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Silica supported polyphosphoric acid (PPA-SiO₂): an efficient and reusable heterogeneous catalyst for the one-pot synthesis of α -amino phosphonates

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An efficient green protocol is described for the preparation of α -amino phosphonates, employing a one-pot three-component condensation reaction between aldehydes, amines, and trialkyl phosphites in the presence of PPA-SiO₂ under solvent-free conditions at 80 °C. The present procedure offer advantages such as high to excellent yields, short reaction time, inexpensiveness, recovery, and reusability of catalyst.

Key Words: α -Amino phosphonates; PPA-SiO₂; heterogeneous catalyst; trialkyl phosphites

Introduction

The development of simple synthesis routes for widely used organic compounds using readily available reagents is one of the most important tasks in organic chemistry.¹ Organophosphorus compounds are synthetic reagents of interest, at least because of their value for a variety of industrial, biological, and chemical synthetic uses.^{2,3} α -Amino phosphonates have been reported as enzyme inhibitors,⁴ HIV protease,⁵ antibiotics,⁶ and antimicrobial agents,⁷ peptide mimics,⁸ anti-thrombotics,⁹ herbicides, insecticides, and fungicides.¹⁰ As a result, a large number of methods have appeared describing novel synthesis for α -amino phosphonates by nucleophilic addition

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reactions between phosphites and imines.^{13–15} However, these reactions cannot proceed in a one-pot reaction because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids.¹⁶

To overcome some of these problems, recently one-pot three-component procedures have been developed. This conversion can proceed using lanthanide triflate,¹⁷ InCl_3 ,¹⁸ scandium tris(dodecyl sulfate),¹⁹ $\text{TaCl}_5\text{-SiO}_2$,²⁰ lithium perchlorate,²¹ $\text{CF}_3\text{CO}_2\text{H}$,²² metal triflates $[\text{M}(\text{OTf})_n]$, $\text{M} = \text{Li, Mg, Al, Cu, Ce}$,²³ $\text{In}(\text{OTf})_3$,²⁴ magnesium perchlorate,²⁵ PhNMe_3Cl ,²⁶ $\text{H}_3\text{PW}_{12}\text{O}_{40}$,²⁷ Amberlite-IR 120,²⁸ Amberlyst-15,²⁹ sulfamic acid,³⁰ TiO_2 ,³¹ oxalic acid,³² microwave assisted,³³ trifluoroethanol,³⁴ AlCl_3 ,³⁵ and (bromodimethyl) sulfonium bromide.³⁶ However, most of these methods displayed drawbacks such as environmental pollution caused by utilization of organic solvents, unsatisfactory yields, long reaction times, drastic reaction conditions, and the help of microwave irradiation. Furthermore, some of these catalysts are either expensive or difficult to prepare and cannot be recovered.

Recently, heterogeneous catalysts have attracted increasing interest due to economic and environmental considerations. One of these heterogeneous catalysts is silica supported polyphosphoric acid (PPA- SiO_2). PPA- SiO_2 was prepared from the reaction of silica gel with polyphosphoric acid.³⁷ PPA- SiO_2 has been explored as a powerful catalyst for various organic transformations under mild conditions.^{37–40} Herein we report a novel, simple, and efficient protocol for a one-pot three-component synthesis of α -amino phosphonates (Figure).

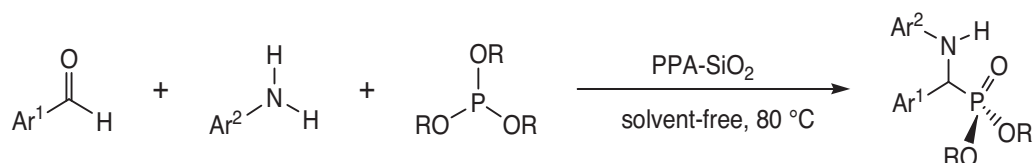


Figure. Synthesis of α -amino phosphonates.

Experimental

General procedure for preparation of α -amino phosphonates: The aldehyde (1 mmol), amine (1 mmol), and PPA- SiO_2 (0.05 g, 0.025 mmol H^+) were stirred for a few minutes. Then trimethyl/triethyl phosphite (1 mmol) was added. The mixture was stirred at 80 °C in an oil bath for the appropriate time (see Table 2). After completion of the reaction (followed by TLC), the reaction mixture was cooled and CH_2Cl_2 (10 mL) was added. The catalyst was separated by simple filtration and the filtrate was washed with H_2O (3×10 mL). Then the organic layer dried over anhydrous Na_2SO_4 and was evaporated. The crude product was purified by silica gel column chromatography with the mixture of n-hexane/EtOAc (7:3) as an eluent to provide pure α -amino phosphonates. Physical and chemical data of the new products are represented below:

