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β-Cyclodextrin as an efficient catalyst for the one-pot synthesis of 1-aminophosphonic esters in water

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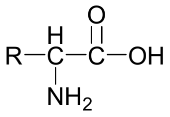
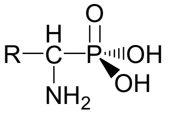
Abstract—A simple, efficient, and general method has been developed for the one-pot synthesis of α-aminophosphonic esters in water using β-cyclodextrin as an efficient catalyst. α-Aminophosphonic esters were obtained in good yields (45–82%) and purity under mild conditions by the reaction of diethyl phosphite with a mixture of aldehyde and amine in water at reflux.

Phosphorus–carbon bond formation has attracted growing attention because of its application in organic synthesis and bioorganic chemistry. α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[1–4] Among α-functionalized phosphonic acids, 1-aminophosphonic acids are an important class of compounds that exhibit a variety of interesting and useful properties. 1-Aminophosphonic acids are important substitutes for the corresponding α-amino acids in biological systems.[5] Indeed a number of potent antibiotics,[6] enzyme inhibitors,[7] and pharmacological agents[8] are 1-aminophosphonic acids or peptide analogues. Aminophosphonic acids are also found as constituents of natural products.[9] Many effective methods for the preparation of 1-aminoalkylphosphonic acids have been developed. Of these, the Kabachnik–Fields[10] synthesis, catalyzed by a base or an acid, is the most convenient. The key step in the Kabachnik–Fields synthesis of 1-aminoalkyl phosphonates is the nucleophilic addition of an amine to a carbonyl compound followed by the addition of a dialkyl or diaryl phosphite to the resulting imine. The formation of 1-hydroxyphosphonates or a product of rearrangement frequently accompanies the formation of 1-aminoalkyl phosphonates.[11] Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3{\cdot}Et_2O$, $ZnCl_2$, $MgBr_2$, and $InCl_3$ have been used as catalysts.[12] However, these reactions cannot be carried out in a one-step operation with the carbonyl compound, amine and dialkyl phosphite because the amine and water present during imine formation can decompose or deactivate the Lewis acids. Recently, metal triflates[13] and perchlorates[14] have been reported as efficient catalysts. However, these catalyzed reactions are often carried out in the presence of stoichio metric amounts of additional reagents such as molecular sieves and $MgSO_4$.



$R-\overset{H}{\underset{NH_2}{C}}-\overset{O}{\overset{\|}{C}}-OH$

α-amino acid



$R-\overset{H}{\underset{NH_2}{C}}-\overset{O}{\overset{\|}{P}}(OH)OH$

1-aminoalkylphosphonic acid

Organic reactions in aqueous media have attracted much recent attention. Water is one of the most abundant, cheapest, and environmentally friendly solvents. Indeed water exhibits unique reactivity and selectivity, which is different from that of conventional organic solvents. Thus, development of novel reactivity and selectivity is one of the challenges of aqueous chemistry.[15]

β-Cyclodextrin (β-CD) is a water-soluble cyclic oligosaccharide possessing hydrophobic cavities, which binds substrates selectively and catalyzes chemical reactions with high selectivity by involving reversible formation of host–guest complexes with noncovalent bonding as seen in enzymes.[16] β-CD can be recovered and reused in subsequent reactions without loss of activity. As part of our efforts to introduce novel methods for the synthesis of organophosphorus compounds,[17] in this report, a

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new method for the one-pot synthesis of 1-aminoalkylphosphonates using β-cyclodextrin as catalyst in water is described (Scheme 1 and Table 1).

