



Synthesis and Bioactivity of α -Aminophosphonates Containing Fluorine

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Abstract: Twenty-one α -aminophosphonates containing fluorine were synthesized by Mannich-type reactions. Their structures were established by elemental analysis, IR, ^1H -NMR and MS. In field tests, some of these new compounds display high antiviral activity against the tobacco mosaic virus (TMV). The molecular geometry of compound **4f** was determined by X-ray diffraction structure analysis.

Keywords: α -Aminophosphonates, synthesis, bioactivity

Introduction

It is known that α -aminophosphonic acids and their derivatives display interesting bioactivities such as antiphytoviral, antitumor, herbicidal and fungicidal activity, therefore they have attracted considerable attention in pesticide and medicine formulation. A large volume of research on their synthesis and biological activities has been reported during the last twenty years [1-8], but little attention has been paid to the synthesis of α -aminophosphonates bearing fluorine. Considering that fluorine has special biomimetic, electronegativity, blocking and lipophilic effects, once introduced into organic compounds, there may be profound and unexpected changes in biological activity of these compounds. In our search for new classes of compounds with high biological activity and low toxicity, a series of simple α -aminophosphonates containing fluorine were synthesized by one-pot Mannich-type reactions. (Figure 1) and their structures were confirmed by ^1H -NMR, IR, MS and elemental analysis.

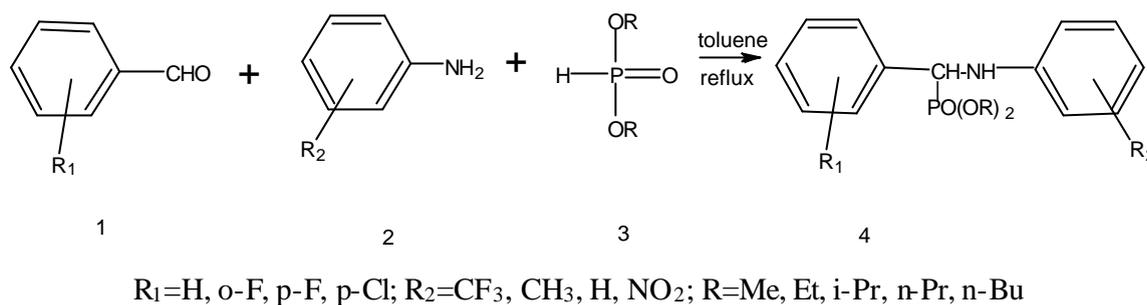


Figure 1. Synthetic scheme.

The biological activity of some of the compounds synthesized was tested in the field against the tobacco mosaic virus (TMV). The test results are shown in Table 1.

Table 1. The anti-TMV bioactivity of some synthesized compounds in the field.

Compound Number	Substituents			% Inhibition at 5×10^4 gL^{-1} Concentration	
	R_1	R_2	R	7days	14days
4a	p-Cl	p-Trifluoromethyl	i-Pr	9.43	39.28
4b	o-F	p-Trifluoromethyl	i-Pr	38.08	64.12
4c	p-F	p-Trifluoromethyl	i-Pr	45.73	52.1
4d	H	p-Trifluoromethyl	i-Pr	45.73	38.77
4e	p-Cl	p-Trifluoromethyl	Et	69.04	13.35
4f	o-F	p-Trifluoromethyl	Et	70.12	84.92
4h	4-Cl	p-Trifluoromethyl	Me	39.89	39.11
4o	p-Cl	p-Trifluoromethyl	n-Bu	23.1	32.1
4j	p-F	p-Trifluoromethyl	Me	4.65	19.32

Results and Discussion

Reaction Conditions

The reaction temperature should be controlled between 95-100°C. The byproducts increase and the yield decreases if the temperature is allowed to exceed 120°C. If the reaction temperature is below 90°C the reaction time will be 1.5 times longer. Toluene is a good solvent for the reaction and other solvents such as ethanol or dichloromethane are not so good, mainly because their reflux temperatures are lower than that of toluene.

