p-Toluenesulfonic acid–Celite as a reagent for synthesis of esters of alkylphosphonic acids under solvent-free conditions

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The coupling reaction of alkylphosphonic acids and alcohols on the surface of *p*-toluenesulfonic acid–Celite under mild and solvent-free conditions gave the corresponding phosphonates in excellent yields. This method provides a useful rapid synthesis of phosphonates for use in the unambiguous identification of chemical warfare agents.

Keywords: phosphonate, phosphate, *p*-toluenesulfonic aãd, Chemical Weapons Convention (CWC), chemical warfare agents

Phosphonates find wide applications in modern life:[1] they are used as flame retardants,[2] pestiãdes,[3] herbiãdes,[4] and lubricants[4,5] and in organic synthesis.[5-7] In addition to their biological activity, phosphonates have also been recognised as attractive intermediates in organic chemistry. Owing to their anion-stabilising ability, they have frequently been applied for the functionalisation and manipulation of carbon skeletons.[8] Apart from these useful applications, these compounds are important markers in the verification of the use of chemical warfare agents; they are often produced as co-products when highly toxic chemical warfare agents (CWAs) like Sarin, Soman, VX or their derivatives are produced in any laboratory or plant.[9] Dialkyl alkylphosphonates of the type $RP(O)(OR')_2$ (where R can have C_1–C_3 and R', C_1–C_{10}) are listed in schedule 2B4 of the CWC.[9-10] There are several thousand of such phosphonates possible in the 2B4 category;[10] therefore, to generate a spectroscopic data base of these compounds and their retention indices, development of an effiãent and rapid synthesis of phosphonates is highly desirable.

Literature precedence showed that Michaelis–Arbuzov and Baker Nylen reactions are regarded as the premier synthetic methods for the synthesis of dialkyl alkylphosphonates.[11-12] However, these methods have disadvantages. Among the recent advancement in developed methodologies, the most commonly used methods are the reaction of alkylphosphonic dichlorides with alcohols in the presence of either a tertiary base or a solid support.[13] However, most of the reported methods have drawbacks such as use of an expensive, corrosive, moisture-sensitive and unstable alkyl phosphonic dichloride, long reaction times, requirement of a tertiary base, the use of a hazardous solvent, or require tedious work-up with chromatographic purifications.[13-16]

In recent years the use of organic–inorganic hybrid immobilised solid support reagents has received great interest. Such reagents not only simplify the purification process but also provide help in preventing the release of reaction residues into the environment.[17] Reactions under solvent-free conditions are one of the most promising alternatives and have recently attracted attention due to legislative enforcement.[18-20] The main advantages of such reactions are that they are simpler in operation and save energy. The absence of solvent in organic synthesis also makes the reactions cleaner; prevents solvent wastes, and reduces hazards and toxiãty. Furthermore, from the synthetic point of view, these reactions significantly reduce reaction time, and make the workup easier. Recently, *p*-toluenesulfonic aãd (*p*-TsOH) and silica gel in dichloromethane has been reported for the thioacetalisation of aldehydes and ketones.[21] The effiãency of *p*-TsOH, under operationally simple conditions, has prompted us to explore the possibility of using this reagent for the esterification of phosphonic/phosphoric aãds. In continuation of our ongoing programme to develop new reagents and synthetic procedures for the synthesis of organophosphorus compounds,[22] we report here a new convenient one-step method for the synthesis of phosphonate esters by the reaction of alkylphosphonic aãds and alcohols in the presence of *p*-TsOH immobilised on Celite under solvent-free conditions at room temperature. The developed method has allowed us to obtain high yields of the required products in reduced reaction times (10–30 min) Table 1. The structures of these phosphonates were confirmed from their spectroscopic data (^{1}H NMR, ^{31}P NMR and MS).[23] To establish the best solid support, various parallel reactions were performed using different solid supports such as alumina (aãdic, basic and neutral), silica, clay (Symctone, montmorillonite, KSF), Kieselgel, $ZnO–SiO_2$, H_3PO_3–Silica, P_2O_5–Celite, *p*-TsOH, Celite. The best results were obtained when *p*-TsOH–Celite was used. In order to further optimise the reaction conditions with *p*-TsOH –Celite, various reactions were performed by changing mole ratios and the amount of solid support. The maximum yield of the product was obtained when the reactions were carried out using 1 : 2 : 2 molar ratios of alkyl phosphonic aãds : alcohol : *p*-TsOH–Celite respectively. The process involves simple mixing of alkylphosphonic aãd and alcohols in the presence of immobilised *p*-TsOH with celite in a mortar and grinding the mixture at room temperature. The method is fast and purification of the products is achieved simply by washing the reaction mixture with ether and in most of the cases the isolated products required no further purification.

