Synthesis of perfluoroalkylated heterocyclic phosphonates

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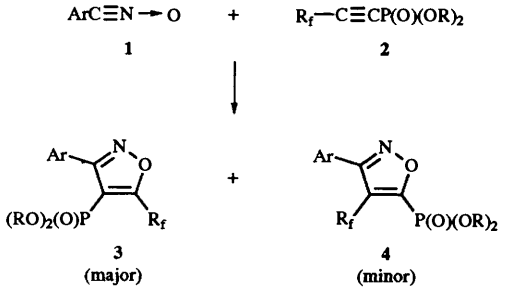
Perfluoroalkylated heterocyclic phosphonates have been conveniently synthesized by 1,3-dipolar cycloaddition of aromatic nitrile oxides (or ethyl diazoacetate or *tert*-butyl azidoacetate) and perfluoroalkylated alkynylphosphonates in good to excellent yields with high regioselectivity.

A large number of phosphonic acids and their derivatives have been shown to exhibit important biological properties, including antibiotic, antileukaemic and insecticidal activity, depending on the nature of substituent on the phosphonic group.[1] Introduction of a fluorine atom or perfluoroalkyl group into compounds with biological properties often leads to pronounced activity enhancement, and organofluorine compounds have been applied increasingly in pharmaceuticals, agrichemicals and other fields.[2] Furthermore heterocyclic compounds, particularly fluorine-containing heterocyclic species, play important roles in the fields of medicinal and agricultural chemistry.[3] Therefore, it is of interest to develop a convenient method for the synthesis of the title compounds since they may be expected to possess biological activity.

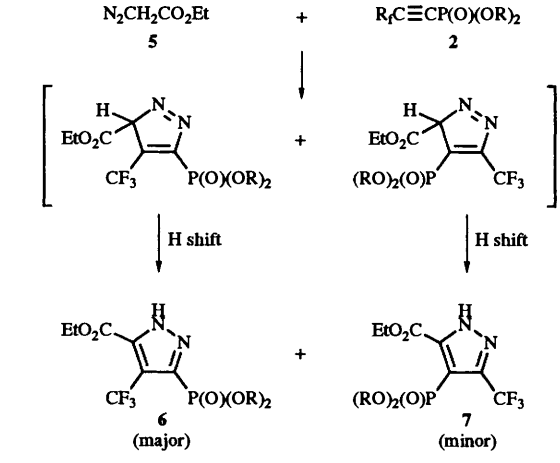
Results and discussions

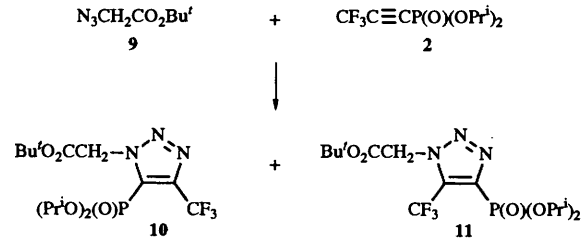
The 1,3-dipolar cycloaddition of nitrile oxides and carbon–carbon unsaturated dipolarophiles is a useful method for the synthesis of heterocyclic compounds.[4] Perfluoroalkylated acetylenes, such as hexafluorobut-2-yne, have been found to be good dipolarphiles, but no 1:1 cycloadducts have been isolated from this reaction.[5] We found that perfluoroalkynylphosphonates could be used as dipolarophiles in reaction with aromatic nitrile oxides to give perfluoroalkylated isoxazolylphosphonates in good to excellent yields.



Aromatic nitrile oxides **1** reacted with perfluoroalkynylphosphonates **2** to give perfluoroalkylated isoxazolylphosphonates (regioisomers **3** and **4**). The reaction is highly regioselective with **3** as the major product. The results are summarized in Table 1. Treatment of ethyl diazoacetate **5** with perfluoroalkynylphosphonates **2** gave perfluoroalkylated pyrazolylphosphonates as a mixture of regioisomers **6** and **7** which could be separated by column chromatography. Regioisomer **6** was obtained as the major product. The results are summarized in Table 2.

