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A Domino Knoevenagel/1,6-Heteroelectrocyclization Sequence to Access Phosphono-2*H*-thiopyrans

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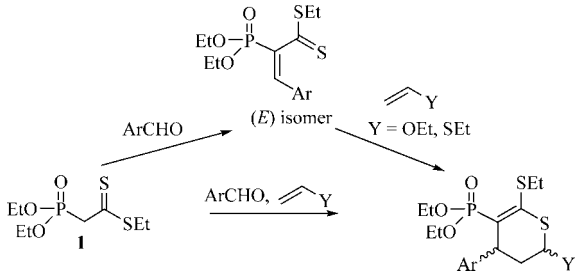
Knoevenagel-type condensation reactions between phosphonodithioacetate **1** and α,β-unsaturated aldehydes **2** directly afford 5-phosphono-substituted 2*H*-thiopyrans **4**. Use of heteroaromatic aldehydes allows the consecutive heteroelectrocyclization of the triene intermediate **3**, provided that the aromatic character of the C5–C6 double bond is sufficiently decreased, which is the case for electron-deficient indole nuclei. This Knoevenagel/1,6-heteroelectrocyclization sequence represents a new domino process.

Introduction

The 1,6-electrocyclization reaction represents a useful synthetic tool to produce cyclohexadiene structures, and it comes as a fine complement to [4 + 2] cycloadditions to afford cyclohexenes. However, the requirement for a (*Z*) central double bond strongly restricts its synthetic applications.[1] Heteroatomic versions, mainly involving 1-oxatrienes and 1-azatrienes as sources of pyrans,[2,3] and dihydropyridines,[2,3d,3e,4] respectively, have been described. In contrast, thiocarbonyl derivatives have been relatively little studied in this field, in spite of the numerous applications of the resulting thiopyrans.[5] To the best of our knowledge, five examples of thiaelectrocyclization are mentioned in the literature: (i) the thermal rearrangement of 2- and 3-(propargylthio)thiophenes to bicyclodihydrothiopyrans,[6] (ii) the thermal evolution of perfluorothioketones into the corresponding dihydrothiopyran,[7] (iii) the electrocyclic ring-closure of a dithiochromenone to a tricyclic dihydrothiopyran,[8] (iv) the electrocyclization of an unsaturated thioamide,[9] and (v) the 6-*endo-trig* cyclization of dithioethers.[10]

Earlier studies in our laboratories dealt with the reactivity of phosphonodithioesters in hetero-Diels–Alder reactions and their applications to the preparation of phosphorus-functionalized dihydrothiopyrans. In particular, it was shown that triethyl phosphonodithioacetate **1** gives access to phosphonodihydrothiopyrans, by two procedures (Scheme 1). The first relies on condensations of **1** with aromatic aldehydes under Knoevenagel conditions, with subsequent Diels–Alder cycloadditions of the resulting thiocarbonyl heterodienes with vinyl ethers or thioethers.[11d] It is noteworthy that the Knoevenagel condensation was totally (*E*)-stereoselective. The second one-pot route is based on a Knoevenagel/hetero-Diels–Alder sequence.[11e]



Scheme 1. One- or two-step Knoevenagel/hetero-Diels–Alder sequence, using phosphonodithioacetate **1**.

This led us to assume that condensing phosphonodithioacetate **1**, under Knoevenagel reaction conditions, with α,β-unsaturated aldehydes **2** should also afford exclusively the (*E*) isomers[12] of the expected heterotrienes **3**, which would be likely to lead, through 1,6-heteroelectrocyclization, to new 5-phosphono-substituted 2*H*-thiopyrans **4** (Scheme 2). The results are presented in this paper.

Results and Discussion

In a first series of experiments, the reactivity of phosphonodithioacetate **1**, prepared according to the literature,[13] toward two commercially available aldehydes, cinnamaldehyde (**2a**) and crotonaldehyde (**2b**), was examined

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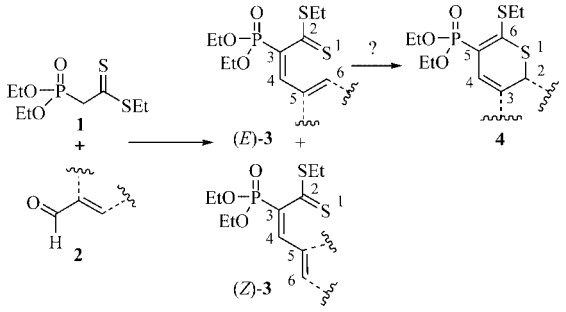
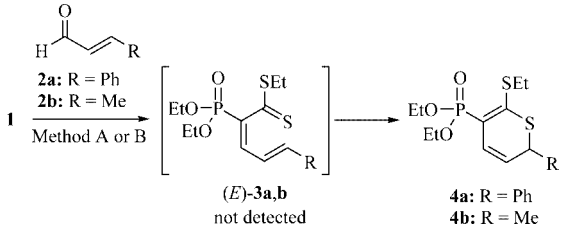


Scheme 2. Expected domino sequence from phosphonodithioacetate **1** and α,β-unsaturated aldehydes.