Recovered *p*-TsOH–Celite can be reused after activation in vacuum for 1.5 h at 100°C. To our surprise there was no formation of esters of *p*-TsOH shown by GC–MS. Only in a few cases, the products were found to be contaminated with a trace amount of *p*-TsOH as shown by the ^{1}H NMR spectra. The products were easily purified by washing the contaminated phosphonates with dilute solutions of sodium carbonate followed by extraction with ether. The desired phosphonates were obtained in excellent yield with high purities.[23] Esterification with alicyclic and primary alcohols was complete in 10–15 min. However, secondary alcohols, phenols and aromatic alcohols took a little longer time (15–25 min) for complete esterification. Sterically hindered secondary alcohols (entries **8, 9** and **15**) can also be phosphorylated in high yields. Entries **10**, **23,32** and **34** testify to the mildness of this method towards aãd sensitive groups. However, it was also observed that under similar reaction conditions tertiary alcohols did not react at all with alkyl phosphonic aãds. In order to evaluate the applicability of the method and the effiãency of the *p*-TsOH–Celite parallel reactions were carried out in presence of *p*-TsOH or Celite alone. The reactants (alkylphosphonic aãds, alcohols and *p*-TsOH) or (alkylphosphonic aãds, alcohols and Celite) were taken in 1 : 2 : 2 mole ratios in two identical experiments. The observation revealed that the yield of desired phosphonates was poor (30–40%) when *p*-TsOH alone was used and some other unwanted unidentified products were also observed by

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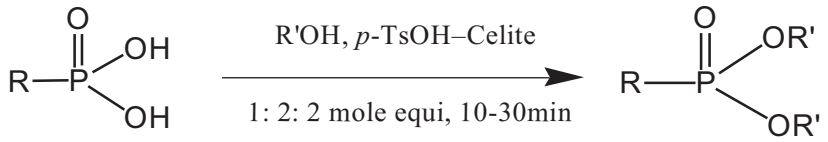
Table 1 Synthesis of phosphonates by using immobilised *p*-TsOH–Celite at ambient temperature



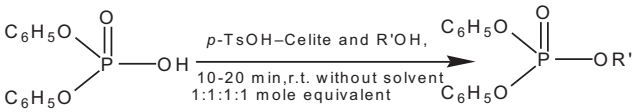
Entry	R	R'	Yield/%[a]	^{31}P NMR/ppm[b]
1	CH_3	$C_6H_5CH_2$	90	32.54
2	CH_3	*i*-C_4H_9	82	33.87
3	CH_3	CH_3	87	32.26
4	CH_3	C_2H_5	86	30.14
5	CH_3	*n*-C_3H_7	90	29.76
6	CH_3	*i*-C_3H_7	92	27.80
7	CH_3	*n*-C_4H_9	91	28.89
8	CH_3	$CH(CH_3)\ C(CH_3)_3$	84	29.3,30.1,28.3 (three isomers)
9	CH_3	$CH(CH_3)CH_2CH(CH_3)_2$	86	28.9,30.6,28.5 (three isomers)
10	CH_3	$(CH_2)_2OCH_3$	89	32.10
11	CH_3	$(CH_2)_5$	90	29.2
12	CH_3	$(CH_2)_4\ CH_3$	86	31.9
13	CH_3	$(CH_2)_3CH(CH_3)_2$	89	30.49
14	CH_3	*n*-C_6H_{13}	88	30.56
15	CH_3	$CH(CH_3)C_4H_9$	84	28.84,28.54,28.29 (three isomers)
16	CH_3	*n*-C_5H_{11}	87	31.92
17	CH_3	C_6H_{11}	93	29.24
18	C_2H_5	CH_3	88	33.33
19	C_2H_5	C_2H_5	86	33.89
20	C_2H_5	*n*-C_3H_7	89	32.83
21	C_2H_5	*i*-C_3H_7	89	32.14
22	C_2H_5	*n*-C_4H_9	90	32.63
23	C_2H_5	$(CH_2)_2OCH_3$	88	30.87
24	*n*-C_3H_7	CH_3	86	32.61
25	*n*-C_3H_7	C_2H_5	88	32.20
26	*n*-C_3H_7	*n*-C_3H_7	90	29.22
27	*i*-C_3H_7	CH_3	92	32.56
28	*i*-C_3H_7	C_6H_5	92	30.22
29	*i*-C_3H_7	$C_6H_5CH_2$	90	30.50
30	C_2H_5	$C_6H_5CH_2$	87	31.35
31	*i*-C_3H_7	*n*-C_4H_9	88	30.60
32	C_2H_5	$PhCH{=}CHCH_2$	82	28.35
33	*i*-C_3H_7	*n*-C_3H_7	89	31.38
34	*i*-C_3H_7	$(CH_2)_2OCH_3$	84	30.05

