Pergamon

Tetrahedron Letters, Vol. 35, No. 23, pp. 3979-3982, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0719-E

One-Pot Sequential Glycosylation: A New Method for the Synthesis of Oligosaccharides

Haruo Yamada, Takeo Harada, Hiroshi Miyazaki† and Takashi Takahashi*

Department of Chemical Engineering, Tokyo Institute of Technology
Meguro, Tokyo 152, JAPAN.

Abstract : Sequential one-pot glycosylations among various glycosidic donors (glycosyl bromide, glycosyl trichloroimidate, glycosyl fluoride), a β-thiophenyl glycoside derivative and a α-methyl glycoside derivative have been attempted to give the corresponding trisaccharides.

Synthesis of the oligosaccharides has made considerable progress as a result of the development of glycosylation procedures[1] and sophisticated protective group strategies. However, only a few methodologies directed to the synthesis of oligosaccharides have been developed, such as the solid-phase synthesis,[2] the one-step synthesis,[3] the enzyme-assisted synthesis,[4] the two-stage activation procedure,[5] and silicon-connected glycosylation[6]. Here we describe the one-pot glycosylation that allows us to construct two glycosidic linkages sequentially in one-pot operations.

Concept of One-Pot Glycosylation

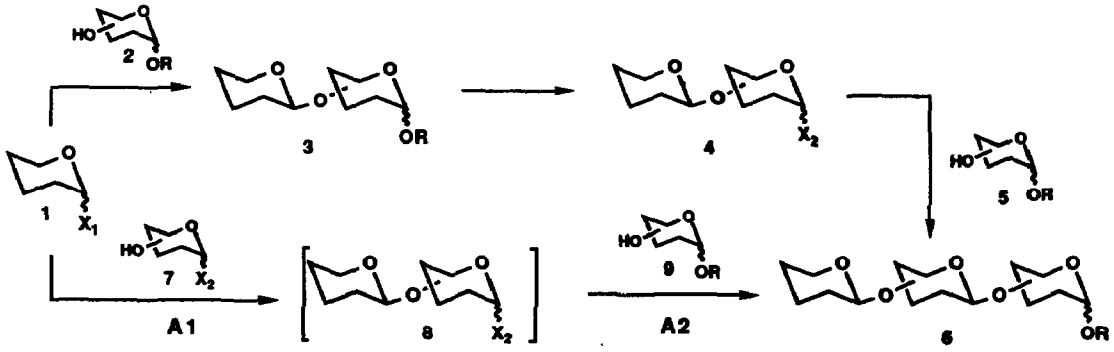


Figure-1

A general approach to the synthesis of the trisaccharide **6** involves the glycosylation of the glycosyl donor **1** with the glycosyl acceptor **2**, followed by the second glycosylation of **4** with **5**. Under such a process, selective removal of the

anomeric protecting group in **3** and conversion of the resulting hydroxyl group into X_2 have to be carried out to activate the sugar **3** as glycosyl donor **4**. The one-pot approach comes from the idea that if the difference in the reactivity between glycosyl donor **1** (X_1) and acceptor **7** (X_2) (figure-1) is large enough to be distinguished by the activator **A1**, the glycosyl donor **1** can be selectively activated in the presence of **A1** to give the disaccharide **8**. Successive activation of X_2 in **8** in the presence of **A2**, followed by coupling with the glycosyl acceptor **9** will provide the trisaccharide **6** in one-pot without the laborious transformation. In our method for the one-pot glycosylation, initial coupling of the glycosyl bromide **1** (X_1=Br) with thioglycoside **7** (X_2=SPh) in the presence of the activator **A1** (AgOTf)[7] would give the disaccharide **8**. While the anomeric phenylthio groups in **7** and **8** are stable to the AgOTf activation, addition of both the second activator **A2** (NIS)[8] and glycosyl acceptor **9** to the reaction mixture promotes the selective activation of the glycosyl donor **8** to give the trisaccharide **6** in one-pot. In this reaction, TfOH generated at first stage is effectively used for the second glycosylation (TfOH/NIS). Reaction of glycosyl fluoride[9] (X_1=F) or glycosyl trichloroimidate[10] (X_1=OC(NH)CCl$_3$) with excess BF_3·OEt_2, followed by addition of both thioglycoside (X_2=SPh) and NIS also allows us to achieve another one-pot glycosylation.

