Lithium Perchlorate-Catalyzed Three-Component Coupling: A Facile and General Method for the Synthesis of α-Aminophosphonates under Solvent-Free Conditions

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Keywords: Lewis acids / Nucleophilic addition / Phosphonate / Solvent effects

A simple, efficient, and general method has been developed for the synthesis of α-aminophosphonates in the presence of solid lithium perchlorate under solvent-free conditions. Thus secondary and tertiary α-aminophosphonates were synthesized relatively quickly in good yields at room temperature.

Introduction

α-Aminophosphonates are an important class of compounds since they are considered as structural analogues of the corresponding α-amino acids. Their utilities as enzyme inhibitors, antibiotics, pharmacological agents and many other applications are well documented.[1] Thus, an efficient synthesis of these compounds has been of great interest in recent years. A number of the synthetic methods for α-aminophosphonates have been developed during the past two decades.[2] Nucleophilic addition of dimethylphosphite or trimethylphosphite to iminium salts or imines is the most convenient method for the preparation of these compounds. The imines are usually activated by Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3{\cdot}Et_2O$, $ZnCl_2$, $MgBr_2$,[3] and a combination of lanthanide triflate, magnesium sulfate,[4] $TaCl_5{\cdot}SiO_2$,[5] and indium(III) chloride.[6] Although, these approaches are satisfactory for a one-pot synthesis of α-aminophosphonate, the harsh reaction conditions, expensive reagents, and long reaction times limit the use of these methods.

Recently, concentrated solutions of lithium perchlorate in diethyl ether (LPDE) have been used in various organic transformations.[7,8] The LPDE solution is a convenient medium in which to carry out reactions under neutral conditions. Furthermore, the LPDE solution is found to retain its activity even in the presence of amines. Drying lithium perchlorate and preparation of its concentrated solution in diethyl ether (ca. 5.0 M; the solution is very hygroscopic) is one disadvantage for this medium. We have already reported the "in situ" preparation of iminium salts or imines in a concentrated solution of lithium perchlorate in diethyl ether (ca. 5.0 M) and their transformation to different organic compounds.[9] In these procedures, a solution of lithium perchlorate in diethyl ether (5.0 M; ca. 4 mL) was used for each transformation on a 2-mmol scale (ca. 2.1 g solid $LiClO_4$).

On the other hand, due to the current challenge for developing solvent-free and environmentally benign synthetic systems[10] and extending our interest in the applications of lithium perchlorate for various organic transformations,[11] we now describe a simple, general and efficient protocol for the synthesis of α-aminophosphonates (secondary and tertiary) using only solid $LiClO_4$, (ca. 0.4 g) under solvent free conditions.

Results and Discussion

The optimized reactant ratios were found to be 1.0 equiv. benzaldehyde, 1.1 equiv. primary amine, and 1.2 equiv. trimethylphosphite in the presence of 2.0 equiv. solid $LiClO_4$. The expected aminophosphonate was produced in 92 % yield after 40 min at room temperature without the use of any solvent (Scheme 1). To show the generality and scope of the lithium perchlorate promoted α-aminophosphonate synthesis, the reaction was examined with various structurally diverse aldehydes, ketones, and trimethylphosphite or triethylphosphite. The results are summarized in Table 1. These data clearly show that different aromatic aldehydes were successfully converted into the corresponding α-aminophosphonate in high yields at room temperature. The presence of electron-withdrawing or electron-donating substituents on the aromatic ring makes no difference to the course of the reaction. The reaction can also proceed with 2-methylpropanal (an enolizable aldehyde) and cyclohexanone. The reaction conditions are very mild, and α-aminophos-

