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Polymer-supported sulfonated magnetic resin: An efficient reagent for esterification of O-alkyl alkylphosphonic-and carboxylic-acids

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ABSTRACT

A mild and efficient synthetic method has been developed for the esterification of O-alkyl alkylphosphonic-and carboxylic-acids using polymer-supported sulfonated magnetic resins. Polymer-supported resins are recovered using an external magnet and reused several times.

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Organophosphorus esters containing P-C bond find large number of applications in the field of pesticides, fungicides, fire retardants and lubricants.¹ In addition to synthetic and pharmaceuticals applications, these compounds are also used for the production of toxic nerve agents like sarin, soman and VX type chemical warfare agents (CWAs).² Organophosphorus esters are also registered as markers of CWAs for the verification of use of CWAs.³⁻⁷ Verification of spillage or use of CWAs is the prime responsibility of Organization for the Prohibition of Chemical Weapons (OPCW).⁸⁻⁹ OPCW ensures the implementation of an international treaty known as chemical weapons convention (CWC). The CWC has been formulated to make the world free from chemical weapons. For verification analysis of CWC, *O,O'*-dialkylalkylphosphonates (DAPs) are required as reference chemicals to facilitate identification of the chemicals related to the CWC.¹⁰⁻¹¹ These DAPs belong to the schedule 2B4 category of CWC.

A number of synthetic methods are reported in literature for the synthesis of DAPs, these methods suffer from one or other kind of disadvantages like requirement of corrosive reagent, long reaction time and chromatographic purification to obtain desired compounds.¹²⁻¹⁵ In recent years polymer-supported reagents are widely used in organic synthesis for various functional group transformations, due to its better ability for product purifications.¹⁶⁻¹⁷ The catalytic activities of sulfonic acids for esterification is well documented in the literature.¹⁸ And magnetically active sulfonated resins are reported for various purposes including analytical and synthetic applications.¹⁹ We contemplated that magnetically active sulfonated resins could be used as a reagent for esterification and due to their superparamagnetic property these could be retrieved and reused; with this concept these resins were selected to study their application as condensation

reagent to prepare phosphonic and carboxylic esters. Sulfonated magnetic resins were prepared by coating magnetic nanoparticles with polystyrene divinylbenzene through emulsion polymerization. Sulfonation of polymer coated resins yielded polymer-supported sulfonated magnetic resins (PSMRs). PSMRs were used for the synthesis of DAPs and carboxylic esters by reacting O-alkyl alkylphosphonic-and carboxylic-acids with alcohols. The PSMRs were prepared as per the available synthetic method, and characterized by FTIR & SEM analysis (supporting information). These resins contain sulfonic acid group attached on the surface of polymer coated Fe₃O₄ particles and catalyze the reaction for the formation of phosphonate ester as well as carboxylic ester. The amount of sulfonic acid present on the synthesized polymer surface was calculated as per the reported procedure and found to be 2.1 mmole/g.^{1,20} The developed synthetic method produces excellent yield (60-82%) within the 30-45 min (figure 1).²¹

To optimize the reaction conditions such as solvent, time, temperature, alcohol and amount of polymer supported catalyst, a pilot reaction of *O*-butyl methylphosphonic acid with butanol was performed. Reactions were performed by varying one parameter at a time, results are summarized in Table 1.

