Tetrahedron Letters, Vol.32, No.48, pp 7065-7068, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A New Glycosylation Reaction Based on a "Remote Activation Concept": Glycosyl 2-Pyridinecarboxylate as a Novel Glycosyl Donor

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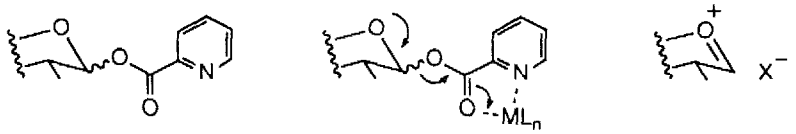
Key Words: glycosylation; glycosyl 2-pyridinecarboxyl; glycosyl donor; stannous triflate; cupric triflate.

Abstract: *A novel glycosyl donor, glycosyl 2-pyridinecarboxylate, was designed based on a variation of the Remote Activation Concept. Glycosylation using glycosyl 2-pyridinecarboxylate could be effected with copper (II) triflate in Et_2O or tin (II) triflate in CH_3CN to give α-glucosides or β-glucosides, respectively.*

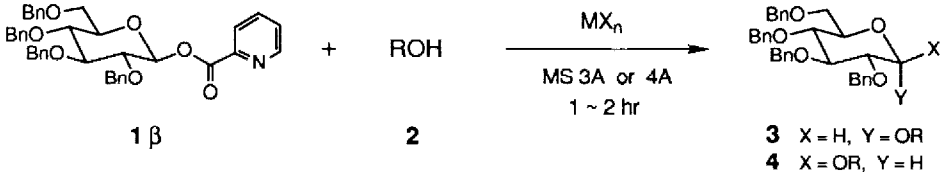
The introductions of glycosyl imidate,[1] and of glycosyl fluoride[2] in the early 1980's have brought a great advance in the field of carbohydrate chemistry, and these derivatives have been widely employed as potential glycosyl donors in the synthesis of physiologically interesting oligosaccharides.[3] However, the development of more efficient and selective glycosylation methods[4,5] by the devising of novel glycosyl donors is certainly still required, especially because of growing interest in the oligosaccharide and glycoconjugate fields.[6]

Among the various glycosyl derivatives glycosyl esters are the most readily accessible, and frequently serve as useful precursors for potential glycosyl donors such as glycosyl halides.[7] However, until now it has not been possible to achieve efficient glycosylation using a glycosyl ester directly as the glycosyl donor[8] probably because activation of such glycosyl esters usually requires rather acidic conditions. We now report a new and selective glycosylation method using glycosyl 2-pyridinecarboxylate as a novel glycosyl donor based on a variation of the *Remote Activation Concept*.[9] We expected that a stable glycosyl 2-pyridinecarboxylate (A) could be activated through coordination to a Lewis acid (B) resulting in generation of a reactive oxonium species (C).

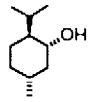
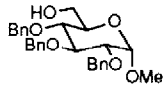
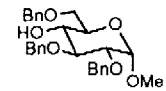
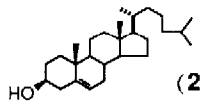
Scheme 1



2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl 2-pyridinecarboxylate (**1**) was easily prepared by esterification of the anomeric hydroxyl group of the sugar under the usual conditions with commercially available picolynoyl chloride in the presence of triethylamine (CH_2Cl_2, 0°C, 90%, α:β=1:3.4). Recrystallization of the epimeric mixture from AcOEt-hexane gave the β-isomer **1β**[10] as white crystals, and the following experiments were carried out using **1β** unless otherwise stated.



1β **2** **3** X = H, Y = OR; **4** X = OR, Y = H

run[a]	ROH (**2**) (1.1 eq.)	activator (2.2 ~ 2.4 eq.)	solvent	**3** + **4** yield[b] (%)	**3** : **4**
1	 (**2a**)	$Cu(OTf)_2$	Et_2O/CH_2Cl_2 (5/1)	91	84 : 16[c]
2		$Sn(OTf)_2$	CH_3CN	82	17 : 83[c]
3	 (**2b**)	$Cu(OTf)_2$	Et_2O	67	71 : 29[c]
4		$Sn(OTf)_2$	CH_3CN	89	19 : 81[c]
5	 (**2c**)	$Cu(OTf)_2$	Et_2O	97	83 : 17[c]
6		$Sn(OTf)_2$	CH_3CN/CH_2Cl_2 (6/1)	77	9 : 91[c]
7	 (**2d**)	$Cu(OTf)_2$	Et_2O/CH_2Cl_2 (5/1)	70	92 : 8[d]
8		$Sn(OTf)_2$	CH_3CN/CH_2Cl_2 (5/1)	70	17 : 83[d]
9	 (**2e**)	$Cu(OTf)_2$	Et_2O/CH_2Cl_2 (5/1)	88	81 : 19[c]
10		$Sn(OTf)_2$	CH_3CN/CH_2Cl_2 (1.7/1)	92	13 : 87[c]

a: Reaction temperature; -50°C for $Cu(OTf)_2$; -50~0°C for $Sn(OTf)_2$. b: Isolated yields. c: YMC-pack 60A SIL (Yamazen Co., Ltd. 5-06). Eluent: 0.3% *i*-PrOH in hexane for run 1~4; 0.8% *i*-PrOH in hexane for run 5~6; 0.2% *i*-PrOH in hexane for run 9~10. d: SSC-ODS (Senshu Kagaku Co., Ltd. 171). Eluent H_2O/MeOH= 1/20.

