$Al(H_2PO_4)_3$ as an Efficient and Reusable Catalyst for One-pot Three-component Synthesis of α-Amino Phosphonates under Solvent-free Conditions

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Synthesis of α-amino phosphonates is described under solvent-free conditions at 100 ℃ from reaction between aldehydes and amines in the presence of trialkyl phosphites using $Al(H_2PO_4)_3$ as an efficient and reusable heterogeneous catalyst. The advantages of this procedure are short reaction time, flexibility and having high to excellent yields.

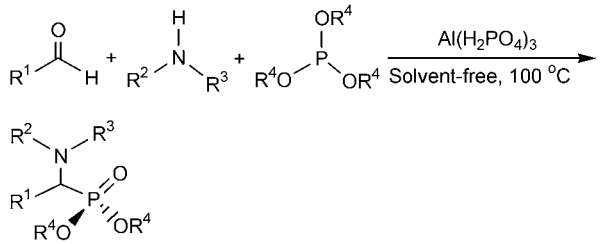
Keywords α-amino phosphonate, $Al(H_2PO_4)_3$, heterogeneous catalyst, aldehyde, trialkyl phosphite

Introduction

α-Amino phosphonates are of growing importance in biological processes, because they are considered to be structural analogues of the corresponding α-amino acids and transition state mimics of peptide hydrolysis. In these connection, the utilities of α-amino phosphonates as enzyme inhibitors,[1] HIV protease,[2] anti-therombotic agents,[3] peptide mimics,[4] antibiotics,[5] herbicides, fungicides, and insecticides,[6] as well as the important uses for antibody generation[7] are well documented. As a result, various methodologies have been developed for the synthesis of α-amino phosphonates. Many of these methods are based on nucleophilic addition of phosphite to imines catalyzed by protic,[8] Lewis acids like BF_3•OEt_2,[9] $SnCl_4$,[10] $ZnCl_2$ and $MgBr_2$,[11] or by base.[12] However, these reactions can not proceed in one-pot procedure from reaction between an aldehyde, an amine and a phosphite, because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids.[13] This drawback has been overcome by some recent methods using metal triflates [$M(OTf)_n$, M＝Li, Mg, Al, Cu, Ce],[14] $InCl_3$,[15] $FeCl_3$,[16] Scandium tris(dodecyl sulfate),[17] $TaCl_5$-SiO_2,[18] lithium perchlorate,[19] CF_3CO_2H,[20] $In(OTf)_3$,[21] magnesium perchlorate,[22] $PhNMe_3Cl$,[23] $H_3PW_{12}O_{40}$,[24] Amberlyst-15,[25] Amberlite-IR 120,[26] sulfamic acid,[27] TiO_2,[28] oxalic acid,[29] trifluroethanol,[30] microwave assisted,[31] ionic liquid[32] and ultrasonic assisted.[33] However, some of these methods displayed drawbacks, such as environmental pollution caused using organic solvent, long reaction times, expensive catalyst or unavailable reagents, unsatisfactory yields, complicated operations and the help of microwave irradiation. Therefore, it is necessary to further develop an efficient one-pot multi-component synthesis of α-amino phosphonates without these problems.

In the recent years, the use of solid acidic catalysts has received considerable attention in organic synthesis due to their important advantages such as, operational simplicity, environmental compatibility, reusability, low cost, non-toxic, and ease of preparation, handling and isolation. Aluminum tris(dihydrogen phosphate) is well known as an efficient heterogeneous catalyst for organic synthesis.[34,35] In this paper, we report a novel, simple and efficient procedure for the one-pot three-component synthesis of α-amino phosphonates from reaction between aldehydes, amines, and trialkyl phosphites in the presence of $Al(H_2PO_4)_3$ as a catalyst under solvent-free conditions at 100 ℃ (Scheme 1).

Scheme 1 Synthesis of α-amino phosphonates



Experimental

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer respectively. The ^1H,

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^{13}C and ^{31}P NMR spectra were obtained on BRUKER DRX-300 and 400 AVANCE instruments with $CDCl_3$ as a solvent. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. All reagents and solvents obtained from Fluka were used without further purification.