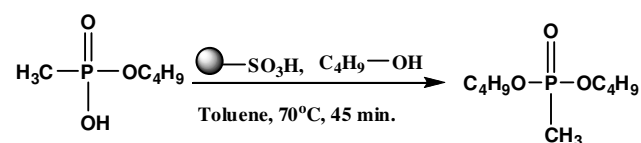


Figure 1. Esterification of *O*-butyl methylphosphonic acid^a

Table 1 Optimization of reaction condition

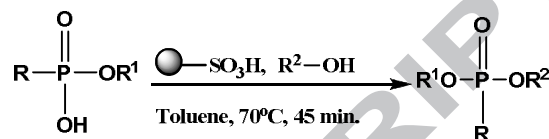
Entry	Solvent	Temp ^(°C)	Time (min.)	Alcohol (mmol)	PSMRs mmoles/g	Yield ^b (%)
1	Toluene	25	45	4	0.1	20
2	Toluene	50	45	4	0.1	55
3	Toluene	70	45	4	0.1	92
4	Toluene	70	45	4	0.2	90
5	Toluene	70	45	4	0.05	65
6	Toluene	70	15	4	0.1	30
7	Toluene	70	30	4	0.1	60
8	Toluene	70	45	1	0.1	28
9	Toluene	70	45	2	0.1	42
10	Toluene	70	45	6	0.1	90
11	Benzene	70	45	4	0.1	85
12	Chloroform	70	45	4	0.1	83
13	Acetonitrile	70	45	4	0.1	70
14	Ethyl acetate	70	45	4	0.1	78
15	1,4-Dioxane	70	45	4	0.1	90
16	Toluene	70	90	4	c	nd

^aReaction condition : *O*-butyl methylphosphonic acid (1 mmol)^bIsolated yield^c Non-sulfonated magnetic polystyrene resins (50 mg)nd: Not detected

Highest yield of dibutyl ester was obtained at 70°C (entry 1-3, Table 1). Requirement of PSMRs in terms of sulfonic acids in mmoles was 0.1 mmoles (entry 4-5, table 1), and minimum reaction time required to get high yield was 45 min (entry 6-7, table 1). Similarly the minimum amount of alcohol required was found to be 1:4 (entry 8-10, table 1). Amongst the various solvents screened toluene and 1,4-dioxane afforded best recoveries of the ester (entry 11-15, table 1). No product was observed when the reaction was carried out by using non-sulfonated polystyrene-divinylbenzene magnetic resins. It illustrates that sulfonic acid function on the resins is required for esterification. Thus finally optimized reaction conditions were solvent toluene, temp 70°C, time 45 min and ratio of phosphonic acid: alcohol: PSMRs (1:4:0.1).

After optimizing the reaction parameters generality of the method was tested with other *O*-alkyl alkylphosphonic acids and alcohols for the synthesis of DAPs. Results summarized in Table 2 indicates that *O*-alkyl alkylphosphonic acids, were converted to their corresponding esters (DAPs) when reacted with alcohols under the optimized reaction conditions. Major advantage of the method is highly convenient isolation of product. PSMRs were isolated from the reaction mixture with the help of an external magnet thus required no filtration or

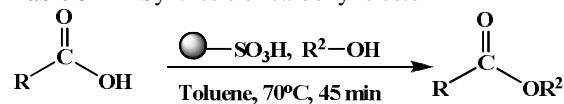
centrifugation. From supernatant, the DAPs were obtained in pure form by distilling off the solvent. High performance of this reaction is attributed to the small size (100 μm) of PSMRs which were dispersed in the reaction mixture homogeneously. Fine dispersion of PSMRs facilitated the condensation reaction of acids and alcohols through efficient mass transfer on the surface of resins. Thus efficiency of the reaction and extremely simple work-up are important attribute of this protocol.

Table 2 Synthesis of *O,O'*-dialkylalkylphosphonate(DAPs).^a

Entry	R	R ¹	R ²	Yield (%)
1	CH ₃	CH ₃	CH ₃ OH	74
2	CH ₃	C ₄ H ₉	C ₃ H ₇ OH	86
3	CH ₃	C ₃ H ₇	C ₃ H ₇ OH	84
4	CH ₃	C ₃ H ₇	ⁱ C ₃ H ₇ OH	92
5	CH ₃	ⁱ C ₃ H ₇	ⁱ C ₃ H ₇ OH	88
6	CH ₃	C ₃ H ₁₀	C ₅ H ₁₀ OH	90
7	CH ₃	C ₈ H ₁₇	C ₈ H ₁₇ OH	88
8	C ₂ H ₅	C ₃ H ₇	C ₂ H ₅ OH	82
9	C ₃ H ₇	ⁱ C ₃ H ₇	C ₃ H ₇ OH	85
10	C ₂ H ₅	ⁱ C ₄ H ₉	C ₂ H ₅ OH	80

^aAll the reactions were carried out in 1:4:0.1 molar ratios of alkyl alkylphosphonic acid, alcohol and (PSMRs) at 70°C in 45 minute by using toluene as a solvent.

