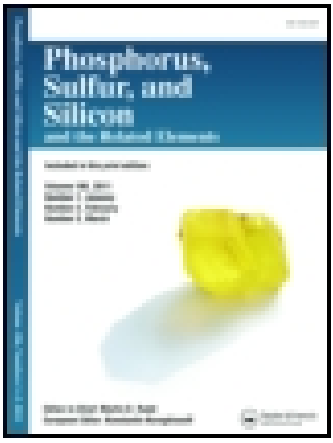

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A Convenient One-Pot Synthesis of β -(Trifluoromethyl)allylaminophosph and Benzylaminophosphonic Acids

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A Convenient One-Pot Synthesis of β-(Trifluoromethyl)allylaminophosphonic and Benzylaminophosphonic Acids

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The reductive condensation of aminoalkylphosphonic acids with β-chloro- or β-ethylthio-(β-trifluoromethyl)acroleins leads to secondary (trifluoromethyl)-allylaminophosphonic acids in moderate to good yields. The method appears to be useful for the preparation of benzylaminophosphonic acids.

Keywords Allylaminophosphonic acids; benzylamino-phosphonic acids; reductive amination; β-(trifluoromethyl)acroleins

INTRODUCTION

Organophosphorus compounds have found a wide range of applications in the areas of biological, medicinal, and synthetic chemistry.[1,2] Aminophosphonic acids constitute an important class of compounds that exhibit very useful properties and utilities.[3] In fact, several aminophosphonic acids are known to act as chelating agents,[4] antibacterial agents (alafosfalin),[5] herbicides (glyphosate),[6] fungicides,[7] enzyme inhibitors,[8] etc. However, the highly ionic character of this class of compounds limits transmembraned transport, and this stimulates the research for new biologically active phosphorus compounds.[9] The introduction of fluorine atoms into the organic structure can change its metabolic stability, binding affinity, and lipophilicity, and thus improve its bioavailability.[10] Recently, numerous fluorinated aminocarboxylic acids were also synthesized and tested, showing increased biological

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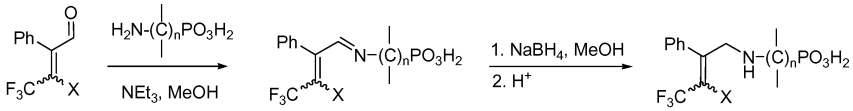
activity[11–13]; however less attention has been paid to the synthesis of their *P*-counterparts. Several fluorinated aminophosphonic acids have already been prepared and revealed high antiviral activity[14]; increased activity as insecticides, fungicides, and plant activators[15]; and showed better enzyme inhibitory effect[16] and stability.[17,18]

3-Chloro-4,4,4-trifluoro-2-phenylbutenal (**1**), easily available (as an E/Z, 40:60 mixture) from the Vilsmaier reaction of 1,1,1-trifluoro-3-phenylacetone,[19] is known to be a versatile building block for the synthesis of both acyclic and cyclic trifluoromethyl-functionalized compounds.[20–22] This acroleine can be converted into 3-ethylsulfanyl-4,4,4-trifluoro-2-phenylbutenal (**2**) by reaction with ethanethiolate (EtSH/NaH).[23]

In this article, we demonstrate a useful approach for applying these two synthons for the synthesis of trifluoromethyl-functionalysed allylaminophosphonic acids.[24]

RESULTS AND DISCUSSION

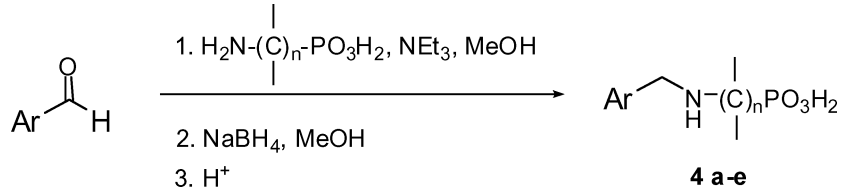
It has been reported that both **1** and **2** react with primary alkyl or arylamines to form stable 1-aza-1,3-dienes, which can be transformed to secondary allylamines by reduction with sodium borohydride.[25] We have investigated these reactions using primary aminophosphonic acids. Starting from aminomethylphosphonic acid, chosen as a model compound, and an equimolar amount of acroleine **1**, we found that no transformation to the imine is taking place (THF, reflux, 48 h), in contrast to alkyl or arylamines.[25] We tried to perform this reaction in various solvents. The best result was obtained in MeOH with the addition of NEt_3 (3 eq). (Aminomethyl)phosphonic acid is only partially soluble in MeOH/NEt_3 solution. After the addition of **1** (1 eq, rt, 2 h), a clear solution was obtained. The reaction time can be shortened by powdering of the starting amino acid. The oily residue obtained after evaporation of the solvent from the sample was dissolved in $CDCl_3$. The ^{1}H NMR spectrum exhibits a multiplet at δ 8.33–8.75 indicating that imine CH=N protons of diastereoisomers of 1-aza-1,3-diene formed as the only product. This azadiene appeared to be not as stable as its non-phosphorylated analogues.[25] For instance, from its solution in chloroform, the amino acid precipitated quantitatively after a few hours. Next, in a one-pot procedure, we reduced the intermediate azadiene in MeOH with sodium borohydride and isolated aminophosphonic acid **3a** as a 42:58 mixture of diastereomers (based on the ^{19}F NMR spectrum and confirmed by ^{31}P NMR spectroscopy). Similarly products **3b–h** were obtained (Scheme 1, Table I).



