A simple and green procedure for the synthesis of α-aminophosphonate by a one-pot three-component condensation of carbonyl compound, amine and diethyl phosphite without solvent and catalyst

Brindaban C. Ranu* and Alakananda Hajra

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta-700 032, India. E-mail: ocbcr@mahendra.iacs.res.in; Fax: 91-33-4732805

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A simple, general, efficient and greener method has been developed for the synthesis of **α**-aminophosphonates through a solvent-free and catalyst-free one-pot three-component condensation of carbonyl compound, amine and diethyl phosphite.

Introduction

α-Aminophosphonates, due to their structural analogy to α-amino acids, have been the subject of considerable current interest.[1] A number of synthetic methods have been developed during past two decades.[2] Of these methods, the nucleophilic addition of phosphites to imines catalyzed by a base or an acid, is the most convenient one. A variety of metal halides such as $TiCl_4$,[2b] $SnCl_4$,[2c] $ZnCl_2$,[2d] $MgBr_2$,[2d] $InCl_3$,[2e] $TaCl_5$–SiO_2[2f] and lanthanide triflates[2g,h] have been used as Lewis catalysts in methylene chloride or other organic solvents to promote this addition. However, organic solvents, particularly chlorinated hydrocarbons are high on the list of damaging chemicals because of their volatile nature, considerable toxicity and use in large quantities for a reaction. On the other hand, the metal halides employed as catalysts in these procedures are not all eco-friendly and often entail severe environment pollution during the process of waste disposal. To avoid these disadvantages a couple of modifications using montmorillonite clay[3a] and alumina[3b] in dry media under microwave irradiation have been reported recently. As a part of our green technology program we would also like to disclose here a more practical green alternative for the synthesis of α-aminophosphonates by a three-component condensation of carbonyl compounds (aldehydes and ketones), amines and diethyl phosphite at 75–80 °C in neat without any solvent and catalyst (Scheme 1).

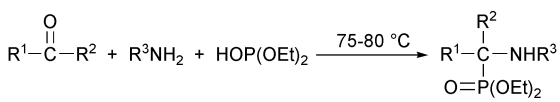
Results and discussion

In a typical experimental procedure, a mixture of carbonyl compound, an amine and diethyl phosphite was heated (75–80 °C) in neat without any solvent and catalyst for few minutes (TLC). The liquid products were isolated by direct distillation from the reaction pot under reduced pressure and the solid ones were recrystallized from ethyl acetate.

A wide range of structurally varied aldehydes and ketones underwent reactions with aromatic and aliphatic amines to produce the corresponding α-aminophosphonates by this procedure. The results are summarized in Table 1. This procedure is equally effective for conversion of open-chain, cyclic, heterocyclic and aromatic aldehydes and ketones to the respective α-aminophosphonates. The presence of electron-withdrawing or electron-donating substituents on the aromatic ring does not make any difference to the course of reaction. Several sensitive functionalities such as OH, OMe, Cl, NO_2, CO_2Me, C=C bond, methylenedioxy are well tolerated under the present reaction conditions.

The reactions are, in general very fast, clean and atom-economic. No side product has been isolated in any reaction leading to a minimum waste. The products obtained after distillation or recrystallization are of high purity and do not require any chromatographic purification. This avoids use of large quantities of volatile organic solvents usually required for work-up and purification in many existing procedures. On the other hand, use of no catalyst in this process makes easier waste disposal.

When the reaction was carried out in a solvent like THF under similar reaction conditions the condensation proceeds to a marginal extent (10–15%) for aldehydes and does not occur at all for ketones. The reaction can be scaled up to the extent of a batch of 10g (not optimized) without any difficulty avoiding use of any organic solvent in any step.



