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Rapid O-Glycosidation of Phenols with Glycosyl Fluoride by Using the Combinational Activator, Cp_2HfCl_2-$AgClO_4$

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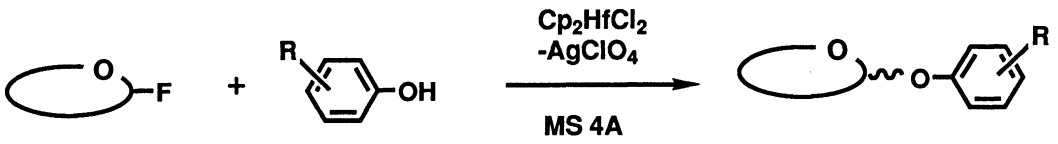
A new and efficient method for O-glycosidation of phenols is described. Cp_2HfCl_2-$AgClO_4$ is a highly effective promoter for the coupling reaction between glycosyl fluoride and phenol in the presence of molecular sieves 4A, which proceeds rapidly at low temperature to give O-aryl glycoside in high yields.

O-Aryl glycosides are widely found in natural products and also have importance as biochemical probes in enzyme assay.[1] The synthesis of these compounds, i.e. O-aryl glycosidation, has attracted historical interest, which has often been executed under harsh reaction conditions, such as in strongly alkaline medium.[2,3] In relation to the synthesis of biologically significant compounds possessing O-aryl glycoside linkages, such as chartreusin[4a] and vancomycin,[4b] there appeared a need for exploiting the O-aryl glycosidation reaction which proceeds under mild conditions in high yield to permit the application to the synthesis of sensitive compounds as exemplified above.

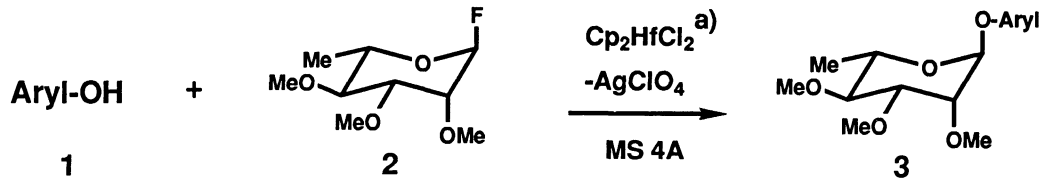
Recently, we uncovered an efficient activator for glycosyl fluorides, that is Cp_2MCl_2-$AgClO_4$ (M = Zr, Hf), which enables the expeditious glycosidation of various types of alcohols including sterically hindered or sensitive ones.[5] Since the O-glycosidation of phenols is known to show considerably different features from that of ordinary alcohols (alkanols) due to the difference of their pKa's, we tested the applicability of this activation method to the glycosidation of phenols.[6] In this communication, we wish to describe the outcome of those attempts, which shows that Cp_2HfCl_2-$AgClO_4$ is highly effective in this context to open a rapid entry into O-aryl glycosides (Eq. 1).[7]

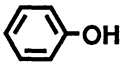
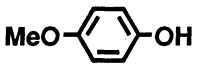
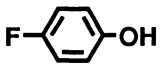
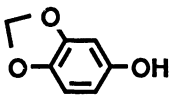
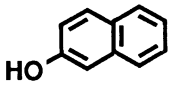
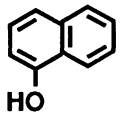


(1)

First, the reactions of fluoride **2**, derived from L-rhamnose, with some representative phenols were examined by using Cp_2HfCl_2-$AgClO_4$ as the reaction promoter.[8,9] The results in Table 1 show the following characteristic features of the method. (1) The reactions proceed quite rapidly to give the O-aryl glycoside in high yield in comparison with the conventional methods. (2) As for

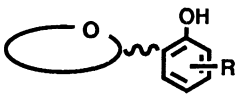
Table 1.[12,13]



Run	Aryl-OH	Solvent	Temperature/°C	Reaction period	Yield/%	α/β
1		CH_2Cl_2	-78	45 min	81	α
2		CH_2Cl_2	-78	30 min	81	α
3		CH_2Cl_2	-78	30 min	85	11/1
4		CH_2Cl_2	-78 → 0	30 min	41	α
5		CH_2Cl_2	-78	30 min	64[b]	α
6		Et_2O	-20 → 0	1 h	79	α
7		CH_2Cl_2	-78	45 min	70[b]	α
8		Et_2O	-20 → rt	1 h	82	α
9		CH_2Cl_2	-78	45 min	63[b]	α
10		Et_2O	-20	20 min	74	α

a) See typical procedure. b) C-glycoside was isolated in ca. 10%.

