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Note

Oxidation of sugar hydroxy groups with triphenylphosphine–*N*-chlorosuccinimide–dimethyl sulfoxide

György Hodosi

Institute for Drug Research, P.O.B. 82, 1325 Budapest (Hungary)

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In our previous paper[1] we reported that the reaction of triphenylphosphine and *N*-bromosuccinimide with *N*,*N*-dimethylformamide afforded the *N*,*N*-dimethylsuccinimidomethanium bromide (**1**). The latter can react with alcohols to give *O*-iminium type intermediates (**2**), which can be converted by heating to give bromides or by quenching with water to give *O*-formyl derivatives. In our present paper we describe the reaction of triphenylphosphine and *N*-chlorosuccinimide with dimethyl sulfoxide to form a dimethylsuccinimidosulfonium[2] salt (**3**), which is a good reagent for the oxidation[3] of primary and secondary alcohols.

Triphenylphosphine reacted with *N*-chlorosuccinimide to give the phosphonium salt (**4**), which, when treated at low temperatures (−40 to −50°C) with dimethyl sulfoxide, afforded a white suspension of dimethylsuccinimidosulfonium[2] chloride (**3**) and triphenylphosphine oxide, probably via intermediate **5**. The ylide **3** can react either with primary or secondary alcohols to give the alkoxysulfonium derivatives[4] **6**, which, in the presence of triethylamine, can be converted mainly into aldehyde **7** (R = alkyl, R′ = H) or ketone **7** (R = R′ = alkyl), and partially into the corresponding (methylthio)methyl ether[5] derivative **8**. In this way the glucofuranose derivative **9** and galactopyranose derivative **12**, both having primary OH groups, were oxidized into the corresponding aldehydes **10** and **13** (ref 6) in good yields (65–70%). While the 1,2-*O*-isopropylidene-α-D-glucofuranose **10** had to be characterized as the *p*-nitrophenylhydrazone derivative **11**, the 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdopyranose (**13**) showed the ^{1}H NMR spectrum of a pure aldehyde. In the case of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**12**), the isolated byproduct was determined to be 6-*O*-(methylthio)methyl ether **14** (ref 7), isolated in 10% yield. A similar side product **18** was observed in the oxidation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**17**), wherein the yield of 3-ulose **20** was very low (20%). Kondo and Takao[8] also oxidized compound **17** and published the 60-MHz ^{1}H NMR spectrum of a byproduct, which was de-

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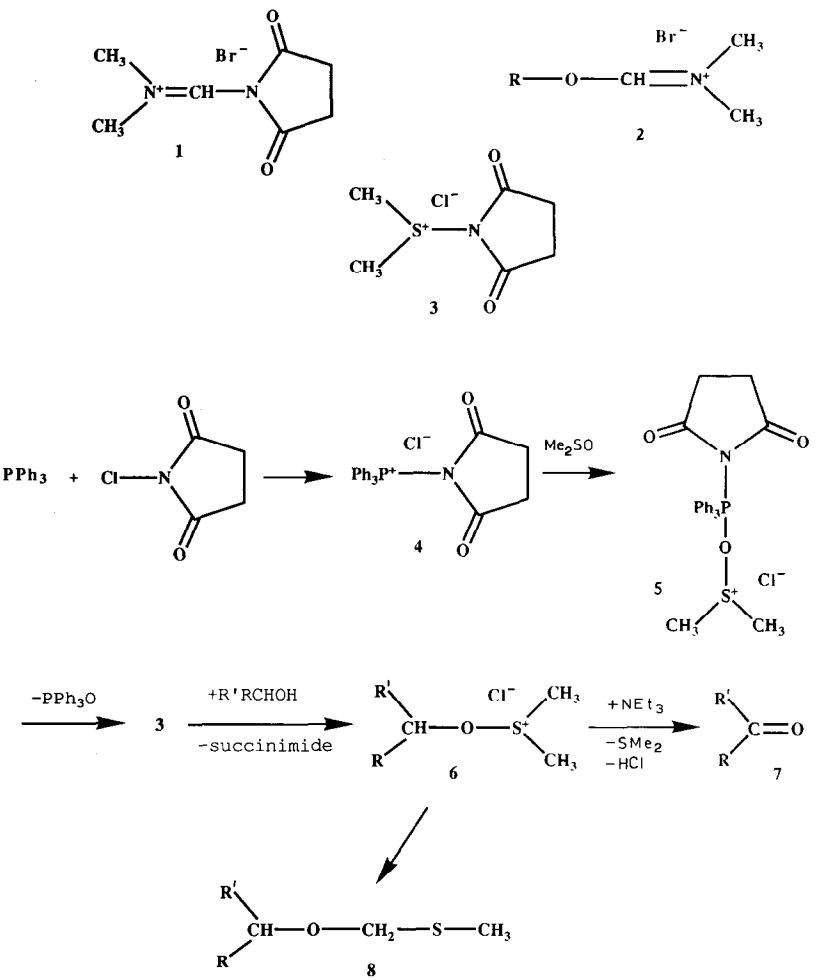
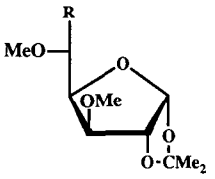
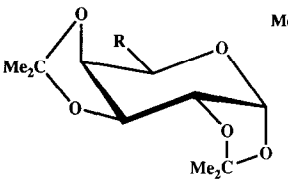
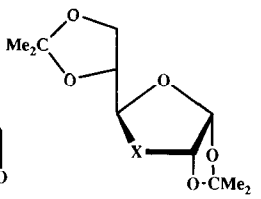


