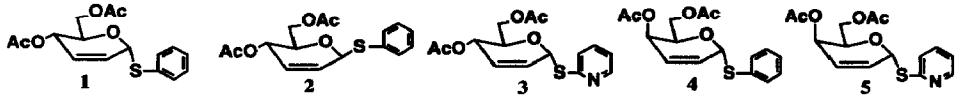
sieves, and disaccharides **12**[13], **13**[14], **14**[15], **15**[16],**16** and **17** were obtained in good yields. A typical glycosylation procedure is described for the reaction of **4** with **11** (run 10) ; to a stirred mixture of $Pd(CH_3CN)_2Cl_2$ (260 mg, 1 mmol) and molecular sieves 4Å (1 g) in CH_2Cl_2 (5 ml) was added AgOTf (257 mg, 1 mmol) under argon atomosphere at room temperature. After stirring for 10 min, a solution of alcohol **11**(232 mg, 0.5 mmol) in CH_2Cl_2 (1 ml) and thioglycosyl donor **4** (322 mg, 1 mmol) in CH_2Cl_2 (1 ml) was added to the reaction mixture. The mixture was stirred at room temperature for 90 min; then the reaction mixture was neutralized with triethylamine, and insoluble materials were removed by filtration. The filtrate was evaporated and the residue was purified by preparative TLC(AcOEt : *n*-hexane=1:4) on silica gel to give **15α**[16](288 mg, 85%), $[\alpha]_D^{25}$ +62.4° (*c* 1, $CHCl_3$). The stereochemistry at C_1 in compounds **12,13,14** and **15** was assigned by means of a NOE study of the H-1 and H-5 signals in the ^{1}H-NMR spectrum[17]. A significant NOE of 2.8%, 6.9-8.8% and 6.0% was observed in compounds **12β,13β** and **14β**, respectively. On the other hand, the NOE experiments of the corresponding **12α,13α,14α** and **15α** showed no evidence of any enhancement. In the glycosylations involving both the 1-thio-2-enosides **A** and 3-thio-2-enoses **B**, the formation of α-anomer was predominant (runs 1-12), while the stereochemistry of the anomeric site was not markedly affected by the anomeric configuration of the donors (runs 2 and 3). *S*-Phenyl and *S*-pyridyl groups as *S*-glycosyl donors did not make any difference in either the anomeric ratio or yields in these glycosylations (runs 1-12). Interestingly, SN2' glycosylations of 3-thiopyridyl -1-enoses **6,7** and **8** also proceeded smoothly, and α compounds were preferentially obtained in good yields (runs 5,6,9 and 12). Further, a general glycosylation involving 1-thioglucoside **9** proceeded by use of this activating system in good yield (runs 13-15). The glycosylation of **9** in an acetonitrile containing dichloromethane solution exhibited a marked β-favored solvent effect compared with a dichloromethane solution (runs 13 and 14). On modification of the ratio of $Pd(CH_3CN)_2Cl_2$ and AgOTf, although the use of $Pd(CH_3CN)_2Cl_2$ and AgOTf in 1:1 ratio provided sufficient high reactivity for glycosylation of the 1-thio-2-enosides **A** or 3-thio-1-enoses **B** (runs 1-12), glycosylation of 1-thioglucoside **9** was faster in 1:2 ratio of $Pd(CH_3CN)_2Cl_2$ and AgOTf than in the 1:1 ratio (runs 13 and 14). These results imply the involvement of different active species. Further, this means that affinity of thioglycoside with the activator may be enhanced by use of a di-triflate complex ($Pd(CH_3CN)_2Cl_2$: AgOTf=1:2) (II) more than by a mono-triflate complex ($Pd(CH_3CN)_2Cl_2$: AgOTf=1:1) (I)[18]. These results may be attributed to the high reactivity of the oxyallylic system of 1-thio-2-enosides **A** or 3-thio-1-enoses **B** than 1-thioglucoside **9** for glycosylation. Further, α-selective glycosylation of 1-thio-2-enosides **A** or 3-thio-1-enoses **B** may occur exclusively on delocalized allyloxy carbonium ions (III) resulting in higher yield of the thermodynamically favored α-anomer due to the anomeric effect [19](Scheme 2).

In conclusion, the reagent system, $Pd(CH_3CN)_2Cl_2$ - AgOTf, may exert highly α-selective effect on the activation of 1-thio-2-enosides **A** and 3-thio-1-enoses **B**. The present method opens up new areas for the potential exploitation of the general glycosylation reaction.

