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Pentafluorophenylammonium triflate (PFPAT): A new organocatalyst for the one-pot three-component synthesis of α-aminophosphonates

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Abstract. In the presence of a catalytic amount of pentafluorophenylammonium triflate (10 mol %), dimethyl phosphite reacts with imines (generated *in situ* from aldehydes and amines) to yield the corresponding coupling products in good yield. The organocatalyst is air-stable, cost-effective, easy to handle, and easily removed from the reaction mixtures.

Keywords. α-Amino phosphonates; nucleophilic addition; Kabachnik–Fields reaction; organocatalyst.

1. Introduction

Owing to their pharmacological and medicinal importance,[1] synthesis of α-aminophosphonates, the structural analogues of α-amino acids, has received increased attention during the last two decades. Their potential as peptidomimetics,[2] enzyme inhibitors[3–5] including HIV protease,[6,7] herbicides,[8] insecticides,[9] fungicides,[10] and antiviral agents,[11] as well as their role for antibody generation[12] is well-documented. Of the variety of reported methods[13–20] for the synthesis of α-aminophosphonates, most are based on nucleophilic addition of phosphates to imine-catalysed base,[21] protic,[22] or Lewis acids such as aluminium(III) chloride,[23] zirconium(IV) chloride,[24] zinc(II) chloride,[25] and boron trifluoride–diethyl ether complex.[26] However, these reactions cannot be carried out in a one-step operation because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids. In recent years, several new efficient methods have been developed including the use of $H_3PW_{12}O_{40}$,[27] magnesium percholorate,[28] $PhNMe_3Cl$,[29] bismuth nitrate pentahydrate,[30] scandium tris (dodecyl sulphate),[31] indium(III) chloride,[32] metal triflates [M(OTf)n, M=La, Li, Mg, Al, Cu, Ce],[33] $LiClO_4$,[34] Al_2O_3,[35] CF_3CO_2H,[36] montmorillonite KSF,[37] (bromodimethyl) sulphonium bromide,[38] lanthanide triflate,[39] $InCl_3$,[40] $TaCl_5$–SiO_2,[41] oxalic acid,[42] trifluoroethanol[43] and succinic acid.[44] These methods show varying degrees of success as well as limitations such as harsh reaction conditions, expensive and detrimental metal reagents, tedious work-up, low product yields, long reaction times, and co-occurrence of several side products. Therefore, a simple, efficient method for the synthesis of α-aminophosphonates remains an attractive goal.

In recent years, increasing attention has been paid to organocatalysts due to economic and environmental considerations.[45–48] Organocatalysts have received extensive recognitions in organic synthesis due to its unique properties of being readily affordable, selectivity, longer catalyst life, negligible equipment corrosion, ease of product separation, nontoxic and reusability. Of these, pentafluorophenylammonium triflate (PFPAT) has emerged as a powerful Brønsted acid catalyst to perform many useful organic transformations[49–57] under mild reaction conditions. Due to the current challenges for developing environmentally benign synthetic processes and in continuation of our interest in the application of new organocatalysts for various organic transformations,[52–57] we report an efficient route for the synthesis of α-aminophosphonate derivatives using PFPAT as a catalyst (scheme 1).

2. Experimental

2.1 *Apparatus and analysis*

NMR spectra were determined on an FT-NMR Bruker AV-400 spectrometer in $CDCl_3$ or DMSO-d_6 and are expressed in δ values relative to tetramethylsilane; coupling constants (J) are measured in Hertz. Melting points were determined on an Electrothermal 9100 apparatus. Infrared spectra were recorded on a Rayleigh WQF-510 Fourier transform instrument. Commercially