1 : X = Cl
2 : X = SEt

SCHEME 1

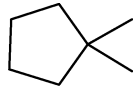
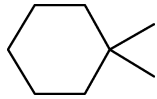
Encouraged by the results obtained with **1** and **2**, we focused our attention on other aldehydes. We found that in contrast to aliphatic aldehydes, reaction with aromatic aldehydes gave very good results (Scheme 2, Table II).



SCHEME 2

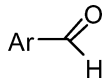
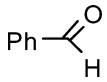
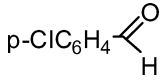
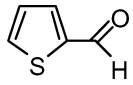
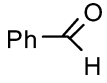
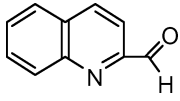
In summary, during our study on the reactivity of β-chloro or β-ethylthio-(β-trifluoromethyl)acroleins towards aminophosphonic

TABLE I Synthesis of β-(Trifluoromethyl)allylaminophosphonic Acids 3a–h by Reductive Amination

	X	—(C)n—	Conditions	Product	Diastereomers ratio[a]	Isolated yield (%)	Mp (°C)
a	Cl	—CH_2—	rt, 2 h	**3a**	58:42	60	97–102
b	Cl	—$(CH_2)_2$—	rt, 2 h	**3b**	35:65	38	205–207
c	Cl	—$(CH_2)_3$—	rt, 14 h	**3c**	39:61	37	168–171
d	Cl		rt, 2 h	**3d**	44:56	56	199–200
e	SEt	—CH_2—	rt, 2 h	**3e**	13:87	54	193–196
f	SEt	—$(CH_2)_2$—	rt, 2 h	**3f**	79:21	42	172–174
g	SEt		rt, 2 h	**3g**	90:10	35	194–195
h	SEt	—$(CH_2)_3$—	40°C, 2.5 h	**3h**	8:92	65	185–187

[a]Based on ^{19}F NMR.

TABLE II Synthesis of Benzylaminophosphonic Acids 4a–e by Reductive Amination

			Conditions	Product	Isolated yield (%)	Mp (°C)
a		—CH_2—	40 min	**4a**	45	274–276
b		—$(CH_2)_2$—	180 min	**4b**	45	276–279
c		PhCH=	30 min	**4c**	60	239–241
d		MeCH=	40 min	**4d**	58	246–247
e		—$(CH_2)_3$—	6 h	**4e**	71	231–233

acids, we found a simple procedure for preparation of both β-(trifluoromethyl)allylaminophosphonic acids and benzyl functionalized aminophoshonic acids. In contrast to the already described reductive amination methods for aminoalkylphosphonic acids,[26,27] our method allows us to avoid chromatography and also gives good yields. Further studies directed towards an application of the intermediate azadiene for the synthesis of new differently functionalized aminophosphonic acids are in progress.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were obtained with a Bruker DPX 250, a Varian Gemini 200, and a Tesla BS 687 spectrometer operating at 250, 200, and 80 MHz, respectively for ^{1}H (TMS); 63, 50, and 20 MHz for ^{13}C; 235 MHz for ^{19}F ($CFCl_3$); and 101 and 80 MHz for ^{31}P (H_3PO_4). The elemental analysis was performed by the Laboratory of Microanalysis of the Centre of Molecular and Macromolecular Studies, Polish Academy of Science in Łódź. Starting acroleines **1** and **2** were obtained according to the method in the literature.[19]

