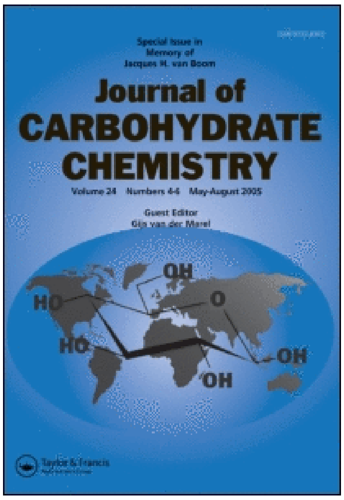

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Synthesis and Reactions of Carbohydrate Trifluoro-Methanesulfonates (Carbohydrate Triplates)

Roger W. Binkley[a]; Michael G. Ambrose[a]
[a] Department of Chemistry, Cleveland State university, Cleveland, Ohio

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SYNTHESIS AND REACTIONS OF CARBOHYDRATE TRIFLUOROMETHANESULFONATES (CARBOHYDRATE TRIFLATES)

Roger W. Binkley* and Michael G. Ambrose

Department of Chemistry
Cleveland State University
Cleveland, Ohio 44115

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I. INTRODUCTION

During the past decade a new leaving group, the trifluoromethanesufonate (triflate), has been used increasingly in displacement reactions in carbohydrate chemistry*. The importance of this group has become progressively more apparent to the synthetic carbohydrate chemist as the examples of triflate displacement have increased. The number of applications of this reaction now has reached a sufficient magnitude that it seems appropriate to review what has been accomplished.

This article, which describes the applications of triflate displacement in carbohydrate chemistry, includes a discussion of the factors which have been found to be significant in understanding the chemistry of these compounds. Also, for individuals interested specifically in knowing which triflates have been synthesized and reacted, a compilation of the compounds studied is found in Tables 1-11. To provide information on the chemistry of carbohydrate triflates which is as current as possible, a series of research papers describing recent developments in the reactions of these compounds follows this article.

II. RELATIVE REACTIVITY OF SEVERAL SULFONIC ESTERS

A reasonable first topic to be discussed in considering the chemistry of a new leaving group is a comparison between its reactivity and that of its more

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*The first report of triflate displacement from a carbohydrate was by Maradufu and Perlin (reference 1).

common counterparts. The new leaving group in this case is, of course, the triflate while the common counterparts are the *p*-toluenesulfonate (tosylate) and methanesulfonate (mesylate). Unless triflate displacement has a clear advantage over the corresponding reactions of tosylates and mesylates, there would seem to be little justification for its use. Some information pertinent to this subject is found in a recent review* of the methods of preparation of perfluoroalkanesulfonic esters and the use of these esters in organic chemistry. This review summarizes the leaving group ability of a number of sulfonates. The relative reactivities of the mesylate, tosylate, and triflate are reported to be 1.00, 0.70, and 56,000, respectively. While the numbers associated with these groups undoubtedly vary somewhat with the particular system under study and the reaction conditions, they provide a real appreciation for the jump in reactivity which takes place when a mesyl or tosyl group is exchanged for a triflyl group.

In light of the relative reactivity of the three types of sulfonic esters mentioned in the preceding paragraph, it is not surprising that triflate displacement often occurs in high yield in carbohydrates for which displacement involving other sulfonic esters requires such drastic conditions that little or no substitution product is obtained. For example, mesylate displacement from 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-methylsulfonyl-α-*D*-allopyranosyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-*D*-glucopyranoside (1) with lithium azide at 105-108 °C in *N*,*N*-dimethylformamide (DMF) for 12 hours gives a complex mixture of products from which the desired azide 3 is isolated with difficulty in only 20% yield (equation 1); in contrast, the corresponding

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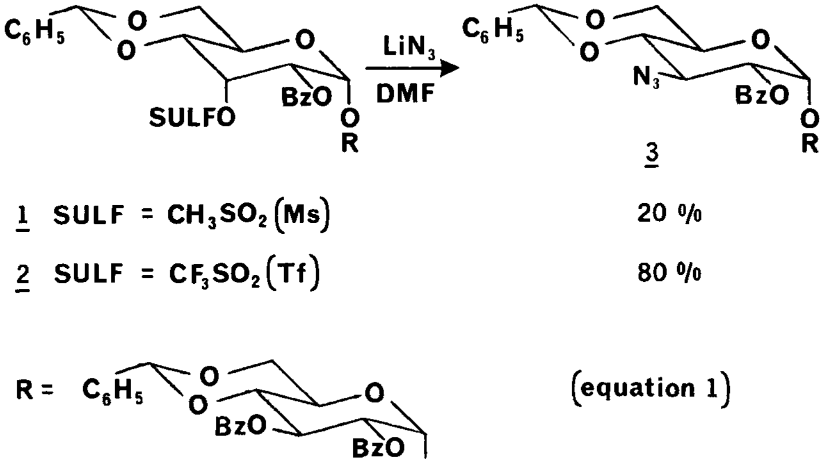
*This review by Stang, Hanack, and Subramanian (reference [58]) contains a wealth of valuable information about triflates. Some examples using carbohydrates are included.



1 SULF = CH_3SO_2(Ms) 20 %

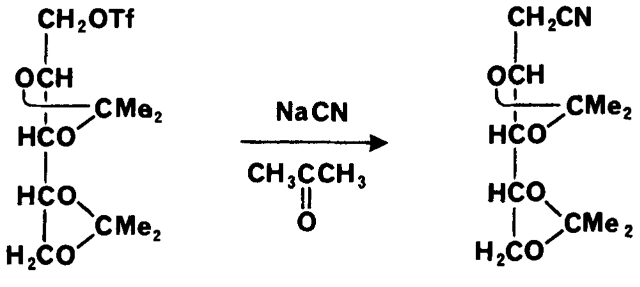
2 SULF = CF_3SO_2(Tf) 80 %

(equation 1)

triflate (2) reacts "almost instantaneously at room temperature" to give the azide 3 in 80% yield (equation 1, Table 2).[7] Another pertinent example is found in the reaction of 2,3:4,5-di-O-isopropylidene-1-O-trifluoromethylsulfonyl-D-arabinitol (4) with cyanide ion at room temperature to give 2,3:4,5-di-O-isopropylidene-D-arabinononitrile (5) (equation 2, Table 6).[41] This reaction is described as being much faster than that of the corresponding tosylate and yielding a product which is easier to purify. These two reactions (equations 1 and 2) illustrate well the reason for the triflate often being the leaving group of choice in a displacement reaction. Simply stated, the advantage the triflate has over other leaving groups is that displacement occurs at a much lower temperature where, in general, there is little or no competition from elimination, rearrangement, or other undesired reactions.

III. SYNTHESIS OF CARBOHYDRATE TRIFLUOROMETHANESULFONATES (CARBOHYDRATE TRIFLATES)

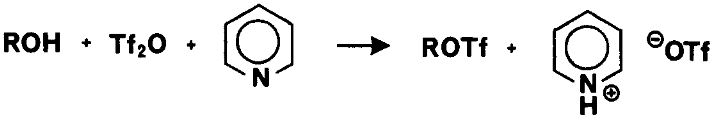
Two methods have been developed for synthesizing carbohydrates which contain the trifluoromethylsulfonyl



4 5

(2)

(triflyl) group. The most widely used of these methods consists of reacting a partially protected carbohydrate with triflic anhydride in the presence of an organic base, usually pyridine or a substituted pyridine (equation 3).



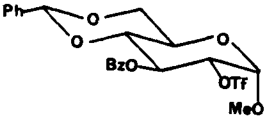
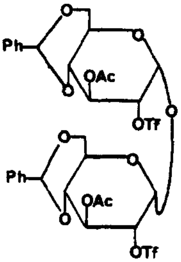
(3)

(The base is present to neutralize any acid produced during esterification.) If a triflyl group is to be introduced into the carbohydrate portion of a nucleoside, a second procedure frequently is used; that is, an unprotected hydroxyl group first is converted into its sodium salt by reaction with sodium hydride (equation 4) and then this salt is treated with triflyl chloride to produce the corresponding triflate (equation 5).

$$2\ ROH + 2\ NaH \longrightarrow 2\ RONa + H_2 \qquad (4)$$

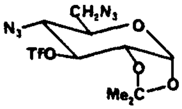
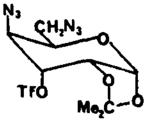
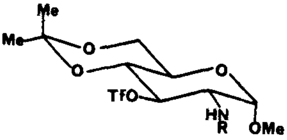
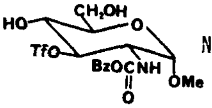
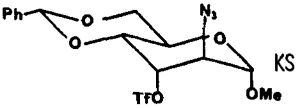
$$RONa + TfCl \longrightarrow ROTf + NaCl \qquad (5)$$

TABLE 1.[A] TRIFLATE DISPLACEMENT FROM THE 2-POSITION OF A PYRANOSE RING

SUBSTRATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., °C	REF.
						
