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(Bromodimethyl)sulfonium bromide: an inexpensive reagent for the solvent-free, one-pot synthesis of α-aminophosphonates☆

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Abstract—A novel solvent-free, one-pot synthesis of α-aminophosphonates in the presence of catalytic (bromodimethyl)sulfonium bromide at room temperature in high yields is reported.

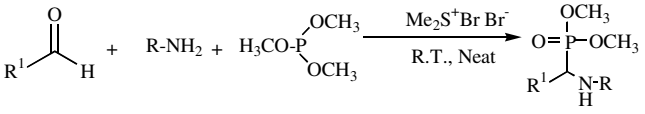
Phosphonate-containing molecules are biologically potent. Their diverse applications include inhibitors of synthase,[1] HIV protease,[2] renin,[3] and PTPases,[4,6] and as antibiotics,[5] enzyme inhibitors,[6] herbicides[7] and as surrogates of α-amino carboxylic acids.[8] α-Aminophosphonates have attracted attention as substrates in the synthesis of phosphonopeptides.[9] As a result, a variety of synthetic approaches has been developed for the synthesis of α-aminophosphonates, for example the Kabachnik–Fields[10] synthesis in which the key step is nucleophilic base- or acid- catalysed condensation of an amine with a carbonyl compound followed by the addition of phosphite to the resulting imine. Lewis acids[11,12] including lanthanide triflates[12c] are known to catalyse these reactions. However, many of these procedures require expensive reagents in stoichiometric amounts, long reaction times and deliver low yields. Some of these reactions cannot be carried out in one step with a carbonyl compound, an amine and a dialkylphosphite because the amine and water present during imine formation can decompose or deactivate the Lewis acid.[12a]

Hence, there is a need to develop a convenient, environmentally benign and practicably feasible method for the synthesis of α-aminophosphonates.

We report for the first time, a simple, one-pot, practical protocol for the synthesis of α-aminophosphonates using (bromodimethyl)sulfonium bromide[13] under solvent-free conditions.

The reaction of aldehyde, amine and trimethylphosphite in the presence of 10 mol % of (bromodimethyl)sulfonium bromide at room temperature resulted almost instantaneously in the formation of α-aminophosphonates in excellent yields (Scheme 1). In all cases, and with a variety of substrates, the reaction proceeded smoothly at ambient temperature affording high yields of the desired products within 15–30 min (Table 1).[14] The reaction conditions are very mild and the α-aminophosphonates were formed without any undesired by-products. The simplicity and mild reaction conditions make it a viable method for α,β-unsaturated aldehydes. Another feature of this method is the survival of olefin, ether, hydroxy and halide groups and no bromination of aromatic rings was observed. Compared to other acid catalysts such as $SnCl_2$, $ZrCl_4$,[15] $AlCl_3$,[16] triflates,[12c] $InCl_3$,[12b] etc., (bromodimethyl)sulfonium bromide was found to be more effective in terms of environmental compatibility, yields, simple work-up and a short reaction time.

In summary we have developed a novel efficient solvent-free protocol for the synthesis of α-aminophosphonates using catalytic (bromodimethyl)sulfonium bromide. The



Scheme 1.

Keywords: α-Aminophosphonates; (Bromodimethyl)sulfonium; Bromide; Imine.

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Table 1.

Product	Amines	Aldehyde	Time (min)	Yield (%)	Mp (°C)
4a	$C_6H_5NH_2$	4-$MeOC_6H_4$	15	95	123
4b	$C_6H_5NH_2$	4-$CH_3C_6H_4$	15	90	114
4c	$C_6H_5NH_2$	3-$PhOC_6H_4$	25	87	125
4d	$C_6H_5NH_2$	2,5-$(MeO)_2C_6H_3$	20	89	130
4e	$C_6H_5NH_2$	3,4,5-$(MeO)_3C_6H_2$	25	89	138
4f	$C_6H_5CH_2NH_2$	3,4,5-$(MeO)_3C_6H_2$	20	89	220
4g	$C_6H_5CH_2NH_2$	4-F-2-$CF_3C_6H_3$	25	88	242
4h	4-$FC_6H_4NH_2$	4-$CH_3C_6H_4$	20	90	110
4i	4-$FC_6H_4NH_2$	4-$MeOC_6H_4$	15	92	125
4j	4-$FC_6H_4NH_2$	4-F-2-$CF_3C_6H_3$	20	90	138
4k	4-$FC_6H_4NH_2$	4-$NO_2C_6H_4$	20	89	135
4l	4-$FC_6H_4NH_2$	4-FC_6H_4	20	91	127
4m	4-$FC_6H_4NH_2$	$C_6H_4CH{=}CH$	25	91	192
4n	4-$FC_6H_4NH_2$	2,5-$(MeO)_2C_6H_3$	20	92	148

method is effective for aromatic as well as α,β-unsaturated aldehydes and provides excellent yields of the product in a very short time, which makes it a novel, environmentally friendly and economically viable process for the synthesis of α-aminophosphonates.

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14. Typical experimental procedure: The amine (5 mmol) and aldehyde (5 mmol) were stirred for a few minutes at room temperature and then trimethyl phosphite (5 mmol) and (bromodimethyl)sulfonium bromide (10 mol %) were added and the mixture stirred for the appropriate time (see Table 1). After completion of the reaction, as indicated by TLC, the mixture was quenched with water (10 mL) and extracted with ethyl acetate to give after concentration the crude product, which was subjected to flash chromatography (hexane–ethyl acetate), 8:2 to afford the pure α-aminophosphonate.
All products gave satisfactory spectral data in accord with the assigned structures.
Data for **4g** as an example, ^{1}H NMR (400 MHz) ($CDCl_3$): 3.55 (3H, d, J = 10.98 Hz OCH_3), 3.62 (3H, d, J = 10.98 Hz, OCH_3), 3.75 (3H, s, OCH_3), 4.75 (1H, d, J = 23.42 Hz, CH), 5.78 (1H, br, NH), 6.60 (2H, d, J = 8.75 Hz, Ar–H), 6.75 (2H, d, J = 8.75 Hz, Ar–H), 6.90 (2H, d, J = 8.75 Hz, Ar–H), 7.30 (2H, d, J = 8.75 Hz, Ar–H). Anal. Calcd For $C_{16}H_{19}FNO_4P$: C, 56.64; H, 5.60; N, 4.12%. Found: C, 56.44; H, 5.88; N, 4.18%.
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