

Tetrahedron Letters 40 (1999) 6423-6426

TETRAHEDRON LETTERS

Formation of the 1,2,6-orthoester of mannose and its utilization in the glycosylation reaction

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Received 30 April 1999; accepted 9 June 1999

Abstract

The synthesis of mannose 1,2,6-orthoester and its utilization in the glycosylation reaction are described. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: orthoesters; glycosidation; pyridinium salts; anhydride.

The use of 1,2-O-alkyl orthoesters in synthetic carbohydrate chemistry has been well documented; for example, ring opening with various catalysts, differentiating the hydroxyl groups, and the glycosylation reaction.¹⁻⁴ As for the glycosylation reaction, it is known that the control of selectivity in glycosylation and ester rearrangement has been the major problem.¹

In our recent study, protection of the primary alcohol of mannose 1,2-orthoester $(1)^{5.6}$ using TBDPSCl and imidazole in DMF failed to give the desired 6-O-silyl product, instead the 1,2,6-orthoester (2) was obtained in good yield. Compound 2 was considered to be formed as a result of the nucleophilic attack by the 6-OH group of 1. Compound 2, however, could be a good glycosylation reagent after protection of the remaining hydroxyl groups, because ring opening of the orthoester could be achieved with 2-OH and 6-OH groups being differentiated concurrently (see Schemes 1 and 2).



Scheme 1.

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Scheme 2.

 Table 1

 Formation of mannose 1,2,6-orthoester

| entry | Reagent (eq) | Solvent | Additive | R | Time | Y | Yield | |
|-------|---|----------|----------------|-----------------|------|-----|-------|--|
| 1 | TBDPSCI (1.2) | DMF | imidazole | allyl | 16 h | 3 a | 88% | |
| 2 | BF ₃ •OEt ₂ (1.2) | pyridine | | aliyi | 24 h | 3 a | 56% | |
| 3 | PPTS (1.2) | pyridine | | aliyi | 12 h | 3 b | 78% | |
| 4 | Py•TfOH (1.2) | pyridine | | allyl | 8 h | 3 a | 89% | |
| 5 | Py•TfOH (0.2) | pyridine | | allyl | 72 h | 3 a | 72%* | |
| 6 | Py•HCI (1.2) | pyridine | | CH3 | 8 h | 3 a | 85% | |
| 7 | imidazole•HCl (1.2 eq) | DMF | imidazole | CH ₃ | 8 h | 3 b | 87% | |
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Triacetate of the starting material was obtained in 12% yield.

In order to obtain compounds 3, several conditions were examined (Table 1).⁷ It was found that $BF_3 \cdot OEt_2$ and pyridinium or imidazolium salts of protonic acids gave the orthoesters $(3a,b)^6$ in good yields. The best result was obtained when 1.2 equivalents of pyridinium trifluoromethanesulfonate was used [89%, after in situ acetylation of the reaction mixture (entry 3)]. The reaction was shown to be catalytic although it proceeded slowly and the starting material was recovered after 3 days (entry 5). Protection of the 2-OH group of 2 can be carried out without intermediate purification. As shown in entries 2 and 6, the solvent was removed after the reaction and the crude residue was subjected to the benzylation reaction using NaH/BnCl in DMF to give 3b.

We then utilized the obtained 1,2,6-orthoester in oligosaccharide synthesis. Previous work on the ring opening of 1,2-orthoesters provides access to 1-OH derivatives,² 1-halogenated derivatives³ and glycosides. In addition, Ogawa et al. reported^{3,4} that the reaction of mannose *O*-alkyl 1,2-orthoesters in the presence of TMSOTf in dichloroethane gave the corresponding rearranged glycosides. Our 1,2,6-orthoester system may have an advantage in glycosidic bond formation reaction as C-1, O-2, and O-6 are protected in such way that a nucleophilic substitution reaction in a stereo- and regiospecific manner should occur to yield the desired glycoside with O-2 and O-6 already differentiated for further reactions.

Initially, TMSOTf, $BF_3 \cdot OEt_2$ and *p*-TsOH were examined as activators for the reaction of compound **3b** with octanol (10 equiv.) to give the expected mannoside (4) (Scheme 3).⁸ The glycosylation reactions were shown to be essentially catalytic; however, silylation of the alcohol was observed when TMSOTf was used as an activator, which resulted in a longer reaction time. In the case that *p*-TsOH was used as an activator, formation of a polar material was observed leading to a lower yield compared to the other two conditions. The reaction with HgBr₂ resulted in the recovery of staring material even when an excess amount of reagent was used.