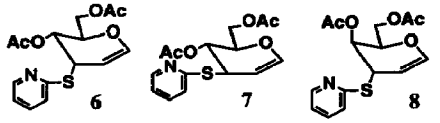


Scheme 2

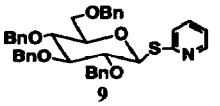
A. 1-thio-2-enoside,



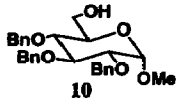
B. 3-thio-1-enose,



C. 1-thio-glucoside,



D. acceptor,



E. glycoside,

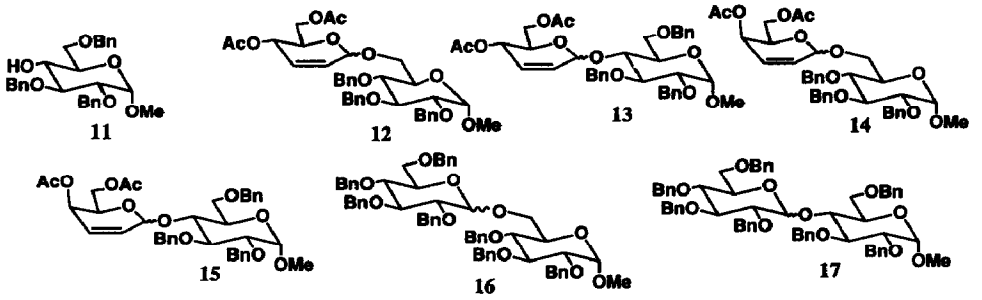


Table 1. Results of glycosylation reactions.

Run[a)]	Thioglycoside	Acceptor	Molar ratio[b)]	Solvent	Temp.(℃)/time	Product[c)]	Yield(%)[d)]	α : β
1	3	10	2:1:2:2	CH_2Cl_2	r.t./43min.	12	94	83:17[e)]
2	1	11	2:1:2:2	CH_2Cl_2	29	13	66	95:5[e)]
3	2	11	3:1:2:2	CH_2Cl_2	28	13	62	98:2[f)]
4	3	11	2:1:2:2	CH_2Cl_2	25	13	68	96:4[f)]
5	6	11	2:1:2:2	CH_2Cl_2	28	13	72	94:6[f)]
6	7	11	2:1:2:2	CH_2Cl_2	90	13	62	90:10[f)]
7	4	10	2:1:2:2	CH_2Cl_2	45	14	81	97:3[f)]
8	5	10	2:1:2:2	CH_2Cl_2	20	14	55	g)
9	8	10	2:1:2:2	CH_2Cl_2	60	14	81	94:6[f)]
10	4	11	2:1:2:2	CH_2Cl_2	90	15	85	g)
11	5	11	4:1:2:2	CH_2Cl_2	17hr	15	87	g)
12	8	11	1:1:1:1	CH_2Cl_2	120	15	68	g)
13	9	10	2:1:2:2	CH_2Cl_2	25	16	80	60:40[e)]
14	9	10	2:1:2:4	CH_2Cl_2	5	16	93	65:35[e)]
15	9	10	2:1:3:6	CH_2Cl_2/CH_3CN[h)]	0℃/20	16	88	13:87[e)]
16	9	11	2:1:3:6	CH_2Cl_2/CH_3CN[h)]	0℃/25	17	93	42:58[e)]

a) All reactions were carried out under argon atmosphere in the presence of $Pd(CH_3CN)_2Cl_2$, AgOTf and molecularsieves 4Å.
b) Corresponds to thioglycoside : acceptor : $Pd(CH_3CN)_2Cl_2$: AgOTf . c) All new compounds were characterized by IR, ^{1}H-NMR (300 and 400 Mz), high resolution mass spectral analysis and elemental analysis: Details will be given in forthcoming full paper. d) Yields were based on acceptors. e) Determined by ^{1}H-NMR (300 and 400 Mz). f) Determined by individual isomer separation. g) Only α-products were detected. h) Activator was prepared in CH_2Cl_2 solution.

