A NOVEL TRIFLATE MEDIATED APPROACH TO ALKALOIDAL GLYCOSIDES

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Abstract- A mild one pot synthesis of alkaloidal glycosides is reported. In the reaction sequence, classical S_N2 displacement of the trifluoromethanesulfonyloxy group in sugar triflate (1) was affected with nucleophilic nitrogen of a variety of naturally occurring alkaloidal bases (2-10) affording alkaloidal N-glycosides (11-19). Deprotection of the sugar moiety in (11), (18) and (19) with boron trichloride afforded the deprotected compounds (20-22). The strategy provides a general method for the preparation of pharmacologically interesting compounds from readily accessible precursors.

The alkaloidal glycosides are a group of natural products which constitute a broad range of physiological activities and claim intrinsic interest from the last two decades.[1] Most of these have been isolated from plants and possess the general O-glycosidic linkage.[2] The N-glycosidic alkaloids are comparatively rare[3] and their syntheses have not, to the best of our knowledge, been previously reported in the literature.

We have previously reported the syntheses of potential monosaccharide derivatives utilizing the excellent leaving group properties of trifluoromethanesulfonyloxy (triflyl) group[4-6]. From the high selectivity observed during these reactions, it appeared that the substitution of triflyl group in partially blocked sugar triflates by the basic nitrogen of the alkaloidal bases should perform the desired C-N coupling between two important group of natural products, providing a new and efficient access to alkaloidal N-glycosides. In this communication we wish to report an account of these studies which not only appear to afford a new route to pharmacologically interesting compounds, but also provide a method for the modification of physiological activity and solubility of the naturally occurring alkaloidal bases.

1,2:3,4-Di-O-isopropylidene-6-triflyl-α-D-galactopyranose (1)[7] was used as partially blocked sugar in the present investigations. The isopropylidene group was selected as protecting group in view of its stability in basic conditions and ease of cleavage.[8] On the other hand, different types of naturally occuring alkaloidal bases were used to demonstrate the scope of the reaction. These included ajmaline (2),[9] isoajmaline (3)[10], sandwicine (4)[11], 17-acetyl ajmaline (5)[12], 17,21-diacetyl

sandwicine (6)[13], harmine (7)[14], harmaline (8)[15], tetrahydroharmine (9)[16] and ephedrine (10)[17]. In a typical reaction (1) was reacted with a four fold excess of the bases (2-10) in dimethylformamide and stirring the reaction mixture at room temperature for 12h. The products and the remaining starting materials were recovered through column chromatography over silica gel. The physical data of the products (11-19) are provided in Table-1.

Table-1: Reaction of alkaloidal bases with sugar triflate (1).

Starting material	Product[a]	Yield[b] (%)	$[\alpha]_D^{20}$ (o)[c]	FDMS M^+ peak [m/z]	R_f[d]
(2)	(11)	80	75.00	568	0.67
(3)	(12)	72	-65.23	568	0.65
(4)	(13)	78	-52.21	568	0.60
(5)	(14)	62	8.57	610	0.61
(6)	(15)	57	-19.36	610	0.58
(7)	(16)	73	-5.69	455	0.42
(8)	(17)	59	-38.65	457	0.45
(9)	(18)	72	-37.95	458	0.56
(10)	(19)	85	-64.59	407	0.61

a: All products were isolated as oil except (19) which formed colourless plates with dichloromethane-hexane (1:1), m.p. 120-2°C.

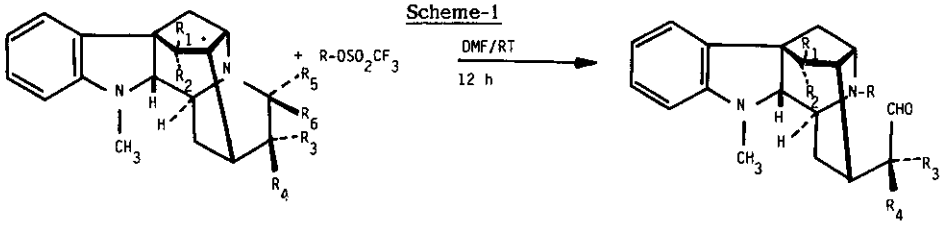
b: Yields refer to isolated substances after column chromatography.

c: Chloroform.

