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New Glycosidation Reaction 2. Preparation of 1-Fluoro-D-Desosamine Derivative and its Efficient Glycosidation by the Use of Cp_2HfCl_2-$AgClO_4$ as the Activator

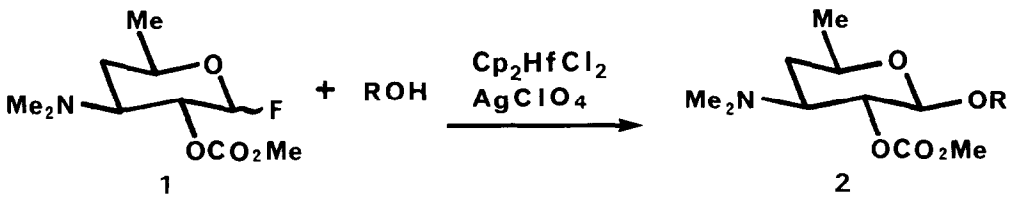
Keisuke Suzuki*, Hideki Maeta, Takashi Matsumoto, and late Gen-ichi Tsuchihashi

Department of Chemistry, Keio University, Hiyoshi, Yokohama 223, Japan

Summary: Preparation of 1-fluoro-D-desosamine derivative 1 and its glycosidation are described. A new activation system for glycosyl fluorides, Cp_2HfCl_2-$AgClO_4$, enables highly efficient glycosidation of 1.

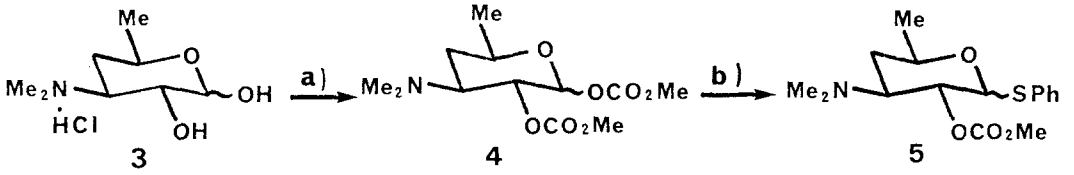
It is doubtless that there are significant needs for newer methods of glycosidation which are mild and efficient.[1] This is especially the case in dealing with the sensitive glycosyl acceptors as typified in the macrolide antibiotics, where the low reactivity and the high chemical sensitivity of the substrates must be considered.[2]

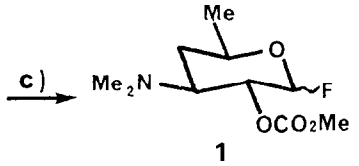
In the synthesis of the mycinamicin macrolide antibiotics,[3] we were confronted with such a problem, that is, the glycosidation of D-desosamine,[4] which is particularly challenging because of the existence of the basic Me_2N-group at C(3) which may interfere the glycosidic activation.[5] Toward this problem, our effort was centered around the preparation and the use of the 1-fluoro-D-desosamine derivative 1 as the glycosyl donor hopefully with a good reactivity and a good shelf stability.[6] Also hoped was that the new activation method for glycosyl fluorides[7,8] is applicable to the glycosidation of this class of amino sugars ubiquitous in the macrolide antibiotics.



This report describes the successful outcome along these lines, that is, the preparation of 1-fluoro-2-O-methoxycarbonyl-D-desosamine (1) and its mild and efficient glycosidation by the new activation system, Cp_2HfCl_2-$AgClO_4$, which satisfied all of our target-oriented criteria.[3]

Although the synthesis of fluoro sugar 1 was not straightforward at the outset, the route eventually exploited was quite efficient (Scheme 1). D-Desosamine hydrochloride (3)[9] was transformed to thioglycoside 5 via 4. Conversion of 5 into fluoride 1 with NBS-DAST[10] failed, for which, we surmised, the competitive attack of NBS to both PhS- and Me_2N-groups might be responsible. For the selective activation of the PhS-moiety, the reaction was performed at low temperature in the presence of $HF\cdot(Pyr)_n$ (for the protection of the amino group in situ), which cleanly afforded fluoride 1.[11] Moreover, gratifyingly, fluoride 1 was a stable oil which can be purified by short-path distillation [Yield 77 %; bp. 70-90 °C / 1 mmHg (oven temp.)].[12,13]





Scheme I

Keys: a) $ClCO_2Me$ (3 equiv.), i-Pr_2NEt (5 equiv.) / CH_2Cl_2, rt, 12 hr (85 %); b) PhSH (2 equiv.), $SnCl_4$ (1 equiv.) / $ClCH_2CH_2Cl$, 80 °C, 2 hr (70 %); c) DAST (2.5 equiv.), NBS(1.5 equiv.), $HF\cdot(Pyr)_n$ / CH_2Cl_2, -50 °C, 20 min (77 %).

