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Hewitt reaction revisited

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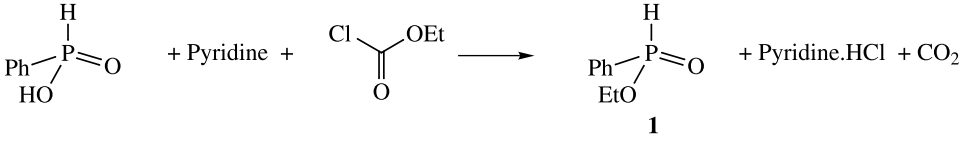
Dedicated to Professor Charles W. Rees FRS on the occasion of his 75th birthday

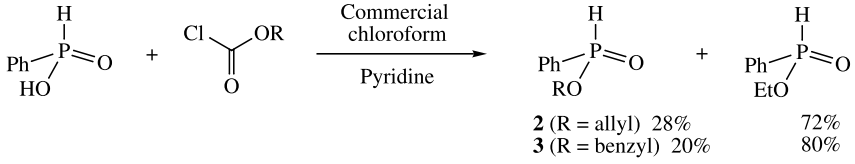
Abstract—A range of alkyl phenylphosphonites are prepared from the reaction of phenylphosphinic acid with the corresponding alkyl chloroformates. A mechanism for this reaction is proposed.

In 1979 Hewitt published a procedure for the transformation of phenylphosphinic acid to its monoethyl ester, compound **1** (Scheme 1).[1] The procedure involves the addition of pyridine to a stirred solution of phenylphosphinic acid and ethyl chloroformate in chloroform. This is followed by an exothermic reaction and rapid effervescence (CO_2 gas) after which the reaction is complete. After a simple workup procedure, the product is obtained essentially pure and in quantitative yield. Although this is an exceptionally efficient and clean method for the preparation of ethyl phenylphosphonite **1**, and has been employed on a number of occasions,[2–6] neither the mechanism nor the generality of the reaction have ever been investigated. Since efficient and practically simple methods for the mono-esterification of phosphinic acids are rare,[7] we became interested in exploiting Hewitt's reaction for the general synthesis of mono esters of phenylphosphinic acid. Here, we report the application of this method to the general preparation of alkyl phenylphosphonites, as well as the observations which enable us to propose a mechanism for this reaction.

To test the generality of the reaction, we carried out reactions of phenylphosphinic acid with allyl chloroformate and benzyl chloroformate under Hewitt's conditions, using chloroform as a solvent. Unexpectedly, the reactions afforded not only the desired allyl and benzyl phenylphosphinates, **2** and **3**, respectively, but also a significant quantity of ethyl phenylphosphinate, **1** (Scheme 2). We presumed that the origins of the ethyl group in **1** must be in the small amount of ethanol which is added to commercially available chloroform. Indeed, when these two reactions were carried out in dichloromethane, which lacks any ethanol as an additive, we obtained compounds **2** and **3** in excellent yields



Scheme 1.



Scheme 2.

