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The Design and Synthesis of β-Trifluoromethylenol Phosphates as Potential Insecticides

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ABSTRACT: *A new group of compounds, β-trifluoromethylenol phosphates [$(RO)_2P(O)OCR{=}CHCF_3$], has been designed and prepared by several methods. Some of them showed good insecticidal activities. In the molecular structure, the designed leaving group can rearrange to a powerful electrophilic agent, β,β-difluorovinyl ketone, which would be a potential enzyme inhibitor.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:304–308, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10147

INTRODUCTION

Enol phosphates are a class of important organic compounds. For example, phosphenol pyruvate (PEP) is a well known as high-energy species that play a vital role in a number of biological processes. Further efforts have been made in the preparation of bioactive enol phosphates. As pesticide, they are a kind of very potent insecticide that has wide field of application. Despite their diverse structure, they own their activity to their capacity to phosphorylate and inhibit the action of cholinesterase, although in some instances the inhibition of other vital enzyme is believed to be involved.

It has been demonstrated that their toxic action is the result of progressive inhibition of cholinesterase in mammals and insects. The complete chemical and physical structure of the enzyme AChE is still not known. The enzyme has two known active sites [1], one is the esteratic site because it attracts ester groups to it; the other is anionic or negative site because it attracts a cation (or an electrically positive section of a compound). Present theory [2] poisoning proposes that an organophosphorus molecule (an ester) forms an intimate complex with AChE, then the serine-OH of AChE is phosphorylated. Thus, AChE cannot split acetylcholine due to the stability of its phosphorylated derivative and is inhibited. The results may probably be considered as indicating that when other condition (especially the steric ones) are similar the inhibitory power depends essentially on the phosphorylating power. Organophosphorus insecticides with the following general structure $(RO)_2P(O$ or $S)X$ are often designed to have a good leaving group X for increasing its phosphorylating power.

Crop protection continually needs the discovery of novel insecticides, particularly, those acting via novel modes of action. Recently, Widlauski [3] reported the synthesis of enol phosphates having leaving group at the 1-position that are mechanism-based phosphatase or phosphodiesterase inhibitors. On the basis of this idea, we designed a new group of

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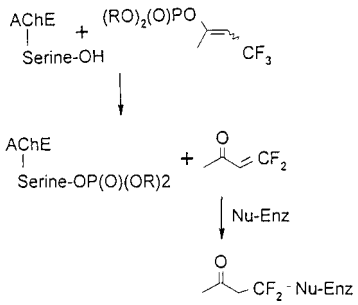
insecticide, β-trifluoromethylenol phosphates. During the course of the phosphorylation of the serine-OH of AChE (or hydrolysis by phosphatase), this compound can give rise to an intermediate that would undergo a rapid chemical rearrangement to a highly reactive compound, β,β-difluorovinyl ketone, which is a powerful electrophilic agent to other nucleophilic residues of enzyme. That is, the leaving group X would also be a potential enzyme inhibitor.



RESULTS AND DISCUSSION

Synthesis

We attempted to prepare β-trifluoromethylenol phosphates from the phosphorylation of the enolates of α-trifluoromethylated ketones. But the experiments showed that the α-trifluoromethylated ketones could not be formed by the reaction of α-bromo or α-iodoketones with trifluoromethylating agent $FO_2SCF_2CO_2Me$ under the conditions described in the literature [4]. Enol phosphates are versatile intermediates in organic synthesis. They can be thought of as an active form of ketones. So we imagined that β-haloenol phosphates may be more reactive substrates than α-haloketones in trifluoromethylation. In this paper β-trifluoromethylenol phosphates **2** have been synthesized from the reaction of β-bromoenol phosphates **1** with $FO_2SCF_2CO_2Me$, as outlined in Scheme 1.

ß-Bromoenol phosphates **1a–f** were prepared by Perkow reaction [5] of trialkyl phosphite with 1-aryl-2,2-dibromo-ethanones which were obtained from bromination of the corresponding 1-aryl-ethanones [6]. **1a–f** were mixtures of Z and E isomers in which the Z isomer predominated. ß-Bromoenol phosphates are also prepared from Atherton–Todd reaction [7]. The separation of pure E isomer failed.