The three-component reaction of benzaldehyde **1a**, aniline **2a**, and diethylphosphite was selected as a model reaction for the one-pot synthesis 1-aminophosphonates **3a** using β-cyclodextrin as catalyst (Table 1). In the absence of any catalyst, reaction in water at reflux for 24 h gave the corresponding 1-aminophosphonate **3a** in 15% yield (entry 1). The reaction yield was not changed by adding 3 equiv of diethyl phosphite to the reaction mixture (entry 2). A mixture of aniline (**2a**) and benzaldehyde (**1a**) with diethyl phosphite in the presence of β-CD in water at reflux, afforded the desired product **3a** in 61% yield (entry 3). Other mixtures of amines and aldehydes also reacted with diethylphosphite in the presence of a catalytic amount of β-CD to give the desired compounds in good yields (entries 4–12). The reaction of cyclohexylamine with benzaldehyde (**1a**) in the presence of diethylphosphite gave the desired product in 45% yield (entry 13). The reactions were clean with no tar formation.[18]

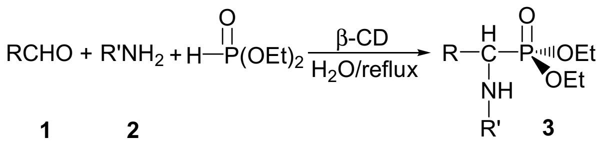
Table 1. One-pot synthesis of 1-aminoalkylphosphonic esters using β-CD in water at reflux

Entry	R **1**	R′ **2**	Reaction time (h)	Yield[a] (%) **3**
1	C_6H_5–	C_6H_5–	24	15[b]
2	C_6H_5–	C_6H_5–	24	15[c]
3	C_6H_5–	C_6H_5–	24	61
4	*p*-$CH_3C_6H_4$–	C_6H_5–	24	82
5	*p*-$(CH_3)_2CHC_6H_4$–	C_6H_5–	24	63
6	*o*-MeC_6H_4–	C_6H_5–	24	53
7	*m*-$MeOC_6H_4$–	C_6H_5–	24	73
8	*n*-C_4H_9–	C_6H_5–	24	62
9	Ph–CH=CH–	C_6H_5–	12	55
10	C_6H_5–	*m*-$O_2NC_6H_4$–	24	45
11	*p*-$CH_3C_6H_4$–	*m*-$O_2NC_6H_4$–	24	72
12	*p*-$(CH_3)_2CHC_6H_4$–	*m*-$O_2NC_6H_4$–	24	70
13	C_6H_5–	Cyclohexyl	24	45

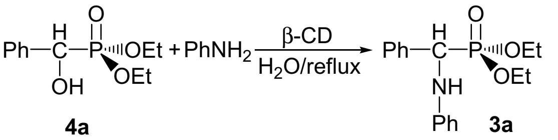
[a] Isolated yield.

[b] Reaction carried out without any catalyst.

[c] Reaction carried out without any catalyst in the presence of 3 equiv of diethylphosphite.



Scheme 1.



Scheme 2.

No 1-hydroxyphosphonates or products of rearrangement were detected during the formation of 1-aminoalkylphosphonates. These results prompted us to examine the conversion 1-hydroxyalkylphosphonates to 1-aminoalkylphosphonates in the presence of amines in water with β-CD as catalyst (Scheme 2).[19] Interestingly, we found that diethyl 1-hydroxyphenylmethyl phosphonate (**4a**) was converted to diethyl 1-aminophenylmethylphosphonate (**3a**) in the presence of aniline in water and β-CD as catalyst (20% yield, reflux, 48 h, Scheme 2).[20] The reaction yield was increased to 55% by adding 1 equiv of diethylphosphite to the reaction mixture.

In summary, a simple work-up, mild reaction conditions, good yields, and relatively clean reactions with no tar formation make this method an attractive and useful addition to present methodologies. Indeed, a wide range of aldehydes and amines were converted to the corresponding α-aminophosphonic esters using this method.

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18. β-CD (0.1 mmol) was dissolved in water (15 ml) by warming to 60 °C until a clear solution was formed. A mixture of an amine (1 mmol) and aldehyde (1 mmol) was added to reaction mixture. Diethyl phosphite (1.5 mmol) was then added and the mixture stirred at reflux until the reaction was complete. The organic material was extracted with ethyl acetate. The organic phase was separated, filtered, and washed with brine. β-CD was recovered by filtration and reused. The organic phase was then dried ($MgSO_4$), filtered, and the solvent was removed under vacuum. The crude product was purified by passing through a column of silica gel using ethyl acetate/*n*-hexane (1:5 to 5:1) as the eluent. All products gave satisfactory spectral data in accord with the assigned structures and literature reports.[14a,17c,21,22]
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