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Mild and efficient esterification of alkylphosphonic acids using polymer-bound triphenylphosphine

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ABSTRACT

Mild and efficient esterification of alkylphosphonic acids using primary alcohols, iodine, imidazole and polymer-bound triphenylphosphine is developed.

Esters of alkylphosphonic acids are of particular importance due to their synthetic and pharmaceuticals applications.[1,2] Besides their useful applications, esters of alkyl (methyl, ethyl, *i*-propyl and *n*-propyl) phosphonic acids are also registered as extremely toxic nerve agents.[3,4] Considering the threat from nerve agents, which form a major class of chemical warfare agents (CWAs), their proliferation is prohibited by an international treaty known as Chemical Weapons Convention (CWC). CWC is administered by an international organisation known as Organisation for Prohibition of Chemical Weapons (OPCW).[5–7] OPCW administers CWC through its verification regime.

One component of verification programme of CWC, dealing with the off-site analysis, requires *O,O′*-dialkyl alkylphosphonates (DAPs) as reference chemicals for identification of the chemicals related to CWC.[8] DAPs are included in the schedule 2B4 category of CWC and most of them are commercially not available. Hence, their synthesis becomes an inevitable activity during verification analysis. These compounds are synthesised by the laboratories involved in international proficiency tests conducted by the OPCW.[8,9] Variety of reactions are reported in the literature for the synthesis of DAPs.[8,10–13] Two approaches are noteworthy, (i) condensation of alkylphosphonic dichlorides with alcohols in the presence of base[13,14] and (ii) condensation of alkylphosphonic acids with alcohols aided by carbodiimide.[8] Former method requires the formation of alkylphosphonic dichlorides by the use of corrosive and environmentally harmful thionylchloride ($SOCl_2$) from alkyl-

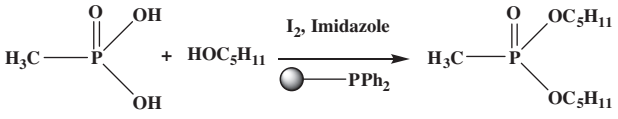

Figure 1. Esterification of methylphosphonic acid.

Table 1
Formation of *O,O′*-dipentyl methylphosphonate[a] from methylphosphonic acid and *n*-pentanol as per Gareg–Samuelsson reaction in different solvents

Entry	Solvents	Yield[b] (%)
1	Dichloromethane	94
2	Chloroform	90
3	Hexane	85
4	Benzene	32
5	Toluene	15
6	Ethyl acetate	12
7	Acetonitrile	10

[a] Reaction conditions: Methyl phosphonic acid (1.0 mmol), iodine (3 mmol), imidazole (6.6 mmol), polymer-bound triphenylphosphine (3 mmol) and alcohol (2.5 mmol) reaction time 50 min.
[b] Isolated yield.

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Table 2
Condensation of alkylphosphonic acid with alcohols in the presence of iodine, imidazole and polymer-bound triphenylphosphine

Entry	R	R′	Product[a]	Time in minutes	Yield[b] (%)
1	CH_3	CH_3	*O,O′*-Dimethyl methylphosphonate	40	85
2	CH_3	C_3H_7	*O,O′*-Dipropyl methylphosphonate	45	90
3	CH_3	C_5H_{11}	*O,O′*-Dipentyl methylphosphonate	50	94
4	CH_3	$C_{10}H_{21}$	*O,O′*-Didecyl methylphosphonate	60	82
5	C_2H_5	C_2H_5	*O,O′*-Diethyl ethylphosphonate	45	90
6	C_2H_5	C_5H_{11}	*O,O′*-Dipentyl ethylphosphonate	50	92
7	C_2H_5	$C_{10}H_{21}$	*O,O′*-Didecyl ethylphosphonate	60	84
8	C_3H_7	CH_3	*O,O′*-Dimethyl propylphosphonate	40	87
9	C_3H_7	C_5H_{11}	*O,O′*-Dipentyl propylphosphonate	50	92
10	C_3H_7	$C_{10}H_{21}$	*O,O′*-Didecyl propylphosphonate	60	83

[a] Reaction conditions: alkyl phosphonic acid (1.0 mmol), iodine (3 mmol), imidazole (6.6 mmol), polymer-bound triphenylphosphine (3 mmol) and alcohol (2.5 mmol).
[b] Isolated yield.

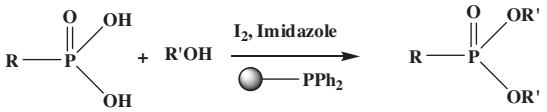


Figure 2. Esterification of alkylphosphonic acid.

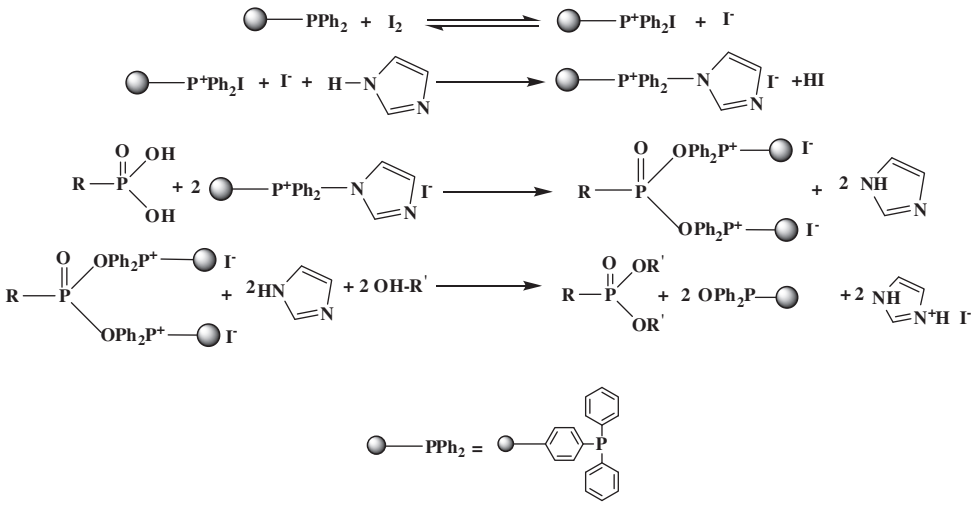
phosphonic acids and latter method generates DAPs with side products requiring chromatographic purification.[8]