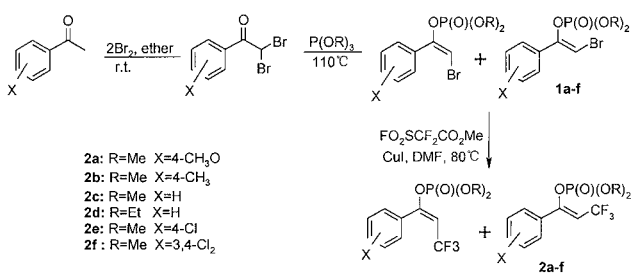
In the presence of CuI, **1a–f** reacted with $FO_2SCF_2CO_2Me$ in DMF at 80°C to give 1-aryl-3,3,3-trifluoro-1-propenyl phosphates (method A) in low yield. Trifluoromethylation maintains configuration [8], trifluoromethylenol phosphates made from Z-ß-bromoenol phosphates are also Z-isomers. The E and Z configurations of all enol phosphates were determined using the Tobey–Pascual substituent shielding constant method [9] and NOE observation in NMR.

The study in details proved that the cleavage of O—P in trifluoromethylenol phosphates by the attack of fluoride ion led to the loss of the phosphoryl group to form trifluoromethyl ketones. If the reaction time was prolonged only trifluoromethylketones were formed [10].

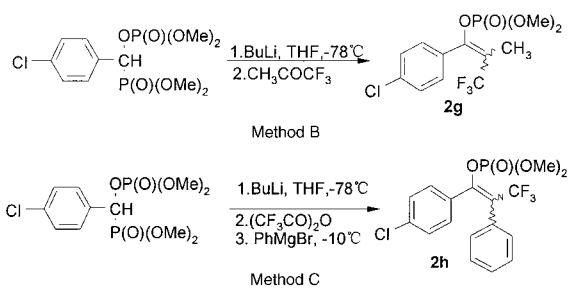
Because of the poor yield of above method, Wittig-type reactions [11,12] that were tried (Scheme 2), but the yields were not improved.

Insecticidal Activity

The compounds were screened for their insecticidal activity against *Mythimna separata* (Walker), *Aphis laburni* (Kaltenback), and *Tetranychus cirinabarinus* (Boisduval). Two of the synthesized compounds showed significant insecticidal activities. At concentration of 500 ppm/insect, compound **2a** showed a broad spectrum of insecticidal activity: 77% mortality against *Mythimna separata*, 75% mortality against *Aphis laburni*, and 67% mortality against *Tetranychus cirinabarinus*. Compound **2d** showed specific insecticidal activity: 100% mortality against *Aphis laburni*, only 8% mortality against *Tetranychus cirinabarinus*, and no insecticidal activity against *Mythimna*



SCHEME 1 Method A.



SCHEME 2 Methods B and C.

separata. All other compounds showed lower activity and did not show any activity against *Mythimna separata* particularly. The examination of the true insecticidal mechanism is in progress.

EXPERIMENTAL

Instrumentation

All melting points were uncorrected. IR spectra were measured with a Y-Zoom CURSOR spectrometer. ^{1}H NMR spectra were recorded on FX-90Q spectrometer using TMS as internal standard. ^{31}P NMR were recorded on an AM-300 spectrometer at 161.97 MHz using $CDCl_3$ as solvent and 85% of H_3PO_4 as external standard. ^{19}F NMR spectra were recorded on an EM-360L spectrometer at 56.4 MHz using TFA as the external standard with positive for upfield shifts. Mass spectra were taken on a Finnigan-4021 spectrometer and HR-MS spectra on a Finnigan MAT8430 spectrometer. Elemental analyses were done by the Elemental Analyses Group of SIOC.

Material

ß-*Bromoenol phosphates* **1a–f** were prepared by Perkow reaction [13] of trialkyl phosphite with 1-aryl-2,2-dibromo-ethanones [6] with purity of >95% (GC). The known compounds were identified in agreement with the literature data, and only the NMR data are reported here.