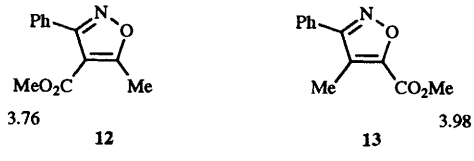
The reaction of *tert*-butyl azidoacetate with diisopropyl 3,3,3-trifluoroprop-1-ynylphosphonate gave trifluoromethylated triazolylphosphonates **10** and **11** (90% yield, ratio **10**:**11** 75:25)





with **10** as the major product. The two regioisomers could be easily separated by column chromatography.

The structures of regioisomers **3** and **4** were assigned by a comparison of their NMR data with reported data for similar compounds. Christl and Huisgen have reported the ^{1}H NMR data of compounds **12** and **13**.[6] The OMe signals in the ^{1}H



NMR spectrum of compound **12** are shifted upfield while those of compounds **13** are shifted downfield. NMR data for two other similar compounds **14** and **15** have also been reported and we assume that the OMe signal of compound **14** is shifted upfield while that of compound **15** is shifted downfield.[7] By

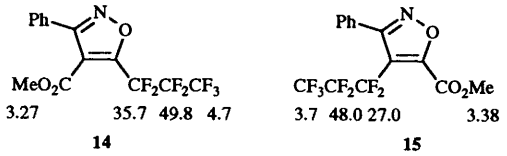


Table 1 Perfluoroalkylated isoxazolylphosphonates prepared

Product	Ar	R	R_f	Yield[a] (%)	Ratio[b] 3:4
3a + 4a	Ph	Ph	C_3F_7	86	98:2
3b + 4b	Ph	Ph	C_2F_5	84	98:2
3c	Ph	Ph	CF_3	80	100:0
3d + 4d	4-ClC_6H_4	Ph	C_3F_7	83	96:4
3e + 4e	4-ClC_6H_4	Ph	C_2F_5	74	97:3
3f	4-ClC_6H_4	Ph	CF_3	80	100:0
3g	4-MeC_6H_4	Ph	C_3F_7	92	100:0
3h	4-MeC_6H_4	Ph	C_2F_5	92	100:0
3i	4-MeC_6H_4	Ph	CF_3	90	100:0
3j + 4j	4-ClC_6H_4	Pr^i	CF_3	90	87:13
3k + 4k	4-FC_6H_4	Pr^i	CF_3	91	88:12

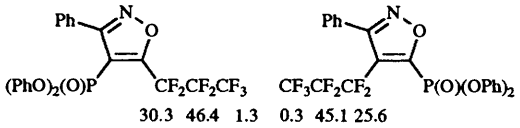
[a] Isolated yields. [b] The ratios of **3**:**4** were estimated from the ^{19}F NMR data.

Table 2 Trifluoromethylated pyrazolylphosphonates prepared

Compound	R_f	R	Yield[a] (%)	Ratio[b] 6:7
6a + 7a	CF_3	Et	89	84:16
6b + 7b	CF_3	Pr^i	94	85:15

[a] Isolated yields. [b] The ratios of **6**:**7** were estimated from the ^{19}F NMR data.

comparing the ^{19}F NMR data of compounds **14** and **15** with the data for compounds **3a** and **4a** we have assigned the regioisomers **3a** and **4a** as shown below, *i.e.* the CF_3 signals of compounds **14** and **3a** are shifted upfield while those of compounds **15** and **4a** are shifted downfield.



Experimental

All mps and bps are uncorrected. IR spectra were recorded on a Shimadzu IR-440 spectrometer. ^{19}F NMR spectra were determined on a Varian EM-360 spectrometer (60 MHz) with trifluoroacetic acid (TFA) as external standard, positive for upfield shifts; ^1H NMR spectra were carried out on a Varian EM-360 or a Bruker AM-300 (300 MHz) instrument with tetramethylsilane (TMS) as reference; $CDCl_3$ was used as solvent. *J* Values are given in Hz. Mass spectra were measured on a Finnigan GC–MS-4021 mass spectrometer.