Scheme 1

Green Context

Minimisation of solvent usage and catalyst waste are key factors in any process. The synthesis of aminophosphonates is typically carried out using an imine and a phosphite, and reacting them together in an organic solvent using one of a wide range of catalysts. Remarkably, this paper indicates that neither is required. Simply heating the two reaction partners together neat is sufficient in many cases to give high yields of pure products. ***DJM***

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Conclusion

The present procedure for the synthesis of α-aminophosphonates by a solvent-free and catalyst-free one-pot reaction of carbonyl compounds, amines and diethyl phosphite provides a very simple, efficient, general, cost-effective and greener methodology. Most significantly, this protocol now throws a challenge to the existing procedures[2] using solvents and catalysts and in general, leads to a new technology of solvent-free, catalyst-free reaction.[4] Finally, we believe that this will present a better and more benign alternative to the existing methodologies[2,3] for the synthesis of α-aminophosphonates to cater the need of academia as well as industries.

Experimental

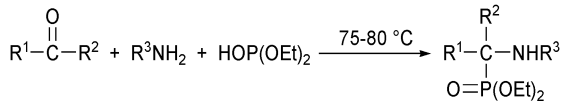
General

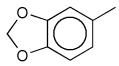
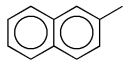
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were run in $CDCl_3$ solutions. Analyses were done on a Perkin Elmer 2400 autoanalyzer. The aldehydes, ketones, amines and diethyl phosphite are all commercial materials and were distilled before use.

General experimental procedure for the synthesis of α-aminophosphonates

Representative procedure for the aminophosphonate listed in entry 8. A mixture of 4-chlorobenzaldehyde (140.6 mg, 1 mmol), 4-chloroaniline (127.6 mg, 1 mmol) and diethyl phosphite (138 mg, 1 mmol) was stirred at 75–80 °C (oil bath) in neat without any solvent for 35 min (monitored by TLC). A solid appeared and was recrystallized from ethyl acetate–hexane (1 : 4) to furnish the corresponding α-aminophosphonate as a colorless solid (342 mg 88%), mp 117–118 °C; ν_{max} (KBr)/cm^{-1} 3292, 1598, 1490, 1230; δ_H 7.46–7.24 (m, 4H), 7.04 (d, J = 8.7 Hz, 2H), 6.50 (d, J = 8.8 Hz, 2H), 4.96 (br, 1H), 4.69 (d, J = 24.2 Hz, 1H), 4.22–3.73 (m, 4H), 1.38–1.08 (m, 6H); δ_C 145.2, 145.0, 134.6, 134.4, 129.7, 129.6, 129.5, 129.4, 123.6, 123.5, 115.3 (2C), 63.9, 63.7, 55.9 (d, J_{CP} = 150.3 Hz), 16.8,

Table 1 Synthesis of α-aminophosphonates



Entry	R^1	R^2	R^3	Time/min	Yield[a] (%)	Ref.
1	Ph	H	Ph	25	92	2*g*
2	Ph	H	*o*-OTsC$_6$H$_4$	30	86	
3	Ph	H	PhCH$_2$	25	93	2*g*
4	Ph	H	Cyclohexyl	30	88	2*e*
5	*p*-OMeC$_6$H$_4$	H	*p*-BrC$_6$H$_4$	30	85	
6	*m*-OMeC$_6$H$_4$	H	*p*-IC$_6$H$_4$	30	88	
7	*p*-ClC$_6$H$_4$	H	*o*-OMeC$_6$H$_4$	35	90	
8	*p*-ClC$_6$H$_4$	H	*p*-ClC$_6$H$_4$	35	88	
9	*p*-NO$_2$C$_6$H$_4$	H	*o*-CO$_2$MeC$_6$H$_4$	35	82	
10	*p*-NMe$_2$C$_6$H$_4$	H	Cyclohexyl	30	85	
11	*o*-OHC$_6$H$_4$	H	*m*-ClC$_6$H$_4$	30	85	
12	*p*-OAllylC$_6$H$_4$	H	*p*-MeC$_6$H$_4$	30	85	
13		H	*p*-ClC$_6$H$_4$	30	94	
14		H	*o*-MeC$_6$H$_4$	30	90	
15		H	Ph	25	88	2*e*
16		H	Ph	25	81[b]	2*g*
17		H	Cyclohexyl	25	85	
18	PhCH=CH(t)	H	Ph	25	80[b]	2*g*
19	n-Bu	H	Me$_2$CH	25	92	2*e*
20	Me$_2$CH	H	PhCH$_2$	25	88	2*e*
21	Me$_2$CH	H	*n*-Bu	25	88	
22	Citral	H	PhCH$_2$	25	80[b]	2*e*
23	Et	Et	PhCH$_2$	140	86	2*e*
24	Me$_2$CHCH$_2$	Me	PhCH$_2$	150	84	
25	Cyclopentanone		PhCH$_2$	45	90	
26	Cyclohexanone		PhCH$_2$	40	94	2*e*
27	Cyclohexanone		Ph	40	94	2*f*
28	Cycloheptanone		PhCH$_2$	50	88	
29	Cyclooctanone		PhCH$_2$	50	88	
30	4-Methylcyclohexanone		n-Bu	45	89	
31	4-*tert*-Butylcyclohexanone		PhCH$_2$	45	88	2*e*
32			PhCH$_2$	180	80	

