

NbCl₅: an efficient catalyst for one-pot synthesis of α -aminophosphonates under solvent-free conditions

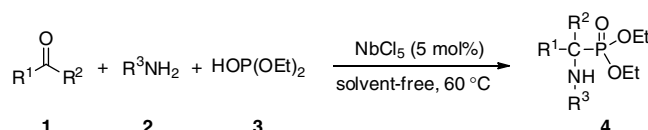
Jun-Tao Hou, Jian-Wu Gao and Zhan-Hui Zhang*

NbCl₅ has been found to be a very effective catalyst for the synthesis of a variety of α -aminophosphonates through the Kabachnik–Fields reaction of carbonyl compound, amine and diethyl phosphite under solvent-free conditions. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: NbCl₅; α -aminophosphonates; Kabachnik–Fields reaction; solvent-free

Introduction

The great importance of α -aminophosphonates is based on their presence in a number of biologically active compounds, as well as on their application as substitutes for the corresponding α -amino acids^[1] and versatile intermediates and catalysts in organic synthesis.^[2] The activity of α -aminophosphonates as peptidomimetics, pharmacogenic agents, antitumor agents, enzyme inhibitors, inhibitors of UDP-galactopyranose mutase and plant glutamine synthetase has been demonstrated.^[3] Consequently, different methods have been developed for the synthesis of α -aminophosphonates.^[4] Among them, the Kabachnik–Fields reaction appears to be still one of the simplest and most direct approaches.^[5] The reaction proceeds via the imine formed upon reaction of carbonyl compounds and amines, where an imine is converted to the corresponding aminophosphonates by reaction with phosphite. This one-pot reaction can be promoted by acid or base catalysts, microwave irradiation or by heating.^[6] Several acid catalysts, such as Lewis acids [recent examples are Al(H₂PO₄)₃,^[7] InCl₃,^[8] BiCl₃,^[9] FeCl₃,^[3a] YbCl₃,^[10] In(OTf)₃,^[11] Ce(OTf)₄,^[12] Al(OTf)₃,^[13] Sn(OTf)₂,^[14] Mg(ClO₄)₂,^[15] LiClO₄,^[16] ZrOCl₂ · 5H₂O,^[17] CAN,^[18] Yb(PFO)₃,^[19] SmI₂,^[20] TaCl₅–SiO₂^[21] and SbCl₃/Al₂O₃^[22]] Brønsted acids (recent examples are hypophosphorus acid,^[23] sulfamic acid^[24] and oxalic acid^[25]), heteropoly acids,^[26] solid acids (montmorillonite KSF,^[27] silica sulfuric acid,^[28] Amberlyst-15^[29] and Amberlite-IR 120^[30]), base catalysts such as CaCl₂^[31] and PPh₃,^[32] as well as other catalysts such as ZnO,^[33] TiO₂,^[34] tosyl chloride,^[35] phenyltrimethylammonium chloride,^[36] (bromodimethyl)sulfonium bromide,^[37] tetramethyl-tetra-3,4-pyridinoporphyrazinato copper (II) methyl sulfate [Cu(3,4-tmtppa)(MeSO₄)₄],^[38] tetra-*tert*-butylphthalocyanine,^[39] β -cyclodextrine (β -CD),^[40] NBS^[41] and mesoporous aluminosilicate nanocage,^[42] have been used to promote this reaction. Although these procedures worked nicely in many cases, sometimes some of these procedures were associated with one or more shortcomings such as long reaction time, low yield, lack of generality, requirement of excess of reagents, the use of expensive or less easily available catalysts and vigorous reaction conditions. Owing to the importance of α -aminophosphonates from pharmaceutical,



Scheme 1. The synthesis of α -aminophosphonates catalyzed by NbCl₅.

industrial and synthetic points of view, introduction of an efficient method for the preparation of these compounds is still in demand.