R=Me	CsF	0.5	DMF	42	130	2
R=Bn	TBAF		DMF	35-60	RT	3
R=Bz	TBAF		DMF	35-60	RT	3
	TBAF		DMF			3
	NaOBz	5	DMF	82	80	4
	NaN_3	2	DMF	86	80	4
	$NaSCH_3$	1	DMF	89	0	4
	$NaSC_6H_5$	6	DMF	83	50	4
	NaOMe	OVERNIGHT	DMF	85	RT	4
	$NaSC_6H_5$		DMF			5

A. SEE TABLE 12 FOR THE MEANING OF ABBREVIATIONS USED.

TABLE 2.[A] TRIFLATE DISPLACEMENT FROM THE 3-POSITION OF A PYRANOSE RING

SUBSTRATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., °C	REF.
	NaN_3	4	DMF	43	65	6
	NaN_3	1	DMF	81	65	6
COMPOUND 2 (EQUATION 1)	LiN_3	IMMEDIATE	DMF-DMSO	80	60	7
						
R=C(O)OBz	$NaSC_6H_5$	OVERNIGHT	DMF	64	5	8
R=Ac[B]	$NaSC_6H_5$	12	DMF	90+	25	9
	$NaSC_6H_5$	OVERNIGHT	DMF	81	5	8
	$KSC(O)CH_3$		DMF	97	-15	10

A. SEE TABLE 12 FOR THE MEANING OF ABBREVIATIONS USED.

B. THIS REACTION WAS ALSO CONDUCTED ON A MIXTURE OF ALPHA- AND BETA-ANOMERS.

TABLE 3.[A] TRIFLATE DISPLACEMENT FROM THE 4-POSITION OF A PYRANOSE RING

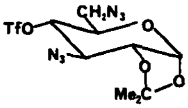
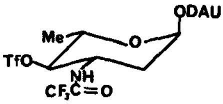
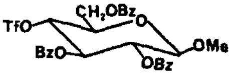
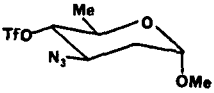
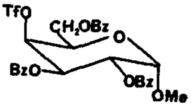
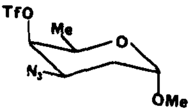
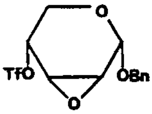
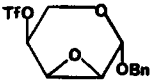
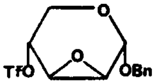
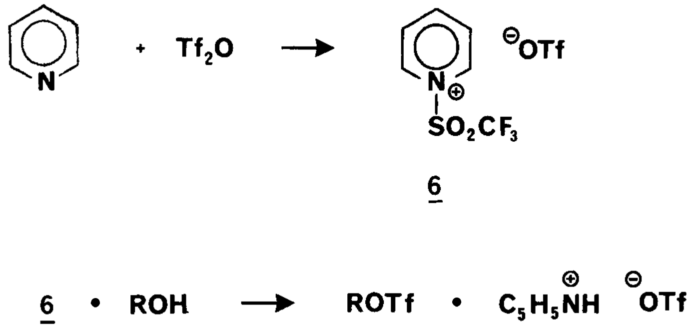
SUBSTRATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., ^{0}C	REF.
	NaN_3	1.0	DMF	83	RT	6
	TBAI			75	30	11
	NaN_3	2	DMF	75	95-100	1
	Bu_4NOAc	0.5	MeCN	88	40	12
	KSCN	12	DMF	80	85	13
	Bu_4NCN	5 MIN.	MeCN	21	30	12

TABLE 3.[A] (CONTINUED)

SUBSTRATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., °C	REF.
	NaN_3		DMF	91	RT	14,15
	NaN_3		DMF	85	RT	14,15
	NaN_3		DMF	80	RT	14,15

A. SEE TABLE 12 FOR THE MEANING OF ABBREVIATIONS USED.

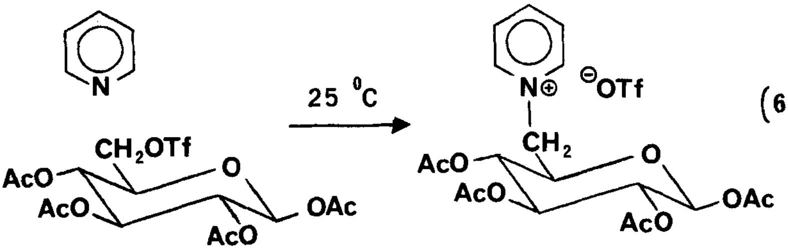
When triflic anhydride and pyridine are combined, the pyridinium salt 6 forms immediately (Scheme 1). This material (6) precipitates from solution in solvents



SCHEME 1

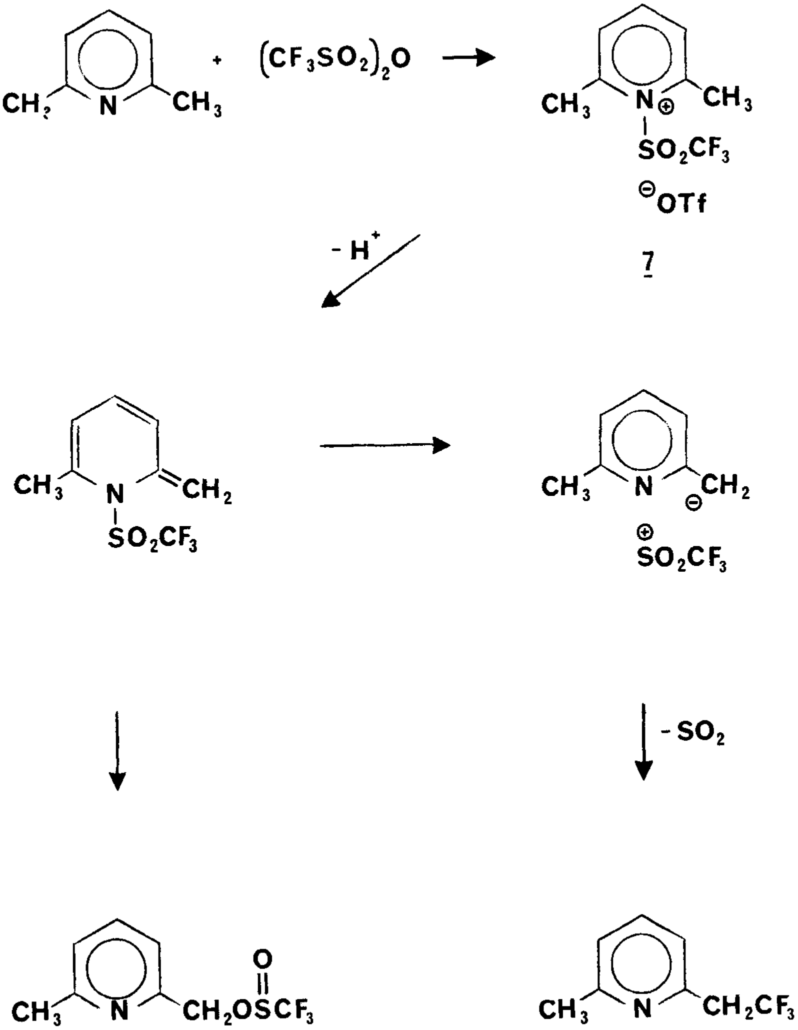
of relatively low dielectric constant (eg., benzene); nevertheless, the salt 6 is an effective esterifying agent which reacts with the added carbohydrate to give high triflate yields (Scheme 1).

The primary disadvantage in using pyridine as a base is that it is also a nucleophile and can become involved in displacement reactions when very reactive triflates are being synthesized (equation 6).[40] One approach to minimizing displacement by pyridine is to replace it with one of its less nucleophilic derivatives, such as 2,4,6-trimethylpyridine or 2,6-dimethylpyridine.[59,60] Although these compounds are less nucleophilic than pyridine itself, and, consequently, are less likely to displace triflate, methyl pyridines complicate the situation by opening new reaction pathways.[61] The initial reaction between 2,6-dimethylpyridine, for example, and triflic anhydride is formation of the quaternary ammonium salt 7 (Scheme 2). This salt serves as a triflating agent but also experiences intra- and intermolecular rearrangement to give new pyridine derivatives (Scheme 2).[61]



(6)

No salt formation or other reaction appears to take place between triflic anhydride and the highly hindered 2,6-di-t-butyl-4-methylpyridine (8); thus, when 8 is used to neutralize the triflic acid formed, none of the complications described above are observed. Under these conditions the triflating agent actually


CH3
N
CH3
+
(CF3SO2)2O
CH3
N⊕
CH3
SO2CF3
⊖OTf
7
- H+
CH3
N
CH2
SO2CF3
CH3
N
⊖CH2
⊕SO2CF3
- SO2
CH3
N
CH2OSCF3
O
CH3
N
CH2CF3

SCHEME 2

appears to be triflic anhydride itself and not a pyridinium salt.

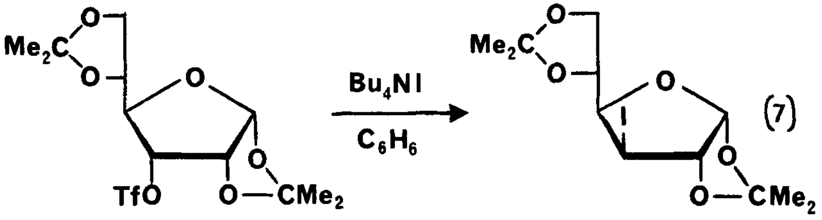
The most common combination of reagents for triflate formation where nucleosides are involved is triflyl chloride and the alkoxide salt formed by reacting the partially protected nucleoside with sodium hydride. Formation of the alkoxide has the advantage that it eliminates the need for an organic base in the reaction mixture; however, alkoxide formation requires quite basic reaction conditions. The disadvantages to the use of triflyl chloride as opposed to triflic anhydride appear to outweigh its advantages. Triflyl chloride is a volatile liquid which is somewhat difficult to measure and transfer without loss of material. Also, it is a chlorinating agent in free radical reactions;[62] thus, the potential exists for reaction processes other than triflate formation. The chloride ion produced by reaction of triflyl chloride can function as a nucleophile and displace the triflyloxy group.[24] Even with these disadvantages, the number of triflates which have been prepared successfully from triflyl chloride demonstrates that it is a useful reagent.

