Coupling of Aldehydes, Amines, and Trimethyl Phosphite Promoted by Amberlyst-15: Highly Efficient Synthesis of α-Aminophosphonates

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Abstract: A three-component reaction promoted by Amberlyst-15 of an amine, an aldehyde, and trimethyl phosphite (Kabachnik–Fields reaction) in one pot under mild conditions affords the corresponding α-aminophosphonate in high yield after a short reaction time at ambient temperature.

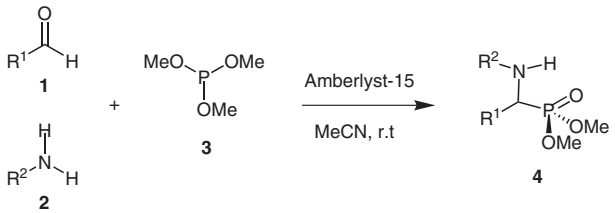
Key words: amines, phosphonates, Amberlyst-15 catalysis, nucleophilic additions, multicomponent reactions

Due to their structural analogy to α-amino acids, α-aminophosphonic acids and their derivatives α-aminophosphonates continue to attract increased interest as synthetic targets. These molecules have found a wide range of applications in the areas of industrial, biological, and medicinal chemistry, as inhibitors of synthase,[1a] HIV protease,[1b] antibiotics,[1c] enzyme inhibitors,[1d] anti-thrombotic agents,[1e] herbicides, fungicides, insecticides,[1f,g] plant growth regulators,[1h] and as substrates in the synthesis of phosphonopeptides.[2] As a result, various synthetic approaches have been developed for the synthesis of α-aminophosphonates. Nucleophilic addition reactions of phosphates with imines is one of the most convenient of these methods, and are usually promoted by base,[3] protic,[4] or Lewis acids such as tin(IV) chloride,[5a] zirconium(IV) chloride,[5b] zinc(II) chloride,[5c] magnesium bromide,[5c] and boron trifluoride–diethyl ether complex.[5d] However, these methods do have some limitations; for example, many imines are hygroscopic and not sufficiently stable to be isolated. In addition, these reactions cannot be carried out in one step with a carbonyl compound, an amine, and a trialkyl phosphite, because the amine and water present during imine formation can decompose or deactivate the Lewis acid.[6] This drawback has been overcome by some recent methods using $H_3PW_{12}O_{40}$,[7a] magnesium perchlorate,[7b] trimethylanilinium chloride,[7c] bismuth nitrate pentahydrate,[7d] scandium tris(dodecyl sulfate),[7e,f] indium(III) chloride,[7g] samarium(II) iodide,[7h] metal triflates [$M(OTf)_n$, M = La, Li, Mg, Al, Cu, Ce],[7i] lithium perchlorate,[7j,k] tantalum(V) chloride–silicon dioxide,[7l] alumina,[7m] trifluoroacetic acid,[7n] montmorillonite KSF,[7o] and (bromodimethyl)sulfonium bromide.[7p] However, many of these methods involve stoichiometric amounts of catalysts, expensive reagents, long reaction times, and high temperatures, result in low yields, and require catalysts that are difficult to prepare. Hence, a convenient, environmentally benign, and practicably feasible method for the synthesis of α-aminophosphonates is desirable.

In recent years, the use of solid acidic catalysts has attracted considerable attention.[8] In this regard, Amberlyst-15 possesses unique properties such as environmental compatibility, nontoxicity, reusability, noncorrosiveness, selectivity, and chemical and physical stability. Owing to the numerous advantages associated with this inexpensive and nonhazardous catalyst, Amberlyst-15 has been explored as a powerful catalyst for various organic reactions.[9]

Amberlyst-15 with a sulfonic acid functionality is strongly acidic and can be handled easily and removed from the reaction mixtures by simple filtration. The ability to be recovered from reaction mixtures and to be reused, the experimental convenience, and being environmentally benign are important advantages of Amberlyst-15 over other conventional catalysts and solid acids. To investigate its recyclability, the Amberlyst-15 catalyst was collected by filtration, washed with acetone, and dried under ambient conditions for one hour after each experiment. The recovered catalyst was reused consecutively several times with only a minimal variation in the yields of the products. In the present work, Amberlyst-15 exhibits relatively good stability, could be regenerated easily, and showed high turnover numbers.