When reactions of **3b** under the same condition without an external nucleophile were examined (Scheme 4), the 1,6-anhydro-mannose derivative was obtained. Although we did not examine the details of the polymerization reactions,⁹ the intramolecular reaction must have dominated to form 9^6 which might undergo further polymerization.¹⁰

Disaccharide $(6)^6$ was obtained in the same manner using the glucose derivative (5) as a nucleophile (Scheme 5). When 1.5 equivalents of 5 were used, reaction of 3b with the 6-hydroxyl group of the mannose residue of the formed disaccharide 6 took place to yield trisaccharide 8 (14%) in addition to



the desired 6 (43%). The formation of the trisaccharide was reduced by using an excess amount of the acceptor (5). Alternatively, *t*-butyldimethylsilyltrifluoromethanesulfonate (TBDMSOTf) could be used as an activator in order to trap the generated hydroxy group to form the silyl ether 7. The best result for the formation of disaccharide was when $BF_3 \cdot OEt_2$ was used (75%).



*Excess amount of acceptor was recovered.

^bReaction proceeded very slowly at 0°C.

Scheme 5.

In conclusion, we have found a new family of 1,2,6-orthoesters which were easily obtained from the corresponding 1,2-orthoesters and demonstrated their usefulness as glycosylation reagents.

Acknowledgements

We are grateful to Dr. Yoshitaka Nagai, director of the Glycobiology Research Group and Dr. Tomoya Ogawa, coordinator of the group, Frontier Research Program of the Institute of Physical and Chemical Research (RIKEN) for their continued support and encouragement of our research. This research was supported in part by the Science and Technology Agency of the Japanese Government.