IV. REACTIONS OF CARBOHYDRATE TRIFLATES

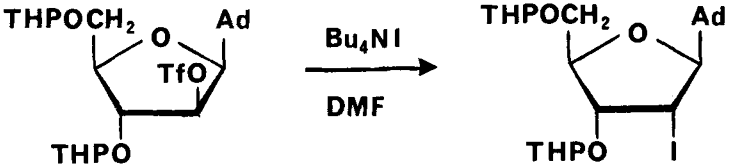
A. SUBSTITUTION REACTIONS

1. FACTORS EFFECTING THE NUCLEOPHILE

The most commonly used nucleophiles for triflate displacement are, of course, negatively charged species and, therefore, must be introduced into a reaction mixture along with a cation. The choice of this cation, which is usually a tetrabutylammonium or alkali metal ion, can be critical to the success of the displacement process. Tetrabutylammonium compounds are soluble in both polar and non-polar solvents; consequently, they have a versatility which is not shared with lithium, sodium, or even cesium compounds, salts which require polar solvents for dissolution. Tetrabutylammonium iodide, for example, has been used for triflate displacements conducted in benzene (equation 7, Table 5)[36] as well as DMF (equation 8, Table 4).[27]

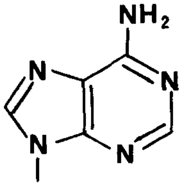


(7)

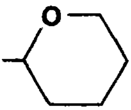


(8)

Ad =



THP =



Triflate displacement with fluoride ion is of particular interest due to the importance of deoxyfluoro sugars in metabolic studies and disease diagnosis. The nucleophilicity of fluoride ion under most conditions is decidedly less than that of other halides; consequently, the enhanced reactivity of the triflyloxy group is essential for some displacements with this ion. One factor which reduces the nucleophilicity of fluoride is its strong association with water (and other polar

TABLE 4.^{A} TRIFLATE DISPLACEMENT FROM THE 2-POSITION IN A FURANOSE RING

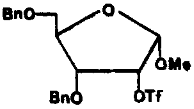
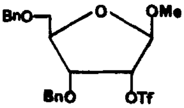
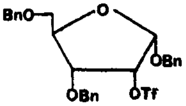
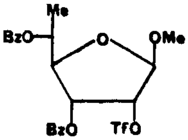
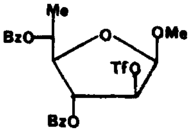
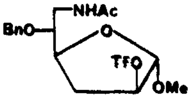
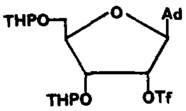
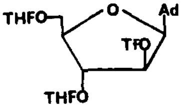
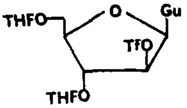
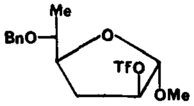
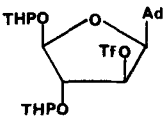
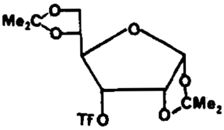
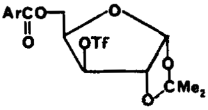
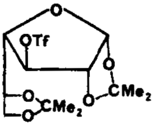
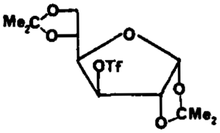
SUBSTRATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., °C	REF.
 9	TBAF	3.5	THF	62	-10	16
	LiCl	20	DMSO-HMPT	67	RT	16
	LiBr	3	DMSO-HMPT	89	RT	16
	NaI	20	DMSO-HMPT	84	RT	16
	LiN_3	0.7	DMSO-HMPT	90	RT	16
 10	TBAF	48	THF	0^B	-10	17
	LiCl	48	DMSO-HMPT	14^B	RT	17
	LiBr	48	DMSO-HMPT	19^B	RT	17
	NaI	48	DMSO-HMPT	19^B	RT	17
	LiN_3	48	DMSO-HMPT	54^B	RT	17
	TBAF	3	THF	50	0	17
	LiCl	20	DMSO-HMPT	64	RT	17
	LiBr	5	DMSO-HMPT	72	RT	17
	NaI	20	DMSO-HMPT	90	RT	17
	LiN_3	3	DMSO-HMPT	84	RT	17
	TBAI	24	BENZENE	82	80	18
	TBAI	24	BENZENE	82	80	18
	NaN_3	2	HMPT	60	RT	19

TABLE 4.[A] (CONTINUED)

SUBSTRATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., °C	REF.
	LiN_3	"FEW MINUTES"	HMPT	61	RT	21
	KSAc		HMPT	88	RT	21
	NaOAc	"FEW HOURS"	HMPT	55	RT	21
	TBAF	2.5	THF	21	4	22
	TBAF	15	THF	40	RT	23
	TBAF	15	THF	32	RT	24
	LiCl	0.5	DMF	36	50	24
	LiBr	0.5	DMF	25	50	24
	NaI	0.5	DMF	34	50	24
	NaN_3	2	HMPT	65	RT	20
	LiN_3	0.2	HMPT	HIGH		25,26
	LiCl		HMPT	HIGH		25
	TBAC	3	DMF	58	80	27
	LiBr		HMPT	HIGH		25
	TBAB	5	DMF	55	70-100	27
	NaI		HMPT	HIGH		27
	TBAI	2	DMF	25	100	27
	NaOAc	"FEW HOURS"	HMPT	HIGH		25
	KSAc		HMPT			25
	TBAF	2	THF	50[B],60		23,27

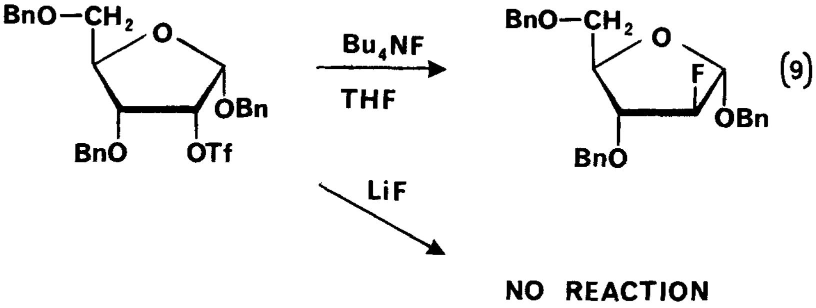
A. SEE TABLE 12 FOR THE MEANING OF ABBREVIATIONS USED.
B. SUBSTITUTION IS ACCOMPANIED BY ELIMINATION; SEE TABLE 11.

TABLE 5.[A] TRIFLATE DISPLACEMENT FROM THE 3-POSITION OF A FURANOSE RING

SUBSTRATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., ^{0}C	REF.
	$NaNH_2$	48	ETHER	32	RT	28
	C_6H_5N	25	PYRIDINE	71	111	29,30
	C.	16	BENZENE	100	25	31
	CsF, TBAF	1.5	DMF	71	-15	32,33,34
	TBAI	12	BENZENE	87	80	35,36,37
	TBAB	12	BENZENE	96	80	36,37
	TBAC	12	BENZENE	85	80	36
	KSCN	20	MeCN	71	70	38
	LiN_3	5	ETHANOL	51[B]	78	39
	LiN_3		HMPT	51[B]	0	39
	Bu_4NN_3		DMF	51[B]	20	39
	TBAI	5	BENZENE	81	80	36
 16	TBAI	18	BENZENE	84	80	35,36
	TBAB	18	BENZENE	42[B]	80	36
	TBAC	18	BENZENE	22[B]	80	36
	KSCN	36	MeCN	53	78	38

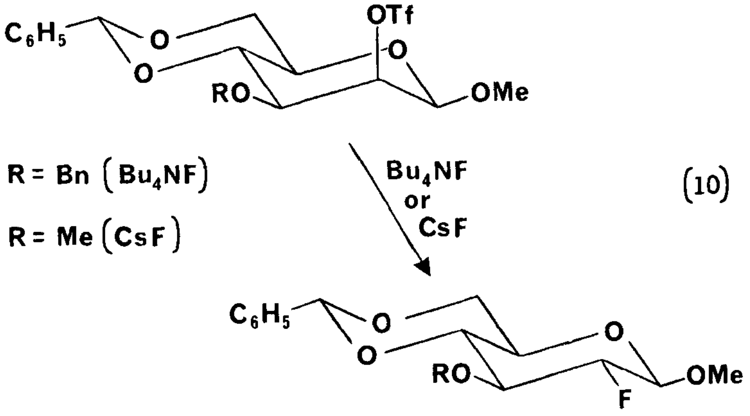
A. SEE TABLE 12 FOR THE MEANING OF ABBREVIATIONS USED.
B. SUBSTITUTION IS ACCOMPANIED BY ELIMINATION; SEE TABLE 11.
C. TETRABUTYLAMMONIUM 2-IODO-4-PHENYL PHENOLATE

molecules); therefore, although anhydrous fluoride salts often are not easy to obtain, they are sometimes essential in displacement reactions. A second factor which influences reactivity is the separation between fluoride ion and its associated cation. Fluoride which is separated from other ions and strongly solvating molecules ("naked fluoride") appears to have nucleophilicity comparable to other halides.[63] One method for separating fluoride from the center of positive charge of the associated cation is to switch from lithium or sodium ions to the tetrabutylammonium ion. In fact, tetrabutylammonium fluoride has been found to be successful in triflate displacement in situations where lithium fluoride has failed[17] (equation 9, Table 4). Cesium fluoride and



