Two Reagent Systems for Converting Hydroxy Compounds into Chlorides using the Triphenylphosphine/Imidazole System

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Efficient procedures, based on the triphenylphosphine/imidazole system, for converting vicinal *trans*-diols into olefins[1], and hydroxy compounds into bromides[2] and iodides[3] have recently been developed.

As chlorinated carbohydrates and nucleosides are finding new uses such as potent sweeteners, male antifertility agents, and antibiotics, new systems for the conversion of hydroxy into chloro compounds should be of general interest. Two new such systems have now been investigated, namely:

- Reagent A, triphenylphosphine dichloride (dichlorotriphenylphosphorane)/imidazole;
- Reagent B, triphenylphosphine/tetrachloromethane/imidazole.

Both systems are derived from previously known reagents. Triphenylphosphine dichloride, discovered by Horner and coworkers[4], has been used for chlorinations of simple alcohols. Triphenylphosphine/tetrachloromethane has been more extensively evaluated. In carbohydrates, mainly primary hydroxy groups are substituted[5].

Imidazole plays an essential role in both of these systems. Reagent A reacts vigorously in the absence of imidazole, giving undesirable side-reactions, often low yields and variable results. Even pyridine was rapidly degraded by this electrophilic reagent in the absence of imidazole. Imidazole probably has a dual role; firstly, as a molecular chlorine scavenger and secondly, by forming a more selective phosphorus intermediate.

In Reagent B, imidazole is essential for obtaining a reactive system capable of substituting secondary hydroxy groups as well as primary ones. Presumably the initial tetrachloromethane/triphenylphosphine adduct reacts with imidazole to form a species of higher reactivity.

It has previously been shown that tribromo- or triiodoimidazole, are good sources of halogen in the triphenylphosphine/imidazole system[2,3]. Trichloroimidazole, by contradistinction, is tedious to prepare and dichloroimidazole, which is more easily obtainable, showed no reactivity towards triphenylphosphine.

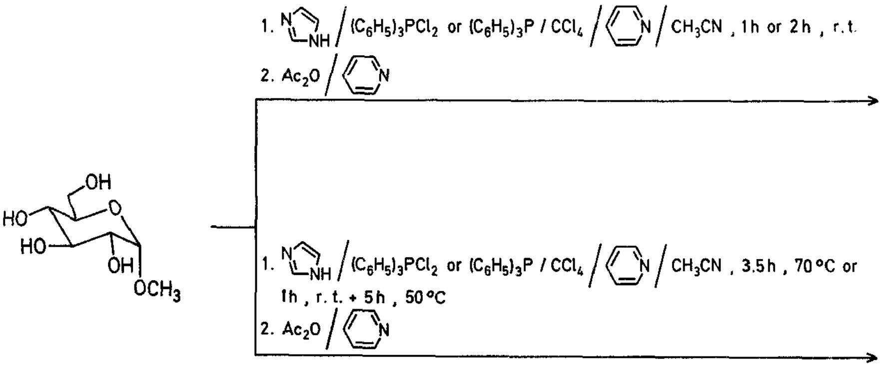
Both Reagents A and B exhibit a good reactivity in acetonitrile, pyridine, or in acetonitrile/pyridine (1 : 1) which gives a homogeneous reaction medium. For particularly unreactive hydroxy groups toluene may be employed as solvent at reflux temperature yielding a liquid-liquid two-phase system. Results obtained are shown in the Table.

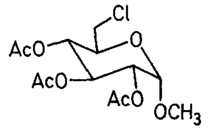
The reagent systems are subject to steric limitations. Thus Reagent B reacted with methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside in toluene at elevated temperature to yield about 10% of the desired 2-chloro-2-deoxy derivative which is far less than the 87% obtained in the corresponding iodination[3] and the 73% in the corresponding bromination[2]. Similarly, 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose gave about 10% of the corresponding 3-chloro-3-deoxy-*allo* derivative whilst iodination[3] proceeded in 78% and bromination[2] in about 30% yield. Methyl β-D-galactopyranoside formed the 3,6-anhydro derivative (88%) on attempted chlorination. Bromination has been shown to give the same compound[2] whereas iodination gave the desired 6-deoxy-6-iodo derivative[3] (63%).

Triphenylphosphine Dichloride:

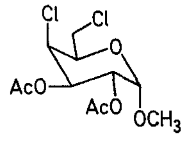
Method A: Triphenylphosphine (26.2 g, 0.10 mol) is dissolved in dichloromethane (50 ml). The solution is stirred at 0°C and chlorine is bubbled through until T.L.C. indicates that all triphenylphosphine has been consumed. Light petroleum (50 ml) is added precipitating triphenylphosphine dichloride as a yellow oil which crystallises on standing. The reagent can be stored at 0°C for several weeks.