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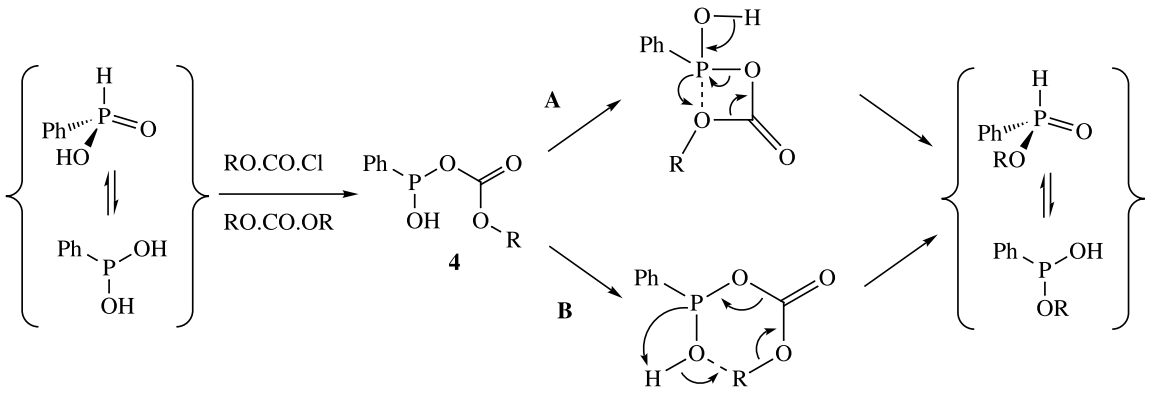
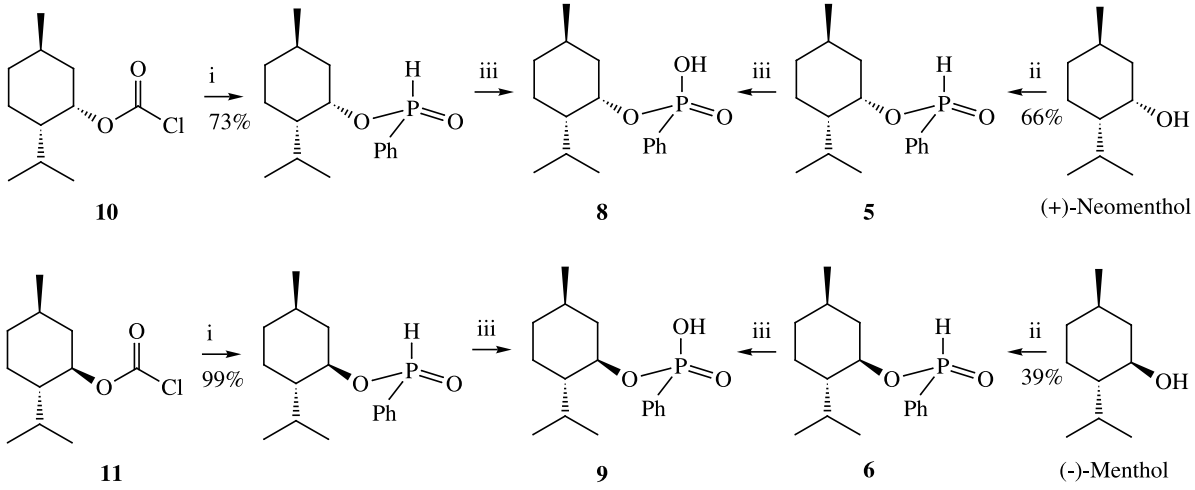


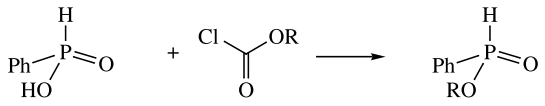
Scheme 3.



Scheme 4. *Reagents and conditions*: (i) toluene, PhP(O)OH, pyridine, reflux; (ii) $PhPCl_2$ **7**, pyridine, reflux, 1 h, then water; (iii) $MeCO_3H$ in $MeCO_2H$ (36%), rt, 2 days.

with no trace of ethyl phenylphosphinate **1** present. However, any ethanol present in the reaction mixture would most likely react with ethyl chloroformate in the presence of pyridine to afford diethyl carbonate. This suggests that the alkylating agent in the Hewitt reaction may be either ethyl chloroformate, EtO.CO.Cl, *or* diethyl carbonate, RO.CO.OR generated in situ during the course of the reaction. Indeed, phenylphosphinic acid reacts with diethyl carbonate in the presence of pyridine to afford **1**, but at a slightly reduced rate. Presumably, in the reactions of phenylphosphinic acid with allyl chloroformate and benzyl chloroformate in chloroform, some allyl ethyl carbonate and benzyl ethyl carbonate are formed that act as alkylating agent transferring either the ethyl or the allyl/benzyl groups.

Proposing a mechanism for Hewitt's reaction is challenging. In solution, phenylphosphinic acid exhibits a tautomerism between a dominant tetracoordinated, pentavalent phosphinic acid form, and a trivalent, tricoordinated phosphinous acid form, which is an ambident nucleophile. As an ambident nucleophile, phenylphosphinic acid may react with acylating and alkylating reagents through both the oxygen and the phosphorus atoms. However, it would be expected that most electrophiles would react at the more nucleophilic phosphorus atom, except for those electrophiles (such as a trimethylsilyl group) that form a considerably stronger bond with oxygen. An esterification mechanism involving formation of a bond between the oxygen atom and a carbon electrophile would be unusual, but explains why the same product is obtained from the reaction with ethyl chloroformate and diethyl carbonate. At any rate, one possible mechanism could be a direct bimolecular nucleophilic displacement on the R group of the chloroformate RO.CO.Cl (Scheme 3). An alternative mechanism would be through formation of a 'mixed anhydride' species **4** (Scheme 3), formed from a chloroformate or a carbonate species. Two different modes for the subsequent steps can be envisaged. Either an attack of the phosphorus on the oxygen atom (route A) or attack of an oxygen atom on a carbon atom



Scheme 5. *Reagents and conditions*: (i) pyridine, CH_2Cl_2, rt (caution: effervescence!) then reflux 15 min.