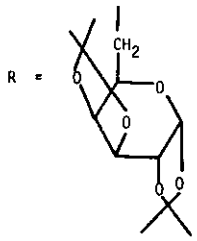
d: Solvent system: benzene:methanol (8:2).

The Rauwolfia bases (2-6) invariably reacted through their aldehyde-imine tautomeric form and the structures of the coupling products (11-15) were fully elucidated through mass, ir, ^1H and ^{13}C-nmr spectral studies (Scheme-1). The existence of carbinol-amine, aldehyde-imine tautomerism in this class of alkaloids has already been established through a series of chemical reactions.[18,19] From the striking similarity in reaction conditions and behaviour observed for these bases, it can be inferred that stereochemical differences at C-17, C-20 and C-21 seem to have no effect on these reactions. In (6), the deacetylation of labile 21-O-acetyl group took place in the solvent medium prior to the coupling reaction. This behaviour has previously been reported in literature to explain the formation of N_b-nitroso and N_b-cyano derivatives from (6).[18,19]

Scheme-1

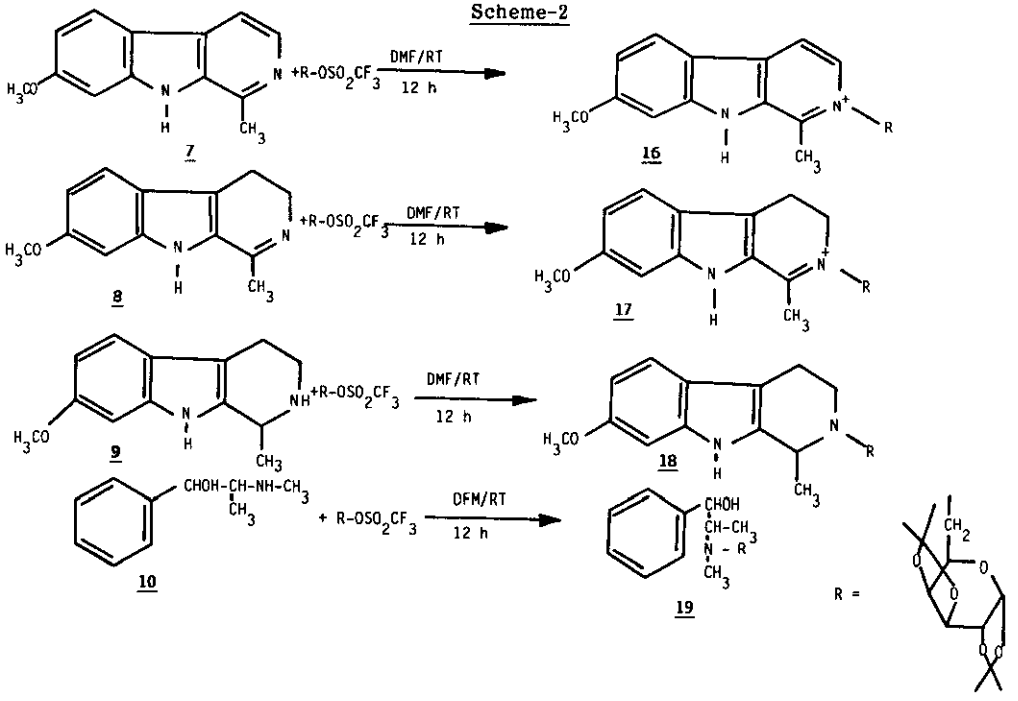


2	$R_1=R_5=OH, R_2=R_3=R_6=H, R_4=Et$	11	$R_1=OH, R_2=R_3=H, R_4=Et$
3	$R_1=R_6=OH, R_2=R_4=R_5=H, R_3=Et$	12	$R_1=OH, R_2=R_4=H, R_3=Et$
4	$R_2=R_5=OH, R_1=R_3=R_6=H, R_4=Et$	13	$R_2=OH, R_1=R_3=H, R_4=Et$
5	$R_1=OAc, R_5=OH, R_2=R_3=R_6=H, R_4=Et$	14	$R_1=OAc, R_2=R_3=H, R_4=Et$
6	$R_2=R_5=OAc, R_1=R_3=R_6=H, R_4=Et$	15	$R_2=OAc, R_1=R_3=H, R_4=Et$



The secondary bases (9) and (10) reacted with (1) to yield the substituted products (18) and (19). On the other hand, the tertiary harmala bases (7) and (8) provided quaternary alkaloidal N-glycosides (16) and (17). Owing to imine-enamine tautomerism in (8)[20] the possibility of the formation of C-glycosidic linkage can not be ruled out. However, imino form predominates in the tautomeric equilibrium[20], explaining the preferential formation of (17), the structure of which was fully elucidated by spectroscopic studies.