β-(Trifluoromethyl)allylaminophosphonic Acids 3a–h: General Procedure

To a suspension of the primary aminophosphonic acid (10 mmol) in MeOH (100 mL), NEt_3 (3.00 g, 30 mmol) was added, and the mixture was stirred at room temperature for 20 min. Next, β-(trifluoromethyl)acroleine (10 mmol), was added and stirring was continued (temperature and time are given in Table I). The clear solution thus obtained was cooled to 0°C, and $NaBH_4$ (1.90 g, 50 mmol) was added cautiously. Stirring was continued for 14 h at room temperature. Then the solvent was evaporated, and the residue extracted with Et_2O (3 × 50 mL, **3a**,**b**,**d**–**g**), or dissolved in MeOH (30 mL, **3c**) or toluene (60 mL, **3h**). If a precipitate was present, it was filtered off. Then the solvent was evaporated (**3c**,**h**) giving an oily residue, or after concentration to ~100 mL, petroleum ether (150 mL, **3a**,**b**,**d**–**g**) was added to precipitate the product. The solids or oils were dissolved in MeOH (30 mL), acidified to pH ~2 by HCl/MeOH (4 mol/dm^3), and evaporated. The residue thus obtained was dissolved in MeOH (20 mL, **3a**,**d**–**g**) or EtOH (20 mL, **3b**) or acetone (40 mL, **3c**,**h**) and filtered, and the filtrate was treated with propylene oxide and left in a refrigerator for a few days. Products **3a–h** precipitated as colorless solids, which constituted a mixture of *Z*/*E* diastereoisomers. Aminoacids **3c**,**d**,**f** required additional purification by crystallization from a MeOH/acetone mixture (3:20).

(3-Chloro-4,4,4-trifluoro-2-phenylbut-2-enylamino)-methylphosphonic Acid (3a)

^{1}H NMR (D_2O/NaOD, 250 MHz): $\delta = 2.48$ (d, $^2J_{PH} = 12.0$ Hz, 2H, CH_2, *Z* or *E*), 2.53 (d, $^2J_{PH} = 12.0$ Hz, 2H, CH_2, *Z* or *E*), 3.82 (s, 2H, CH_2N, $Z + E$), 7.27–7.46 (m, 5H, C_6H_5, $Z + E$). ^{13}C NMR (D_2O/NaOD, 20 MHz): $\delta = 49.4$ (d, $^1J_{PC} = 137.9$ Hz, CH_2, $Z + E$), 53.7 (dq, $^3J_{PC} = 16.5$ Hz, $^4J_{CF} = 4.0$ Hz, C-1, *E*), 56.8 (d, $^3J_{PC} = 15.9$ Hz, C-1, *Z*), 121.0 (q, $^2J_{CF} = 36.0$ Hz, C-3, *Z* or *E*), 121.2 (q, $^2J_{CF} = 37.2$ Hz, C-3, *Z* or *E*), 122.1 (q, $^1J_{CF} = 271.8$ Hz, C-4, *Z* or *E*), 122.7 (q, $^1J_{CF} = 271.8$ Hz, C-4, *Z* or *E*), 129.3–131.2 (CH_{arom}, $Z + E$), 137.9 (C-*i*, *Z* or *E*), 139.4 (C-*i*, *Z* or *E*), 147.9 (C-2, *Z* or *E*), 149.1 (C-2, *Z* or *E*). ^{31}P NMR (D_2O/NaOD, 101 MHz): $\delta = 16.0$, 15.9 (58 : 42). ^{19}F NMR (D_2O/NaOD, 235 MHz): $\delta = -59.2$, -60.0 (42 : 58). Anal. Calcd for $C_{11}H_{12}ClF_3NO_3P$: C, 40.08; H, 3.67; N, 4.25%. Found: C, 40.11; H, 3.60; N, 4.27%.