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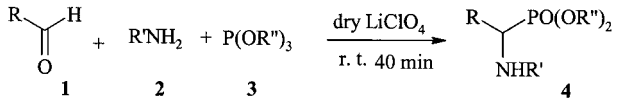
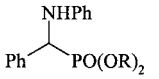
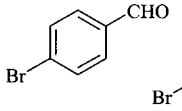
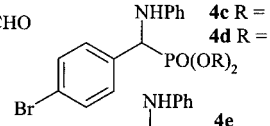
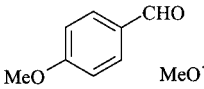
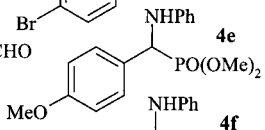
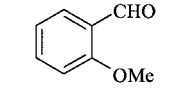
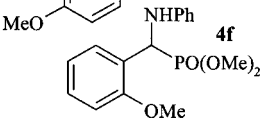
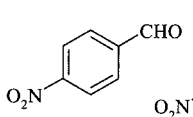
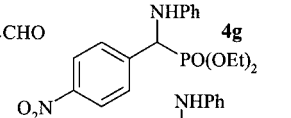
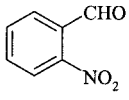
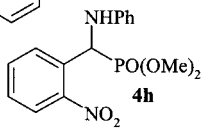
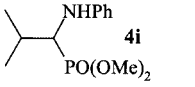
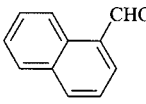
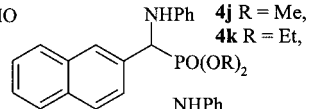
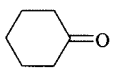
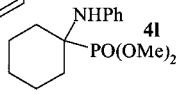
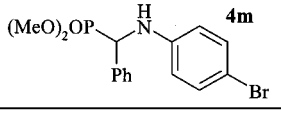
phonate is exclusively obtained without formation of any side products such as α-hydroxyphosphonate. Longer reaction times did not increase the yields of the reactions. In the absence of $LiClO_4$ only the starting materials were recovered.

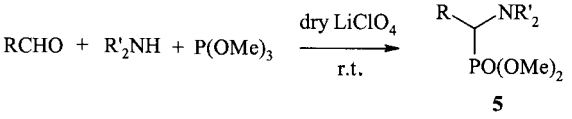


Scheme 1

Table 1. Solvent-free synthesis of α-aminophosphonates **4** mediated by dry lithium perchlorate (isolated yields are given)

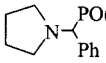
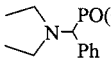
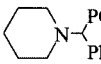
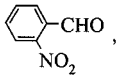
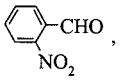
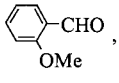
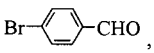
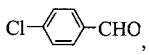
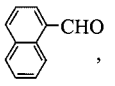
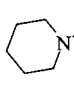
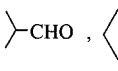
Entry	Starting material	Product	%Yield
1 2	PhCHO		**4a** R = Me, 92 **4b** R = Et, 88
3 4			**4c** R = Me, 86 **4d** R = Et, 85
5			**4e** 78
6			**4f** 88
7			**4g** 80
8			**4h** 84
9			**4i** 76
10 11			**4j** R = Me, 78 **4k** R = Et, 83
12			**4l** 76
13	PHCHO		**4m** 70

This protocol is also very efficient for the synthesis of tertiary α-aminophosphonates. The reaction of an aldehyde, a secondary amine and trimethylphosphite in the presence of two equivalents of solid lithium perchlorate at ambient temperatures resulted in the formation of tertiary α-aminophosphonate in good yields. The reaction proceeded smoothly and was completed within 20−45 min. Aliphatic aldehydes also afforded the corresponding phosphonate in relatively good yield (Scheme 2, Table 2).



Scheme 2

Table 2. Lithium perchlorate-mediated synthesis of α-aminophosphonates **5** under solvent-free conditions (isolated yields are given)

Entry	Starting materials	Product	%Yield
1 2	PhCHO, 		**5a** R= Me 90 **5b** R = Et 86
3	PhCHO, 		**5c** 78
4	PhCHO, 		**5d** 84
5	PhCHO, $Me_2NSi(Me_3)_2$		**5e** 82
6			**5f** 80
7			**5g** 82
8			**5h** 88
9			**5i** 83
10			**5j** 78
11			**5k** 80
12			**5l** 65

Furthermore, unsaturated aldehydes, such as cinnamaldehydes, gave the corresponding phosphonate without any polymerization under the above reaction conditions.

