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The use of 2-*O*-propagyloxycarbonyl protecting group in the selective formation of 1,2-*trans*-glycosidic linkage

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Abstract—The effect of *N*-phenylcarbamoyl (Car) and propagyloxycarbonyl (Poc) protecting groups at the O-2 position of donors was examined. The usefulness of Poc group in the selective formation of 1,2-*trans*-glycosidic linkage is shown by comparing the reactivity of donors having Car or acyl (Bz) groups.

Simple, efficient, and selective synthesis of oligosaccharides has been an ongoing challenge in carbohydrate chemistry.[1] In our previous paper,[2] we presented the construction of four types (*cis*-α, *trans*-α, *cis*-β, *trans*-β) of glycosidic linkages between readily available glucosyl donors and primary alcohol groups of carbohydrates that involves the participation of a neighboring *N*-phenylcarbamoyl (Car) group and the S_N2 displacement reaction at C-2. The Car group at O-2 is particularly important for the construction of the four glycosidic linkage types. Because of the difficulty in the deprotection process,[3] the Car group, which is stable from pH 1 to 12, has not been widely employed for the protection of hydroxyl groups. However, our research group has developed a novel deprotection procedure that does not affect other protecting groups such as acyl, silyl, methoxymethyl, benzylidene acetal, and isopropylidene acetal groups.[4] Consequently, the Car group has become a useful and unique tool in the synthesis of complex oligosaccharides that requires delicate chemical differentiation of various protecting groups under mild conditions.[5,6] Unfortunately, the Car group did not per- form to our satisfaction for stereo-controlled trans-glycosidations with secondary alcohols of carbohydrates. Herein, we report on the use of a propagyloxycarbonyl (Poc)[7] protection group in an improved strategy in oligosaccharide synthesis. The Poc group was first reported by Chandrasekaran et al.[7] for the selective protection of a hydroxyl function in carbohydrates—the group can be removed under neutral conditions using tetrathiomolybdate (MoS_4^{2-}) in CH_3CN at rt, which does not affect benzylidene nor benzylidene acetal, benzyl ether, acetyl and levulinoyl ester, and benzyl carbonate groups. Furthermore, the Poc protection group is stable under acidic and glycosidation conditions.[3] In this Letter, we describe the effects of the Car and Poc groups in comparison to the commonly used 2-*O*-benzoyl (Bz) in the stereo-controlled trans-glycosidation between donors and the primary and secondary alcohols of carbohydrates.

Donors **1** and **2** were synthesized from ethyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside via ethyl 4,6-*O*-benzylidene-3-*O*-benzyl-2-*O*-methoxymethyl-1-thio-β-D-glucopyranoside;[2] donors **10** and **11** were obtained using phenyl 4,6-*O*-benzylidene-3-*O*-benzoyl-1-thio-β-D-gluco-pyranoside. Acceptors **3**, **4**, **12**, and **13** were synthesized in the usual manner. The trans-glycosidation reactions between the donor and acceptor were carried out as follows: a mixture of donor (1.2 equiv), acceptor (1.0 equiv), and MS 4A in CH_2Cl_2 was stirred for 30 min under argon. To the cooled, stirred mixture (−20 °C) was added dry *N*-iodosccinimide (1.5 equiv), followed by the dropwise addition of trifluoromethanesulfonic acid (0.3 equiv) in CH_2Cl_2, and the reaction mixture was maintained at −20 °C. Upon disappearance of the starting acceptor (monitored by TLC), the mixture was neutralized using Et_3N, diluted with $CHCl_3$, filtered, and successively washed with aqueous $NaHCO_3$, water (twice), and then brine. The organic layer was dried with anhydrous $MgSO_4$, and evaporated to give the corresponding disaccharide, which was purified using silica

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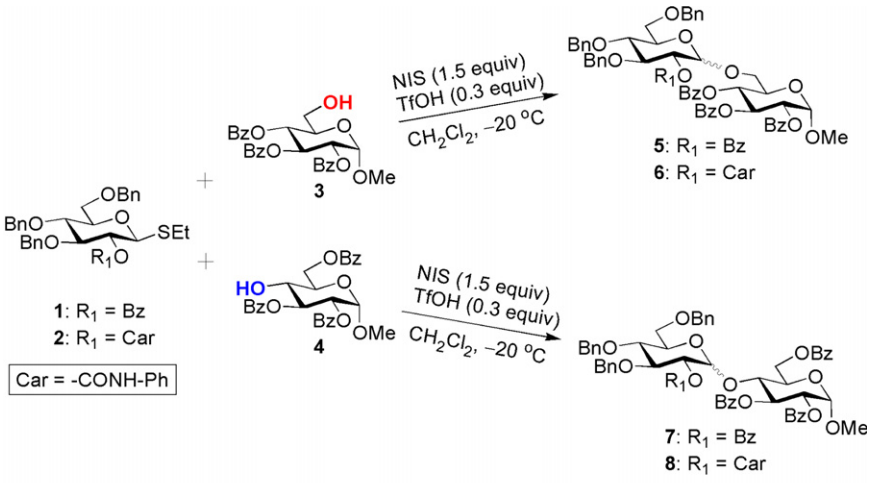
Table 1. Glycosidation of 2-*O*-Bz-and Car-protected thioglucosyl donors **1**, **2** with acceptors **5**–**8**