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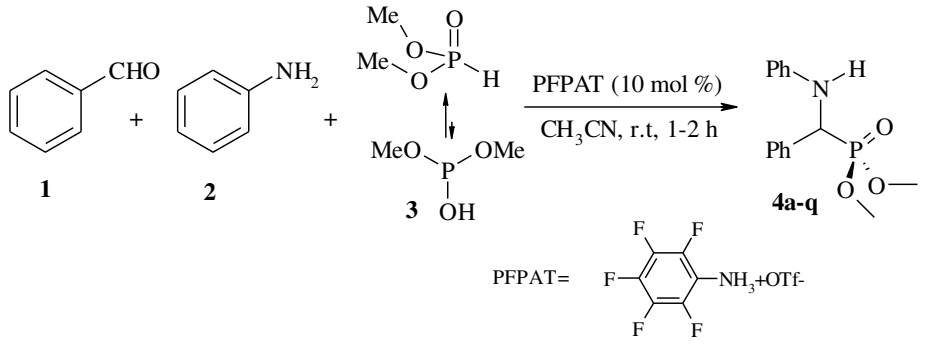


Scheme 1. Synthesis of α-aminophosphonates **4** from various aldehydes and amines.

available reagents were used throughout without further purification.

2.2 *General procedure for the synthesis of α-aminophosphonate derivatives*

A mixture of amine (1 mmol), aldehyde (1 mmol), and dimethyl phosphite (1 mmol) dissolved in 3 mL toluene, and PFPAT (10 mol%) was stirred for 1 h at room temperature. The reaction was monitored by TLC. The reaction mixture, after being cooled to room temperature was poured onto crushed ice and stirred for 5–10 min. The crystalline product was collected by filtration under suction (water aspirator), washed with ice-cold water (40 ml) and then recrystallized from hot ethanol to afford pure products. Products were characterized by comparison of their physical and spectral data with those of authentic samples.[27] Spectroscopic data for selected examples are shown here.

2.3 *Spectroscopic data for selected examples*

Compound (**4a**): White solid, mp 87°C; 1H NMR (400 MHz, $CDCl_3$): δ = 3.51 (d, J = 10.5 Hz, 3H), 3.81 (d, J = 10.6 Hz, 3H), 4.82 (d, J = 24 Hz, 1H), 4.84 (br s, 1H), 6.64 (d, J = 8.0 Hz, 2H), 6.74 (t, J = 7.2 Hz, 1H), 7.1 (t, J = 7.7 Hz, 2H), 7.3 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.5 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 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), 68.5 (CH), 114.3 (CH), 119.0 (CH), 128.2 (d, $^3J_{p-c}$ = 5.8 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).

Compound (**4b**): White solid, mp 60°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (m, 1H), 3.79 (d, J = 11.8 Hz, 3H), 3.83 (d, J = 10.1 Hz, 3H), 5.2 (d, J = 24 Hz, 1H), 6.8–7.28 (m, 5H), 7.3 (d, J = 8.5 Hz, 2H), 7.5 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 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 (C), 140.0 (C), 146.6 (d, $^2J_{p-c}$ = 14.5 Hz, C).

Compound (**4e**): Viscous yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.6 (d, J = 10.6 Hz, 3H), 3.8 (d, J = 10.6 Hz, 3H), 4.5 (br s, 1H), 5.0 (d, J = 23.8 Hz, 1H), 6.37–7.40 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50 (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 (CH), 119.5 (CH), 129.9 (d, $^3J_{p-c}$ = 5.6 Hz, CH), 143.1 (CH), 146.3 (d, $^2J_{p-c}$ = 13.3 Hz, C),149.4 (C).

Compound (**4k**): Viscous yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.49 (d, 3H, J = 10.5 Hz), 3.71 (d, 3H, J = 10.6 Hz), 4.71–4.79 (d, 1H, $^1J_{P-H}$ = 23.9 Hz), 6.5–7.25 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.9 (CH), 54.03 (OCH_3), 54.3 (OCH_3), 114.0 (CH), 121.9 (CH), 125.7 (CH), 129.3 (CH), 130.1 (CH), 131.2 (C), 135.0 (C), 149.2 (C).

Compound (**4p**): White solid, mp 104°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33–1.50 (m, 6H), 1.54–2.10 (4H, m), 3.64 (d, J = 10.4 Hz, 3H), 3.66 (d, J = 10.4 Hz, 3H), 4.84 (br s, 1 H), 7.00 (t, J = 7.1 Hz, 1H),

Table 1. Effect of different PFPAT and solvents on formation of **4**.

