C-Arylglycosylation of Unprotected Free Sugar

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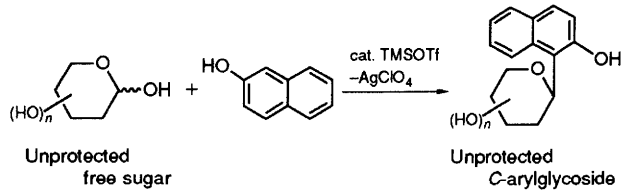
Highly regio- and stereo-selective *C*-arylglycosylations of the protected free sugars **1–4**, the unprotected methyl glycosides **6–9** and the unprotected free sugars **10** and **11** with 2-naphthol **5** are effectively realized by the combined use of TMSOTf–$AgClO_4$ (TMSOTf = trimethylsilyloxytrifluoromethanesulfonate) as a catalytic activator.

Simplification of a glycosyl donor, as well as development of new functional groups at the anomeric position and their activating reagents, is of great advantage to the efficiency of the glycosylation reaction. From this concept, we have recently announced a mild and efficient method for β-stereoselective *C*-arylglycosylations[1,2] of *O*-protected methyl and acetyl glycosides with 2-naphthol by using a novel catalyst system, TMSOTf–$AgClO_4$ (TMSOTf = trimethylsilyloxytrifluoromethanesulfonate) as the activator. However, unprotected free (1-OH) sugar is undoubtedly much simpler than those glycosyl donors. In our previous observations, it was found that a TMSOTf–$AgClO_4$ catalyst system cleanly cleaved *O*-alkylglycosidic bonds and then smoothly formed *C*-arylglycosidic bonds in the presence of naphthol. So, we expected that if the TMSOTf–$AgClO_4$ combined activator was not deactivated by any hydroxy group of the glycosyl donor and could activate the 1-OH group effectively, *C*-arylglycosylation of unprotected free sugar would be achieved (Scheme 1). In this communication, we report that the protected free sugars **1–4**, the unprotected methyl glycosides **6–9** and the unprotected free sugars **10** and **11** were effectively coupled with 2-naphthol **5** with high regio- and stereo-control in the presence of a catalytic amount of TMSOTf-$AgClO_4$ as the activator.

In our first preliminary experiments, we have examined the *C*-arylglycosylations of the protected free sugars **1–4** with 2-naphthol **5** to assay the ability of the TMSOTf–$AgClO_4$ catalyst to activate the 1-OH group of the sugar. Four types of sugar, which mainly occurred as glycosidic components in representative *C*-arylglycoside antibiotics,[3] were selected for the present glycosylation studies as shown in Fig. 1. All reactions were carried out by using TMSOTf–$AgClO_4$ (1 : 1) in CH_2Cl_2. The results summarized in Table 1 as entries 1–4 showed that these glycosylation reactions proceeded smoothly under mild conditions to afford the corresponding protected aryl β-*C*-glycosides **14–17**† with high stereoselectivity in high



Scheme 1

† All new compounds were purified by silica gel column chromatography and were fully characterized by spectroscopic means.