In all cases, α-hydroxyphosphonate (an adduct between the aldehydes and trimethylphosphite) was not obtained under these conditions, due to the rapid formation of iminium salts in the presence of $LiClO_4$.

In conclusion, anhydrous lithium perchlorate is found to be an efficient Lewis acid for promoting three-component coupling reactions of carbonyl compounds, amines and trialkylphosphite under solvent-free conditions. The simplicity, efficiency, mild reaction conditions, high yields, short reaction times, easy work-up, and the need for only a small amount of $LiClO_4$ make it the preferred procedure for the preparation of different kinds of α-aminophosphonate

under solvent-free conditions. Although $LiClO_4$ is relatively cheap in comparison with many other Lewis acids used for these transformations, due to the stability of $LiClO_4$ in water, it is possible to recover it by simple filtration and reactivate it by heating in vacuo at 160 °C.

Experimental Section

General: NMR spectra were recorded with a Bruker ACF 500. IR spectra were measured with a Perkin−Elmer 1600 FTIR spectrometer. Column chromatography was performed on silica gel, Merck grade 60. CH_2Cl_2 was distilled before use. All reactions were performed under argon. Anhydrous lithium perchlorate and other chemicals were purchased from Fluka or Merck. All compounds were characterized on the basis of spectroscopic data (IR, NMR, MS) and were compared with the literature.

General Procedure for the Preparation of the α-Aminophosphonate 4: The aldehyde (2 mmol), $LiClO_4$ (4 mmol, 0.42 g) and an amine (4.4 mmol) were placed in a 5 mL flask under argon and stirred at room temperature for 5 min. Trimethylphosphite or triethylphosphite (2.5 mmol) was added and the mixture was stirred at room temperature for about 20−45 min. Dichloromethane was added after the reaction was complete and the precipitated $LiClO_4$ was recovered by filtration. The filtrate was washed with water. The organic phase was separated, dried with $MgSO_4$, and the solvent removed using a rotary evaporator. Further purification was carried out by column chromatography on basic alumina eluting with petroleum ether/ethyl acetate, if necessary.

Dimethyl [Phenyl(phenylamino)methyl]phosphonate (4a):[5,9a] IR (KBr): $\tilde{\nu}$ = 3305 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 500 MHz): δ = 3.48 (d, J = 6.1 Hz, 3 H), 3.78 (d, J = 10.7 Hz, 3 H), 4.50 (br. s, 1 H, NH), 5.12 (dd, J = 24.3, 10.2 Hz, 1 H), 6.61−6.72 (m, 3 H), 7.28−7.50 (m, 7 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 53.68 (d, $^2J_{P,C}$ = 6.6 Hz), 54.2 (d, $^2J_{P,C}$ = 7.6 Hz), 55.6 (d, $^1J_{P,C}$ = 150.6 Hz), 114.2, 119.2, 123.4, 129.0, 129.8 (d, $J_{P,C}$ = 4.5 Hz), 130.2, 135.9 (d, $J_{P,C}$ = 2.5 Hz), 146.4 (d, $J_{P,C}$ = 14.7 Hz) ppm.

Dimethyl [(4-Bromophenyl)(phenylamino)methyl]phosphonate (4c):[6,9a] IR (KBr): $\tilde{\nu}$ = 3316 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 500 MHz): δ = 3.55 (d, J = 10.6 Hz, 3 H), 3.78 (d, J = 10.7 Hz, 3 H), 4.83 (d, J = 24.6 Hz, 1 H), 4.85 (br. s, 1 H, NH), 6.62−7.46 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 53.70 (d, $^2J_{P,C}$ = 6.6 Hz), 54.2 (d, $^2J_{P,C}$ = 6.0 Hz) 55.02 (d, $^1J_{P,C}$ = 154 Hz), 114.0, 119.1, 129.0, 129.6 (d, $J_{P,C}$ = 8.1), 129.9, 130.2, 134.2 (d, $J_{P,C}$ = 3.9 Hz), 146.4 (d, $J_{P,C}$ = 15.0 Hz) ppm.