Dimethyl 1-(4-methoxylphenyl)-2-bromoethenyl phosphate **1a**: oil, yield 80%. ^{1}H NMR (CCl_4, 90 MHz): 6.77–7.67 (m, 4H); 6.40 (s, 0.38 H_E); 6.00 (s, 0.62 Hz); 3.73 (d, $J = 10$ Hz, 6H); 3.80 (s, 3H). ^{31}P NMR: −4.1713, −3.5413. IR (film): 3093, 2959, 1608, 1513, 1285, 1256, 1182, 1039. EI-MS: 336 (M^+, 6.76), 257 (100.00), 229 (9.85), 199 (5.07), 132 (7.95), 109 (42.62), 93 (21.73). Anal. calcd. for $C_{11}H_{14}BrO_5P$: C 39.18, H 4.19; Found: C 38.97, H 4.25.

Dimethyl 1-(4-methylphenyl)-2-bromoethenyl phosphate **1b**: oil, yield 82%. ^{1}H NMR (CCl_4, 90 MHz): 7.20 (m, 4H); 6.38 (m, 0.2H_E); 6.08 (s, 0.8 Hz); 3.74 (d, $J = 10$ Hz, 6H); 2.38 (s, 3H). ^{31}P NMR: −4.2095, −3.5928. IR (film): 3105, 2959, 1625, 1509, 1299, 1180, 1048, 906. EI-MS: 320 (M^+, 10.96), 241 (100.00), 219 (3.85), 195 (2.56), 127 (5.20), 109 (9.48), 93 (4.25). Anal. calcd. for $C_{11}H_{14}BrO_4P$: C 41.14, H 4.40; Found: C 40.87, H 4.34.

Dimethyl 1-phenyl-2-bromoethenyl phosphate **1c** *[9]*: ^{1}H NMR (CCl_4, 90 MHz): 7.40 (m, 5H); 6.20 (m, 1H); 3.75 (d, $J = 10$ Hz, 6H).

Diethyl 1-phenyl-2-bromoethenyl phosphate **1d** *[13]*: ^{1}H NMR (CCl_4, 90 MHz): 7.36 (m, 5H); 6.20 (M, 1H); 4.07 (m, 4H); 1.22 (t, 6H).

Dimethyl 1-(4-chlorophenyl)-2-bromoethenyl phosphate **1e** *[13]*: ^{1}H NMR (CCl_4, 90 MHz): 7.38 (m, 4H); 6.20 (s, 1H); 3.76 (d, $J = 10$ Hz, 6H).

Dimethyl 1-(3,4-dichlorophenyl)-2-bromoethenyl phosphate **1f**: oil, yield 75%. ^{1}H NMR ($CDCl_3$, 90 MHz): 7.52 (m, 3H); 6.30 (d, $J = 2$ Hz, 1H); 3.80 (d, $J = 10$ Hz, 6H). ^{31}P NMR: −4.170. IR (film): 3080, 1618, 1554, 1475, 1390, 1300, 1045, 933; EI-MS: 374 (M^+, 4.11), 294 (100.00), 250 (2.99), 235 (41.35), 127 (2.74), 109 (53.40), 93 (10.10). Anal. calcd. for $C_{10}H_{10}BrCl_2O_4P$: C 31.94, H 2.68; Found: C 32.63, H 2.65.

Dimethyl 1-(dimethoxyphosphinyl)-1-(p-chlorophenyl)methyl phosphate was prepared from the reaction of 4-chlorobenzoylphosphonate with dimethyl phosphite according to the reference method [14]. ^{1}H NMR ($CDCl_3$, 90 MHz): 7.46 (m, 4H); 5.60 (d–d, $J_1 = 12$ Hz, $J_2 = 9$ Hz, 1H); 3.80 (m, 12H). EI-MS: 358 (M^+, 2.95), 248 (100.00), 232 (12.07), 218 (10.86), 187 (10.71), 139 (14.03), 109 (77.92).

PREPARATION OF β-*TRIFLUOROMETHYLENOL PHOSPHATES*

Method A: A mixture of **1a–f** (1 mmol), $FO_2SCF_2CO_2Me$ (1.5 mmol), CuI (1.5 mmol), and DMF (5 ml) was stirred at 80°C for 3 h under a nitrogen atmosphere. Then the reaction mixture was cooled, filtered, poured into water and extracted with diethyl ether. The organic extract was combined, washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by flash column chromatography using a mixture of petroleum ether (bp 60–90°C) and ethyl acetate (20–25:1) to give **2a–f**.