Preparation of $Al(H_2PO_4)_3$

The catalyst was prepared by taking a mixture of alumina (neutral) and concentrated phosphoric acid (88%) in a silica boat maintaining with the molar ratio of alumina-H_3PO_4 as 1∶3 and heating at 200—220 ℃ in a hot sand bath. The mixture was stirred at the stipulated temperature until the swampy mass solidified, and then the temperature was lowered to around 100 ℃. The whole solidified product was then placed in a vacuum desiccator and cooled to ambient temperature. The catalyst thus prepared was finally transferred and stored in an air tight sample vial.[35]

General procedure

The aldehyde (1 mmol), amine (1 mmol) and $Al(H_2PO_4)_3$ (60 mg) were stirred for a few minutes. Then trimethyl/triethyl phosphite (1 mmol) was added. The mixture was stirred at 100 ℃ in oil bath for the appropriate time (see Table 1). After completion of the reaction (monitored by TLC), the reaction mixture was cooled and EtOAc (15 mL) was added to separate the catalyst by simple filtration. The filtrate was washed with distilled water (10 mL×3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by silica gel column chromatography with the mixture of *n*-hexane/EtOAc (V∶V =7∶3) as an eluant to provide pure α-amino phosphonates. Spectral data for the new products are represented below.

Compound 13 Yellow solid, m.p. 92—94 ℃. ^1H NMR ($CDCl_3$, 400 MHz) 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); ^{13}C NMR ($CDCl_3$, 100 MHz) 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),

Table 1 Synthesis of α-amino phosphonates catalyzed by $Al(H_2PO_4)_3$

Entry	R^1	R^2	R^3	R^4	Time/min	Yield[a]/%	Ref.[b]
1	Ph	Ph	H	Me	15	95	22
2	Ph	Ph	H	Et	90	93	28
3	4-NO_2-C_6H_4	Ph	H	Me	5	91	23
4	4-NO_2-C_6H_4	Ph	H	Et	50	90	26
5	3-NO_2-C_6H_4	Ph	H	Et	55	90	26
6	4-Cl-C_6H_4	Ph	H	Me	12	95	29
7	4-Cl-C_6H_4	Ph	H	Et	80	93	28
8	3-Cl-C_6H_4	Ph	H	Me	15	90	25
9	3-Cl-C_6H_4	Ph	H	Et	85	89	28
10	4-NMe_2-C_6H_4	Ph	H	Me	17	93	25
11	4-OH-C_6H_4	Ph	H	Me	20	87	22
12	4-F-C_6H_4	Ph	H	Et	80	91	26
13	2-Cl-6-F-C_6H_3	Ph	H	Me	5	97	[c]
14	2,4-di-OMe-C_6H_3	Ph	H	Me	25	97	[c]
15	2,5-di-OMe-C_6H_3	Ph	H	Me	25	97	[c]
16	2-Me-C_6H_4	Ph	H	Me	30	95	[c]
17	4-Me-C_6H_4	Ph	H	Et	120	93	28
18	3-NO_2-C_6H_4	3-NO_2-C_6H_4	H	Et	70	91	21
19	4-NO_2-C_6H_4	4-NO_2-C_6H_4	H	Me	15	89	22
20	4-OMe-C_6H_4	4-OMe-C_6H_4	H	Me	35	93	22
21	4-OMe-C_6H_4	3-NO_2-C_6H_4	H	Et	120	86	21
22	4-OMe-C_6H_4	4-NO_2-C_6H_4	H	Et	130	90	21
23	*n*-Propyl	Ph	H	Me	300	75	23
24	Ph	$PhCH_2$	H	Me	300	83	29
25	Ph	Et	Et	Me	300	No reaction	—
26	4-OMe-C_6H_4	$H_2NCH_2CH_2$	H	Et	300	35	28

[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. [c] The new compounds synthesized in this work.

130.20, 145.77 (d, J=14.5 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz) δ: 23.00; IR (KBr) v: 3313 (NH), 1246 (P=O), 1056, 1033 (P—O—Me) cm^{-1}; 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 14 White solid, m.p. 146—148 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) 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); ^{13}C NMR ($CDCl_3$, 100 MHz) 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); ^{31}P NMR ($CDCl_3$, 161 MHz) δ: 26.21; IR (KBr) v: 3290 (NH), 1233 (P=O), 1050, 1027 (P—O—Me) cm^{-1}; 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.

