Tetrahedron Letters,Vol.29,No.29,pp 3567-3570,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

New Glycosidation Reaction 1. Combinational Use of Cp_2ZrCl_2-$AgClO_4$ for Activation of Glycosyl Fluorides and Application to Highly β-Selective Gylcosidation of D-Mycinose

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

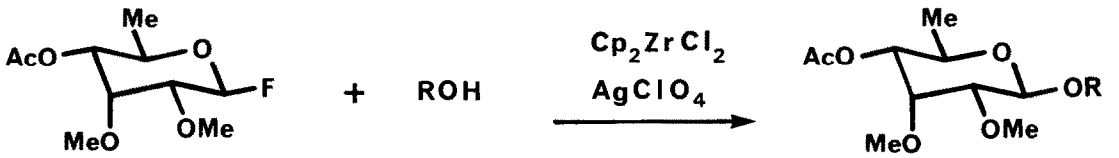
Department of Chemistry, Keio University, Hiyoshi, Yokohama 223, Japan

Summary: The combination of Cp_2MCl_2-$AgClO_4$ (M=Zr, Hf) is effective for the activation of glycosyl fluorides, which enables the highly β-selective glycoside formation of D-mycinose by performing the reaction in benzene.

Glycosidation reaction is one of the oldest but yet unresolved problems in organic synthesis. Recent uncoverage of a number of biologically active glycosidic compounds has stimulated a renewed and ever-increasing interest in this reaction in light of the overall efficiency as well as the stereochemical control in the formation of glycosidic linkages.[1)]

Our interest in this issue stemed from the total synthesis of the mycinamicin macrolide antibiotics which called for a β-selective glycosidation of the aglycon to D-mycinose.[2,3)] For this purpose, we intended to use the glycosyl fluoride, a new class of shelf-stable glycosyl donor which is effectively activated under specific conditions.[4)]

Although the glycosidation of D-mycinosyl fluoride 1[5,6)] employing the known methods[4)] proceeded in excellent yields, the stereoselectivity did not reach the synthetically useful level. This issue represents a more general problem encountered in the glycosidation processes, i.e., the stereocontrol of the "non-Königs-Knorr" sugars with the non-participating protection at C(2)-OH. Thus, we explored a newer method for the activation of glycosyl fluorides.

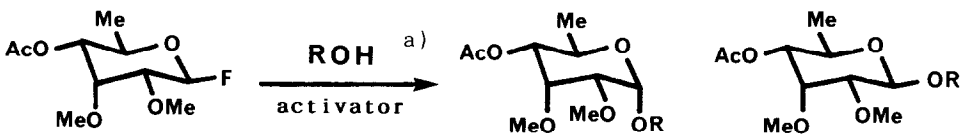


In this communication, we wish to describe a new and efficient system for the activation of glycosyl fluorides, Cp_2ZrCl_2-$AgClO_4$, which enables highly β-selective glycosidation of D-mycinose in high yield.

In contrast to the activators for the glycosyl chlorides or bromides which are classified as the salts of late transition metals (e.g. Hg, Ag etc.) with the soft characters,[1] the ones for the glycosyl fluorides are the derivatives of the hard elements of group IVb (Si, Sn).[4] Here, we examined an unexplored possibility for the activation of glycosyl fluorides, that is, the use of early transition metal salts in expectation of their hard characters.

Specifically, use of group IVa metallocenes (Cp_2MCl_2: M=Ti, Zr, Hf) was investigated along these lines. Although the reagent itself was essentially inert as the activator, the coupled use with the equimolar amount of $AgClO_4$[7] gave rise to *an impressively rapid and clean reaction*. The results of the reactions using cyclohexylmethanol as the model acceptor are shown in Table 1, which reveals the rough order of the reactivity as Zr ≧ Hf ≫ Ti. The Zr-system exhibited the most powerful reactivity and the reaction was almost instantaneous at -20 °C. The Hf-system is slightly less reactive and the consumption of fluoride 1 required 30 min. The Ti-system showed a much lower reactivity compared with the above two systems: no reaction occurred at -20 °C, nonetheless, which also led to an excellent yield at 0 °C.

