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A simple and convenient procedure for the synthesis of 1-aminophosphonates from aromatic aldehydes

Babak Kaboudin* and Khavar Moradi

Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), Gava Zang, Zanjan 45195-1159, Iran

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Abstract—A simple, efficient, possible industrial process has been developed for the synthesis of 1-aminophosphonic acids from simple starting materials. As described below, treatment of aromatic aldehydes with ammonia and reaction with diethyl phosphite gives diethyl *N*-(arylmethylene)-1-aminoaryl methylphosphonates, which can be easily hydrolyzed to diethyl 1-aminoaryl-methylphosphonates. This method is easy, rapid, and good yielding for the synthesis of 1-aminoalkylphosphonates from simple starting materials.

Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates.[1] α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[2–4] Among α-functional phosphonic acids, 1-aminophosphonic acids are an important class of compounds that exhibit a variety of interesting and useful properties. The 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 thereof. Aminophosphonic acids are also found as constituents of natural products. A number of synthetic methods for the synthesis of 1-aminoalkyl phosphonates have been developed during the past 20 years.[9] Of these methods, the Kabachnik-Field's[10–14] synthesis of 1-aminoalkyl phosphonates, catalyzed by a base or an acid, is the most convenient. The key step in the Kabachnik-Field's 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. However, the formation of 1-hydroxyphosphonates or a product of its rearrangement frequently accompanies the formation of 1-aminoalkyl phosphonates.[15] 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. However, these reactions cannot be carried out in a one-step operation using the carbonyl compound, amine and dialkyl phosphite because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids.[16] A typical procedure is a Strecker-type reaction,[17] which involves the treatment of an aldehyde with ammonia and a dialkyl phosphite. This method, however, is not high yielding and is unsuitable for large-scale production since the reaction is performed in a sealed vessel at 100 °C. As a part of our efforts to introduce novel methods for the synthesis of organophosphorus compounds,[18] in this letter, a new method for the synthesis of α-aminophosphonates is described.

We have found that reaction of aromatic aldehydes with ammonia solution followed by reaction with diethyl phosphite, gives 1-aminophosphonates in good yields (Scheme 1). Thus the reaction of benzaldehyde, chosen as the model compound, was studied. As described below, treatment of benzaldehyde (**1a**) with ammonia followed by treatment with diethyl phosphite, gave diethyl *N*-(phenylmethylene)-1-aminophenyl methylphosphonate (**2a**) (92%) (Scheme 1). The ^1H NMR spectrum of **2a** exhibited a doublet at δ 8.42 indicative of HC ~ P coupling ($^4J_{HP}$ = 4.7 Hz). Hydrolysis of **2a** with *p*-toluenesulfonic acid and neutralization of the sulfonate salt,

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* Corresponding author. Tel.: +98 241 4153220; fax: +98 241 4249023; e-mail: kaboudin@iasbs.ac.ir

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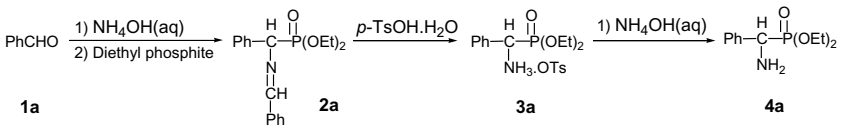
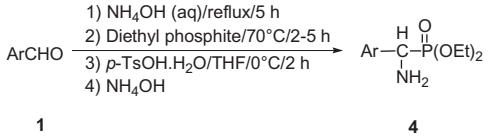


Scheme 1.

Table 1. Synthesis of 1-aminophosphonates from aldehydes

	Ar **1**	Reaction time (h)	Yield[a] (%) **4**
a	C_6H_5–	4	61
b	*p*-ClC_6H_4–	2	76
c	*p*-$(CH_3)_2CHC_6H_4$–	5	66
d	*p*-$MeOC_6H_4$–	5	70
e	*p*-BrC_6H_4–	3	81
f	*m*-ClC_6H_4–	2	79
g	*m*-MeC_6H_4–	3	68
h	1-Naphthyl	5	51
i	2-Naphthyl	5	53
j	*n*-C_6H_{13}–	5	—[b]

[a] Isolated yields.
[b] Unknown products.



Scheme 2.

gave 1-(aminophenylmethyl)phosphonate (**4a**) (Scheme 1). This process was successfully applied to other aromatic aldehydes as summarized in Table 1. As shown, substituted benzaldehydes react with ammonia followed by reaction with diethyl phosphite to afford the desired 1-aminophosphonates in good yields (**4b–g**). Naphthalene carbaldehydes also reacted with diethyl phosphite in the presence of ammonia to give the desired 1-aminophosphonates in good yields (**4h** and **4i**) (Scheme 2).

In summary, this method is an attractive and useful contribution to present methodology. A wide range of aromatic aldehydes was converted to the corresponding 1-aminophosphonic acids using this method. Reaction of aliphatic aldehydes with diethylphosphite in the presence of ammonia gave unidentified mixed products.[19]

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19. The aldehyde (15 mmol) was added to ammonium hydroxide (30%, 15 mL) and the solution was stirred for 5 h at reflux. During this time, a white precipitate formed. The precipitate was removed by filtration and dried. Diethyl phosphite (6 mmol) was added to this solid and the resulting solution was stirred for 2–5 h at 70 °C. *p*-Toluenesulfonic acid (6 mmol) in 50 mL THF was added to the reaction mixture, which was stirred for 2 h

at 0 °C. The precipitate was removed by filtration and washed with THF (20 mL). The precipitate was added to 15 mL aqueous ammonium hydroxide (10%) and stirred for 30 min at room temperature. Extraction with ether (3×50 mL), evaporation of the solvent, and chromatography on silica gel with EtOAc/*n*-hexane (9:1) gave the pure products as oils in 51–81% yields. All products gave satisfactory spectral data in accord with the assigned structures and literature reports.[18,20]

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