Pergamon

Tetrahedron Letters, Vol. 37, No. 9, pp. 1477-1480, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00043-3

A New Promoter System for the Sulfoxide Glycosylation Reaction

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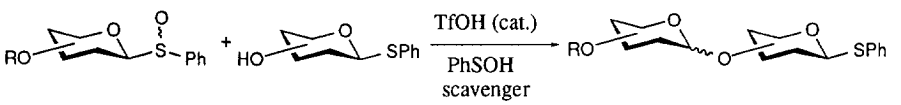
Abstract: *Sulfinylglycosides are efficiently activated by the system TfOH/TEP in the glycosylation reaction to afford disaccharides in good yields.*

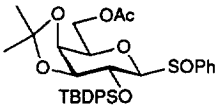
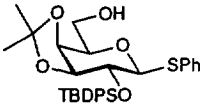
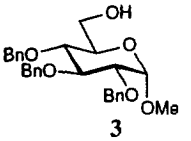
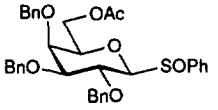
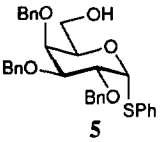
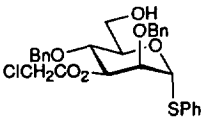
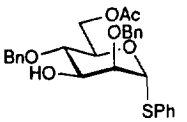
In the last decades there has been an increased interest towards oligosaccharides, since a great number of biological studies have revealed the vital roles played by the glycone of glycoconjugates and antibiotics in molecular recognition for the transmission of biological information. As a consequence considerable and fascinating progress has been made in the synthesis of these complex biomolecules,[1] but still no single type of reaction or set of reaction conditions is successful in every instance. So new methodologies are continuously being developed. Among the glycosylation reactions recently developed, the sulfoxide methodology is particularly attractive especially when rather unreactive nucleophiles are used as glycosyl acceptors.[2] The effectiveness of a glycosylation reaction is not only dependent on the glycosyl donor used, but also and in a large extent on the promoter used to activate it. Up to date, two types of promoter systems for sulfinylglycosides have been described. The first one uses Tf_2O[3] or TfOTMS[4] in stoichiometric amount, while the second one uses a catalytic amount of triflic acid (TfOH) in the presence of large excess of methyl propiolate as acid scavenger.[5] Using the second system and taking advantage of the fact that the reactivity of phenylsulfinylglycosides can be regulated by the substituent in the *para* position of the phenyl ring, D. Kahne succeeded in the synthesis of the cyclamycin O trisaccharide in a one-step manner. In a project aimed to the synthesis of an octasaccharide putative second messenger of the hormone insulin, we tried to apply Kahne´s methodology for the preparation of the tetragalactose moiety in a one-step manner. However, according to our results[6] as well as others[4], this system is not effective for sulfinyl glycosides other than 2-deoxy sugars. In this communication we describe that the use of TEP (triethyl phosphite) as acid scavenger allow the use of TfOH in a catalytic amount in the preparation of several disaccharides in acceptable yield.



Scheme 1

The acid activation of a sulfinylglycoside leads to the release of 1 equiv of a sulfenic acid. It is known that sulfenic acids are highly reactive species and undergo a rapid bimolecular reaction promoted by hydrogen bonding (scheme 2) affording 1 equiv. of thiosulfinate and 1 equiv. of water[8] which can hydrolyze the half of the oxonium ion. In the case of less reactive glycosyl donors this reaction can

Table I: TfOH/TEP catalysed glycosylation reactions.[a]

Entry	Donor	Acceptor	T(°C)	Products α:β ratio	Yield(%)[b]	Thioglycoside recovered (%)[g]
1	 **1**	 **2**	-40	80:20	68 (98)	26
2	**1**	 **3**	-25	75:25	65 (98)	31
3	 **4**	**3**	-40	45:55	79 (96)	38
4[c,d]	**4**	 **5**	-40	55:45	40 (--)	--
5	**4**	**5**	-20	46:54	63 (99)	38
6	**1**	 **6**	-30	77:23	52 (98)	28
7[e]	**1**	 **7**	-30	100:0	26 (>99)	24
8[f]	**4**	**3**	-40	48:52	92 (--)	21

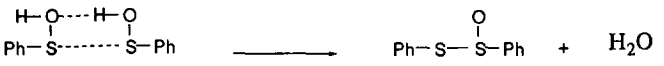
[a] All reactions were conducted in ether:CH_2Cl_2 3:1, using 3 equiv. of the donor, 1 equiv. of the acceptor, 4 equiv. of TEP, 1 equiv. of TfOH, in the presence of 4Å molecular sieves, until otherwise indicated. [b] Yield in transformed glycosyl acceptor in brackets. [c] 2 equiv. of donor and a mixture of ether-CH_2Cl_2 1:1 as solvent were used. [d] Only TfOH was used as a promoter and 2.2 equiv were needed. Without MS.