2-(3-Chloro-4,4,4-trifluoro-2-phenylbut-2-enylamino)-ethylphosphonic Acid (3b)

^{1}H NMR (D_2O/NaOD, 250 MHz): $\delta = 1.35$–1.52 (m, 2H, CH_2, $Z + E$), 2.60–2.73 (m, 2H, CH_2, $Z + E$), 3.74 (s, 2H, CH_2N, $Z + E$), 7.23–7.47 (m,

5H, C_6H_5, $Z + E$). ^{13}C NMR (D_2O/NaOD, 20 MHz): $\delta = 27.2$ (d, $^1J_{PC} = 125.1$ Hz, CH_2, $Z + E$), 46.2 (d, $^2J_{PC} = 1.8$, CH_2), 49.7 (q, $^4J_{CF} = 3.7$ Hz, C-1, E), 52.5 (C-1, Z), 121.7 (q, $^1J_{CF} = 274.0$ Hz, C-4, Z or E), 122.3 (q, $^1J_{CF} = 274.0$ Hz, C-4, Z or E), 124.2 (q, $^2J_{CF} = 36.6$ Hz, C-3, Z or E), 124.9 (q, $^2J_{CF} = 37.8$ Hz, C-3, Z or E), 129.5–131.3 (CH_{arom}, $Z + E$), 135.1 (C-*i*, Z or E), 136.8 (C-*i*, Z or E), 142.4 (q, $^3J_{CF} = 2.4$ Hz, C-2, Z or E), 142.8 (q, $^3J_{CF} = 2.0$ Hz, C-2, Z or E). ^{31}P NMR (D_2O/NaOD, 101 MHz): $\delta = 19.3$, 19.2 (63 : 37). ^{19}F NMR (D_2O/NaOD, 235 MHz): $\delta = -59.3$, -60.1 (35 : 65). Anal. Calcd for $C_{12}H_{14}ClF_3NO_3P$: C, 41.94; H, 4.11; N, 4.08%. Found: C, 41.97; H, 4.15; N, 4.11%.

3-(3-Chloro-4,4,4-trifluoro-2-phenylbut-2-enylamino)-propylphosphonic Acid (3c)

^1H NMR (D_2O/NaOD, 250 MHz): $\delta = 1.09$ (s br, 2H, CH_2, $Z + E$), 1.33 (s br, 2H, CH_2, $Z + E$), 3.40 (s br, 2H, CH_2N, $Z + E$), 6.78–6.98 (m, 5H, C_6H_5, $Z + E$). ^{13}C NMR (D_2O/NaOD, 20 MHz): $\delta = 23.0$ (d, $^2J_{PC} = 4.3$ Hz, CH_2, $Z + E$), 27.9 (d, $^1J_{PC} = 130.6$, CH_2, $Z + E$), 47.9 (q, $^4J_{CF} = 3.4$ Hz, C-1, E), 50.4 (d, $^3J_{PC} = 14.1$ Hz, CH_2, $Z + E$), 52.9 (C-1, Z), 121.7 (q, $^1J_{CF} = 273.7$ Hz, C-4, Z or E), 122.3 (q, $^1J_{CF} = 273.7$ Hz, C-4, Z or E), 123.7 (q, $^2J_{CF} = 36.0$ Hz, C-3, Z or E), 124.2 (q, $^2J_{CF} = 38.8$ Hz, C-3, Z or E), 129.5–131.9 (CH_{arom}, $Z + E$), 135.6 (C-*i*, Z or E), 137.2 (C-*i*, Z or E), 143.3 (q, $^3J_{CF} = 2.4$ Hz, C-2, Z or E), 144.0 (q, $^3J_{CF} = 1.2$ Hz, C-2, Z or E). ^{31}P NMR (D_2O/NaOD, 101 MHz): $\delta = 22.4$. ^{19}F NMR (D_2O/NaOD, 235 MHz): $\delta = -59.2$, -60.0 (39 : 61). Anal. Calcd for $C_{13}H_{16}ClF_3NO_3P$: C, 43.65; H, 4.51%. Found: C, 43.64; H, 4.43%.

1-(3-Chloro-4,4,4-trifluoro-2-phenylbut-2-enylamino)-cyclopentylphosphonic Acid (3d)

