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Cp_2ZrCl_2-$AgClO_4$: Efficient Promoter for the Friedel-Crafts Approach to C-Aryl Glycosides

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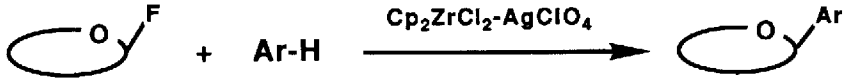
Summary: *Combination of Cp_2ZrCl_2-$AgClO_4$ is highly effective for promoting the Friedel-Crafts coupling of glycosyl fluoride and aromatic compounds. Regiochemical aspects of the reactions of some naphthalene derivatives are described.*

Considerable attention is now paid to a new class of antibiotics possessing a unique general structural feature, that is, the C-aryl glycosidic linkage(s), as exemplified by aquayamycin and ravidomycin.[1] Some of the compounds of this class are known to exhibit potent antitumor properties, which are, therefore, ranked as one of the challenging targets in current organic synthesis.[2]

An easily conceivable and, *if viable*, the most straightforward synthetic approach toward these structures would be the Friedel-Crafts-type connection of aromatics to the anomeric center of sugars, which has additional attractiveness in relation to their putative biosynthesis.[3] Viability of such an approach critically depends on the efficiency of the C-aryl glycosidation protocol employed.[4]

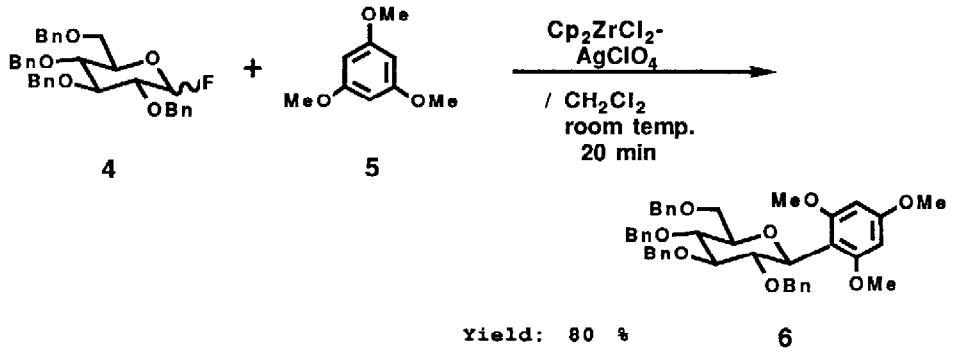
Recently, we found a novel method for the activation of glycosyl fluoride by using the combinational promoter, Cp_2MCl_2-$AgClO_4$ where M are the Group IVa elements, i.e. Ti, Zr, Hf.[5] Considering the high level of glycosidic activation thereby achievable, we set out to examine the potentiality of this new method in the area of C-aryl glycoside synthesis.[6] Herein, we report that *Cp_2ZrCl_2-$AgClO_4$ is effective indeed in promoting this type of glycosyl-aromatic coupling reactions.*



1 **2** **3**

Preliminary experiments were carried out for the reaction of tetra-O-benzyl-D-glucosyl fluoride (**4**) and 1,3,5-trimethoxybenzene (**5**) using either of the three promoters: Cp_2MCl_2-$AgClO_4$ (M = Ti, Zr, Hf). Among them, Cp_2ZrCl_2-$AgClO_4$ showed a promising reaction profile. The starting material was consumed almost instantaneously at room temperature to afford β-C-glycoside **6** as the sole product. The surrogate promoter, Cp_2HfCl_2-$AgClO_4$, seemed to have a higher reactivity, however, which

destroyed the product to give multi spots. Attempted modulation of the reactivity by changing the solvent or the temperature was not fruitful. Cp_2TiCl_2-$AgClO_4$ showed a much lower reactivity.



4 5 6

Yield: 80 %

Next, we proceeded to examine the reaction of naphthalene derivatives (**7a** - **7d**) shown in Table 1. With particular attention to the regiochemical problem, tri-O-methyl-L-rhamnosyl fluoride (**8**)[7] was employed for simplifying the NMR analysis of the aromatic region of the products.