(Scheme 3, Table 1). Two kinds of reaction conditions were tested. The first (Method A) used "classical" Knoevenagel conditions:[14] the reagents were warmed at reflux in benzene or cyclohexane[15] in the presence of a catalytic amount of piperidine. The second (Method B), based on Lenhert's work,[16] consisted of the use of a Lewis acid catalyst ($TiCl_4$) to promote the phosphonate/aldehyde condensation, in THF at room temperature and in the presence of an excess of pyridine.



Scheme 3. Reactions between phosphonodithioacetate **1** and cinnamaldehyde (**2a**) and crotonaldehyde (**2b**).

Table 1. Reactions between phosphonodithioacetate **1** and aldehydes **2a** and **2b**.

Entry	Aldehyde	Method [a]	Time [d]	Product	Yield [%][b]
1	**2a**	A (C_6H_6)	1	**4a**	60
2	**2a**	A (C_6H_{12})	1	**4a**	62
3	**2a**	B	7	**4a**	74
4	**2b**	A (C_6H_6)	1	**4b**	<5[c]
5	**2b**	B	7	**4b**	67

[a] Method A: piperidine, solvent (benzene or cyclohexane), reflux; Method B: $TiCl_4$, THF, 0 °C, pyridine, room temp. [b] Isolated yields after chromatography. [c] Degradation of the reaction mixture.

Whatever the method used, the reaction between phosphonoacetate **1** and cinnamaldehyde (**2a**) led to 2*H*-thiopyran **4a** as a single product, without any trace of triene **3a** (Table 1, Entries 1–3). This result, however, suggests that (*E*)-**3a** was the reactive intermediate in the transformation. By Method A, **4a** was formed in 1 d in a 60–62% yield[17] (Entries 1 and 2). With Method B, 7 d were necessary to attain a comparable yield (74%, Entry 3).

The same reaction conditions (Methods A and B) were applied to crotonaldehyde (**2b**). In this case, Method A afforded only traces of thiopyran **4b** (Entry 4), probably due to degradation of the reaction mixture at high temperature. In contrast, with Method B the desired cycloadduct could be obtained in a satisfying 67% yield when the reaction was allowed to proceed for 7 d (Entry 5). Interestingly, when phosphonodithioacetate **1** was replaced with carbonyl analogues such as the phosphonoacetate $(i\text{PrO})_2\text{P(O)CH}_2\text{CO}_2\text{Et}$ or the β-ketophosphonate $(\text{MeO})_2\text{P(O)CH}_2\text{C(O)Me}$, the process stopped at the Knoevenagel product stage.[18]

Encouraged by the first results, we attempted to extend the scope of this sequence to heteroaromatic aldehydes. This challenging endeavour, which implied the participation of an aromatic double bond in the cyclization process, was thought likely to open a new route to polycyclic skeletons interesting in medicinal chemistry. The following heteroaromatic aldehydes were selected for this study: thiophene-2-carbaldehyde (**2c**), furfuraldehyde (**2d**), 1-tosyl- and 1-trifluoromethylsulfonyl-1*H*-pyrrole-2-carbaldehydes (**2e** and **2f**), and 1-tosyl- and 1-trifluoromethylsulfonyl-1*H*-indole-2-carbaldehydes (**2g** and **2h**). Treatment of phosphonodithioacetate **1** with aldehydes **2c**–**f**, according to Lenhert's procedure (Method B), led at room temperature after 2 d to Knoevenagel diene products **3c**–**f** as their (*E*) isomers in good yields (59–78%, Table 2, Entries 1–4). No trace of the corresponding thiopyrans **4c**–**f** was observed. Extending the reaction time up to 7 d did not afford the desired thiopyrans.

Table 2. Reactions between phosphonodithioacetate **1** and heteroaromatic aldehydes **2c**–**h**.