X-Ray diffraction data [9]

To further confirm the structure of the compounds synthesized single-crystals of compound **4f** were obtained by recrystallization from anhydrous ethanol at room temperature. Determination of the unit cell and the data collection were performed with Moka radiation ($\lambda=0.71073\text{\AA}$) on an Enraf-Nonions CAD4 four-circle diffractometer. Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication no. CCDC 201543 [9]. The crystallography parameters and conditions of data collection of intensity are summarized as follows: $C_{18}H_{20}F_4NO_3P$; (M.W. 405.32). The crystal data are triclinic, space group P-1 with unit cell dimensions $a=8.301(3)$, $b=9.358(4)$, $c=12.731(5)\text{\AA}$, $\alpha=79.8^\circ(6)$, $\beta=89.2^\circ(7)$, $\gamma=87.4^\circ(7)$, $z=2$, $D_x=1.384\text{mg/m}^3$, $V=172.4\text{\AA}^3$, $F(000)=420$, scan type w/zQ , $0=\theta=25^\circ$, crystal size $0.3\times 0.30\times 0.2\text{mm}$, reflections collected /unique 3332/2751 [$R(\text{inf})=0.0236$].

The corrections for L_p factors and semi empirical absorption were applied to the intensities. The other non-hydrogen atoms were determined with successive difference Fourier syntheses. The final refinement by full matrix least-square method with isotropic thermal parameters for F(2) atom was converged with outweighted and weighted agreement factors of 0.061 and 0.097. The highest peak on the final difference Fourier map had a height of $0.62/\text{\AA}^3$.

The distance of P(1)-C(5) is $1.814(4)\text{\AA}$ which is longer than the sum of Van der Waals radii between the atoms of phosphorus and carbon which shows that there is no coordinated bond from the carbonyl oxygen to the central phosphorus atom. Comparison with the difference between the standard tetrahedral geometry and the bond angle of O(1)-P-O(3)(98.91) shows that the compound is 4-coordinated triclinic with a distorted tetrahedral geometry. The distances of the two N-C bonds are 1.398 and 1.447. It may be the result of the steric effect of the proximity to the bulky phosphorus-containing substituent. The molecular structure is shown in Figure 2. The packing diagram of the unit cell is shown in Figure 3.

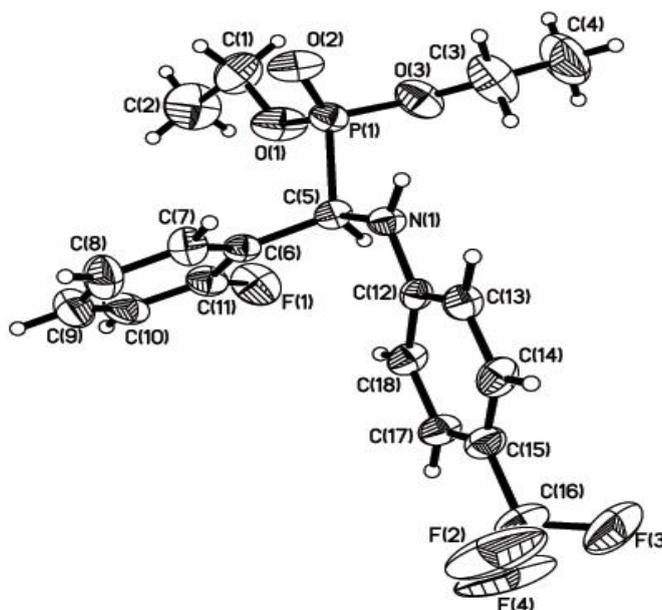


Figure 2. The molecular structure figure of $C_{18}H_{18}F_4NO_3P$.