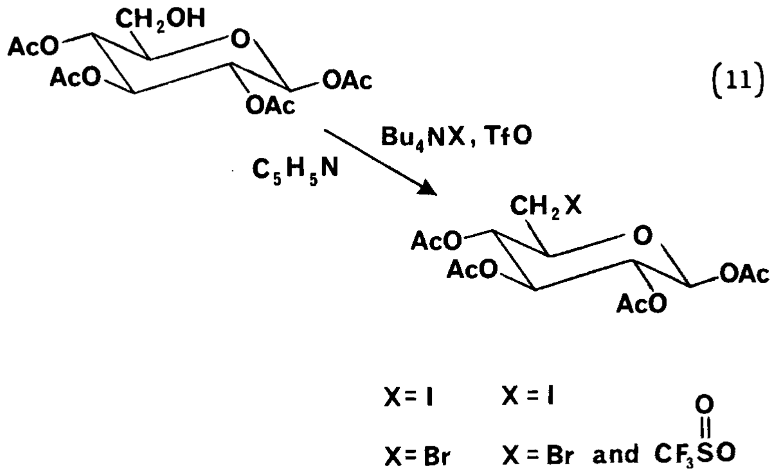
tetrabutylammonium fluoride both have been used in reactions where displacement is known to be difficult (equation 10, Table 1).[2,3] The large cesium ion may be comparable to the tetrabutylammonium ion in its ability to activate fluoride.

The simplest method for triflate synthesis and displacement should be to combine all the reactants (*i.e.*, triflic anhydride, base, partially protected sugar, and nucleophile) at the same time in a single flask (a "one-pot" reaction)). This approach worked well, at least in one instance where iodide ion was



(10)

the nucleophile (equation 11, Table 6).[40] It was less successful, however, when bromide ion was involved because bromide reacted with triflic anhydride to give a new nucleophile ($CF_3SO_2^-$) (equations 12 and 13).[40] This new nucleophile competed with bromide and produced a new type of substitution product (equation 11, Table 6).[40] (It is probable that the same reactions (equations 12 and 13) take place with iodide ion and triflic anhydride but it is also probable that $CF_3SO_2^-$ does not compete effectively in triflate displacement with the iodide ion present in solution.) An attempt at a similar one-pot reaction using chloride ion gave only unreacted starting material (no triflate formation). Lack of reaction apparently was the result of the water associated with the quarternary ammonium chloride reacting with triflic anhydride in preference to the sugar. Displacements by bromide and chloride occurred normally to give the corresponding deoxyhalogeno sugars in high yields (Table 6) in one-pot reactions if triflate formation was allowed to occur prior to nucleophile introduction. Triflate formation and reaction with halides, therefore, can take place in a single flask if the reagents are added in a speci-



(11)

$$Br^{\ominus} + (CF_3SO_2)_2O \longrightarrow CF_3SO_2Br + CF_3SO_3^{\ominus} \qquad (12)$$

$$Br^{\ominus} + CF_3SO_2Br \longrightarrow Br_2 + CF_3SO_2^{\ominus} \qquad (13)$$

fic order. Only for deoxyiodo sugar synthesis can all reagents be combined at the same time.

2. INFLUENCE OF THE SOLVENT

A number of solvents (benzene, methylene chloride, DMF, THF, HMPT, and DMSO)* have been used for triflate displacement reactions. Although a thorough study of the relationship between solvent and reactivity has not been conducted, the information available for these reactions suggests that, as with other S_N2 displacements, reaction occurs most readily in dipolar, aprotic solvents. One noteworthy finding is that solvent mixtures may offer real advantages in triflate displacement. The

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*See Table 12 for the meaning of abbreviations used in this article.

TABLE 6.[A] DISPLACEMENT OF THE TRIFLATE GROUP FROM PRIMARY POSITIONS IN CARBOHYDRATES

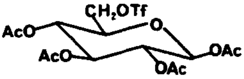
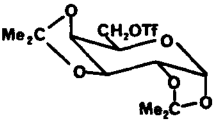
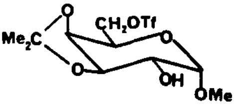
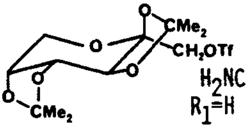
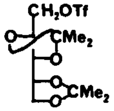
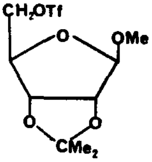
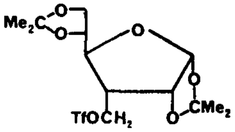
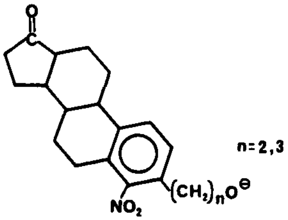
SUBSTRATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., °C	REF.
	TBAI	3.0	CH_2Cl_2	97	25	40
	TBAB	3.0	CH_2Cl_2	94	25	40
	$Bn(Et)_3NCl$	3.0	CH_2Cl_2	85	25	40
	TBAF	15	BENZENE	27	80	40
	KSO_2CF_3	3.0	CH_2Cl_2	62	25	40
	C_6H_5N	1.0	CH_2Cl_2	84	25	40
	TBAI	2.0	BENZENE	94	80	35,36
	TBAB	2.0	BENZENE	89	80	36
	TBAC	2.0	BENZENE	87	80	36
	NH_3	OVERNIGHT	$CHCl_3$	100	RT	28
	C_6H_5N	1.5	CH_2Cl_2	90	RT	29,30
	B.	16	BENZENE	100	RT	31
	TBAI	2.0	BENZENE	62	80	36
	TBAI	15	BENZENE	99	80	35,36
	$H_2NCHR_1COOR_2$					
	R_1=H R_2=Et	6 H.	DMF	75	153	83
	R_1=Me R_2=Me	8 MIN.	DMF	42	153	83
	R_1=i-Pr R_2=Me	18 MIN.	DMF	63	153	83
	R_1=i-Bu R_2=Et	25 MIN.	DMF	85	153	83
	R_1=2-Bu R_2=Me	25 MIN.	DMF	83	153	83

TABLE 6.[A] (CONTINUED)

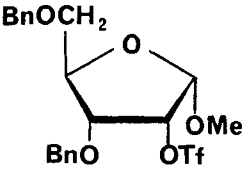
SUBSTRATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., °C	REF.
	NaI	OVERNIGHT	ACETONE	86	RT	41
	NaCN	OVERNIGHT	DMF	21	RT	41[D]
	TBAI	1.0	CH_2Cl_2	87	RT	35,36,43
	C.	18	BENZENE	65	RT	42
	TBAI	1.5	CH_2Cl_2	73	-78	43

A. SEE TABLE 12 FOR THE MEANING OF ABBREVIATIONS USED.
B. TETRABUTYLAMMONIUM 2-IODO-4-PHENYLPHENOLATE
C. NUCLEOPHILE=

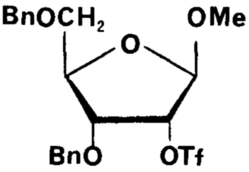


D. FOR APPLICATION OF THIS REACTION, SEE REFERENCES 84 AND 85.

reaction of methyl 3,5-di-*O*-benzyl-2-*O*-triflyl-α-*D*-ribopyranoside (**9**) and methyl 3,5-di-*O*-benzyl-2-*O*-triflyl-β-*D*-ribopyranoside (**10**) with various nucleophiles is quite slow in DMSO. In HMPT there is considerable decomposition but in a mixture of these solvents displacement occurs readily (Table 4).[16]



9

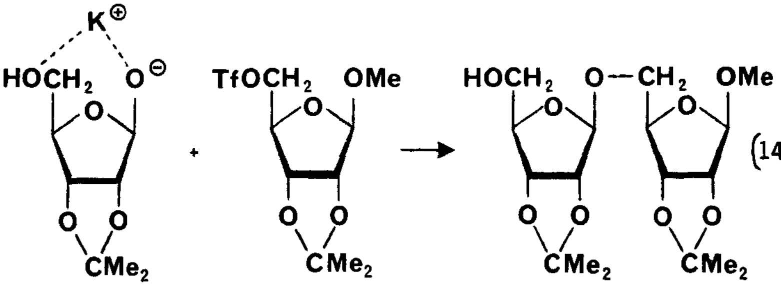


10

B. *O*-ALKYLATION REACTIONS

1. DISACCHARIDE SYNTHESIS

Carbohydrate triflates themselves function as *O*-alkylating agents in the synthesis of disaccharides. Typically, a sodium or potassium alkoxide derived from one carbohydrate is used as the nucleophile to displace a triflate from another sugar (equation 14, Table 7).[44] The configuration at the anomeric center where glycoside formation is taking place is determined by the anomeric



(14)

11 **12**

configuration of the alkoxide salt. For example, the potassium salt 11 is thought to prefer, due to internal complexation, a β-configuration. When 11 reacts with methyl 2,3-O-isopropylidene-5-O-triflyl-β-D-ribofuranoside (12), the newly formed glycosidic linkage is β.[44] The smaller sodium ion is not believed to be internally complexed in the same manner but rather to exist preferentially in the α-configuration. An α glycoside forms when the sodium salt is treated with compound 12 (Table 7).