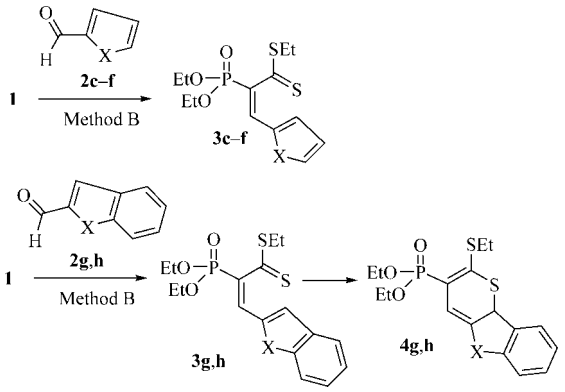
Entry	Aldehyde	Heterocycle (X)	Product (yield)[a]	**3**/**4**[d]
1	**2c**	thiophene (S)	**3c** (65%)	–
2	**2d**	furan (O)	**3d** (73%)	–
3	**2e**	pyrrole (NTs)	**3e** (78%)	–
4	**2f**	pyrrole (NTf)	**3f** (59%)	–
5	**2g**	indole (NTs)	**3g** + **4g** (72%)[b]	24:76
6	**2h**	indole (NTf)	**3h** + **4h**[c] (55%)[b]	13:87

[a] Isolated yields. [b] Yield of the inseparable mixture of **3** + **4**. [c] Unstable compound. [d] Ratio **3**/**4** in the crude mixture, by ^{31}P NMR spectroscopy.

The effects of pressure on electrocyclic reactions have been the object of relatively little attention, and the cyclization of heterotrienes under these conditions have, to the best of our knowledge, never been considered. However, precedents on the isomerization of substituted Dewar benzene suggest that the activation volume (ΔV^*) could be negative for this family of reaction and would thus be favoured under hyperbaric conditions.[19] Exposing compounds **3c**–**f** to hyperbaric conditions (12 kbar), at 50 °C and in the presence of $BF_3{\cdot}OEt_2$, however, did not afford the desired thiopyrans.

The dearomatization of these heterocycles probably goes through high-lying transition states that cannot be reached under the conditions used. Now, the decreased aromaticity of *N*-sulfonylindoles may lower the LUMO energy of the double bond sufficiently to favour the cyclization, since both *N*-tosyl- and *N*-triflylindoles gave the desired thiopyrans **4g** and **4h** as main products, together with the corresponding dienes **3g** and **3h**, respectively (Scheme 4, Table 2,

Entries 5 and 6). Exposing the **3g** + **4g** mixture to hyperbaric conditions (12 kbar) did not improve the **4g**/**3g** ratio.



Scheme 4. Reactions between phosphonodithioacetate **1** and heteroaromatic aldehydes **2c**–**h**.

The proportion of **4h** in the **3** + **4** mixture was slightly higher than that of **4g** (87:13 vs. 76:24). In both cases the separation of the thiopyran from its open-chain precursor by chromatography on silica gel was not possible; moreover, degradation occurred on the column.

Conclusions

The reactions between phosphonodithioacetate **1** and α,β-unsaturated aldehydes such as cinnamaldehyde and crotonaldehyde under Knoevenagel conditions led directly to 5-phosphono-substituted 2*H*-thiopyrans, probably through the electrocyclization of a 1-thioxatriene intermediate. When the reaction was extended to heteroaromatic aldehydes, including thiophene, furan, and pyrrole heterocycles, heterotrienes were the only products recovered, while the electron-deficient *N*-sulfonylindole nuclei underwent the cyclization process. To the best of our knowledge, such a Knoevenagel/1,6-heteroelectrocyclization domino sequence is unprecedented. Other applications as well as theoretical aspects[20] of this reaction are currently under examination.

Experimental Section

General: NMR analyses were obtained with a Bruker spectrometer (300, 250 or 200 MHz), in $CDCl_3$. Chemical shifts (δ) are given in ppm and the coupling constants (J) in Hertz (Hz). IR spectra were recorded by transmission with an IRTF spectrometer. The mass spectra were obtained under electron impact (EI) conditions at 70 eV ionizing potential; ammonia (NH_3) was used for chemical ionization (CI). High-resolution mass spectra were recorded with a QTOF Micro Waters spectrometer in the positive-ion electrospray-ionization mode. Elemental analyses were obtained with a THERMOQUEST NA 2500 apparatus. Thin layer chromatography (TLC) was carried out on Merck 5735 Kieselgel 60 F_{254} fluorescent plates. The silica gel used for flash chromatography was of 0.040–0.063 mm size. All reagents were of reagent grade and were used as such or distilled prior to use. THF was dried using a PURESOLV apparatus developed by Innovative Technology Inc. Aldehydes **2e**–**h** were synthesized according to described procedures.[21–23]