[a] The yields refer to pure products characterized by spectral and analytical data. [b] The reaction was started at −20 °C and then temperature was riased to 75 °C.

16.5. (Found: C, 52.51; H, 5.08; N, 3.53. $C_{17}H_{20}NO_3PCl_2$ requires C, 52.61; H, 5.15; N, 3.61%).

This procedure is followed for the synthesis of all the aminophosphonates listed in Table 1. The liquid products are distilled directly from the reaction vessel under reduced pressure. The products are characterized by their IR, ^{1}H NMR , ^{13}C NMR spectral data and elemental analysis.

Spectral and analytical data of the α-aminophosphonates , not reported earlier are presented below in order of their entries in Table 1.

Entry 2. ν_{max} (neat)/cm^{-1} 3442, 1610, 1456, 1232; δ_H 7.86 (d, J = 8.3 Hz, 2H), 7.33–7.23 (m, 7H), 6.95–6.87 (m, 2H), 6.55 (t, J = 7.9 Hz, 1H), 6.34 (d, J = 8.0 Hz, 1H), 5.31 (br, 1H), 4.68 (dd, J = 5.3, 23.9 Hz, 1H), 4.12–3.77 (m, 4H), 2.19 (s, 3H), 1.28–1.16 (m, 6H); δ_C 145.8, 139.7, 139.5, 137.5, 135.6, 135.5, 133.2, 130.3 (2C), 129.0 (2C), 128.9, 128.3, 128.1, 128.0, 122.8, 117.9, 113.6, 63.9, 63.6, 56.0 (d, J_{CP} = 149.1 Hz), 22.2, 16.9, 16.6. (Found: C, 58.78; H, 5.72; N, 2.81. $C_{24}H_{28}NO_6SP$ requires C, 58.89; H, 5.77; N, 2.86%).

Entry 5. Mp 108–109 °C; ν_{max} (KBr)/cm^{-1} 3456, 1615, 1452, 1226; δ_H 7.34 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 6.85 (d, J = 7.8 Hz, 2H), 6.46 (d, J = 8.1 Hz, 2H), 4.65 (m, 1H), 4.10–3.83 (m, 4H), 3.77 (s, 3H), 3.69 (m, 1H), 1.36–1.10 (m, 6H); δ_C 159.8, 145.7, 132.2 (2C), 129.3, 128.9, 126.8, 115.9 (2C), 114.5, 110.5, 63.8, 63.6, 55.8 (d, J_{CP} = 151.2 Hz), 55.6, 16.8, 16.6. (Found: C, 50.31; H, 5.37; N, 3.22. $C_{18}H_{23}NO_4PBr$ requires C, 50.48; H, 5.41; N, 3.27%).