General procedure for the preparation of perfluoroalkylated isoxazolyl phosphonates 3 and 4

To a solution of a diphenyl perfluoroalkynylphosphonate[8] **2** (0.6 mmol) and an arylcarbohydroximoyl chloride (0.5 mmol) in diethyl ether (5 cm^3) was slowly added triethylamine (0.6 mmol) at 0 °C over 0.5 h. The mixture was stirred at 0 °C for 2 h, then warmed to room temperature and stirred for a further 2 h. The triethylamine hydrochloride formed was filtered off. Removal of the solvent under reduced pressure gave a residue which was purified by column chromatography on silica gel eluting with light petroleum–chloroform (7:3) to give the products **3** and/or **4**). After recrystallization from light petroleum pure regioisomer **3** was obtained. In the cases of **j** and **k**, **3j** and **4j** (or **3k** and **4k**) could be separated by column chromatography on silica gel eluting with light petroleum–acetone (40:1 to 20:1).

Diphenyl (5-heptafluoropropyl-3-phenyl-1,2-oxazol-4-yl)phosphonate 3a. Mp 48–49 °C; ν/cm^{-1} 1590, 1240, 1120 and 1020; δ_H 6.72–7.71 (15 H, m); δ_F 1.3 (3 F, t, *J* 8), 30.3 (2 F, q, *J* 8) and 46.4 (2 F, s); *m/z* 545 (M^+, 22%), 452 (5), 376 (12) and 77 (100) (Found: C, 53.1; H, 3.0. $C_{24}H_{15}F_7NO_4P$ requires C, 52.86; H, 2.77%).

Diphenyl (5-pentafluoroethyl-3-phenyl-1,2-oxazol-4-yl)phosphonate 3b. Mp 60–61 °C; ν/cm^{-1} 1600, 1240, 1110 and 1010; δ_H 6.75–7.75 (15 H, m); δ_F 4.0 (3 F, s) and 32.2 (2 F, s); *m/z* 495 (M^+, 100%), 402 (13), 376 (24) and 77 (95) (Found: C, 55.9; H, 3.2. $C_{23}H_{15}F_5NO_4P$ requires C, 55.77; H, 3.05%).

Diphenyl (3-phenyl-5-trifluoromethyl-1,2-oxazol-4-yl)phosphonate 3c. Mp 65–66 °C; ν/cm^{-1} 1600, 1220, 1160 and 1030; δ_H 6.74–7.82 (15 H, m); δ_F −17.6 (3 F, s); *m/z* 445 (M^+, 64%), 376 (22), 352 (9) and 77 (95) (Found: C, 59.2; H, 3.4. $C_{22}H_{15}F_3NO_4P$ requires C, 59.34; H, 3.39%).

Diphenyl [3-(4-chlorophenyl)-5-heptafluoropropyl-1,2-oxazol-4-yl]phosphonate 3d. Mp 78–79 °C; ν/cm^{-1} 1590, 1210, 1170 and 1020; δ_H 6.75–7.72 (14 H, m); δ_F 1.2 (3 F, t, *J* 8), 30.0 (2 F, q, *J* 8) and 46.0 (2 F, s); *m/z* 579 (M^+, 12%), 486 (6), 410 (13) and 77 (100) (Found: C, 49.9; H, 2.3. $C_{24}H_{14}ClF_7NO_4P$ requires C, 49.72; H, 2.43%).

Diphenyl [3-(4-chlorophenyl)-5-pentafluoroethyl-1,2-oxazol-4-ylphosphonate 3e. Mp 61–62 °C; ν/cm^{-1} 1590, 1220, 1160 and 1020; δ_H 6.65–7.73 (14 H, m); δ_F 4.0 (3 F, s) and 32.0 (2 F, s); *m/z* 529 (M^+, 10%), 436 (6), 410 (11) and 77 (100) (Found: C, 52.1; H, 2.6. $C_{23}H_{14}ClF_5NO_4P$ requires C, 52.14; H, 2.66%).

Diphenyl [3-(4-chlorophenyl)-5-trifluoromethyl-1,2-oxazol-4-yl]phosphonate 3f. Bp 140 °C/0.1 Torr; ν/cm^{-1} 1590, 1200, 1160 and 1020; δ_H 6.76–7.72 (14 H, m); δ_F −17.5 (3 F, s); *m/z* 479 (M^+, 95%), 410 (41), 386 (14) and 77 (100) (Found: C, 55.2; H, 2.8. $C_{22}H_{14}ClF_3NO_4P$ requires C, 55.08; H, 2.94%).