scribed as the 2,3-oxidodimethylene derivative **19**; however, the integral of the crucial part was omitted. The published spectrum was in agreement with our spectrum of 3-*O*-(methylthio)methyl ether **18**. The integral of our spectrum corresponds to two protons of the methylene group of the CH_3SCH_2O substituent at C-3, thus proving the structure. (It should also be mentioned that Defaye et al.[9], who cited Kondo and Omura without revision, correctly ascribed the structure of the by-product **18**, but their assignment of the ^1H NMR spectrum was not completely correct.) Swern and Omura[5] studied the mechanisms of side reactions, and for cases where large amounts of *O*-(methylthio)methyl derivative were formed, they suggested the use of a sterically hindered base to avoid the side reaction. We attempted to improve the yield of 3-ulose **20** by using diazabicycloundecene (DBU), but the yield was still rather low, perhaps because of severe steric

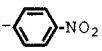






9 R = CH_2OH

10 R = CHO

11 R = CH=N-NH-  -NO_2

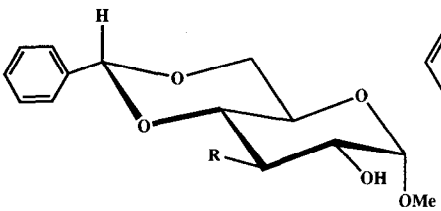
12 R = CH_2OH

13 R = CHO

14 R = $CH_2OCH_2SCH_3$

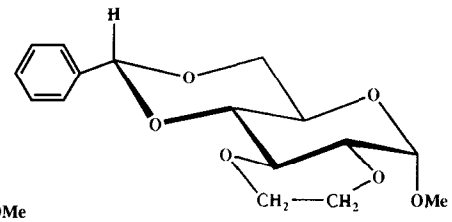
15 X = CHOH (D-gluco)

16 X = CO

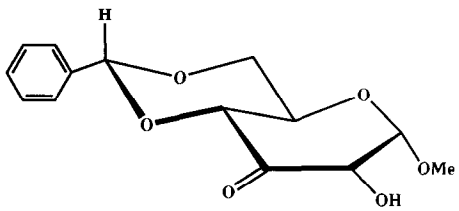


17 R = OH

18 R = OCH_2SCH_3



19



20

hindrance. In this case, the use of the sterically less hindered dimethylsulfoxonium salts instead of the dimethylsuccinimidosulfonium salt (**3**) can lead to a higher yield[5]. The oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**15**) giving **16** (ref 10) was much more successful, and the yield was quite good (68%). The disadvantage of the reported oxidation reactions is the formation of large amounts of triphenylphosphine oxide; however, in the case of protected ketones and aldehydes, which are soluble in organic solvents, triphenylphosphine oxide can be removed by partial crystallization either from diethyl ether or a 1:1 ethyl acetate–hexane mixture.