Dimethyl 1-(4-methoxylphenyl)-2-trifluoroethenyl phosphate **2a**: oil, yield 11%. ^{1}H NMR (CCl_4, 90 MHz): 7.45 (d, $J = 7$ Hz, 2H); 6.85 (d, $J = 7$ Hz, 2H); 5.44 (q, $J = 6$ Hz, 1H); 3.73 (m, 9H). ^{19}F NMR (CCl_4): −20.5 (d, $J = 6$ Hz). ^{31}P NMR:−4.917. EI-MS: 326 (M^+, 10.20), 306 (3.93), 243 (30.19), 214 (16.79), 200 (100.00), 181 (22.75), 109 (18.80): IR (film): 3080, 2964, 1669, 1610, 1516, 1338, 1135, 1039, 929. Anal. calcd. for $C_{12}H_{14}F_3O_5P$: C 44.18, H 4.33; Found: C 43.71, H 4.48.

Dimethyl 1-(4-methylphenyl)-2-trifluoroethenyl phosphate **2b**: oil, yield 16.2%. ^{1}H NMR (CCl_4, 90 MHz): 6.50 (d, $J = 7$ Hz, 2H); 6.25 (d, $J = 7$ Hz, 2H); 5.60 (q, $J = 7$ Hz, 1H); 3.75 (d, $J = 12$ Hz, 6H); 2.42 (s, 3H). ^{19}F NMR (CCl_4): −20.2 (d, $J = 7$ Hz). ^{31}P NMR: −4.963. EI-MS: 310 (M^+, 38.60), 291 (100.00), 241 (25.48), 198 (5.03), 184 (9.63), 165 (12.04), 127 (22.77). IR (film): 2964, 1671, 1453,

1336, 1282, 1127, 1039, 1017, 929. HR-MS: 310.0567 (M^+: $C_{12}H_{14}F_3O_4P$, calcd. 310.0582).

Dimethyl 1-phenyl-2-trifluoroethenyl phosphate **2c**: oil, yield 20%. ^{1}H NMR (CCl_4, 90 MHz): 7.40 (m, 5H); 5.55 (q, $J = 7.5$ Hz, 1H); 3.70 (d, $J = 12$ Hz, 6H). ^{19}F NMR (CCl_4): −20.3. ^{31}P NMR: −4.911. EI-MS: 296 (M^+, 39.58), 256 (5.12), 227 (6.30), 184 (8.16), 170 (100.00), 151 (19.09), 127 (7.06). IR (film): 3076, 2964, 1672, 1450, 1340, 1281, 1134, 1043, 934. HR-MS: 296.0425 (M^+: $C_{11}H_{12}F_3O_4P$, calcd. 296.0425).

Diethyl 1-phenyl-2-trifluoroethenyl phosphate **2d**: oil, yield 22%. ^{1}H NMR (CCl_4, 90 MHz): 7.30 (m, 5H); 5.45 (q, $J = 7.5$ Hz, 1H); 3.90 (m, 4H); 1.10 (t, $J = 7$ Hz, 6H). ^{19}F NMR (CCl_4): −25.0. ^{31}P NMR: −7.421. EI-MS: 324 (M^+, 18.60), 305 (50.17), 257 (13.28), 229 (6.45), 198 (25.19), 170 (100.00), 151 (49.15). IR (film): 2989, 1672, 1450, 1341, 1279, 1134, 1040, 985. Anal. calcd. for $C_{13}H_{16}F_3O_4P$: C 48.15, H 4.98; Found: C 48.22, H 4.99.

Dimethyl 1-(4-chlorophenyl)-2-trifluoroethenyl phosphate **2e**: mp 50–51°C, yield 17%. ^{1}H NMR ($CDCl_3$, 90 MHz): 7.45 (m, 4H); 5.60 (q, $J = 7.5$ Hz, 1H); 3.75 (d, $J = 10$ Hz, 6H). ^{19}F NMR ($CDCl_3$): −20.0 (d, $J = 7.5$ Hz). ^{31}P NMR: −4.934. EI-MS: 330 (M^+, 41.79), 311 (6.99), 261 (4.92), 247 (5.59), 218 (6.38), 204 (100.00), 109 (45.52). IR (KBr): 3093, 1673, 1496, 1337, 286, 1127, 1081, 1019, 927. Anal. calcd. for $C_{11}H_{11}ClF_3O_4P$: C 39.96, H 3.36; Found: C 39.84, H 3.15.