Dimethyl [(2-Nitrophenyl)(phenylamino)methyl]phosphonate (4h):[6,9a] IR (KBr): $\tilde{\nu}$ = 3330 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 500 MHz): δ = 3.64 (d, J = 10.7 Hz, 3 H), 3.83 (3 H, J = 10.7 Hz), 4.99 (d, J = 25.0 Hz, 1 H), 5.12 (br. s, 1 H, NH), 6.62−6.73 (m, 3 H), 7.11−7.13 (m, 2 H), 7.88−8.40 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 54.1 (d, $^2J_{P,C}$ = 6.8 Hz), 54.6 (d, $^2J_{P,C}$ = 5.9 Hz), 54.8 (d, $^1J_{P,C}$ = 155.0 Hz), 114.2 (d, $J_{P,C}$ = 11.2 Hz), 119.3 (d, $J_{P,C}$ = 11.4 Hz), 123.2, 129.7 (d, $J_{P,C}$ = 4.5 Hz), 130.0 (d, $J_{P,C}$ = 11.2 Hz), 134.3 (d, $J_{P,C}$ = 3.9 Hz), 139.9, 145.9 (d, $J_{P,C}$ = 13.8 Hz), 148.9 (d, $J_{P,C}$ = 2.5 Hz) ppm.

Diethyl [(1-Naphthyl)(phenylamino)methyl]phosphonate (4k):[3d] IR (KBr): $\tilde{\nu}$ = 3320 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.77 (t, J = 6.9 Hz, 3 H), 1.37 (t, J = 7.0 Hz, 3 H), 3.26 (m, 1 H), 3.79 (m, 1 H), 4.26 (m, 2 H), 5.01 (br. s, 1 H, NH), 5.75 (d, J = 24.1 Hz, 1 H), 6.63−6.70 (m, 3 H), 7.06−7.09 (m, 2 H), 7.45−7.93 (m, 6 H), 8.33−8.35 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 16.3 (d, $^3J_{P,C}$ = 2.3 Hz), 17.0 (d, $^3J_{P,C}$ = 5.8 Hz), 51.8 (d, $^1J_{P,C}$ = 151 Hz), 63.6 (d, $^2J_{P,C}$ = 6.5 Hz), 63.9 (d, $^2J_{P,C}$ = 5.8 Hz), 113.9, 114.1, 118.6, 123.4 (d, $J_{P,C}$ = 6.6 Hz), 126.2, 126.2, 126.7, 128.8, 129.0, 129.4, 129.6 (d, $J_{P,C}$ = 10.6 Hz), 132.0 (d, $J_{P,C}$ = 5.0) 134.3, 146.6 (d, $J_{P,C}$ = 14.5 Hz) ppm.

Dimethyl [1-(Phenylamino)cyclohexyl]phosphonate (4l):[6,9a] IR (KBr), 3320 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 500 MHz), δ_H = 1.13−2.13 (m, 10 H), 3.45 (br. s, NH), 3.54 (d, J = 10.2 Hz, 6 H), 6.66−7.05 (m, 5 H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ_C = 20.2 (d, $J_{P,C}$ = 10.5 Hz), 25.6, 30.5, 53.3 (d, $J_{P,C}$ = 7.7 Hz), 58.1 (d, $J_{P,C}$ = 159.0 Hz), 118.6 (d, $J_{P,C}$ = 10.5 Hz), 119.6 (d, $J_{P,C}$ = 13.2 Hz), 129.0 (d, $J_{P,C}$ = 6.7 Hz), 146.1.

General Procedure for the Preparation of α-Aminophosphonate (5): The aldehyde (2 mmol), $LiClO_4$ (4 mmol, 0.42 g) and an amine (4.5 mmol) were placed in a 5 mL flask under argon and stirred at room temperature for 5 min. Trimethylphosphite or triethylphosphite (2.5 mmol) was added and the mixture stirred at room temperature for about 20−45 min. Dichloromethane was added after the reaction was completed. $LiClO_4$ was precipitated out and recovered by filtration. The filtrate was washed with water. The organic phase was separated, dried with $MgSO_4$, and the solvent removed using a rotary evaporator.