First, the reactions among glycosyl bromide **10**, thioglycoside **11**, and glycosyl acceptors **12**, **14**, **16** were examined and the results are summarized in Table 1. One-pot sequential glycosylation was carried out as follows. To a solution of **10**[11] (1.2 eq.), **11** (1.0 eq.) and molecular sieves (MS) 4A in CH_2Cl_2 was added 3-5 eq. of AgOTf in toluene in a few portions at room temperature, and the mixture was stirred for 30 min. To the solution, 6-hydroxyglucose **12** in CH_2Cl_2 and 10 eq. of NIS were added and the mixture was stirred for 1 h. The reaction was quenched with Et_3N and purified by column chromatography on silica gel afforded the corresponding triglucose **13** in 84% yield.[12] It is worthy of note that addition of base such as collidine in the first glycosylation step leads the second glycosylation into failure, probably because the presence of pyridinium salt interferes with the activation of the anomeric phenylthio group in **11**. In a similar way, one-pot glycosylation using **10**, **11** and 3-hydroxyglucose **14** was also proceeded to give trisaccharide **15** in 79% yield. (run 2) One-pot coupling of the less reactive 4-hydroxy derivative **16** was also carried out to give the trisaccharide **17** in 44% yield. (run 3)

Next, one-pot glycosylations of the glycosyl trichloroimidate and glycosyl fluoride were examined. We have found that the thiophenyl glycoside can be effectively activated in the presence of BF_3·OEt_2 and NIS to construct glycosidic linkage.[13] Thus, this method was applied to the one-pot glycosylations of the glycosyl trichloroimidate **18** and the glycosyl fluoride **20**. Treatment of the glycosyl trichloroimidate **18** (1 eq.), phenylthio glycoside **11** (0.9 eq.), and MS 4A with 10 eq. of BF_3·OEt_2 in CH_2Cl_2 at -45 °C gave the disaccharide, which was subjected to the second glycosylation with **12** (1.2 eq.) and NIS (5 eq.) at room temperature to afford the triglucose **19** in 62%

overall yield. (run 4) Excess $BF_3 \cdot OEt_2$ was used for the activation of the anomeric carbons at both stages of the glycosylation. Similarly, use of the glycosyl fluoride **20** as first glycosyl donor with $BF_3 \cdot OEt_2$ provided the another combination of one-pot glycosylation. To a solution of **20** (1.5 eq), **11** (1.0 eq.) and MS 4A in CH_2Cl_2 was added $BF_3 \cdot OEt_2$ (10 eq.) at 0 °C and the mixture was stirred for 30 min. at room temperature. The mixture were treated with **12** (1.0 eq.) and NIS (2 eq.) to give the triglucose **19** in 76 % overall yield. (run 5)

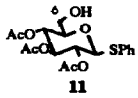
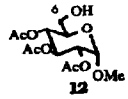
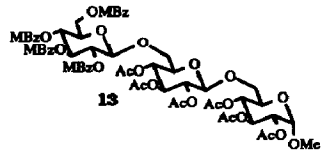
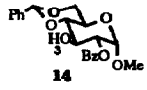
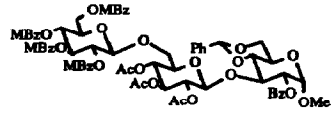
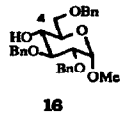
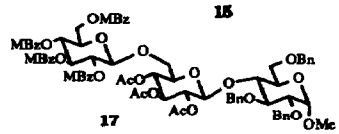
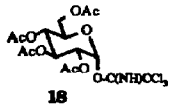
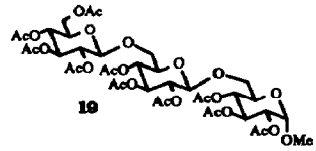
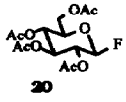
run	A	B	C	Yield	Products
1	 **10**	 **11**	 **12**	84%	 **13**
2	**10**	**11**	 **14**	79%	 **15**
3	**10**	**11**	 **16**	44%	 **17**
4	 **18**	**11**	**12**	62%	 **19**
5	 **20**	**11**	**12**	76%	**19**