Diphenyl [5-heptafluoropropyl-3-(*p*-tolyl)-1,2-oxazol-4-yl]-phosphonate 3g. Mp 69–70 °C; ν/cm^{-1} 1590, 1200, 1170 and 960; δ_H 6.63–7.67 (14 H, m) and 2.38 (3 H, s); δ_F 1.7 (3 F, t, *J* 8), 30.1 (2 F, q, *J* 8), 46.3 (2 F, s); *m/z* 559 (M^+, 100%), 446 (21), 390 (21) and 77 (95) (Found: C, 53.6; H, 3.0. $C_{25}H_{17}F_7NO_4P$ requires C, 53.68; H, 3.06%).

Diphenyl [5-pentafluoroethyl-3-(*p*-tolyl)-1,2-oxazol-4-yl]-phosphonate 3h. Mp 52–53 °C; ν/cm^{-1} 1590, 1200, 1160 and 980; δ_H 6.47–7.58 (14 H, m) and 2.42 (3 H, s); δ_F 4.0 (3 F, s) and 32.1 (2 F, s); *m/z* 509 (M^+, 89%), 416 (43), 390 (53) and 77 (100) (Found: C, 56.4; H, 3.3. $C_{24}H_{17}F_5NO_4P$ requires C, 56.59; H, 3.36%).

Diphenyl [3-(*p*-tolyl)-5-trifluoromethyl-1,2-oxazol-4-yl]phosphonate 3i. Bp 165 °C/0.5 Torr; ν/cm^{-1} 1590, 1200, 1160 and 980; δ_H 6.85–7.68 (14 H, m) and 2.40 (3 H, s); δ_F −17.8 (3 F, s), *m/z* 459 (M^+, 100%), 390 (30), 366 (22) and 77 (95) (Found: C, 60.4; H, 3.4. $C_{23}H_{17}F_3NO_4P$ requires C, 60.14; H, 3.73%).

Diisopropyl [3-(4-chlorophenyl)-5-trifluoromethyl-1,2-oxazol-4-yl]phosphonate 3j. Colourless oil; ν/cm^{-1} 1605, 1270, 1230 and 1020; δ_H 7.71–7.76 (2 H, m), 7.46–7.50 (2 H, m), 4.72 (2 H, hept., *J* 6.2), 1.29 (6 H, d, *J* 6.2) and 1.18 (6 H, d, *J* 6.2); δ_F −16.8 (3 F, s); *m/z* 411 (M^+, 5%), 369 (13) and 258 (100) (Found: C, 46.8; H, 4.4; N, 3.5. $C_{16}H_{18}ClF_3NO_4P$ requires C, 46.67; H, 4.41; N, 3.40%).

Diisopropyl [3-(4-chlorophenyl)-4-trifluoromethyl-1,2-oxazol-5-yl]phosphonate 4j. Colourless oil; ν/cm^{-1} 1600, 1270, 1230 and 1020; δ_H 7.74–7.58 (4 H, m), 4.96 (2 H, hept., *J* 6.2) and 1.34–1.46 (12 H, m); δ_F −24.0 (3 F, s); *m/z* 411 (M^+, 18%), 413 (6), 369 (11) and 246 (100) (Found: C, 46.8; H, 4.4; N, 3.4. $C_{16}H_{18}ClF_3NO_4P$ requires C, 46.67; H, 4.41; N, 3.40%).

Diisopropyl [3-(4-fluorophenyl)-5-trifluoromethyl-1,2-oxazol-4-yl]phosphonate 3k. Colourless oil; ν/cm^{-1} 1605, 1270, 1230 and 1020; δ_H 7.76–7.80 (2 H, m), 7.15–7.21 (2 H, m), 4.73 (2 H, hept., *J* 6.2), 1.28 (6 H, d, *J* 6.2), 1.17 (6 H, d, *J* 6.2); δ_F −16.6 (3 F, s) and 32.0 (1 F, s); *m/z* 396 (M^+ + 1, 13%), 354 (11) and 242 (100) (Found: C, 48.3; H, 4.5; N, 3.5. $C_{16}H_{18}F_4NO_4P$ requires C, 48.62; H, 4.59; N, 3.54%).

