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CHEMISTRY OF 1-(DIMETHYLAMINO)ETHYLIDENE AND α-(DIMETHYLAMINO)BENZYLIDENE ACETALS: UTILITY AS BLOCKING GROUP FOR DIOLS AND FOR SELECTIVE ESTERIFICATION.

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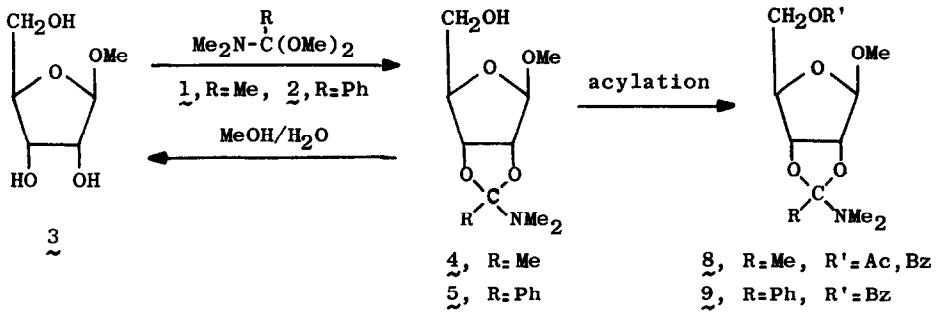
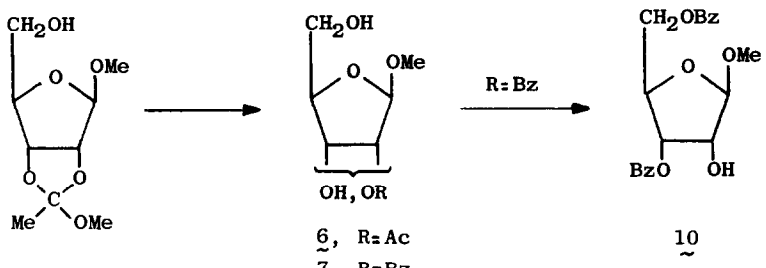
In connection with our studies involving the synthetic utility of amide halides and amide acetals in carbohydrates[1] in general and nucleosides[2] in particular, we report on some novel aspects of the synthetic applications of dimethyl acetals of (1) N,N-dimethylacetamide[3] and (2) benzamide[4]. Methyl β-D-ribofuranoside[5] (3) was chosen as a model because it contains a cis diol group and a primary hydroxyl group, structural features suitable for chemical transformations and also found in the biologically important ribonucleosides. Treatment of 3 with two equivalents of 1 in a chlorinated hydrocarbon such as 1,1,2-trichloroethane[6] at room temperature for one hour in the dark affords the corresponding methyl 2,3-O-[1-(dimethylamino)ethylidene]-β-D-ribofuranoside 4 as a 2:1 mixture of diastereoisomers in over 90% yield; bp 103-108°/0.4mm. The corresponding methyl 2,3-O-[α-(dimethylamino)benzylidene]-β-D-ribofuranoside 5 was also prepared in high yield (r.t., 18 h).





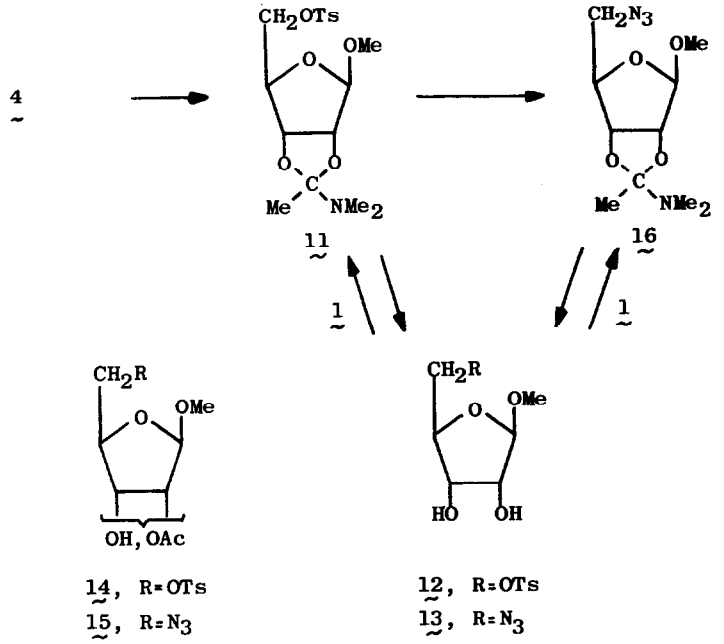
The acetal group in these compounds can be easily hydrolyzed off by 3% aq. methanol (reflux, 1 h) to regenerate the starting diol 3. Treatment of 4 with 95% acetic acid at pH 4-5 during 2-4 h resulted in selective hydrolysis of the acetal to give a mixture of the 2- and 3-monoacetates 6 in approximately equal amount (nmr)*. A crystalline 2,5-bis (p-nitrobenzoate) was prepared from this mixture and a pure isomer (nmr) was separated from it by fractional recrystallization, mp 147.5-148°[7] $[\alpha]_D$ 37° ($CHCl_3$). Acid hydrolysis of 5 afforded a mixture of monobenzoates 7 as the sole products, with the 3-benzoate predominating (nmr). Selective benzoylation of this product gave crystalline methyl 3,5,di-O-benzoyl-β-D-ribofuranoside, mp 132-133°, the identity of which was established by nmr spectroscopy[8]. The structures of compounds 6 and 7 were further substantiated by converting them into methyl 2,3,5-tri-O-acetyl and benzoyl-β-D-ribofuranosides on one hand and by deesterification to 3 on the other.