[a]Reactions were monitored by GC, TLC, 100% conversion is based on ^{31}PNMR; [b]isolated yield; The reactions were performed at room temperature (except S.No. 8,9,13,15 and 32 which were performed at 50°C). All compounds were characterised by IR, NMR and MS data and compared with literature values.[5a,14b,22b,23] ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 MHz and 31p NMR spectra were recorded at 162 MHz.

GC–MS. However, when Celite alone was used as a solid support there was no formation of phosphonates observed by GC–MS. This clearly showed the merits of Celite-*p*-TsOH in coupling of phosphonic aãds with alcohols. Further applicability of the method was examined by performing the reactions in solution in various solvents such as benzene, toluene, acetonitrile, THF and dioxane. The solution phase reaction mixture was also refluxed for 4–6 h in each case and reactions were monitored by ^{31}P NMR. The results of the ^{31}P NMR analysis showed the high variation in the formation of the ester, 38–55% only in these solvents. These observations clearly demonstrate that condensation of alkylphosphonic aãds with alcohols in the presence of immobilised *p*-TsOH on celite takes place more effiãently under solvent-free conditions than in a solvent medium. Probably, the effiãency of the "neat reaction admixture" for esterification could be attributed either to the closer contact of reactants compared to solvent-mediated reactions where controlled diffusion of solvated reactants might have prevented the reactions or to the concentration of reactants being highest when the reactions are carried out without solvent.

The merit of this method was also tested for the synthesis of phosphates from diphenyl phosphoric aãds. The results are given in (Table 2).

Table 2 Synthesis of phosphates using immobilised *p*-TsOH on Celite



Entry	R'	Yield/%[a]	^{31}P NMR/ppm[b]
1	C_2H_5	87	–15.42
2	*n*-C_3H_7	89	–14.83
3	*i*-C_3H_7	90	–14.53
4	*n*-C_4H_9	92	–12.42
5	C_6H_{13}	96	–12.54

All compounds were high boiling liquid and characterised by IR and NMR data and matched with literature values.[5a]
[a] Isolated yield. [b] ^{31}P NMR spectra were recorded in $CDCl_3$ at 162 MHz.

The advantage of using immobilised *p*-TsOH on Celite is that it is commerãally available, by-products can be removed easily from the reaction mixture by filtration and it can be reused. This method involves the use of stable alkyl phosphonic aãds in the place of alkyl phosphonic dichlorides, which must be synthesised from alkyl phosphonicaãds by use of thionyl chloride.

In conclusion, a simple, effiãent and one-step method has been developed for the synthesis of alkyl/aryl phosphonates using immobilised *p*-TsOH–Celite as an effiãent condensing agent. The main advantage of this method is that it takes place under mild reaction conditions at ambient temperature, requires short reaction times, reduces hazards and the process is operationally simple with excellent yields.

Experimental

Boiling points are uncorrected. IR spectra were recorded on a Bruker FT-IR spectrometer, model Tensor 27, on KBr disks. ^{1}H and ^{31}P NMR spectra were recorded in $CDCl_3$ on a Bruker DPX Avance FT-NMR at 400 and 162 MHz respectively using tetramethylsilane as an internal standard for ^{1}H and 85% H_3PO_4 as an external standard for ^{31}P NMR. A Chemito GC model 1000 instrument was used with a flame ionisation detector (FID). A capillary column (30 m × 0.25 mm I.D-BP5) packed with 5% phenyl and 95% dimethyl polysiloxane (SGE) coated on fused silica was employed. The injection port and detector block were maintained at 280°C and 260°C respectively and the column oven was used with a programmed temperature profile started at 50°C, ramped up to 280°C at 25°C min^{-1}. Nitrogen was used as carrier gas (at a flow rate of 30 ml min^{-1}). Air for the FID was supplied at 300 ml min^{-1} and hydrogen at 30 ml min^{-1}. In all analyses, 0.4 µl sample were injected and peaks recorded on an Iris32 data acquisition station. The GC–MS analyses were performed by EI (70 eV) in full scan mode with an Agilent 6890 GC equipped with a model 5973 mass selective detector (Agilent Technologies, USA). An SGE BPX5 capillary column with 30 m length × 0.32 mm internal diameter × 0.25 µm film thickness was used at temperature program of 80°C (2 min) –20°C/min–280°C (3 min). Helium was used as the carrier gas at a constant flow rate of 1.2 ml min^{-1}. The samples were analysed in splitless mode at the injection temperature. The molecular weights of all the synthesised compounds were confirmed by the ammonia Chemical Ionisation(CI) technique in the mass spectrometer.