To find the optimum conditions for the three-component reaction (Scheme 1), we stirred a solution of benzaldehyde (**1**, R^1 = Ph) and aniline (**2**, R^2 = Ph) in acetonitrile for five minutes before adding Amberlyst-15 and trimethyl phosphite (**3**) at ambient temperature. The reaction was complete in 25 minutes and afforded dimethyl [anilino(phenyl)methyl]phosphonate (**4a**) in 92% yield (Table 1, entry 1).



Scheme 1

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Table 1 Synthesis of α-Aminophosphonates **4** from Various Aldehydes and Amines

Entry	R^1	R^2	Time (min)	Product **4**	Yield[a] (%)
1	Ph	Ph	25	**4a**	92
2	3-ClC_6H_4	Ph	35	**4b**	94
3	4-ClC_6H_4	Ph	40	**4c**	87
4	tolyl	Ph	30	**4d**	89
5	4-$O_2NC_6H_4$	Ph	35	**4e**	86
6	4-$Me_2NC_6H_4$	Ph	20	**4f**	96
7	4-HOC_6H_4	Ph	35	**4g**	87
8	PMP	Ph	35	**4h**	83
9	2-furyl	Ph	25	**4i**	96
10	Ph	4-ClC_6H_4	45	**4j**	83
11	Ph	PMP	30	**4k**	89
12	PMP	PMP	35	**4l**	91
13	Ph	4-HOC_6H_4	35	**4m**	87
14	cinnamyl	Ph	90	**4n**	89
15	prop-1-enyl	Ph	90	**4o**	84
16	*n*-Pr	Ph	60	**4p**	84
17	*n*-pentyl	Ph	60	**4q**	87
18	$(CH_2)_2Ph$	Ph	60	**4r**	84
19	*i*-Pr	Ph	60	**4s**	87

[a] Yield of isolated product.

This method was applied to a variety of substrates, and in all cases the reaction proceeded smoothly at ambient temperature to give the desired products in high yields.[10] The results are summarized in Table 1. Both electron-deficient and electron-releasing benzaldehydes react efficiently with aniline to give the corresponding α-aminophosphonates (Table 1, entries 2–8). 2-Furaldehyde also gave the corresponding α-aminophosphonate in high yield (Table 1, entry 9). Similarly substituted anilines reacted with trimethyl phosphite and benzaldehyde or 4-methoxybenzaldehyde to afford the corresponding α-aminophosphonates in high yields (Table 1, entries 10–13). When α,β-unsaturated aldehydes reacted with aniline and trimethyl phosphite in acetonitrile in the presence of Amberlyst-15 a longer reaction time was required for the reaction to be completed and to give the 1,2-addition products in high yields (Table 1, entries 14 and 15).

In addition, this method is even effective with aliphatic aldehydes, which normally produce low yields due to their intrinsic lower reactivity (Table 1, entries 16–19). However, it is interesting that the reactions of ketones and aromatic amines with trimethyl phosphite under similar reaction conditions give the corresponding α-aminophosphonates in low yield only. The present method does not require any additives or promoters to facilitate the reaction.

In summary, we have successfully demonstrated the use of Amberlyst-15 as an efficient catalyst for the three-component synthesis of α-aminophosphonates at room temperature. This procedure is attractive owing to its operational simplicity and generally high yields of products.