EXPERIMENTAL

General methods.—Organic solutions were dried over $MgSO_4$ and concentrated under reduced pressure. Optical rotations were determined on 1% solutions in

TABLE I

Reaction conditions, yields and chromatography condition for the oxidation products

Compd	Reagent (mol equiv)				Yield (%)	Solvent [b]	Ref
	Ph_3P	NCS [a]	Me_2SO	Et_3N			
10	1.7	1.7	2.0	3.0	72.5	*C*	
13	1.7	1.7	2.0	3.0	65.6	*C*	6
14	1.7	1.7	2.0	3.0	9.8	*D*	7
16	2.2	2.2	2.4	3.5	67.5	*C*	10
18	1.7	1.7	2.0	3.5	22.0	*C*	9
20	1.7	1.7	2.0	3.5	20.1	*B*	9

[a] *N*-Chlorosuccinimide. [b] Solvent used in column chromatography (see general methods in Experimental section).

$CHCl_3$ at 20°C unless stated otherwise. Solutions were cooled in ice, unless stated otherwise. TLC was performed on Silica Gel G with EtOAc (*A*) and EtOAc–hexane mixtures (*B*, 1:1; *C*, 1:2; and *D*, 1:3) with detection by charring with H_2SO_4. ^1H NMR spectra (250 MHz) were recorded with a Bruker AC 250 NMR spectrometer on solutions in $CDCl_3$ (internal Me_4Si) unless stated otherwise.

General procedure for the preparation of oxo compounds from hydroxyl derivatives.—Triphenylphosphine (16.9 mmol) was added in three portions to a dry ice-cooled (−50 to −40°C) and stirred solution of anhyd Me_2SO (18.4 mmol) and *N*-chlorosuccinimide (16.9 mmol) in anhyd CH_2Cl_2 (30 mL) under N_2. After 70 min the solution of a hydroxy compound (7.7 mmol) in anhyd CH_2Cl_2 (10 mL) was added to the white, dense suspension. After 1.5 h Et_3N (26.95 mmol) was added, and after an additional 10 min the cooling bath was removed. The solution was stirred at 20°C for 1.5 h and worked up as follows. Chloroform (200 mL) was added to the mixture, and this mixture was washed twice with satd aq $NaHCO_3$ (50 mL), dried, filtered, and evaporated. Triphenylphosphine oxide partially crystallized either from diethyl ether solution or solvent *B*. The crystals were filtered, washed either with cooled diethyl ether or solvent *B*. The filtrate was evaporated and purified by column chromathography. The yields of oxo derivatives and reaction conditions are given in Table I.

*1,2-O-Isopropylidene-3,5-di-O-methyl-α-D-*gluco*-hexodialdo-1,4-furanose* (**10**).—Prepared from **9**, compound **10** had $[\alpha]_D^{20}$ −25.5° (*c* 1.0, EtOH) and R_f 0.6 (solvent *B*). Compound **10** was characterized as the 4-nitrophenylhydrazone **11**. ^1H NMR data: (90 MHz), δ 8.00 (dd, 2 H, Ar), 6.80–7.30 (m, 3 H, Ar and CH=N), 5.85 (d, 1 H, H-1), 4.6 (t, 1 H, H-2), 4.00–4.50 (m, 2 H, H-3, H-5), 3.80 (t, 1 H, H-4), 3.50, 3.40 (each s, 1 H, MeO) 1.50, 130 (each s, 3 H, CMe_2). Anal. Calcd for $C_{17}H_{23}N_3O_7$: C, 53.54; H, 6.08; N, 11.02. Found: C, 53.65; H, 5.98; N, 11.00.

*1,2:3,4-di-O-Isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose* (**13**) *(ref 6).*—Prepared from **12**, compound **13** had $[\alpha]_D^{20}$ −132°, R_f 0.7 (solvent *B*); lit.[6] $[\alpha]_D^{20}$ −131° (*c* 0.9). ^1H NMR data: δ 9.63 (s, 1 H, CHO), 5.68 (d, 1 H, H-1), 4.67 (dd, 1 H, H-3), 4.60 (dd, 1 H, H-4), 4.40 (dd, 1 H, H-2), and 4.22 (d, 1 H, H-5); $J_{1,2}$ 4.8,

$J_{2,3}$ 2.4, $J_{3,4}$ 7.8, and $J_{4,5}$ 2.1 Hz. These data are in agreement with the published partial spectrum[6].