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10) Compounds **3**,**6** and **7** were synthesized by the reaction of 3,4,6-tri-*O*-acetyl-**D**-glucal with 1.1 equiv. of 2-mercaptopyridine in the presence of 1.1 equv. of $SnCl_4$ in CH_2Cl_2 for 20 min at room temperature.(yield; **3**, 25%, **6**, 37%, **7**, 29%). On the other hand, the reaction of 3,4,6-tri-*O*-acetyl-D-glucal with 1.5equiv. of 2-mercaptopyridine in the presence of 1.5 equv. of $SnCl_4$ gave only compound **3** (69 %) in CH_2Cl_2 for 3 hr at -20 ℃. **3**; $[\alpha]_D^{26}$ +364.3° (*c* 0.46, $CHCl_3$), ^{1}H-NMR($CDCl_3$,300Mz) 4.28(C_5-H, dt, *J* =5.0, 8.5 Hz, 1H), 5.42(C_4-H, ddt, *J*=2.0, 2.5, 8.5 Hz, 1H), 5.90(C_3-H, ddd, *J*=1.5, 2.0, 10.0 Hz, 1H), 6.09 (C_2-H, ddd, *J*=2.0, 3.0, 10.0, 1H), 6.61(C_1-H, ddd, *J*=1.5, 2.5, 3.0 Hz, 1H). **6**; $[\alpha]_D^{24}$ +135.2° (*c* 0.63, $CHCl_3$), ^{1}H-NMR ($CDCl_3$,300Mz) 4.30(C_5-H, ddd, *J*=2.0, 5.0, 10.0 Hz, 1H), 4.92(C_2-H, t, *J*=6.0, 1H), 5.10(C_3-H, ddd, *J*=1.0, 4.5, 6.0 Hz, 1H), 5.38(C_4-H, dd, *J*=4.5, 10.0 Hz, 1H), 6.43(C_1-H, dd,*J*=1.0, 6.0 Hz, 1H). **7**; $[\alpha]_D^{24}$+39.7° (*c* 1.55, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 300Mz) 4.20(C_5-H, ddd, *J*=2.5, 6.5, 7.5 Hz,1H), 4.77(C_3-H, ddd, *J*=2.0, 3.0, 7.0 Hz, 1H), 4.92(C_2-H, dd, *J*=3.0, 6.0 Hz, 1H), 5.32(C_4-H, dd, *J*=7.0, 7.5 Hz, 1H), 6.43(C_1-H, dd, *J*=2.0, 6.0 Hz, 1H).
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12) Compounds **5** and **8** were synthesized by the reaction of 3,4,6-tri-*O*-acetyl-**D**-galactal with 1.2 equiv. of 2-mercaptopyridine in the presence of 1.5 equv. of $SnCl_4$ in CH_2Cl_2 at 0 ℃~room temperature for 24 hr. (yield; **5**, 15%, **8**, 65%, starting material, 6%). On the other hand, the reaction of 3,4,6-tri-*O*-acetyl-**D**-galactal with 1.1equiv.of 2-mercaptopyridine in the presence of 1.0 equiv. of $SnCl_4$ gave 24% of **5**, a trace of **8** and 63% of starting material in CH_2Cl_2 for 5 hr at -20 ℃, while compound **8** was obtained in 59% yield as a single product by use of 1.5 equiv. of 2-mercaptopyridine and 2.0 equiv. of $SnCl_4$ at room temperature. **5**; 15%,$[\alpha]_D^{23}$+64.7° (*c* 0.17, $CHCl_3$), ^{1}H-NMR($CDCl_3$,300Mz) 4.53(C_5-H, ddd, *J*=2.5, 6.0, 7.0 Hz, 1H), 5.13 (C_4-H, dd, *J*=2.5, 5.0 Hz, 1H), 6.14(C_3-H, ddd, *J*=1.5, 5.0, 10.0 Hz, 1H), 6.24(C_2-H, dd, *J*=3.5, 