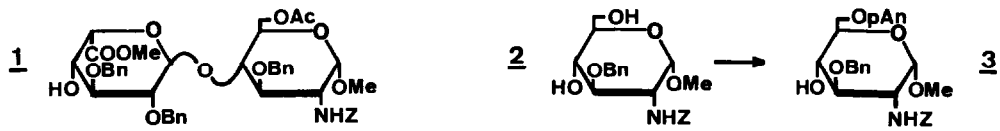
Tetrahedron Letters,Vol.29,No.12,pp 1389-1390,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

p-ANISYL ETHERS IN CARBOHYDRATE CHEMISTRY: SELECTIVE PROTECTION OF THE PRIMARY ALCOHOL FUNCTION

M. Petitou*, P. Duchaussoy and J. Choay
Institut Choay, 46 Avenue Théophile Gautier, 75016 Paris, France

Summary : A p-anisyl ether is selectively introduced at the primary position of a carbohydrate. It is remarkably stable yet easily removed without affecting other protecting groups.

To synthesize a pentasaccharide analog of the antithrombin binding site of heparin[1] we needed the protected intermediate 1. Such an iduronic acid containing disaccharide can be obtained from a suitable idose containing precursor by oxidation at C-6'[2]. The preparation of this precursor involves glycosylation of a glucosamine derivative by an idosyl halide, best with an halide having an acyl group at C-2 which, owing to participation, secures a highly stereoselective reaction. Following this strategy to obtain 1, we then had to deacylate the resulting disaccharide (5) and to perform benzylation at positions 2' and 3' of the idose moiety of the derivative thus obtained. This precluded the introduction, at the very beginning of the synthesis, of the desired acetyl group at C-6 of the glucosamine unit. Instead, a base-stable goup was temporarily needed at this position to allow alkylation and later acetylation. The ideal group should be selectively introduced on the primary position and subsequently removed without acid, conditions met by p-anisyl ethers, reported to be resistant under a wide range of conditions and to be easily cleaved by ceric ammonium nitrate (CAN)[3].

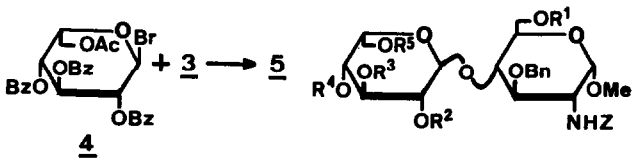


Ac: acetyl; Bn: benzyl; Bz: benzoyl; Me: methyl; pAn: p-Anisyl; Z: benzyloxycarbonyl

p-Anisyl ethers can be obtained[3] by means of the Mitsunobu reaction. For diol 2, we predicted that the inertness of position 4 towards such an inversion would result in the exclusive introduction of the p-anisyl at position 6. This is the fact: a solution of 2[4] (0.7g, 1.7 mmoles) in tetrahydrofuran (5 ml) was heated at 80°C with triphenylphosphine (2.2 mmoles), diethylazodicarboxylate (2.2 mmoles) and p-methoxyphenol (5.1 mmoles). The reaction was complete after 1h to give a single compound (t.l.c.), which was isolated after passage through a column of silica gel (toluene/ether; 4/1 then 2/1; v/v). The residue (0.73g; 82%) was crystallized (hexane-ethyl acetate; m.p. 135°C). NMR analysis confirmed structure 3, particularly the presence of a single p-anisyl group at position 6.[5]

Alcohol 3 was then condensed with bromide 4[6] in the presence of silver triflate at -25°C resulting in a 85% yield of isolated 5. Removal of acyl groups (MeONa, MeOH) was followed by benzylidenation (C_6H_5CHO; CF_3COOH) and benzylation ($C_6H_5CH_2Br$, BaO, $Ba(OH)_2$) thus yielding crystalline 6 (m.p. 208°C) in 52% overall yield. The removal of the p-anisyl group was then performed as follows: to a solution of 6, (0.1g; 0.1 mmole) in acetonitrile/water (4/1; v/v) CAN (0.28g; 0.5 mmole) was added. After 5 min the mixture was diluted with chloroform, washed (satd NaCl, water), dried, concentrated and chromatographed on silica gel, yielding 7 (0.073g; 80%). This disaccharide was then converted into 1 by the following route: $(CH_3CO)_2$, pyridine; CF_3COOH 70% in CH_2Cl_2; TrCl, pyridine; levulinic acid, DCC; $HClO_4$; CrO_3/H_2SO_4; NH_2NH_2; CH_2N_2.

In conclusion, its selective introduction, remarkable stability and cleavage specificity make the p-anisyl an attractive protective group for the primary alcohol function of carbohydrates. For secondary alcohols, the possibility of inversion of configuration with concomitant protection is also a useful possibility.



	R^1	R^2	R^3	R^4	R^5
5	pAn	Bz	Bz	Bz	Ac
6	pAn	Bn	Bn	Benzylidene	
7	H	Bn	Bn	Benzylidene	

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3. Fukuyama T., Laird A.A. and Hotchkiss L.M., Tetrahedron Lett., 26 (1985) 6291-6292.
4. Petitou M., Duchaussoy P., Lederman I., Choay J., Jacquinet J.-C., Sinaÿ P. and Torri G., Carbohydr. Res., 167 (1987) 67-75.
5. All compounds gave satisfactory elemental analysis. NMR data were in accord with the expected structures.
6. Halide 4 was obtained from 1,6-anhydro-2,3,4-tri-O-benzoyl-L-idopyranose after acetolysis followed by halogenation (HBr/ACOH).

(Received in France 23 December 1987)