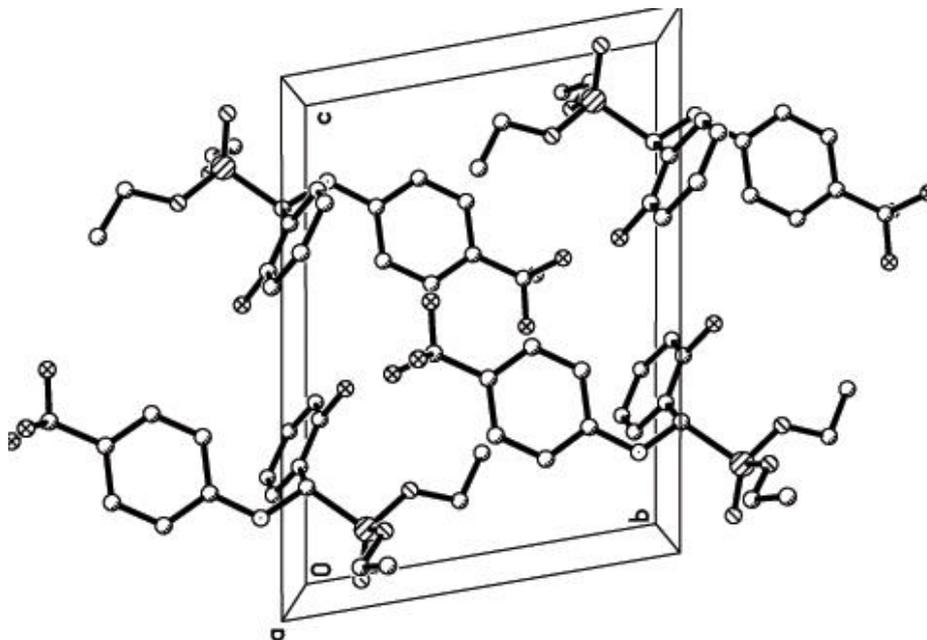


Figure 3. The packing diagram of the unit cell.

Biological activities against TMV

The bioassays show that all compounds tested had significant toxicity against TMV in the field. The activity showed large variability depending on the substituent groups. The best results were obtained when R is Et. The inhibitory rate of compound **4f** towards TMV was 84.92% at the concentration of 500 mg L⁻¹.

Acknowledgements

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Experimental

General

Melting points were measured on a Tech X-4 melting point apparatus and they are not corrected. ¹H-NMR spectra was recorded on a Varian INOVO400 (400MHz) pulse Fourier-transform NMR spectrometer in CDCl₃ using tetramethylsilane as an internal standard. The IR spectra were recorded on a Bruker VECTOR22 spectrometer. The X-ray diffraction data recorded on an Enraf-Nonious CAD4 four-circle diffractometer. The mass spectra were taken on an HP5988A spectrometer. Elemental

analysis was performed with a Vario-II CHN analyzer. The reagents were all analytical reagent grade or of high chemical purity.

Typical experimental procedure for synthesis of 4a-s.

A substituted aryl benzaldehyde (**1**, 5mmol), 4-aminobenzotrifluoride (**2**, 5.3mmol) and toluene (15mL) were placed in a three-necked 25mL flask. Dialkyl phosphate (**3**, 5.3mmol) was added with stirring and the reactants were refluxed for 2-5hrs. The progress of reactions was checked by TLC (petroleum ether-ethyl acetate = 1:3). Toluene was evaporated under vacuum and the residue was recrystallized from ethanol and water to give the target compound **4**.

Yields and physicochemical properties:

1-(4-trifluoromethylphenylamino)-1-(4-chlorophenyl)-o,o-diisopropylphosphonate (4a). Yield 64%; m.p.127-128°C; Calculated for C₂₀H₂₄ClNF₃PO₃ (449.5): 53.40%C, 5.38%H, 3.11%N; found: 53.40%C, 5.39%H, 2.96%N; ¹H-NMR: 6.57-7.40 (m, 9H, Ar-H+NH), 4.49-5.18 (m, 3H, 2CH + CH), 2.18 (s, 3H, -CH₃), 0.98-1.33 (m, 12H, 4CH₃); IR: 3301.7 (?N-H), 1228.4 (?P=O), 1063.0 (?P-O-C), 1100 (?C-F), 121 (?C-F); MS: 449 (M⁺), 284, 172, 145, 123, 111, 82.

1-(4-trifluoromethylphenylamino)-1-(2-fluorophenyl)-o,o-diisopropylphosphonate (4b). Yield 68.0%; m.p.117-118°C; Calculated for C₂₀H₂₄NF₄PO₃(433): 55.43%C, 5.58%H, 3.23%N; found: 55.40%C, 5.36%H, 3.20%N; ¹H-NMR: 6.63-7.49 (m, 9H, Ar-H+NH), 4.42-5.24 (m, 3H, 2CH + CH), 0.86-1.35 (m, 12H, 4CH₃); IR: 3302.8 (?N-H), 1231.9 (?P=O), 1065.2 (?P-O-C); MS: 433(M⁺), 268, 172, 145, 123, 95, 92.