Extensive complexation of the sodium ion by the oxygen atoms in the sodium salt of 2,3:5,6-di-O-isopropylidene-D-mannofuranose causes this salt (13, Table 7) to favor the β-configuration and to react to form a β-glycoside. In contrast, the α-anomer (14, Table 7) is the only reactant if complexation of the sodium cation with the oxygen atoms of the sugar is prevented by prior complexation with a crown ether.[45] Cation complexation is not the only factor which has been found to be significant in determining configuration in these O-alkylation reactions. The identity of C-6 substituents in pyranoside derivatives[46] and reaction temperature[47] also are influential.

2. DERIVATIVE FORMATION

Many alkyl triflates are powerful O-alkylating agents which can easily derivatize and protect carbohydrates. Methyl triflate, the most widely used of these reagents, is responsible for the synthesis of a large number of methylated carbohydrates (Table 9). Methylation typically takes place in high yield even when the reactant carbohydrate has more than one unprotected hydroxyl group (equation 15, Table 9).[53] Benzyl triflate, which is a much more potent alkylating agent than methyl triflate, reacts with free hydroxyl groups at -60 °C to form benzyl ethers (equation 16, Table 8).[48]

TABLE 7.[A] DISACCHARIDE SYNTHESIS VIA TRIFLATE DISPLACEMENT
(FURTHER EXAMPLES OF TRIFLATE DISPLACEMENT FROM THE PRIMARY POSITIONS IN CARBOHYDRATES)

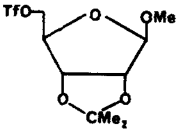
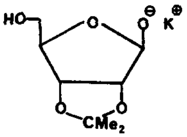
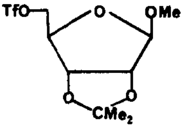
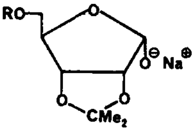
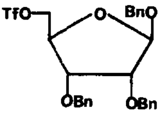
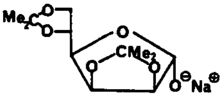
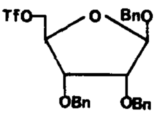
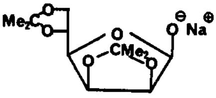
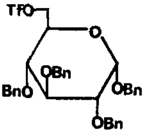
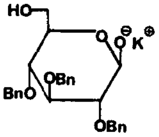
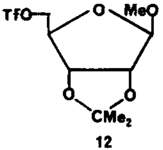
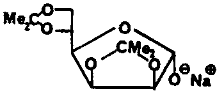
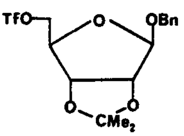
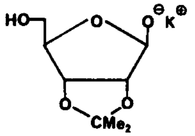
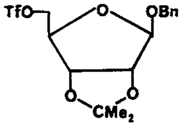
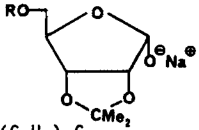
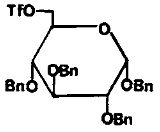
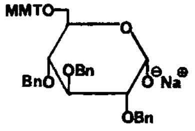
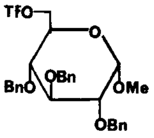
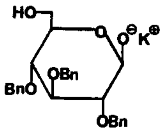
SUBSTRATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., °C	REF.
 12	 11	5-20	THF	89	RT	44
 12						
	$R=(C_6H_5)_3C$	5-20	THF	87	RT	44
	$R=Me_3CSiMe_2$	5-20	THF	86	RT	44
	R=H	6-20	THF	93	RT	44
	 14		THF-BENZENE	68	RT	45,47
	 13		THF	90	RT	45,47
			THF	54	RT	46

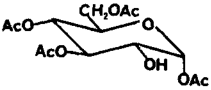
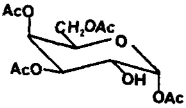
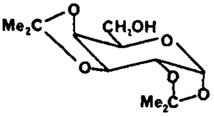
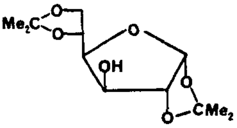
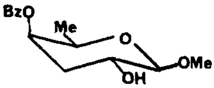
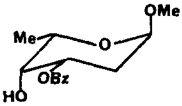
TABLE 7.[A] (CONTINUED)

SUBSTRATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., ^{0}C	REF.
 12	 14		THF-BENZENE	72	RT	45
		5-20	THF	72	RT	44
						
	R=$(C_6H_5)_3C$	5-20	THF	74	RT	44
	R=Me_3CSiMe_2	5-20	THF	77	RT	44
	R=H	5-20	THF	87	RT	44
			THF	80	-10	46
			THF	51	RT[B]	46

A. SEE TABLE 12 FOR THE MEANING OF ABBREVIATIONS USED.

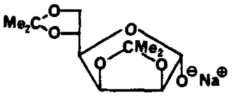
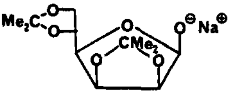
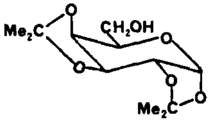
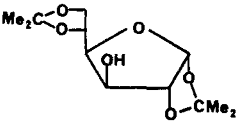
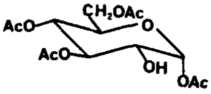
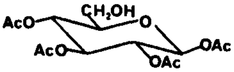
B. STUDIES OF TEMPERATURE DEPENDENCE OF THIS REACTION SHOW THAT THE BETA-ISOMER IS ALSO FORMED (REFERENCE 47).

TABLE 8.[A] *O*-ALKYLATION OF CARBOHYDRATE HYDROXYL GROUPS WITH BENZYL TRIFLATE

CARBOHYDRATE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., °C	REF.
	120	CH_2Cl_2	63	-60	48
	120	CH_2Cl_2	79	-60	48
	0.5[B]	CH_2Cl_2	60	-70[B]	49
	0.5[B]	CH_2Cl_2	93	-70[B]	49
	0.5[B]	CH_2Cl_2	89	-70[B]	49
	120	CH_2Cl_2		-60	50
	120	$CHCl_3$		-60	51

A. SEE TABLE 12 FOR THE MEANING OF ABBREVIATIONS USED.
B. REACTION MIXTURE WARMED TO ROOM TEMPERATURE BEFORE WORK-UP.

TABLE 9.[A] *O*-ALKYATION OF CARBOHYDRATE HYDROXYL GROUPS WITH METHYL TRIFLATE[B]

CARBOHYDRATE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., °C	REF.
		THF-BENZENE	66	RT	45
		THF	61	RT	45
	12	CH_2Cl_2	95	43	49
	12	CH_2Cl_2	90	43	49
	2.5	CH_2Cl_2	80+	80	52
	72	CH_2Cl_2	36	43	49
	24	CH_2Cl_2	93	43	49

(continued)

TABLE 9.^{A} (CONTINUED)

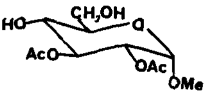
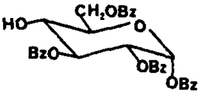
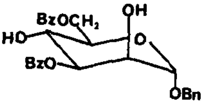
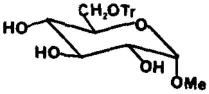
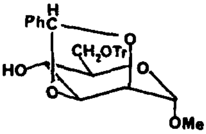
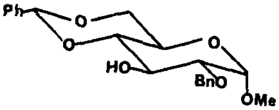
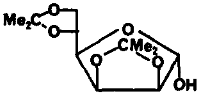
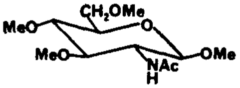
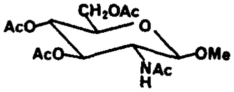
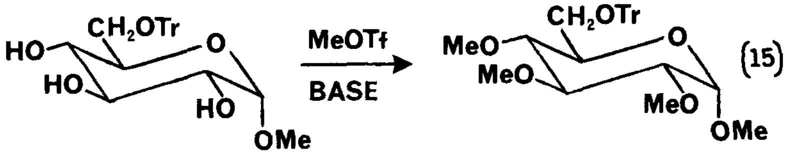
CARBOHYDRATE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., ^{0}C	REF.
	2.5	CH_2Cl_2	80+	43	52
	2.5	CH_2Cl_2	89	80	53
	2.5	CH_2Cl_2	89	80	53
	2.5	CH_2Cl_2	93	80	53
	2.5	CH_2Cl_2	81	80	53
	2.5	CH_2Cl_2	88	80	53

TABLE 9.[A] (CONTINUED)

CARBOHYDRATE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., °C	REF.
	2.5	CH_2Cl_2	80	80	53
	2.5	CH_2Cl_2	90	80	53
	2.5	CH_2Cl_2	84	80	53

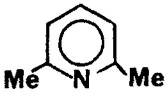
A. SEE TABLE 12 FOR THE MEANING OF ABBREVIATIONS USED.

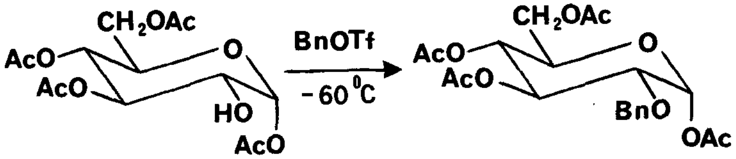
B. FOR EXAMPLES OF THE USE OF METHYL TRIFLATE IN STRUCTURE DETERMINATION IN COMPLEX CARBOHYDRATES; SEE REFERENCES 54 AND 55.