Method B: Chlorine is bubbled through a solution of triphenylphosphine (26.2 g, 0.10 mol) in dichloromethane (150 ml), stirred at 0°C, until T.L.C. indicates that all triphenylphosphine had been consumed. Nitrogen gas is flushed through the solution to remove some excess chlorine. The solution is transfered to a bottle, diluted with dichloromethane to give a 0.5 molar solution of reagent and sealed under ni-





2a



3a

trogen. Before reaction, a measured volume of the reagent solution is transfered into the reaction solvent acetonitrile/pyridine (1:1) and dichloromethane is removed under reduced pressure.

General Procedure for the Conversion of Hydroxy into Chloro Compounds:

With Reagent A (triphenylphosphine dichloride/imidazole): The solvents of choice are acetonitrile/pyridine (1:1) (from room temperature to 80 °C), acetonitrile (same temperature range) or toluene at reflux for particularly unreactive hydroxy groups. The ratio of alcohol/triphenylphosphine dichloride/imidazole is ~1:2:4; for reaction temperature and time, see Table.

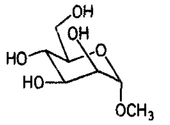
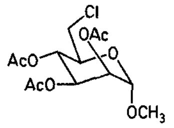
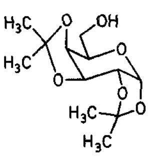
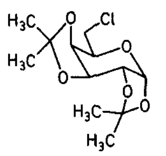
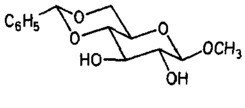
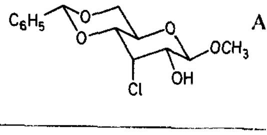
With Reagent B (triphenylphosphine/tetrachloromethane/imidazole): Solvents of choice are the same as for system A. The ratio of alcohol/triphenylphosphine/tetrachloromethane/imidazole is ~1:2:10:4; for reaction temperature and time, see Table.

General Procedure for Work-up and Acetylation; Compounds 2 and 3: Work-up can be effected in a variety of ways. If the chlorinated substrate is water-soluble, work-up is most easily performed in the following manner: The reaction mixture is quenched through the addition of some ice, stirred for a few minutes and concentrated at reduced pressure to almost dryness. The residue is partitioned between toluene and water (the toluene phase contains triphenylphosphine oxide). The water phase is concentrated to dryness. The residue is acetylated with acetic anhydride/pyridine, concentrated at reduced pressure and dissolved in toluene/water (1:1). The organic phase is collected, washed with water, 3% hydrochloric acid, saturated aqueous sodium hydrogen carbonate and water, dried with magnesium sulfate, filtered and concentrated to give a pure product (Table).

Methyl 4,6-*O*-Benzylidene-3-chloro-3-deoxy-β-D-*allo*-pyranoside (2d); Typical Procedure:

Triphenylphosphine dichloride (1.10 g, 3.30 mmol) is added to a stirred solution of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (0.50 g, 1.77 mmol) and imidazole (0.45 g, 6.60 mmol) in acetonitrile/pyridine (1:1, 20 ml). The mixture is stirred at 70 °C for 4 h, cooled to room temperature, diluted with ethanol (15 ml) and evaporated to dryness. The residue is filtered through a layer of silica gel and eluted with ethyl acetate/ethanol (1:1). The filtrate is concentrated and the residue is subjected to chromatography on silica gel using ethyl acetate/toluene (2:1) as eluent to yield the title compound; yield: 0.46 g (87%); m.p. 130–132 °C; $[\alpha]_D^{22}$: −24° (c 1.6, $CHCl_3$) [Lit.[6], m.p. 129–131 °C; $[\alpha]_D$: −24°, $CHCl_3$].

Table. Chloro Compounds **2** and **3** prepared

Educt	Product	Reagent System	Reaction Conditions[a] temperature/time	Yield [%]	m.p. [°C] found	m.p. [°C] reported	$[\alpha]_D^{22}$ (c, solvent) found	$[\alpha]_D^{22}$ (c, solvent) reported
1a	**2a**	A	20–25 °C/1 h	80	98–100°	96.5–98.5°[7]	+166° (1.0, pyridine)	+159°[7]
		B	20–25 °C/2 h	84				
	3a	A	70 °C/3.5 h	89	104–106°	103.5–105°[7]	+191° (1.3, pyridine)	+190°[7]
		B	20–25 °C/1 h then 50 °C/5 h	88				
1b 	**2b** 	A	20–25 °C/1 h	89	85–87°	—[b]	+ 59° (1.1, $CHCl_3$)	—[b]
		B	20–25 °C/2 h	89				
1c 	**2c** 	A	50 °C/1 h	93	—	—	− 63° (1.0, $CHCl_3$)	− 66°[8]
1d 	**2d** 	A	see experimental procedure[9]					

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[a] Solvent: acetonitrile/pyridine, 1:1.

[b] $C_{13}H_{19}ClO_8$ (338.7) calc. C 46.09 H 5.65 Cl 10.47
found 46.23 5.72 10.47

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[9] The procedures are essentially the same as described for the hydroxy-iodine exchange; Ref.[3].