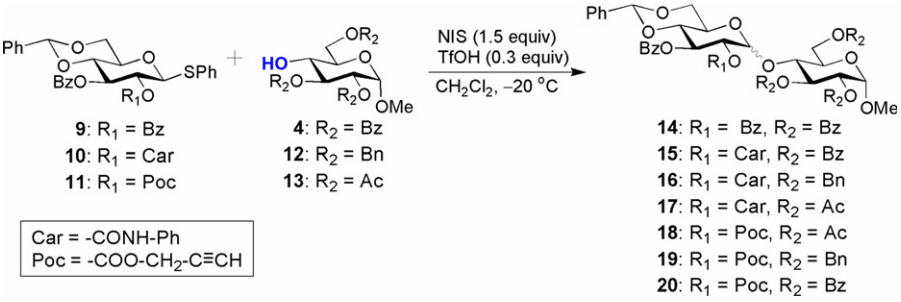
Entry	Donor (R_1)	Acceptor	Product	α/β[a]	Yield[b] (%)
1	1 (Bz)	**3** (primary OH)	5	1/8	98
2	2 (Car)	**3**	6	1/8	93
3	1 (Bz)	**4** (secondary OH)	7	1/8	80
4	2 (Car)	**4**	8	No reaction	

[a] Determined by ^{1}H NMR spectrum.
[b] Isolated yield.

gel column chromatography. Based on ^{1}H NMR spectroscopy, the structures were confirmed using the purified products, whereas the ratios of the α- and β-linkages were determined using the crude products (prior to purification).

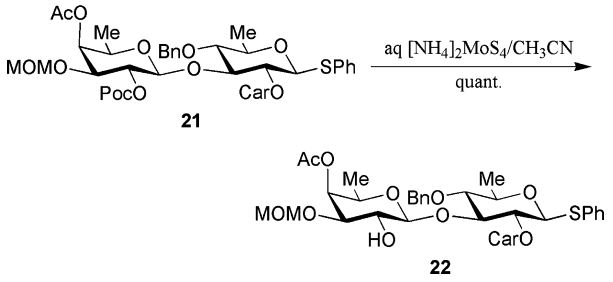
As shown in Table 1, the reactions between donors **1** or **2** with primary alcoholic acceptor **3** (entries 1 and 2) gave the corresponding β-linked disaccharides **5** and **6** exclusively in good yields. The reaction of donor **1** with secondary alcohol acceptor **4** (entry 3) gave the expected neighboring group participation product **7** in a moderate yield. Because the reaction between donor **2** and secondary alcohol acceptor **4** (entry 4) did not afford the expected disaccharide **8**, additional studies were carried out to elucidate the effects of the donors' O-2 group and the acceptors' protecting group using donors **9** and **10** with acceptors **4**, **12**, and **13** (entries 5–8). As shown in Table 2, the reaction between **9** and **4** (entry 5) gave the corresponding disaccharide **14** (α/β = 1:12) in 81%

Table 2. Glycosidation of 2-*O*-Bz, Car-, and Poc-protected thioglucosyl donors **9**–**11** with acceptors **4**, **12**, **13**



Entry	Donor (R_1)	Acceptor (R_2)	Product	α/β[a]	Yield[b] (%)
5	**9** (Bz)	**4** (Bz)	**14**	1/12	81
6	**10** (Car)	**4** (Bz)	**15**	No reaction	
7	**10** (Car)	**12** (Bn)	**16**	1/6	13
8	**10** (Car)	**13** (Ac)	**17**	1/6	63
9	**11** (Poc)	**4** (Bz)	**18**	1/9	51
10	**11** (Poc)	**12** (Bn)	**19**	1/9	73
11	**11** (Poc)	**13** (Ac)	**20**	1/10	78

[a] Determined by ^{1}H NMR spectrum.
[b] Isolated yield.



Scheme 1. Selective deprotection of Poc group in disaccharide **21** using tetrathiomolybdate.

yield. In contrast, due to the bulkiness of the acceptors' protecting group, the reactions of **10** with the acceptors (entries 6–8) resulted in lower yields; in the case of acceptor **4**, the coupling reaction was not observed. Because such behavior has not been observed for the coupling reactions between 2-*O*-Bz donors and carbohydrate secondary alcohol acceptors, it can be suggested that the Car group adopts a rigid conformation and/or may appear more bulkier than expected. This is in accordance with the observation that the solubilities of the crystalline Car-protected sugar derivatives decrease with the number of the protecting groups. In contrast to the Car derivatives, the Poc compounds are less hindered in terms of neighboring group participation for the glycosidations. As shown in entries 9–11, the yields and β-selectivities are better than those of Car, but worse than those of Bz.

In summary, we have compared the effects of the donors' 2-*O*-Car and -Poc groups in β-selective glycosidations with the alcohol group of sugars. Our results demonstrate the usefulness of the 2-*O*-Poc derivatives as universal glucosyl donors in the construction of disaccharides,[2] and for synthesizing naturally occurring bioactive products, such as the partially acylated β-linked oligosaccharide esters.[6]

Additionally, we have examined the selective deprotection of Poc group of disaccharide **21**, protected Ac, Car, MOM, and Bn, by using tetrathiomolybdate (MoS_4^{2-}) in CH_3CN at rt[7] in order to confirm (Scheme 1). Under these conditions, Poc group is successfully cleaved without affecting other protecting groups.[8]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.083.

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