In recent years, the use of niobium catalysts for organic synthesis has been an ever-growing research area, and a variety of reactions have been developed, such as cyanosilylation of ketones,^[43] regioselective dealkylation of alkyl aryl ethers,^[44] alkoxide rearrangements,^[45] conversion of aldehydes and ketones to allylic halides,^[46] conversion of carboxylic acids to carboxamides^[47], deprotection of methoxy methyl ether^[48] and synthesis of pyranoquinoline derivatives,^[49] α -aminonitriles,^[50] 1,1-diacetates,^[51] β -hydroxyethers^[52] and hydrazide.^[53] However, to the best of our knowledge, there is no report on the synthesis of α -aminophosphonates using niobium pentachloride as a reagent. As part of our continuing interest in the development of new synthetic methodologies,^[54] we report herein an efficient and convenient procedure for the synthesis of α -aminophosphonates by one-pot three-component reaction of carbonyl compound, amine and diethyl phosphite catalyzed by NbCl₅ under solvent-free conditions (Scheme 1).

Experimental

Melting points were determined using an X-4 apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8900

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spectrometer. NMR spectra were taken with a Bruker DRX-500 spectrometer at 500 (^1H), 125 (^{13}C) and 201 MHz (^{31}P) using CDCl_3 as the solvent. Elemental analyses were carried out on a Vario EL III CHNOS elemental analyzer.

General Procedure for the Preparation of α -Aminophosphonates

A mixture of an aldehyde (1 mmol), aniline (1 mmol), diethyl phosphate (1.1 mmol) and NbCl_5 (0.05 mmol) was heated in an oil bath at 60°C for an appropriate time. The progress of the reaction was monitored by TLC using hexane and ethyl acetate as eluent. After completion, the reaction mixture was cooled to room temperature and treated with water (10 ml). The resulting mixture was extracted with ethyl acetate (3×5 ml). Drying (Na_2SO_4) and evaporation of the solvent under reduced pressure gave a residue that was purified by chromatography on silica gel (hexane/ethyl acetate). All the physical and spectroscopic data of the known compounds were in agreement with those reported in the literature.

Spectral and Analytical Data for New Compounds

[Benzo[1,3]dioxol-5-yl-(4-nitrophenylamino)-methyl]-phosphonic acid diethyl ester (**4o**)

Yellow solid; IR (KBr): 3265, 1596, 1504, 1481, 1413, 1286, 1230, 1110, 1049, 1022, 962, 837, 752 cm^{-1} ; ^1H NMR δ_{H} 1.17 (t, $J = 7.0$ Hz, 3H, $-\text{OCH}_2\text{Me}$), 1.32 (t, $J = 7.0$ Hz, 3H, $-\text{OCH}_2\text{Me}$), 3.68–3.76 (m, 1H, $-\text{OCH}_2\text{Me}$), 3.94–4.02 (m, 1H, $-\text{OCH}_2\text{Me}$), 4.08–4.19 (m, 2H, $-\text{OCH}_2\text{Me}$), 4.70 (dd, $J = 24.0, 7.5$ Hz, 1H, *CHP*), 5.57 (dd, $J = 10.0, 7.5$ Hz, 1H, *NH*), 5.96 and 5.98 (AB system, $J = 2.0$ Hz, 2H, $-\text{OCH}_2\text{O}-$), 6.57 (d, $J = 9.0$ Hz, 2H, *ArH*), 6.78 (d, $J = 7.5$ Hz, 1H, *ArH*), 6.89–6.92 (m, 2H, *ArH*), 8.03 (d, $J = 9.0$ Hz, 2H, *ArH*); ^{13}C NMR δ_{C} 16.2 (d, $^3J_{\text{PC}} = 5.7$ Hz), 16.4 (d, $^3J_{\text{PC}} = 5.7$ Hz), 55.2 (d, $^1J_{\text{PC}} = 152.5$ Hz), 63.3 (d, $^2J_{\text{PC}} = 7.2$ Hz), 63.8 (d, $^2J_{\text{PC}} = 7.2$ Hz), 101.3, 107.8 (d, $J_{\text{PC}} = 4.6$ Hz), 108.5 (d, $J_{\text{PC}} = 2.6$ Hz), 112.4, 121.3 (d, $J_{\text{PC}} = 6.4$ Hz), 126.0, 128.2 (d, $J_{\text{PC}} = 3.2$ Hz), 139.0, 147.7, 148.2, 151.8 (d, $J_{\text{PC}} = 13.8$ Hz); ^{31}P NMR δ_{P} 21.2. Anal. calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_7\text{P}$: C, 52.94; H, 5.18; N, 6.86. Found: C, 53.06; H, 4.99; N, 7.03.