With fluoride 1 in hand, model reactions with cyclohexanol were examined using the new activtion system Cp_2MCl_2-$AgClO_4$.[8] In this case, Cp_2ZrCl_2-$AgClO_4$ turned out to be ineffective (yield 12 %), despite which is the combination of choice in the reaction of a neutral sugar (D-mycinose).[8] Instead, the surrogate system, Cp_2HfCl_2-$AgClO_4$, exhibited a high reactivity to afford the glycoside in 92 % yield. For the purpose of comparison, the conventional methods were also examined. While TMSOTf[7b] was less effective (yield 51 %), $SnCl_2$-$AgClO_4$[7a] appeared as another useful candidate for the glycosidation of 1 (yield 95 %).

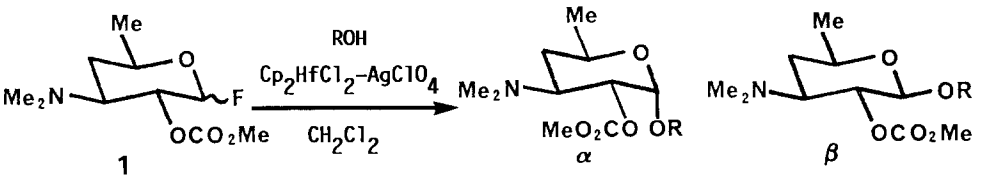
Results of the Cp_2HfCl_2-$AgClO_4$-promoted reactions[14] with some other alcohols are summarized in Table 1. The efficiency of the method is evident in light of the extremely rapid reaction rates (the four runs in Table 1 were complete within 15 min at -20 °C). Even t-butanol or 2,4-dimethyl-3-pentanol can be smoothly glycosylated in high yield.

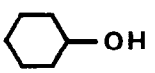
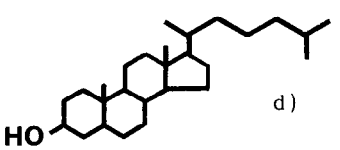
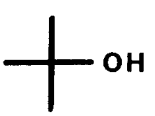
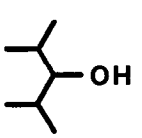
Another notable feature is the uniformly excellent stereoselectivity. It is seemingly a matter of course expected from the participation effect, which, however, is not always true as seen in the example below.[15]

The results by the $SnCl_2$-$AgClO_4$ method,[7a] another option found in the model study (vide supra), are also shown in Table 1. The method is effective so far as the simple sec-alcohols are concerned (run 1, 2), however which suffers from the substantial decrease of the yield (run 3) or the stereoselectivity (run 4) when the bulkier glycosyl acceptors are concerned.

In summary, the combination of Cp_2HfCl_2-$AgClO_4$ is an effective activator for the glycosyl fluorides, which is useful in the formation of β-D-desosaminyl glycoside in high yield and in high stereoselectivity. Application to the macrolide synthesis is described in the accompanying paper.[3]

Table 1 Cp_2HfCl_2-$AgClO_4$-Promoted Glycosidation of 1[12]



Run	ROH[a]	Yield (%)	α : β[b]
1		91	β
		(95	β)[c]
2	 d)	92	β
		(97	β)[c]
3		93	1 : 26
		(16	β)[c]
4		91	1 : 50
		(64	1 : 4)[c]

a) Stoichiometry: 1:ROH:Cp_2HfCl_2:$AgClO_4$=1:2:5:5; b) Determined by ^1H NMR (400 MHz) and isolation; c) By $SnCl_2$-$AgClO_4$ method (ref. 7a); d) 3-β-Cholestanol.

