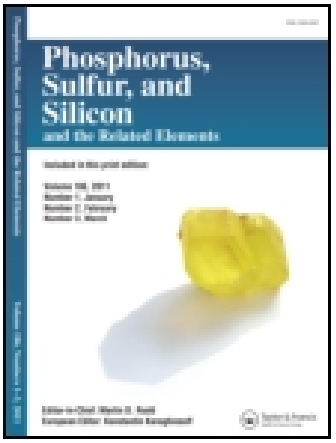

Phosphorus, Sulfur, and Silicon and the Related Elements

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A Novel and Efficient Synthesis of α-Aminophosphonates by Use of Triphenyl Phosphite in Acetic Acid Media

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A NOVEL AND EFFICIENT SYNTHESIS OF α-AMINOPHOSPHONATES BY USE OF TRIPHENYL PHOSPHITE IN ACETIC ACID MEDIA

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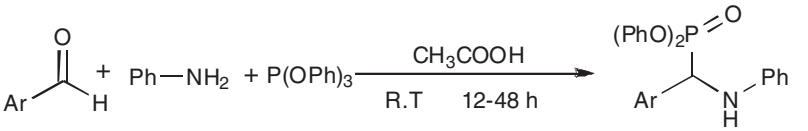
GRAPHICAL ABSTRACT



Abstract *For the first time, α-aminophosphonates were obtained by a simple and efficient one-pot method from the reaction between aldehyde, aniline, and triphenyl phosphite in the presence of acetic acid as a catalyst and solvent at room temperature.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Acetic acid; α-aminophosphonates; multicomponent reaction; triphenyl phosphite

INTRODUCTION

In recent years, there has been increasing interest in the synthesis of organophosphorus compounds. This is due to the value of such compounds that have biological effects and medicinal importance (enzyme inhibitors,[1] HIV protease,[2] antibiotics,[3] herbicides, fungicides, insecticides,[4] plant growth regulators,[5] and antithrombotic agents,[6] as well as peptidases and proteases).[7] Thus a variety of synthetic approaches for the synthesis of α-aminophosphonates is desirable. Among the available methods, the nucleophilic addition

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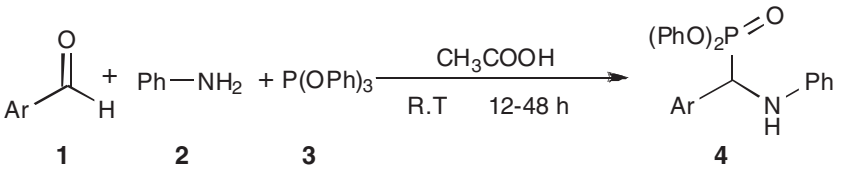

Figure 1 Synthesis of α-aminophosphonates.

of phosphites to imines is the most convenient and is usually activated by Lewis acids including lantanide triflate,[8] samarium diiodide,[9] $InCl_3$,[10] $TaCl_5$–SiO_2,[11] bromodimethylsulfonium bromide,[12] $LiClO_4$,[13] montmorillonite KSF,[14] $ZrCl_4$,[15] alumina-supported reagents as catalysts,[16] Amberlite-IR 120,[17] $H_3PW_{12}O_{40}$,[18] oxalic acid,[19] and TiO_2,[20] and generally dialkyl or trialkyl phosphites were used as phosphorus reagents. However, there is no report for the synthesis of α-aminophosphonates using triaryl phosphite as a reagent. We now describe a mild and efficient protocol for the synthesis of α-aminophosphonates using triphenyl phosphite in acetic acid as solvent and catalyst at room temperature (Figure 1).

RESULTS AND DISCUSSION

In the current work, initially benzaldehyde was used to react with aniline and triphenyl phosphite in the presence of acetic acid as both solvent and catalyst at room temperature to give the corresponding α-aminophosphonate in 98% yield.

In addition, several aldehydes were employed in a series of experiments for generation of the other corresponding α-aminophosphonates in high to excellent yields. The results are summarized in Table 1.