[(4-Bromophenylamino)-(4-nitrophenyl)-methyl]-phosphonic acid diethyl ester (**4r**)

Yellow solid; IR (KBr): 3294, 2985, 2902, 1593, 1487, 1390, 1344, 1209, 1163, 958, 904, 815, 696 cm^{-1} ; ^1H NMR δ_{H} 1.19 (t, $J = 7.5$ Hz, 3H, $-\text{OCH}_2\text{Me}$), 1.31 (t, $J = 7.5$ Hz, 3H, $-\text{OCH}_2\text{Me}$), 3.83–3.91 (m, 1H, $-\text{OCH}_2\text{Me}$), 3.99–4.06 (m, 1H, $-\text{OCH}_2\text{Me}$), 4.09–4.19 (m, 2H, $-\text{OCH}_2\text{Me}$), 4.80 (d, $J = 26.0$ Hz, 1H, *CHP*), 4.86 (br s, 1H, *NH*), 6.41 (d, $J = 9.0$ Hz, 2H, *ArH*), 7.20 (d, $J = 9.0$ Hz, 2H, *ArH*), 7.63 (dd, $J = 8.5, 2.5$ Hz, 2H, *ArH*), 8.21 (d, $J = 8.5$ Hz, 2H, *ArH*); ^{13}C NMR δ_{C} 16.2 (d, $^3J_{\text{PC}} = 6.9$ Hz), 16.4 (d, $^3J_{\text{PC}} = 6.9$ Hz), 55.4 (d, $^1J_{\text{PC}} = 148.0$ Hz), 63.5 (d, $^2J_{\text{PC}} = 7.0$ Hz), 63.7 (d, $^2J_{\text{PC}} = 6.8$ Hz), 110.8, 115.3, 123.7, 129.5 (d, $J_{\text{PC}} = 5.1$ Hz), 132.0, 143.5, 144.6 (d, $J_{\text{PC}} = 14.4$ Hz), 147.6; ^{31}P NMR δ_{P} 20.4. Anal. calcd for $\text{C}_{17}\text{H}_{20}\text{BrN}_2\text{O}_5\text{P}$: C, 46.07; H, 4.55; N, 6.32. Found: C, 46.25; H, 4.72; N, 6.18.

[(4-Ethoxy-2-nitrophenylamino)-(4-nitrophenyl)-methyl]-phosphonic acid diethyl ester (**4u**)

Reddish brown solid; IR (KBr): 3369, 2979, 2903, 1635, 1608, 1573, 1525, 1469, 1419, 1299, 1215, 1149, 1110, 1097, 1014, 862, 783,

690 cm^{-1} ; ^1H NMR δ_{H} 1.28 (t, $J = 7.0$ Hz, 3H, $-\text{OCH}_2\text{Me}$), 1.30 (t, $J = 7.0$ Hz, 3H, $-\text{OCH}_2\text{Me}$), 1.38 (t, $J = 7.0$ Hz, 3H, ArOCH_2Me), 3.98 (q, $J = 7.0$ Hz, 2H, ArOCH_2Me), 4.02–4.19 (m, 4H, $-\text{OCH}_2\text{Me}$), 4.97 (dd, $J = 26.0, 7.0$ Hz, 1H, *CHP*), 6.46 (d, $J = 9.0$ Hz, 1H, *ArH*), 7.00 (dd, $J = 9.0, 3.0$ Hz, 1H, *ArH*), 7.65 (dd, $J = 9.0, 2.0$ Hz, 2H, *ArH*), 7.67 (d, $J = 3.0$ Hz, 1H, *ArH*); 8.23 (d, $J = 9.0$ Hz, 2H, *ArH*); 8.76 (dd, $J = 11.5, 7.0$ Hz, 1H, *ArH*); ^{13}C NMR δ_{C} 14.6, 16.3 (d, $^3J_{\text{PC}} = 5.3$ Hz), 16.4 (d, $^3J_{\text{PC}} = 5.3$ Hz), 55.6 (d, $^1J_{\text{PC}} = 148.1$ Hz), 63.7 (d, $^2J_{\text{PC}} = 6.6$ Hz), 64.0 (d, $^2J_{\text{PC}} = 7.1$ Hz), 64.3, 108.9, 115.5, 123.3 (d, $J_{\text{PC}} = 2.8$ Hz), 126.7, 128.4 (d, $J_{\text{PC}} = 4.5$ Hz), 133.1, 138.4 (d, $J_{\text{PC}} = 13.6$ Hz), 142.8 (d, $J_{\text{PC}} = 3.5$ Hz), 147.8, 150.2; ^{31}P NMR δ_{P} 28.5. Anal. calcd for $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_8\text{P}$: C, 50.33; H, 5.34; N, 9.27. Found: C, 50.21; H, 5.50; N, 9.07.