Dimethyl [Phenyl(pyrrolidino)methyl]phosphonate (5a):[3d] ^1H NMR (500 MHz, $CDCl_3$): δ = 1.66 (m, 4 H), 2.55 (m, 4 H), 3.34 (d, J = 10.4 Hz, 3 H), 3.75 (d, J = 10.5 Hz, 3 H), 3.92 (d, J = 17.2 Hz, 1 H), 7.22−7.24 (m, 5 H) ppm.

Dimethyl [(Diethylamino)(phenyl)methyl]phosphonate (5c):[3d] ^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.2 Hz, 6 H), 2.22 (m, 2 H), 2.89 (m, 2 H), 3.37 (d, J = 10.5 Hz, 3 H), 3.77 (d, J = 10.4 Hz 3 H), 4.00 (d, J = 24.9 Hz, 1 H), 7.16−7.38 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.5 (CH_3), 45.1 (d, J = 8.25 Hz, CH_2), 52.8 (d, J = 6.8 Hz, CH_3), 54.5 (d, J = 7.2 Hz, CH_3), 61.9 (d, J = 163.3 Hz, CH), 128.2 (CH), 128.4 (CH), 130.7 (d, J = 8.8 Hz, CH), 133.2 (d, J = 4.7 Hz, C) ppm. IR (KBr): $\tilde{\nu}$ = 1452 cm^{-1}.

Dimethyl [(Dimethylamino)(phenyl)methyl]phosphonate (5e):[12] ^1H NMR (500 MHz, $CDCl_3$): δ = 2.13 (s, 6 H), 3.20 (d, J = 10.5 Hz, 3 H), 3.59 (d, J = 10.7 Hz, 3 H), 3.61 (d, J = 20.8 Hz, 1 H), 7.12−7.26 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 43.8 (d, J = 9.3 Hz), 53.2 (m, CH_3), 68.1 (d, J = 160.4 Hz, CH), 128.4 (CH), 130.6 (CH), 130.7 (CH), 132.2 (C) ppm.

Dimethyl [1-Phenyl(piperidino)methyl]phosphonate (5d):[12] ^1H NMR (500 MHz, $CDCl_3$): δ = 1.38 (m, 2 H), 1.41−1.54 (m, 4 H), 2.38 (m, 2 H), 2.86 (m, 2 H), 3.43 (d, J = 10.5 Hz, 3 H), 3.9 (d, J = 10.3 Hz, 3 H), 4.08 (d, J = 23.8 Hz, 1 H), 7.36−7.94 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.3 (CH_2), 26.7 (CH_2), 31.2 (CH_2), 52.9 (m), 68.4 (d, J = 161.8 Hz, CH), 128 (d, J = 11.6 Hz,), 130.1 (d, J = 9.1 Hz), 132 (d, J = 2.7 Hz) ppm.

Dimethyl (2-Methoxyphenyl)(pyrrolidino)methyl]phosphonate (5h):[12] ^1H NMR (500 MHz, $CDCl_3$): δ = 1.68 (m, 4 H), 2.64 (m, 4 H), 3.46 (d, J = 10.4 Hz, 3 H), 3.75 (d, J = 10.5 Hz, 3 H), 3.85 (s, 3 H), 4.65 (d, J = 18.0 Hz, 1 H), 6.89−7.74 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.5 (CH_2), 52.6 (CH_2), 52.7 (d, J = 9.1 Hz, CH_3), 53.4 (d, J = 6.6 Hz, CH_3), 55.9 (CH_3), 57.2 (d, J = 145.1 Hz, CH), 111.0 (CH), 120.7 (CH), 122.9 (C), 129.3 (CH), 131.5 (d, J = 4.1 Hz, CH), 157.8 (d, J = 9.2 Hz, C) ppm. IR (KBr): $\tilde{\nu}$ = 1490 cm^{-1}.

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