Alkylation of Carbohydrates with Alkyl Trifluoromethanesulfonates

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Alkylation of hydroxyl groups is a common reaction in carbohydrate chemistry. Methylation in particular is important in structural studies and for preparative purposes, *e.g.* in modification of carbohydrate-containing antibiotics.

The application of benzyl or methyl trifluoromethanesulfonates (triflates) as alkylating agents in the field of carbohydrate chemistry has been reported.[1-3] In these reactions *O*-acetyl and *O*-isopropylidene groups are stable and the alkylated products are obtained in high yields.

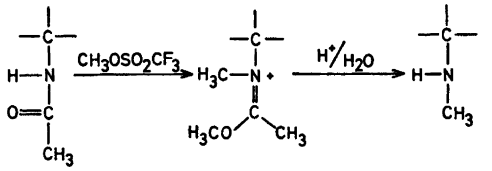
We now report further studies on triflate alkylation of neutral carbohydrates substituted with different protecting groups and of 2-acetamido-2-deoxyhexose derivatives.

The substrate was dissolved in dry dichloromethane and 2,6-di-*tert*-butyl-4-methylpyridine, followed by methyl or ethyl triflate, was added. The reaction mixture, in a sealed vial, was heated at 80 °C. The products were isolated by chromatography and identified from their m.p. and spectral properties and by GLC-MS of the derived alditol acetates.[4]

Table 1 gives starting materials, products and yields for some alkylation reactions. It is evident that *O*-benzoyl, *O*-benzyl, *O*-benzylidene, *O*-isopropylidene, *O*-tosyl and *O*-triphenylmethyl groups are suitable protecting groups and that the yields of *O*-alkyl ether derivatives are essentially quantitative. These results are in agreement with the earlier observation that *O*-acetyl, *O*-isopropylidene groups and glycosidic linkages are stable during methylation with methyl triflate.[2,3] An exception was, however, observed in the present investigation. Thus, methylation of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose gave some cleavage of the 2,3-*O*-isopropylidene acetal. Likewise, during methylation of 1,3,4,6-tetra-*O*-acetyl-α-D-glucose partial migration of an acetyl group from *O*-1 to *O*-2 was noted.[3]

Two compounds, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and 1,2,3,6-tetra-*O*-benzoyl-α-D-glucopyranose, were subjected to ethylation using ethyl triflate. The yields of *O*-ethyl ethers were 81 and 92 %, respectively. These results confirm, as expected, that ethylation is equally efficient as methylation.

Methylation of 2-acetamido-2-deoxyhexosides with the Hakomori procedure yields the 2-*N*-methylacetamido derivatives whereas the Haworth, Purdie and Kuhn procedures give *N*-methylation in variable extents.[5] Methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranoside and methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside were methylated using methyl triflate. The products were either treated with aqueous acetic acid or, in the latter example, subjected to de-*O*-acetylation and treatment with acidic ion-exchange resin. Methyl 2-deoxy-2-*N*-methylamino-3,4,6-tri-*O*-methyl-β-D-glucopyranoside and methyl 2-deoxy-2-*N*-methylamino-β-D-glucopyranoside hydrochloride were obtained in 90 and 84 % yield, respectively. Thus, in both examples *N*-methylation was obtained but with concomitant de-*N*-acetylation. A possible mechanism for this reaction, involving a methyl acetimidate group, is depicted in



Scheme 1.

Scheme 1. Methyl imidates have earlier been obtained in the methylation of acetamido sugar derivatives with silver oxide, silver perchlorate and methyl iodide in chloroform – benzene.[6] Subsequent acid hydrolysis gave the corresponding amine salts.[6] The *N*-acetyl to *N*-methyl exchange obtained with methyl triflate may be of interest in modifications of acetamido-sugar derivatives.

Experimental. Concentrations were performed under reduced pressure at bath temperatures not exceeding 40 °C. Preparative TLC was performed on Merck Silica Gel F_{254}. ^{1}H NMR and mass spectra were recorded using Varian XL-100 and M-T11 instruments, respectively. Methyl and ethyl ethers were identified from their ^{1}H NMR spectra and, after deblocking, by GLC-MS of the derived alditol acetates. The aminosugar derivatives were identified from their ^{1}H NMR spectra only.

O-Alkylation of neutral sugars. The sugar derivative (0.2 mmol), contained in a serum vial, was dissolved in dichloromethane (5 ml), 2,6-di-*tert*-butyl-4-methyl-pyridine (4.0 mmol) was added and the vial was sealed and flushed with nitrogen.[2] Alkyl triflate (2.0 mmol) was added with a syringe and the vial was heated at 80 °C for 2.5 h (methylation) or 8 h (ethylations and compound I). Methanol (5 ml) was added and the reaction mixture was concentrated to dryness. The products were then isolated by preparative TLC.

*Methyl 2-deoxy-2-*N*-methylamino-3,4,6-tri-*O*-methyl-β-D-glucopyranoside.* Methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-glucopyranoside (20 mg) was methylated as described

Table 1. Alkylations with alkyl trifluoromethanesulfonates.