Dimethyl 1-(3,4-dichlorophenyl)-2-trifluoroethenyl phosphate **2f**: mp 82°C, yield 11%. ^{1}H NMR ($CDCl_3$, 90 MHz): 7.50 (m, 3H); 5.62 (q, $J = 7$ Hz, 1H); 3.80 (d, $J = 10$ Hz, 6H). ^{19}F NMR ($CDCl_3$): −20.0 (d, $J = 7$ Hz). ^{31}P NMR: −4.863. EI-MS: 364 (M^+, 2.30), 344 (37.74), 294 (6.14), 237 (55.40), 219 (16.09), 173 (35.37), 109 (46.57). IR (KBr): 3093, 2962, 1677, 1477, 1392, 1289, 1129, 1028, 946. Anal. calcd. for $C_{11}H_{10}Cl_2F_3O_4P$: C 36.19, H 2.77; Found: C 36.55, H 2.57.

Method B: *n*-BuLi (1.6 M, 1.2 mmol) was added dropwise to a stirred solution of dimethyl 1-(dimethoxyphosphinyl)-1-(*p*-chlorophenyl)methyl phosphate 430 mg (1.2 mmol) in absolute THF (15 ml) at −78°C under N_2. The mixture was stirred at −78°C for further 15 min, and CH_3COCF_3 134 mg (1.2 mmol) was added to it. Stirring was continued for 2 h at −78°C then warmed to r.t. The reaction mixture was acidified with acetic acid, then diluted with ether, washed and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was purified by flash column chromatography, eluting with a mixture of petroleum ether (60–90°C) and ethyl acetate to give *dimethyl 1-(4-chlorophenyl)-2-trifluoro-2-methylethenyl phosphate* **2g** 70 mg, yield 17%. ^{1}H NMR ($CDCl_3$, 90 MHz): 7.45 (m, 4H); 3.60 (d, $J = 12$ Hz, 6H); 1.80 (s, 3H). ^{19}F NMR ($CDCl_3$): −17.00. ^{31}P NMR: −4.610. EI-MS: 344 (M^+, 5.89), 323 (5.66), 288 (6.88), 218 (46.23), 183 (100.00), 149 (23.14), 127 (13.28). IR (film): 2963, 1680, 1597, 1493, 1336, 1267, 1133, 1060, 891. HR-MS: 344.0179 (M^+: $C_{12}H_{13}ClF_3O_4P$, calcd. 344.0192).

Method C: *n*-BuLi (1.6 M, 1.3 mmol) was added dropwise to a stirred solution of dimethyl 1-(dimethoxyphosphinyl)-1-(*p*-chlorophenyl)methyl phosphate 450 mg (1.3 mmol) in absolute THF (15 ml) at −78°C under N_2. The mixture was stirred at −78°C for further 30 min, and $(CF_3CO)_2O$ (1.3 mmol) was added to it in one portion. Stirring was continued for 1 h at −78°C then warmed to −10°C, after which PhMgBr (2.6 mmol) in THF was added dropwise to the mixture, which was stirred for 5 h at −10°C. The reaction mixture was acidified with acetic acid, then diluted with ether, washed and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was purified by flash column chromatography, eluting with petroleum ether (60–90°C) and ethyl acetate to give *dimethyl 1-(4-chlorophenyl)-2-trifluoro-2-phenylethenyl phosphate* **2h** 130 mg, mp 63–64°C, yield 25%. ^{1}H NMR ($CDCl_3$, 90 MHz): 7.50 (m, 9H), 3.20 (d, $J = 12$ Hz, 6H). ^{19}F NMR ($CDCl_3$): −21.0 and −19.5. ^{31}P NMR: −4.661 (q, $J = 5.4$ Hz) and −4.854 (q, $J = 5.4$ Hz). EI-MS: 406 (M^+, 23.81), 384 (39.15), 281 (38.61), 246 (16.56), 214 (8.97), 165 (11.96), 139 (58.64). IR (KBr): 2960, 1667, 1495, 1334, 1282, 1172, 1105, 1016. Anal. calcd. for $C_{17}H_{15}ClF_3O_4P$: C 50.19, H 3.72; Found: C 50.36, H 3.73.

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