Regioselective addition of alkyl phosphites on 6-(aryliminomethyl)-furobenzopyran-5-one derivatives

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Received 1 March 2012
Accepted 13 May 2012

Egyptian Pharmaceutical Journal
2012,11:109–115

Aim
Trialkyl phosphites **2a,b** attack 6-(aryliminomethyl)furobenzopyran-5-ones **1a–e** regiospecifically at the carbon–carbon double bond of the γ-pyrone ring to yield new 1,2-addition phosphonate products for which structures **3a–e** have been respectively assigned.
Methods
The alkyl phosphites **2a,b** attacked the monoanils **1a–e** at the azomethine carbon of the C=N bond to yield corresponding phosphonate adducts **5a–e** when reactions were carried out in the presence of a controlled amount of acetic acid. Phosphonates **5a–e** could also be obtained by the reaction of dialkyl phosphites **4a,b** with anils **1a–e**. Structures of the new phosphonates **3a–e** were elucidated by elemental analyses as well as spectroscopic methods. The ^{1}H and ^{13}C nuclear magnetic resonance and infrared measurements were helpful tools in confirming the structures of the new products.
Results and conclusion
The insecticidal activities of phosphonates **3a–e** and their respective regioisomers **5a–e** against adult *Aphis gossypii* (Glover), which infest cotton crops, were determined. The structure–activity relationship has been discussed.

Keywords:
6-(aryliminomethyl)furobenzopyran-5-ones, ^{13}C nuclear magnetic resonance, insecticidal activities, phosphorylation, regioselectivity, spectroscopic evidences, structural elucidation

Egypt Pharm J 11:109–115

1687-4315

Introduction

It is evident that compounds of phosphorus play vital roles in the living process. Our interest in the field of organophosphorus chemistry led us to study the preparation of organophosphorus compounds because of their increasing importance in industry and biology [1–3]. Aldehydes [4–6], ketones [7,8], aldimines [9–11] and ketimines [12–14] are suitable substrates for the preparation of members of this class of compounds. Recently, we have reported on the reaction of monoarylimines **1a–e**, derived from 4-methoxy-5-oxo-5H-furo[2,3-*g*]benzopyran-6-carboxaldehyde and 4,9-dimethoxy-5-oxo-5H-furo[2,3-*g*]benzopyran-6-carboxaldehyde, with dialkyl phosphites **4a,b** [1]. Now, with our growing interest in the field of organophosphorus chemistry of arylimines derived from carbonyl compounds [9,12–14], we have studied the behaviour of trialkyl phosphites **2a,b** towards the monoarylimines **1a–e** under different reaction conditions.

Subjects and methods

Solvents were purified and dried according to usual procedures. Trialkyl phosphites are commercially available from Aldrich Chem. Co. (New Jersey, USA) and were freshly distilled immediately before use. The starting compounds **1a** [1], **1b** [1], **1c** [15], **1d** [1] and **1e** [1] were prepared according to the given procedures. Melting points were recorded on an electrothermal melting point apparatus and were uncorrected. The infrared spectra were obtained from KBr disks using a Brüker Vector 22 infrared spectrophotometer (Germany) and/or a JASCO FT/IR-300E fourier transform infrared spectrophotometer (Japan) and reported in cm^{-1}. ^{1}H-nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury VX-300 spectrometer (Japan) (at 300 MHz) and/or a JEOL JNM-EX 270 FT spectrometer (Japan) (at 270 MHz). Proton chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. ^{13}C NMR spectra were recorded on a JEOL JNM-EX 270 FT (at 68 MHz) and/or a JOEL 500 AS (at 125 MHz) spectrometer. Mass spectra were recorded on a Finnigan SSQ 7000 spectrometer (Japan) and/or a Shimadzu GC MS-Q 1000 EX spectrometer at 70 eV (Electron Impact, Japan). Microanalyses were carried out at the Microanalytical Unit, Cairo University (Cairo, Egypt).

Experimental

Reactions of *1a–e* with trialkyl phosphites *2a,b*

General procedure

A mixture of the appropriate anil **1a–e** (0.005 mol) and trialkyl phosphite (TAP) **2a** (or **2b**; 0.01 mol) was heated in the absence of a solvent at 100°C until the starting anil

1687-4315 © 2012 Division of Pharmaceutical and Drug Industries Research, National Research Centre
DOI: 10.7123/01.EPJ.0000421666.94096.f5

could no longer be detected (TLC) [TLC silica gel aluminum sheet (type 60 F254, Merk, Damstadt, Germany)]. After removal of the volatile materials *in vacuo*, the residual substance was washed with cold diethyl ether and then recrystallized from petroleum ether at 60–80°C to yield the respective phosphonates **3a–e** in yellow crystalline forms.

