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Amberlite-IR 120 catalyzed three-component synthesis of α-amino phosphonates in one-pot

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Abstract

A simple, efficient, and environmentally benign method for a three-component reaction of an amine, an aldehyde or a ketone, and diethyl phosphite catalyzed by Amberlite-IR 120 resin has been developed to afford α-amino phosphonates in high yields and short reaction times under solvent-free reaction conditions. The major advantages of the present method are good yields, inexpensive, ecofriendly and reusable catalyst, mild and solvent-free reaction conditions and tolerance towards various functionalities present in the substrates.

Keywords: α-Amino phosphonates; Aldehydes; Amines; Alkyl phosphite; Ion-exchange resin; Multi-component reaction

1. Introduction

The synthesis of α-amino phosphonates has attracted much attention recently due to their significant biological activities and structural analogy to α-amino acids. They have been reported to act as peptide mimics,[1] haptens of catalytic antibodies,[2] antibiotics and pharmacological agents[3] and herbicides.[4] Further, phosphinic acid and phosphinic amino acid analogues have also been reported to be enzyme inhibitors.[5] Various synthetic approaches have been reported for the synthesis of α-amino phosphonates, however, nucleophilic addition reaction of phosphites with imines is one of the most preferred methods, which is usually catalyzed by an alkali metal alkoxide, for example, NaOEt or Lewis acids[6] such as $ZnCl_2$, $SnCl_2$, $SnCl_4$, $BF_3{\cdot}Et_2O$ and $MgBr_2$.[7,8] However, these reactions cannot proceed in one-pot from a carbonyl compound, an amine and a phosphite because the water that is generated during the course of the reaction can decompose or deactivate the Lewis acid.[9] This drawback has been overcome by one of our recent methods utilizing bismuth nitrate pentahydrate as an efficient Lewis acid as it is able to tolerate trace amounts of water.[10] As α-amino phosphonate synthesis via three-component reactions is important acid-mediated reactions, the development of a reaction that uses an environmentally benign and reusable catalyst should be of great interest.

The use of solid acidic catalysts has gained importance in organic synthesis due to several advantages such as, operational simplicity, nontoxicity, reusability, low cost, and ease of isolation after completion of the reaction. Amberlite-IR 120 resin has emerged as an efficient heterogeneous catalyst for various chemical transformations.[11–13] Owing to the numerous advantages associated with this cheap and nonhazardous catalyst, we considered Amberlite-IR 120 resin to be an ideal heterogeneous acid catalyst for the synthesis of α-amino phosphonates. Also, it is widely reported in the literature[14–18] that application of microwave irradiation enables realization of reactions, which otherwise require harsh conditions and are too slow for practical purposes. Moreover, microwave-assisted reactions are believed to satisfy the demands of 'green chemistry' allowing for solvent-free conditions to be employed.

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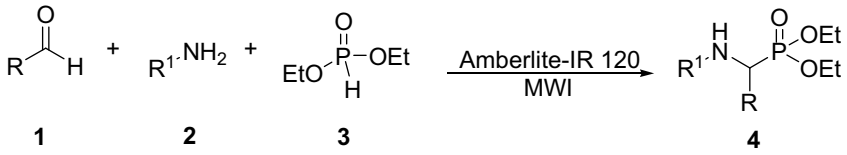


Scheme 1.

Herein, we report a novel one-pot synthesis of α-amino phosphonates catalyzed by Amberlite-IR 120 resin under solvent-free reaction conditions using microwave irradiation (Scheme 1).

2. Results and discussions

Initially, benzaldehyde was reacted with aniline and diethyl phosphite in the presence of Amberlite-IR 120 and irradiated with microwaves for 2 min to give the corresponding α-amino phosphonate in 90% yield (Table 1, entry 1). Several structurally diverse carbonyl compounds and aniline/substituted anilines were subjected to this novel procedure to give the corresponding α-amino phosphonates in high to excellent yields. The results are summarized in Table 1. The presence of electron-donating groups on the aldehyde resulted in the corresponding products in low yields and the reaction was sluggish, however, aldehydes possessing electron-withdrawing groups afforded the corresponding α-amino phosphonates in shorter reaction times and in higher yields. Also, amines possessing electron-donating groups gave the corresponding products in good yields. However, in the case of a diene aldehyde (entry 24), the corresponding product was obtained in poor yield. The wide applicability of the present method is evident from the fact that it is tolerant towards various functional groups including alkoxy, halides, nitro, methylenedioxy, carboxylic and hydroxy groups. Moreover, the catalyst can be reused without affecting the yield of the desired product and reaction time thus, making it environmentally friendly.