Compound 11: White solid, mp 133-135 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 2.53$ (s, 3H), 3.41 (d, $J = 10.5$ Hz, 3H), 3.80 (d, $J = 10.5$ Hz, 3H), 4.60 (br, 1H), 5.06 (d, $J = 23.8$ Hz, 1H), 6.58 (d, $J = 8.5$ Hz, 2H), 6.72 (t, $J = 7.3$ Hz, 1H), 7.10-7.28 (m, 5H), 7.55 (d, $J = 2.7$ Hz, 1H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 19.68$, 51.89 (d, $J = 151.2$ Hz), 53.72 (d, $J = 6.9$ Hz), 53.85 (d, $J = 6.9$ Hz), 113.81, 118.69, 126.64 (d, $J = 2.9$ Hz), 127.21 (d, $J = 4.5$ Hz), 128.96, 129.25, 130.65 (d, $J = 2.5$ Hz), 133.68, 136.33 (d, $J = 6.7$ Hz), 145.79 (d, $J = 14.4$ Hz) ppm; $^{31}\text{P-NMR}$ (161 MHz, CDCl_3): $\delta = 25.86$ ppm; IR (KBr, cm^{-1}): 3314 (NH),

1234 (P=O), 1060, 1019 (P|O|Me); MS m/z (%): 305 (M^+ , 21), 196 (100), 194 (18), 109 (12), 104 (64), 91 (18), 77 (75); Anal. Calcd for $C_{16}H_{20}NO_3P$: C, 62.94; H, 6.60; N, 4.59. Found: C, 62.90; H, 6.74; N, 4.50.

Compound 12: Yellow solid, mp 92-94 °C. 1H -NMR (400 MHz, $CDCl_3$): δ = 3.66 (d, J = 10.7 Hz, 3H), 3.89 (d, J = 10.7 Hz, 3H), 5.20 (br, 1H), 5.61 (d, J = 27.1 Hz, 1H), 6.61-6.77 (m, 3H), 6.95-7.01 (m, 1H), 7.10-7.21 (m, 4H) ppm; ^{13}C -NMR (100 MHz, $CDCl_3$): δ = 51.75 (d, J = 152.5 Hz), 53.54 (d, J = 7.0 Hz), 54.28 (d, J = 7.0 Hz), 113.75, 115.50, 119.07, 122.97, 125.64, 129.35, 129.83 (d, J = 2.6 Hz), 129.93 (d, J = 2.6 Hz), 130.20, 145.77 (d, J = 14.5 Hz) ppm; ^{31}P -NMR (161 MHz, $CDCl_3$): δ = 23.00 ppm; IR (KBr, cm^{-1}): 3313 (NH), 1246 (P=O), 1056, 1033 (P|O|Me); MS m/z (%): 345 ($M+2$, 3), 343 (M^+ , 10), 234 (100), 198 (21), 109 (11), 107 (15), 93 (51), 77 (47); Anal. Calcd for $C_{15}H_{16}ClFNO_3P$: C, 52.42; H, 4.69; N, 4.08. Found: C, 52.62; H, 4.71; N, 4.19.

Compound 13: White solid, mp 146-148 °C. 1H -NMR (400 MHz, $CDCl_3$): δ = 3.48 (d, J = 10.4 Hz, 3H), 3.78 (s, 3H), 3.82 (d, J = 10.4 Hz, 3H), 3.92 (s, 3H), 4.42 (br, 1H), 5.30 (d, J = 24.2 Hz, 1H), 6.46-6.72 (m, 5H), 7.10-7.42 (m, 3H) ppm; ^{13}C -NMR (100 MHz, $CDCl_3$): δ = 47.42 (d, J = 155.9 Hz), 53.67 (d, J = 6.9 Hz), 53.81 (d, J = 6.9 Hz), 55.31, 55.84, 98.55 (d, J = 2.0 Hz), 104.93 (d, J = 2.5 Hz), 113.88, 116.21, 118.49, 129.08 (d, J = 4.7 Hz), 129.55, 145.87 (d, J = 14.7 Hz), 158.17 (d, J = 6.1 Hz), 160.63 (d, J = 2.6 Hz) ppm; ^{31}P -NMR (161 MHz, $CDCl_3$): δ = 26.21 ppm; IR (KBr, cm^{-1}): 3290 (NH), 1233 (P=O), 1050, 1027 (P|O|Me); MS m/z (%): 351 (M^+ , 24), 242 (100), 227 (10), 149 (48), 109 (21), 93 (30), 77 (20); Anal. Calcd for $C_{17}H_{22}NO_5P$: C, 58.18; H, 6.31; N, 3.99. Found: C, 58.28; H, 6.44; N, 3.87.

Results and discussion

Initially, we tried to optimize the amount of PPA-SiO₂ for the reaction between benzaldehyde, aniline, and trimethyl phosphite under solvent-free conditions at 80 °C (Table 1). As can be seen in Table 1, maximum yield was obtained with 0.05 g (0.025 mmol H⁺) of the catalyst.