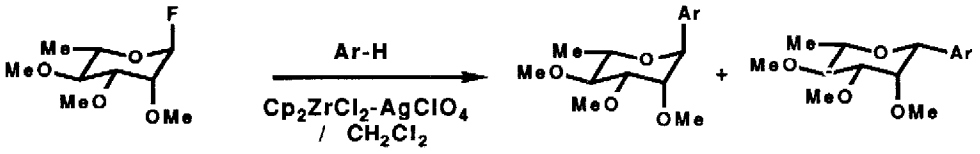
C-Naphthyl glycosides (**9a** - **9d**) were obtained in good to excellent yields and, more importantly, the regiochemistry of aromatic substitution was selective in line with the HOMO coefficient of the starting naphthalenes **7**.[8] The arrows indicate the sites where the new C-C bonds were actually formed. It should be noted that none of the positional isomers were isolated in run 1-9. Cases of **7d** (run 10-12) were exceptional in this regard, where the reaction occurred preferentially at C(3) rather than at C(8) with the largest coefficient, presumably due to the steric congestion around the C(8) center.

It is noteworthy that even the catalytic amount of the promoter can effect the coupling reaction cleanly. Generally, however, use of stoichiometric amount (preferably more than two equivalents) offers the more synthetically useful rates of the reaction.

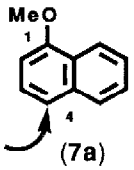
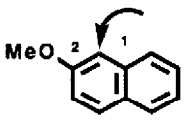
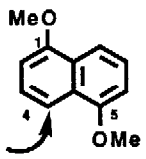
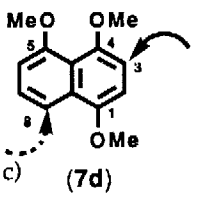
Comparison of the α/β selectivities for the stoichiometric and the catalytic cases provides an intriguing implication. The stoichiometric reaction gave β-**9** in high selectivity, while partial (run 12) or even predominant (run 3, 6) formation of α-**9** was observed in the catalytic conditions. This divergence is well understood by regarding the α-anomer as the kinetic product and the β-isomer as the thermodynamic product, respectively. Kinetically, it is reasonable to assume that the aromatics attack the **8**-derived oxonium species from the top face to afford α-**9**. It may be interesting to note that the α-isomers of **9b** and **9d** prefer the flipped conformation [$^4C_1$ (L)] disposing the C(1)-aryl at *equatorial* rather than the $^1C_4$ (L) conformer depicted in Table 1.[9] The kinetic α-anomers undergo *in situ*-anomerization to more stable β-epimers under the stoichiometric conditions.[4c] In fact, Cp_2ZrCl_2-$AgClO_4$ was capable of epimerizing the pre-formed α-anomer to the β-counterpart.

The present method enables a rapid and flexible assembly of aromatics and sugars to afford C-aryl glycosidic compounds. Further study is now in progress.

Table 1 Friedel-Crafts Reaction of Naphthalenes [7,9]



8 room temp. α-9 (a ~ d) β-9 (a ~ d)

Run	Naphthalene [a] (Ar-H)	Reagent (equivalents)	Reaction Period	Yield (%)	α : β [b]
1	 (7a)	5.0	20 min	96	β
2		2.0	45 min	91	1 : 12
3		0.3	2 hr	79	2 : 1
4	 (7b)	5.0	30 min	77	1 : 13
5		2.0	30 min	58	2 : 1
6		0.2	15 hr	40	21 : 1
7	 (7c)	5.0	20 min	59	β
8		2.0	20 min	64	β
9		0.2	75 min	50	β
10	 (7d)	5.0	30 min	67 [c]	β
11		2.0	30 min	89 [c]	1 : 7
12		0.5	10 min	66 [c]	1 : 2

a) Two equivalents were used; b) Determined by weighing the separated isomers; c) In addition, the C(8) positional isomer was also isolated in the yields of 15 % (run 10; α/β=1/7), 10 % (run 11; α/β=1/1), and 10 % (run 12; α/β=1/10), respectively.