*Diisopropyl 6-((4-fluorophenylimino)methyl)-4-methoxy-5-oxo-6,7-dihydro-5H-furo[3,2-g]chromen-7-ylphosphonate (**3a**, $C_{25}H_{27}FNO_7P$)*

Yield 81%, melting point (MP) 128–130°C; IR (KBr, cm^{-1}): 3096, 3064 (C–H aromatic), 2982 (C–H aliphatic, asymmetric), 2936 (C–H aliphatic, symmetric), 1713 (exocyclic C = O of a saturated 4-pyranone ring), 1647 (C = N), 1611, 1552 (C = C), 1247 (P = O), 1135 (C – O) and 1015 (P – O – C). ^{1}H NMR (DMSO-d_6): 1.00, 1.05, 1.10, 1.14 (12, O–CH–(CH_3)$_2$, 4d, J_{HH} = 6.0 Hz), 4.03 (1H, CH–C*H*–CH = N, dd, J_{HH} = 8.0 Hz, J_{HP} = 10.8 Hz), 4.08 (3H, –OCH_3, s), 4.51 (2H, O–C*H*–CH_3, dsp, J_{HH} = 6.0 Hz, J_{HP} = 10.8 Hz), 5.43 (1H, O–C*H*–P, dd, J_{HH} = 8.0 Hz, J_{HP} = 18.0 Hz), 6.90 (1H, O – CH – C*H*, furan ring d, J_{HH} = 7.17 (2H, aromatic *meta* to F atom, d, AB system, J_{HH} = 9 Hz); 7.26 (2H, aromatics *ortho* to F atom, d, AB system, J_{HH} = 9 Hz), 7.40 (1H, aromatic, s), 7.82 (1H, C*H* = N, d, $^3J_{HH}$ = 10.8 Hz), 7.91 (1H, O–C*H*, furan, d, J_{HH} = 2.0 Hz).

^{13}C NMR (DMSO-d_6): 21.02 (P–O–CH–*C*H_3), 23.67 (P–C–*C*H–CH = N, $^2J_{CP}$ = 28.0 Hz), 60.84 (O–*C*H_3), 70.71 (P–O–*C*H–CH_3, d, $^2J_{CP}$ = 25.0 Hz), 74.45 (O–*C*H–P, d, $^1J_{CP}$ = 146.4 Hz), 94.88 (*C*–H aromatic), 98.37 (quaternary aromatic carbon), 106.05 (O–CH–*C*H, furan), 112.25 (quaternary aromatic carbon), 116.80 (carbons *ortho* to fluorine atom, d,$^2J_{CF}$ = 22.62 Hz), 118.36 (carbons *meta* to fluorine atom, d, $^3J_{CF}$ = 8.3 Hz), 137.26 (C = N–*C*), 143.48 (O–*C*H furan), 145.27 (*C*H = N), 154.92 (*C*–OCH3), 157.81, 158.56 (quaternary aromatic carbons), 171.97 (*C*–F) and 181.25 (*C* = O). MS *m/z* (%): 503 $[M]^+$ (3%). Anal. calcd (%) for $C_{25}H_{27}FNO_7P$ (503.46): C, 59.64; H, 5.41; F, 3.77; N, 2.78; P, 6.15. Found (%): C 59.76; H, 5.28; 2.61; P, 5.22.

*Diisopropyl 6-((4-chlorophenylimino)methyl)-4-methoxy-5-oxo-6,7-dihydro-5H-furo[3,2-g]chromen-7-ylphosphonate (**3b**, $C_{25}H_{27}ClNO_7P$)*

Yield 80%; MP 118–120°C. IR (KBr, cm^{-1}): 3110, 3066 (C–H aromatic), 2980 (C–H aliphatic, asymmetric), 2934 (C–H aliphatic, symmetric), 1717 (exocyclic C = O of a saturated 4-pyranone ring), 1645 (C = N), 1601, 1553 (C = C); 1246 (P = O); 1129 (C – O), and 983 (C – Cl aromatic). ^{1}H NMR (DMSO-d_6): 0.966, 1.04, 1.11, 1.18 (6H, O–CH(CH_3)$_2$, 4d, J_{HH} = 8.1 Hz), 4.03 (1H, CH–C*H*–CH = N, d, J_{HH} = 10.8 Hz), 4.06 (3H, OCH_3, s), 5.41 (1H, P–C*H*–CH, dd, J_{HH} = 10.8 Hz, J_{HP} = 15.5 Hz), 6.87 (1H, O–CH–C*H* furan, d, J_{HH} = 3 Hz), 7.12 (2H, aromatic *meta* to chlorine, AB system, d, J_{HH} = 8.1 Hz), 7.25 (2H, aromatics *ortho* to chlorine, AB system, d, J_{HH} = 8.1 Hz), 7.41 (1H, s, aromatic), 7.80 (1H, –C*H* = N, d, J_{HH} = 10.8 Hz), 7.88 (1H, O–C*H* furan, d, J_{HH} = 3.0 Hz). MS *m/z* (%): $[M]^{+\bullet}$ at 519 and 521 (2.7% and 0.83%). Anal. calcd (%) for $C_{25}H_{27}ClNO_7P$ (519.92): C, 57.75; H, 5.23; Cl, 6.82; N, 2.69; P, 5.96. Found (%): C, 57. 86; H, 5.02; Cl, 6.57; N, 2.61; P, 6.12.