(15)

$Tr = C(C_6H_5)_3$

BASE = 



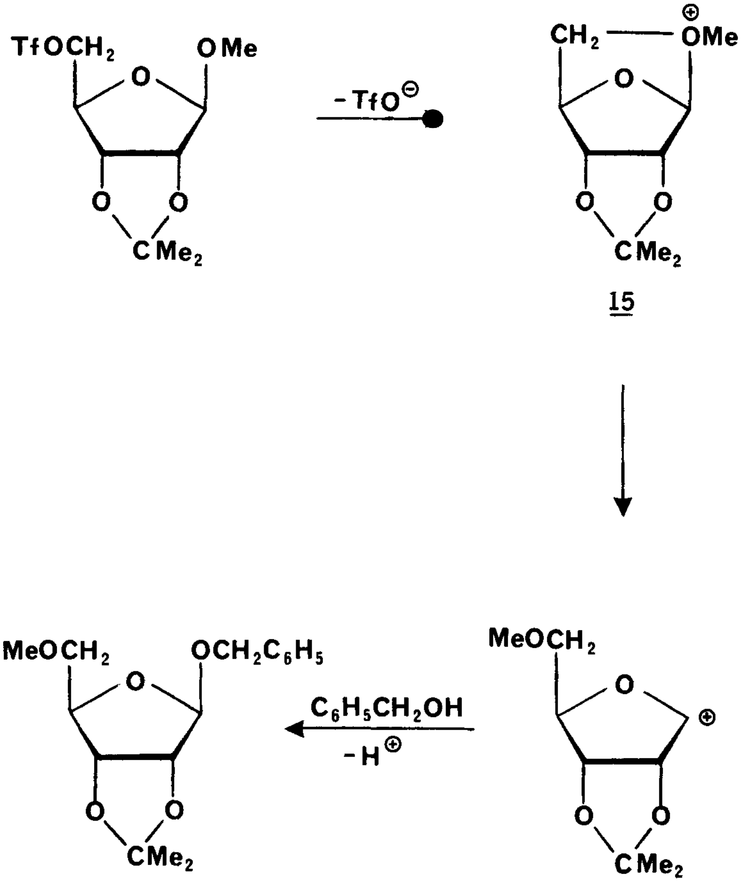
(16)

C. REARRANGEMENTS

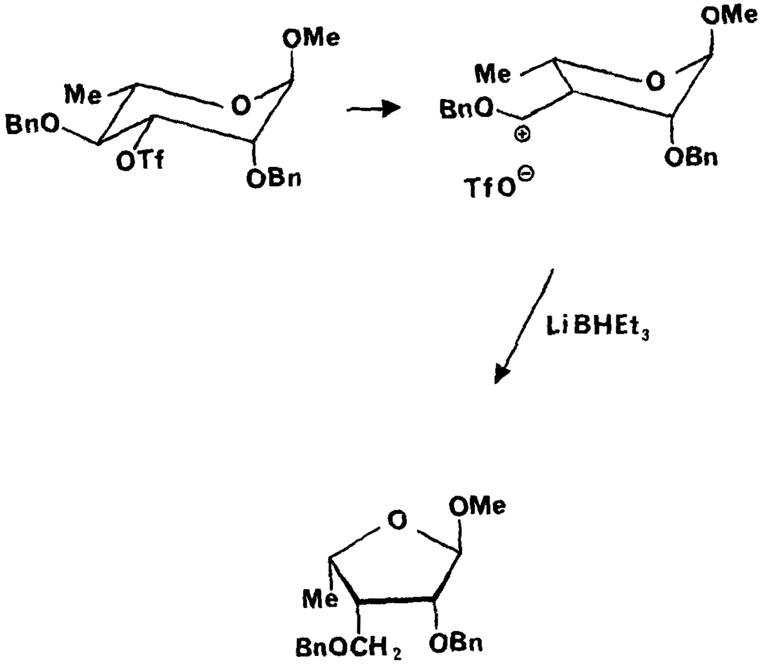
Five rearrangements of carbohydrate triflates have been observed. They each are related to processes known to occur in cyclic systems containing very reactive leaving groups. In the first of these five, an oxygen atom in a methoxy group internally displaces a triflate to produce a bridged, bicyclic cation 15 (Scheme 3).[65] Ring-opening of this cation (15) results in migration of the methoxy group. In a second type of rearrangement, participation of the 4,5-bond in a pyranose ring in the departure of an equatorial triflyloxy group attached to C-3, causes ring-contraction (Scheme 4).[66] Simultaneous hydride migration and carbonyl formation, a third rearrangement, provide sufficient driving-force for ring opening in a compound where subsequent closure to a new ring system takes place (Scheme 5).[11] The fourth rearrangement is, in some respects, a combination of the first two. A ring-contraction process is made possible by a preceeding intramolecular triflate displacement (Scheme 6).[67] Finally, loss of a benzyl group can accompany intramolecular displacement (Scheme 7).[86]

D. ELIMINATION REACTIONS

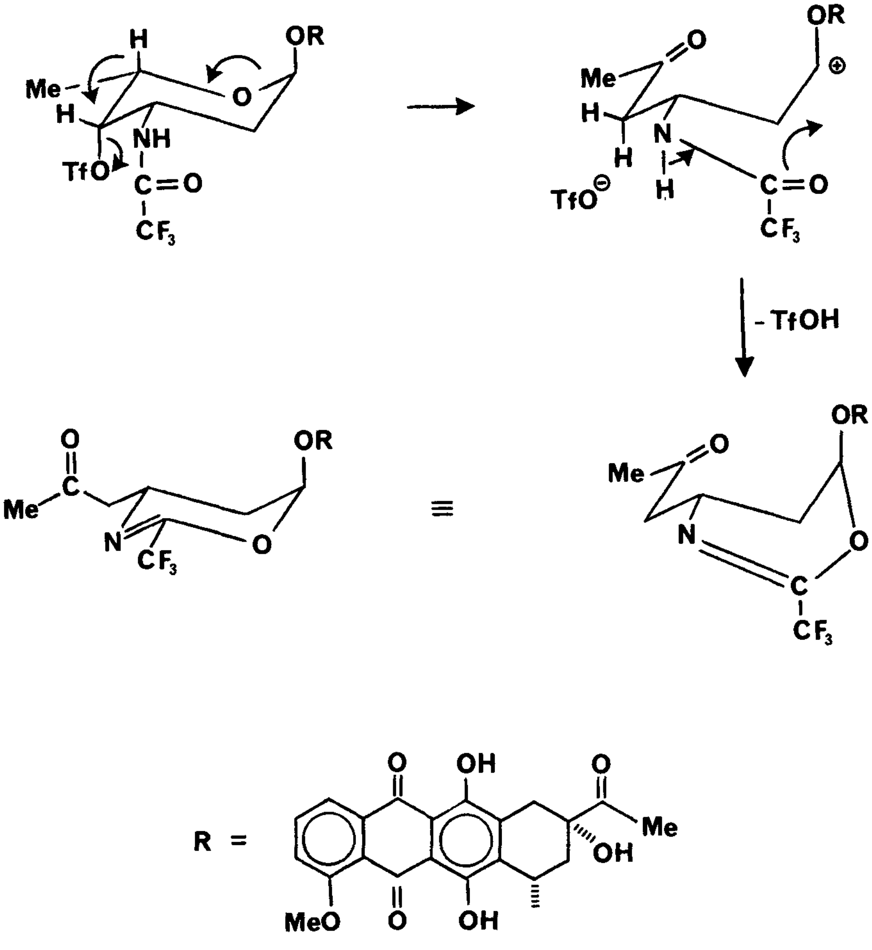
Base-catalyzed elimination of the elements of triflic acid from a carbohydrate is a relatively rare event when compared to eliminations involving other sulfonate esters; in fact, one of the reasons for use of the triflate in S_N2 substitution processes is that it is usually possible to avoid the elimination reactions that, along with rearrangement and other competing processes, complicate displacements of less reactive sulfonate esters. The reported examples of unsaturated compounds being formed from reactions of triflates arise primarily from those molecules for which substitution is made difficult by steric and electronic factors. For such compounds elimination becomes a significant competing reaction.


