Pergamon

Tetrahedron Letters 39 (1998) 4537–4540

TETRAHEDRON LETTERS

AgOTfa/SnCl4: A Powerful New Promoter Combination in the Aryl C-Glycosidation of a Diverse Range of Sugar Acetates and Aromatic Substrates.

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Received 4 March 1998; revised 15 April 1998; accepted 17 April 1998

Abstract:

SnCl4/AgOTfa was shown to be a powerful combination for promoting aryl C-glycosidation between various sugar acetates and aromatic substrates. This promoter activates otherwise unreactive peracetylated glycosides, leaving them susceptible to reaction with low electron-donating aromatics. A survey of the reaction application is described.

Keywords: Carbohydrate mimetics; Coupling reagents; Friedel-Crafts reactions; Glycosidation.

Aryl C-glycosides are naturally-occurring, structurally diverse compounds that have attracted considerable attention because they exhibit a vast array of important biological activities[1]. Synthesis of aryl C-glycosides that do not occur in nature, but that are congeners of biologically important aryl O-glycosides or are mimics of biologically important glycoepitopes, may eventuate in the discovery of lead compounds having novel biological activities and pharmaceutical value. These compounds would have the advantage of being very stable against acidic hydrolysis and less vulnerable to enzymatic digestion[2].

Several useful methods for aryl C-glycosidation have been developed[3-20]. Suzuki's O→C glycoside rearrangement method[7-9], in particular, is an excellent method that was successfully applied to the synthesis of natural aryl C-glycoside antibiotics[1,21,22].

Several problems inherent to seeking biologically active aryl C-glycosides were revealed during the course of our synthetic studies. A close examination of the existing methods revealed that most of them were focused primarily on aromatics, such as high electron-donating trimethoxybenzene or β-naphthol, or on reactive glycosyl donors protected with benzyl groups or 2-deoxy sugars[7-16]. There appeared to be no systematic survey of the

0040-4039/98/$19.00
PII: S0040-4039(98)00825-9

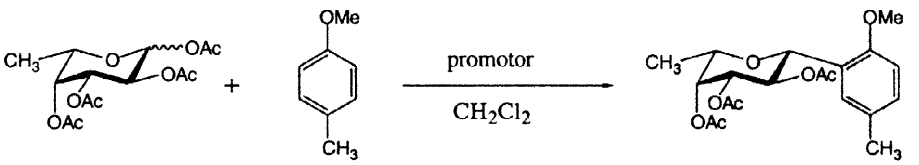
glycosidation between the monosaccharides commonly found on the cell surface glycoconjugates and the relatively unreactive aromatics.

In this communication, we wish to report on a new powerful promoter combination of silver trifluoroacetate/tin tetrachloride (AgOTfa/$SnCl_4$) that activates even relatively unreactive peracetylated glycosides in a Friedel-Crafts-type reaction and that affords aryl C-glycosides. The application of this new promoter combination to a diverse range of sugars and aromatics is described.

Rather than being utilized as a glycosyl donor, glycosyl acetates are commonly the intermediate species for preparation of more active donors. Thus, providing they can be properly activated, their merit lies in their ready availability, stability and ease of handling.

To this end, fucose tetraacetate was selected as a glycosyl donor, along with p-methoxytoluene as a low electron-donating aromatic substrate, for the screening of aryl C-glycosidation promoters. The results are summarized in Table 1.

Table 1: The Effect of Additives on the Glycosidation of Fucose Tetraacetate



Entry	Promotor	Isolated Yield	α/β ratio[a)]
1.	$SnCl_4$	42	71 / 29
2.	$SnCl_4$ / AgOTf	27	ND[b)]
3.	$SnCl_4$ / $AgClO_4$	41	1 / 99
4.	$SnCl_4$ / $Hg(OAc)_2$	83	13 / 87
5.	$SnCl_4$ / $Hg(OTfa)_2$	72	2 / 98
6.	$SnCl_4$ / AgOTfa	89	1 / 99
7.	$SnCl_4$ / $Sn(OTf)_2$	56	ND[b)]
8.	$SnCl_4$ / $Tl(OTfa)_2$	35	ND[b)]
9.	$SnCl_4$ / TMSOTf	55	28 / 72
10.	$GaCl_3$ / AgOTfa	76	3 / 97

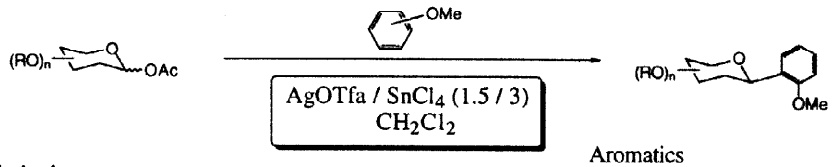
The reaction was carried out in CH_2Cl_2 at 0 °C - R.T. for several hours using the following eqivalency:
Fucose tetraacetate / p-Methoxytoluene / $SnCl_4$ / Additive = 1 / 2 / 1.5 / 3
a) determined by HPLC b) ND means not determined