*Diisopropyl 6-((4-bromophenylimino)methyl)-4-methoxy-5-oxo-6,7-dihydro-5H-furo[3,2-g]chromen-7-ylphosphonate (**3c**, $C_{25}H_{27}BrNO_7P$)*

Yield 83%, MP 150–152°C. IR (KBr, cm^{-1}): 3066 (C–H, aromatic), 2979 (C–H aliphatic, asymmetric), 2933 (C–H aliphatic, symmetric), 1717 (exocyclic C = O of a saturated 4-pyranone ring), 1645 (C = N), 1601, 1553 (C = C), 1246 (P = O) and 1127 (P–O–C).

^{1}H NMR (DMSO-d_6): 0.09, 1.04, 1.11, 1.17 (12H, CH–(CH_3)$_2$, four doublets, each of $^{1,3}J_{HH}$ = 5.4 Hz), 4.04 (1H, CH–C*H*–CH = N, d, J_{HH} = 10.8 Hz), 4.06 (3H, O–CH_3), 4.48 (2H, O–C*H*–(CH_3)$_2$, m), 5.41 (1H, O–C*H*–CH, dsp, J_{HH} = 10.8 Hz, J_{HP} = 19.3 Hz), 6.87 (1H, O–CH–C*H*, furan ring, d, J_{HH} = 2 Hz), 7.15 (2H, aromatic meta to bromine, AB system, d, J_{HH} = 8.1 Hz), 7.33 (2H, aromatic *para* to bromine, AB system, d, J_{HH} = 8.1 Hz), 7.56 (1H, aromatic, s), 7.82 (1H, C*H* = N, d, J_{HH} = 10.8 Hz),7.88 (1H, O–C*H*, furan, d, J_{HH} = 2.0 Hz). MS *m/z* (%): $[M]^{+\bullet}$ at 564 and 566 (2.3 and 2.4%). Anal. calcd (%) for $C_{25}H_{27}BrNO_7P$ (564.37): C, 53.21; H, 4.82; Br, 14.16; N, 2.48; P, 5.49. Found (%): C, 53.58; H, 4.57; Br, 14.00; N, 2.24; P, 5.62.

*Diisopropyl 6-((4-fluorophenylimino)methyl)-4,9-dimethoxy-5-oxo-6,7-dihydro-5H-furo[3,2-g]chromen-7-ylphosphonate (**3d**, $C_{26}H_{29}FNO_8P$)*

Yield 79%; MP 98–100°C. IR (KBr, cm^{-1}): 3135, 3072 (C–H aromatic), 2983, 2935 (C–H aliphatic), 1714 (exocyclic C = O of a saturated 4-pyranone ring), 1644 (C = N), 1605, 1553 (C = C aromatic), 1240 (P = O) and 1197 (P–O–C). ^{1}H NMR (DMSO-d_6): 1.05, 1.11, 1.15, 1.16 (12H, CH(CH3), four doublets each with J_{HH} = 6.0 Hz), 3.86 (1H, CH–C*H*–CH = N, dd, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 8.3 Hz), 3.88 (3H, OCH_3,s), 3.92 (3H,OCH_3,s), 4.47 (2H, C*H*(CH_3)$_2$,dsp, J_{HH} = 6.3 Hz, J_{HP} = 11.5 Hz), 5.46 (1H, O–C*H*–P, dd, $^3J_{HH}$ = 6.8 Hz, $^2J_{HP}$ = 15 Hz), 7.07 (1H, O–CH–C*H*, furan ring, d, J_{HH} = 2.0 Hz), 7.21 (2H, aromatics *meta* to fluorine, AB system, ^{3}d, J_{HH} = 8.1 Hz), 7.36 (2H, aromatics *ortho* to fluorine, AB system, d, $^3J_{HH}$ = 8.1 Hz). 7.77 (1H, CH–C*H* = N, d, J_{HH} = 9.3 Hz), 7.88 (1H, O–C*H*, furan ring, d, J_{HH} = 2.0 Hz). ^{13}C NMR (DMSO-d_6): 21.56 (O–CH–(*C*H_3)$_2$), 24.25 (*C*H–CH = N), d, $^2J_{CP}$ = 14.31), 61.42 (O*C*H_3), 61.75 (O*C*H_3), 71.41 (O–*C*H–(CH_3)$_2$, d, $^2J_{CP}$ = 7.2 Hz), 74.41 (O–*C*H–P, d, $^1J_{CP}$ = 156.3 Hz), 98.79 (quaternary aromatic carbon), 105.99 (CH–*C*H furan), 113.79 (quaternary fused aromatic carbon), 116.92 (two carbons *ortho* to fluorine, d, $^2J_{CF}$ = 13.6 Hz), 118.52 (two carbons *meta* to fluorine, d, $^3J_{CF}$ = 5.4 Hz), 129.91 (C = N–*C*), 143.97 (O–*C*H furan), 145.86 (*C*H = N), 148.99, 149.49, 150.84, 159.02 (quaternary aromatic carbons), 172.67 (*C*–F), 181.25 (*C* = O). MS *m/z* (%): 533 (5%). Anal. Calcd. (%) for $C_{26}H_{29}FNO_8P$ (533.49): C, 58.54; H, 5.48; F, 3.56; N, 2.63; P, 5.81. Found (%): C, 58.28; H, 5.20; F, 3.31; N, 2.59; P, 5.95.

