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A simple and efficient synthesis of [²H₁₀]deuterated bromfenvinphos by the Perkow reaction

Bogumiła Huras, Leszek Konopski,* and Jerzy Zakrzewski

(E,Z)-2-bromo-1-(2,4-dichlorophenyl)vinyl bis[ethyl-²H₅] phosphate ([²H₁₀]bromfenvinphos), a regiospecifically deuteriumlabelled pesticide, was synthesized in two steps starting from [²H₆]ethanol, phosphorus trichloride and 2,4dichlorophenacylidene bromide, and fully characterized. The deuterated biologically active bromfenvinphos is an important compound for the advancement of environmental degradation testing and some mass spectrometric studies.

Keywords: bromfenvinphos; deuterium labelling; acaricide; insecticide; Perkow reaction

Introduction

Bromfenvinphos, (*E*,*Z*)-2-bromo-1-(2,4-dichlorophenyl)vinyl diethyl phosphate (1a), has been known for almost 40 years. It was first used as an insecticide against Colorado potato beetle (Leptinotarsa decemlineata Say.)^{1,2} and recently as an acaricide (varroacide) against a honey bee parasite Varroa destructor,³ or as a biocide in anti-insect veterinary products.⁴ The bromfenvinphos impurities have been intensively investigated.^{5,6} Bromfenvinphos is synthesized by the Perkow reaction⁷ from 2,4-dichlorophenacylidene bromide and (2) and triethyl phosphite $(3a)^{8-12}$ (Scheme 1). To the best of our knowledge, the synthesis of $[{}^{2}H_{10}]$ bromfenvinghos (**1b**) has not been previously described, hence the current paper describes its synthesis and full characterization. 1b will be used as a reference and comparative material to study the hydrolysis and thermal degradation of **1a** as well as to examine the mass spectrometry fragmentation pathways (GC/MS (EI, CI)) of 1a,b.

Experimental

General

 $[{}^{2}H_{6}]$ Ethanol (certified to be 99.5 atom% D) and *N*,*N*-diethylaniline (99%) were purchased from Aldrich and used without further purification. Phosphorus trichloride (99%, Aldrich) and hexane (laboratory grade) were distilled before use. ¹H, ¹³C and ³¹P NMR spectra were recorded on a UNITYplus 500 spectrometer at 500, 125 and 202 MHz, respectively. GC analysis was carried out using a Varian 3400 gas chromatograph. Low-resolution El (70 eV) or Cl (methane) mass spectra (*m/z*, int.%) were recorded using an Agilent MSD 5975B series mass detector. Low-resolution ESI mass spectra (ESI MS, *m/z*, int.%) were measured using an ES+ Micromass LCT apparatus. High-resolution El mass spectra (El HRMS) were recorded using an AMD 604 sector instrument at 70 eV, and high-resolution ESI mass spectra (ESI HRMS) were measured using an ES+ Micromass LCT TOF mass spectrometer. FTIR (ν , cm⁻¹, film) data were recorded using a Jasco 420 infrared spectrophotometer.

[²H₁₅]Triethyl phosphite (3b)

3b was synthesized according to¹⁴ using [²H₆]ethanol instead of ethanol. Five gram (0.096 mol) of [²H₆]ethanol afforded 3.3 g of **3b** (57%) as a colorless liquid; bp 44–48°C/7 Torr (50–51°C/12 Torr¹³). ¹³C NMR δ_{C} (CDCl₃): 15.8 (septet of doublets) J_{CD} = 19.2 Hz, J_{CP} = 4.9 Hz, OCD₂**C**D₃, 57.1 (quintet of doublets), J_{CD} = 21.9 Hz, J_{CP} = 12.0 Hz, O**C**D₂**C**D₃; ³¹P NMR δ_{P} (CDCl₃): 138.8 (139.3¹³); GC: R_t = 4.17 min (purity 92.7%), El MS: 183(2), 182(5), 181(55, M⁺⁻), 180(5), 167(2), 153(1), 152(4), 151(73), 150(4), 149(10), 133(26), 131(34), 119(89), 117(17), 115(25), 101(11), 99(37), 95(15), 87(86), 85(94), 83(61), 67(100), 50(14), 47(17), 34(56); El HRMS m/z M⁺⁻ calcd. for C₆D₁₅O₃P: 181.17003, found 181.17091; FTIR: 2229, 2147, 2100 (C-D), 1183, 1102, 991.