The ^1H (500 MHz) and ^{13}C (125 MHz) NMR data reported below for selected products were determined on a Bruker Avance DRX 500 spectrometer. The spectroscopic and physical data for all compounds corresponded to those given in the literature: **4a**,[7a–c,11] **4b**,[10] **4c**,[7a–c] **4d**,[7p] **4e**,[7c] **4f**,[7b] **4g**,[7b] **4h**,[7l] **4i**,[7b] **4j**,[11] **4k**,[7l] **4l**,[7b] **4m**,[7c] **4n**,[7b] **4o**,[7l] **4p**,[7c] **4q**,[7c] **4r**,[7b] and **4s**.[7b]

α-Aminophosphonates 4; General Procedure

The amine **2** (2.2 mmol) and aldehyde **1** (2 mmol) were stirred for a few minutes at r.t. in MeCN (4 mL) before the $P(OMe)_3$ (**3**; 2.2 mmol) and Amberlyst-15 (0.2 g) were added and the mixture was stirred for the appropriate time (see Table 1). After completion of the reaction (followed by TLC), the catalyst was separated by filtration. The solvent was evaporated and the reaction mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (15 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated under vacuum, and the crude mixture was purified by column chromatography (hexane–EtOAc, 8:2); this afforded the pure dimethyl phosphonate **4**.

Dimethyl [Anilino(phenyl)methyl]phosphonate (4a)[7a–c,11]

^1H NMR (500 MHz, $CDCl_3$): δ = 3.50 (d, *J* = 10.5 Hz, 3 H), 3.80 (d, *J* = 10.6 Hz, 3 H), 4.82 (d, *J* = 24 Hz, 1 H), 4.84 (br s, 1 H), 6.60–7.50 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.1 (d, $^2J_{P-C}$ = 7.0 Hz, OCH_3), 54.2 ($^2J_{P-C}$ = 6.8 Hz, OCH_3), 56.2 (d, $^1J_{P-C}$ = 150 Hz, CH), 128.4 (d, $^3J_{P-C}$ = 3.1 Hz, CH), 129.1 (CH), 131.2 (CH), 136.0 (C), 146.6 (d, $^2J_{P-C}$ = 14.5 Hz, C).

Dimethyl [Anilino(4-chlorophenyl)methyl]phosphonate (4c)[7a,c]

^1H NMR (500 MHz, $CDCl_3$): δ = 3.50 (m, 1 H), 3.80 (d, *J* = 11.8 Hz, 3 H), 3.83 (d, *J* = 10.1 Hz, 3 H), 5.20 (d, *J* = 24 Hz, 1 H), 7.30–8.20 (m, 9 H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 56.1 (d, $^2J_{P-C}$ = 7.0 Hz, OCH_3), 56.2 (d, $^2J_{P-C}$ = 6.8 Hz, OCH_3), 57.2 (d, $^1J_{P-C}$ = 150 Hz, CH), 114.3 (CH), 120.0 (CH), 128.2 (d, $^3J_{P-C}$ = 5.8 Hz, CH), 128.4 (d, $^3J_{P-C}$ = 3.1 Hz, CH), 130.1 (CH), 131.2 (CH), 140.0 (C), 146.6 (d, $^2J_{P-C}$ = 14.5 Hz, C).

Dimethyl [Anilino(4-nitrophenyl)methyl]phosphonate (4e)[7c]

^1H NMR (500 MHz, $CDCl_3$): δ = 3.70 (d, *J* = 10.1 Hz, 3 H), 3.74 (br s, 1 H), 3.74 (d, *J* = 10.3 Hz, 3 H), 5.00 (d, *J* = 10.7 Hz, 1 H), 7.30–8.40 (m, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 58.1 (d, $^2J_{P-C}$ = 7.0 Hz, OCH_3), 58.2 ($^2J_{P-C}$ = 6.8 Hz, OCH_3), 58.3 (d, $^1J_{P-C}$ = 150 Hz, CH), 115.3 (CH), 119.0 (CH) 129.2 (d, $^3J_{P-C}$ = 5.8 Hz, CH), 129.4 (d, $^3J_{P-C}$ = 3.1 Hz, CH), 130.1 (CH), 131.2 (CH), 136.0 (C), 147.6 (d, $^2J_{P-C}$ = 4.5 Hz, C).

