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Surface-mediated solid phase reactions: a simple, efficient and base-free synthesis of phosphonates and phosphates on Al_2O_3

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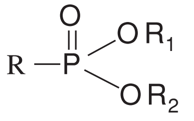
Al_2O_3-supported solvent free condensation of alkylphosphonic dichlorides with alcohols at room temperature yielded phosphorus esters in excellent yields.

Keywords: phosphonate, Al_2O_3, phosphate, CWC, alcoholysis, solid support

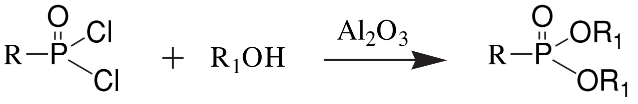
In the realm of organophosphorus chemistry, phosphonates and phosphates are important and interesting complements in terms of biological activities.[1-8] In addition to their biological utility, the phosphonates have also been recognised as attractive intermediates in organic chemistry. Owing to their anion stabilising ability, they have been frequently applied for the functionalisation and manipulation of carbon skeletons.[9] Furthermore, phosphonates have currently been also recognised as "markers" of chemical warfare agents, for verification purposes of the Chemical Weapons Convention (CWC).[10] Therefore, alkylphosphonates are covered in the list of CWC text under schedule 2 B4 category.[11] Large numbers of compounds can be made for this particular category by substituting the alkyl groups as per the CWC text. Phosphonates, with only methyl, ethyl, *n*-propyl and isopropyl groups are included in CWC, where O-alkyl groups may vary from C_1 to C_{10} carbon skeleton including all isomers. The general structure of such phosphonates is given below.



$R = -CH_3, -C_2H_5, -{}^nC_3H_7, -{}^iC_3H_7$

R_1, R_2 = Alkyl, Cycloalkyl, Alkenyl, Aryl

To meet the requirements of the verification program of the CWC, the synthesis of such a large number of phosphonates requires the development of rapid synthetic methods. Rapid synthesis of these compounds is necessary to fulfill two important aspects of the verification mechanism, first for the development of a spectral data base and second for the preparation of reference chemicals during Official Proficiency Tests (OPTs). Several methods have been reported in the literature for their synthesis.[12] However, only two deserve mention here as convenient laboratory methods. The first is alcoholysis of alkyl dichlorophosphines in the presence of base followed by oxidation,[13] and the second is the alcoholysis of alkyl phosphonic dichlorides in the presence of base.[14] Although these methods provide straightforward routes to prepare these materials, they suffer from many disadvantages. Both the methods are time consuming, require a base, solvent, refluxing, tedious work up and often chromatographic techniques to afford the compounds in the desired purity. It is worth noting that the purity of a substance is essential to generate authentic spectral data and retention indices.[10] In recent years use of inorganic solid oxides as catalysts and solid support has received much attention because of their chemoselectivity, environmental compatibility and economic availability. Amongst the various kinds of solid supports such as silica gel, zeolites, clay and alumina, alumina has attracted attention as it facilitates many reactions.[15]



Scheme 1

Despite the availability of a wide range of synthetic methods, so far no attempt has been made to use readily accessible neutral Al_2O_3 as a solid support for the synthesis of phosphonates. Recently, Al_2O_3 has been reported as a solid support for the acylation of amines and alcohols.[15] Such methods are simple, economical and upgradeable for large scale preparations. The efficiency and simplicity of Al_2O_3-supported acylations prompted us to explore the possibility of Al_2O_3-supported phosphorylations of alcohols. We found that neutral Al_2O_3-served as an effective solid support for the condensation of alkylphosphonic dichlorides with different alcohols in the absence of solvent.

Results and discussion

The general scheme for the synthesis of phosphonates is depicted in Scheme 1. Table 1 shows the range of phosphonates that were synthesised using this methodology together with % yields of products that were obtained, both with and without the use of Al_2O_3.

Reactions of alkyl phosphonic dichlorides and alcohols were performed at room temperature without using any solvent. It is evident from Table 1, that yields of phosphonates varied from 50 to 98 % on Al_2O_3, whereas, without alumina the yields were 10–25 % under similar reaction conditions. Reactions with alicyclic and primary aliphatic alcohols were complete within 10–20 minutes with excellent yields. Secondary alcohols, phenols and aromatic alcohols took comparatively longer times (30 min) to complete the reaction, while tertiary alcohols did not react at all.

