Tetrahedron Letters,Vol 25,No.49,pp 5697-5700,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

C-GLYCOSIDES THROUGH THE WITTIG-CYCLIZATION PROCEDURE: OBSERVATIONS ON THE INFLUENCE OF THE NATURE OF THE SUBSTRATE.

Francesco Nicotra, Fiamma Ronchetti, Giovanni Russo*, and Lucio Toma

Istituto di Chimica Organica e Centro per lo Studio delle Sostanze Organiche Naturali del CNR, Via Venezian 21, 20133 Milano, Italy.

Summary: The Moffatt C-glycosidation procedure was examined on different pyranoses; in glucopyranoses competitive elimination was observed in the Wittig reaction; all the other glycopyranoses investigated gave the Wittig product without elimination.

The synthesis of C-glycosides has become an increasing important area in synthetic organic chemistry; these compounds are in fact chiral templates for complex synthetic targets[1] and potential enzyme inhibitors.[2] Moreover a wide variety of medically important C-nucleosides[3] and other important C-glycosides have been discovered.[4]

One widely used procedure for the synthesis of C-glycosides is the Wittig reaction between a sugar and (ethoxycarbonylmethylene)triphenylphosphorane, followed by Michael cyclization (Moffatt procedure).[5]

We now describe here some interesting observations regarding the applicability of the Moffatt C-glycosidation procedure on pyranoses.

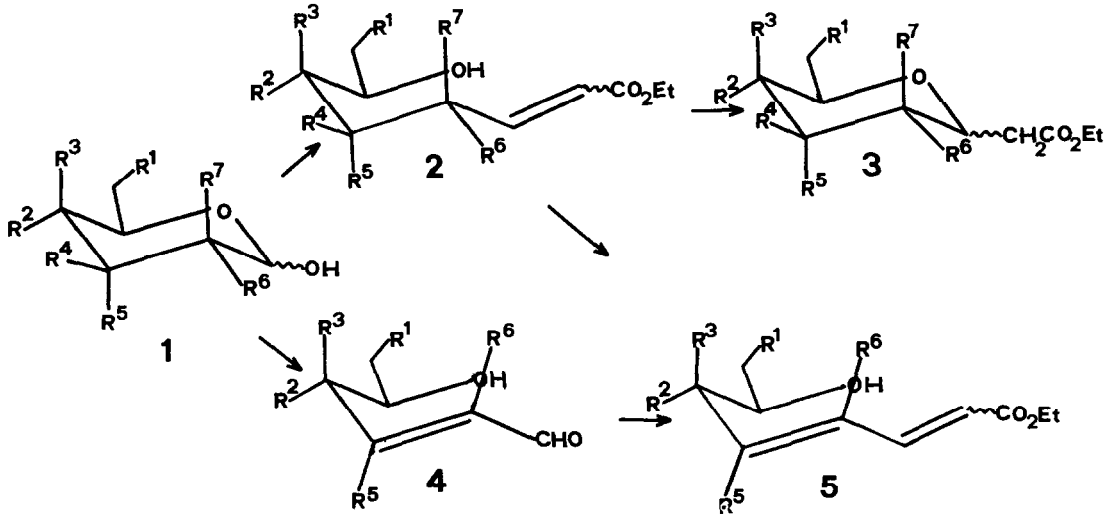
During the course of our efforts towards the synthesis of the phosphono analogues of α- and ß-D-glucose 1-phosphate[2b], we tried to apply the Moffatt procedure to the commercially available (Fluka AG) 2,3,4,6-tetra-O-benzyl-D-glucopyranose (**1a**); surprisingly the Wittig reaction afforded the elimination product **5a** in 80% yield (δ 7.20, d, J=16Hz, H-3; 6.30, d, J=16Hz, H-2; 5.53, d,J=9Hz, H-5).[6] All attempts to find reaction conditions avoiding the unwanted

elimination (entry 2,3 and 4 in table) failed. The same elimination was observed when we did the Wittig reaction on 2-O-benzyl-3,4,6-tri-O-acetyl-D-glucopyranose (**1c**), and in part also in the case of 2,3,4,6-tetra-O-acetyl-D-glucopyranose (**1b**). These results are unusual in that reactions of sugar derivatives with (ethoxycarbonylmethylene)triphenylphosphorane have been described which readily afford the α,β-unsaturated carboxylic ester **2**[5-7] or, directly, the cyclization product **3**.[5,8,9] It is worty of note however that in most reported cases, the reaction was effected on furanoses, which require shorter reaction times, or on pyranoses with an hydroxyl group at C-3.

The recent interest on C-pyranosides as chiral templates has made desirable to know to which substrate the Moffatt C-glycosidation procedure may be successfully applied.