Table 1 Cp_2MCl_2-$AgClO_4$-Promoted Glycosidation of 1



1 α β

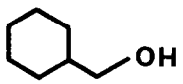
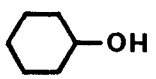
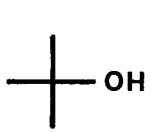
Activator	Conditions[b]	Yield(%)	α : β[d]
Cp_2TiCl_2-$AgClO_4$	0 °C, 2 hr	90[c]	1 : 1.8
Cp_2ZrCl_2-$AgClO_4$	-20 °C, 5 min	90	1.2 : 1
Cp_2HfCl_2-$AgClO_4$	-20 °C, 30 min	86	1.7 : 1

a) Cyclohexylmethanol (2 equiv.) was used; b) Performed in CH_2Cl_2; c) No reaction at -20 °C (30 min); d) By ^1H NMR (400 MHz).

Our attention was then turned to the problem of stereoselectivity, for which the solvent effect was extensively examined on the Cp_2ZrCl_2-$AgClO_4$-promoted protocol (Table 2). The reaction is α-selective in Et_2O, whereas β-selective in CH_3CN, although the ratios are not particularly high.

In sharp contrast, however, the stereochemical outcome was markedly altered *when carried out in benzene leading to the highly selective formation of the β-glycoside* (run 5).[8] This dramatic solvent effect is also valid for the cases of secondary or tertiary alcohols (run 7, 9), and proved to be useful also in the macrolide synthesis.[2] This exceptional stereoselectivity clearly illustrates another attractive feature of the present method, since this level of selectivity is otherwise unattainable.[9]

Table 2 Solvent Effect in Cp_2ZrCl_2-$AgClO_4$-Promoted Glycosidation of 1[10)]

Run	ROH[a)]	Solvent	Conditions	Yield (%)	α : β[c)]
1		CH_2Cl_2	-20 °C, 5 min	90	1.2 : 1
2		$ClCH_2CH_2Cl$	-20 °C, 50 min	99	1.3 : 1
3		Et_2O	-20 °C, 1 hr	99	2.4 : 1
4		CH_3CN	0 °C, 2 hr[b)]	72	1 : 1.3
5		C_6H_6	rt, 10 min	92	1 : 16
6		CH_2Cl_2	-20 °C, 20 min	99	1 : 1.2
7		C_6H_6	rt, 15 min	89	1 : 16
8		CH_2Cl_2	-20 °C, 40 min	93	1.4 : 1
9		C_6H_6	rt, 30 min	59	β

a) Stoichiometry: 1:ROH:Cp_2ZrCl_2:$AgClO_4$=1:2:5:5 (see typical procedure); b) No reaction at -20 °C; c) Determined by ^1H NMR (400 MHz) and isolation.

A typical procedure is as follows: To a mixture of 1 (12.8 mg, 54.2 μmol) and cyclohexylmethanol (12.4 mg, 108 μmol) and powdered molecular sieves 4A (ca. 100 mg) in benzene (2.5 ml) was added Cp_2ZrCl_2 (79.3 mg, 271 μmol) followed by $AgClO_4$ (56.2 mg, 271 μmol), and the mixture was stirred for 10 min at room temperature. 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 (hexane/Et_2O=1/1) gave the glycoside in 92 % yield.

In summary, the reagent system Cp_2MCl_2-$AgClO_4$ (M=Zr, Hf) is highly efficient for the activation of glycosyl fluorides. The present method offers a new and promising possibility in the glycosidation reactions.