3. Conclusion

In conclusion, Amberlite-IR 120 was found to be an efficient catalyst for the one-pot reaction of aldehydes, amines, and diethyl phosphite to afford α-amino phosphonates in good to excellent yields. The main advantages of the present synthetic protocol are mild, solvent-free conditions, ecofriendly catalyst and easy reaction work-up procedure. It is expected that the present methodology will find application in organic synthesis.

4. Experimental

4.1. Typical experimental procedure

Carbonyl compound (1 mmol), amine (1 mmol), diethylphosphite (1 mmol) and Amberlite-IR 120 (100 mg) were taken in a Pyrex test tube and exposed to microwave irradiation (Kenstar Model No. OM-9918 C; 2450 MHz, 2350 W) for the appropriate time (see Table 1). After completion of the reaction (TLC), the reaction mixture was cooled and DCM (25 mL) was added. The catalyst was filtered from the reaction mixture and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (100–200 mesh) eluting with petroleum ether–ethyl acetate (15–30%) to afford the corresponding pure α-amino phosphonates. All the products were characterized from their spectral data.

4.1.1. Compound **4d**

Solid; mp 98–99 °C; ^{1}H NMR (200 MHz, Acetone-d_6, TMS): $\delta = 7.41$–6.56 (m, 9H), 4.70 (d, $^1J_{PH} = 23.0$ Hz, 1H), 4.19–3.63 (m, 4H), 3.77 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.13 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (50 MHz, Acetone-d_6, TMS): $\delta = 159.3$, 146.5, 129.2, 129.0, 128.9, 127.7, 118.4, 114.1, 114.0, 113.9, 63.37 (d, $^2J_{PC} = 7.3$ Hz, –O*C*H$_2$CH$_3$), 63.23 (d, $^2J_{PC} = 7.0$ Hz, –O*C*H$_2$CH$_3$), 55.3 (d, $^1J_{PC} = 152.2$ Hz, –*C*HP), 55.2, 16.5 (d, $^3J_{PC} = 5.5$ Hz, –OCH$_2$*C*H$_3$), 16.3 (d, $^3J_{PC} = 5.5$ Hz, –OCH$_2$*C*H$_3$); MS (ESI): $m/z = 388$ $[M+K]^+$, 372 $[M+Na]^+$, 350 $[M+H]^+$. Anal. Calcd for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 4.01. Found: C, 61.90; H, 6.86; N, 3.95.

4.1.2. Compound **4m**

Solid; mp 97–98 °C; ^{1}H NMR (200 MHz, Acetone-d_6, TMS): $\delta = 7.99$–7.29 (m, 9H), 5.57 (d, $^1J_{PH} = 12.8$ Hz, 1H), 3.92–3.44 (m, 4H), 0.94 (m, 6H); ^{13}C NMR (50 MHz, Acetone-d_6, TMS): $\delta = 167.6$, 138.0, 137.4, 132.2, 132.0, 129.2, 128.8, 126.5, 125.2, 124.6, 124.4, 63.8 (d, $^2J_{PC} = 7.0$ Hz, –O*C*H$_2$CH$_3$), 62.6 (d, $^2J_{PC} = 7.3$ Hz, –O*C*H$_2$CH$_3$), 59.2 (d, $^1J_{PC} = 153.7$ Hz, –*C*HP), 16.0 (d, $^3J_{PC} = 5.1$ Hz, –OCH$_2$*C*H$_3$), 15.8 (d, $^3J_{PC} = 6.9$ Hz, –OCH$_2$*C*H$_3$); MS (ESI): $m/z = 384$ $[M-H_2O+K]^+$, 368 $[M-H_2O+Na]^+$, 346 $[M-H_2O+H]^+$. Anal. Calcd for $C_{18}H_{22}NO_5P$: C, 59.50; H, 6.10; N, 3.85. Found: C, 59.15; H, 6.02; N, 3.78.

4.1.3. Compound **4s**

Solid; mp 168–169 °C; ^{1}H NMR (200 MHz, Acetone-d_6, TMS): $\delta = 6.95$–6.42 (m, 7H), 5.81 (s, 2H), 4.63 (d, $^1J_{PH} = 24.3$ Hz, 1H), 4.05–3.56 (m, 4H), 1.11 (t, $J = 7.1$ Hz, 3H), 0.98 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, Acetone-d_6, TMS): $\delta = 149.7$, 147.7, 147.1, 140.0, 131.1, 121.9, 115.4, 115.5, 108.5, 107.6, 101.1, 62.5 (d, $^2J_{PC} = 7.3$ Hz, –O*C*H$_2$CH$_3$), 62.3 (d, $^2J_{PC} = 7.3$ Hz, –O*C*H$_2$CH$_3$), 55.9 (d, $^1J_{PC} = 153.3$ Hz, –*C*HP), 15.9 (d,