A typical experimental procedure is as follows: To a mixture of 1 (17.4 mg, 74.0 μmol), Cp_2HfCl_2 (141 mg, 370 μmol), $AgClO_4$ (77 mg, 370 μmol) and powdered molecular sieves 4A (ca. 100 mg) was added cyclohexanol (14.8 mg, 148 μmol) in CH_2Cl_2 (1.5 ml) at -20 °C. The mixture was stirred for 30 min at -20 °C, to which was added satd. $NaHCO_3$ solution and the mixture was filtered through a Celite pad. Extractive workup followed by purification on SiO_2 TLC (AcOEt, 1 % Et_3N) afforded the glycoside as an oil (21.2 mg, 91 %).[12]

Acknowledgments: The authors are grateful to the Kawakami Memorial Foundation and the Foundation of Research on Medicinal Resources for financial support.

References and Notes

1) a) K. Igarashi, Adv. Carbohydr. Chem. Biochem., 34, 243 (1977); b) A. F. Bochkov and G. E. Zaikov, "Chemistry of the O-Glycosidic Bond," Pergamon, Oxford, 1979; c) H. Paulsen, Angew. Chem., Int. Ed. Engl., 21, 155 (1982); idem, Chem. Soc. Rev., 13, 15 (1984).

2) S. Masamune and P. A. McCarthy, in "Macrolide Antibiotics", S. Ōmura Ed., Academic, Orlando, pp 127-198 (1984).

3) See the accompanying communication in this issue.

4) D-Desosamine is the constituent of a number of macrolides such as erythromycin, narbomycin, pikromycin, methymycin and so on. For the relevant glycosidation in the total synthesis, see a) Methymycin: S. Masamune, H. Yamamoto, S. Kamata, and A. Fukuzawa, J. Am. Chem. Soc., 97, 3513 (1975); b) Erythromycin: R. B. Woodward et al., ibid., 103, 3215 (1981).

5) It is well recognized that the glycosidation of N-containing sugars is often problematic (See refs. 4). Also see, K. C. Nicolaou, S. P. Seitz, and M. R. Pavia, J. Am. Chem. Soc., 104, 2030 (1982).

6) The corresponding bromo sugar is known to be highly unstable even as the HBr salt and also under the glycosidation conditions (ref. 4a).

7) For pioneering works in this area, a) T. Mukaiyama, Y. Murai, and S. Shoda, Chem. Lett., 1981, 431; b) S. Hashimoto, M. Hayashi, and R. Noyori, Tetrahedron Lett., 25, 1379 (1984).

8) See the preceding communication in this issue.

9) E. H. Flynn, M. V. Sigal, P. F. Wiley, and K. Gerzon, J. Am. Chem. Soc., 76, 3121 (1954).

10) K. C. Nicolaou, R. E. Dolle, D. P. Papahatjis, and J. L. Randall, J. Am. Chem. Soc., 106, 4189 (1984).

11) The amount of $HF\cdot(Pyr)_n$ relative to DAST is crucial for the success of the reaction. Experimentally, use of the same volume amount to DAST gave the best result.

12) All new compounds were fully characterized by ^1H NMR (400 MHz), IR and high-resolution MS.

13) The fluoride was obtained as a 4/1 mixture of α/β-anomers. Selected NMR data ($CDCl_3$) for α-1: H(1) δ 5.71 (dd, $J_{H(1),H(2)}$=2.9 Hz, $J_{H(1),F}$=54.7 Hz); C(1) δ 105.2($J_{C(1),F}$=224.3 Hz). Data for β-1: H(1) δ 5.20 (dd, $J_{H(1),H(2)}$=6.4 Hz, $J_{H(1),F}$=53.2 Hz); C(1) δ 108.4 (d, $J_{C(1),F}$=213.8 Hz). The $J_{H(2),F}$ values are 23.9 Hz (α-1) and 12.2 Hz (β-1): L. D. Hall, J. F. Manville, and N. S. Bhacca, Can. J. Chem., 47, 1 (1969).

14) Mixture of the anomers was used in the reaction. No noticeable difference in reactivity was observed between the anomers.

15) Slight decrease of the stereoselectivity was observed in the reactions at higher temperature, typically 0 °C or above.

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