Dimethyl [Anilino(2-furyl)methyl]phosphonate (4i)[7b]

^1H NMR (500 MHz, $CDCl_3$): δ = 3.60 (d, *J* = 10.6 Hz, 3 H), 3.80 (d, *J* = 10.6 Hz, 3 H), 4.50 (br s, 1 H), 5.00 (d, *J* = 23.8 Hz, 1 H), 6.37–7.40 (m, 8 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 50.0 (d, $^1J_{P-C}$ = 159.6 Hz, CH), 54.1 (d, $^2J_{P-C}$ = 5.8 Hz, OCH_3), 54.4 (d, $^2J_{P-C}$ = 6.9 Hz, OCH_3), 109.4 (d, $^3J_{P-C}$ = 6.8 Hz, CH), 111.2 (CH), 114.4 (d, CH), 119.5 (CH), 129.9 (d, CH), 143.1 (CH), 146.3 (d, $^2J_{P-C}$ = 13.3 Hz, C), 149.4 (C).

Dimethyl [4-Hydroxyanilino(phenyl)methyl]phosphonate (4m)[7c]

^{1}H NMR (90 MHz, $CDCl_3$): δ = 3.7 (dd, J_{P-C} = 10.5 Hz, 6 H), 4.8 (d, J_{P-H} = 27 Hz, 1 H), 7.1–8.0 (m, 10 H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 51.9 (CH), 54.0 (OMe), 54.3 (OMe), 114.0 (CH), 121.9 (CH), 125.7 (CH), 129.3 (CH), 130.1 (CH), 131.2 (CH), 135.0 (C), 149.2 (C).

Dimethyl (1-Anilinohexyl)phosphonate (4q)[7c]

^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.7 (t, *J* = 7.5 Hz, 3 H), 1.2–1.8 (m, 8 H), 3.6 (br s, NH), 3.7 (d, *J* = 9.9 Hz, 3 H), 3.8 (d, *J* = 9.9 Hz, 3 H), 3.9 (m, 1 H), 6.5–7.5 (m, 5 H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 13.5 (CH_3), 21.9 (CH_2), 25.3 (d, $^3J_{P-C}$ = 12.4 Hz, CH_2), 30.3 (d, $^3J_{P-C}$ = 3.3 Hz, CH_2), 31.1 (CH_2), 52.2 (d, $^2J_{P-C}$ = 7.42 Hz, OCH_3), 53.2 (d, $^2J_{P-C}$ = 7.4 Hz, OCH_3), 53.7 (d, $^1J_{P-C}$ = 135 Hz, CH), 113.2 (CH), 118.0 (CH), 129.4 (CH), 149.0 (C).

Dimethyl (1-Anilino-3-phenylpropyl)phosphonate (4r)[7b]

^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.2–1.5 (m, 2 H), 2.1–2.4 (m, 2 H), 2.9 (br s, NH, 1 H), 3.5 (m, CH, 1 H), 3.8–3.9 (dd, *J* = 8.9, 9.0 Hz, 6 H), 6.5–7.5 (m, Ar, 10 H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 31.8 (CH_2), 36.6 (CH_2), 52.1 (OCH_3), 58.9 (CH_3), 69.1 (CH), 112.8 (CH), 115.1 (CH), 118.4 (CH), 126.0 (CH), 128.5 (CH), 129.3 (CH), 140.9 (C), 146.6 (C).

References

(1) (a) Sikosrki, J. A.; Miller, M. J.; Braccolino, D. S.; Cleary, D. G.; Corey, S. D.; Ream, J. E.; Schnur, D.; Shah, A.; Walker, M. C. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *76*, 375. (b) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625. (c) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29. (d) Peyman, A.; Budt, K.-H.; Paning, J. S.; Stowasser, B.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 4549. (e) Meyer, J. H.; Barlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4600. (f) Maier, L. *Phosphorus, Sulfur Silicon Relat. Elem.* **1990**, *53*, 43. (g) Maier, L.; Spoerri, H. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *61*, 69. (h) Emsley, J.; Hall, D. *Chemistry of Phosphorus*; Harper & Row: London, **1976**, 494.