Entry	PFPAT amount (mol %)	Condition/solvent	Time (h)/ yield
1	0	r.t/CH_3CN	12/0
2	5	r.t/ CH_3CN	5/60
3	10	r.t / CH_3CN	1/90
4	10	r.t/ toluene	8/50
5	10	r.t/CH_2Cl_2	5/65
6	10	r.t/THF	5/55
7	10	r.t/ethanol	3/60
8	10	r.t/H_2O	5/20
9	10	r.t/diethyl ether	8/10
10	15	r.t / CH_3CN	1/90

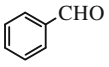
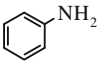
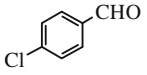
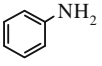
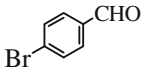
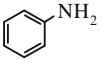
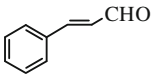
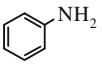
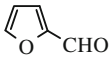
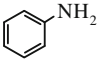
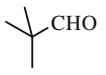
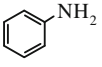
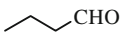
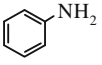
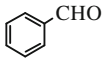
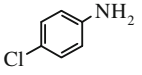
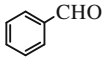
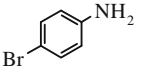
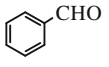
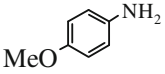
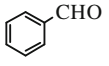
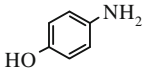
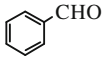
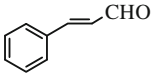
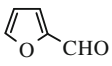
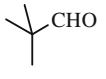
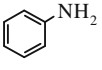
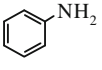
7.13 (d, $J = 8.1$ Hz, 2H), 7.16 (t, $J = 8.1$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $d = 19.7$ (CH_2), 25.6 (CH_2), 25.1 (CH_2), 52.2 (d, $^2J_{P-C} = 7.4$ Hz, OCH_3), 53.2 (d, $^2J_{P-C} = 7.4$ Hz, OCH_3), 65.2 (d, $J_{P-C} = 155.1$ Hz, C), 118.2 (CH), 118.3 (CH), 129.1 (CH), 145.5 (C).

3. Results and discussion

In order to optimize the reaction conditions, we chose the condensation of the reaction of benzaldehyde, aniline and dimethyl phosphite catalysed by PFPAT under different conditions both in the absence and in the presence of PFPAT and results are given in table 1.

It is noteworthy that in the absence of catalyst, no product formation was observed even after long reaction times (table 1, entry 1). Then, the effect of temperature, the amount of catalyst, and the reaction time on the yield of the product were examined. It was found that this condensation reaction was affected by various solvents (table 1, entries 3–9). Among them, acetonitrile provided the highest yield at room temperature

Table 2. PFPAT-Catalyzed one-pot synthesis of α-amino phosphonate derivatives.

Entry	Aldehyde/Ketone	Amine	Time (min)	Product	Yield (%)
1			60	**4a**	90
2			60	**4b**	95
3			60	**4c**	95
4			90	**4d**	85
5			60	**4e**	95
6			120	**4f**	80
7			120	**4g**	80
8			100	**4h**	85
9			90	**4i**	88
10			90	**4j**	90
11			120	**4k**	85
12			60	**4l**	90
13			70	**4m**	85
14			60	**4n**	90
15			60	**4o**	85
16			120	**4p**	80
17			120	**4q**	80

after 1 h (table 1, entry 3). Then, we examined the optimal amount of catalyst using the same model reaction (table 1, entries 1–3). We observed that 10 mol% of PFPAT was sufficient to catalyse the reaction smoothly. Increasing either the amount of catalyst and/or prolonging the reaction time did not improve the yield (table 1, entry 10), while reducing these factors led to a reduction in product yield (table 1, entry 2).

Having optimized the reaction conditions, the scope and efficiency of this approach was explored for the synthesis of a wide variety of substituted α-amino phosphonate and results are summarized in table 2.