*Diethyl 6-((4-chlorophenylimino)methyl)-4,9-dimethoxy-5-oxo-6,7-dihydro-5H-furo[3,2-g]chromen-7-ylphosphonate (**3e**, $C_{24}H_{25}ClNO_8P$)*

Yield 86%; MP 198–200°C. IR (KBr, cm^{-1}): 3131, 3083 (C – H aromatic); 2975 (C – H aliphatic, asymmetric);

2930 (C – H aliphatic, symmetric); 1715 (exocyclic C = O of a saturated 4-pyranone ring); 1645 (C = N), 1600, 1552 (C = C); 1246 (P = O); 1129 (P–O–C); 984 (C – Cl aromatic). ^{1}H NMR (DMSO-d$_6$): 1.08 (6H, CH$_2$–C*H*$_3$, t, J_{HH} = 7.1 Hz), 3.92 (3H, OC*H*$_3$, s), 3.71 (1H, C*H*–CH = N, dd, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 8.3 Hz) 3.97 (3H, OC*H*$_3$, s), 3.93–4.00 (4H, OC*H*$_2$CH$_3$, m), 5.58 (1H, O–C*H*–P, dd, $^3J_{HH}$ = 10.0 Hz, $^2J_{HP}$ = 15.0 Hz), 7.15 (1H, O–C–C*H*, furan, d, $^3J_{HH}$ = 3.2 Hz), 7.40–7.45 (4H, aromatic, m), 7.85 (1H, C*H* = N, d, $^3J_{HH}$ = 10.2 Hz), 7.96 (1H, O–C*H* furan, d, J_{HH} = 3.2 Hz). ^{13}C NMR (DMSO-d$_6$): 16.18 (OCH$_2$–*C*H$_3$, d, $^3J_{CP}$ = 5.4 Hz), 38.72 (P–CH–*C*H, d, $^2J_{CP}$ = 20.9 Hz), 60.92 (O*C*H$_3$), 61.34 (O*C*H$_3$), 62.28 (P–O–*C*H$_2$–CH$_3$, d, $^2J_{CP}$ = 16.3 Hz), 74.20 (O–*C*H–P, d, $^1J_{CP}$ = 162.0 Hz), 98.95 (quaternary aromatic carbon), 105.34 (O–CH–*C*H, furan), 113.13 (quaternary aromatic carbon), 117.61 (carbons *meta* to chlorine), 127.25 (carbons *ortho* to chlorine), 129.39, 129.54 (quaternary aromatic carbons), 139.17 (C = N–*C*), 142.47 (O–*C*H, furan), 145.51 (*C*H = N), 148.36, 149.10, 150.39 (quaternary aromatic carbons) and 180.79 (*C* = O). MS: *m*/$\underset{\sim}{z}$ (%): 521and 523 (3 and 0.92%). Anal. calcd (%) for $C_{24}H_{25}ClNO_8P$ (521.89): C, 55.23; H, 4.83; Cl, 6.79; N, 2.68; O, 24.53; P, 5.93. Found (%): C, 55.01; H, 4.69; Cl, 6.51; N, 2.50; P, 6.19.

Reactions of *1a–e* with trialkyl phosphites *2a,b* in the presence of acetic acid

General procedure

A mixture of the appropriate anil **1a–e** (0.005 mol), trialkyl phosphite **2a** (or **2b**; 0.01 mol) and a few drops of acetic acid was heated in the absence of a solvent at 100°C until the starting anil could no longer be detected (TLC). After removal of the volatile materials *in vacuo*, the residual substance was washed with cold diethyl ether and then recrystallized from ethanol to yield the respective phosphonates as yellow crystalline products, which were identified to be the corresponding phosphonates **5a–e** (MP, mixed MP, comparative TLC and comparative IR) [1].

Insecticidal evaluation

Toxicity of the tested compounds was studied under laboratory conditions using the slide-dip method [16] at the Central Agricultural Laboratory of Pesticides, Cairo, Egypt. Concentrations were prepared by dissolving each compound (0.05 g) in 5 ml of acetone and then diluting it with water in a ratio of 2 : 3 (this dilution did not cause any mortality in insects). *Aphis gossypii* was transferred onto a slide using a fine brush and then adults were affixed to a double-face scotch tape and fixed tightly onto the slide on their dorsal side. The slides were then dipped into the toxicant solution for 10 s and the excess toxicant was blotted off with filter paper. Mortality counts were carried out 2 h after treatment. A mortality of 50% for each compound was determined from the corresponding average mortality percentage that was corrected, if necessary, using Abbott's formula [17].