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- 6. Selected physical data: compound 2; ¹H NMR (CDCl₃) δ 5.77 (1H, d, J=5.9, H-1), 4.42 (1H, dd, J=2.3, 5.9, H-2), 4.04 (1H, d, J=13.0, H-6), 4.02 (1H, m, H-5), 3.97 (1H, dd, J=1.0, 7.6, H-4), 3.84 (1H, dd, J=3.0, 13.0, H-6), 3.63 (1H, dd, J=1.0, 7.6, H-4), 3.84 (1H, dd, J=3.0, 13.0, H-6), 3.63 (1H, dd, J=1.0, 7.6, H-4), 3.84 (1H, dd, J=3.0, 13.0, H-6), 3.63 (1H, dd, J=1.0, 7.6, H-4), 3.84 (1H, dd, J=3.0, 13.0, H-6), 3.63 (1H, dd, J=1.0, 7.6, H-4), 3.84 (1H, dd, J=3.0, 13.0, H-6), 3.63 (1H, dd, J=1.0, 7.6, H-4), 3.84 (1H, dd, J=3.0, 13.0, H-6), 3.63 (1H, dd, J=1.0, 7.6, H-4), 3.84 (1H, dd, J=3.0, 13.0, H-6), 3.63 (1H, dd, J=3.0, 13.0, H-6), 3.64 (1H, dd, J=3.0, H-6), 3.64 (1H, d J=2.3, 7.6, H-3), 1.65 (3H, s, CH₃). ¹³C NMR (CDCl₃) δ 123.31 (ortho), 100.13 (C-1), 80.54 (C-5), 76.52 (C-2), 71.79 (C-3), 70.37 (C-4), 69.88 (C-6), 23.99 (CH₃). Note: pure compound 2 was obtained by deacetylation of compound 3a because of difficulty in isolation. Compound 3a; ¹H NMR (CDCl₃) & 5.81 (1H, d, J=5.9, H-1), 5.15 (1H, dd, J=8.2, H-4), 5.10 (1H, dd, J=2.0, 8.2, H-3), 4.54 (1H, dd, J=2.0, 5.9, H-2), 4.12 (1H, dd, J=3.3, 12.9, H-6), 4.03 (1H, dd, J=1.0, 12.9, H-6), 4.01 (1H, dd, J=1.0, 3.3, H-5), 2.15, 2.09, 1.68 (3H×3, s, CH₃). ¹³C NMR (CDCl₃) δ 170.80, 170.53 (C=O), 123.43 (ortho), 99.17 (C-1), 78.54 (C-5), 73.40 (C-2), 70.82 (C-4), 70.08 (C-3), 68.91 (C-6), 23.63, 21.04, 20.88 (CH₃). Compound 3b; ¹H NMR (CDCl₃) δ 7.20–7.10 (10H, m, aromatic), 5.67 (1H, d, J=5.6, H-1), 4.44 (1H, dd, J=2.3, 5.9, H-2), 4.42 (1H, d, J=1.3, 7.6, H-4), 4.05 (1H, dd, J=1.3, 3.6, H-5), 4.03 (1H, dd, J=11.3, 7.6, H-4), 3.98 (1H, d, J=12.9, H-6), 3.65 (1H, dd, J=2.3, 7.6, H-3), 3.50 (1H, dd, J=3.6, 12.9, H-6), 1.64 (3H, s, CH₃). ¹³C NMR (CDCl₃) δ 137.97–127.57 (aromatic), 122.93 (ortho), 99.30 (C-1), 79.07 (C-5), 77.11 (C-4), 77.11 (C-3), 73.80 (C-2), 69.71 (C-6), 23.67 (CH₃). Compound 9; ¹H NMR (CDCl₃) δ 7.39–7.26 (10H, m, aromatic), 5.44 (1H, s, H-1), 4.83 (1H, dd, J=2.0, 5.6, H-2), 4.55 (1H, m, H-5), 4.23 (1H, dd, J=1.0, 7.3, H-6), 4.04 (1H, dd, J=1.7, 5.6, H-3), 3.45 (1H, bt, J=1.7), 2.12 (3H, s, CH₃). ¹³C NMR (CDCl₃) δ 170.24 (C=O), 138.37-127.22 (aromatic), 99.35 (C-1), 76.43 (C-4), 74.39 (C-5), 74.20 (C-3), 69.63 (C-2), 64.98 (C-6), 20.86 (CH₃). Compound 6; ¹H NMR (CDCl₃) δ 7.30-7.10 (15H, m, aromatic), 5.43 (1H, dd, J=1.7, 3.3 Hz, M-2), 4.84 (1H, bs, M-1), 4.36 (1H, d, J=7.9, G-1), 3.94 (1H, dd, J=3.3, 9.2, M-3), 3.95-3.60 (7H, m, octyl-CH2, M-3, G-3, G-6, M-4, M-5, M-6), 3.50-3.40 (4H, m, G-2, G-4, G-5, octyl-CH2), 2.13 (3H, s, CH3), 1.78-1.24 (12H, broad), 0.87 (3H, bt). ¹³C NMR (CDCl₃) δ 170.13 (C=O), 138.40–127.62 (aromatic), 103.52 (G-1), 97.81 (M-1), 84.71 (G-3), 82.21 (G-2), 77.65 (G-4), 77.61 (G-3), 73.87 (G-5, M-4), 71.77 (M-5), 70.12 (octyl-CH), 68.30 (M-2), 66.11 (G-6), 61.89 (M-6), 31.79, 29.69, 29.38, 29.20, 26.15, 22.61 (octyl-CH₂), 21.01 (acetyl-CH₃), 14.05 (octyl-CH₃).
- 7. Representative procedure: Pyridinium trifluoromethanesulfonate (104.8 mg, 0.457 mmol) was added to a solution of 1 (R=allyl, 100 mg, 0.381 mmol) dissolved in pyr. (3 mL), and the mixture was stirred at room temperature for 8 h. Ac₂O (0.1 mL) was added and the mixture was stirred for 8 h. The reaction mixture was extracted with EtOAc. The organic layer was dried (MgSO₄) and concentrated. Purification by column chromatography (hexane:EtOAc=5:1) afforded **3a** (98 mg, 89%).
- 8. Representative procedure: To a solution of 3b (25 mg, 0.065 mmol) and 1-octanol (102 μL, 0.65 mmol) in dichloroethane (1 mL), BF₃·OEt₂ (1.6 mL, 0.013 mmol) was added slowly at room temperature. The mixture was stirred for 1.5 h at the same temperature, then extracted with EtOAc. The organic layer was dried (MgSO₄), concentrated and purified on a column of silica gel using hexane:EtOAc (3:1) as eluent. Note: 1,6-anhydro compound 9 was not observed probably due to the amount of acceptor used in the reaction (10 equivalents).
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