Carbohydrate Research, 44 (1975) C5–C7
© Elsevier Scientific Publishing Company, Amsterdam – Printed in Belgium

Preliminary communication

Methylation of carbohydrates with methyl trifluoromethanesulfonate

JAN ARNARP, LENNART KENNE, BENGT LINDBERG, and JÖRGEN LÖNNGREN

Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm, S-104 05 Stockholm (Sweden)

(Received August 27th, 1975; accepted for publication, September 1st, 1975)

Methylation of hydroxyl groups is an important reaction in carbohydrate chemistry which is used both for preparative purposes and, especially, in structural studies. In most of the methylation procedures, methyl sulfate or methyl iodide is used together with a strong base, such as sodium hydroxide, silver oxide, or methylsulfinyl anion. *O*-Acyl groups present in the sugar reactants are cleaved or may migrate. Carbohydrates containing base-labile substituents can, however, be methylated with diazomethane–boron trifluoride[1]. The presence of a strong Lewis acid, however, limits the scope of this reaction. The high reactivity of methyl trifluoromethanesulfonate (methyl triflate) should make it a suitable reagent for methylation of carbohydrates under mild conditions, and we now report studies with this reagent.

On alkylation with a triflate[2], a base should be present to neutralize the liberated acid. In preliminary experiments, methyl 2,4,6-tri-*O*-methyl-β-D-glucopyranoside (50 mg) in dichloromethane (3 ml) at 80° was treated with methyl triflate (330 mg), using solid potassium carbonate[2] as the base. The reaction was monitored by g.l.c. All starting material had disappeared after 30 min, but in addition to the expected methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside, the corresponding α-D-glucoside was also formed. The ratio of α- to β-glucoside was approximately 1 : 1, but increased on prolonged reaction time. The anomerization is obviously caused by the strong acid, demonstrating that the neutralization with potassium carbonate is not sufficiently effective.

On benzylation using benzyl triflate, Lemieux and Kondo[3] used 2,4,6-trimethylpyridine as base. This substance, however, was rapidly *N*-methylated in the presence of methyl triflate. The strongly sterically hindered bases 2,6-di-*tert*-butylpyridine and 2,6-di-*tert*-butyl-4-methylpyridine proved to be satisfactory, and, using the procedure given below, the following substances were methylated: methyl 2,3-di-*O*-acetyl-α-D-glucopyranoside, methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside, 1,2,3,2′,3′,4′,6′-hepta-*O*-acetyl-β-maltose, and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose.

The substance (0.2 mmol) and the base (4.0 mmol) in a 10-ml serum flask were dissolved in dry dichloromethane (3 ml). The flask was sealed with a rubber cap and flushed with nitrogen, and methyl triflate (2.0 mmol) was added with a syringe. The solution was heated for 2.5 h at 80° and then allowed to cool. The product was purified by chromatography on silica gel, using ethyl acetate–light petroleum (1 : 1 v/v).

The yields of isolated products were 80% or better. Only a single component was obtained in each reaction, as demonstrated by g.l.c. and t.l.c. The structures of the products were demonstrated by comparison with authentic materials, by n.m.r. spectroscopy, and by hydrolysis and sugar analysis[4], when the expected methylated sugars were obtained. The m.p. of the maltose derivative also agreed with the literature value[5].

The high reactivity of methyl triflate limits the choice of solvent for the methylation. This is a restriction for the methylation of hydrophilic carbohydrates, such as unprotected glycosides and polysaccharides. Polysaccharides partially substituted with lipophilic groups may, however, be methylated, as demonstrated with a commercially available cellulose acetate of d.s. 2.40.

Cellulose acetate (5 mg) in a 10-ml serum flask was dissolved in dry *p*-dioxane (2 ml). The flask was sealed with a rubber cap and flushed with nitrogen, and 2,6-di-*tert*-butyl-4-methylpyridine (200 mg) was added, followed by methyl triflate (90 mg). The solution was kept at 80° for 4 h, dialysed against water, and lyophilized. The product was hydrolysed, and the methylated sugars were analysed, as their alditol acetates, by g.l.c.–m.s.[4] (Table I).

TABLE I

METHYLATED SUGARS IN THE HYDROLYSATE OF METHYLATED CELLULOSE ACETATE (d.s. 2.40)

D-*Glucose derivative, methylated in positions*	*Found (mol %)*	*Calc. (mol %)*
2,3,6	1.3	1.8
2,6	1.7	3.4
3,6	3.1	2.3
2,3	2.4	1.1
6	19.8	20.7
2	4.7	9.3
3	6.9	9.7
0	62.0	51.6

The distribution of *O*-acetyl groups in this cellulose acetate has been determined[6], and the expected percentages of the different methylated glucoses, assuming complete methylation, are given in Table I. The results show that most, but not all, free hydroxyl groups have been methylated, probably because part of the cellulose acetate was not dissolved. Thus, the d.s. of methoxyl groups in the product is 0.49 compared to the theoretical value of 0.60.

In conclusion, reaction with methyl triflate and a sterically hindered, weak base seems to be a versatile method for methylation of carbohydrates containing base- and/or acid-labile groups and might open interesting possibilities in structure elucidation of natural products.

ACKNOWLEDGMENTS

We are indebted to Dr. I. J. Goldstein for a gift of 1,2,3,2′,3′,4′,6′-hepta-*O*-acetylmaltose, and to the Swedish Natural Science Research Council for financial support.

REFERENCES

1 I. O. Mastronardi, S. M. Flematti, J. O. Deferrari, and E. G. Gros, *Carbohyd. Res.*, 3 (1966) 177–183.
2 C. D. Beard, K. Baum, and V. Grakauskas, *J. Org. Chem.*, 38 (1973) 3673–3677.
3 R. U. Lemieux and T. Kondo, *Carbohyd. Res.*, 35 (1974) C4–C6.
4 H. Björndal, C. G. Hellerqvist, B. Lindberg, and S. Svensson, *Angew. Chem. Int. Ed. Engl.*, 9 (1970) 610–619.
5 H. Arita, M. Isemuva, T. Ikenaka, and Y. Matsushima, *Bull. Chem. Soc. Jap.*, 43 (1970) 818–823.
6 H. Björndal, B. Lindberg, and K.-G. Rosell, *J. Polym. Sci., Part C*, 36 (1971) 523–527.