The utility of the 1-(dimethylamino)ethylidene and α-(dimethylamino)benzylidene acetals as blocking groups in synthesis was explored. Acetylation of the acetal 4 with acetic anhydride in pyridine gave the 5-acetate 8 as a syrup in 90% yield[9]. At pH 4 in the presence of aqueous acetic acid, this product was hydrolyzed to give a mixture of 2,(3),5-diacetates in 75% yield.

Tosyl chloride in pyridine during 24 h at 25° converted 4 into the 5-p-toluenesulfonate 11 obtained as a homogeneous syrup in good yield[9]. Alternatively, the same 11 could be obtained from methyl 5-O-p-tolylsulfonyl-β-D-ribofuranoside (12) and a slight excess of 1 in the dark at room temperature during 24 h. Hydrolysis of 11 in dilute acetic acid as described above afforded the corresponding 2,(3)-monoacetates 14.

The sulfonyloxy group in 11 could be displaced by treatment with sodium azide in DMF during 6 h at 90° to give the corresponding 5-azide 16, characterized as the crystalline 2,3-bis(p-toluenesulfonate)[10], mp 120-121°, thus demonstrating the compatibility of the acetal group with conventional procedures of nucleophilic displacement reactions in non-aqueous, aprotic solvents. Alternatively, treatment of methyl 5-azido-5-deoxy-β-D-ribofuranoside (13) with two equivalents of 1 in 1,1,2-trichloroethane at room temperature overnight gave the same acetal 16 in good yield. Under controlled conditions, other types of acylations are also possible in the presence of 1-(dimethylamino)ethylidene acetals

* Selective acetylation in the 2- and 3- positions of 3 could also be achieved by hydrolysis of the corresponding methoxyethylidene derivative, which is considerably less stable than 4 and comparatively less useful from a preparative standpoint.

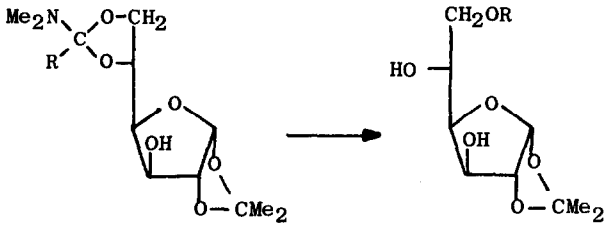


14, R=OTs
15, R=N_3

12, R=OTs
13, R=N_3

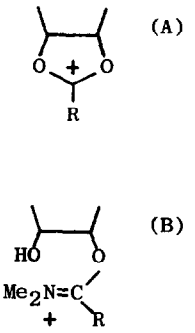
in marked contrast to 1-(dimethylamino)methylene acetals, derived from ribonucleosides and N,N-dimethylformamide dimethyl acetal[11]. Acylation in the presence of α-(dimethylamino)benzylidene acetals is also possible, as demonstrated by the benzoylation of 5 with benzoyl chloride in pyridine, followed by mild hydrolysis to give the crystalline dibenzoate 10 in high yield.

In the case of 1,2-O-isopropylidene-α-D-glucofuranose, reaction with 1 and 2 during 48 h at room temperature resulted in a selective acetalation to give the 5,6-acetals 17 and 18, respectively, in over 80% yield. Hydrolysis with aqueous acetic acid at pH 4 for 2 h at room temperature gave 6-O-acetyl-1,2-O-isopropylidene-α-D-glucofuranose (19), mp 145-147°; reported mp 145-146° [12], and the corresponding 6-benzoate, mp 194-195°, reported, mp 196° [13]. These reactions represent efficient, indirect procedures for the preferential esterification of the primary hydroxyl groups in acyclic diols. The preponderant formation of one of two possible esters can be explained by the stereoselective collapse of a cyclic orthoester derived from an acyloxonium intermediate (A) or from the ring-opening of a protonated acetal to give an iminium intermediate (B).



17, R=Me
18, R=Ph

19, R=Ac
20, R=Bz



The 1-(dimethylamino)ethylidene and α-(dimethylamino)benzylidene acetal groups are thus useful protecting groups for 1,2-diols[14]. Their particular advantages include their relative stability and compatibility with various acylation and nucleophilic-displacement reactions. Moreover, these acetals lend themselves to a variety of transformations that take advantage of the presence of the dimethylamino group, such as the formation of benzoxonium and acetoxonium ions. These and other aspects of the chemistry of amide acetals will be dealt with separately.

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References

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