10.0 Hz, 1H), 6.70(C_1-H, dd, *J*=1.5, 3.5 Hz, 1H). **8**; 65%,$[\alpha]_D^{25}$+54.5° (*c* 1.02, $CHCl_3$), ^{1}H-NMR($CDCl_3$,300Mz) 4.42(C_3-H, br.dd, *J*=1.0, 1.5, 5.0 Hz, 1H), 4.44(C_5-H, ddd, *J*<1, *J*=4.5, 7.5 Hz, 1H), 4.86(C_2-H, ddd, *J*=2.0, 5.0, 6.0 Hz, 1H), 5.22(C_4-H, ddd, *J*<1, *J*=1.5, 2.0 Hz, 1H), 6.60(C_1-H, dd, *J*=1.0, 6.0 Hz, 1H).
13) **1 2α**; $[\alpha]_D^{24}$+52.8° (*c* 0.33, $CHCl_3$), ^{1}H-NMR($CDCl_3$,400Mz) 4.02(C_5-H, ddd, *J*=2.0, 5.0, 9.0 Hz, 1H), 5.11(C_1-H, t, *J*=1.0 Hz, 1H), 5.30(C_4-H, dt, *J*=1.0, 9.0 Hz, 1H), 5.84(C_2-H, dt, *J*=1.0, 10.0 Hz, 1H), 5.87(C_3-H,dt, *J*=1.0, 10.0 Hz, 1H). **1 2β**; $[\alpha]_D^{23}$+78.2 ° (*c* 0.55, $CHCl_3$), ^{1}H-NMR($CDCl_3$,400Mz) 3.96(C_5-H, dt, *J*=4.0, 6.0 Hz, 1H), 5.07(C_1-H, q,*J*=1.5 Hz, 1H), 5.18 (C_4-H, ddt, *J*=1.5, 3.5, 6.0 Hz, 1H), 5.84(C_2-H, dt, *J*=1.5, 10.5 Hz, 1H), 5.94(C_3-H, ddd, *J*=1.5, 3.5, 10.5 Hz, 1H).
14) **1 3α**; $[\alpha]_D^{26}$+53.3° (*c* 0.9, $CHCl_3$), ^{1}H-NMR($CDCl_3$,400Mz) 3.76(C_5-H, ddd, *J*=3.0, 5.0, 9.5 Hz, 1H), 5.21(C_4-H, dd, *J*=2.5, 9.5 Hz, 1H), 5.47(C_1-H, dd, *J*=2.5, 3.0 Hz, 1H), 5.51(C_3-H, ddd, *J*=2.5, 3.0, 10.0Hz, 1H), 5.77(C_2-H, dd, *J*=2.5, 10.0 Hz, 1H). **1 3β**; $[\alpha]_D^{24}$+59.0° (*c* 0.19, $CHCl_3$), ^{1}H-NMR($CDCl_3$,300Mz) 3.80(C_5-H, ddd, *J*=4.0, 5.5, 7.5 Hz, 1H), 5.20(C_4-H, ddt, *J*=1.5, 2.5, 7.5 Hz,1H), 5.32(C_1-H, q, *J*=1.5, 1H), 5.65(C_2-H, dt, *J*=1.5, 10.0 Hz, 1H), 5.77(C_3-H, ddd, *J*=1.5, 2.5, 10.0 Hz, 1H).
15) **1 4α**; $[\alpha]_D^{23}$-63.8° (*c* 0.21, $CHCl_3$), ^{1}H-NMR($CDCl_3$,300Mz) 4.29(C_5-H, ddd, *J*=2.5, 5.5, 7.5 Hz, 1H), 5.00(C_4-H, dd, *J*=2.5, 5.0 Hz, 1H), 5.15(C_1-H, d,*J*=2.5 Hz, 1H), 6.04(C_2-H, dd, *J*=2.5, 10.0 Hz, 1H), 6.10(C_3-H, dd, *J*=5.0, 10.0 Hz, 1H), **1 4β**; $[\alpha]_D^{24}$-56.6° (c 0.35, $CHCl_3$), ^{1}H-NMR($CDCl_3$,400Mz) 4.00(C_5-H, dt, *J*=3.0, 6.5 Hz, 1H), 5.06(C_4-H, dddd, *J*=1.0, 2.0, 3.0, 4.5 Hz, 1H), 5.10(C_1-H, dt, *J*=1.0, 2.0 Hz, 1H), 5.91(C_2-H, dt, *J*=1.0, 10.5 Hz, 1H), 6.07(C_3-H, ddd, *J*=1.0, 4.5, 10.5 Hz, 1H).
16) **1 5α**; $[\alpha]_D^{25}$+62.4° (*c*1, $CHCl_3$), ^{1}H-NMR($CDCl_3$,400Mz) 4.06-4.10(C_5-H, m, 1H), 4.91(C_4-H, br.d, *J*=5.5 Hz, 1H), 5.50 (C_1-H, dd, *J*=1.0, 3.0 Hz, 1H), 5.69(C_2-H, dd, *J*=3.0, 10.0 Hz, 1H), 6.00(C_3-H, ddd, *J*=1.0, 5.5, 10.0 Hz, 1H).
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