A New One-pot Synthesis of α-Amino Phosphonates Catalyzed by Butyldimethyl(1-phenylethyl)ammonium Bromide

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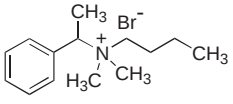
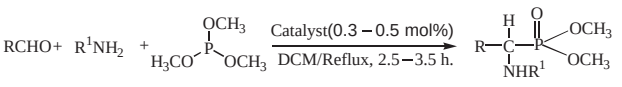
Butyldimethyl(1-phenylethyl)ammonium bromide is found to be an efficient catalyst for the three-component reaction of an aldehyde, aromatic amine, and trimethylphosphite in refluxing CH_2Cl_2 to afford corresponding α-amino phosphonate in high yield.

α-Amino phosphonates have acquired great attention in synthetic organic chemistry due to their structural analogy to α-amino acids and their varied utility as herbicides,[1] peptidemimics,[2] potent antibiotics,[3] enzyme inhibitors,[4] haptens of catalytic antibodies,[5] and pharmacological agents.[6] In view of their versatile biological activity, a variety of synthetic methodologies have been developed.[7] Pudovik,[8] the pioneer of this chemistry, used imines under catalytic conditions of NaOMe for this transformation and notable are some of the recent methods in which Lewis acids such as $SnCl_4$,[9] $ZrCl_4$,[10] $InCl_3$,[11] $ZnCl_2/MgBr_2$,[12] $AlCl_3$,[13] lithium perchlorate in diethyl ether (LPDE),[14] lanthanide triflates,[15] scandium tris(dodecylsulfate),[16] and polystyrene-supported sulphonic acid ($PS\text{-}SO_3H$)[17] are used to give better yields of α-amino phosphonates. However, many of these methods lack simplicity of one-pot, one-step synthesis, and use dialkylphosphite along with a desiccant and in some cases the Lewis acids are used in stoichiometric amounts. In view of this there is still a need to develop new catalytic procedures for the synthesis of α-amino phosphonates. Therefore we envisaged use of butyldimethyl(1-phenylethyl)ammonium bromide (**I**) as catalyst in one-pot, one step, three component reaction. The catalyst **I** is a stable quaternary ammonium salt which can be prepared easily in the laboratory. We have explored its utility as an efficient catalyst for oxidation, esterification, alkylation reactions,[18] and Biginelli's cyclocondensation reaction.[19]



I

In the present paper, we wish to report the use of **I** as a catalyst for the synthesis of α-amino phosphonates (Scheme 1). The three-component reaction is performed under relatively simple reaction conditions by heating together an aldehyde (**1**), aromatic amine (**2**), trimethylphosphite (**3**) in the ratio of 1.2:1:1 and the catalyst (0.35–0.5 mol %) in refluxing dichloromethane



1 **2** **3** **4 a – o**

Scheme 1.

to afford the α-amino phosphonates (**4a**–**4o**) in high yields (>81%) and in shorter reaction time (2.5–3.5 h).[20] The results obtained are summarized in Table **1**. The generality of this reaction is further extended to ketones and secondary amines. Ketones such as methy lisobutyl ketone and cyclohexanone reacted with aniline to afford dimethyl (1-anilino-1,3-dimethylbutyl)-phosphonate and dimethyl (1-anilinocyclohexyl)phosphonate in 75 and 88% yield, respectively. Benzaldehyde reacted with secondary amines such as piperidine and pyrrolidine to afford dimethyl phenyl(piperidino)methylphosphonate and dimethyl phenyl(pyrrolidin-1-yl)methylphosphonate in 76 and 77% yield, respectively. These results indicate the scope and versatility of the reaction of various aldehydes or ketones with aromatic as well as secondary amines. Catalysts like tetrabutylammonium bromide (TBAB, 0.65 mol %) gave lower yield of product **4a** (48%) in comparison to **I** under similar reaction conditions (Table 1).

The compounds **4j**, **4k**, **4l**, **4m** are synthesized for the first time and their structures have been unequivocally assigned by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic data. It is interesting to note that a doublet at δ 4.68–4.88 ppm in all these compounds with a coupling constant of 25 Hz due to $^2J_{H,P}$ coupling is assignable to proton α to phosphonate moiety and it is diagnostic for α-amino phosphonates.

The reaction is presumed to proceed through the hydrolysis of trimethyl phosphite by water generated during imine formation to yield dimethyl phosphite, which in turn react with imines to form α-amino phoshonates.

