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USE OF *O*-THALLIUM(I) SALTS IN THE SYNTHESIS OF PHOSPHATE, SULFITE, AND RELATED ESTER DERIVATIVES OF CARBOHYDRATES

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ABSTRACT

O-Thallium(I) salts are shown to promote a variety of rapid, high-yield, substitution reactions at an anomeric, a primary, or a secondary position of carbohydrate derivatives. Syntheses are described of phosphates, phosphites, sulfites, and xanthic ester derivatives. Preparation of the thallous salt involves a facile exchange between thallous ethoxide and an alcohol group of the carbohydrate. The substitution reaction with the appropriate reagent (*e.g.*, a phosphorochloridate) is then conducted in such solvents as benzene or acetonitrile, in which thallous salts are usually soluble. The configuration of an organo-phosphate moiety introduced at the anomeric position is strongly influenced by the choice of solvent, so that a preponderance of either the α- or β-phosphate may be obtained.

INTRODUCTION

Recently, the reaction between the 1-*O*-thallium(I) salt of an aldose and thionyl chloride was employed[1] for a synthesis of glycosyl chlorides. As this reaction, as well as many others[2,3] that are mediated by thallium, affords excellent yields of product, we were prompted to examine the properties of *O*-thallium salts of carbohydrates in a variety of substitution reactions, other than alkylation[4]. The present article describes several examples of this kind, namely, syntheses of phosphate, phosphite, sulfite, and xanthic ester derivatives.

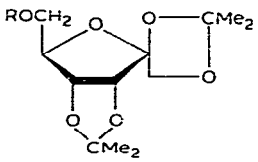
RESULTS AND DISCUSSION

A number of methods are available[5–9] for the phosphorylation of carbohydrates. Reactions whereby the phosphate group is introduced through the use of a phosphorochloridate, $(RO)_2POCl$, are generally catalyzed by such bases as pyridine. The present procedure differs from those, in that the carbohydrate (**1**) is first converted into the *O*-thallium salt (**2**); the latter then undergoes substitution, to give **3**.

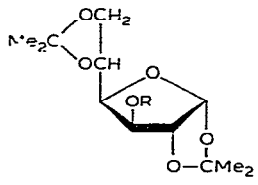
$$\underset{\mathbf{1}}{\text{R-O-H}} \xrightarrow[C_6H_6]{TlOEt} \underset{\mathbf{2}}{\text{R-O-Tl}} \xrightarrow[C_6H_6\ (MeCN)]{(R'O)_2POCl} \underset{\mathbf{3}}{\text{R-O-PO(OR')}_2} + TlCl$$

Equimolar amounts of the carbohydrate (**1**) and thallium ethoxide were admixed for 10–15 min in benzene or benzene–oxolane, and the ethanol evolved was removed by evaporation. Additional benzene, or acetonitrile, was introduced as a solvent for the residual salt (**2**), followed by an equimolar amount of the phosphorochloridate. A precipitate of thallium chloride soon formed, usually quantitatively, within 1–2 h, and the product (**3**) was isolated by evaporation of the solution.

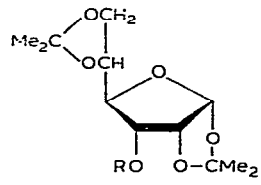
Syntheses conducted in this way were found, in some instances, to be as effective as established procedures, and more satisfactory in others. For example, the reaction of 1,2:3,4-di-*O*-isopropylidene-α-D-psicofuranose (**4**) with diphenyl chlorophosphate in the presence of pyridine had been shown[10] to give an almost quantitative yield of the



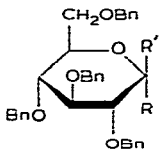
4 R = H
5 R = $PO(OPh)_2$
6 R = Tl



7 R = H
8 R = Tl
9 R = $P(OEt)_2$
10 R = $PO(OEt)_2$
11 R = $PO(OPh)_2$
12 R = CSSTl
13 R = CSSMe
14 R = SOCl
15 R = SOEt
16 R = SOPh