Recently, esterification of carboxylic acid is reported by exploiting Garegg–Samuelsson reaction.[15] In this reaction, an efficient esterification of carboxylic acids by the intermediacy of phosphonium-carboxylate salt was achieved by using triphenylphosphine, iodine and imidazole. In this reaction, purification of synthesised esters, required chromatographic removal of triphenylphosphine oxide. Recently, the use of polymer-bound triphenylphosphine has been reported for the synthesis of olefins and aryl ethers, and its use as dehydrating reagent is also documented.[16–18] To the best of our knowledge, so far this reaction is not reported for the synthesis of phosphorous esters that is *O,O′*-dialkyl alkylphosphonates. Promoted by the efficiency and mildness of the reaction and given the scope for improvement by use of commercially available polymer-bound triphenylphosphine, we explored this reaction for synthesis of DAPs.[19] We envisaged that after completion of reaction, the byproduct triphenylphosphine oxide could be removed by simple filtration thereby avoiding the chromatographic purification.

To optimise the reaction conditions such as time, temperature and solvent, condensation of methylphosphonic acid with *n*-pentanol (as a pilot reaction) was performed in the presence of imidazole, iodine (I_2) and polymer-bound triphenylphosphine (Fig. 1)

Reaction was performed as per details presented in the experimental section and *O,O′*-dipentyl methylphosphonate was obtained in excellent yield at 45–50 °C within 50 min. The effect of solvent on yield was also studied and results are summarised in Table 1

It is evident from these results that best yields were obtained in dichloromethane or chloroform. Therefore, further reactions were performed in dichloromethane with different alkylphosphonic acids and alcohols. Results of these reactions are presented in Table 2. Reactions afforded all esters in excellent yields; the noteworthy point is that alcohols C_1–C_{10} reacted with almost equal efficiency under the employed reaction conditions (Fig. 2). Whereas condensations of alkylphosphonic dichlorides with higher alcohols (C_5–C_{10}) produce less yields with the formation of pyrophosphonates as side products.[11] The important feature of reaction is isolation of final product from the reaction mixture. As stated in experimental section, after completion of reaction, the polymer-bound triphenylphosphine oxide and imidazolium iodide were removed by filtration and the product was obtained from dichloromethane after removing the solvent by distillation. Further purification of crude product was done by vacuum distillation.



Scheme 1. Mechanistic proposal for the esterification of phosphonic acids by using iodine, imidazole and polymer-bound triphenylphosphine.

The reaction mechanism is hypothesised similar to the one described by Morcillo et al. for carboxylic acids.[15] Dicationic salt of alkylphosphonic acid and polymer-bound triphenylphosphine are formed as per the scheme presented in Scheme 1. This salt undergoes nucleophilic attack by alcohol, generating DAPs and releasing polymer-bound triphenylphosphine oxide and imidazolium iodide.

When more hindered secondary alcohols were used in this reaction, the yield of corresponding esters was reduced to a great extent. For example, reaction of methylphosphonic acid with isopropyl alcohol gave rise to 30–35% yield in comparison to the 90% yield obtained with *n*-propanol. This trend was observed with other secondary alcohols also. Thus, this method can be further exploited to prepare esters with primary alcohols in the presence of secondary and tertiary alcohols. The study is in progress and will be reported in due course of time.

In conclusion, we have developed an efficient and convenient method for the synthesis of a variety of *O,O′*-dialkyl alkylphosphonates from corresponding alkylphosphonic acids using polymer-bound triphenylphosphine. Main feature of this reaction is removal of triphenylphosphine oxide by simple filtration, as polymer-bound triphenylphosphine is used as dehydrating agent. Thus, this reagent is an effective dehydrating reagent which obviates the use of carbodiimide, and avoids chromatography to remove the triphenylphosphine oxide.

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19. *General experimental procedure*: A mixture of iodine (3 mmol), 1 g polymer-bound triphenylphosphine (3 mmol/g obtained from M/s Sigma–Aldrich, New Delhi, cat. No.–93093), and dry dichloromethane (2 mL) was stirred at room temperature for 15 min. Excess of imidazole (6.6 mmol) was added and stirred at room temperature for 15 min. Alkylphosphonic acid (1 mmol) was added to the reaction mixture and stirred at 45–50 °C for further 30 min. Then the reaction mixture was brought to room temperature and alcohol (2.5 mmol) was added. The reaction mixture was stirred for another 40–60 min at 45–50 °C. Finally, the reaction mixture was cooled to room temperature and filtered through filter paper. From filtrate the solvent was removed by distillation to get the colourless liquid. ^{1}H and ^{31}P NMR spectra at 400 MHz were recorded in $CDCl_3$. Electron ionisation (EI^+) mass spectra were recorded on a Waters GC/MS system.