Entry 6. Mp 112–114 °C; ν_{max}(KBr)/cm^{-1} 3429, 1624, 1457, 1231; δ_H 7.33 (d, J = 8.7 Hz, 2H), 7.25–6.77 (m, 4H), 6.37 (d, J = 8.7 Hz, 2H), 4.65 (d, J = 24.0 Hz), 4.14–3.78 (m, 4H), 3.75 (s, 3H), 3.68–3.65 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H); δ_C 160.3, 146.5, 138.1 (2C), 137.4, 130.1, 130.0, 120.5, 116.4 (2C), 113.8, 113.7, 63.9, 63.6, 56.3 (d, J_{CP} = 149.8 Hz), 55.6, 16.9, 16.6. (Found: C, 45.31; H, 4.77; N, 2.87. $C_{18}H_{23}NO_4PI$ requires C, 45.49; H, 4.88; N, 2.95%).

Entry 7. ν_{max}(neat)/cm^{-1} 3419, 1600, 1510, 1244; δ_H 7.42–7.23 (m, 4H), 6.76–6.64 (m, 3H), 6.34–6.31 (m, 1H), 5.28 (br, 1H), 4.72 (d, J = 24.1 Hz, 1H), 4.13-3.88 (m, 3H), 3.85 (s, 3H), 3.83-3.72 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); δ_C 147.7, 136.4, 135.2, 134.0, 129.6, 129.5, 129.1, 129.0, 121.3, 118.3, 111.5, 110.0, 63.8, 63.5, 55.9, 55.8 (d, J_{CP} = 149.9 Hz), 16.8, 16.6. (Found: C, 56.21; H, 6.01; N, 3.55. $C_{18}H_{23}NO_4PCl$ requires C, 56.33; H, 6.04; N, 3.65 %).

Entry 9. Mp 82–84 °C; ν_{max}(KBr)/cm^{-1} 3317, 1685, 1519, 1232; δ_H 8.90–8.84 (m, 1H), 8.16 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 2.2, 8.7 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H), 6.60 (t, J = 7.3 Hz, 1H), 6.32 (d, J = 8.5 Hz, 1H), 4.94 (dd, J = 7.1, 25.3 Hz, 1H), 4.15–3.89 (m, 4H), 3.89 (s, 3H), 1.24 (t, J = 7.1 Hz, 6H); δ_C 169.1, 149.4, 149.2, 148.0, 144.2, 134.9, 132.2, 129.0, 128.9, 124.5, 124.0, 117.0, 112.3, 64.2, 63.8, 55.6 (d, J_{CP} = 148.1 Hz), 52.2, 16.8 (2C). (Found: C, 53.93; H, 5.37; N, 6.56. $C_{19}H_{23}N_2O_7P$ requires C, 54.03; H, 5.49; N, 6.63%).

Entry 10. ν_{max}(neat)/cm^{-1} 3444, 1614, 1519, 1236; δ_H 7.20 (dd, J = 2.2, 8.8 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 4.11–4.01 (m, 5H), 2.92 (s, 6H), 2.35-1.03 (m, 18H); δ_C 150.4, 129.5 (2C), 124.2, 112.7 (2C), 63.3, 62.8, 57.1 (d, J_{CP} = 154.8 Hz), 53.5, 53.3, 40.9, 34.7, 32.3, 26.5, 25.3, 24.8, 16.9, 16.6. (Found: C, 53.90; H, 5.41; N, 6.52. $C_{19}H_{23}N_2O_7P$ requires C, 54.03; H, 5.49; N, 6.63%).

Entry 11. ν_{max}(neat)/cm^{-1} 3480, 2927, 1610, 1222; δ_H 9.16 (br, 1H), 7.36–6.54 (m, 8H), 5.27 (d, J = 23.7 Hz, 1H), 4.90 (br, 1H), 4.25–3.82 (m, 4H), 1.39–1.07 (m, 6H); δ_C 155.9, 148.1, 135.2, 130.6, 129.8, 129.1, 121.7, 120.6, 118.8, 117.2, 114.2, 112.5, 64.3, 64.1, 51.4 (d, J_{CP} = 154.5 Hz), 16.8, 16.5. (Found: C, 55.08; H, 5.59; N, 3.70. $C_{17}H_{21}NO_4PCl$ requires C, 55.22; H, 5.72; N, 3.79%).