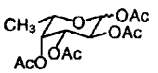
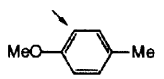
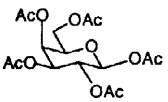
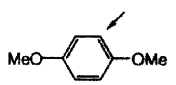
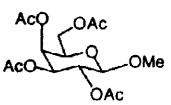
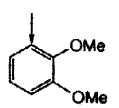
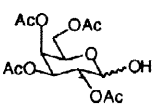
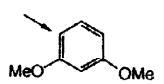
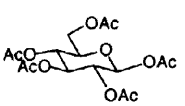
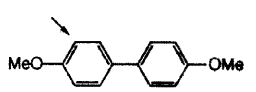
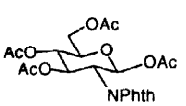
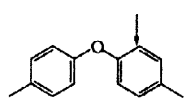
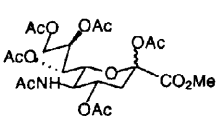
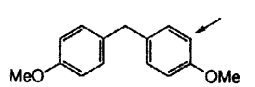
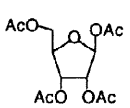
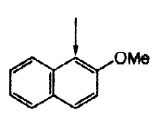
Among the number of typical Lewis acids examined, only $SnCl_4$ afforded the coupled product, although the yield and α/β selectivity were less than satisfactory (entry 1). The use of AgOTf or $AgClO_4$ with $SnCl_4$[23], popular coupling reagents in O-glycosidation, was too strong and afforded a complex mixture mainly from the decomposition of the fucose moiety (entry 2,3). A search directed to identifying milder coupling reagents revealed that the use of $Hg(OAc)_2$, $Hg(OTfa)_2$ or AgOTfa as an additive provided a clean reaction; especially AgOTfa, which afforded the best results in yield and selectivity (entry 6). Other metal salts of acids produced no improvement. Of trials with Lewis acid $GaCl_3$, $GaCl_3$/AgOTfa showed promising result (entry 10).

With this new promoter combination in hand, we turned our attention to applying it to a diverse range of sugars and aromatics. The data are summarized in Table 2. It is evident from these results that not only fucose peracetate but also that of galactose, glucose and N-phthaloyl glucosamine reacted with p-methoxytoluene to

afford the aryl C-glycosides in good yields (entries 2,5 and 6). Entries 3 and 4 are noteworthy in that they show that not only the acetate but also the 1-methoxy or 1-hydroxy of sugars can be the donors in the reaction.

Table 2: Application of AgOTfa/$SnCl_4$ to a Wide Range of Sugers and Aromatics[a)]



Entry	Carbohydrates react with	Isolated Yield (%) (α/β) ratio[b)]	Entry	Aromatics react with	Isolated Yield (%)[c)]
1.		89 (β only)	9.		78
2.		78 (")	10.		82
3.		60 (")	11.		67
4.		42 (")	12.		42
5.		65 (")	13.		66
6.		77 (")	14.		74
7.		31 (84:16)	15.		62
8.		62 (26:74)	16.		61

a) The arrow indicates where the carbohydrate is accepted. b) Determined by HPLC. c) Only β-anomer was obtained.

Further trials involving sialic acid and ribose acetates show that these also can be donors; however, they exhibited only fair stereocontrol and yields. Examination of reactions between galactose pentaacetate and various

aromatics (entry 9-16) indicated that almost all types of aromatics activated with at least one methoxy group can serve as substrates for this aryl C-glycosidation.

Noteworthy is the coupling of N-acetyl-2,4,7,8,9-penta-*O*-acetyl-α,β-neuraminic acid methyl ester with a reactive 1,3-dimethoxybenzene as this affords an aryl C-sialoside in 78% yield (α:β = 89:11), which is an interesting glycomimetic of sialosylated glycoepitopes.

The application of this reaction to the synthesis of biologically interesting aryl C-glycosides is currently in progress.

A typical procedure is represented by the reaction of fucose tetraacetate and p-methoxytoluene:

To a mixture of L-fucose tetraacetate (332mg, 1.0mmol), p-methoxytoluene (250μl, 2.0mmol) and AgOTfa (333mg, 1.5mmol) in CH_2Cl_2 (5ml) at 0°C was added a 1M $SnCl_4$ CH_2Cl_2 solution (3ml, 3.0mmol) under N_2 gas atmosphere. After the reaction mixture was stirred for 4h at 0°C, $NaHCO_3$ aqueous solution was added and stirred for 20 min. The inorganic material was filtered off over a Celite^R pad and the filtrate was extracted several times with CH_2Cl_2. The combined CH_2Cl_2 solution was washed with brine and dried over anhydrous $MgSO_4$, then concentrated under reduced pressure. A small amount of crude product was subjected to HPLC analysis, and the remainder was purified by column chromatography on silica gel (hexane/EtOAc = 2/1) to afford 4-methoxy-3-(2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl)toluene (352mg, 0.89mmol).

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