[(4-Ethoxy-2-nitrophenylamino)-(3-nitrophenyl)-methyl]-phosphonic acid diethyl ester (**4v**)

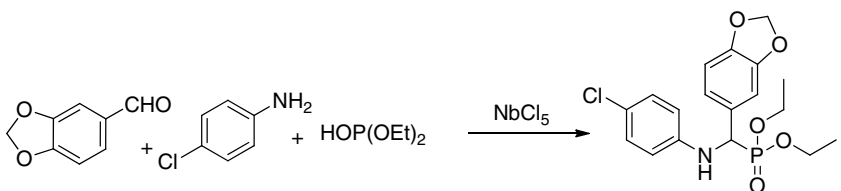
Yellow solid; IR (KBr): 3350, 2983, 1635, 1573, 1521, 1481, 1415, 1350, 1259, 1225, 1137, 1101, 1047, 979, 817, 682 cm^{-1} ; ^1H NMR δ_{H} 1.29 (t, $J = 7.0$ Hz, 6H, $-\text{OCH}_2\text{Me}$), 1.35 (t, $J = 7.0$ Hz, 3H, ArOCH_2Me), 3.99 (q, $J = 7.0$ Hz, 2H, ArOCH_2Me), 4.06–4.19 (m, 4H, $-\text{OCH}_2\text{Me}$), 4.97 (dd, $J = 26.0, 7.0$ Hz, 1H, *CHP*), 6.50 (d, $J = 9.0$ Hz, 1H, *ArH*), 7.01 (dd, $J = 9.0, 3.0$ Hz, 1H, *ArH*), 7.57 (t, $J = 9.0$ Hz, 1H, *ArH*), 7.68 (d, $J = 3.0$ Hz, 1H, *ArH*); 7.83 (d, $J = 8.0$ Hz, 1H, *ArH*); 8.19 (d, $J = 8.0$ Hz, 1H, *ArH*); 8.32 (s, 1H, *ArH*), 8.76 (dd, $J = 11.5, 7.0$ Hz, 1H, *ArH*); ^{13}C NMR δ_{C} 14.6, 16.2 (d, $^3J_{\text{PC}} = 5.3$ Hz), 16.4 (d, $^3J_{\text{PC}} = 5.3$ Hz), 54.8 (d, $^1J_{\text{PC}} = 148.1$ Hz), 63.7 (d, $^2J_{\text{PC}} = 7.0$ Hz), 64.0 (d, $^2J_{\text{PC}} = 7.1$ Hz), 64.3, 108.9, 115.5, 112.6 (d, $J_{\text{PC}} = 4.8$ Hz), 123.3 (d, $J_{\text{PC}} = 2.8$ Hz), 126.7, 129.9, 133.0, 133.4 (d, $J_{\text{PC}} = 4.5$ Hz), 137.8 (d, $J_{\text{PC}} = 3.5$ Hz), 138.4 (d, $J_{\text{PC}} = 13.6$ Hz), 148.4 (d, $J_{\text{PC}} = 3.0$ Hz), 150.2; ^{31}P NMR δ_{P} 18.7. Anal. calcd for $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_8\text{P}$: C, 50.33; H, 5.34; N, 9.27; Found: C, 50.18; H, 5.53; N, 9.10.