Scheme-2



Considering the fact that the compounds with deprotected sugar moiety claim greater pharmacological interest, a variety of acidic reagents were tried for the selective removal of isopropylidene group. However, the best results were achieved with boron trichloride. The general applicability of this reagent was demonstrated by using one representative from each of the three classes of alkaloidal glycosides described in the foregoing, namely (11), (18) and (19). In the reaction sequence, three fold excess of boron trichloride was carefully added to a solution of either (11), (18) or (19) in dichloromethane at -70°C. The reaction mixture was kept at room temperature for 15 minutes, worked up in the usual manner, and chromatographed over silica gel to separate the desired deprotected alkaloidal glycosides (20-22) respectively. The physical data of these products are provided in Table-2.

Table-2: Deprotection of alkaloidal glycosides with boron trichloride.

Starting material	Product[a]	Yield[b] (%)	$[\alpha]_D^{20}$ (o)	FDMS[d] M^+ peak [m/z]	R_f[e]
(11)	(20)	67	12.50	848	0.49
(18)	(21)	59	11.12	666	0.31
(19)	(22)	73	-14.28	687	0.36

a: All products were isolated as oil.
b: Yields refer to isolated substances after column chromatography.
c: Chloroform.
d: As trimethylsilyl derivatives.
e: Solvent system: toluene:methanol (8:2).

REFERENCES

1. R.T. Brown and R.S. Kapil, Alkaloids NY 17, 1979, 546.
2. G.N. Smith, J.Chem.Soc.Chem.Commun., 1968, 912; A.R. Battersby, A.R. Burnett and P.G. Parsons, J.Chem.Soc.Sec.C., 1969, 1193.
3. A.U. Rahman, H.U. Rehman, I. Ali, M. Alam, and S. Perveen, J.Chem.Soc.Perk. Trans.I, 1987, 1701.
4. A. Malik, N. Afza, M. Roosz, and W. Voelter, J.Chem.Soc.Chem.Commun., 1984, 1530.
5. N. Afza, A. Malik, and W. Voelter, Z.Naturforsch., 1984, 39(b), 840.
6. W. Kowollik, A. Malik, N. Afza, and W. Voelter, J.Org.Chem., 1985, 50(18), 3325.
7. O.T. Schmidt, Methods Carbohyd.Chem., 1963, 11, 324; L. Hall and D.C. Miller,

Carbohyd.Res., 1975, 40, C1.

8. T.J. Tewson and M.J. Welch, J.Org.Chem., 1978, 43, 1090.
9. S.Siddiqui and R.H.Siddiqui, J.Ind.Chem.Soc., 1931, 8, 669.
10. S.Siddiqui, J.Ind.Chem.Soc., 1939, 16, 421.
11. M. Gorman, M. Neuss, C.D. Jerassi, J.P. Kutney, and P.J. Scheuer, Tetrahedron, 1957, 1, 328.
12. M. Muquet, J.L. Pousset, and J. Poisson, Acad.Sci., Paris, Ser.C., 1968, 266(21), 1542.
13. F. Ronchetti, G. Russo, E. Bombardelli, and A. Bonati, Phytochemistry, 1971, 10, 1385.
14. R.H.F. Manske, W.H. Perkin, and R. Robinson, J.Chem.Soc., 1927, 1.
15. F. Goebel, Liebigs Ann.Chem., 1841, 38, 363.
16. S.Siddiqui, Pak.J.Sci.Ind.Res., 1962, 5, 207.
17. N. Nagai, Pharm.Ztg., 1887, 32, 700.
18. S.Siddiqui, S.A. Warsi, M. Alauddin, and V.U. Ahmad, Pak.J.Sci.Ind.Res., 1959, 2, 86.
19. A. Malik, N. Afza, N. Sultana, and S. Siddiqui, Heterocycles, 1981, 16, 1101.
20. A.U. Rahman and T. Burney, Pak.J.Sci.Ind.Res., 1972, 15, 9.

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