Typical procedure is described for the reaction of 7a and 8: To a stirred mixture of glycosyl fluoride **8** (21.7 mg, 104 μmol), 1-methoxynaphthalene (**7a**; 49.5 mg, 313 μmol) and powdered molecular sieves 4A (ca. 200 mg) in CH_2Cl_2 (1.5 mL) was added Cp_2ZrCl_2 (153 mg, 522 μmol) followed by $AgClO_4$ (108 mg, 522 μmol) at room temperature. After stirring for 20 min, the reaction was stopped by the addition of saturated $NaHCO_3$ solution. Filtration (Celite), extractive workup, and purification by TLC (SiO_2; hexane/AcOEt=6/4) afforded β-**9a** as a colorless oil (34.5 mg, 96 %).

References and Notes

1) a) Aquayamycin: M. Sezaki, S. Kondo, K. Maeda, H. Umezawa, and M. Ohno, *Tetrahedron*, **26**, 5171 (1970); b) Ravidomycin: J. A. Findlay, J.-S. Liu, L. Radics, and S. Rakhit, *Can. J. Chem.*, **59**, 3018 (1981).

2) For the relevant synthetic endeavors, see A. D. Patten, N. H. Nguyen, and S. J. Danishefsky, *J. Org. Chem.*, **53**, 1003 (1988), and the references cited therein. Also see G. A. Kraus and M. T. Molina, *ibid.*, **53**, 752 (1988).

3) R. Misra, H. R. Tritch, III, and R. C. Pandey, *J. Antibiot.*, **38**, 1280 (1985).

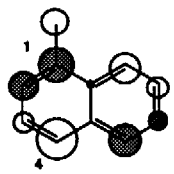
4) For the former examples of C-aryl glycosidation reactions, see a) H. Ohrui, H. Kuzuhara, and S. Emoto, *Agric. Biol. Chem.*, **36**, 1651 (1972); b) A. O. Stewart and R. M. Williams, *J. Am. Chem. Soc.*, **107**, 4289 (1985); c) R. R. Schmidt and M. Hoffmann, *Tetrahedron Lett.*, **23**, 409 (1982).

5) T. Matsumoto, H. Maeta, K. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, **29**, 3567, 3571, 3575 (1988).

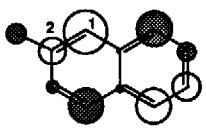
6) For an optional approach based on the rearrangement of O-aryl glycosides to their C-congeners, which showed a different and complementary regiochemical features from those obtained by the present method, see T. Matsumoto, M. Katsuki, and K. Suzuki, *Tetrahedron Lett., in press.*

7) Fluoride **8** was the α-L-anomer, which was obtained almost exclusively by treating the corresponding C(1)-OH derivative with $HF\cdot(pyr)_n$ in CH_2Cl_2 (0°C, 2 hr; 86 %). Bp: 65-85°C / 3 mmHg (oven temp.); NMR (δ, $CDCl_3$): H(1) 5.60 (dd, $J_{1,2}$=1.5 Hz, $J_{1,F}$=50.5 Hz); C(1) 105.5 (d, $J_{C(1),F}$=221.5 Hz).

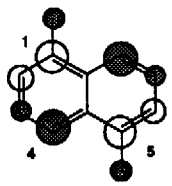
8) HOMO of the naphthalenes are shown based on the simple Hückel MO calculation.



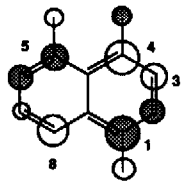
7a



7b



7c



7d

9) All new compounds exhibited satisfactory physical properties [^1H NMR (400 MHz), ^{13}C NMR (100 MHz), IR, and HRMS]. Regiochemistry of aromatic substitution was rigorously determined by the NOE study. Anomeric stereochemistry is based on the following ^1H NMR data ($CDCl_3$).

	δ, (Hz)	9a	9b	9c	9d
α	H(1) ($J_{1,2}$)	5.56 (4.9)	5.93 (8.8)	———	5.57 (7.3)
	H(4) ($J_{3,4}$; $J_{4,5}$)	3.37 (6.4; 6.4)	3.49 (4.4; 2.0)		3.72 (4.9; 2.9)
β	H(1) ($J_{1,2}$)	5.07 (~ 0)	5.33 (1.0)	5.63 (~ 0)	4.84 (~ 0)
	H(4) ($J_{3,4}$; $J_{4,5}$)	3.28 (9.3; 9.3)	3.45 (9.3; 9.3)	3.25 (9.3; 9.3)	3.25 (9.3; 9.3)

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