A wide range of structurally varied aldehyde reacted smoothly and quickly to give the corresponding α-amino phosphonate in high yield and purity as listed in table 2. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields. It could also be concluded that the aldehydes bearing electron-withdrawing groups required shorter time and gave higher yields (table 1, entries 2 and 3). This method is even effective with aliphatic aldehydes, which normally produce low yields due to their intrinsic lower reactivity. In addition, when α,β-unsaturated aldehydes reacted with aniline and dimethyl phosphite in acetonitrile in the presence of PFPAT, a longer reaction time was required for the reaction to be completed and to give the 1,2-addition products in high yields (table 2, entry 4). This method is also effective with ketones. No α-hydroxy phosphonate (an adduct between an aldehyde and dimethyl phosphite) was obtained under these reaction conditions. This is due to rapid formation and activation of the imines or iminium salts by PFAPT. Moreover, the highly hydrophobic pentafluorophenyl moiety effectively repels H_2O produced by the dehydration steps.

Arylamines with electron-donating substituents such as alkyl and methoxyl groups and with weak electron-withdrawing groups such as chloro and bromo all gave good yields of products.

In addition, the PFPAT catalyst was easily removed from the reaction mixture after work-up, by washing with an aqueous NaOH solution to remove the CF_3SO_3H, followed by distillation under reduced pressure ($C_6F_5NH_2$: bp 153°C at 760 mmHg).[42]

4. Conclusion

In conclusion, we have developed an efficient synthesis of α-aminophosphonate derivatives via the one-pot three-component coupling reaction of aldehydes, amines and dimethyl phosphite under mild conditions using PFPAT as an efficient organocatalyst. In contrast to the existing methods using potentially hazardous catalysts/additives, the present method offers the following competitive advantages: PFPAT is easy-to prepare from commercially available pentafluoroaniline and triflic acid; short reaction time; ease of product isolation/purification by non-aqueous work-up; absence of side reaction; low cost and simplicity in process and handling; and an environmentally benign process.

Supplementary information

Supplementary data associated with this article synthesis and NMR spectra can be found in the online version (ww.ias.ac.in/chemsci).

Acknowledgement

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References

1. Bartlett P A, Hanson J E and Giannousis P P 1990 *J. Org. Chem.* **55** 6268
2. Kafarski P and Lejczak B 1991 *Phosphorus Sulfur Silicon Relat. Elem.* **63** 193
3. Allen M C, Fuhrer W, Tuck B, Wade R and Wood J M 1989 *J. Med. Chem.* **32** 1652
4. Logusch E W, Walker D M, McDonald J F, Leo G C and Franz J E 1988 *J. Org. Chem.* **53** 4069
5. Giannousis P P and Bartlett P A 1987 *J. Med. Chem.* **30** 1603
6. Peyman A, Budt K H, Spanig J, Stowasser B and Ruppert D 1992 *Tetrahedron Lett.* **33** 4549
7. Stowasser B, Budt K H, Jian-Qi I, Peyman A and Ruppert D 1992 *Tetrahedron Lett.* **33** 6625
8. Natchev I A 1988 *Liebigs Ann. Chem.* 861
9. Emsley J and Hall D 1976 *The chemistry of phosphorus* (London: Harper and Row) p. 494
10. Maier L and Spörri H 1991 *Phosphorus Sulfur Silicon Relat. Elem.* **61** 69
11. Huang J and Chen R 2000 *Heteroatom Chem.* **11** 480
12. Smith A B, Taylor C M, Benkovic S J and Hirschmann R 1994 *Tetrahedron Lett.* **35** 6853
13. Kim D Y and Yong Rhie D 1997 *Tetrahedron* **53** 13603
14. Afarinkia K, Cadogan J I G and Rees C W 1990 *Synlett* 415
15. Yuan C, Chen S and Wang G 1991 *Synthesis* 490
16. Sasai H, Shigeru A, Tahara Y and Shibasaki M 1995 *J. Org. Chem.* **60** 6656
17. Laschat S and Kunz H 1992 *Synthesis* 90
18. Manjula A, Vittal R B and Parvathi N 2003 *Synth. Commun.* **33** 2963
19. Genet J P, Uziel J, Port M, Touzin S, Roland A M, Thorimbert S and Tanier S 1992 *Tetrahedron Lett.* **33** 77
20. Laschat S and Kunz H 1992 *Synthesis* 90