2,4-Dichlorophenacylidene bromide (2) (according to an unpublished procedure, Institute of Industrial Organic Chemistry, Report # 8558, 1996, with some modifications)

Bromine (64 g, 0.4 mol) was added dropwise to 2,4-dichloroacetophenone (37.8 g, 0.2 mol) at 35–40°C during 1 h, at such a rate to keep the reaction mixture colorless. Stirring was continued for the next 2 h. Hydrogen bromide was removed under reduced pressure (up to 1 Torr). The residue, crude **2** (57 g, yellowish oil) was dissolved in hexane (230 mL) and stirred at 40°C for 30 min. The resulting solution was gradually cooled to 0°C for 2 h. When the temperature reached 10°C the solution was seeded

Institute of Industrial Organic Chemistry, Annopol 6, 03-236 Warsaw, Poland

*Correspondence to: Leszek Konopski, Institute of Industrial Organic Chemistry, Annopol 6, 03-236 Warsaw, Poland. E-mail: konopski@ipo.waw.pl



Scheme 1. Synthesis of bromfenvinphos (**1a**,**b**). (i) Br₂, 40°C, 3 h, 51% (ii) PhNEt₂, hexane, reflux, 1 h, 57% (**3b**, X=D) (iii) Br₂, 50°C, 1 h, 63% (**1a**, X=H), 79% (**1b**, X=D).

with a crystal of **2**. The crystallizing **2** was kept at 0°C for 30 min. The crystals were rapidly filtered off, washed with small amount of chilled hexane, and dried to afford **2** (44 g). The above crystallization procedure was repeated (175 mL of hexane) to afford colorless, crystalline 2,4-dichlorophenacylidene bromide (**2**), yield 35.5 g, (51%), purity (GC): 99.3%, mp 27–30°C; (28.5–29.5°C⁶).

(E,Z)-2-bromo-1-(2,4-dichlorophenyl)vinyl bis[ethyl-²H₅] phosphate (1b)

 $[^{2}H_{15}]$ triethyl phosphite (**3b**) (3.05 g, 0.016 mol) was added with stirring to 2,4-dichlorophenacylidene bromide (2, 5.3 g, 0.015 mol) at 30°C. The temperature rose to 50°C, and the stirring was continued at this temperature for 1 h. The title product (1b) was then isolated from the reaction mixture by distillation under vacuum, yield 5.0 g (79%), bp 120-135°C/ 0.02 Torr. Purity (GC): 94% (sum of E and Z isomers), $R_t = 17.26 \text{ min}$ (*E*, 3.52%,), 17.56 min (*Z*, 90.44%). ¹H NMR δ_H (CDCl₃): 6.06 (d, 1H, J_{PH} = 1 Hz, CHBr), 7.28 (dd, 1H, J = 2.0, 8.3 Hz, H_{ar}), 7.42 (d, 1H, J = 8.3 Hz, H_{ar}), 7.44 (d, 1H, J = 2 Hz, H_{ar}); ¹³C NMR $\delta_{\rm C}({\rm CDCI}_3)$: 14.9, septet, $J_{\rm CD}$ = 19.6 Hz, $J_{\rm CP}$ = 6.7 Hz, ${\rm OCD}_2$ **C** ${\rm D}_3$), 64.0 (quintet of doublets, $J_{CD} = 22.9 \text{ Hz}$, $J_{CP} = 5.9 \text{ Hz}$, OCD₂CD₃), 97.7 (d, $J_{CP} = 9.3 \text{ Hz}$, C = CHBr), 127.0 (C_{ar}), 129.7 (C_{ar}), 131.4 (d, $J_{CP} = 1.5 \text{ Hz}, C_{ar}-C = CHBr), 132.4 (d, J_{CP} = 1.0 \text{ Hz}, C_{ar}), 134.0 (C_{ar}),$ 136.3 (C_{ar}), 146.4 (d, $J_{CP} = 7.8$ Hz, -C = CHBr); ³¹P NMR $\delta_P(CDCl_3)$: -7.5. EI MS: 377(4, MH⁺-HCl), 333(58, MH⁺-HBr), 313(8), 301(16), 269(100), 250(6), 237(3), 234(3), 204(5), 188(2), 173(7), 170(19), 160(15), 145(3), 135(5), 123(11), 115(8), 109(4), 99(8), 95(4), 83(24), 74(5), 67(2), 50(3); CI MS: 441(9, MEt⁺) 413(51, MH⁺), 165(100); ESI MS 853(7), 851(11), 849(9), 847(4, [2M+Na]⁺), 439(30), 437(62), 435(41, [M+Na]⁺), 417(46), 415(100), 413(56, $[MH]^+$). ESI HRMS m/z MH⁺ calcd. for C₁₂H₅D₁₀BrCl₂O₄P: 412.9891, found 412.9886; FTIR: 3090, 3073 (C-H arom.), 2250, 2232, 2150, 2119 (C-D), 1639, 1584, 1470, 1289, 1070, 1025, 912.

Results and discussion

 $[{}^{2}H_{15}]$ Triethyl phosphite **3b** was obtained in 57% yield from ethanol-d₆ and phosphorus trichloride in the presence of *N*,*N*-diethylaniline in hexane.^{13,14} **3b** was condensed with 2,4-dichlorophenacylidene bromide (**2**) in the Perkow reaction. After elimination of $[{}^{2}H_{5}]$ ethyl bromide, the labelled target compound – $[{}^{2}H_{10}]$ bromfenvinphos (**1b**) was obtained in 79% yield (Scheme 1).

The structures of synthesized compounds and the location of deuterium-labelled sites were confirmed using spectral methods.

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