Results and discussion

Chemistry

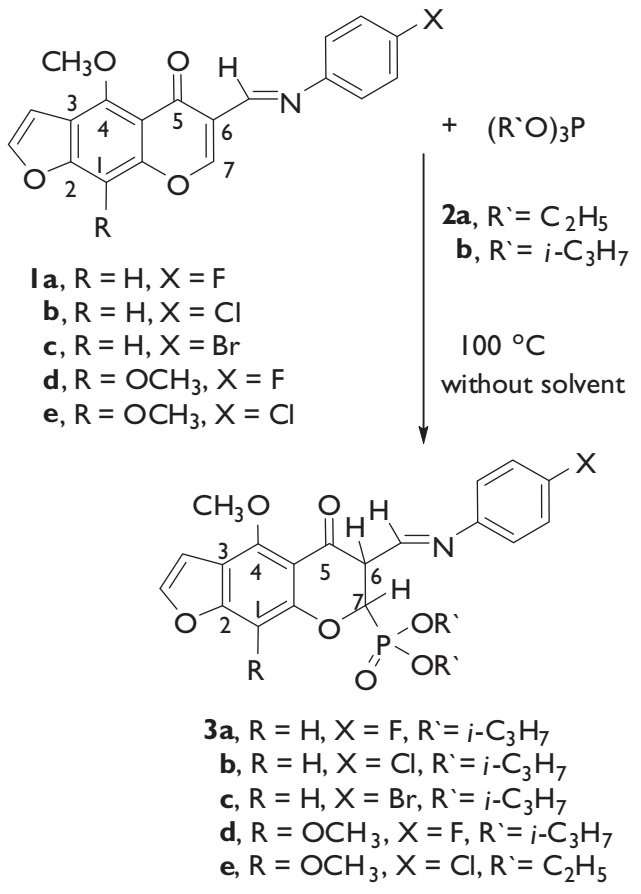
On performing the reaction of monoanils **1a–e** with trialkyl phophites **2a,b** in the absence of a solvent at 100 °C, yellow crystalline products were obtained. They were assigned the phosphonate structures **3a–e** (Scheme 1). However, phosphonates **3a–e** were found to be isomeric (microanalyses and mass spectrometry) but not identical (comparative MPs, TLC, IR and ^{1}H NMR spectra) to phosphonates **5a–e** [1] that were obtained from the reaction of anils **1a–e** with dialkyl phosphites **4a,b** (Scheme 2). In contrast, the reaction of anils **1a–e** with phosphites **2a,b**, in the presence of a few drops of acetic acid, was found to yield phosphonates **5a–e** [1] (MP, mixed MP, TLC and IR, Scheme 2).

Thus, it is clear that anils **1a–e** behave differently towards alkyl phosphites depending on the nature of the reagent and/or the reaction conditions.

The spectroscopic measurements, particularly decoupled and distortionless enhancement by polarization transfer ^{13}C NMR experiments, IR and ^{1}H NMR, have provided valuable evidence in confirming the structure of phosphonates **3a–e**. The assigned structure **3a** is established by analytical and spectral data:

(1) The IR spectrum (KBr) showed intense bands at 1247, 1135 and 1015 cm^{-1}, corresponding to P = O, C–O and P–O–C alkyl stretching vibrations [18,19], respectively. Absorption bands of the carbonyl group appeared at 1650 cm^{-1} in anil **1a** and at 1647 cm^{-1} in

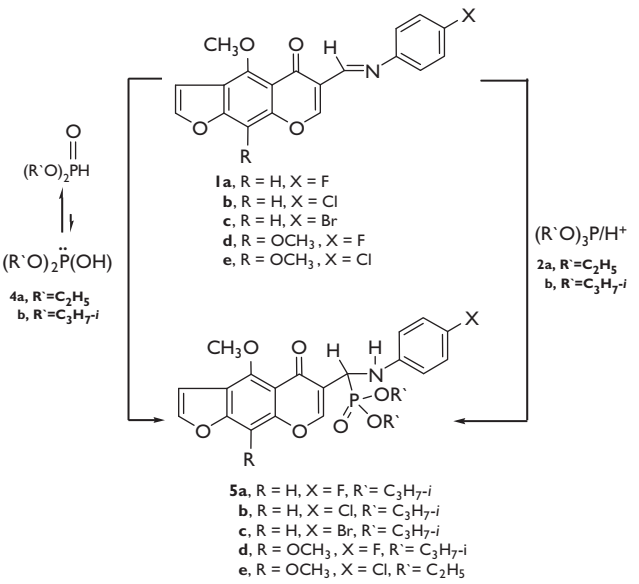
Scheme 1



3a, R = H, X = F, R`= *i*-C_3H_7
b, R = H, X = Cl, R`= *i*-C_3H_7
c, R = H, X = Br, R`= *i*-C_3H_7
d, R = OCH_3, X = F, R`= *i*-C_3H_7
e, R = OCH_3, X = Cl, R`= C_2H_5