^1H NMR (D_2O/NaOD, 250 MHz): $\delta = 1.29$–1.97 (m, 8H, C_5H_8, $Z + E$), 3.92 (s, 2H, CH_2N, Z or E), 3.97 (s, 2H, CH_2N, Z or E), 7.30–7.52 (m, 5H, C_6H_5, $Z + E$). ^{13}C NMR (D_2O/NaOD, 20 MHz): $\delta = 26.3$ (d, $^3J_{PC} = 7.9$ Hz, CH_2, $Z + E$), 26.9 (d, $^3J_{PC} = 7.3$ Hz, CH_2, $Z + E$), 35.8 (d, $^2J_{PC} = 7.9$ Hz, CH_2, $Z + E$), 36.5 (CH_2, $Z + E$), 47.9 (dq, $^4J_{CF} = 1.8$ Hz, $^3J_{PC} = 5.5$ Hz, C-1, E), 51.2 (d, $^3J_{PC} = 4.9$ Hz, C-1, Z), 66.6 (d, $^1J_{PC} = 142.8$ Hz, Cq), 120.3 (q, $^2J_{CF} = 36.0$ Hz, C-3, Z or E), 120.5 (q, $^2J_{CF} = 37.8$ Hz, C-3, Z or E), 122.2 (q, $^1J_{CF} = 273.4$ Hz, C-4, Z or E), 122.8 (q, $^1J_{CF} = 274.3$ Hz, C-4, Z or E), 129.4–130.4 (CH_{arom}, $Z + E$), 138.1 (C-*i*, Z or E), 139.5 (C-*i*, Z or E), 148.5 (C-2, Z or E), 149.4 (C-2, Z or E). ^{31}P NMR (D_2O/NaOD, 101 MHz): $\delta = 23.0$, 22.8 (56 : 44). ^{19}F NMR (D_2O/NaOD, 235 MHz): $\delta = -59.4$, -60.1 (44 : 56). Anal. Calcd for $C_{15}H_{18}ClF_3NO_3P$: C, 46.95; H, 4.73%. Found: C, 46.91; H, 4.91%.

(3-Ethylsulfanyl-4,4,4-trifluoro-2-phenylbut-2-enylamino)-metylphosphonic Acid (3e)

^{1}H NMR (D_2O/NaOD, 250 MHz): $\delta = 1.02$ (t, $^3J_{HH} = 7.4$ Hz, 3H, CH_3, *Z* or *E*), 1.28 (t, $^3J_{HH} = 7.3$ Hz, 3H, CH_3, *Z* or *E*), 2.45 (d, $^2J_{PH} = 12.6$ Hz, 2H, CH_2, $Z + E$), 2.85 (q, $^3J_{HH} = 7.4$ Hz, 2H, CH_2, $Z + E$), 3.83 (s, 2H, CH_2, *Z* or *E*), 4.03 (s, 2H, CH_2, *Z* or *E*), 7.22–7.44 (m, 5H, C_6H_5, $Z + E$). ^{13}C NMR (D_2O/NaOD, 20 MHz): $\delta = 11.6$ (CH_3, *Z* or *E*), 12.0 (CH_3, *Z* or *E*), 27.1 (SCH_2, *Z* or *E*), 27.8 (SCH_2, *Z* or *E*), 46.0 (d, $^1J_{PC} = 137.2$ Hz, CH_2, $Z + E$),), 51.4 (dq, $^3J_{PC} = 17.4$ Hz, $^4J_{CF} = 3.0$ Hz, C-1, *E*), 54.4 (d, $^3J_{PC} = 14.0$ Hz, C-1, *Z*), 120.5 (q, $^2J_{CF} = 30.8$ Hz, C-3, $Z + E$), 121.5 (q, $^1J_{CF} = 275.5$ Hz, C-4, $Z + E$), 125.6–128.1 (CH_{arom}, $Z + E$), 136.3 (C-*i*, *Z* or *E*), 137.4 (C-*i*, *Z* or *E*), 156.2 (C-2, $Z + E$). ^{31}P NMR (D_2O/NaOD, 101 MHz): $\delta = 16.1$. ^{19}F NMR (D_2O/NaOD, 235 MHz): $\delta = -55.6, -55.7$ (13 : 87). Anal. Calcd for $C_{13}H_{17}F_3NO_3PS$: C, 43.95; H, 4.82%. Found: C, 43.87; H, 4.99%.

2-(3-Ethylsulfanyl-4,4,4-trifluoro-2-phenylbut-2-enylamino)-ethylphosphonic Acid (3f)