To investigate if any generalization can be made concerning the elimination process observed in the case of D-glucopyranoses, we submitted to the Wittig reaction pyranoses with different configurations to the gluco-isomer at C-2 and/or at C-3. No elimination was observed in the manno-, altro-, or allo-hexopyranoses (**1d, 1e, and 1f**, respectively). Also no elimination occurred in the C-4 stereoisomer (note the case of 2,3,4,6-tetra- O-benzyl-D-galactopyranose **1g**). The behaviour of 2,3,4,6-tetra-O-benzyl-D-glucopyranose stands in contrast to the behaviour of 4,6-O-benzylidene-D-glucopyranoses. Both 4,6-O-benzylidene-2,3-di-O-benzyl--D-glucopyranose(**1i**), and 4,6-O-benzylidene-2,3-di-O-acetyl-D-glucopyranose (**1h**), afforded the C-glycosidation product **3** (in the case of **1i** also the α,β-unsaturated octenoate **2i** was isolated, see table). No elimination product was detected.

The above results are worthy of note, as D-glucose is a cheap, chiral starting material widely employed in synthesis.



a $R^1=R^2=R^4=R^6=PhCH_2O-$; $R^3=R^5=R^7=H$ (gluco)

b $R^1=R^2=R^4=R^6=AcO-$; $R^3=R^5=R^7=H$ (gluco)

c $R^1=R^2=R^4=AcO-$; $R^6=PhCH_2O-$; $R^3=R^5=R^7=H$ (gluco)

d $R^1=R^2=R^4=R^7=PhCH_2O-$; $R^3=R^5=R^6=H$ (manno)

e $R^1=R^2=R^5=R^7=PhCH_2O-$; $R^3=R^4=R^6=H$ (altro)

f $R^1=R^2=R^5=R^6=PhCH_2O-$; $R^3=R^4=R^7=H$ (allo)

g $R^1=R^3=R^4=R^6=PhCH_2O-$; $R^2=R^5=R^7=H$ (galacto)

h $R^1,R^2=PhCH(O-)_2$; $R^4=R^6=AcO-$; $R^3=R^5=R^7=H$ (gluco)

i $R^1,R\delta2=PhCH(O-)_2$; $R^4=R^6=PhCH_2O-$; $R^3=R^5=R^7=H$ (gluco)

Table

Entry	Substrate	Reaction conditions	Isolated products[7]
1	**a**	CH_3CN, rfx 16h, 2eq of $Ph_3P=CHCO_2Et$	**5**
2	**a**	" " 7h, 1.2eq "	**5** (traces of **1**)
3	**a**	THF " 40h, 1.2eq "	**1**
4	**a**	Toluene " 50h, 1.2eq "	**5**
5	**b**	CH_3CN, " 20h, 2eq "	**3+5** (7:3)
6	**c**	" " " " "	**5**
7	**d**	" " " " "	**2**
8	**e**	" " " " "	**2**
9	**f**	" " " " "	**2**
10	**g**	" " " " "	**3** (traces of**2**)
11	**h**	" " " " "	**3**
12	**i**	" " 14h " "	**3+2** (4:1)

References and Notes

1. a) M.D. Lewis, J.K. Cha and Y. Kishi, J.Am.Chem.Soc.,104, 4976 (1982) and references cited therein; b) G.E. Keck and J.B. Yates, ibid., 104, 5829 (1982); c) A.P. Kozikowski and K.L. Sorgi, Tetrahedron Lett., 23, 2281 (1982); d) R.R. Shmidt and M. Hoffman, ibid, 23, 409 (1982).

2. a) F. Nicotra, F. Ronchetti and G. Russo, J.Chem.Soc., Chem.Commun., 470 (1982); b) F. Nicotra, F. Ronchetti and G. Russo, J.Org.Chem., 47, 4459 (1982); c) M. Chmielewski, J.N. Be Miller and D.P. Cerretti, Carbohydr.Res., 97, C1-C4 (1981).

3. R.J. Suhadolnik, Nucleoside Antibiotics, 1970, J. Wiley and Sons Inc.

4. For example see R.A. Eade and H-P. Pham, Aust.J.Chem., 32, 2483 (1979).

5. H. Orui, G.H. Jones, J.G. Moffatt, M.L. Maddox, A.T. Christensen and S.K. Byram, J.Am.Chem.Soc., 97, 4602 (1975).

6. The trans configuration of the **4**, which indicates an anti elimination, was deduced by NOE experiments (5% NOE).

7. Satisfactory elemental analyses, ^{1}H and ^{13}C NMR spectra, consistent with the assigned structures, were obtained for all new compounds.

8. F. Nicotra, F. Ronchetti and G. Russo, J.Org.Chem., 47, 5381 (1982).

9. F. Nicotra, G. Russo, F. Ronchetti and L. Toma, Carbohydr.Res., C5-C7 (1983).

10. The formation of **2i** in the reaction of **1i** whith (ethoxycarbonylmethylene)tryphenylphosphorane has been reported by L.A. Reed, Y. Ito, S. Masamune and K.B. Sharpless, J.Am.Chem.Soc., 104, 6468 (1982).

(Received in UK 19 September 1984)