[(4-Nitrophenylamino)-thiophen-2-yl-methyl]-phosphonic acid diethyl ester (**4aa**)

Yellow solid; IR (KBr): 3255, 3197, 1598, 1502, 1481, 1315, 1230, 1114, 1051, 1014, 839, 754, 646 cm^{-1} ; ^1H NMR δ_{H} 1.22 (t, $J = 7.0$ Hz, 3H, $-\text{OCH}_2\text{Me}$), 1.29 (t, $J = 7.0$ Hz, 3H, $-\text{OCH}_2\text{Me}$), 3.84–3.91 (m, 1H, $-\text{OCH}_2\text{Me}$), 4.05–4.10 (m, 1H, $-\text{OCH}_2\text{Me}$), 4.13–4.23 (m, 2H, $-\text{OCH}_2\text{Me}$), 5.16 (d, $J = 24.0$ Hz, 1H, *CHP*), 6.56 (br s, 1H, *NH*), 6.73 (d, $J = 8.5$ Hz, 2H, *ArH*), 6.98 (s, 1H, *ArH*), 7.23–7.29 (m, 2H, *ArH*), 8.03 (d, $J = 8.5$ Hz, 2H, *ArH*); ^{13}C NMR δ_{C} 16.3 (d, $^3J_{\text{PC}} = 5.7$ Hz), 16.4 (d, $^3J_{\text{PC}} = 5.7$ Hz), 51.2 (d, $^1J_{\text{PC}} = 158.4$ Hz), 63.7 (d, $^2J_{\text{PC}} = 7.1$ Hz), 64.0 (d, $^2J_{\text{PC}} = 7.1$ Hz), 112.3, 125.8 (d, $J_{\text{PC}} = 3.5$ Hz), 126.0, 126.9 (d, $J_{\text{PC}} = 6.8$ Hz), 127.3 (d, $J_{\text{PC}} = 2.6$ Hz), 137.9, 139.0, 152.1 (d, $J_{\text{PC}} = 12.0$ Hz); ^{31}P NMR δ_{P} 19.4. Anal. calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_5\text{PS}$: C, 48.64; H, 5.17; N, 7.56; Found: C, 48.81; H, 5.01; N, 7.75.

[1-(4-Nitrophenylamino)-1-phenyl-ethyl]-phosphonic acid diethyl ester (**4af**)

Yellow solid; IR (KBr): 3240, 1635, 1618, 1600, 1487, 1325, 1276, 1222, 1113, 1051, 1024, 875, 617 cm^{-1} ; ^1H NMR δ_{H} 1.24 (t, $J = 7.0$ Hz, 6H, $-\text{OCH}_2\text{Me}$), 2.04 (d, $J = 16.0$ Hz, 3H, *COMe*), 3.84–4.03 (m, 4H, OCH_2Me), 5.64 (br s, 1H, *NH*), 6.36 (d, $J = 8.0$ Hz, 2H, *ArH*), 7.32 (t, $J = 7.0$ Hz, 1H, *ArH*), 7.37 (t, $J = 7.0$ Hz, 2H, *ArH*), 7.52 (d, $J = 7.0$ Hz, 2H, *ArH*), 7.90 (d, $J = 8.0$ Hz, 2H, *ArH*); ^{13}C NMR δ_{C} 16.3 (d, $^3J_{\text{PC}} = 5.4$ Hz), 20.6 (d, $^3J_{\text{PC}} = 3.0$ Hz), 59.7 (d, $^1J_{\text{PC}} = 148.4$ Hz), 63.8 (d, $^2J_{\text{PC}} = 7.1$ Hz), 64.0 (d, $^2J_{\text{PC}} = 7.1$ Hz), 114.7, 125.4, 127.7 (d, $J_{\text{PC}} = 4.8$ Hz), 127.9 (d, $J_{\text{PC}} = 3.1$ Hz), 128.6, 136.6 (d, $J_{\text{PC}} = 7.8$ Hz), 138.7, 150.7 (d, $J_{\text{PC}} = 14.6$ Hz); ^{31}P NMR δ_{P}

Table 1. Investigation of the amounts of catalyst and temperature effects on the reaction of piperonal, *p*-chloroaniline and diethyl phosphite


Entry	Catalyst loading (mol%)	Temperature (°C)	Time (min)	Yield (%) ^a
1	No	60	120	30
2	3	60	35	84
3	5	60	35	95
4	7	60	35	96
5	10	60	35	96
6	5	40	120	75
7	5	50	45	92
8	5	70	35	96

^a Isolated yields

24.0. Anal. calcd for $C_{18}H_{23}N_2O_5P$: C, 57.14; H, 6.13; N, 7.40; Found: C, 57.32; H, 5.98; N, 7.59.

{1,4-Phenylenebis[(4-nitrophenylamino)methylene]}bis-(phosphonic acid tetraethyl ester) (**4ag**)