^{1}H NMR (D_2O/NaOD, 250 MHz): $\delta = 1.01$ (t, $^3J_{HH} = 7.4$ Hz, 3H, CH_3, *Z* or *E*), 1.29 (t, $^3J_{HH} = 7.4$ Hz, 3H, CH_3, *Z* or *E*), 1.77–1.95 (m, 2H, CH_2P), 2.52 (q, $^3J_{HH} = 7.4$ Hz, 2H, CH_2, *Z* or *E*), 2.90 (q, $^3J_{HH} = 7.4$ Hz, 2H, CH_2, *Z* or *E*), 3.15–3.28 (m, 2H, CH_2), 4.34 (s, 2H, CH_2, *Z* or *E*), 4.59 (s, 2H, CH_2, *Z* or *E*), 7.31–7.51 (m, 5H, C_6H_5, $Z + E$). ^{13}C NMR (D_2O/NaOD, 20 MHz): $\delta = 14.8$ (CH_3, *Z* or *E*), 15.3 (CH_3, *Z* or *E*), 30.2 (SCH_2, *Z* or *E*), 31.0 (SCH_2, *Z* or *E*), 31.2 (d, $^1J_{PC} = 127.0$ Hz, CH_2, $Z + E$),), 52.3 (q, $^4J_{CF} = 3.0$ Hz, C-1, *E*), 55.8 (C-1, *Z*), 124.0 (q, $^2J_{CF} = 30.5$ Hz, C-3, *Z* or *E*), 124.8 (q, $^2J_{CF} = 30.5$ Hz, C-3, *Z* or *E*), 125.0 (q, $^1J_{CF} = 275.3$ Hz, C-4, *Z* or *E*), 125.5 (q, $^1J_{CF} = 275.3$ Hz, C-4, *Z* or *E*), 128.9–130.5 (CH_{arom}, $Z + E$), 139.8 (C-*i*, *Z* or *E*), 140.9 (C-*i*, *Z* or *E*), 159.5 (q, $^3J_{CF} = 2.4$ Hz, C-2, *Z* or *E*), 159.9 (q, $^3J_{CF} = 2.4$ Hz, C-2, *Z* or *E*). ^{31}P NMR (D_2O/NaOD, 101 MHz): $\delta = 18.3, 18.2$ (78 : 22). ^{19}F NMR (D_2O/NaOD, 235 MHz): $\delta = -56.3, -56.6$ (79 : 21). Anal. Calcd for $C_{14}H_{19}F_3NO_3PS$: C, 45.53; H, 5.19%. Found: C, 45.37; H, 5.12%.

1-(3-Ethylsulfanyl-4,4,4-trifluoro-2-phenylbut-2-enylamino)-cyclohexylphosphonic Acid (3g)

^{1}H NMR (D_2O/NaOD, 250 MHz): $\delta = 0.94–1.58$ (m, 13H, C_6H_{10} + CH_3, $Z + E$), 2.52 (q, $^3J_{HH} = 7.4$ Hz, 2H, CH_2, *Z* or *E*), 2.86 (q, $^3J_{HH} = 7.4$ Hz, 2H, CH_2, *Z* or *E*), 3.98 (s, 2H, CH_2, *Z* or *E*), 4.14 (s, 2H, CH_2, *Z* or *E*), 7.29–7.45 (m, 5H, C_6H_5, $Z + E$). ^{13}C NMR (D_2O/NaOD, 20 MHz): $\delta = 14.9$ (CH_3, *Z* or *E*), 15.3 (CH_3, *Z* or *E*), 21.5 (d, $^3J_{PC} = 9.2$ Hz,CH_2, $Z + E$), 26.1 (CH_2, *Z* or *E*), 26.5 (CH_2, *Z* or *E*), 30.3 (CH_2, *Z* or *E*), 31.1

(CH_2, *Z* or *E*), 31.8 (CH_2, *Z* or *E*), 47.7 (q, $^4J_{CF} = 3.5$ Hz, C-1, *E*), 50.5 (C-1, *Z*), 58.7 (d, $^1J_{PC} = 141.6$ Hz, Cq, $Z + E$), 124.0 (q, $^2J_{CF} = 30.5$ Hz, C-3, $Z + E$), 124.9 (q, $^1J_{CF} = 275.3$ Hz, C-4, $Z + E$), 129.3–131.8 (CH_{arom}, $Z + E$), 139.5 (C-*i*, *Z* or *E*), 159.3 (C-2, $Z + E$). ^{31}P NMR (D_2O/NaOD, 101 MHz): $\delta = 22.1$, 21.9 (91 : 9). ^{19}F NMR (D_2O/NaOD, 235 MHz): $\delta = -55.5$, -55.6 (90 : 10). Anal. Calcd for $C_{18}H_{25}F_3NO_3PS$: C, 51.06; H, 5.95%. Found: C, 50.90; H, 5.73%.