After successfully synthesizing DAPs from *O*-alkyl alkylphosphonic acids, we further extended this work for the synthesis of carboxylic esters from carboxylic acids by using PSMRs and alcohols. Results summarized in Table 3 reveal that PSMRs could be used as condensing reagent for the synthesis of carboxylic esters as well.

Table 3 Synthesis of carboxylic ester^a

Entry	Substrate	Alcohol	Product	Yield (%)
1	Propanoic Acid	C ₂ H ₅ OH	Ethyl Propionate	88
2	Nonanoic Acid	C ₃ H ₇ OH	Propyl Nonanoate	86
3	Benzoic Acid	C ₂ H ₅ OH	Ethyl Benzoate	90
4	4-Methoxy benzoic acid	C ₃ H ₇ OH	Propyl 4-Methoxy benzoate	80
5	4-Nitro benzoic Acid	C ₃ H ₇ OH	Propyl 4-Nitro benzoate	88

^aAll the reaction were carried out in 1:4:0.1 molar ratios of carboxylic acid, alcohol and (PSMRs) at 70°C in 45 minute by using toluene as a solvent.

The attribute of this synthetic protocol is the isolation of final product from the reaction mixture. After completion of the reaction polymer-supported catalyst was removed by using an external magnet. The separated PSMRs could be further reused by washing with organic solvent like dichloromethane and treatment with hydrochloric acid. After removing the PSMRs from the reaction mixture, excess of solvent is removed by distillation. Products were further purified by vacuum distillation.

Synthesis of *O,O'*-dialkyl alkylphosphonate starting from dibasic alkylphosphonic acids using PSMRs was also attempted. Dibasic alkylphosphonic acids afforded DAPs no higher than 25% when reacted with alcohols in the presence of PSMRs under the reaction conditions optimized for mono basic acids. Varying the time, temperature and solvent also did not improve the yield. Less reactivity of dibasic acids could be attributed to their relatively lesser nucleophilicity originating from stabilization of oxyanion over three oxygen atoms. This study is in progress and will be reported in due course.

In conclusion, we have developed an efficient process, for the synthesis of *O,O'*-dialkyl alkylphosphonate & carboxylic esters using PSMRs as recyclable catalyst. The PSMRs were able to efficiently promote the esterification of a variety of *O*-alkyl alkylphosphonic acid as well as carboxylic acid with different alcohols in high yields under mild reaction conditions. After completion of the reaction the PSMRs were removed by an external magnet, which could be reused.

Supplementary data

Experimental details and spectroscopic data of synthesized compounds are presented in supporting information.

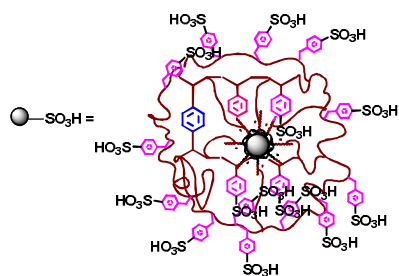
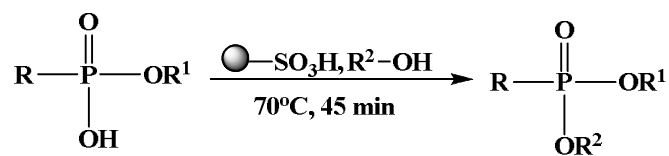
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21. General experimental procedure: A mixture of 50 mg polymer-supported sulfonated magnetic resins (0.1 mmol) and alkyl alkylphosphonic acid / carboxylic acid (1mmol) and dry toluene (0.5ml) was stirred at room temperature for 15 minute. After that excess of alcohol (4 mmol) was added to the reaction mixture and stirred at 70°C for further 30 min. Progress of the reaction was monitored by TLC and ³¹P NMR. After completion, the reaction mixture was cooled to room temperature and placed near by a strong external magnet and supernatant layer was separated from the reaction mixture. Finally, excess of solvent was removed by distillation to get the colourless liquid. ¹H and ³¹P NMR spectra at 400 MHz were recorded in CDCl₃. Electron ionization (EI+) mass spectra were recorded on Agilent GC-MS system.

Graphical Abstract



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