1-(4-trifluoromethylphenyl)-1-(4-fluorophenyl)-O,O-diisopropylphosphonate (4c). Yield 65.0%; m.p. 108-113°C; Calculated for C₂₀H₂₄NF₄PO₃ (433): 55.43%C, 5.58%H, 3.23%N; found: 55.40%C, 5.45%H, 3.20%N; ¹H-NMR: 6.45-7.41 (m, 9H, Ar-H+NH), 4.50-4.71 (m, 3H, 2CH+CH), 2.18 (s, 3H, -CH₃), 0.99-1.32 (m, 12H, 4CH₃); IR: 3313.4 (?N-H), 1233.6 (?P=O), 1103.8 (?P-O-C).

*1-(4-trifluoromethylphenyl)-1-phenyl-O,O-diisopropylphosphonate (4d).*Yield 60.3%; m.p.140-142°C; Calculated for C₂₀H₂₅NF₃PO₃ (414): 57.83%C, 6.07%H, 3.37%N; found: 58.00%C, 5.95%H, 3.30%N; ¹H -NMR: 6.59-7.45 (m, 10H, Ar-H+NH), 4.42-4.72 (m, 3H, 2CH+CH), 0.88-1.33 (m, 12H, 4CH₃); IR: 3305.1 (?N-H), 1230.8 (?P=O), 1062.3 (?P-O-C).

1-(4-trifluoromethylphenyl)-1-(4-chlorophenyl)-O,O-diethylphosphonate (4e). Yield 63.13%; m.p. 135-139°C; Calculated for C₁₈H₂₀ClNF₃PO₃ (421.5): 51.26%C, 4.78%H, 3.32%N; found: 51.28%C, 4.50%H, 3.21%N; ¹H-NMR: 6.50-7.41 (m, 9H, Ar-H+NH), 4.05-5.14 (m, 5H, 2CH₂+ CH), 1.06-1.30 (m, 6H, 2CH₃).

1-(4-trifluoromethylphenyl)-1-(2-fluorophenyl)-O,O-diethylphosphonate(4f). Yield 44.4%; m.p. 110-111°C; Calculated for $C_{18}H_{20}NF_4PO_3$ (405): 53.34% C, 4.97% H, 3.46% N; found: 53.36% C, 4.76% H, 3.34% N; 1H -NMR: 6.59-7.46 (m, 10H, Ar-H+NH), 3.90-5.52 (m, 5H, 2CH₂ + CH), 1.03-1.31 (m, 6H, 2CH₃); MS: 405(M⁺), 268, 172, 145, 109, 95, 81.

1-(4-trifluoromethylphenyl)-1-phenyl-O,O-diethylphosphonate (4g). Yield 24.9%; m.p. 141-142°C; Calculated for $C_{18}H_{21}NF_3PO_3$ (387): 55.82% C, 5.46% H, 3.62% N; found: 55.76% C, 5.29% H, 3.43% N; 1H -NMR: 6.59-7.45 (m, 9H, Ar-H+NH), 4.42-4.72 (m, 5H, 2CH₂+ CH), 1.05-1.31 (m, 6H, 2CH₃).

1-(4-trifluoromethylphenyl)-1-(4-chlorophenyl)-O,O-dimethylphosphonate (4h). Yield 30.1%; m.p. 134-135°C; Calculated for $C_{16}H_{16}ClNF_3PO_3$ (393.5): 48.81% C, 4.10% H, 4.10% N; found: 48.80% C, 3.98% H, 3.45% N; 1H -NMR: 6.54-7.36 (m, 9H, Ar-H+NH), 3.46-4.61 (m, 7H, 2CH₃+ CH).

1-(4-trifluoromethylphenyl)-1-(2-fluorophenyl)-O,O-dimethylphosphonate (4i). Yield 26.6%; m.p. 110-111°C; Calculated for $C_{16}H_{16}NF_4PO_3$ (377): 50.94% C, 4.27% H, 3.71% N; found: 50.80% C, 4.15% H, 3.65% N; 1H -NMR: 6.60-7.47 (m, 9H, Ar-H+NH), 3.46-5.26 (m, 7H, 2CH₃+ CH).

1-(4-trifluoromethylphenyl)-1-(4-fluorophenyl)-O,O-dimethylphosphonate (4j). Yield 22.5%; m.p. 139-141°C; Calculated for $C_{16}H_{16}NF_4PO_3$ (377): 50.94% C, 4.27% H, 3.71% N; found 50.94% C, 4.15% H, 3.71% N; 1H NMR: 6.55-7.41(m,9H,Ar-H+NH), 3.46-4.62(m,7H,2CH₃+ CH).