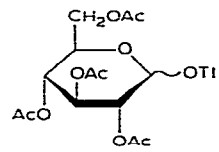


17 R = Tl
18 R = $PO(OEt)_2$
19 R = $PO(OPh)_2$



20 R , R^1 = H.OTl
21 R = $OPO(OEt)_2$.R^1 = H
22 R = H.R^1 = $OPO(OEt)_2$
23 R = $OPO(OPh)_2$.R^1 = H
24 R = H,R^1 = $OPO(OPh)_2$

Bn = $PhCH_2$



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6-diphenyl phosphate (**5**). By use of the thallium salt (**6**) as an alternative to pyridine as the catalyst, an equally high yield of crystalline **5** was produced. An example of a more efficient synthesis involved the introduction of a diethylphosphite substituent

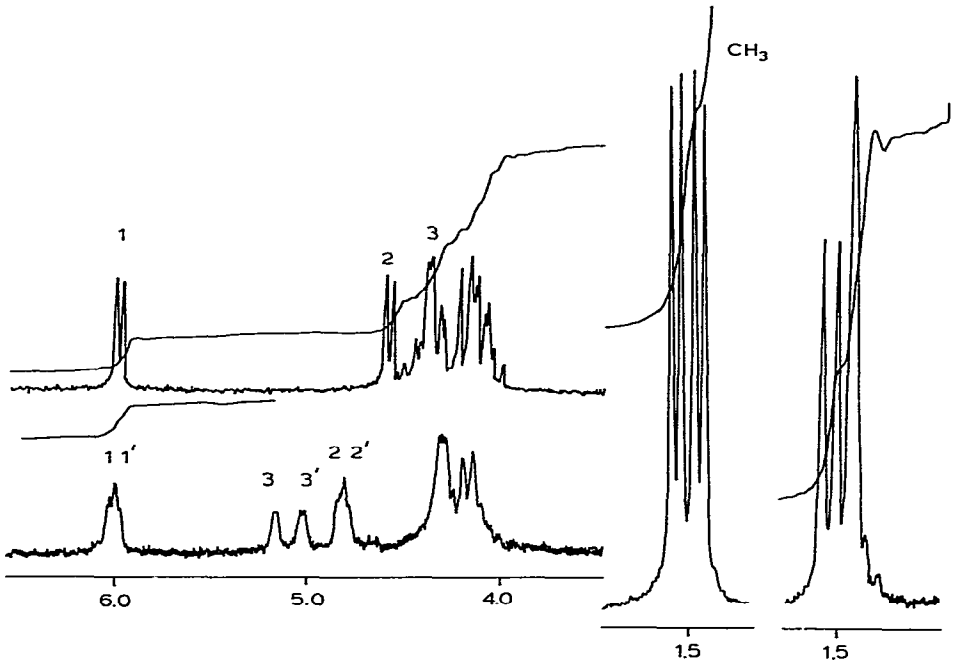

Fig. 1. ^{1}H-N.m.r. spectra (100 MHz) of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**) (upper trace and left group of CH_3 signals), and its 3-(chlorosulfite) derivative (**14**) (lower trace and right group of CH_3 signals). [Similar spectra were obtained for the 3-(ethylsulfite) (**15**) and 3-(phenylsulfite) (**16**) derivatives. At 60 MHz, the distance separating ^{1}H-peaks 3 and 3′ was correspondingly smaller.]

at C-3 of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**). Thus, the reaction of diethyl chlorophosphite with the 3-*O*-thallium salt (**8**) gave **9** in 84% yield, whereas 45% of this compound was recovered[8] from the analogous substitution reaction catalyzed by pyridine.

The thallium salt **8** was also employed in synthesis of the 3-diethylphosphate **10** (in 84% yield) and 3-diphenylphosphate **11** (in 63% yield). Analogous compounds, *i.e.*, **17** (in 61% yield) and **18** (in 96% yield) were obtained by appropriate substitution of the 3-*O*-thallium salt of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**19**).

Products of the reaction[11] between thallous alkoxides (*e.g.*, isopropoxide) and carbon disulfide are unstable, and rapidly decompose to form thionocarbonates or orthocarbonates. However, the addition of carbon disulfide to the thallous salt of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**) produced a xanthate (probably **12**) of sufficient stability to undergo subsequent alkylation with methyl iodide, which thereby afforded the known[12] xanthate (**13**) in 93% yield.