The reaction of **1β** and *l*-menthol[11] (**2a**) as a model glycosyl acceptor was then examined. As expected, the compound **1β**, while being stable, was activated even by mild Lewis acids such as $CuCl_2$ and $SnCl_2$. After a systematic survey of various metal salts, $Cu(OTf)_2$ and $Sn(OTf)_2$ were found to be more effective than other reagents such as BF_3 etherate and TMSOTf. Particularly, high α-selectivity and β-selectivity were observed in the case of the $Cu(OTf)_2$-Et_2O/CH_2Cl_2 system (run 1) and the $Sn(OTf)_2$-CH_3CN system (run 2), respectively.

When a 5:1 epimeric mixture of **1**α:**1**β was used, *l*-menthyl glycosides **3a** and **4a** were obtained in almost the same ratio as when pure **1**β was used. It was also found that no reaction occurred when the isomeric glycosyl 4-pyridinecarboxylate was treated with $Cu(OTf)_2$ and *l*-menthol even at *room temperature*. These results clearly suggest that the generation of an oxonium species (C) is achieved through the formation of a five-membered chelation complex. Initial activation thus takes place at a remote site from the anomeric carbon, and we propose that the present methodology is based on the *Remote Activation Concept*.[9]

The reaction of **1**β with other glycosyl acceptors using $Cu(OTf)_2$ and $Sn(OTf)_2$ was also examined, and these results are summarized in Table.[14] Characteristic features of the present methodology are as follows: (1) The glycosyl donor can be prepared very easily and is stable. No detectable decomposition of **1** was observed even after several months at room temperature. (2) The activators required are non-toxic, and other additives such as silver perchlorate are not necessary. (3) The mildness of the reaction conditions is noteworthy, and it was confirmed that the relatively unstable β-isomer **4a** did not undergo any decomposition nor epimerization to the thermodynamically more stable **3a** under the reaction conditions. (4) α-Glucosides and β-glucosides can selectively be obtained from the same glycosyl donor in good to excellent yields by the proper choice of metal salt and solvent.

In summary we have demonstrated that glycosyl 2-pyridinecarboxylate can serve as a potential glycosyl donor in carbohydrate chemistry, and we are currently applying this methodology to the synthesis of other oligosaccharides. Furthermore, from a conceptual point of view, the introduction of a bidentate ligand as a leaving group as well as the variation of the *Remote Activation Concept* we have introduced here should be useful in the development of more efficient and selective glycosylation methods.

Acknowledgement

This work was financially supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (Dynamic Aspects of Natural Product Chemistry) from the Ministry of Education, Science, and Culture, Japan. We also thank Central Glass Co., Ltd. for a generous donation of tin (II) triflate.

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9. The term "*Remote Activation*" was originally introduced by Hanessian in relation to Hg(II)-promoted glycosylation with pyridylthio glycoside. Hg(II) probably coordinates to the sulfur atom next to the anomeric carbon in this process. Consequently, we use the term *Remote Activation* in a rather different sense: Hanessian, S.; Bacquet, C.; Lehong, N. *Carbohydr. Res.* **1980**, *80*, C17-C22.
10. All new compounds described here gave satisfactory elemental and spectroscopic (IR, NMR, and MS) analysis. Some typical data are as follows. ^{1}H-NMR ($CDCl_3$, 400MHz) data are shown only for anomeric proton for each compound: **1β**; m.p. 119~120°C, $[\alpha]_D^{23}$ -13.8°(*c* 1.00, $CHCl_3$), ^{1}H-NMR δ 5.94 (d, *J*=7.7Hz). **3a**; $[\alpha]_D^{22}$ +37.9°(*c* 4.12, $CHCl_3$), ^{1}H-NMR δ 5.01 (d, *J*=5.0Hz). **4a**; m.p. 82~83°C, $[\alpha]_D^{23}$ -17.2°(*c* 1.05, $CHCl_3$), ^{1}H-NMR δ 4.47 (d, *J*=7.7Hz). **3b**[12]; $[\alpha]_D^{23}$ +41.5°(*c* 0.61, $CHCl_3$), ^{1}H-NMR δ 5.13 (d, *J*=3.7Hz). **4b**[12]; m.p. 93.0~96.5°C, $[\alpha]_D^{23}$ +19.9°(*c* 1.60, $CHCl_3$). **3c**[13]; m.p. 101.0°C, $[\alpha]_D^{23}$ +57.1°(*c* 1.97, $CHCl_3$), ^{1}H-NMR δ 4.97 (d, *J*=2.9Hz). **4c**[13]; m.p. 133~135°C, $[\alpha]_D^{23}$ +18.6°(*c* 0.49, $CHCl_3$), ^{1}H-NMR δ 4.34 (d, *J*=7.7Hz). **3d**[13]; $[\alpha]_D^{23}$ +47.5°(*c* 0.71, $CHCl_3$), ^{1}H-NMR δ 5.69 (d, *J*=3.7Hz). **4d**[12]; m.p. 87~88°C, $[\alpha]_D^{23}$ +24.2°(*c* 2.23, $CHCl_3$). **3e**[1]; m.p. 142~143°C, $[\alpha]_D^{23}$ +50.4°(*c* 0.72, $CHCl_3$), ^{1}H-NMR δ 4.93 (d, *J*=3.7Hz). **4e**[1]; m.p. 124~125°C, $[\alpha]_D^{23}$ +0.3°(*c* 2.48, $CHCl_3$), ^{1}H-NMR δ 4.50 (d, *J*=7.7Hz).
11. The merit of employing *l*-menthol as a model glycosyl acceptor is that the ratio of **3a** and **4a** can readily be determined by HPLC analysis.
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14. All reactions were carried out in the presence of molecular sieves (3A or 4A depending on the solvent used) in order to prevent competitive hydrolysis caused by a trace amount of water present in the reaction mixture.

(Received in Japan 16 August 1991)