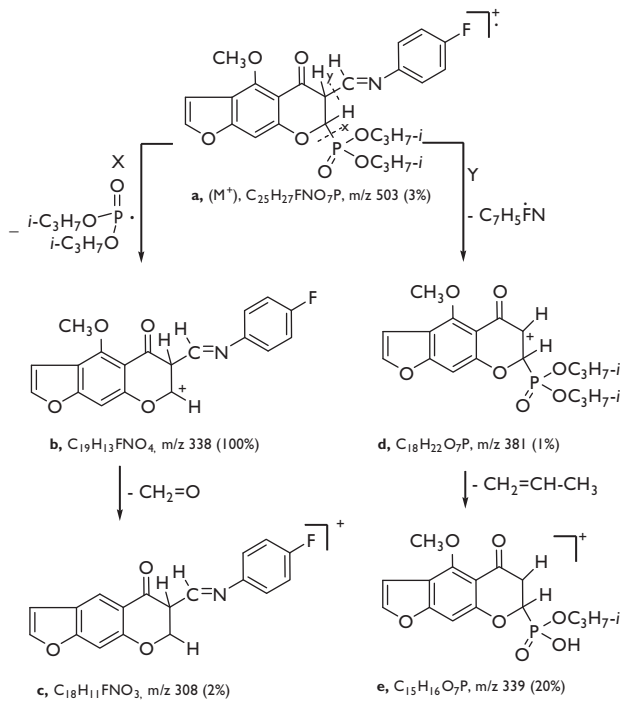
Preparation of phosphonate compounds (**3a-e**).

Scheme 2



Preparation of phosphonate compounds (**5a-e**).

Scheme 3



MS fragmentation of **3a**.

phosphonate **5a** [1], whereas in phosphonate **3a**, it appeared at 1713 cm^{-1}, a value that is typical for exocyclic C = O of a saturated six-membered ring [19]. Moreover, the spectrum of **3a** indicated the presence of C = N absorption at 1647 cm^{-1} (which appeared in the IR spectrum of **1a** at 1616 cm^{-1}) [1] and the absence of any absorption band because of the NH group, which generally appears in the region of 3350–3300 cm^{-1} [18,19] (which appeared in the spectrum of **5a** at 3303 cm^{-1}) [1].

(2) The ^{1}H NMR spectrum of **3a** (DMSO-d_6, δ ppm) showed four doublets at 1.00, 1.05, 1.10 and 1.14 ppm, each with J_{HH} = 6.0 Hz, because of protons of the four methyl groups of the two isopropoxy groups attached to phosphorus. Apparently, the asymmetry of the molecule because of the presence of a stereocenter would render the four methyl groups diastereotopic, and hence anisochronous, thus resulting in the observed splitting pattern [20,21]. Moreover, the isopropoxy-C*H* protons attached to phosphorus (2H) appeared as a doublet of septet at 4.51 ppm (with $^3J_{HH}$ = 6.0 Hz and $^3J_{PH}$ = 10.8 Hz) because of coupling with the methyl groups and the phosphorus atom, respectively. Signals were also recorded at 4.03 ppm (1H, CH–C*H*–CH = N, dd, $^{1,3}J_{HH}$ = 8.0 Hz, $^{1,3}J_{HH}$ = 10.8 Hz) and 5.43 ppm (1H, O – C*H* – P, dd, $^{1,3}J_{HH}$ = 8.0 Hz and $^{1,2}J_{HP}$ = 18.0 Hz) [22,23]. Moreover, the doublet ($^{1,3}J_{HH}$ = 10.8 Hz) that appeared at δ of 7.82 ppm could be attributed to the azomethine C*H* = N proton. The spectrum also lacked absorption due to D_2O-exchangeable protons (N*H* or O*H*).

(3) The ^{13}C NMR spectrum of **3a** showed signals at 181.25 and 145.27 ppm because of carbon atoms of *C* = O and *C*H = N groups, whose signals appeared at 180.48 and 144.48 ppm, respectively, in the spectrum of **1a**. The signals present at 111.31 and 154.17 ppm in the ^{13}C NMR spectrum of **1a** because of carbon-6 and carbon-7, respectively, disappeared in the spectrum of phosphonate **3a**. Instead, two doublets centred at 23.67 ppm ($^2J_{CP}$ = 28.0 Hz) and 74.45 ppm ($^1J_{CP}$ = 146.4 Hz) appeared in the spectrum of **3a**, assignable to carbon-6 and carbon-7, respectively. The last doublet was in the region of *ter*-carbon–oxygen chemical shifts and its large *J*-value was typical for spin–spin coupling between directly bonded carbon and phosphorus atoms [24,25]. Meanwhile, in phosphonate **5a**, the signal because of the carbon attached to phosphorus appeared at δ of 42.22 ppm ($^1J_{CP}$ = 147.0 Hz) [1], cf. Experimental.