1-(4-trifluoromethylphenyl)-1-phenyl-O,O-dimethylphosphonate (4k). Yield 30%; m.p. 97-99°C; Calculated for $C_{16}H_{17}NF_3PO_3$ (359): 53.48% C, 4.77% H, 3.90% N; found: 53.94% C, 4.51% H, 3.90% N; 1H -NMR: 6.57-7.42 (m, 10H, Ar-H+NH), 3.40-4.64 (m, 7H, 2CH₃+CH).

1-(4-trifluoromethylphenyl)-1-(4-chlorophenyl)-O,O-dipropylphosphonate (4l). Yield 25.0%; m.p. 91-95°C; Calculated for $C_{20}H_{24}ClNF_3PO_3$ (449.5): 53.40% C, 5.38% H, 3.11% N; found: 53.35% C, 5.20% H, 2.99% N; 1H -NMR: 6.53-7.39 (m, 9H, Ar-H+NH), 3.62-4.78 (m, 5H, 2CH₂+CH), 1.45-1.65 (m, 4H, 2CH₂), 0.76-0.93 (m, 6H, 2CH₃); MS: 449(M⁺), 284, 172, 145, 123, 111, 82.

1-(4-trifluoromethylphenyl)-1-(2-fluorophenyl)-O,O-dipropylphosphonate(4m). Yield 28.0%; m.p. 109-111°C; Calculated for $C_{20}H_{24}NF_4PO_3$ (433): 55.43% C, 5.58% H, 3.23% N; found: 55.45% C, 5.40% H, 3.12% N; 1H -NMR: 6.60-7.34 (m, 9H, Ar-H+NH), 3.79-5.23 (m, 5H, 2CH₂+CH), 1.38-1.658 (m, 4H, 2CH₂), 0.71-0.94 (m, 6H, 2CH₃).

1-(4-trifluoromethylphenyl)-1-(4-fluorophenyl)-O,O-dipropylphosphonate (4n). Yield 29.8%; m.p. 95-96°C; Calculated for $C_{20}H_{24}NF_4PO_3$ (433): 55.43% C, 5.58% H, 3.23% N; found: 55.45% C, 5.30% H, 3.15% N; 1H -NMR: 6.53-7.40 (m, 8H, Ar-H), 3.97-4.79 (m, 6H, 2CH₂+CH+NH), 1.47-1.65 (m, 4H, 2CH₂), 0.75-0.92 (m, 6H, 2CH₃); MS: 433(M⁺), 268, 172, 145, 123, 95, 82.

1-(4-trifluoromethylphenyl)-1-(4-chlorophenyl)-O,O-dibutylphosphonate (4o). Yield 69.5%; m.p. 93-95°C; Calculated for C₂₂H₂₈ClNF₃PO₃ (477.5): 55.29%C, 5.91%H, 2.93%N; found: 55.45%C, 6.15%H, 2.89%N; ¹H-NMR: 6.53-7.34 (m, 9H, Ar-H+NH), 4.01-4.77 (m, 5H, 2CH₂+CH), 1.23-1.30 (m, 4H, 4CH₂), 0.76-0.90 (m, 6H, 2CH₃).

1-(4-trifluoromethylphenyl)-1-(4-fluorophenyl)-O,O-dibutylphosphonate (4p). Yield 80.2%; m.p. 92-94°C; Calculated for C₂₂H₂₈NF₄PO₃ (461): 57.27%C, 6.11%H, 3.04%N; found 57.17%C, 5.95%H, 3.09%N; ¹H-NMR: 6.54-7.42 (m, 9H, Ar-H+NH), 3.63-4.76 (m, 5H, 2CH₂+CH), 1.19-1.62 (m, 4H, 4CH₂), 0.76-0.90 (m, 6H, 2CH₃).

Biological tests

A field trial was carried out at Guizhou University using spring tobacco, cv.Hung. The experiment was arranged with 4 replicates per concentration per test compound on randomized plots of 60.0m². The compounds **4a-4h**, **4j** and **4o** were formulated as a 30% WP which was then diluted with water to give AI concentrations of 500 mg litre⁻¹. Disease assessment of TMV was estimated 7 days and 14 days after application when untreated control plants had 10-15% infected leaf area. Results are expressed as the inhibition rate calculated on the basis of % infected leaf area.

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9. CCDC 201543 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the URL <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).