Yellow solid; IR (KBr): 3276, 3070, 1597, 1541, 1485, 1442, 1296, 1280, 1228, 1110, 1020, 979, 837, 754 cm^{-1} ; 1H NMR δ_H 1.06 (t, $J = 7.0$ Hz, 6H, $-OCH_2Me$), 1.29 (t, $J = 7.0$ Hz, 6H, $-OCH_2Me$), 3.62–3.67 (m, 2H, $-OCH_2Me$), 3.88–3.95 (m, 2H, $-OCH_2Me$), 4.14–4.23 (m, 4H, $-OCH_2Me$), 4.87 (dd, $J = 23.5, 8.5$ Hz, 2H, CHP), 6.63 (d, $J = 9.0$ Hz, 4H, ArH), 7.51 (s, 4H, ArH), 7.97 (d, $J = 9.0$ Hz, 4H, ArH); ^{13}C NMR δ_C 16.2 (d, $^3J_{PC} = 2.6$ Hz), 16.3 (d, $^3J_{PC} = 2.6$ Hz), 16.4 (d, $^3J_{PC} = 2.5$ Hz), 16.5 (d, $^3J_{PC} = 2.5$ Hz), 54.9 (d, $^1J_{PC} = 153.8$ Hz), 63.4 (d, $J = 3.5$ Hz), 63.5 (d, $^2J_{PC} = 3.5$ Hz), 63.4 (d, $^2J_{PC} = 3.5$ Hz), 63.6 (d, $^2J_{PC} = 3.5$ Hz), 63.7 (d, $^2J_{PC} = 3.5$ Hz), 112.0, 126.0, 128.4, 135.2, 138.6, 152.4 (d, $J_{PC} = 7.1$ Hz); ^{31}P NMR δ_P 20.7. Anal. calcd for $C_{28}H_{36}N_4O_{10}P_2$: C, 51.69; H, 5.58; N, 8.61; Found: C, 51.82; H, 5.76; N, 8.43.

Results and Discussion

In the initial experiment, the one-pot, three-component reaction of *p*-chloroaniline, piperonal and diethyl phosphite was chosen as the model reaction to optimize the reaction conditions. We were pleased to find that the reaction occurred efficiently to afford the corresponding α -aminophosphonates in 95% yield when 5 mol% $NbCl_5$ was used at 60 °C under solvent-free conditions (Table 1, entry 3). Moreover, we observed that the yields were obviously affected by the amount of $NbCl_5$ loaded and the reaction temperature. Lowering the amount of the catalyst or the reaction temperature led to the formation of the product in lower yields. Importantly, only 30% yield of the product was obtained in the absence of $NbCl_5$. The above results showed that $NbCl_5$ was essential to the reaction, and the best results were obtained when the reaction was carried out with 5 mol% of $NbCl_5$ under solvent-free conditions at 60 °C.

Under the optimized conditions, the substrate scope of the Kabachnik–Fields reaction was investigated, and a range of α -aminophosphonates were prepared (Table 2). Various aromatic aldehydes containing electron-withdrawing groups and electron-donating groups gave the corresponding α -aminophosphonates in high to excellent yields (Table 2, entries 1–23). In general, the electronic properties of the substituents of aromatic aldehydes did not affect the yields. However, α,β -unsaturated aldehyde (entry 24) and heterocyclic aromatic aldehydes (entries 25–28) were found to be less reactive in this reaction and gave slightly lower yields of the desired products; incomplete conversion of the starting materials to the product was observed by GC or TLC. Moreover, it was noteworthy that the methodology worked well for cyclic ketone (entry 31). However, poor yield was obtained when the reaction was applied to unactivated ketones such as acetophenone (entry 32). On the other hand, various amines were examined as substrates for this three-component reaction. The nature of the substituents on the aromatic ring of aniline had a delicate effect on this conversion. The presence of an electron-withdrawing group on the benzene ring decreased the reactivity and required longer reaction times. Furthermore, bis(α -aminophosphonates) were also obtained successfully under similar conditions (entries 33–35). These compounds are multidentate ligands which may be used for the extraction of metals and can be employed as the monomers for the preparation of macrocyclic or polymeric compounds carrying phosphonate and amine moieties.^[3a] No competitive side reactions such as aromatic nucleophilic substitution of halogen atom, nucleophilic cleavage of the *O*-Me group or decomposition of acid sensitive substrates were observed.