21. Pudovik A N 1952 *Dokl. Akad. Nauk SSSR* **83** 865; 1953 *Chem. Abstr*. **47** 4300
22. Petrov K A, Chauzov V A and Erkhina T S 1974 *Usp. Khim.* **43** 2045; 1975 *Chem. Abstr*. **82** 449
23. Manjula A, Rao V and Neelakanthan P 2003 *Synth. Commun.* **33** 2963
24. Yadav J S, Reddy B V S, Raj S, Reddy K B and Prasad A R 2001 *Synthesis* 22
25. Zon J 1981 *Pol. J. Chem.* **55** 643
26. Ha H J and Nam G S 1992 *Synth. Commun.* **22** 1143
27. Heydari A, Hamadi H and Pourayoubi M 2007 *Catal. Commun.* **8** 1224
28. Bhagat S and Chakraborti A K 2007 *J. Org. Chem.* **72** 1263
29. Heydari A and Arefi A 2007 *Catal. Commun.* **8** 1023
30. Bhattacharya A K and Kaur T 2007 *Synlett* 745
31. Qian C and Huang T 1998 *J. Org. Chem.* **63** 4125
32. Ranu B C, Hajra A and Jana J 1999 *Org. Lett.* **1** 1141
33. Firouzabadi H, Iranpoor N and Sobhani S 2004 *Synthesis* 2692
34. Heydari A, Karimian A and Ipaktschi J 1998 *Tetrahedron Lett.* **39** 6729
35. Kaboudin B and Nazari R 2001 *Tetrahedron Lett.* **42** 8211
36. Akiyama T, Sanada M and Fuchibe K 2003 *Synlett* 1463
37. Yadav J S, Reddy B V S and Madan C 2001 *Synlett* 1131
38. Kudrimoti S and Bommena Roa V 2005 *Tetrahedron Lett.* **46** 1209
39. Qian C and Huang T 1998 *J. Org. Chem.* **63** 4125
40. Ranu B C, Hajra A and Jana U 1999 *Org. Lett.* **1** 1141
41. Chandrasekhar S, Prakash S J, Jagadeswar V and Narsihmulu C 2001 *Tetrahedron Lett.* **42** 5561
42. Vahdat S M, Baharfar R, Tajbakhsh M, Heydari A, Baghbanian S M and Khaksar S 2008 *Tetrahedron Lett.* **49** 6501
43. Heydari A, Khaksar S and Tajbakhsh M 2009 *Tetrahedron Lett.* **50** 77
44. Hazeri N, Maghsoodlou M T, Habibi-Khorassani S M, Aboonajmi J, Lashkari M and Sajadikhah S S 2014 *Res. Chem. Intermed.* **40** 1781
45. List B 2007 *Chem. Rev.* **107** 5413
46. Schreiner P R 2003 *Chem. Soc. Rev.* **32** 289
47. Doyle A G and Jacobsen E N 2007 *Chem. Rev.* **107** 5713
48. Dalko P I and Moisan L 2004 *Angew. Chem., Int. Ed.* **43** 5138
49. Funatomi T, Wakasugi K, Misaki T and Tanabe Y 2006 *Green Chem.* **8** 1022
50. Iida A, Osada J, Nagase R, Misaki T and Tanabe Y 2007 *Org. Lett.* **9** 1859
51. Nagase R, Osada J, Tamagaki H and Tanabe Y 2010 *Adv. Synth. Catal.* **352** 1128
52. Khaksar S, Vahdat S M and Rezaee F 2013 *C R Chim.* **16** 144
53. Khaksar S and Behzadi N 2012 *Comb. Chem. High T. Scr.* **15** 845
54. Khaksar S and Ostad S M 2011 *J. Fluorine Chem.* **132** 937
55. Khaksar S, Fattahi E and Fattahi E 2011 *Tetrahedron Lett.* **52** 5943
56. Khaksar S, Vahdat S M and Moghaddamnejad R N 2012 *Monatsh. Chem.* **143** 1671
57. Khaksar S, Vahdat S M, Tajbakhsh M, Jahani F and Heydari A 2010 *Tetrahedron Lett.* **51** 6388