Entry 12. ν_{max}(neat)/cm^{-1} 3432, 1609, 1460, 1238; δ_H 7.36–6.48 (m, 8H), 6.01–5.90 (m, 1H), 5.36–3.62 (m, 10H), 2.14 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H); δ_C 158.6, 144.6, 133.6, 129.6 (2C), 129.4, 129.3, 128.6, 128.5, 127.5, 115.2, 115.1, 114.4 (2C), 69.0, 63.4, 63.3, 56.01 (d, J_{CP} = 151.2 Hz), 20.7, 16.9, 14.5. (Found: C, 64.61; H, 7.19; N, 3.51. $C_{21}H_{28}NO_4P$ requires C, 64.77; H, 7.25; N, 3.60%).

Entry 13. mp 114–115 °C; ν_{max}(KBr)/cm^{-1} 3460, 1612, 1460, 1254; δ_H 7.02–6.50 (m, 7H), 5.87 (s, 2H), 4.84 (br, 1H), 4.60 (d, J = 23.9 Hz, 1H), 4.14–3.69 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H); δ_C 148.4, 147.8, 145.4, 129.6, 129.3 (2C), 123.3, 121.7, 115.4 (2C), 108.7, 108.4, 101.5, 63.8, 63.6, 56.2 (d, J_{CP} = 151.8 Hz), 16.8, 16.6. (Found: C, 54.22; H, 5.27; N, 3.41. $C_{18}H_{21}NO_5PCI$ requires C, 54.35; H, 5.32; N, 3.52%).

Entry 14. ν_{max}(neat)/cm^{-1} 3430, 1608, 1452, 1236; δ_H 7.91–6.39 (m, 11H), 4.99–4.75 (m, 2H), 4.13-3.58 (m, 4H), 2.31 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 0.86 (t, J = 7.1 Hz, 3H); δ_C 144.9, 134.1, 130.7, 128.9, 128.4, 128.3, 128.2, 128.1, 127.5, 127.1, 126.6, 126.5, 125.4, 124.9, 118.7, 111.8, 63.7, 63.6, 56.9 (d, J_{CP} = 148.6 Hz), 18.1, 16.6, 14.6. (Found: C, 68.81; H, 6.75; N, 3.52. $C_{22}H_{26}NO_3P$ requires C, 68.92; H, 6.83; N, 3,65 %).

Entry 17. ν_{max}(neat)/cm^{-1} 3422, 1601, 1458, 1252; δ_H 7.13–6.85 (m, 3H), 4.32 (d, J = 22.0 Hz, 1H), 4.08–3.75 (m, 4H), 2.40–0.92 (m, 18H); δ_C 141.2, 127.1, 126.3, 125.2, 63.7, 63.1, 54.1, 53.5 (d, J_{CP} = 159.2 Hz), 34.5, 32.3, 26.3, 25.2, 24.7, 16.8, 16.5. (Found: C, 54.22; H, 7.85; N, 4.16. $C_{15}H_{26}NO_3SP$ requires C, 54.36; H, 7.91; N, 4.23%).

Entry 21. ν_{max}(neat)/cm^{-1} 3452, 1658, 1235; δ_H 4.04–3.92 (m, 4H), 2.70–2.63 (m, 1H), 2.51–2.44 (m, 2H), 1.98–1.96 (m, 1H), 1.34–0.74 (m, 20H); δ_C 61.8, 61.5, 61.1 (J_{CP} = 140.6 Hz), 49.9, 32.9, 29.3, 21.0, 20.8, 20.5, 18.2, 16.8, 14.2. Found: C, 54.21; H, 10.48; N, 5.17. $C_{12}H_{28}NO_3P$ requires C, 54.32; H, 10.54; N, 5.28%).

Entry 24. ν_{max}(neat)/cm^{-1} 3446, 1454, 1228; δ_H 7.39–7.20 (m, 5H), 4.20–3.89 (m, 7H), 2.04–0.96 (m, 18H); δ_C 141.5, 129.1 (2C), 128.5 (2C), 127.1, 62.3, 62.0, 57.6 (J_{CP} = 137.9 Hz), 48.1, 42.6, 25.7, 25.4, 23.4, 21.1, 17.0, 16.6. (Found: C, 62.24; H, 9.21; N, 4.22. $C_{17}H_{30}NO_3P$ requires C, 62.37; H, 9.24; N, 4.28%).