the substituent of the phenolic component, either OMe (run 2) or F (run 3) has essentially no influence on the rate and yield (Cf. run 1), while mesomerically electron-withdrawing group (Ac: run 4) markedly retards the reaction. (3) In the cases of a more electron-rich phenol (run 5) or naphthols (runs 7, 9), the yields were slightly lowered.

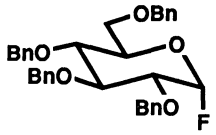


4

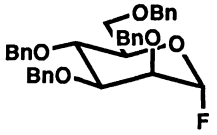
This is due to the side reaction, i.e. formation of C-aryl glycoside as **4** via the rearrangement of the initially-formed O-glycosides,[10,11] which can be effectively suppressed by using Et_2O as the solvent (runs 6, 8, 10). (4) Except for one case

(run 3), the anomeric stereochemistry of the products was exclusively α-oriented reflecting the large anomeric effect inherent in the particular sugar moiety of **3** derived from L-rhamnose.

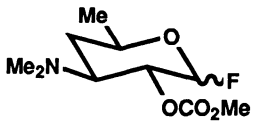
Next, we applied the method to some other glycosyl fluorides **5a-5d** (Table 2). As for perbenzylated fluorides **5a** (gluco), **5b** (manno), the reactions were incomplete at -78 °C, however, which proceeded cleanly around -30 °C to give the products in high yields.



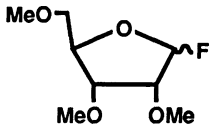
5a



5b



5c

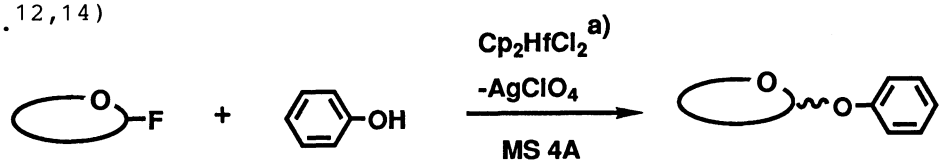


5d

Glycosidation of **5c**, derived from D-desosamine,[5] also proceeded in excellent yield. Unexpectedly, the reaction gave more of the α-anomer rather than the β-anomer anticipated from the neighboring-group participation. Apart from this stereochemical issue, it is one of the prominent features of the present method that the anomeric activation is not damaged by the basic amino group.

The product from fluoride **5d** (ribo) was particularly prone to the O-C rearrangement (vide supra) and the corresponding C-aryl glycoside was formed even at -78 °C. Here again, use of the donor solvents, Et_2O and CH_3CN, suppressed this undesired reaction and the O-glycoside **6d** was formed in high yield. Interestingly, the α/β ratios of the product were reversed in these cases.

Table 2.[12,14]



5a-5d **6a-6d**

Run	Fluoride	Solvent	Temperature/°C	Reaction period	Yield/%	α / β
1	**5a**	CH_2Cl_2	-78 → -30	2.5 h	82	1 / 1.1
2	**5b**	CH_2Cl_2	-78 → -20	25 min	90	α
3	**5c**	CH_2Cl_2	0 → rt	1 h	93	2.2 / 1
4	**5d**	CH_2Cl_2	-78	20 min	74[b]	1 / 3.1
5		Et_2O	-20	50 min	86	8.7 / 1
6		CH_3CN	-20	30 min	86	1 / 5.8

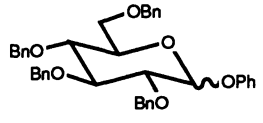
a) See typical procedure. b) In addition, 5% of C-glycoside was isolated.

In summary, the combination of Cp_2HfCl_2 and $AgClO_4$ is proved to be a highly effective promoter for the reaction of phenol and glycosyl fluoride, which provides a rapid and versatile method for the synthesis of O-aryl glycosides.