Table 1. Butyldimethyl(1-phenylethyl)ammonium bromide (**I**) catalyzed formation of α-amino phosphonates

Product[a]	R	R′	Time/h	Yield/%[b]
4a	C_6H_5	C_6H_5	2.5	89
4b	4-ClC_6H_4	C_6H_5	2.5	91
4c	4-$CH_3C_6H_4$	C_6H_5	3.0	92
4d	4-HOC_6H_4	C_6H_5	2.5	87
4e	4-$O_2NC_6H_4$	C_6H_5	2.5	90
4f	2-ClC_6H_4	C_6H_5	2.5	85
4g	2-HOC_6H_4	C_6H_5	3.0	87
4h	3-BrC_6H_4	C_6H_5	3.5	85
4i	C_6H_5	4-$CH_3OC_6H_4$	3.0	85
4j	C_6H_5	2-HOC_6H_4	3.5	87
4k	C_6H_5	4-FC_6H_4	3.0	87
4l	3-HO,4-$CH_3OC_6H_4$	C_6H_5	3.0	86
4m	C_6H_5	3-$O_2NC_6H_4$	3.0	89
4n	CH_3-$(CH_2)_4$	C_6H_5	3.5	82
4o	CH_3-$(CH_2)_8$	C_6H_5	3.5	81

[a]All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy, [b]Isolated and unoptimised yields.

Table 2. Effect of solvents on the synthesis of **4a**

Entry	Solvent[a]	Catalyst/mol %	Yield/%
1	Toluene	0.35	37
2	THF	0.35	74
3	Acetonitrile	0.35	68
4	Dichloromethane	0.35	89
5	Dichloromethane[b]	none	trace

[a]Reflux temperature for 3.5 h.; [b]Reflux for 10 h.

The effect of solvent on the synthesis **4a** is studied in different organic solvents and the results are summarized in Table 2. Dichloromethane was found to be the solvent of choice for carrying out the three-component reaction.

In summary the results reveal that the catalyst is effective in catalytic amount to synthesize α-amino phosphonates in high yield without using any desiccant. Moreover, the catalyst can be prepared in the laboratory and insensitive to moisture unlike the conventional Lewis acid catalysts.

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20 General procedure for the synthesis of α-amino phosphonates **4**: A mixture containing an aldehyde (12 mmol), amine (10 mmol), trimethyl phosphite (10 mmole) and quaternary ammonium bromide salt (0.35 mol %) in dichloromethane (15 mL) was refluxed for appropriate time as mentioned in Table 1. After completion of the reaction, as indicated by TLC, the reaction mixture was washed with water (2×15 mL), dried over Na_2SO_4, concentrated under vacuum and the crude mixture was purified by column chromatography on silica gel (Hexane: EtOAc 8:2) to afford pure product. Spectroscopic data: Dimethyl [(2-hydoxyphenyl)amino]-(phenyl)methylphosphonate (**4j**): mp. 120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.43 (d, $J = 10.57$ Hz, 3H, $-OCH_3$), 3.90 (d, $J = 10.48$ Hz, 3H, $-OCH_3$), 4.89 (d, $J = 25.8$ Hz, 1H, –CH), 5.7 (brs, 1H, –NH, D_2O exchangeable), 6.49–6.52 (m, 2H, Ar), 6.60 (t, $J = 7.5$ Hz, 1H, Ar), 6.75 (d, $J = 8.8$ Hz, 1H, Ar), 7.09–7.1 (m, 3H, Ar), 7.39 (d, $J = 7.8$ Hz, 2H, Ar), 9.2 (brs, 1H, –OH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.97, 54.53, 56.68, 111.91, 114.36, 118.36, 119.88, 127.89, 127.96, 128.57, 134.59, 134.80, 135.34, 145.11. FABMS: m/z (%) 307 (18) (M^+), 198 (100), 154 (8), 77 (10). IR (KBr) $\nu = 3275$, 2985, 2140, 1275, 1210, 1040 cm^{-1}. Dimethyl [(4-Fluorophenyl)-amino](phenyl)methylphosphonate (**4k**): mp. 82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.41 (d, $J = 10.58$ Hz, 3H, $-OCH_3$), 3.78 (d, $J = 10.54$ Hz, 3H, $-OCH_3$), 4.68 (d, $J = 24.31$ Hz, 1H, –CH), 5.26 (brs, 1H, NH, D_2O exchangeable), 6.49–6.52 (m, 2H, Ar), 6.76 (t, $J = 7.8$ Hz, 2H, Ar), 7.24–7.36 (m, 3H, Ar), 7.44 (d, $J = 7.5$ Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 54.01, 58.58, 56.73, 114.62, 115.01, 115.36, 115.44, 115.55, 127.72, 127.95, 128.57, 135.22, 142.23, 155.27, 157.15; FAB MS: m/z (%) : 309 (20), (M^+), 200 (100), 77 (4), 57 (3); IR (KBr) $\nu = 3320$, 2980, 1520, 1480, 1230, 1020, 825 cm^{-1}.

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