[e] Temperature was raised to room temperature then a reaction progress was observed.

[f] A mixture of 0.33 equiv. of TfOH and 1.3 equiv. of TEP in ether, 0.03 and 0.13M respectively, was used as a promoter.

[g] Coming from the reduction of the glycosyl donor.

compete efficiently with the glycosylation reaction. Thus, the use of a very effective acid scavenger able to react with sulfenic acid at low temperatures is essential.



Scheme 2

Michael acceptors such as methyl propiolate do not fulfill this requirement, especially at the low temperature at which the reaction is conducted.[9] Comparison of the yield of disaccharide obtained in the presence (Table, entry 5) and in the absence (entry 4) of TEP are indicative of the effectiveness of TEP as sulfenic acid scavenger. The use of this promoter system allowed the preparation of several disaccharides[7] in acceptable isolated yields and in excellent yield based on the transformed glycosyl acceptor as it can be seen from table 1 (entries 1-3, 5. 6 and 8).

The only important side product obtained in the reaction is the thioglycoside coming from the reduction of the glycosyl donor. The amount of thioglycoside is in relation with the amount of TEP employed (compare entries 3 and 8) which is known to be an effective deoxygenating agent.[10] Nevertheless, this thioglycoside is a valuable intermediate that needs only one step of oxidation to be reused. It is worth noting the mildness of the reaction conditions as indicated by the use of labile acid groups either in the glycosyl donor or acceptor (entry 1, 2, 6 and 7). This system also enable the selective activation of sulfinylglycosides in the presence of thioglycosides (entries 1, 5, 6 and 7). As thioglycosides are known to be good glycosyl donors, the disaccharide thus obtained in these cases can be used as glycosyl donor. The α,β ratio depends on the structure of the glycosyl donor, compound **1** gives better α-selectivity than **4**. Unfortunately, when a more hindered acceptor was employed (entry 7) disaccharide was formed in low yield although the yield on transformed product was excellent. Special attention has to be paid to the result given in entry 8 where lowering the amount of TEP (0.43 equiv./1 equiv. of the donor) and TfOH (0.11 equiv./1 equiv. of the donor) enhance the yield of the disaccharide (92 %). This result is indicative of the mechanism by which the reaction occurs and, indicates also that the yield when using secondary alcohols as glycosyl acceptors may be improved by changing the amount of the promoter system.

In conclusion, we have shown for the first time that TfOH/TEP[11] is an effective, mild and selective promoter system of sulfinylglycosides. The fact that triflic acid acts in a catalytic amount opens the way to the construction of various glycosidic linkages in a one-step synthesis using many types of sulfinylglycosides. Toward this end we are now trying to improve the results with secondary acceptors.

Acknowledgment. We gratefully acknowledge the dirección General de Investigacíon Cientifica y Técnica (Grant PB-93-0127) and Europharma S. A. for financial support .

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7. **General procedure for the glycosylation reaction.** To a solution of 0.04 mmoles (1 equiv) of acceptor, 0.12 mmoles (3 equiv) of donor and 100 mg of powdered molecular sieves (4 Å) in ether-dichloromethane 3:1 (4 ml) at -40°C under argon atmosphere, 0.16 mmoles (4 equiv.) of triethyl phosphite and 0.04 (1 equiv.) of TfOH were added. Stirring was continued and the reaction followed by T.L.C. although it seems to be immediate. Then, a saturated solution of $NaHCO_3$ (15 ml) was added and the reaction mixture was extracted with dichloromethane (2X15 ml). The combined organic layers were washed with brine (15 ml), dried (Na_2SO_4) and evaporated. The crude mixture was purified by flash chromatography.
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11. No glycosidation reaction of the liberated ethanol (coming from the reaction of H_2O and $P(OEt)_3$) has been observed in any case.

(*Received in UK* 24 *October* 1995; *revised* 20 *December* 1995; *accepted* 8 *January* 1996)