Entry 25. ν_{max}(neat)/cm^{-1} 3446, 1452, 1228; δ_H 7.31–7.16 (m, 5H), 4.18–3.87 (m, 6H), 1.99–1.22 (m, 15H); δ_C 141.7, 128.6 (2C), 128.4 (2C), 127.1, 64.2 (d, J_{CP} = 145.2 Hz), 62.2, 61.1, 48.7, 34.7, 34.6, 24.8, 24.7, 17.1, 17.0. (Found: C, 61.59; H, 8.29; N, 4.38. $C_{16}H_{26}NO_3P$ requires C, 61.72; H, 8.42; N, 4.50%).

Entry 28. ν_{max}(neat)/cm^{-1} 3446, 1456, 1234; δ_H 7.38–7.21 (m, 5H), 4.20–4.10 (m, 4H), 3.92–3.91 (m, 2H), 2.00–1.25 (m, 19H); δ_C 141.9, 128.6 (2C), 128.5 (2C), 127.1, 62.1, 62.0, 59.7 (d, J_{CP} = 135.0 Hz), 48.0, 34.2, 34.1, 30.4 (2C), 22.3, 22.2, 17.1, 17.0. (Found: C, 63.58; H, 8.79; N, 4.09. $C_{18}H_{30}NO_3P$ requires C, 63.70; H, 8.91; N, 4.13%).

Entry 29. ν_{max}(neat)/cm^{-1} 3442, 1450, 1230; δ_H 7.43–7.17 (m, 5H), 4.24–3.83 (m, 6H), 2.39–0.90 (m, 21H); δ_C 141.8, 128.8 (2C), 128.5 (2C), 127.1, 62.0, 61.9, 59.7 (d, J_{CP} = 134.8 Hz), 48.0, 30.0, 29.5 (2C), 28.5, 24.9, 21.4, 21.3, 17.1, 17.0. (Found: C, 60.01; H, 6.83; N, 3.61. $C_{19}H_{32}NO_3P$ requires C, 60.14; H, 6.91; N, 3.69 %).

Entry 30. ν_{max}(neat)/cm^{-1} 3444, 1455, 1234; δ_H 3.95–3.83 (m, 4H), 2.47–2.44 (m, 2H), 1.55-0.67 (m, 26H); δ_C 61.6, 61.5, 55.4 (d, J_{CP} = 141.0 Hz), 42.4, 33.5, 32.4, 29.9, 29.2, 28.7, 28.5, 22.8, 20.6, 16.9, 16.8, 14.3. (Found: C, 58.90; H, 10.51; N, 4.48. $C_{15}H_{32}NO_3P$ requires C, 58.99; H, 10.56; N, 4.59%).

Entry 32. ν_{max}(neat)/cm^{-1} 3442, 1452, 1236; δ_H 7.35–7.05 (m, 7H), 4.18–3.57 (m, 7H), 2.81–2.78 (m, 2H), 2.24–2.03 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); δ_C 141.0, 140.8, 133.3, 128.7 (2C), 128.6 (2C), 127.9, 127.2, 122.0, 63.5, 62.8, 58.9 (d, J_{CP} = 153.0 Hz), 47.8, 29.7, 25.3, 21.0, 16.9, 16.7. (Found: C, 60.01; H, 6.82; N, 3.59. $C_{19}H_{26}NO_3PS$ requires C, 60.14; H, 6.91; N, 3.69%).

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4 Although there are a couple of isolated examples of solvent-free, catalyst-free reactions like preparation of hydrazone under microwave irradiation (see: M. Joselink, R. S. Varma, S. Palanc and M. Kocevar, *Chem. Commun*, 2001, 1716); this protocol has not been explored for multi-component condensation or any complex reaction to any great extent.