Compound 15 White solid, m.p. 121—123 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.49 (d, J=10.5 Hz, 3H), 3.73 (s, 3H), 3.82 (d, J=10.5 Hz, 3H), 3.91 (s, 3H), 4.58 (br, 1H), 5.42 (d, J=24.5 Hz, 1H), 6.65—6.87 (m, 5H), 7.07—7.14 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 47.99 (d, J=153.8 Hz), 53.74 (d, J=7.1 Hz), 53.84 (d, J=7.1 Hz), 55.66, 56.43, 111.83 (d, J=1.8 Hz), 113.87, 113.97, 114.06, 118.61, 125.15, 129.16, 145.80 (d, J=14.3 Hz), 151.46 (d, J=6.2 Hz), 153.92 (d, J=3.3 Hz); ^{31}P NMR ($CDCl_3$, 161 MHz) δ: 25.80; IR (KBr) v: 3322 (NH), 1231 (P=O), 1061, 1040 (P—O—Me); MS *m/z* (%): 351 (M^+, 9), 242 (100), 227 (41), 212 (42), 149 (10), 109 (9), 77 (28). Anal. calcd for $C_{17}H_{22}NO_5P$: C 58.12, H 6.31, N 3.99; found C 58.23, H 6.44, N 3.90.

Compound 16 White solid, m.p. 133—135 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 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); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 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); ^{31}P NMR ($CDCl_3$, 161 MHz) δ: 25.86; IR (KBr) v: 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.

Results and discussion

First, benzaldehyde was treated with aniline and trimethyl phosphite in the presence of $Al(H_2PO_4)_3$ under solvent-free conditions at 100 ℃. The reaction proceeded smoothly to give the corresponding α-amino phosphonate in excellent yield (95%) after 15 min (Table 1, Entry 1). With respect to the initial results of first experiment, several reactions were investigated between different aldehydes, amines, and trialkyl phosphites in the presence of $Al(H_2PO_4)_3$ as a catalyst under solvent-free conditions at 100 ℃. The results are summarized in Table 1. As shown in Table 1, benzaldehydes with electron-deficient and/or electron-releasing group reacted efficiently with anilines to give the corresponding α-amino phosphonates in high to excellent yields. Substituents on the benzene ring such as NO_2, NMe_2, OMe, Cl, F, and OH were tolerated during the reaction. In all cases, the reaction proceeded to afford α-amino phosphonates exclusively. On the basis of experimental results, the rate of all reactions in the presence of triethyl phosphite were reduced in comparison with trimethyl phosphite under constant conditions. We have also prepared 4 new analogues of these compounds in excellent yields (Entries 13—16). These new compounds were characterized by melting point, IR, NMR (^{1}H, ^{13}C and ^{31}P) and mass spectroscopies.

The reusability of the catalyst is an important factor from economical and environmental point of views and has attracted much attention in recent years. Therefore, the reusability of aluminum tris(dihydrogen phosphate) was examined in the reaction between 2,4-dimethoxybenzaldehyde, aniline and trimethyl phosphite under solvent-free conditions at 100 ℃. Since $Al(H_2PO_4)_3$ is a heterogeneous catalyst, it was separated and reused after being washed with methanol and dried at 100 ℃ for 60 min. The results showed that the catalyst can be used 5 times without significant loss of its activity (Table 2).

Table 2 Investigation on reusability of the catalyst in the reaction of 2,4-dimethoxybenzaldehyde with aniline and trimethyl phosphite

Run no.	Yield[a]/%
1	97
2	96
3	95
4	92
5	90

[a] Yields refer to the pure recovered catalyst.

Conclusion

In conclusion, we have developed an efficient method for the synthesis of α-amino phosphonate derivatives by an one-pot three-component reaction under thermal solvent-free conditions. The use of $Al(H_2PO_4)_3$ as a highly efficient, inexpensive, easy handling, non-toxic, and reusable catalyst makes the present procedure eco-friendly and economically acceptable. Furthermore, this method with noteworthy advantages such as short reaction time, high yields and easy work-up can

be considered as a valid contribution to the existing methodologies.

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