TfOCH2
OMe
O
O
O
CMe2
-TfO⊖
CH2
⊕
OMe
O
O
O
CMe2
15
MeOCH2
OCH2C6H5
O
O
O
CMe2
C6H5CH2OH
-H⊕
MeOCH2
O
⊕
O
O
CMe2

SCHEME 3


OMe
Me
BnO
O
OTf
OBn
OMe
Me
BnO
O
⊕
OBn
TfO⊖
LiBHEt₃
O
OMe
Me
BnOCH₂
OBn

SCHEME 4



SCHEME 5

TABLE 10.^{A} O-ALKYLATION OF CARBOHYDRATE HYDROXYL WITH ADDITIONAL ALKYL TRIFLATES

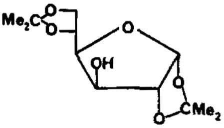
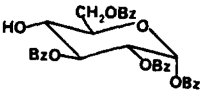
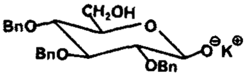
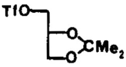
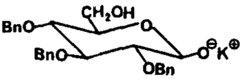
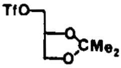
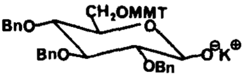
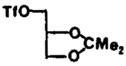
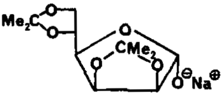
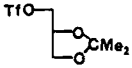
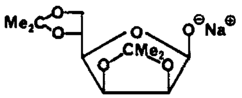
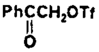
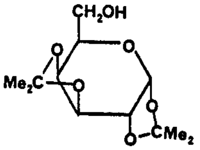
TRIFLATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., ^{0}C	REF.
CH_3CH_2OTf		8.0	CH_2CL_2	81	80	53
CH_3CH_2OTf		8.0	CH_2CL_2	92	80	53
$CH_3(CH_2)_{17}OTf$			THF	43	RT	45,46
			THF	79	B.	46
			THF	65	B.	47
			THF- BENZENE	48	RT	45,47

TABLE 10.^{A} (CONTINUED)

TRIFLATE	NUCLEOPHILE	REACTION TIME, H.	SOLVENT	PRODUCT YIELD, %	TEMP., ^{0}C	REF.
			THF	59	RT	45,47
 $PhC(=O)CH_2OTf$			$CL_2CH_2CH_2CL_2$	62	80	56

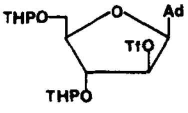
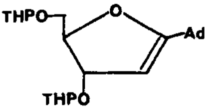
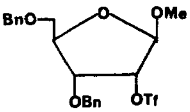
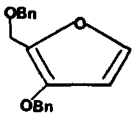
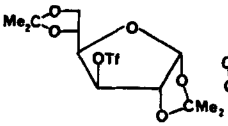
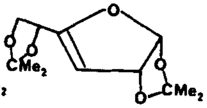
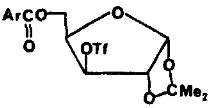
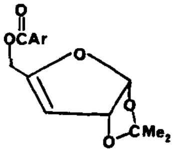
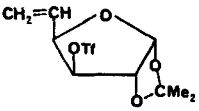
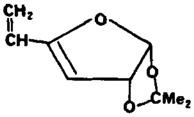
A. SEE TABLE 12 FOR THE MEANING OF ABBREVIATIONS USED.
B. ANOMER COMPOSITION IS TEMPERATURE DEPENDENT.

One example of the competition which can be introduced between elimination and substitution by stereoelectronic factors is seen in the difference in reactivity between the anomers 9 and 10 (equations 17 and 18, Tables 4 and 11).[16] Approach of a nucleophile to the 2-position in 9 is relatively unhindered and, consequently, substitution is the exclusive process. In contrast, substitution at the same position in 10 requires the nucleophile to enter into close proximity to the methoxy group. A negatively charged nucleophile will be sterically and electronically repelled by the electron rich methoxy oxygen.[16]

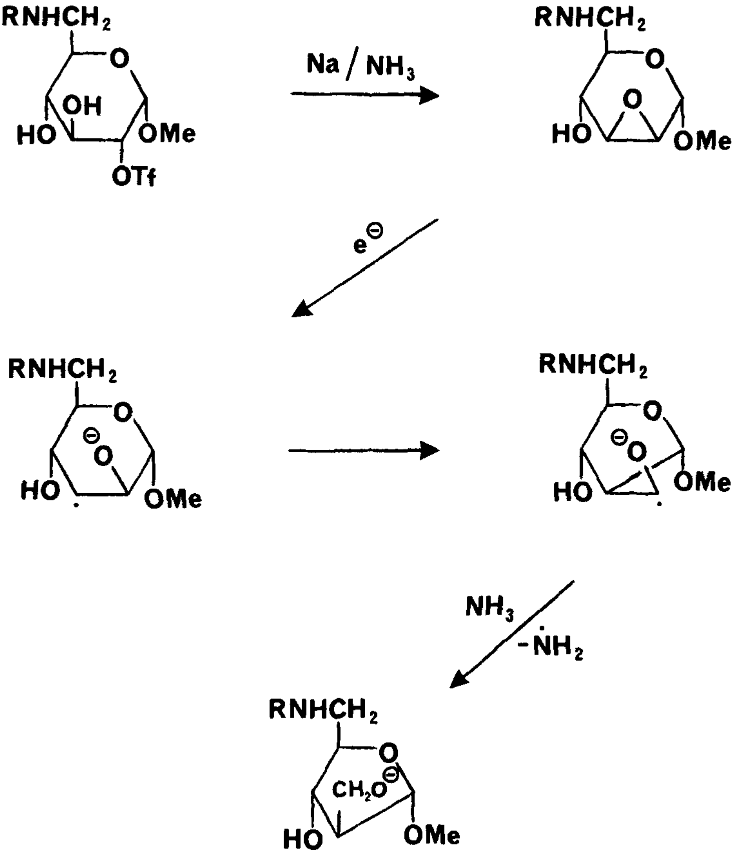
The reported triflate elimination reactions (Table 11) all involve loss of the elements of triflic acid from a furanose ring system. This fact suggests that a triflyloxy group attached to a furanose ring is more susceptible to elimination than one attached to a pyranose ring.

It is, of course, typical of E_2 eliminations that the stronger the base the more facile the elimination

TABLE 11.[A] ELIMINATION REACTIONS INVOLVING LOSS OF TRIFLATE

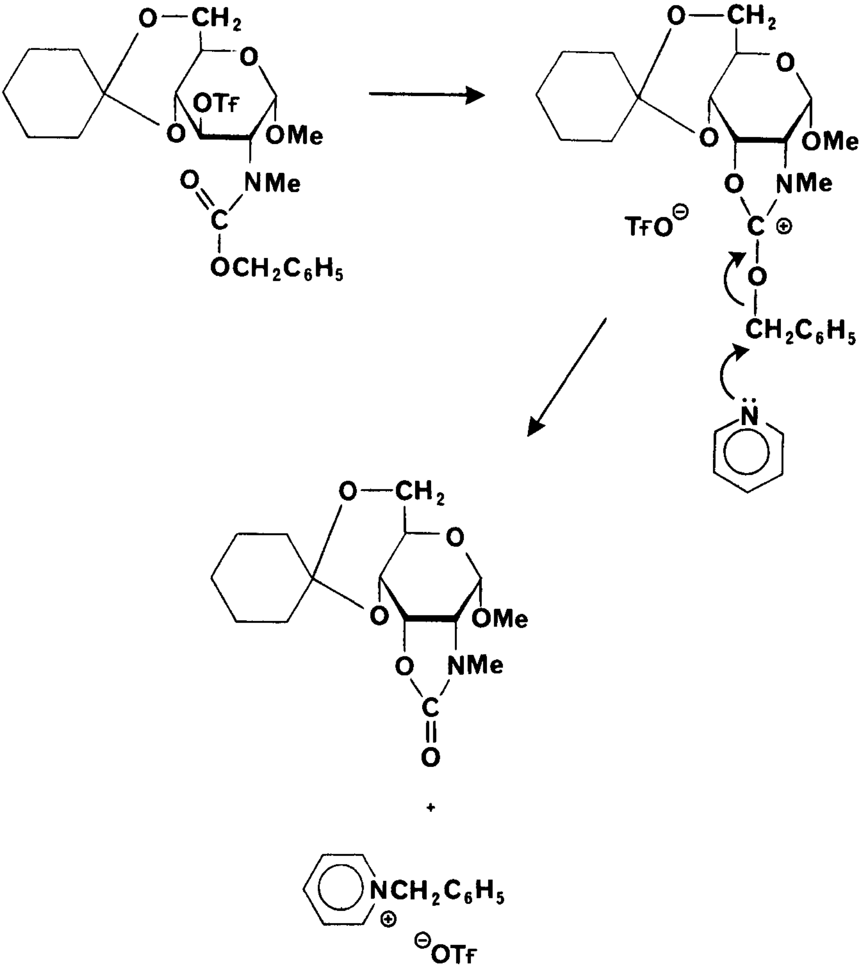
TRIFLATE	PRODUCT	BASE	SOLVENT	% YIELD	REF.
		TBAF	THF	30^B	24
		TBAF	THF	76^B	15
		LiCl	DMSO-HMPT		15
		LiBr	DMSO-HMPT		15
		NaI	DMSO-HMPT		15
		DBU	ETHER	98	28
		$KOC(CH_3)_3$	ETHER	67	28
		C.	BENZENE	100	31
		TBAB	BENZENE	43^B	36
		TBAC	BENZENE	82^B	36
		$KOC(CH_3)_3$	BENZENE	25	28
		LiN_3	ETHANOL	41^B	39
		DBU	ETHER	100	57

A. SEE TABLE 12 FOR THE MEANING OF ABBREVIATIONS USED.
B. ELIMINATION IS ACCOMPANIED BY SUBSTITUTION.
C. TETRABUTYLAMMONIUM 2-IODO-4-PHENYLPHENOLATE

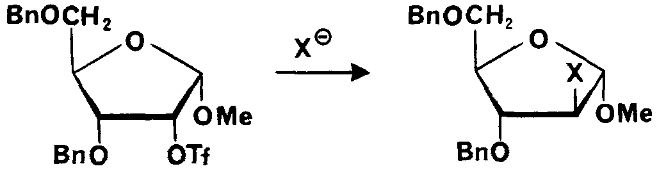


R = Ts or H

SCHEME 6



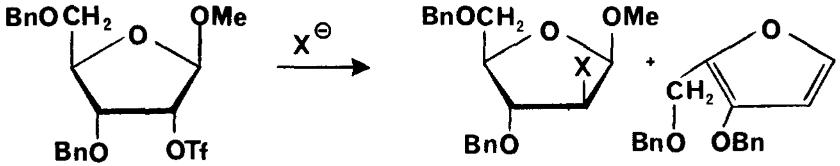
SCHEME 7



9

(17)