Table 1. Optimization of the amount of PPA-SiO₂ for the reaction between benzaldehyde, aniline, and trimethyl phosphite under solvent-free conditions at 80 °C.

Entry	Catalyst (g)	Time (min)	Yield (%) ^a
1	0.01	80	81
2	0.02	65	89
3	0.03	45	94
4	0.05	35	97
5	0.1	10	96

^aIsolated yields.

Hence, several reactions between different aldehydes, amines, and trialkyl phosphites were examined in the presence of PPA-SiO₂ as a catalyst under solvent-free conditions at 80 °C. The results are summarized in Table 2.

Table 2. The synthesis of α -amino phosphonates catalyzed by PPA-SiO₂.

Entry	Ar ¹	Ar ²	R	Time (min)	Yield (%) ^a	Ref. ^b
1	Ph	Ph	Me	35	97	25
2	Ph	Ph	Et	120	95	31
3	3-NO ₂ -C ₆ H ₄	Ph	Et	80	94	28
4	4-NO ₂ -C ₆ H ₄	Ph	Me	15	95	26
5	4-NO ₂ -C ₆ H ₄	Ph	Et	80	91	28
6	4-Cl-C ₆ H ₄	Ph	Me	20	95	32
7	4-Cl-C ₆ H ₄	Ph	Et	100	92	31
8	4-NMe ₂ -C ₆ H ₄	Ph	Me	20	95	29
9	4-F-C ₆ H ₄	Ph	Et	90	92	28
10	4-Me-C ₆ H ₄	Ph	Et	180	95	31
11	2-Me-C ₆ H ₄	Ph	Me	45	96	–
12	2-Cl-6-F-C ₆ H ₃	Ph	Me	10	98	–
13	2,4-di-OMe-C ₆ H ₃	Ph	Me	35	98	–
14	2,5-di-OMe-C ₆ H ₃	Ph	Me	35	98	36
15	3-NO ₂ -C ₆ H ₄	3-NO ₂ -C ₆ H ₄	Et	115	92	24
16	4-NO ₂ -C ₆ H ₄	4-NO ₂ -C ₆ H ₄	Me	25	94	25
17	Ph	4-OMe-C ₆ H ₄	Et	100	95	20
18	Ph	4-Cl-C ₆ H ₄	Me	35	94	33
19	Ph	4-Me-C ₆ H ₄	Me	30	96	33
20	4-OMe-C ₆ H ₄	4-F-C ₆ H ₄	Et	130	91	31
21	4-OMe-C ₆ H ₄	4-OMe-C ₆ H ₄	Me	40	93	25
22	4-NO ₂ -C ₆ H ₄	4-OMe-C ₆ H ₄	Me	15	95	33

^a Yields refer to the pure isolated products.

^b All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.

Each benzaldehyde with electron-deficient or electron-releasing groups reacts efficiently with aniline or substituted aniline to give the corresponding α -amino phosphonates in high to excellent yields. Sensitive functionality groups such as NO₂, NMe₂, OMe, F, and Cl were unaffected during the reaction. In all cases the one-pot three-component reaction proceeded smoothly to yield the corresponding α -amino phosphonates exclusively without any undesired side products. Moreover, on the basis of experimental results, the rate of all reactions in the presence of trimethyl phosphite was increased in comparison with triethyl phosphite under constant conditions. The wide applicability of the present method is evident from the fact that it is tolerant towards various functional groups including alkoxy, halides, and nitro groups. We have also prepared 3 new analogues of these compounds in excellent yields (entries 11-13).

The reusability of the catalyst is an important factor from economical and environmental point of views and has attracted much attention in recent years. Thus, the reusability of PPA-SiO₂ was examined in the reaction between 2,4-dimethoxy benzaldehyde, aniline, and trimethyl phosphite under solvent-free conditions at

80 °C. As PPA-SiO₂ is a heterogeneous catalyst, it was separated and reused after being washed with methanol and drying at 100 °C for 30 min. The results showed that the catalyst can be used 5 times without loss of its activity (Table 3).

Table 3. Investigation of reusability of the catalyst in the reaction between 2,4-dimethoxy benzaldehyde, aniline, and trimethyl phosphite in the presence of PPA-SiO₂.

Run no.	Yield (%) ^a
1	98
2	96
3	92
4	90
5	86

^aIsolated yields

Conclusion

We have developed a novel and efficient method for the synthesis of α -amino phosphonates with the one-pot three-component reaction under thermal solvent-free conditions. The use of PPA-SiO₂ as an efficient, inexpensive, easy to handle, non-toxic, and reusable heterogeneous catalyst makes the present procedure eco-friendly and economically acceptable. In addition, the thermal solvent-free green procedure offers noteworthy advantages such as short reaction times, easy work-up, and high to excellent yields, which make this method a valid contribution to the existing methodologies.

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