*1,2:3,4-di-*O*-Isopropylidene-6-*O*-(methylthio)methyl-α-*D*-galactopyranose* (**14**) *(ref 7).*—Prepared from **12**, compound **14** had $[\alpha]_D^{20}$ −108.8°, R_f 0.8 (solvent *B*); lit.[7] $[\alpha]_D^{20}$ −85.0° (*c* 0.9). ^{1}H NMR data: δ 5.65 (d, 1 H, H-1), 4.85 (d, 1 H, O-CH_a-S), 4.75 (d, 1 H, O-CH_b-S), 4.72 (dd, 1 H, H-3), 4.42 (dd, 1 H, H-2), 4.36 (dd, 1 H, H-4), 4.09 (td, 1 H, H-5), 3.88 (dd, 1 H, H-6a) 3,77 (dd, 1 H, H-6b), 2.25 (s, 3 H, CH_3-S), 1.63, 1.56 (each s, 3 H, Me_2C), and 1.43 (s, 6 H, Me_2C); $J_{1,2}$ 5.1, $J_{2,3}$ 2.4, $J_{3,4}$ 7.8, $J_{4,5}$ 1.8, $J_{5,6a}$ 5.1, $J_{5,6b}$ 7.2, $J_{6a,6b}$ 10.3, and $J_{O\text{-}CHa\text{-}S,O\text{-}CHb\text{-}S}$ 11.4 Hz. These data are in agreement with the published partial spectrum[7].

*1,2:5,6-di-*O*-Isopropylidene-α-*D*-*ribo*-hexofuranose-3-ulose* (**16**) *(ref 10).*—Prepared from **15**, compound **16** had $[\alpha]_D^{20}$ +118.1°, R_f 0.65 (solvent *B*); lit.[10] $[\alpha]_D$ +107°. ^{1}H NMR spectra: δ 6.15 (d, 1 H, H-1), 4.38 (d, 1 H, H-2), 4.36–4.32 (m, 2 H, H-4,6a), 4.0–4.05 (m, 2 H, H-5,6b), 1.47, 1.42 (each s, 3 H, Me_2C), and 1.32 (s, 6 H, Me_2C); $J_{1,2}$ 4.5 Hz. These data are in agreement with the published partial spectrum[10].

*Methyl 4,6-*O*-benzylidene-3-*O*-(methylthio)methyl-α-*D*-glucopyranoside* (**18**) *(ref 9).*—Prepared from **17**, compound **18** had mp 136–138°C, $[\alpha]_D^{20}$ +142.7°, R_f 0.6 (solvent *B*); lit.[9] mp 138–140°C, $[\alpha]_D^{20}$ +122° (*c* 1.04, CH_2Cl_2). ^{1}H NMR spectra: δ 7.5–7.35 (m, 5 H, Ar), 5.55 (s, 1 H, benzylidene), 4.97 (d, 1 H, O-CHa-S), 4.87 (d, 1 H, O-CHb-S), 4.81 (d, 1 H, H-1), 4.29 (dd, 1 H, H-4), 4.07 (t, 1 H, H-6a), 3.84 (td, 1 H, H-5), 3.75 (t, 1 H, H-3), 3.67 (dd, 1 H, H-2), 3.59 (t, 1 H, H-6b), and 3.47 (s, 3 H, MeO); $J_{1,2}$ 9, $J_{2,3}$ 9.5, $J_{3,4}$ 9.8, $J_{4,5}$ 4.5, $J_{5,6a}$ 9.3, $J_{5,6b}$ 9.3 $J_{6a,6b}$ 9.3 and $J_{O\text{-}CHa\text{-}S,O\text{-}CHb\text{-}S}$ 11.4 Hz. These data are partially in agreement with the published partial spectrum[9].

*Methyl 4,6-di-*O*-benzylidene-α-*D*-*ribo*-hexopyranoside-3-ulose* (**20**) *(ref 9).*—Prepared from **17**, compound **20** had mp 190–191°C, $[\alpha]_D^{20}$ +101.2°, R_f 0.3 (solvent *B*); lit.[9] mp 192–193°C, $[\alpha]_D^{23}$ +123° (*c* 0.3, acetone). These data were in reasonable agreement with those published[9].

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