Finally, the efficacy of $NbCl_5$ was compared with that of other catalysts reported earlier the synthesis of **4a** was considered as a representative example (Table 3). As demonstrated in Table 3, $NbCl_5$ is an equally or more efficient catalyst for this three-component reaction in terms of yield and reaction rate.

Conclusion

In conclusion, we have developed a simple, mild and practical protocol for the synthesis of α -aminophosphonates through

Table 2. Scope for NbCl₅-catalyzed synthesis of α -aminophosphonates

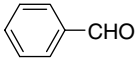
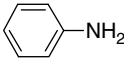
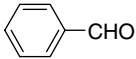
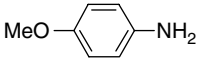
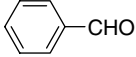

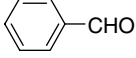
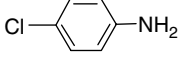
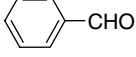
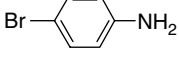
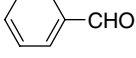
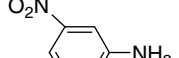
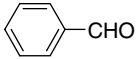
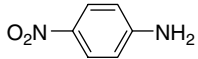
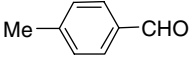
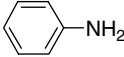

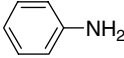
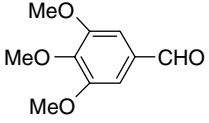
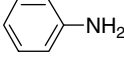
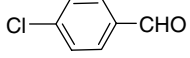
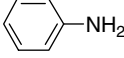
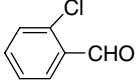
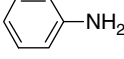
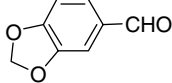
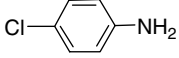
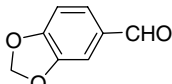

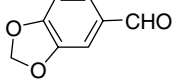
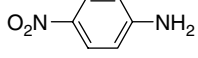
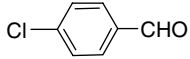
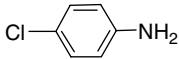

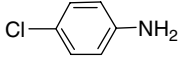

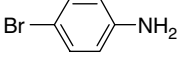
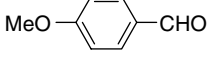
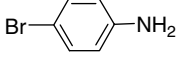

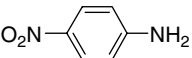

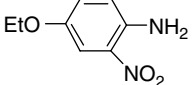
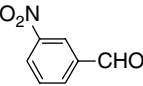
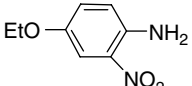
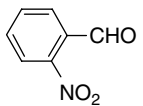
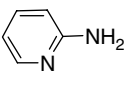
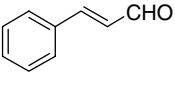
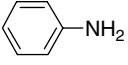
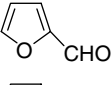
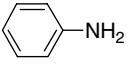
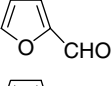
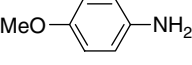
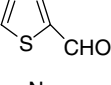
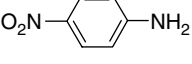
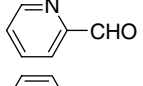
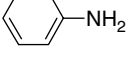
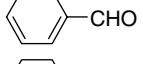
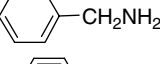
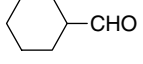
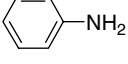
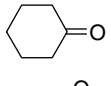
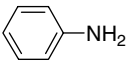
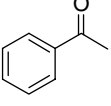
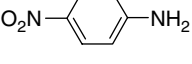
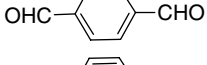
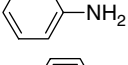
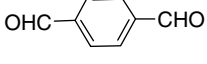
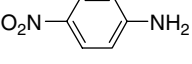
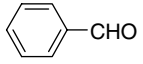
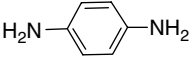
Entry	Aldehyde/ketone	Amine	Product	Time (min)	Yield (%) ^a	Melting point (°C)	
						Found	Reported
1			4a	30	95	90–91	89–90 ^[4c]
2			4b	35	92	71–72	70–73 ^[4c]
3			4c	30	95	116–117	117–118 ^[26b]
4			4d	40	92	113–114	112–113 ^[26b]
5			4e	45	93	121–122	121–123 ^[32]
6			4f	50	92	129–130	128–130 ^[32]
7			4g	50	90	146–147	145–147 ^[32]
8			4h	50	87	64–65	63–65 ^[6b]
9			4i	50	90	102–103	102–103 ^[6b]
10			4j	60	89	109–110	107–109 ^[32]
11			4k	25	92	58–59	57 ^[34]
12			4l	28	93	88–89	88 ^[34]
13			4m	35	95	115–116	114–115 ^[6a]
14			4n	30	92	102–103	102–104 ^[55]
15			4o	30	95	150–151	
16			4p	30	90	178–179	117–118 ^[6a]
17			4q	30	96	150–151	149–150 ^[26b]
18			4r	30	94	181–183	
19			4s	40	92	107–108	106–108 ^[6a]