Diisopropyl [3-(4-fluorophenyl)-4-trifluoromethyl-1,2-oxazol-5-yl]phosphonate 4k. Colourless oil; ν/cm^{-1} 1605, 1270, 1230 and 1020; δ_H 7.60–7.64 (2 H, m), 7.15–7.22 (2 H, m), 4.90–5.00 (2 H, m) and 1.32–1.47 (6 H, m); δ_F −23.8 (3 F, s) and 32.0 (1 F, s); *m*/*z* 396 (M^+ + 1, 8%), 354 (4) and 230 (100) (Found: C, 48.4; H, 4.5; N, 3.4. $C_{16}H_{18}F_4NO_4P$ requires C, 48.62; H, 4.59; N, 3.54%).

General procedure for the preparation of trifluoromethylated pyrazolylphosphonates 6 and 7

To a solution of dialkyl 3,3,3-trifluoroprop-1-ynylphosphonate[9] **2** (R_f = CF_3, 1 mmol) in diethyl ether (2 cm^3) was slowly added ethyl diazoacetate **5** (1.1 mmol) at 0 °C. The mixture was stirred at room temperature for 5 h. Evaporation of the solvent gave a residue which was purified by column chromatography eluting with light petroleum–isopropyl alcohol (40:1 gave **6**; 20:1 gave **7**).

Diethyl (5-ethoxycarbonyl-4-trifluoromethylpyrazol-3-yl)-phosphonate 6a. Mp 68–69 °C; ν/cm^{-1} 1740, 1490, 1240 and 1030; δ_H 13.95 (1 H, br s), 4.46 (2 H, q, *J* 7.2), 4.14–4.31 (4 H, m), 1.41 (3 H, t, *J* 7.2) and 1.34 (6 H, t, *J* 7.2); δ_F −22.0 (3 F, s); *m*/*z* 345 (M^+ + 1, 29%), 317 (9), 299 (15) and 272 (100) (Found: C, 38.2; H, 4.7; N, 7.8. $C_{11}H_{16}F_3N_2O_5P$ requires C, 38.38; H, 4.68; N, 8.14%).

Diethyl (5-ethoxycarbonyl-3-trifluoromethylpyrazol-4-yl)-phosphonate 7a. Colourless oil; ν/cm^{-1} 1740, 1440 and 1240; δ_H 13.95 (1 H, br s), 4.45 (2 H, q, *J* 7.2), 4.17–4.31 (4 H, m) and 1.32–1.43 (9 H, m); δ_F −16.6 (3 F, s); *m*/*z* 345 (M^+, 20%), 317 (15), 299 (19) and 272 (100) (Found: C, 38.3; H, 4.6; N, 7.9. $C_{11}H_{16}F_3N_2O_5P$ requires C, 38.38; H, 4.68; N, 8.14%).

Diisopropyl (5-ethoxycarbonyl-4-trifluoromethylpyrazol-3-yl)phosphonate 6b. Mp 90–91 °C; ν/cm^{-1} 1740, 1260 and 1240; δ_H 9.90 (1 H, br s), 4.75 (2 H, hept., *J* 6.2), 4.45 (2 H, q, *J* 7.2), 1.35–1.44 (9 H, m) and 1.25 (6 H, d, *J* 6.2); δ_F −22.8 (3 F, s); *m*/*z* 373 (M^+ + 1, 10%), 317 (9), 330 (20), 289 (75) and 243 (100) (Found: C, 41.9; H, 5.3; N, 7.3. $C_{13}H_{20}F_3N_2O_5P$ requires C, 41.94; H, 5.41; N, 7.52%).

Diisopropyl (5-ethoxycarbonyl-3-trifluoromethylpyrazol-4-yl)phosphonate 7b. Mp 99–100 °C; ν/cm^{-1} 1740, 1260 and 1220; δ_H 9.90 (1 H, br s), 4.84 (2 H, hept., *J* 6.2), 4.37 (2 H, q, *J* 7.0) and 1.23–1.48 (15 H, m); δ_F −18.2 (3 F, s); *m*/*z* 373 (M^+ + 1, 16%), 331 (14) and 289 (100) (Found: C, 41.7; H, 5.2; N, 7.4. $C_{13}H_{20}F_3N_2O_5P$ requires C, 41.94; H, 5.41; N, 7.52%).