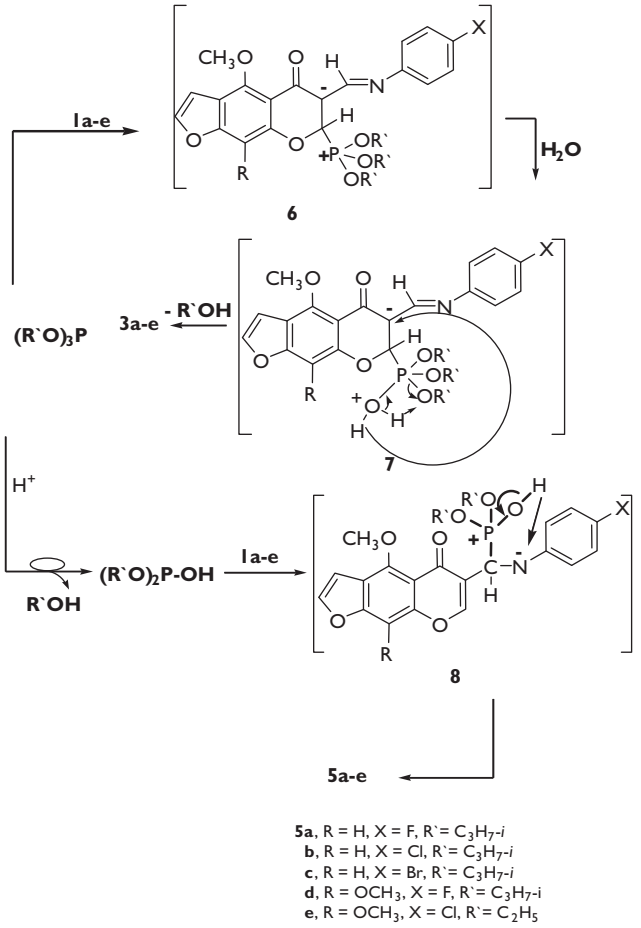
(4) In the mass spectrum of **3a**, the molecular ion peak ($M^{+\bullet}$; the cation radical **a**) appeared at *m*/*z* 503 (3%), showing its relative instability under electron bombardment. Cleavage of $[M]^{+\bullet}$ at axis *x* produced the base peak cation **b** at *m*/*z* 338 (100%), which released a neutral CH_2O molecule from the methoxy group to yield cation **c** at *m*/*z* 308 (2%). Radical (cation **a**) $[M]^{+\bullet}$ was also cleaved at axis *y* to yield cation **d** at *m*/*z* 381 (1%), which in turn lost a neutral 1-propene molecule to yield cation **e** at *m*/*z* 339 (20% Scheme 3).

Thus, in their reactions with anils **1a–e**, phosphites **3a** and **3b** undergo a Michael-type addition reaction [26,27] in which the phosphite–phosphorus atom regiospecifically attacks carbon-7 of the C = C bond in the γ-pyrone ring to yield 1,2-addition phosphonate products **3a–e** exclusively (Scheme 4). The negative charge, formed on carbon-6 in phosphonium betaine intermediate **6**, is

resonance stabilized through conjugation with the carbonyl and/or imine groups. This conjugation reduces the activation energy for addition. Thereafter, the betaine **6** undergoes solvation to yield intermediate **7** with pentacovalent phosphorus similar to that in many phosphobetaine structures [28]. Collapse of **7** through the release of an alcohol molecule yielded the respective phosphonates **3a–e**.

However, when the reactions were performed in acetic acid, trialkyl phosphites **2a,b** were hydrolysed first to the corresponding dialkyl analogous **4a,b**, which in turn reacted with anils **1a–e** to yield phosphonates **5a–e**. Apparently, the regiochemistry of the nucleophilic addition of alkyl phosphites **2** and **4** to anils **1a–e** may be attributed to the steric and electronic nature of both reactants. Thus, in terms of the hard–soft acid–base principle [29,30], alkyl phosphites are considered to be soft bases. However, trialkyl phosphites are softer bases than dialkyl phosphites because of the tautomerism shown by the latter (Scheme 2). However, because of the +R effect exerted by the adjacent oxygen atom, carbon-7 may be relatively less positively polarized (softer acid) than the azomethine carbon of the C = N bond. Therefore, it may be energetically more favourable for alkyl phosphites **2a,b** (softer base) with their relatively bulky size to add to carbon-7 (softer acid), rather than to the azomethine carbon, to avoid the steric crowding [31] exerted by the substituted phenyl group on nitrogen in the transition states, leading to intermediates **6** and **7**. However, phosphites **4** (harder base), with their relatively smaller size, tend to add preferentially at the more electrophilic azomethine carbon atom (harder acid) of the polarized C = N bond to yield **5**. In this case, delocalization of the negative charge that developed on nitrogen over the substituted phenyl group stabilized the intermediate transition state.