Table 2. (Continued)

Entry	Aldehyde/ketone	Amine	Product	Time (min)	Yield (%) ^a	Melting point (°C)	
						Found	Reported
20			4t	45	90	115–116	115 ^[11]
21			4u	35	95	111–112	
22			4v	50	86	146–148	
23			4 w	50	80	144–145	143–145 ^[56]
24			4x	30	85	105–106	104 ^[34]
25			4y	60	86	51–52	50–52 ^[6b]
26			4z	50	90	Oil	Oil ^[41]
27			4aa	60	83	146–147	
28			4ab	60	89	89–90	90 ^[8]
29			4ac	30	90	Oil	Oil ^[6c]
30			4ad	30	92	Oil	Oil ^[18]
31			4ae	60	90	109–110	108–109 ^[6c]
32			4af	60	45	140–141	
33 ^b			4ag	80	90	185–186	184–185 ^[57]
34 ^b			4 ah	90	89	264–266	
35 ^c			4ai	50	91	200–201	199–200 ^[57]

^a Isolated yields. ^b Two equivalents of amines were used. ^c Two equivalents of benzaldehyde were used.

the three-component reaction of carbonyl compound, amine and diethyl phosphite catalyzed by NbCl₅ under solvent-free conditions. The methods allow the preparation of a wide variety of α -aminophosphonates in good to excellent yields in short time.

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Table 3. Comparison of our results with previously reported data for synthesis of **4a**

Entry	Catalyst	Reaction conditions	Time	Yield (%)	Reference
1	Al(H ₂ PO ₄) ₃	Solvent-free/100 °C	90 min	93	[7]
2	InCl ₃	THF/r.t.	11 h	92	[8]
3	BiCl ₃	CH ₃ CN/reflux	6 h	92	[9]
4	FeCl ₃	THF/60 °C	0.75 h	92	[3a]
5	YbCl ₃	CH ₃ CN/r.t.	24 h	93	[10]
6	In(OTf) ₃	THF/reflux	21 h	79	[11]
7	Ce(OTf) ₄	Solvent-free/50 °C	20 min	94	[12]
8	Mg(ClO ₄) ₂	Solvent-free/80 °C	5 h	99	[15]
9	CAN	Solvent-free/reflux	30 min	96	[18]
10	TaCl ₅ -SiO ₂	CH ₂ Cl ₂ /r.t.	22 h	92	[21]
11	TiO ₂	Solvent-free/50 °C	3.5 h	98	[34]
12	ZnO	Solvent-free/r.t.	9 h	90	[33]
13	NBS	Solvent-free/50 °C	3 h	99	[41]
14	Silica sulfuric acid	CH ₃ CN/r.t.	5 h	87	[28]
15	3D mesoporous aluminosilicate nanocage	CH ₃ CN/80 °C	4 h	86	[42]
16	Cu(3,4-tmtppa)(MeSO ₄) ₄	H ₂ O/80 °C	0.5 h	96	[38]
17	β-CD	H ₂ O/reflux	24 h	61	[40]
18	CaCl ₂	Solvent-free/60 °C	3 h	90	[31]
19	PPh ₃	Solvent-free/60 °C	1 h	87	[32]
20	NbCl ₅	Solvent-free/50 °C	30 min	95	This work

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