Trityl Salt Catalyzed Stereoselective Glycosylation of Alcohols with 1-Hydroxyribofuranose

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(Received October 20, 1995)

In the presence of a catalytic amount of several trityl salts, 2,3,5-tri-*O*-benzyl-D-ribofuranose smoothly reacted with alcohols to give various β-ribofuranosides in high yields with high stereoselectivity while reversed stereoselectivity was observed in the coexistence of lithium perchlolate.

Development of a new and efficient method for the synthesis of glycosides becomes more and more important with rapid progress of carbohydrate chemistry.[1] In general, glycosylation reaction involves: i) initial introduction of a suitable leaving group at anomeric position, and ii) its activation by a suitable activator to generate an oxocarbenium ion intermediate which in turn is attacked by a nucleophile such as alcohol to form a glycoside.

Glycosylation reaction starting just from 1-hydroxy sugars is a more convenient and desirable method than the conventional one since a step of introducing a leaving group at anomeric carbon is eliminated. But methods of this concept have not yet been satisfactorily developed because of the following two reasons caused by 1-hydroxy sugar: poor reactivity as a glycosyl donor but strong susceptibility to self coupling reaction.

For this purpose, several new attempts using a cationic activator or a Lewis acid catalyst were recently reported,[2] though these reactions still needed *in situ* generation of second active species by some additional reagents. Then, a development of new and simple conditions starting just from 1-hydroxy sugars and free alcohols was studied. In this communication, we would like to report on the useful method for glycosylation of 1-hydroxyribofuranose with several alcohols giving the corresponding *O*-ribofuranosides in high yields with high stereoselectivities by using several trityl salt catalysts.[3,4]

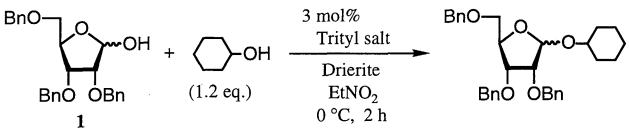
First, the reaction of 2,3,5-tri-*O*-benzyl-D-ribofuranose **1** with cyclohexanol was examined using a catalytic amount of several trityl salts in the coexistence of Drierite, a dehydrating agent (Table 1). The reaction proceeded at 0 °C to yield the corresponding *O*-ribofuranoside with high β-selectivities by using these trityl salts except when using trityl tetrafluoroborate. Of trityl salts examined, trityl tetrakis(pentafluorophenyl)borate [5] was chosen as catalyst because of the easiness in handling as it is moisture- and air-resistant.

Next, the effect of solvents was examined (Table 2). A remarkable solvent effect on yield and stereoselectivity was observed when nitroalkane was used. When 20 vol% of nitroethane was mixed with non-polar solvent such as dichloromethane, the similar effect was observed as in the case of using nitroalkane alone.

Several examples of the present glycosylation reaction are demonstrated in Table 3. In every case, the desired β-D-ribofuranosides were prepared in high yields with high stereoselectivities.

Finally, in order to obtain reversed stereoselectivity, lithium perchlorate, the additive already reported from our laboratory,[3a] was added in the above reaction. As a result, this addition of 150 mol% of lithium perchlorate yielded almost complete reversed stereoselectivity when cyclohexanol was used as a nucleophile (Scheme 1).

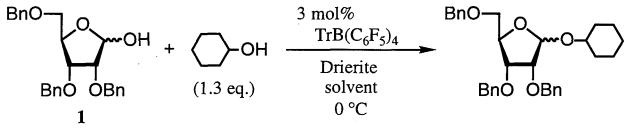
Table 1. Effect of Trityl Salts



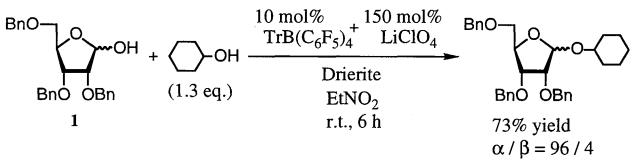
Trityl salt	Yield / %	α / β
$TrBF_4$	4	32 / 68
$TrClO_4$	53 (87)[b]	21 / 79 (4 / 96)[b]
$TrSbCl_6$	91	4 / 96
$MMTrSbCl_6$[a]	trace (73)[c]	- (5 / 95)[c]
$TrB(C_6F_5)_4$	90	5 / 95

[a]MM = Monomethoxy. [b]10mol% catalyst was used.
[c]The reaction was carried out at room temperture.

Table 2. Effect of Solvent

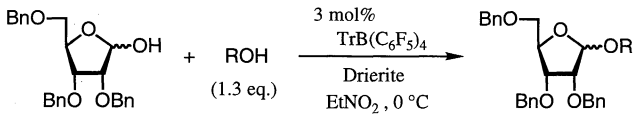


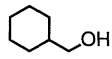
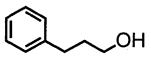
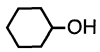
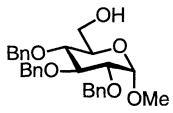
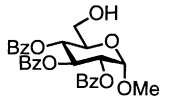
Solvent	Time / h	Yield / %	α / β
Et_2O	6	94	7 / 93
Toluene	6	87	4 / 96
CH_2Cl_2	6	49	9 / 91
CH_3CN	6	18	28 / 72
$MeNO_2$	2	79	5 / 95
$EtNO_2$	2	91	4 / 96
$^nPrNO_2$	2	89	7 / 93
CH_2Cl_2 - $EtNO_2$ (4 : 1)	6	90	6 / 94



Scheme 1. Reversal of Stereoselectivity

Table 3. Synthesis of β-D-Ribofuranosides



ROH	Time / h	Yield / %	α / β
$CH_3(CH_2)_7OH$	2	94	4 / 96
	2	90	5 / 95
	2	90	7 / 93
	2	91 (95)[a]	4 / 96
3β-Cholestan-1-ol[b]	6	94	7 / 93
	6	90	9 / 91
	6	92	4 / 96

[a]Alcohol (1.5 eq.) was used. [b]Solvent: CH_2Cl_2 / $EtNO_2$ = 4 / 1

The typical experimental procedure is as follows: to a stirred suspension of trityl tetrakis(pentafluorophenyl)borate (5.5 mg, 6 μmol) and Drierite (450 mg) in nitroethane (2 ml) was successively added a nitroethane (1 ml) solution of cyclohexanol (26.0 mg, 0.26 mmol) and a nitroethane (1 ml) solution of 2,3,5-tri-*O*-benzyl-D-ribofuranose (84.1 mg, 0.2 mmol) at 0 °C. The reaction mixture was stirred for 2 hours at 0 °C, then it was quenched by adding saturated aqueous sodium hydrogen carbonate. By usual work-up and purification with preparative TLC (silica gel), 1-*O*-cyclohexyl-2,3,5-tri-*O*-benzyl-D-ribofuranose (91.5 mg, 91% yield) was isolated. The ratio of anomer was determined by HPLC analysis.

Thus, the synthesis of various β-ribofuranosides starting just from 1-hydroxy sugar and several alcohols is now successfully carried out in high yields with high stereoselectivity by using a catalytic amount of several trityl salts while by adding lithium perchlorate to the above reaction mixture achieved reversed stereoselectivity.

A development of another useful glycosylation reaction using trityl tetrakis(pentafluorophenyl)borate is now in progress.

The present research is partially supported by Grant-in-Aids for Scientific Research from Ministry of Education, Science and Culture.

We are grateful to Dr. Masaaki Yamabe, Asahi Glass Co., Ltd., for the generous gift of trityl tetrakis(pentafluorophenyl) borate.

References and Notes

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