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

References and Notes

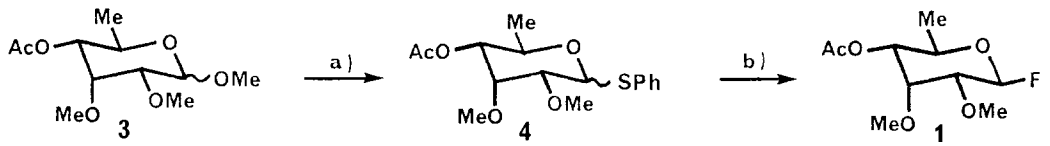
1) a) K. Igarashi, Adv. Carbohydr. Chem. Biochem., 34, 243 (1977); b) A. F. Bochkov and G. E. Zaikov, "Chemistry of the O-Glycosidic Bond," Pergamon, Oxford, 1979; c) H. Paulsen, Angew. Chem., Int. Ed. Engl., 21, 155 (1982); idem, Chem. Soc. Rev., 13, 15 (1984).

2) See the accompanying communications in this issue.

3) D-Mycinose is also the sugar constituent of tylosin. For the glycosidation of this sugar in macrolide synthesis, see K. Tatsuta, Y. Amemiya, Y. Kanemura, H. Takahashi, and M. Kinoshita, Tetrahedron Lett., 23, 3375 (1982); K. C. Nicolaou, M. R. Pavia, and S. P. Seitz, J. Am. Chem. Soc., 104, 2027, 2030 (1982).

4) 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).

5) The fluoride 1 was prepared from 3 (J. S. Brimacombe, M. Stacey, and L. C. N. Tucker, Proc. Chem. Soc., 1964, 83.). For the fluorination, see K. C. Nicolaou, R. E. Dolle, D. P. Papahatjis, and J. L. Randall, J. Am. Chem. Soc., 106, 4189 (1984).



a) ZnI_2,n-Bu_4NI,Me_3SiSPh/CH_2Cl_2, 60°C, 3 hr (79 %); b) DAST,NBS/CH_2Cl_2, -15 °C (79 %).

An alternative synthesis of D-mycinose and its fluoride has been developed in this laboratory (Unpublished results of M. Hirasawa and M. Katsuki).

6) Fluoride 1 was the essentially pure β-anomer judging from the NMR ($CDCl_3$) data: H(1) δ 5.46 (dd, $J_{H(1),H(2)}$=6.8 Hz, $J_{H(1),F}$=54.2 Hz); C(1) δ 108.3 ($J_{C(1),F}$=212.4 Hz). The α-anomer of 1, prepared by the partial isomerization (BF_3.OEt_2 / THF), showed H(1) δ 5.61 (dd, $J_{H(1),H(2)}$=2.9 Hz, $J_{H(1),F}$=53.2 Hz); C(1) δ 104.1 ($J_{C(1),F}$=234.2 Hz). The $J_{H(2),F}$ values provide the basis to this assignment: $J_{H(2),F}$=11.7 Hz for β-1 (Cf. $J_{H(2),F}$=26.9 Hz for α-1): L. D. Hall, J. F. Manville, and N. S. Bhacca, Can. J. Chem., 47, 1 (1969).

7) Combinational use of two metal salts to gain the entirely new reactivities has been extensively studied by Mukaiyama et al.; for example, see S. Kobayashi, M. Tamura, and T. Mukaiyama, Chem. Lett., 1988, 91, and the references cited therein.

8) The β-selectivity is particularly prominent for the Zr-system. Use of benzene as the reaction medium for the other cases, 1) Cp_2HfCl_2-$AgClO_4$ (α/β=1/2.5), 2) $SnCl_2$-$AgClO_4$ (α/β=1.7/1), 3) TMSOTf (α/β=1/3.4).

9) The results obtained by methods (refs. 4) claimed to be β-selective (in the gluco-series) are 1) $SnCl_2$-$AgClO_4$ in CH_3CN: α/β=1/1.7; 2) TMSOTf, cyclo-$C_6H_{11}OTMS$ in CH_3CN α/β=1/2.2.

10) All new compounds exhibited satisfactory ^1H NMR (400 MHz), IR, and HRMS.

(Received in Japan 14 March 1988)