Table-1 One-pot glycosylation of glycosyl bromide, glycosyl imidate and glycosyl fluoride as glycosyl donors
MBz : p-methylbenzoate

The ability to control the reactivity of the glycosyl donors suggests the novel strategy for the synthesis of oligosaccharides in one-pot operation. The one pot glycosylation should be widely applicable for the synthesis of various oligosaccharides and the extension of this one-pot concept could possibly form the basis for an automated carbohydrate synthesizer.

Acknowledgments

This work was supported by Grant-in-Aid for Scientific Research on Priority Area Nos 04220212 from the Ministry of Education, Science and Culture, Japan.

References and notes

† Visiting scientist from Nippon Steel Corporation.

1) a) H. Paulsen, *Angew. Chem. Int. Ed. Engl.*, **1982**, 21, 155. b) R. R. Schmidt, Angew. *Chem. Int. Ed. Engl.*, **1986**, 25, 212.

2) Danishefsky, S. J., *Science*, **1993**, 260, 1307.

3) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.*, **1993**, 115, 1580.

4) a) Ito, Y.; Paulson, J. C. *J. Am. Chem. Soc.*, **1993**, 115, 1603. b) Liu, K. K.-C.; Danishefsky, S. J. *ibid.*, **1993**, 115, 4933. c) Ichikawa, Y.; Lin, Y.-C.; Dumas, D. P.; Shen, G.-J.; Garcia-Junceds, E.; Williams, M. A.; Bayer, R.; Ketcham, C.; Walker, L. E.; Paulson, J. C.; Wong, C.-H. *J. Am. Chem. Soc.*, **1992**, 114, 9283. d) Ichikawa, Y.; Shen, G.-J.; Wong, C.-H. *J. Am. Chem. Soc.*, **1991**, 113, 4698.

5) a) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.*, **1984**, 106, 4189. b) Nicolaou, K. C.; Randall, J. L.; Furst, G. T. *ibid.*, **1985**, 107, 5556.

6) Stork, G.; Kim, G. *J. Am. Chem. Soc.*, **1992**, 114, 1087.

7) a) Igarashi, K. *Adv. Carbohydr. Chem. Biochem.*, **1977**, 34, 243. b) Spijker, N. M.; Boeckel, C. A. A. *Angew. Chem. Int. Ed. Engl.*, **1991**, 30, 180.

8) a) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.*, **1983**, 105, 2430. b) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.*, **1990**, 31, 1331.

9) a) Hayashi, M.; Hashimoto, S.; Noyori, R. *Chem. Lett.*, **1984**, 1747. b) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.*, **1984**, 49, 3063. c) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.*, **1984**, 25, 1379. d) Kuntz, H.; Sager, W. *Helv. Chim. Acta*, **1990**, 31, 6863. e) Wessel, H. P.; Ruiz, N. *J. Carbohydr. Chem.*, **1991**, 10, 901.

10) Schmidt, R. R. *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 212.

11) The one-pot glycosylation of α-bromo tetraacetylglucose with **11** has resulted in the formation of the ortho-ester at the first stage of the reaction. To avoid this side reaction, all hydroxyl groups on glycosyl bromide **10** were protected as p-methylbenzoates.

12) Stepwise glycosylation is also examined as follows. First glycosylation of the glycosyl bromide **10** with **11** and column purification were carried out to give the disaccharide (86%), which are subjected to second glycosylation with **12** under NIS/trifluoromethanesulfonic acid to give trisaccharide in 65% yield. Overall yield of the stepwise reaction is 56%. The one-pot glycosylation have resulted in a saving time and labor.

13) Coupling of peracetyl derivative of β-phenylthio glucose with 6-hydroxy glucose **12** was mediated by $BF_3 \cdot OEt_2$ (3 eq.) and NIS (4 eq.) at room temperature to afford the disaccharide in 72% yield. The details of the glycosylation will be published elsewhere.

(*Received in Japan* 28 *December* 1993; *accepted* 22 *March* 1994)