

DCC–Celite hybrid immobilized solid support as a new, highly efficient reagent for the synthesis of *O*-alkyl hydrogen alkylphosphonates under solvent-free conditions

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Abstract

An efficient and solvent-free synthesis of *O*-alkyl hydrogen alkyl phosphonates is described. The methodology involves the condensation of alkyl phosphonic acids using DCC–Celite under solvent-free conditions.

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Phosphorus compounds containing the P–C bond are not particularly abundant in nature but they have diverse biological activity and have attracted considerable synthetic and pharmacological interest.^{1,2} Besides beneficial applications, their use in the production of the lethal compounds sarin, soman, and VX type chemical warfare agents (CWAs) is of note.³ However, these compounds are prone to hydrolysis to produce the corresponding *O*-alkyl hydrogen alkylphosphonates. These hydrolyzed products of CWAs are persistent and provide good evidence of the specific agent used or produced.

The literature precedent reveals that alkyl hydrogen alkylphosphonates can be obtained either by partial hydrolysis of diesters of alkylphosphonic acids, alkaline hydrolysis of *O*-alkyl alkylphosphonic chloride, or by alcoholysis of alkylphosphonic acid anhydride.^{4–6} However, only a few reports are available for selective esterification of alkylphosphonic acids to yield monoesters.^{6,7} Recently, the selective esterification of alkylphosphonic acids was reported using phenylarsonic acid as the condensing agent.⁸ This method has several drawbacks, such as the

long reaction time (28 h), continuous azeotropic removal of water, and the use of toxic phenylarsonic acid and a solvent. Therefore, there is a need to develop an efficient method for the synthesis of these compounds.

In recent years, the use of organic–inorganic hybrid immobilized solid supported reagents has been of interest.^{9–11} Reactions under solvent-free conditions have also recently attracted attention.^{12–14}

Dicyclohexylcarbodiimide (DCC) alone or in combination with 4-dimethylaminopyridine (DMAP) and DMAP-hydrochloride has frequently been used for the activation of carboxylic acids in solution phase chemistry.¹⁵ The use of DCC has also been reported for the synthesis of various thioesters.¹⁶ Recently, DCC under solvent-free conditions was reported for the synthesis of sulfinate esters.¹⁷ To the best of our knowledge, the use of DCC for the mono-esterification of alkylphosphonic acids has not been reported. In continuation of our ongoing program to develop new reagents and synthetic procedures for the synthesis of organophosphorus compounds,¹⁸ we report here a new and convenient one-step method for the synthesis of phosphonate monoesters under solvent-free conditions using alkylphosphonic acids and alcohols in the presence of DCC immobilized on Celite.¹⁹ High yields of the required

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Table 1
Synthesis of *O*-alkyl hydrogen alkylphosphonates using DCC–Celite

$\begin{array}{c} \text{HO} \quad \text{O} \\ \quad \parallel \\ \text{HO}-\text{P}-\text{R} \end{array} \xrightarrow[\text{solvent-free, 30-60 min}]{\text{R'OH and DCC-celite}} \begin{array}{c} \text{HO} \quad \text{O} \\ \quad \parallel \\ \text{HO}-\text{P}-\text{R} \\ \text{R'O} \end{array}$ /mole ratio 1 : 1 : 2						
Entry	Substrate	Product	Bp/mmHg	Yield ^a (%)	Reaction time ^b (min)	³¹ P NMR ^c (ppm)
1	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3-\text{P}-\text{OC}_2\text{H}_5 \\ \text{OH} \end{array}$	108–110/0.1	80	30	31.20
2	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3-\text{P}-\text{OC}_3\text{H}_7 \\ \text{OH} \end{array}$	112–116/0.1	82	40	31.61
3	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3-\text{P}-\text{O}^i\text{C}_3\text{H}_7 \\ \text{OH} \end{array}$	102–104/0.1	85	35	31.50
4	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3-\text{P}-\text{OC}_5\text{H}_{11} \\ \text{OH} \end{array}$	45–48 (mp) 110–111/0.1	90	45	31.0
5	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3-\text{P}-\text{OCH}-\text{C}(\text{CH}_3)_3 \\ \text{OH} \quad \text{CH}_3 \end{array}$	114–116/0.1	92	60	31.50
6	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_2\text{H}_5-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_2\text{H}_5-\text{P}-\text{O}^i\text{C}_3\text{H}_7 \\ \text{OH} \end{array}$	98–100/0.1	80	40	33.58
7	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_2\text{H}_5-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_2\text{H}_5-\text{P}-\text{OCH}_2\text{CH}_2\text{OCH}_3 \\ \text{OH} \end{array}$	Oil	86	45	33.12
8	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_2\text{H}_5-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_2\text{H}_5-\text{P}-\text{O}^n\text{C}_6\text{H}_{13} \\ \text{OH} \end{array}$	52–54 (mp)	91	50	32.88
9	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_2\text{H}_5-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_2\text{H}_5-\text{P}-\text{OCH}-\text{CH}-\text{CH}_3 \\ \text{OH} \quad \text{CH}_3 \quad \text{CH}_3 \end{array}$	105–106/1	89	80	32.79
10	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_3\text{H}_7-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_3\text{H}_7-\text{P}-\text{OC}_2\text{H}_5 \\ \text{OH} \end{array}$	122–124/0.15	83	40	34.10
11	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_3\text{H}_7-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_3\text{H}_7-\text{P}-\text{O}^n\text{C}_4\text{H}_9 \\ \text{OH} \end{array}$	Oil	84	60	33.80
12	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_3\text{H}_7-\text{P}-\text{OH} \\ \text{OH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_3\text{H}_7-\text{P}-\text{OCH}_2-\text{CH}(\text{CH}_3)_2 \\ \text{OH} \end{array}$	Oil	84	70	33.38