When thionyl chloride was added to **7**, a chromatographically pure, although unstable, oil was obtained in 83% yield. Undoubtedly, this product was the chlorosulfite[13] (**14**), because it was converted into the corresponding *O*-ethyl and *O*-phenyl derivatives (**15** and **16**, respectively) by treatment with thallous ethoxide or thallous

phenoxide. Noteworthy in the ^{1}H-n.m.r. spectrum of **14**, **15**, or **16** (see Fig. 1) was the presence of three pairs of signals (1:1 intensity) for H-1, H-2, and H-3 (other signals were not adequately resolved), attributable to the pair of diastereoisomers generated for each compound by the chiral sulfur atom present in these molecules.

Related substitution-reactions were promoted by thallium at the anomeric centre of aldose derivatives. A benzene solution of the 1-*O*-thallium salt of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**20**), to which was added diethyl chlorophosphate or diphenyl chlorophosphate, yielded a 2:1 mixture or a 1:2 mixture, respectively, of the corresponding α- and β-D-glucosyl phosphate derivatives (*i.e.*, **21** and **22**, or **23** and **24**, respectively). By contrast, the use of acetonitrile as the solvent for the diphenyl reagent sufficiently altered the anomeric ratio of products that only the α anomer was formed; that is, crystalline **23** was obtained in 83% yield. With the thallous salt of the corresponding tetra-*O*-acetylaldose (**25**), diethylphosphorylation yielded a 3:17 α:β mixture (**26** + **27**) when benzene was the solvent, whereas this ratio was reversed when the reaction was conducted in acetonitrile*. These marked differences are reminiscent of large solvent-effects observed[14,15] in syntheses of *O*-acyl esters, and may reflect differences in the anomeric composition of **20** and **25** during the substitution reaction**, as well as in the relative reactivities of the two anomers. Similarly, phosphorylation reactions at the anomeric center employing *O*-acylglycosyl halides and metal organophosphates exhibit[7,8] wide variations in the anomeric composition of the products, and the source of these variations is also uncertain.

It is worth noting that each of the thallium compounds described was appreciably soluble in benzene, even when the alcohol from which it was prepared was only sparingly soluble; in a few instances, oxolane was introduced to increase the solubility. This characteristic enhanced the rate of the thallation step, which was invariably rapid (<15 min). By contrast, the thallium chloride formed during the substitution reactions, being insoluble in benzene or acetonitrile, was readily removed simply by filtration or centrifugation, or both, after which the solution was evaporated. Consequently, the overall procedure was rapid and expedient. Furthermore, the product usually needed little purification, because the reactants were used in stoichiometric amounts and generally gave only one product, in almost quantitative yield (t.l.c. and n.m.r. evidence). In some applications, therefore, these features may offer appreciable advantages over procedures now in general use.

EXPERIMENTAL

General methods. — Solutions were usually evaporated below 40° under diminished pressure. Solvents were dried with molecular sieves 4A. Plates of Silica

*The reaction of **25** with diethyl chlorophosphite also gave a mixture of phosphates (**26** and **27**), rather than the corresponding phosphites. This is in agreement with the finding[8] that the reaction between tetra-*O*-acetyl-α-D-glucopyranosyl bromide and silver diethylphosphite produced a phosphate, instead of the expected phosphite.

The ^{1}H-n.m.r. spectrum of **20 in benzene-d_6 showed that, before the addition of a phosphorylation reagent, an almost equimolar mixture of the two anomers is present in solution.

Gel G were used for t.l.c., and the developing solvent was 1 : 2 ethyl acetate–petroleum ether. Elemental analyses were performed by Guelph Chemical Laboratories, Guelph, Ont. Optical rotations were determined at room temperature for solutions in 1-dm tubes, with a Perkin–Elmer polarimeter (model 141). I.r. spectra were recorded with a Perkin–Elmer infrared spectrophotometer (model 298). Mass spectra were recorded at the Biomedical Mass Spectrometry Unit, McGill University. Proton magnetic resonance spectra were recorded with a Varian T-60 or HA-100 spectrometer, and ^{13}C- and ^{31}P-n.m.r. spectra with a Bruker WH-90 spectrometer. Chemical shifts (δ) are reported with reference to tetramethylsilane.