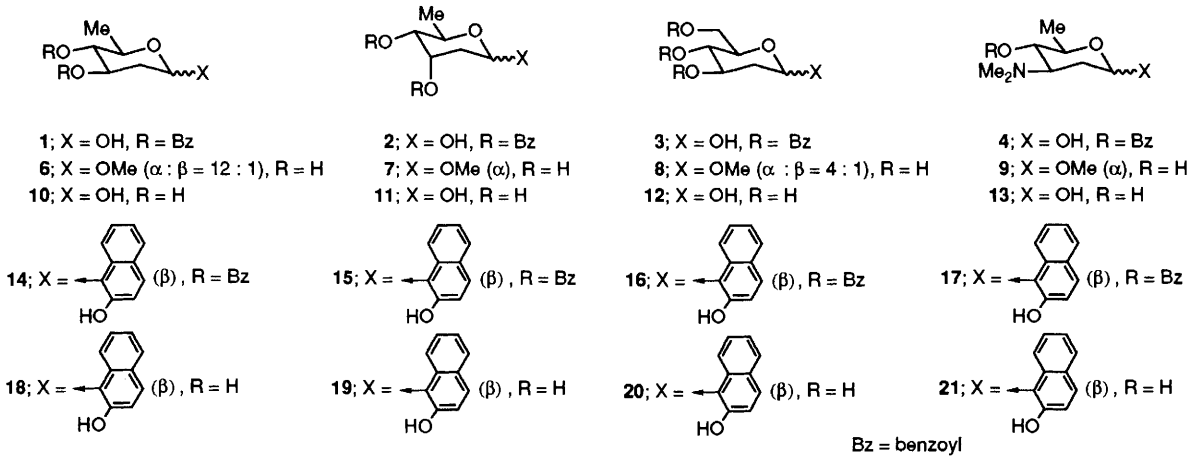


Fig. 1

Table 1 *C*-Arylglycosylations by the TMSOTf–$AgClO_4$ catalyst[a]

Sugar + **5** $\xrightarrow[CH_2Cl_2 \text{ or MeCN}]{\text{cat. TMSOTf–}AgClO_4\ (1:1)}$ Aryl *C*-glycosides

Entry	Sugar	Mol% of catalyst	Solvent	*T*/°C	*t*/h	Yield[b] (%)	α:β Ratio[c]
	Protected 1-OH (free) sugars						
1	**1**	20	CH_2Cl_2	0→25	0.5	99	1:70
2	**2**	20	CH_2Cl_2	0→25	0.5	90	1:15
3	**3**	20	CH_2Cl_2	0→25	1	85	1:>99
4	**4**	50	CH_2Cl_2	0→40	2	83	1:>99
	Unprotected 1-OMe glycosides						
5	**6**	20	MeCN	0→25	1	91	1:>99
6	**7**	20	MeCN	0→25	1	92	1:32
7	**8**	50	MeCN	0→25	1	86	1:>99
8	**9**	50	CH_2Cl_2	0→40	2	72	1:>99
	Unprotected 1-OH (free) sugars						
9	**10**	20	MeCN	0→25	1	92	1:>99
10	**11**	20	MeCN	0→25	1	84	1:97

[a] All reactions were carried out by use of 2.0 equiv. of 2-naphthol **5** to the glycosyl donor. [b] Isolated yields after purification by column chromatography. [c] α:β Ratios were determined by ^1H NMR (270 MHz) spectroscopy and/or isolation of pure isomers.

to excellent yields. These results clearly indicated that the TMSOTf–$AgClO_4$ catalyst was suitable to activate not only methyl and acetyl groups[1] but also the 1-OH group of the sugar. Our second preliminary attempts were the *C*-arylglycosylations of the unprotected methyl glycosides **6–9** with **5** to examine the activating capacity of the TMSOTf–$AgClO_4$ system in the presence of other hydroxy groups of the glycosyl donor. In the case of the glycosyl donors **6–8**, MeCN was used as an appropriate solvent instead of CH_2Cl_2 considering their solubility. However, use of CH_2Cl_2 as a solvent was crucial for the effective glycosylation of the amino sugar **9**. The results summarized as entries 5–8 in Table 1 showed an additional feature of our method. Even the trihydroxy sugar **8** and the monohydroxy amino sugar **9** were smoothly glycosylated with **5** by use of 50 mol% of the present activator to give the corresponding unprotected aryl β-*C*-glycosides **20**† and **21**,† respectively, in high yields. These results suggested that the ability of the TMSOTf–$AgClO_4$ system as a catalytic activator was not significantly influenced by any hydroxy group of sugar. From these favourable results, we finally tried the *C*-arylglycosylations of totally unprotected free sugar by using the present catalyst system. Although the glycosyl donors **12** and **13** were not able to be applied to the glycosylation reaction owing to their low solubility in MeCN‡ and CH_2Cl_2, respectively, both glycosylations of **10** and **11** with **5** in MeCN were effectively achieved under similar conditions to afford the unprotected aryl β-*C*-glycosides **18**† and **19**,† respectively, with satisfactory chemical yield and stereoselectivity (entries 9 and 10 in Table 1).

In conclusion, the catalytic combined use of TMSOTf–$AgClO_4$ gave a significant new entry to the efficient *C*-arylglycosylation method and should find wide applications in the synthesis of aryl *C*-glycosides.

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‡ Other polar solvents, MeOH, Pr^iOH, Bu^tOH, DMF and THF were examined and found to be not suitable for the present glycosylation reaction. DMF = dimethylformamide, THF = tetrahydrofuran.