Table 1.

	R	Yield (%)	δ_p (ppm)	δ_p (PH) (ppm)	J_{PH} (Hz)
1	Me	73	28.3	7.57	566
2	Et	99	25.9	7.57	562
3	*i*-Pr	88	23.4	7.63	559
4	Allyl	80	26.3	7.64	565
5	Benzyl	91	26.2	7.65	566
6	Cholestyl	93	23.4	7.65	560
7	Decyl	85	26.1	7.59	562
8	2-(Benzyloxy)ethyl	85	27.7	7.66	569

(mode B). The key difference between the two proposed routes is on which C–O bond is broken. Therefore, we designed an experiment that would help to resolve the issue.

The two diastereomeric menthyl phenylphosphinates **5** and **6** were obtained from the reaction of corresponding (+)-neomenthol and (−)-menthol and dichlorophenylphosphine **7**. This reaction is known to proceed through a *O*-phosphinylation (a P–O bond formation) and therefore the asymmetry at the carbon atom C-1 is preserved. Although the phosphorus atom is asymmetric, due to its tautomerism it was not possible to isolate the diastereomers in a kinetically stable form in either case (Scheme 4). Therefore, we decided to oxidise the phosphorus atom to make it a non-asymmetric atom. The phosphorus atom in the product is no longer asymmetric and therefore the products of oxidation, compounds **8** and **9**, are diastereomerically pure. We then carried out the reactions between (+)-neomenthol chloroformate and (−)-menthyl choroformate, **10** and **11**, and phenylphosphinic acid in toluene in the presence of pyridine. As before, we oxidised the phosphorus atom.

Analysis of the products from the reactions showed that the phenylphosphinate esters obtained from reactions between (−)-menthol and dichlorophenylphosphine, and between (−)-menthyl choroformate and phenylphosphinic acid to be identical. However, they were different from the two identical phenylphosphinate esters obtained from reactions between (+)-neomenthol and dichlorophenylphosphine, and between (+)-neomenthyl choroformate and phenylphosphinic acid. In other words, the chirality of the ester at C-1 is not affected during the course of the reaction. This observation supports our proposed mechanism in which a P–O bond is formed rather than a C–O bond.

As has already been alluded to, a variety of phenylphosphinate esters can be prepared from the corresponding chloroformates. To demonstrate further the generality of the reaction, we also carried out the reaction of a number of other chloroformates with phenylphosphinic acid (Scheme 5, Table 1).[8,9] The chloroformates derived from a range of primary and secondary alcohols undergo the reaction and afford the corresponding phenylphosphinate esters in excellent yield.

In summary, we have demonstrated that monoesters of phenylphosphinic acids can be easily and efficiently prepared from the reaction between phenylphosphinic acid and a chloroformate in a simple, practical manner. We are currently investigating further the mechanism of this interesting and useful reaction and will report our results in due course.

Acknowledgements

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8. All compounds were fully characterised.
9. Typical experimental procedure. **Benzyl phenylphosphinate**: pyridine (9.68 ml, 0.12 mol) was carefully added to a vigorously stirred solution of benzyl chloroformate (17.13 ml, 0.12 mol) and phenylphosphinic acid (16.8 g, 0.12 mol) in DCM (250 ml) at room temperature. Once effervescence had stopped, the solution was refluxed for 15 min, then allowed to cool to room temperature. The solution was poured into 0.1 M hydrochloric acid (90 ml) and the organic layer was separated. After washing with water (150 ml) and drying over Na_2SO_4, the solvent was removed in vacuo to give benzyl phenylphosphinate as a colourless oil (25.31 g, 91%). δ_H (500 MHz, $CDCl_3$) 5.12 (2H, 2×dd, J_1 9, J_2 12, OCH_2Ph), 7.28–7.40 (5H, m, Aromatic H), 7.49–7.54 (2H, m, aromatic H), 7.58–7.63 (1H, m, aromatic H), 7.65 (1H, d, J_P 566, PH), 7.71–7.83 (2H, m, aromatic H); δ_P (145.67 MHz, $CDCl_3$) 26.22; δ_c (125 MHz, $CDCl_3$) 67.64 (OCH_2Ph), 127.36–133.62 (aromatic C); *m*/*z* (EI) 232 (90), 167 (917), 141 (9), 126 (87), 107 (55), 91 (100), 79 (89), 65 (22), 51 (12).