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose 3-(diethylphosphate) (**10**). — A solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**) (0.52 g, 2 mmol) in dry benzene (15 mL) was transferred to a flask fitted with a rubber septum. Dry nitrogen was passed through the solution, thallium(I) ethoxide* (Aldrich, 0.53 g, 2.1 mmol) was added, and the solution was stirred for 15 min, and evaporated (to remove ethanol). The residue was dissolved by the addition of benzene (15 mL), and diethyl chlorophosphate (0.36 g, 2.1 mmol) was introduced, leading to the formation of a white precipitate. The suspension was stirred for 2 h, filtered through Celite, and the filtrate evaporated, affording a syrup that was purified by distillation (150°/10 μm Hg); yield, 0.71 g (84%); $[\alpha]_D$ −33° (*c* 1.6, chloroform). Its ^1H-n.m.r. spectrum confirmed the presence of two ethyl groups.

Anal. Calc. for $C_{16}H_{29}O_9P$: C, 48.5; H, 7.4; P, 7.8. Found: C, 48.6; H, 7.6; P, 7.7.

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose 3-(diethylphosphite) (**9**). — Under the conditions just described, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (0.52 g, 2 mmol) was treated with thallium(I) ethoxide (0.53 g, 2.1 mmol) and then diethyl chlorophosphite (0.35 g, 2.2 mmol), affording a colorless syrup (0.63 g, 84%); $[\alpha]_D$ −45° (*c* 1.6, chloroform) (lit.[8] $[\alpha]_D$ −48° (chloroform)); ^1H-n.m.r. data ($CDCl_3$): δ 5.90 (d, 1 H, H-1), 4.68 (dd, 1 H, H-3), 4.60 (d, 1 H, H-2), 4.4–3.7 [m, 8 H, H-4–6′ and $P(OCH_2)_2$], 1.55, 1.45 [2 s, 6 H, $(CH_3)_2C$], 1.38 [s, 6 H, $(CH_3)_2C$], and 1.30 (t, 6 H, CH_3CH_2); $J_{1,2}$ 3.6 Hz; these data are closely similar to those reported[8] for **9**.

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose 3-(chlorosulfite) (**14**), *3-(ethylsulfite)* (**15**), and *3-(phenylsulfite)* (**16**). — 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (0.52 g, 2 mmol) was converted, as already described, into the 3-*O*-thallium salt (**8**); this was dissolved in benzene (20 mL), thionyl chloride (0.26 g, 2.1 mmol) was added, and the resulting suspension was stirred for 1 h. At this stage, one of three different procedures was employed.

(*i*) The suspension was filtered through Celite, and the filtrate was evaporated, affording **14** as a colorless, unstable, syrup; ^1H-n.m.r. data ($CDCl_3$): δ 6.1–6.0 (overlapping d, 1 H, H-1), 5.23, 5.00 (2 d, 1 H, H-3), 4.9–4.8 (overlapping d, 1 H,

**As thallium compounds are extremely toxic, rubber gloves should be worn, and operations conducted in a hood.*

H-2), 4.5–4.0 (m, 4 H, H-4–6'), 1.64, 1.58 [2 s, 6 H, $(CH_3)_2C$], and 1.48 [s, 6 H, $(CH_3)_2C$] (see Fig. 1).

(*ii*) Thallium ethoxide (0.53 g, 2.1 mmol) was added; 30 min later, the suspension was filtered through Celite, and the filtrate was evaporated, affording **15** as a colorless syrup. The product was purified by "flash" column-chromatography[16] on silica gel with 1 : 2 ethyl acetate–hexane; yield, 0.65 g (93%); ^{1}H-n.m.r. data ($CDCl_3$): δ 6.0–5.9 (overlapping d, 1 H, H-1), 5.20, 5.03 (2 d, 1 H, H-3), 4.8–4.7 (overlapping d, 1 H, H-2), 4.4–4.0 [m, 6 H, H-4–6' and $SO(OCH_2)$], 1.55, 1.47 [2 s, 6 H, $(CH_3)_2C$], and 1.4–1.3 [m, 9 H, $(CH_3)_2C$, CH_3CH_2].