(continued on next page)

Table 1 (continued)

Entry	Substrate	Product	Bp/mmHg	Yield ^a (%)	Reaction time ^b (min)	³¹ P NMR ^c (ppm)
13			122–124/1	81	55	38.23
14			Oil	87	60	39.82
15			Oil	88	70	41.68

^a Isolated yield.^b Reactions in entries 4, 5, 8, 9, and 15 were performed at 50–60 °C.^c ³¹P NMR spectra were recorded in CD₃OD at 162 MHz.

products were obtained in short reaction times (30–60 min), Table 1. The structures of the monoesters were confirmed by their spectral data (¹H NMR, ³¹P NMR, and MS).²⁰ To find an effective combination of the solid support with condensing agent, various reactions were performed using a variety of reagents such as alumina (acidic, basic, and neutral), silica, clay (Symctone, Montmorillonite, and KSF), Kieselgel, ZnO–SiO₂, H₃PO₃–Silica, P₂O₅–Celite, *p*-TsOH, TiCl₄, and DCC–Celite. The best results were obtained with DCC–Celite.

To optimize further the reaction conditions with DCC–Celite, reactions were carried out using different mole ratios and amounts of the solid support. The maximum yield of the alkyl hydrogen alkylphosphonate was obtained when the reactions were carried out using 1:1:2 molar ratios of the alkyl phosphonic acid, the alcohol, and DCC–Celite, respectively. The process involves mixing the alkylphosphonic acid and the alcohol in the presence of the immobilized DCC–Celite in a mortar and grinding the mixture at room temperature for 30–60 min, Table 1. The method was found to be fast with purification of the products achieved simply by washing the reaction mixture with ether. In most cases, the isolated products required no further purification.

Mono-esterification with alicyclic and primary alcohols was complete within 30–45 min, while secondary alcohols took longer (45–60 min). Tertiary alcohols did not react with the alkyl phosphonic acids under these conditions.

The advantages of using DCC–Celite are that it is commercially available and the only by-product dicyclohexylurea is removed by filtration. To summarize, we have described a general and efficient procedure for the rapid synthesis of alkyl hydrogen alkylphosphonates.

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19. Typical experimental procedure for the synthesis of *O*-alkyl hydrogen alkyl phosphonates. The alkylphosphonic acid (0.1 mol), DCC–Celite (0.2 mol), and the alcohol (0.1 mol) were ground with a pestle in a mortar at room temperature. The progress of reaction was monitored by TLC and ^{31}P NMR after drawing a few milligrams of the reaction mixture and extracting with ether. After the disappearance of the phosphonic acid signal (as per the time given in Table 1) in the ^{31}P NMR, the reaction mixture was washed with ether and the solvent was evaporated. The residue was distilled under vacuum to afford the pure compound. The mass spectrometric and ^{31}P NMR data of the synthesized compounds were matched with the spectral library available in the latest official database of the Organization for the Prohibition of Chemical Weapons (e-OCAD).
20. Central OPCW Analytical Database, Version 6, Released on September, 2004, Technical Secretariat of OPCW, The Hague.