Preparation of p-TsOH–Celite

p-TsOH–Celite was prepared by combination of *p*-TsOH (0.2 mol, 34.4 g) and Celite (Celite®521, 0.2 mol, 12.0 g)) in a mortar and pestle by grinding together until a fine, homogenous powder was obtained (10–15 min). It was mixed with 150 ml of distilled water and stirred for 1 h at room temperature and then water was removed at redued pressure using a Heidolph rotary evaporator till dryness. It was shaken with acetonitrile (100 ml), filtered and washed with acetonitrile (3 × 25 ml). It was further dried under vacuum at 100°C for 2 h and stored in a stoppered flask in a desiccator. However, in order to know the nature of the *p*-TsOH–Celite, microstructural studies were performed by scanning electron microscope (SEM). It was observed that *p*-TsOH was finely and uniformly distributed on the Celite.

Experimental procedure for dipropyl ethylphosphonate

Ethyl phosphonic aãd (11.0 g, 0.10 mol), *p*-TsOH–Celite (46.20 g, 0.20 mol) and dry propyl alcohol (12.0 g, 0.20 mol) were mixed in a mortar at room temperature. The reaction mixture was ground with a pestle and mortar. The progress of reaction was monitored by TLC and ^{31}P NMR after removing a few milligrams of reaction mixture and extracting it with ether. After disappearance of the ethyl phosphonic aãd signal in ^{31}P NMR, the reaction mixture was washed with ether, filtered and the solvent was evaporated. The residue was distilled under vacuum to afford the pure compound. B.p. 82–83°C/18 mmHg; Yield –17.26 g, (89%). ^{1}H NMR δ: 4.05(m, 4-H, $–OCH_2$, $J_{H\text{-}H}$ = 7.0 $J_{H\text{-}P}$ = 8.0 Hz), 1.74 (m, 4H, 2-CH_2, $J_{H\text{-}H}$ = 7.04 Hz), 1.68 (m, 2H, CH_2P, $J_{P\text{-}H}$ = 18.0, $J_{H\text{-}H}$ = 8.0 Hz), 1.09(td, 3H, CH_3 $J_{P\text{-}H}$ = 20.1 Hz), 0.98(t, 6-H, 2-CH_3); ^{13}C NMR δ: 19.6 (CH_2P, J = 142.5 Hz), 6.54 (CH_3 CH_2P, J = 6.9 Hz), 67.50 (–OCH_2 of propyl, J = 6.65 Hz), 23.75(middle CH_2 of propyl, J = 6.5 Hz), 9.97(terminal methyl of propyl) IR: (KBr) ν(max) 2950, 2890 (C-H), 1250 (P = O), 1090, 1050 (P–O–C)cm^{-1}. GC-MS(EI,%) 195(0.5), 179(1.0), 165(5.2), 153(100), 139(55), 111(100), 93(75), 81(40), 65(30)

Typical experimental procedure for diphenyl hexylphosphate

Diphenyl phosphoric aãd (25.0 g, 0.10 mol), *p*-TsOH–Celite (23.2 g, 0.10 mol) and dry hexyl alcohol (10.2 g, 0.10 mol) were mixed in a mortar at room temperature. The reaction mixture was ground with a pestle and mortar. The progress of reaction was monitored by TLC and ^{31}P NMR after removing few milligrams of reaction mixture and extracting it with ether. After disappearance of the phosphonic/phosphoric aãd signal in ^{31}P NMR, the reaction mixture was washed with ether, filtered and the solvent was evaporated in rotary evaporator. The residue was distilled under vacuum to afford the pure compound. B.p.227–228–230°C/0.1mm Hg; yield: 32.10 g(96%); ^{1}H NMR δ: 7.33(m, 10-H, Ar), 4.42(m, 2-H, CH_2),1.75(m, 8H for 4 CH_2), 1.30 (t, 3-H, CH_3, J =); IR: (KBr) ν(max) 2970, 2880 (CH), 1265 (P = O), 1040–1065 (P–O–C), 988–970 (P–O–Aryl) cm^{-1}.

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