3-(3-Ethylsulfanyl-4,4,4-trifluoro-2-phenylbut-2-enylamino)-propylphosphonic Acid (3h)

^{1}H NMR (D_2O/NaOD, 250 MHz): $\delta = 1.00$ (t, $^3J_{HH} = 7.4$ Hz, 3H, CH_3, *Z* or *E*), 1.14–1.28 (m, 5H, CH_2+ CH_3, $Z + E$), 1.40–1.52 (m, 2H, CH_2N, $Z + E$), 2.47(t, $^3J_{HH} = 7.2$ Hz, 2H, CH_2, $Z + E$), 2.81 (q, $^3J_{HH} = 7.4$ Hz, 3H, SCH_2, $Z + E$), 3.74 (s, 2H, CH_2, *Z* or *E*), 3.95 (s, 2H, CH_2, *Z* or *E*), 7.21–7.43 (m, 5H, C_6H_5, $Z + E$). ^{13}C NMR (D_2O/NaOD, 20 MHz): $\delta = 14.8$ (CH_3, *Z* or *E*), 15.3 (CH_3, *Z* or *E*), 24.0 (d, $^2J_{PC} = 3.1$ Hz, CH_2), 28.3 (d, $^1J_{PC} = 130.6$ Hz, CH_2, $Z + E$), 30.1 (SCH_2, *Z* or *E*), 30.9 (SCH_2, *Z* or *E*), 50.7 (d, $^3J_{PC} = 15.9$ Hz, CH_2, $Z + E$), 54.6 (C-1, $Z + E$), 124.9 (q, $^1J_{CF} = 275.9$ Hz, C-4, $Z + E$), 127.1 (q, $^2J_{CF} = 31.1$ Hz, C-3, $Z + E$), 129.1–130.9 (CH_{arom}, $Z + E$), 138.1 (C-*i*, *Z* or *E*), 139.4 (C-*i*, *Z* or *E*), 155.8 (C-2, $Z + E$). ^{31}P NMR (D_2O/NaOD, 101 MHz): $\delta = 22.3$. ^{19}F NMR (D_2O/NaOD, 235 MHz): $\delta = -55.5$, -55.7 (8 : 92). Anal. Calcd for $C_{15}H_{21}F_3NO_3PS$: C, 47.00; H, 5.52%. Found: C, 46.78; H, 5.45%.

Benzylaminophosphonic Acids 4a–e: General Procedure

To the suspension of primary aminophosphonic acid (10 mmol) in MeOH (100 mL), NEt_3 (3.00 g, 30 mmol) was added, and the solution was stirred at room temperature for 20 min. Next, the aromatic aldehyde (10 mmol) was added, and stirring was continued at room temperature (time is given in Table II). The clear solution thus obtained was cooled to 0°C, and $NaBH_4$ (1.90 g, 50 mmol) was added cautiously. Stirring was continued for 14 h at room temperature. Then the solvent was evaporated, and the residue treated with toluene (60 mL, **4a**,**c**) or water (30 mL, **4b**,**d**,**e**), stirred for 5 min, and the solvent was evaporated. The residue thus obtained was dissolved in MeOH (30 mL, **4a**,**c**) or water (30 mL, **4b**,**d**,**e**), acidified to pH ~2 by HCl/MeOH (4 mol/dm^3, **4a**,**c**) or by HCl/H_2O (4 mol/dm^3, **4b**,**d**,**e**), and evaporated. For the preparation of **4d**, the residue was crystallized from water and washed with MeOH providing the product as colorless crystals. For **4a–c**,**e** the residue was dissolved in MeOH/acetone (2:1, 50 mL, **4a**), MeOH (50 mL, **4b**,**c**), or EtOH/acetone (1:1, 30 mL, **4e**). The precipitate, if present, was filtered

off, and the filtrate was treated with propylene oxide and left in the refrigerator for 12 h. Products **4a–c**,**e** precipitated as white colorless solids. All products gave satisfactory spectroscopic data in accord with the assigned structures.

(Benzylamino)methylphosphonic Acid (4a)

^{1}H NMR (D_2O/NaOD, 250 MHz): $\delta = 2.54$ (d, $^2J_{PH} = 12.5$ Hz, 2H, CH_2), 3.74 (s, 2H, CH_2), 7.30–7.35 (m, 5H, C_6H_5). ^{13}C NMR (D_2O/NaOD, 20 MHz): $\delta = 47.7$ (d, $^1J_{PC} = 130.6$ Hz, CH_2), 54.9 (d, $^3J_{PC} = 12.8$ Hz, CH_2), 130.4–131.1 (CH_{arom}), 135.9 (C-*i*). ^{31}P NMR (D_2O/NaOD, 80 MHz): $\delta = 15.7$. Anal. Calcd for $C_8H_{12}NO_3P$: C, 47.77; H, 6.01; N, 6.96%. Found: C, 47.54; H, 6.11; N, 6.88%.