Table 1
One-pot synthesis of α-amino phosphonates catalyzed by Amberlite-IR 120

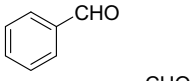
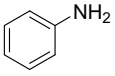
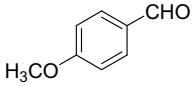
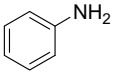
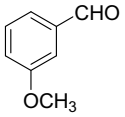
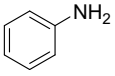
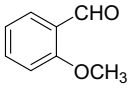
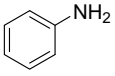
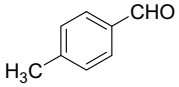
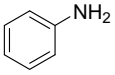
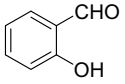
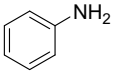
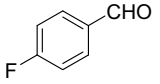
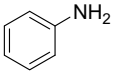
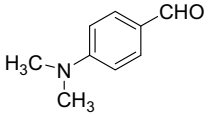
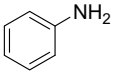
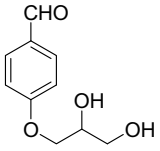
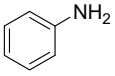
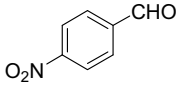
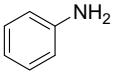
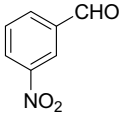
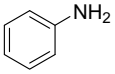
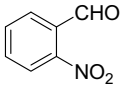
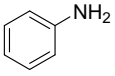
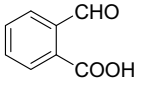
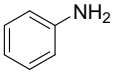
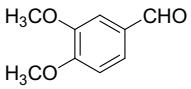
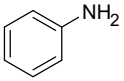
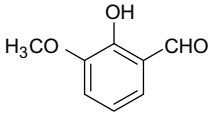
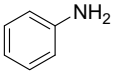
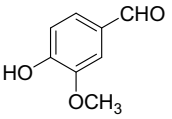
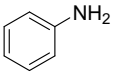
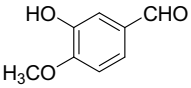
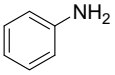
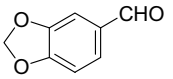
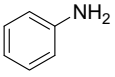
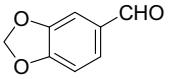
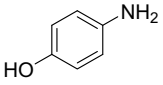
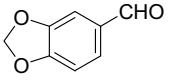
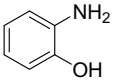
Entry	R–CHO	R^1–NH_2	Product	Time (min)	Yield[a] (%)
1			**4a**	2	90
2			**4b**	5	81
3			**4c**	1	92
4			**4d**	1	87
5			**4e**	1	89
6			**4f**	1.5	91
7			**4g**	1	87
8			**4h**	3	70
9			**4i**	2	67
10			**4j**	1	95
11			**4k**	2.5	88
12			**4l**	3	75
13			**4m**	1	78
14			**4n**	2	90
15			**4o**	2	95

Table 1 (*continued*)

Entry	R–CHO	R^1–NH_2	Product	Time (min)	Yield[a] (%)
16			**4p**	2	90
17			**4q**	2	87
18			**4r**	2	92
19			**4s**	3	98
20			**4t**	2	79
21			**4u**	2	91
22			**4v**	1	81
23			**4w**	1	87
24			**4x**	1	11
25			**4y**	3	78
26			**4z**	2	84

[a] Yields refer to those of pure isolated products fully characterized by spectral data.

$^3J_{PC} = 5.9$ Hz, $-OCH_2CH_3$), 15.7 (d, $^3J_{PC} = 5.9$ Hz, $-OCH_2CH_3$); MS (ESI): $m/z = 418$ $[M+K]^+$, 402 $[M+Na]^+$, 380 $[M+H]^+$. Anal. Calcd for $C_{18}H_{22}NO_6P$: C, 56.99; H, 5.85; N, 3.69. Found: C, 56.60; H, 5.73; N, 3.62.

4.1.4. Compound **4t**

Solid; mp 132–133 °C; ^{1}H NMR (200 MHz, Acetone-d_6, TMS): $\delta = 6.97$–6.47 (m, 7H), 5.87 (s, 2H), 4.79 (d, $^1J_{PH} = 25.0$ Hz, 1H), 4.32–3.69 (m, 4H), 1.29 (t,

$J = 7.1$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, Acetone-d_6, TMS): $\delta = 147.9$, 147.3, 145.3, 135.0, 129.6, 121.6, 119.9, 118.4, 114.3, 112.0, 108.5, 108.3, 101.1, 64.2 (d, $^2J_{PC} = 7.0$ Hz, –O*C*H$_2$CH$_3$), 63.7 (d, $^2J_{PC} = 7.0$ Hz, –O*C*H$_2$CH$_3$), 55.7 (d, $^1J_{PC} = 155.9$ Hz, –*C*HP), 16.4 (d, $^3J_{PC} = 5.9$ Hz, –OCH$_2$*C*H$_3$), 16.2 (d, $^3J_{PC} = 5.9$ Hz, –OCH$_2$*C*H$_3$); MS (ESI): $m/z = 402$ [M+Na]$^+$, 380 [M+H]$^+$. Anal. Calcd for $C_{18}H_{22}NO_6P$: C, 56.99; H, 5.85; N, 3.69. Found: C, 56.65; H, 5.77; N, 3.60.

