2-METHOXYBENZYLIDENE ACETALS, EFFICIENT PROTECTING GROUPS FOR ALDOHEXOPYRANOSIDES

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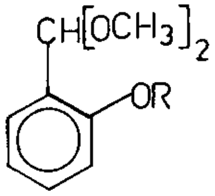
Abstract - 2-Methoxybenzaldehyde dimethyl acetal is an excellent protecting group for aldohexopyranosides by way of the formation of their 4,6-0-(2-methoxybenzylidene) acetals.

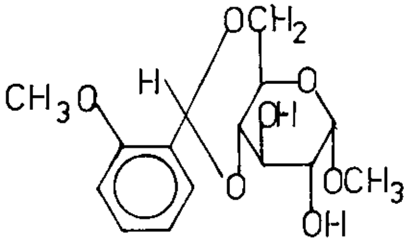
During the course of our explorations for new protecting groups for the aldohexopyranosides, we observed the very high yield formation of 4,6-0- acetals while using variously substituted 2-alkoxybenzaldehyde dimethyl acetals (1) as the reagents in acetal exchange reactions, performed similarly to the method developed by M.E. Evans[1]. We now wish to describe the use of 2-methoxybenzaldehyde dimethyl acetal (2) in the preparation of the 4,6-0-(2-methoxybenzylidene) acetals of methyl α-D-glucopyranoside (3) and methyl β-D-galactopyranoside (4), and further to strongly recommend the use of these derivatives, as they appear to be more efficacious than the classical benzylidene acetals by virtue of their easier and higher yield preparation and their comparable stabilities in normal reaction conditions.[2]

The reagent, 2-methoxybenzaldehyde dimethyl acetal (2) was made in very high yield by methylating salicylaldehyde using dimethyl sulphate with potassium carbonate in acetone; followed by acetalation of the 2-methoxybenzaldehyde using trimethyl orthoformate in anhydrous methanol with p-toluenesulphonic acid,(PTSA) as catalyst, at about 32°C. Each reaction proceeded nearly quantitatively, so providing a nearly pure sample of the reagent (2), δ_{CDCl_3} 3.33 (6H,s), 3.77 (3H,s), 5.63 (1H, s), 6.67 to 7.67 (4H, m); which was used without further purification. The reaction of the methyl glycopyranoside in anhydrous dimethylformamide with the reagent (2) and a catalytic amount of PTSA, under reduced pressure (water pump) at 85°C, for 35 minutes, routinely yielded the 4,6-0-(2-methoxybenzylidene) acetals in greater than 90% yield. Thus the acetals (3) and (4) were prepared in 96% and 93% yields respectively. In a typical preparation, a 500 ml quickfit round bottomed flask containing methyl α-D-glucopyranoside (0.1 mole), DMF (50 mls), the reagent (2) (0.1 mole) and PTSA (0.1 gms) was attached to a rotary evaporator and heated in a water bath at 85°C, for 35 minutes, while rotating the evaporator and evacuating with a water pump. The DMF was then removed by rotatory evaporation at lower pressure provided by an oil pump, to yield a

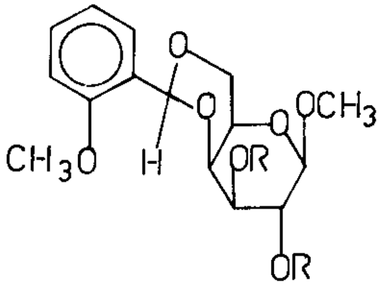


(1) R = alkyl

(2) R = CH_3

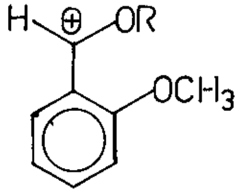


(3)



(4) R = H

(5) R = Ac



(6) R = CH_3 or glycoside

yellow, solid residue, which was triturated with 10% sodium carbonate solution (100 mls), recovered by filtration and washed with cold water (2 x 100 mls). The dried solid was then recrystallised from acetone/60-80° petrol to yield 30.0 gms. (96%) of the compound (**3**). (**3**), m.p. 198-199°C, $[\alpha]_D^{25}$ + 122.5 (c = 1.20, $CHCl_3$) showed δ_{CDCl_3} 3.42 and 3.80 (each 3H, s), 4.72 (1H, d, J = 3Hz, anomeric proton), 5.88 (1H, s, 'benzylidene proton') and 6.67 to 7.67 (4H, m). The multiplicity of the anomeric proton and the coupling constant observed, clearly showed that the anomeric carbon was not affected by the reaction.

The preparation of the non-crystalline compound (**4**) was similar to that of (**3**), save that after the DMF had been removed by evaporation, the gum obtained was thoroughly stirred with 10% sodium carbonate solution (100 mls) to remove the acid catalyst. After decantation of the aqueous solution, the gum was thoroughly stirred with toluene/60-80° petrol (1:1, 150 mls) to remove traces of a coloured material. The gum remaining after decantation was dissolved in ethyl acetate, the solution was dried over sodium sulphate and then the solvent removed, thus yielding a foam of (**4**) pure by T.L.C., in 93% yield.

(**4**), $[a]_D^{25}$ - 32.4° (C = 1.73 gms/100 mls, $CHCl_3$) showed δ_{CDCl_3} 3.48 and 3.77 (each 3H, s), 5.82(1H, s) and 6.67 to 7.67 (4H, m). In order to ascertain the relative configuration at C-1, the compound (**4**) was acetylated using acetic anhydride/pyridine, so yielding the diacetate (5) quantitatively. (**5**), m.p. 182-184°C, $[\alpha]_D^{25}$ + 43.5° (c = 1.45, $CHCl_3$) showed ν_{max} 1740 cm^{-1}; δ_{CDCl_3} 1.98 and 2.03 (each 3H, s), 3.48 and 3.75 (each 3H, s), 4.55 (1H, dd, J = 10 and 3Hz, H-3), 5.37 (1H, dd, J = 10 and 8 Hz, H-z), 5.82 (1H, s) and 6.67 to 7.83 (4H, m). The signals shown by H-2 and H-3 clearly demonstrated that the anomeric carbon again had not been affected by the reaction.

The formation of methyl 4,6-O-benzylidene-glucopyranoside by acetal exchange with benzaldehyde dimethyl acetal has been reported to proceed in yields as high as 84%, but required long reaction times.[3] We suggest that the improvement in yield and the shortened reaction encountered in the use of 2-methoxybenzaldehyde dimethyl acetal was due to the more efficient stabilisation of the carbonium ion intermediate (**6**) by the 2-methoxy group, and to the removal of the methanol from the reaction mixture.

References and notes

All new compounds reported gave satisfactory analytical data.

1. M.E. Evans, Carbohydr. Res., 21, 473 (1972)
2. The 2-methoxybenzylidene acetals are very stable in neutral and basic solutions but are about eleven times as labile as the benzylidene acetals in dilute methanolic HCl. This is decidedly advantageous when it is necessary to remove the protecting acetal group. See too T.H. Fife and L.K. Jao, J. Org. Chem., 30, 1492 (1965) for the reactivities of

arylidene acetals.

3. D.R. Bundle, J.C.S. Perkin I, 2751 (1979).

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