Reactions with alumina were completed within the 30 minutes, and without alumina even the extended reaction time (up to 12 h) had no significant enhancement on the isolated yields. Thus, these results clearly demonstrate the applicability of alumina for the preparation of dialkyl alkylphosphonates at room temperature. In addition, the reaction on neutral alumina also gave relatively pure products in comparison to reported methods.[12]

Thus, facile condensation of alcohols with phosphonic dichlorides on Al_2O_3 is an excellent alternative for the preparation of the phosphorus esters. The main features of these reactions were: (a) no requirement of solvent as medium; (b) there was no need of base to remove generated HCl; (c) all the reactions were complete within 15–30 min at room temperature; (d) products were isolated by merely washing with diethyl ether, which is distilled off after filtration and

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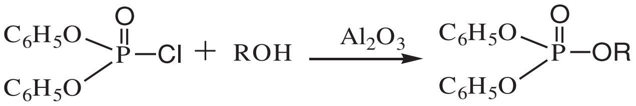
Table 1 Isolated yields of phosphorus esters formed from reactions of neat chloridates and alcohols[a]

Entry	Phosphonates R	R_1	% Yield[b] With Al_2O_3	Without Al_2O_3	B.P./°C (mm Hg)	^{31}P ppm	^{31}P ppm(lit[16])
1	CH_3	CH_3	95	25	65(12)	33.8	32.3
2	CH_3	C_2H_5	97	22	67(11)	31.1	30.0
3	CH_3	n-C_3H_7	98	22	83(5)	30.8	29.6
4	CH_3	i-C_3H_7	97	–	70(5)	30.9	27.4
5	CH_3	n-C_4H_9	85	–	73(5)	30.1	28.6
6	CH_3	i-C_4H_9	82	–	72(3)	30.0	29.1
7	CH_3	C_6H_5	54	11	155(1)	24.1	23.5
8	CH_3	$CH_2C_6H_5$	70	17	175(0.5)	28.2	27.3
9	CH_3	$C_6H_4CH_3$	65	12	180(0.5)	25.8	24.5
10	CH_3	$C_6H_3(CH_3)_2$	61	–	182(0.2)	26.2	–
11	CH_3	$CH_2CH{=}CH_2$	75	16	72(4)	29.3	28.5
12	CH_3	C_5H_9	80	12	78(5)	29.2	30.3
13	CH_3	C_6H_{11}	81	–	82(4)	28.7	29.5
14	C_2H_5	CH_3	96	22	75(5)	32.9	33.5
15	C_2H_5	C_2H_5	96	–	72(4)	34.3	33.8
16	C_2H_5	n-C_3H_7	97	19	70(2)	33.0	32.6
17	C_2H_5	i-C_3H_7	93	14	68(2)	32.9	32.1
18	C_2H_5	n-C_4H_9	88	–	97(1)	31.5	31.0
19	C_2H_5	i-C_4H_9	82	–	95(1)	31.3	31.6
20	C_2H_5	C_6H_5	50	10	155(0.5)	24.5	25.6
21	C_2H_5	$C_6H_5CH_2$	68	14	182(0.3)	27.8	28.4
22	C_2H_5	$C_6H_4CH_3$	65	–	180(0.3)	25.1	–
23	C_2H_5	$C_6H_3\ (CH_3)_2$	63	–	190(0.2)	25.9	–
24	C_2H_5	$CH_2CH{=}CH_2$	76	–	75(4)	28.8	27.7
25	C_2H_5	C_5H_9	82	14	80(4)	28.4	29.5
26	C_2H_5	C_6H_{11}	84	12	92(4)	28.1	33.0
27	n-C_3H_7	CH_3	92	–	85(6)	32.1	32.6
28	n-C_3H_7	C_2H_5	92	18	86(4)	31.8	32.3
29	n-C_3H_7	n-C_3H_7	90	15	96(3)	31.1	29.5
30	n-C_3H_7	i-C_3H_7	89	–	95(3)	30.9	29.3
31	n-C_3H_7	n-C_4H_9	81	–	103(1)	30.7	29.0
32	n-C_3H_7	i-C_4H_9	80	–	102(1)	29.3	–
33	n-C_3H_7	C_6H_5	50	10	158(0.4)	24.2	26.8
34	n-C_3H_7	$CH_2C_6H_5$	68	14	185(0.2)	27.5	25.5
35	n-C_3H_7	$C_6H_4CH_3$	64	–	188(0.2)	24.7	–
36	n-C_3H_7	$C_6H_3(CH_3)_2$	62	–	198(0.2)	24.5	–
37	n-C_3H_7	$CH_2CH{=}CH_2$	76	12	78(2)	28.1	27.2
38	n-C_3H_7	C_5H_9	81	–	80(2)	27.7	27.0
39	n-C_3H_7	C_6H_{11}	80	14	85(1)	27.6	26.8
40	i-C_3H_7	CH_3	90	15	70(4)	31.9	32.7
41	i-C_3H_7	C_2H_5	91	–	64(2)	31.7	32.2
42	i-C_3H_7	n-C_3H_7	86	–	88(2)	30.9	31.6
43	i-C_3H_7	i-C_3H_7	85	12	85(2)	31.1	31.8
44	i-C_3H_7	n-C_4H_9	81	10	101(1)	28.9	30.5
45	i-C_3H_7	i-C_4H_9	83	–	98(1)	28.5	–
46	i-C_3H_7	C_6H_5	51	11	155(0.4)	24.5	–
47	i-C_3H_7	$CH_2C_6H_5$	56	14	181(0.2)	27.2	26.0
48	i-C_3H_7	$C_6H_4CH_3$	54	–	185(0.2)	24.5	–
49	i-C_3H_7	$C_6H_3\ (CH_3)_2$	51	–	196(0.2)	24.3	–
50	i-C_3H_7	$CH_2CH{=}CH_2$	72	15	76(2)	27.9	27.0
51	i-C_3H_7	C_5H_9	81	17	80(1)	27.1	28.5
52	i-C_3H_7	C_6H_{11}	81	–	88(1)	27.4	29.0