Anal. Calc. for $C_{14}H_{24}O_8S$: C, 47.7; H, 6.9. Found: C, 47.5; H, 6.5.

(*iii*) Thallium phenoxide (0.62 g, 2.1 mmol) was added, and the reaction mixture was processed as under (*ii*), affording **16** as a yellow syrup (0.66 g, 83%) that was purified by distillation (160°/10 μm Hg); $[\alpha]_D$ −6.5 °(*c* 2.0, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.4–7.1 (m, 5 H, Ph), 6.1–5.9 (overlapping d, 1 H, H-1), 5.15, 5.00 (2 d, 1 H, H-3), 5.8–5.6 (overlapping d, 1 H, H-2), 4.4–4.0 (m, 4 H, H-4–6'), 1.60, 1.50 [2 s, 6 H, C-$(CH_3)_2$], and 1.40 [s, 6 H, C-$(CH_3)_2$].

Anal. Calc. for $C_{18}H_{24}O_8S$: C, 54.0; H, 6.0. Found: C, 54.7; H, 5.7.

1,2:5,6-Di-O-isopropylidene-3-O-[(methylthio)thiocarbonyl]-α-D-glucofuranose (**13**). — Carbon disulfide (0.19 g, 2.5 mmol) was added to a benzene solution (40 mL) of thallous salt **8** [prepared as before from 0.52 mg (2.0 mmol) of **7**] followed, after 10 min, by methyl iodide (1.2 mL). The suspension was stirred for 24 h (during which time its color changed from dark brown to yellow), filtered through Celite, and the filtrate evaporated, affording a yellow oil (0.67 g, 93%) that was purified by distillation (155°/50 μm Hg); $[\alpha]_D$ −29° (*c* 9, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 5.90 (m, 2 H, H-1,3), 4.65 (d, 1 H, H-2), 4.4–3.9 (m, 4 H, H-4–6'), 2.56 (s, 3 H, CH_3S), 1.52, 1.40 [2 s, 6 H, $(CH_3)_2C$], and 1.30 [s, 6 H, $(CH_3)_2C$].

Anal. Calc. for $C_{14}H_{22}O_6S_2$: C, 48.0; H, 6.3; S, 18.3. Found: C, 48.1; H, 6.6; S, 18.0.

2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl diphenylphosphate (**23**). — To a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (1.08 g, 2 mmol) in 1 : 1 benzene–oxolane (20 mL) was added thallous ethoxide (0.52 g, 2.1 mmol), as described for the preparation of **10**. After evaporation of the solution, the residual thallous salt (**20**) was dissolved in acetonitrile (7.0 mL) and, while cooling with ice, diphenyl chlorophosphate (2.1 mmol) was introduced. The suspension was stirred for 2 h at room temperature, filtered through Celite, and the filtrate evaporated, affording a solid; m.p., after recrystallization from ether–hexane, 98–99°, $[\alpha]_D$ +68° (*c* 3, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.25 (m, 30 H, 6 Ph), 6.05 (dd, 1 H, H-1), 5.0–4.4 (m, 8 H, CH_2), and 3.9–3.4 (m, 6 H, H-2–6'); $J_{1,2}$ 3.5, $J_{1,P}$ 7.0 Hz; ^{13}C-n.m.r. data ($CDCl_3$): δ 186.3 (d, Ph-C, $J_{C,P}$ 10.0), 138.5–38.45, 129.6, 128.4–127.9, 125.5, 120.5–120.0 (Ph), 97.0 (d, C-1, $J_{C,P}$ 7.3), and 81.0–67.5 (C-2–6, CH_2); ^{31}P-n.m.r. data ($CDCl_3$): −11.3 p.p.m. (from H_3PO_4).

Anal. Calc. for $C_{46}H_{45}O_9P \cdot 0.5\ H_2O$: C, 70.6; H, 5.9. Found: C, 70.7; H, 6.0.

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