(2) (a) Maier, L.; Lea, P. J. *Phosphorus Sulfur Relat. Elem.* **1983**, *17*, 1. (b) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603. (c) Gancarz, R.; Wieczorek, J. S. *Synthesis* **1977**, 625. (d) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845. (e) Hilderbrand, R. L. *The Role of Phosphonates in Living Systems*; CRC Press: Boca Raton USA, **1982**. (f) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Relat. Elem.* **1991**, *63*, 193.

(3) Pudovik, A. N. *Dokl. Akad. Nauk SSSR* **1952**, *83*, 865; *Chem. Abstr.* **1953**, *47*, 4300.

(4) Petrov, K. A.; Chauzov, V. A.; Erkhina, T. S. *Usp. Khim.* **1974**, *43*, 2045; *Chem. Abstr.* **1975**, *82*, 449.

(5) (a) Laschat, S.; Kunz, H. *Synthesis* **1992**, 90. (b) Yadav, J. S.; Reddy, B. V. S.; Raj, S.; Reddy, K. B.; Prasad, A. R. *Synthesis* **2001**, 2277. (c) Zon, J. *Pol. J. Chem.* **1981**, *55*, 643. (d) Ha, H. J.; Nam, G. S. *Synth. Commun.* **1992**, *22*, 1143.

(6) Yokomatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 7930.

(7) (a) Heydari, A.; Hamadi, H.; Pourayoubi, M. *Catal. Commun.* **2007**, *8*, 1224. (b) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 1263. (c) Heydari, A.; Arefi, A. *Catal. Commun.* **2007**, *8*, 1023. (d) Bhattacharya, A. K.; Kaur, T. *Synlett* **2007**, 745. (e) Manabe, K.; Kobayashi, S. *Chem. Commun.* **2000**, 669. (f) Qian, C.; Huang, T. *J. Org. Chem.* **1998**, *63*, 4125. (g) Ranu, B. C.; Hajra, A.; Jana, J. *Org. Lett.* **1999**, *1*, 1141. (h) Xu, F.; Luo, Y.; Deng, M.; Shen, Q. *Eur. J. Org. Chem.* **2003**, 4728. (i) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Synthesis* **2004**, 2692. (j) Azizi, N.; Saidi, M. R. *Eur. J. Org. Chem.* **2003**, 4430. (k) Heydari, A.; Karimian, A.; Ipaktschi, J. *Tetrahedron Lett.* **1998**, *39*, 6729. (l) Chandrasekhar, S.; Prakash, S. J.; Jagadeshwar, V.; Narsihmulu, C. *Tetrahedron Lett.* **2001**, *42*, 5561. (m) Kaboudin, B.; Nazari, R. *Tetrahedron Lett.* **2001**, *42*, 8211. (n) Akiyama, T.; Sanada, M.; Fuchibe, K. *Synlett* **2003**, 1463. (o) Yadav, J. S.; Reddy, B. V. S.; Madan, C. *Synlett* **2001**, 1131. (p) Kudrimoti, S.; Bommena Roa, V. *Tetrahedron Lett.* **2005**, *46*, 1209.

(8) Ko, S.; Yao, C. F. *Tetrahedron Lett.* **2006**, *47*, 8827.

(9) (a) Tian, Q.; Zhang, S.; Yu, Q.; He, M. B.; Yang, J. S. *Tetrahedron* **2007**, *63*, 2142. (b) Sabou, R.; Hoelderich, W. F.; Ramprasad, D.; Weinand, R. *J. Catal.* **2005**, *232*, 34. (c) Yadav, J. S.; Subba Reddy, B. V.; Vishnumurthy, P. *Tetrahedron Lett.* **2005**, *46*, 1311. (d) Honkela, M. L.; Root, A.; Lindblad, M.; Krause, A. O. I. *Appl. Catal., A* **2005**, *295*, 216.

(10) Kaboudin, B.; Moradi, K. *Tetrahedron Lett.* **2005**, *46*, 2989.

(11) Zhang, W.; Zou, J. P.; Mu, X. J. *Tetrahedron Lett.* **2006**, *47*, 1125.