[a] Reactions were carried out at ambient temperature and monitored by TLC and GC. All the reactions were completed within 10–30 min.
[b] Isolated yields; all the products had satisfactory IR, NMR and MS data and were compared with authentic samples.

purified products were obtained by vacuum distillation; (e) there were no side products such as pyrophosphonates and telomerised products, which are generally obtained with other classical methods; and (f) the recovered alumina could be recycled just after activating in an oven at 150°C. It seems that alumina facilitated the reaction by providing solid support which brought the reactants in closure contact, and presumably it also scavenged the generated HCl, which is otherwise detrimental to the reaction.

To extend the applicability of the method for preparation of phosphates, a few reactions were also attempted with diphenyl chlorophosphate (Scheme 2). These reactions also produced corresponding phosphates in high yields (Table 2). Thus, this protocol of alcoholysis is not only applicable to synthesis of CWC related phosphorus esters, but also to other phosphates as well, which have synthetic and medicinal utility.[17] Note that hindered alcohols such as menthol also efficiently reacted with diphenylchlorophosphate on alumina (entry 14, Table 2).



$$(C_6H_5O)_2P(O)Cl + ROH \xrightarrow{Al_2O_3} (C_6H_5O)_2P(O)OR$$

Scheme 2

Attempts to prepare cyclic phosphonates were not successful by this method. Reactions of alkane diols with alkylphosphonic dichlorides gave only 10–15% cyclic phosphonates in Al_2O_3 supported condensations. It is noteworthy that diols (bifunctional species) are likely to undergo polymerisation on reaction with bifunctional dichloridates. To avoid polymerisation it is recommended that the reaction is performed under high a degree of dilution[17], which is not achievable on a solid support.

Table 2 Isolated yields of diphenyl phosphate esters formed from reactions of diphenyl chlorophosphates and alcohols[c].

Entry	Phosphates	% Yield[d]		B.P. /°C (mm Hg)	^{31}P ppm	^{31}P ppm(lit)
	R	With Al_2O_3	Without Al_2O_3			
1	CH_3	84	25	158(0.3)	-14.5	-15.5
2	C_2H_5	84	22	162(0.2)	-14.1	-15.3
3	*n*-C_3H_7	82	22	166(0.2)	-13.5	-14.9
4	*i*-C_3H_7	82	20	165(0.2)	-13.9	-14.5
5	*n*-C_4H_9	81	21	174(0.2)	-12.8	-12.0
6	*i*-C_4H_9	80	18	173(0.2)	-12.3	-11.8
7	C_6H_5	41	16	195(0.3)	-18.9	-17.3
8	$CH_2C_6H_5$	67	24	201(0.2)	-17.7	–
9	$C_6H_4CH_3$	65	20	203(0.2)	-17.8	–
10	$C_6H_3(CH_3)_2$	62	21	212(0.2)	-17.2	–
11	$CH_2CH{=}CH_2$	75	22	162(0.2)	-18.3	-19.5
12	C_5H_9	78	18	178(0.2)	-12.1	-11.5
13	C_6H_{11}	79	22	181(0.2)	-11.4	-12.1
14	Menthyl	67	18	194(0.2)	-10.8	–

[c] Reactions were carried out at ambient temperature and monitored by TLC and GC. All the reactions were completed within 5–15 min.
[d] Isolated yields; all the products had satisfactory IR, NMR and MS data and were compared with authentic samples.

In conclusion, we have developed a simple, efficient, environmentally benign, economically viable, base-free and reduced solvent synthetic protocol for preparation of phosphates and phosphonates which find several applications. Further, the application of alumina-supported synthesis of other CWC related compounds is in progress and will be reported in due course.

Experimental procedure

In a typical experimental procedure, neutral activated alumina (0.306 g, 3.0 mmol) was added to an alcohol (2.2 mmol) in a single neck 25 ml round bottom flask. This was sealed with a rubber septum and then alkyl phosphonic dichloride (1.0 mmol.) was added with a syringe at 0 °C. The resultant dispersion was shaken occasionally at room temperature. The progress of reaction was monitored by TLC and GC by drawing a few milligrams of mixture and suspending in 1 ml of diethyl ether. When the reaction was complete the dispersion mixture was extracted with ether (3 × 5 ml) and filtered. The solvent was removed and the residue was distilled under vacuum to get the pure product. The mass spectrometric data and ^{31}P NMR data of the synthesised compounds were matched with the library spectra available in the latest official analytical data base of OPCW (e-OCAD) and elsewhere.[16] The proton decoupled ^{31}P chemical shift values of all the compounds are given in the respective tables.

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