The structures of compounds 4a–p were deduced from IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and mass spectra, and elemental analyses. Compounds 4a–p are chiral, but racemic mixtures were obtained because both the reactants and the reaction medium were achiral. In

Table 1 Preparation of α-aminophosphonates

Entry	Ar	Product	Yield[a] (%)	Mp (°C)
1	Phenyl	**4a**	98	134–136
2	2-Nitrophenyl	**4b**	82	137–139
3	3-Nitrophenyl	**4c**	90	128–129
4	4-Nitrophenyl	**4d**	85	147–149
5	3-Chlorophenyl	**4e**	80	126–128
6	4-Chlorophenyl	**4f**	83	130–132
7	2,4-Dichlorophenyl	**4g**	88	136–138
8	2,6-Dichlorophenyl	**4h**	80	123–125
9	2-Fluorophenyl	**4i**	85	117–119
10	3-Fluorophenyl	**4j**	83	119–121
11	4-Fluorophenyl	**4k**	91	103–105
12	2,3-Dimethoxyphenyl	**4l**	65	110–112
13	2,5-Dimethoxyphenyl	**4m**	80	115–117
14	2-Methylphenyl	**4n**	84	114–116
15	3-Methylphenyl	**4o**	80	125–127
16	4-Methylphenyl	**4p**	85	124–126

[a]Yields refer to the pure isolated products.

summary, we have efficiently prepared novel α-aminophosphonates by a one-pot reaction between triphenyl phosphite, various aromatic aldehydes, and aniline in the presence of acetic acid at room temperature.

EXPERIMENTAL

Melting points and IR spectra were measured on an Electro thermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured on a Bruker DRX-400 Avance spectrometer with $CDCl_3$ as solvent. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on an Agilent Technology (HP) spectrometer operating at an ionization potential of 70 eV.

Synthesis of α-Aminophosphonates: General Procedure

A mixture of aromatic aldehyde (1 mmol), aniline (1 mmol), and triphenyl phosphite (1 mmol) in acetic acid (5 mL) was stirred at room temperature for the appropriate time (12–48 h). After completion of the reaction (as indicated by TLC), the solution was filtered, and the solid phase (product) was washed with water to afford pure α-aminophosphonates. In the case that the α-aminophosphonate was soluble in acetic acid, water was added to the solution and the mixture was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the generated precipitate was washed with cold diethyl ether to afford pure α-aminophosphonates.

Complete physical and spectroscopic data for compounds 4a–p can be found online in the Supplemental Materials.

Selected Data for Compound 4o

White crystals, mp 125–127°C. IR (KBr) (υ_{max}, cm^{-1}): 3342 (NH). ^{1}H NMR (400 MHz): δ 2.35 (3H, s, CH_3), 4.79 (1H, bs, NH), 5.17 (1H, d, $^{2}J_{HP}$ = 24.6 Hz, CHP), 6.71–7.41 (19H, m, aromatic). ^{13}C NMR (100.6 MHz) δ: 21.46 (s, CH_3), 55.96 (d, $^{1}J_{CP}$ = 153.9 Hz, CHP), 114.20 (s, 2 C_{ortho}, NHPh), 118.95 (s, C_{para}, NHPh), 120.36, 120.75 (2d, $^{3}J_{CP}$ = 4.3 Hz, 4 C_{ortho}, 2 OPh), 125.24, 125.39 (2s, 2 C_{para}, 2 OPh), 125.41 (s, C4), 128.71 (d, $^{3}J_{CP}$ = 2.1 Hz, C6), 128.95 (d, $^{3}J_{CP}$ = 6.2 Hz, C2), 129.25 (s, C5), 129.29 (s, 2 C_{meta}, NHPh), 129.61, 129.76 (2s, 4 C_{meta}, 2 OPh), 134.40 (s, C3), 138.51 (d, $^{2}J_{CP}$ = 2.5 Hz, C1), 145.63 (d, $^{3}J_{CP}$ = 14.7 Hz, C_{ipso}, NHPh), 150.29, 150.40 (2d, $^{2}J_{CP}$ = 10.1 Hz, 2 C_{ipso}, 2 OPh). ^{31}P NMR (161.97 MHz) δ: 15.51. MS *m/z* (%): 429 (17) [M^+], 196 (100), 178 (15), 140 (20), 104 (34), 77 (42). Anal. Calcd for $C_{26}H_{24}NO_3P$: C, 72.72; H, 5.63; N, 3.26%. Found: C, 72.51; H, 5.70; N, 3.39%.

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