2-(4-Chlorobenzylamino)ethylphosphonic Acid (4b)

^{1}H NMR (D_2O/NaOD, 250 MHz): $\delta = 1.56$–1.72 (m, 2H, CH_2), 2.96–3.09 (m, 2H, CH_2), 3.96 (s, 2H, CH_2), 7.10–7.50 (m, 4H, C_6H_4). ^{13}C NMR (D_2O/NaOD, 50 MHz): $\delta = 30.6$ (d, $^1J_{PC} = 124.4$ Hz, C-1), 48.4 (C-2), 133.1 (CH_{arom}), 134.9 (CH_{arom}), 136.3 (Cq_{arom}), 138.1 (Cq_{arom}). ^{31}P NMR (D_2O/NaOD, 80 MHz): $\delta = 18.5$. Anal. Calcd for $C_9H_{13}ClNO_3P$: C, 43.30; H, 5.25; N, 5.61%. Found: C, 43.15; H, 5.23; N, 5.62%.

Phenyl(thiophen-2-ylmethylamino)methylphosphonic Acid (4c)

^{1}H NMR (D_2O/NaOD, 250 MHz): $\delta = 3.60$ (AB, $J = 14.1$ Hz, 1H, CH), 3.64 (d, $^2J_{PH} = 7.8$ Hz, 1H, CH), 3.74 (AB, $J = 13.9$ Hz, 1H, CH), 6.80–6.89 (m, 2H, CH_{arom}), 7.18–7.32 (CH_{arom}). ^{13}C NMR (D_2O/NaOD, 63 MHz): $\delta = 43.2$ (d, $^3J_{PC} = 12.6$ Hz, CH_2), 60.4 (d, $^1J_{PC} = 131.2$ Hz, CH), 124.2–127.3 (CH_{arom}), 136.7 (Cq_{arom}), 137.9 (Cq_{arom}). ^{31}P NMR (D_2O/NaOD, 101 MHz): $\delta = 16.0$. Anal. Calcd for $C_{12}H_{14}NO_3PS$: C, 50.88; H, 4.98; N, 4.94%. Found: C, 50.74; H, 5.01; N, 4.97%.

1-(Benzylamino)ethylphosphonic Acid (4d)

^{1}H NMR (D_2O/NaOD, 80 MHz): $\delta = 1.44$ (dd, $^3J_{HH} = 7.2$ Hz, $^3J_{PH} = 13.6$ Hz, 3H, CH_3), 3.09 (dq, $^3J_{HH} = 7.2$ Hz, $^2J_{PH} = 12.7$ Hz, 1H, CH), 4.28 (s, 2H, CH_2), 7.52 (s, 5H, C_6H_5). ^{13}C NMR (D_2O/NaOD, 50 MHz): $\delta = 17.1$ (C-2), 54.0 (d, $^3J_{PC} = 6.5$ Hz, CH_2), 56.5 (d, $^1J_{PC} = 133.4$ Hz, C-1), 132.9–133.5 (CH_{arom}), 137.5 (Cq_{arom}). ^{31}P NMR (D_2O/NaOD, 80 MHz): $\delta = 18.1$. Anal. Calcd for $C_9H_{14}NO_3P$: C, 50.23; H, 6.56; N, 6.51%. Found: C, 50.14; H, 6.48; N, 6.65%.

3-(Quinolin-2-ylmethylamino)propylphosphonic Acid (4e)

^{1}H NMR (D_2O/NaOD, 250 MHz): $\delta = 1.15$–1.29 (m, 2H, CH_2), 1.47–1.59 (m, 2H, CH_2), 2.45 (t, $^3J_{HH} = 7.3$ Hz, 2H, CH_2), 3.77 (s, 2H, CH_2), 7.29–8.09 (m, 6H, CH_{arom}). ^{13}C NMR (D_2O/NaOD, 63 MHz): $\delta = 21.4$ (C-2), 25.2 (d, $^1J_{PC} = 130.2$ Hz, C-1), 47.9 (d, $^3J_{PC} = 17.6$ Hz, C-3), 51.3 (CH_2), 117.1–155.2 (C_{arom}). ^{31}P NMR (D_2O/NaOD, 101 MHz): $\delta = 22.3$. Anal. Calcd for $C_{13}H_{17}N_2O_3P$: C, 55.71; H, 6.11; N, 10.00%. Found: C, 55.67; H, 6.09; N, 9.98%.

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