Typical procedure is described for the reaction of **2** and phenol: To a mixture of phenol (13.6 mg, 145 μmol), Cp_2HfCl_2 (82.1 mg, 216 μmol), $AgClO_4$ (44.8 mg, 216 μmol) and powdered molecular sieves 4A (ca. 200 mg) in CH_2Cl_2 (1 ml), glycosyl fluoride **2** (15.0 mg, 72.1 μmol) in CH_2Cl_2 (1 ml) was added at -78 °C, and the mixture was stirred for 45 min. After the addition of satd. $NaHCO_3$ solution and filtration through a Celite pad, the mixture was extractively worked up. Purification on SiO_2-TLC ($CHCl_3/Et_2O$=9/1) gave the glycoside (16.5 mg, 81%).

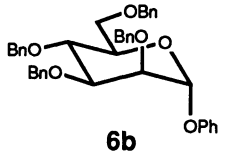
References

1) S. M. Hopkinson, Quart. Rev., 23, 98 (1969).
2) Review: K. Igarashi, Adv. Carbohydr. Chem. Biochem., 34, 243 (1977); H. Paulsen, Angew. Chem., Int. Ed. Engl., 21, 155 (1982).
3) K. Brewster, J. M. Harrison, and T. D. Inch, Tetrahedron Lett., 1979, 5051, and references cited therein.
4) a) Chartreusins: W. Eisenhuth, O. A. Stamm, and H. Schmid, Helv. Chim. Acta, 47, 1475 (1964); b) Vancomycins: C. M. Harris, H. Kopecka, and T. M. Harris, J. Am. Chem. Soc., 105, 6915 (1983), and the references cited therein.
5) T. Matsumoto, H. Maeta, K. Suzuki, and G. Tsuchihashi, Tetrahedron Lett., 29, 3567, 3571, 3575 (1988).
6) For recent mehtods by Lewis acidic catalysis, see the following: L.-F. Tietze, R. Fischer, and H.-J. Guder, Tetrahedron Lett., 23, 4661 (1982); R. R. Schmidt and J. Michel, Angew. Chem., Int. Ed. Engl., 19, 731 (1980).
7) Recently, $BF_3 \cdot OEt_2$-promoted O-aryl glycosidation of glycosyl fluoride using hindered base was reported; Ya. V. Voznyi, I. S. Kalicheva, and A. A. Galoyan, Bioorg. Khim., 10, 1256 (1984) [Chem. Abstr., 102, 95930q (1985)].
8) Related combinations, Cp_2MCl_2-$AgClO_4$ (M = Zr, Ti), were less effective.
9) Other Lewis acids gave lower yields of the product. For example, the reaction of **2** and p-methoxyphenol under the similar reaction conditions (CH_2Cl_2, -78 °C) gave the following results: (1) $BF_3 \cdot OEt_2$, 52%; (2) Me_3SiOTf, 69%; (3) $SnCl_2$-$AgClO_4$, 76% (-20 °C; no reaction at -78 °C).
10) For the precedent of this side reaction, see R. B. Conrow and S. Bernstein, J. Org. Chem., 36, 863 (1971).
11) For the positive use of this reaction in the synthesis of C-aryl glycosides: see T. Matsumoto, M. Katsuki, and K. Suzuki, Tetrahedron Lett., in press.
12) All new compounds were fully characterized by ^1H NMR (400 MHz), IR, and HRMS.
13) All the α-products listed in table 1 uniformly showed $J_{1,2}$ value of 1.8 Hz. $^1C_4$(L)-Conformation is supported by the values $J_{3,4}$ (9 Hz) and $J_{4,5}$ (9 Hz).
14) For ^1H NMR of H-1 of **6a-6d** listed in Table 2, see below:



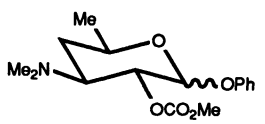
6a

α 5.69 ($J_{1,2}$=3.4 Hz)
β 5.18 ($J_{1,2}$=7.3 Hz)



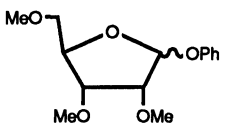
6b

α 5.60 ($J_{1,2}$=1.5 Hz)



6c

α 5.75 ($J_{1,2}$=3.4 Hz)
β 5.66 ($J_{1,2}$=7.8 Hz)



6d

α 5.66 ($J_{1,2}$=4.4 Hz)
β 4.97 ($J_{1,2}$=0 Hz)

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