4.1.5. Compound **4u**

Syrupy liquid; ^{1}H NMR (200 MHz, Acetone-d_6, TMS): $\delta = 6.96$–6.39 (m, 7H), 5.93 (s, 2H), 5.27 (t, $J = 8.0$ Hz, 1H), 4.67 (dd, $^1J_{PH} = 24.0$, 8 Hz, 1H), 4.16–3.85 (m, 4H), 3.88 (s, 3H) 1.28 (t, $J = 7.2$ Hz, 3H), 1.20 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, Acetone-d_6, TMS): $\delta = 148.0$, 147.9, 147.3, 136.0, 129.8, 121.4, 121.0, 117.7, 111.2, 109.6, 108.3, 108.2, 101.1, 63.4 (d, $^2J_{PC} = 7.0$ Hz, –O*C*H$_2$CH$_3$), 63.2 (d, $^2J_{PC} = 7.0$ Hz, –O*C*H$_2$CH$_3$), 55.6 (d, $^1J_{PC} = 152.6$ Hz, –*C*HP), 16.5 (d, $^3J_{PC} = 5.8$ Hz, –OCH$_2$*C*H$_3$), 16.3 (d, $^3J_{PC} = 5.8$ Hz, –OCH$_2$*C*H$_3$); MS (ESI): $m/z = 432$ [M+K]$^+$, 416 [M+Na]$^+$, 394 [M+H]$^+$. Anal. Calcd for $C_{19}H_{24}NO_6P$: C, 58.01; H, 6.15; N, 3.56. Found: C, 57.78; H, 6.10; N, 3.46.

4.1.6. Compound **4v**

Syrupy liquid; ^{1}H NMR (200 MHz, Acetone-d_6, TMS): $\delta = 7.35$–6.77 (m, 8H), 5.97 (s, 2H), 4.13–3.77 (m, 6H), 3.52 (d, $^1J_{PH} = 13.3$ Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, Acetone-d_6, TMS): $\delta = 147.9$, 147.4, 139.3, 129.4, 128.4, 128.3, 127.2, 122.4, 108.7, 108.2, 101.1, 62.9 (t, $^2J_{PC} = 6.6$, 7.3 Hz, –2O*C*H$_2$CH$_3$), 59.2 (d, $^1J_{PC} = 155.2$ Hz, –*C*HP), 51.0 (d, $^3J_{PC} = 17.6$ Hz, –NH*C*H$_2$Ph), 16.4 (t, $^3J_{PC} = 6.2$, 5.6 Hz, –2OCH$_2$*C*H$_3$); MS (ESI): $m/z = 416$ [M+K]$^+$, 400 [M+Na]$^+$, 378 [M+H]$^+$. Anal. Calcd for $C_{19}H_{24}NO_5P$: C, 60.47; H, 6.41; N, 3.71. Found: C, 60.29; H, 6.28; N, 3.62.

4.1.7. Compound **4x**

Syrupy liquid; ^{1}H NMR (200 MHz, Acetone-d_6, TMS): $\delta = 7.13$–6.54 (m, 5H), 5.12–4.95 (m, 2H), 4.38 (dd, 1H, $^1J_{PH} = 20.7$ Hz, $^3J_{CH} = 9.4$ Hz), 4.15–3.97 (m, 4H), 2.06–1.97 (m, 2H), 1.72–1.71 (m, 2H), 1.61 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 1.27–1.17 (m, 6H); ^{13}C NMR (50 MHz, Acetone-d_6, TMS): $\delta = 146.8$, 141.6, 131.8, 129.1, 123.6, 119.9, 118.4, 113.9, 63.1 (d, $^2J_{PC} = 6.6$ Hz, –O*C*H$_2$CH$_3$), 62.8 (d, $^2J_{PC} = 7.3$ Hz, –O*C*H$_2$CH$_3$), 50.6 (d, $^1J_{PC} = 158.5$ Hz, –*C*HP), 39.6, 26.2, 25.6, 17.7, 17.1, 16.5, 16.4; MS (ESI): $m/z = 404$ [M+K]$^+$, 388 [M+Na]$^+$, 366 [M+H]$^+$. Anal. Calcd for $C_{20}H_{32}NO_3P$: C, 65.73; H, 8.83; N, 3.83. Found: C, 65.62; H, 8.76; N, 3.72.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.102.

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