X = I, Br, Cl, F, N_3



10

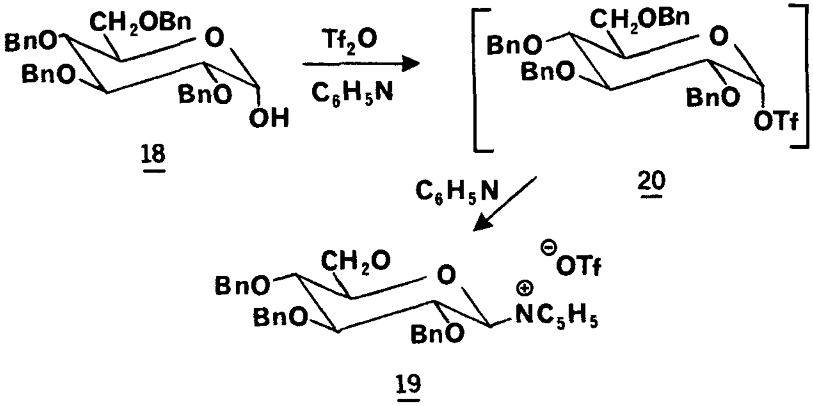
(18)

reaction. Although there has not been a study deliberately designed to test this generalization using carbohydrate triflates, the elimination reactions reported in Table 11 appear to support this principle. With 1,2:5,6-di-O-isopropylidene-α-3-O-triflyl-glucofuranose (16), for example, reaction with chloride ion produces more alkene than bromide while iodide reaction gives only substitution.[36]

With two exceptions, reactions of compounds 16 and 17 (Table 11), eliminations involving carbohydrate triflates have resulted from attempted substitutions. It is possible that elimination reactions involving triflates and non-nucleophilic bases could be conducted, in general, under mild conditions and that triflates could become valuable intermediates in the synthesis of unsaturated compounds.

E. GLYCOSIDE FORMATION (ANOMERIC TRIFLATES)

Considerable effort has been devoted to the study of glycoside formation under conditions where anomeric triflates may be reaction intermediates.* Although the evidence for the intermediacy of these compounds, is convincing in certain situations, this evidence is indirect. For instance, the reaction of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (18) with triflic anhydride in pyridine produces the pyridinium salt 19.[59,60] It would appear that by far the most reasonable explanation for the formation of 19 involves the triflate 20 (Scheme 7). Even though there is indirect evidence of this type supporting the existence of anomeric triflates, at present there is no report of the isolation or direct observation of one of these extremely reactive compounds.



There are two distinctly different sets of reagents and reaction conditions which lead to glycoside formation and which may involve the intermediacy of an anomeric triflate. The first of these is that mentioned in the previous paragraph and is a set of conditions similar to the most commonly used for triflate generation

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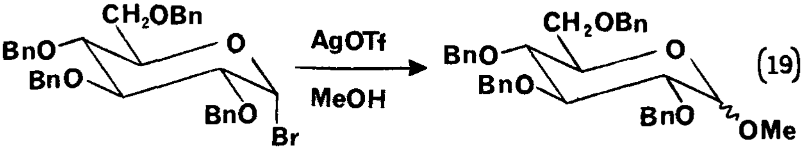
*For reviews containing some discussion of this subject see references 68 and 69.

(Section IIIA), that is, reaction of the partially protected carbohydrate with triflic anhydride in the presence of a hindered, organic base. (The reaction requires a hindered base (e.g., collidine); otherwise, a reaction such as that shown in Scheme 7 will take place). The intermediacy of an anomeric triflate under these conditions is quite probable.

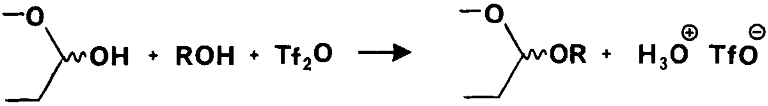
A second and more widely used procedure, one which may involve anomeric triflates, consists of treatment of a glycosyl halide with silver triflate in the presence of an appropriate alcohol (equation 19).[70] The intermediacy of an anomeric triflate in these reactions is much less certain since silver triflate could catalyze ionization of the carbon-halogen bond to give a carbocation without the intermediacy of an anomeric triflate. Glycoside formation involving silver ion and a glycosyl halide is a complex process which has been carefully and extensively studied.[70-72] The α/β ratio of the glycosides produced is a function of a number of variables including the identity of the anion, the solvent, the method of combination of reagents, and the

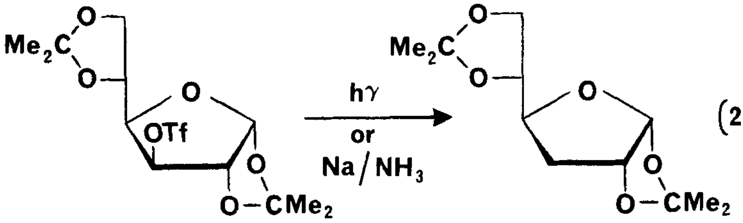


(19)

relative concentration of the reagents. With such a complicated process the question of whether or not an anomeric triflate is an intermediate in the sequence of events becomes a very difficult one to answer.

A third method of glycoside formation that could involve an anomeric triflate uses triflic anhydride but does not require the presence of an organic base (equation 20).[73,74] It is unlikely, however, that an anomeric triflate is involved in this type of reaction because the absence of a base means that triflic acid, one of the strongest acids known, is present in the reaction mixture. Under these conditions, acid-catalyzed glycoside formation is the expected process.[75] A significant driving-force for the reaction is the removal of triflic acid and water from the reaction mixture by precipitation of the salt $H_3O^+TfO^-$.


(20)



16

(21)

F. ADDITIONAL REACTIONS

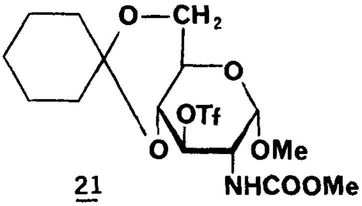
Several carbohydrate triflates (16, 21, and 22) when photolyzed or treated with sodium in liquid ammonia form the corresponding deoxy sugars (equation 21).[67] The photochemical reaction is analogous to that reported for acetylated carbohydrates.[76,77] A mechanism for this photochemical reaction has been proposed.[78]

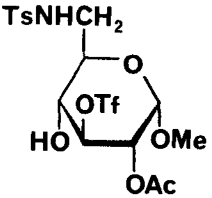
Two remaining examples of triflate displacement are similar to reactions already described but the reactants are sufficiently different from those listed in Tables 1-11 to prevent their inclusion. Compound

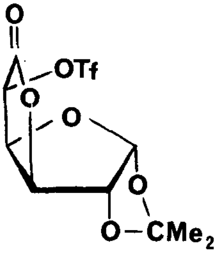
TABLE 12. ABBREVIATIONS

SYMBOL	MEANING
Ac	ACETYL
Ad	9-ADENINYL
DAU	DAUNOMYCINONE
Bn	BENZYL($C_6H_5CH_2$-)
Bu	BUTYL($CH_3CH_2CH_2CH_2$-)
2-Bu	2-BUTYL($CH_3CHCH_2CH_3$)
Bz	BENZOYL($C_6H_5C(O)$-)
DBU	1,8-DIAZABICYCLO(5.4.0)UNDEC-7-ENE
DMF	*N*,*N*-DIMETHYLFORMAMIDE
DMSO	METHYL SULFOXIDE
Et	ETHYL(CH_3CH_2-)
Gu	9-(2-(2-METHYLPROPANOYL))GUANINYL
H	HOUR(S)
HMPT	HEXAMETHYLPHOSPORIC TRIAMIDE
i-Pr	ISOPROPYL($(CH_3)_2CH$-)
Me	METHYL(CH_3-)
MIN	MINUTE(S)
MMT	MONOMETHOXYTRITYL
TBAB	TETRABUTLAMMONIUM BROMIDE
TBAC	TETRABUTYLAMMONIUM CHLORIDE
TBAF	TETRABUTYLAMMONIUM FLUORIDE
TBAI	TETRABUTYLAMMONIUM IODIDE
RT	ROOM TEMPERATURE
Tf	TRIFLUOROMETHYLSULFONYL OR TRIFLUOROMETHANESULFONYL
THF	TETRAHYDROFURAN OR 2-TETRAHYDROFURANYL
THP	2-TETRAHYDROPYRANYL

23 undergoes triflate displacement with sodium benzoate to invert the configuration at C-5.[79] Inversion of configuration also takes place when several carbohydrate containing antibiotics are treated with sodium benzenethioxide [80,81] and tetrabutylammonium fluoride.[82]


21


22


23

V. CONCLUSION

The number of examples of the displacement of the triflate group from carbohydrates now is sufficiently large to state with confidence that this reaction can be used in a wide variety of situations. The high level of reactivity of this group, when compared to other sulfonic esters, should mean that for carbohydrates, where S_N2 displacements are typically more difficult than for other organic molecules, the triflate often should be the leaving group of choice. Use of triflate displacement in carbohydrate chemistry should continue to increase in the future, perhaps, at an even more rapid pace.

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