Procedure for the preparation of trifluoromethylated triazolylphosphonates 10 and 11

To a solution of diisopropyl 3,3,3-trifluoroprop-1-ynylphosphonate[9] **2** (R_f = CF_3, R = Pr^i, 1 mmol) in diethyl ether (2 cm^3) was slowly added *tert*-butyl azidoacetate (1 mmol) at room temperature. The mixture was stirred at room temperature for 20 h. Evaporation of the solvent gave a residue which was purified by column chromatography eluting with light petroleum–ethyl acetate (10:1 gave **10**, 2:1 gave **11**).

Diisopropyl (1-*tert*-butoxycarbonylmethyl-4-trifluoromethyl)-1*H*-1,2,3-triazol-5-yl)phosphonate 10. Colourless oil; ν/cm^{-1} 1750, 1260 and 1240; δ_H 5.53 (2 H, s), 4.75–4.82 (2 H, m), 1.51 (9 H, s), 1.40 (6 H, d, *J* 6.2) and 1.28 (6 H, d, *J* 6.2); δ_F −18.2 (3 F, s); *m*/*z* 416 (M^+ + 1, 4%), 360 (4), 300 (12), 258 (44) and 57 (100) (Found: C, 43.2; H, 6.1; N, 10.2. $C_{15}H_{25}F_3N_3O_5P$ requires C, 43.38; H, 6.07; N, 10.12%).

Diisopropyl (1-*tert*-butoxycarbonylmethyl-5-trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)phosphonate 11. Mp 86–87 °C; ν/cm^{-1} 1750, 1270 and 1240; δ_H 5.25 (2 H, s), 4.86–4.91 (2 H, m), 1.46 (9 H, s), 1.40 (6 H, d, *J* 6.2) and 1.35 (6 H, d, *J* 6.2); δ_F −21.5 (3 F, s); *m*/*z* 416 (M^+ + 1, 3%), 374 (5), 332 (10) and 57 (100) (Found: C, 43.0; H, 5.9; N, 9.9. $C_{15}H_{25}F_3N_3O_5P$ requires C, 43.38; H, 6.07; N, 10.12%).

Acknowledgements

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References

1 (*a*) R. Engel, *Chem. Rev.*, 1977, **77**, 349; (*b*) E. Castagnino, S. Corsano and B. Serena, *Gazz. Chim. Ital.*, 1983, **113**, 97; (*c*) S. Hanessian, Y. L. Bennani and D. Delorme, *Tetrahedron Lett.*, 1990, **31**, 6461.
2 *Biochemical Aspects of Fluorine Chemistry*, eds. R. Filler and Y. Kobayashi, Kodasha Ltd, Tokyo and Elsevier Biomedical, Amsterdam, New York, Oxford, 1982; J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
3 R. Filler, *J. Fluorine Chem.*, 1986, **33**, 361; K. Tamura, H. Mizukami, K. Maeda, H. Watanabe and K. Uneyama, *J. Org. Chem.*, 1993, **58**, 32 and references cited therein.
4 J. E. Baldwin, C. Hoskins and L. Kruse, *J. Chem. Soc., Chem. Commun.*, 1976, 795; A. A. Hagedorn, B. J. Miller and J. O. Nagy, *Tetrahedron Lett.*, 1980, **21**, 229.
5 Y. Kobayashi, I. Kumadaki and S. Fujino, *Heterocycles*, 1977, **7**, 871.
6 M. Christl and R. Huisgen, *Chem. Ber.*, 1973, **106**, 3283.
7 Y.-C. Shen, J.-H. Zheng and Y.-Z. Huang, *Synthesis*, 1985, 970.
8 Y.-C. Shen, Y.-K. Lin and Y.-K. Xin, *Tetrahedron Lett.*, 1985, **26**, 5137.
9 Y.-C. Shen and M. Qi, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2153.

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