Scheme 4



Mechanism of preparation phosphonates compounds **(5a-e)**.

Insecticidal activity

Pesticidal activities are associated with a variety of organophosphorus compounds [32,33], which may become less effective as a result of development of crossresistance in pests. Therefore, continuous efforts are being made towards developing a new generation of these pesticides. This led us to study the effect of phosphonates **3a–e** and **5a–e** on *A. gossypii* (Glover) using actillic (*O*-[2-(diethylamino0–6-methyl-4-pyridiminyl]*O*,*O*-dimethylphosphorothioate) as a standard reference (cf. Experimental). This sucking aphid pest infests cotton crops worldwide. It affects cotton yield by direct feeding and fibre quality by excreting honeydew, which supports the growth of harmful microorganisms. The results for the insecticidal activity of phosphonates **5a–e** have been reported [1]. However, as the biological and pharmaceutical activities of many organic compounds [34,35], including phosphonate derivatives [36–38], strongly depend on the position of a given group in a certain class of compounds, it will be interesting to report the insecticidal activity for phosphonates **3a–e** and compare it with the activity of their regioisomers **5a–e** (Table 1).

From the results in Table 1, it is evident that:

(1) The LC_{50} values indicated that all of the tested compounds showed insecticidal activity against adult *A. gossypii* (Glover).

Table 1 Effect of treatment with phosphonates *3a–e* and *5a–e* on adults of *Aphis gossypii* (Glover)

Compound	LC_{50}^{a} (ppm)	TI[b] (%)	Compound	$LC_{50}^{a,c}$ (ppm)	TI[b,c] (%)
Actilic[d] (pirimiphosmethyl)	1240.67	100			
3a	1489.71	83.28	**5a**	2520.48	49.22
3b	2816.69	44.05	**5b**	4912.93	25.25
3c	1567.55	79.15	**5c**	1907.59	65.03
3d	5377.57	23.07	**5d**	3906.69	31.75
3e	14714.36	8.43	**5e**	6303.25	19.68

[a]LC_{50}: lethal concentration that killed 50%.
[b]TI: toxicity index = LC_{50} of the most effective compound × 100/LC_{50} of the tested compound.
[c]Values for phosphonates **5a–e** have been reported previously in reference [1].
[d]The standard pesticide actillic: *O*-[2-(diethylamino0-6-methyl-4-pyridiminyl]*O*,*O*-dimethyl phosphorothioate.

(2) Among phosphonates **3** and **5**, compound **3a** was found to be the most effective, with a toxicity index (TI) value of 83.28% ($LC_{50} = 1489.71$), when compared with the reference insecticide actillic (TI = 100%, $LC_{50} = 1240.67$). Compound **3e** was found to be the least effective (TI = 8.43%, $LC_{50} = 14714.36$). The order of decreasing activity was as follows: **3a > 3c > 5c > 5a > 3b > 5d > 5b > 3d > 5e > 3e**.

(3) Among phosphonates **3**, the order of decreasing activity was **3a > 3c > 3b > 3d > 3e,** whereas for phosphonates **5**, the order was **5c > 5a > 5d > 5b > 5e**.

(4) For the phosphonates that were derived from compound **1a** (R = H), **3a–c**, in which the phosphorus atom is linked to carbon-7, were found to be more active than their respective regioisomers **5a–c**, in which the phosphorus atom is linked to the azomethine carbon. However, for the derivatives of **1b** ($R = OCH_3$), phosphonates **5d** and **5e** (phosphorus–azomethine carbon bond) were found to be more active than phosphonates **3d** and **3e** (phosphorus–carbon-7 bond), respectively.

(5) Phosphonates **3e** and **5e** that have the diethylphosphoryl moiety ($R' = C_2H_5$) are less effective than the other derivatives that have the diisopropylphosphoryl moiety ($R' = i\text{-}C_3H_7$).

Conclusion

The present study clearly shows that anils **1a–e** behave as ambident electrophiles, as they could be attacked by the phosphite reagents **2** and/or **4** either on carbon-7 or the azomethine carbon, yielding a variety of phosphonate regioisomers. The regioselectivity of attack depends on the steric and electronic nature of both the reagents and the substrates as well as the reaction conditions. Thus, although trialkyl phosphites **2** regiospecifically attack carbon-7 in anils **1a–e** to yield phosphonates **3a–e** exclusively, the dialkyl phosphites **4** attack the azomethine carbon regiospecifically to yield phosphonates **5a–e** [1]. However, the reaction of **2** with **1** in the presence of a few drops of acetic acid yielded phosphonates **5**. The new phosphonates **3a–e** which is derived from furochromones belong to many biologically active centers which can be used as drugs [39,40]. They also belong to the pharmacologically interesting α-aminophosphonates [41–43]. Insecticidal activity tests have confirmed that the phosphonate adduct **3a** shows marked potency against adult *A. gossypii* (Glover), which infest cotton crops. Moreover, there is a marked difference in activity between the respective regioisomers, which confirms the structure–activity relationship principle.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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