Starting material	Product	M.p. °C	Yield %
1,2,3,6-Tetra-*O*-benzoyl-α-D-glucopyranose	4-*O*-Methyl-1,2,3,6-tetra-*O*-benzoyl-α-α-glucopyranose (I)	Oil	89
Benzyl 3,6-di-*O*-benzoyl-α-D-mannopyranoside	Benzyl 2,4-di-*O*-methyl-3,6-di-*O*-benzoyl-α-D-mannopyranoside	Oil	89
Methyl 6-*O*-triphenylmethyl-α-D-glucopyranoside	Methyl 2,3,4-tri-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside	150–153	93
Benzyl 2,3-*O*-benzylidene-6-*O*-triphenylmethyl-α-D-mannopyranoside	Benzyl 2,3-*O*-benzylidene-4-*O*-methyl-6-*O*-triphenylmethyl-α-D-mannopyranoside	Oil	81
Methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranoside	Methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-tosyl-α-D-glucopyranoside	153–154	88
Benzyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside	Benzyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside	120–121	86
2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose	Methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside	Oil	80
	Methyl 2,3-di-*O*-methyl-5,6-*O*-isopropylidene-α-D-mannofuranoside	Oil	10
Methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranoside	Methyl 2-deoxy-2-*N*-methylamino-3,4,6-tri-*O*-methyl-α-D-glucopyranoside	Oil	90
Methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside	Methyl 2-deoxy-2-*N*-methylamino-β-D-glucopyranoside hydrochloride (product after de-*O*-acetylation)	Amorphous	84
1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose	3-*O*-Ethyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose	Oil	81
1,2,3,6-Tetra-*O*-benzoyl-α-D-glucopyranose	4-*O*-Ethyl-1,2,3,6-tetra-*O*-benzoyl-α-D-glucopyranose	73–75	92

above. After concentration, the reaction mixture was treated with 70 % aqueous acetic acid (10 ml) for 14 h at room temperature. The mixture was concentrated and partitioned between 0.1 M HCl and chloroform. The acidic phase was neutralized with sodium hydrogen carbonate and extracted with chloroform. The chloroform phase was then extracted with 0.1 M acetic acid. The combined aqueous phases were made strongly alkaline and finally extracted with chloroform. On concentration, the title compound was obtained as an oil (16 mg) which did not crystallize. ^{1}H NMR (methanol-d_4) showed, *inter alia*, signals at δ 3.30, 3.39, 3.41, 3.51 (4×3 H, 4 s, OMe groups), δ 2.38 (3 H, s, *N*-methyl group) and δ 4.06 (1 H, d, $J_{1,2}$ 8.0 Hz, anomeric proton).

*Methyl-2-deoxy-2-*N*-methylamino-β-*D*-glucopyranoside hydrochloride.* Methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (50 mg) was methylated as described above. After concentration, the reaction mixture was dissolved in methanol (20 ml), a piece of sodium (~10 mg) was added and the mixture left at room temperature for 2 h. Excess of Dowex 50 (H^+) and water (5 ml) were added and the mixture was stirred at room temperature overnight. The resin was filtered off and washed with methanol and 0.2 M HCl. Elution of the resin with 2 M HCl and concentration

yielded the title compound as its hydrochloride in amorphous form (28 mg). ^{1}H NMR (D_2O, 85 °C) showed, *inter alia*, δ 3.60 (3 H, s, OMe group), δ 2.86 (3 H, s, *N*-methyl group) and δ 4.73 (1 H, d, $J_{1,2}$ 8.5 Hz, anomeric proton).

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The Exhaustive Baeyer-Villiger Oxidation of Cyclic α,α-Dimethyl-substituted Ketones: δ-Lactones from 1,1-Dimethyl-2-decalones and Triterpene-3-ones

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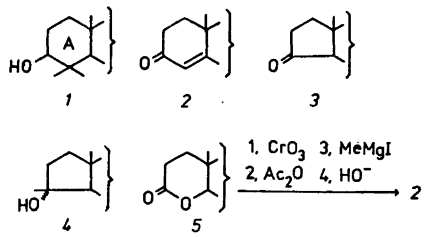
The reconstruction of a triterpenoid ring A (*1*) into a steroid-type 4-en-3-one system (*2*) is a problem of long standing.[1] The Voser procedure [2,3] and later modifications [4–10] involve the dehydration and oxidation of *1* to a ring A cyclopentan-3-one (*3*) followed by methylation (to give *4*), ring cleavage and cyclisation to furnish *2* in 5–7 steps and 2–11 % overall yield. The ketone *3* may also be oxidised to the ring A 4-oxa-3-one (*5*) which will then give *2* as shown in 39 % yield [11,12] (9.4 % overall from *1*).



Another route [13] is based on the photochemical cleavage of the 4-derived nitrite, giving *2* in 6 % yield from 3. The most efficient among the published 4,4-bisdemethylation procedures utilised [14] the second-order Beckmann oxime cleavage (from 5α*H*-lanostan-3-one), giving the corresponding 4-en-3-one (*2*) in 8 steps in 25 % overall yield. A related route has been used [15] to effect 4,4-bisdemethylation without 4,5-dehydrogenation in unspecified yield in 8 steps.

One of us has reported [16] a case of exhaustive Bayer-Villiger oxidation of the pentacyclic triterpene allobetulone (*6*), giving *11* in 50 % yield on treatment with peracetic acid and $BF_3.Et_2O$. Provided this reaction is general, a short new route for the 4,5-dehydrogenative 4,4-bisdemethylation (*1* → *2*) of triterpenes and related compounds would be at hand, as the lactones *5* can be transformed to the enones *2* in 4 steps in *ca.* 40 % yield.[11,12]

Further studies now reported show that the reaction is general for condensed cyclic α,α-dimethyl-substituted ketones. The ketones (*7*–*10*) are oxidised with peracetic acid/boron trifluoride etherate to give the lactones *12*–*15*