General Procedure (Method A): A solution of phosphonodithioacetate **1** (128 mg, 1 equiv., 0.5 mmol), aldehyde (1 equiv., 0.5 mmol) and piperidine (0.1 equiv., 0.05 mmol) in cyclohexane or benzene (2 mL) was heated at reflux in a Dean–Stark apparatus. The reaction was monitored by TLC until completion (the reaction times are indicated in Table 1), and the reaction mixture was then cooled to room temp. and concentrated under reduced pressure. The residue was diluted in CH_2Cl_2 and hydrolyzed with water. The organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel and afforded the final products **4** (yields are given in Table 1).

General Procedure (Method B): A solution of aldehyde (1 equiv., 0.5 mmol) in dry THF (1 mL), and a solution of phosphonodithioacetate **1** (128 mg, 1 equiv., 0.5 mmol) in dry THF (5 mL) were added successively to a solution of $TiCl_4$ (2 equiv., 1 mmol in 250 μL CCl_4) in dry THF (4 mL). The mixture was stirred at room temp. for 15 min and then cooled to 0 °C. A solution of pyridine (4 equiv., 2 mmol) in dry THF (3 mL) was added dropwise over 1 h, and the resulting mixture was stirred at room temp. until completion. The reaction mixture was poured at 0 °C into an aqueous HCl solution (1 M, 10 mL) and vigorously stirred for 1 h. The organic compounds were extracted three times with CH_2Cl_2 (3×20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel and afforded the final products **3** or **4** (yields are given in Tables 1 and 2).

Diethyl [6-(Ethylthio)-2-phenyl-2*H*-thiopyran-5-yl]phosphonate (4a): This compound was prepared according to the general procedure (Method A or B). Purification by flash chromatography on silica gel (AcOEt/cyclohexane, 60:40) gave 144 mg (62%, according to Method A) or 137 mg (74% yield, according to Method B) of product as a beige solid; m.p. 66 °C (AcOEt/cyclohexane, 60:40). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.5 Hz, 3 H), 1.33 (dt, J = 9.0 and 6.8 Hz, 6 H), 2.84–3.05 (m, 2 H), 4.02–4.17 (m, 4 H), 4.68 (d, J = 5.7 Hz, 1 H), 5.73 (ddd, J = 9.8, 5.7 and 1.9 Hz, 1 H), 6.70 (ddd, J = 9.8, 8.7 and 1.1 Hz, 1 H), 7.27–7.38 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 16.6 (d, J = 7.0 Hz), 31.0, 44.8, 62.2, 117.5 (d, J = 11.5 Hz), 120.3 (d, J = 189.9 Hz), 128.2, 128.3, 128.9, 129.3 (d, J = 9.4 Hz), 139.8, 148.6 (d, J = 10.8 Hz) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 16.7 ppm. IR (neat): $\tilde{\nu}$ = 1473, 1234, 1024, 910, 740 cm^{-1}. EIMS (70 eV): m/z (%) = 370 (83) $[M]^+$, 341 (100). HRMS (FAB): calcd. for $C_{17}H_{23}PO_3S_2$ $[MH^+]$ 370.0826; found 370.0832. $C_{17}H_{23}O_3PS_2$ (370.5): calcd. C 55.11, H 6.26, S 17.31; found C 55.05, H 6.23, S 17.53.

Diethyl [6-(Ethylthio)-2-methyl-2*H*-thiopyran-5-yl]phosphonate (4b): This compound was prepared according to the general procedure (Method B). Purification by flash chromatography on silica gel (AcOEt/cyclohexane, 60:40) gave 103 mg (67%) of product as a yellow oil (slightly contaminated with unidentified by-products, which did not contain phosphorus). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27–1.35 (m, 12 H), 2.93–3.17 (m, 2 H), 3.49 (dq ≈ q, J = 6.7 and 6.7 Hz, 1 H), 4.04–4.12 (m, 4 H), 5.57 (ddd, J = 9.2, 6.0, 1.9 Hz, 1 H), 6.40 (dd ≈ t, J = 9.2, 9.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.5, 16.6 (d, J = 6.5 Hz), 20.1, 31.0, 35.9, 62.2 (d, J = 5.8 Hz), 120.1 (d, J = 190.0 Hz), 120.3 (d, J = 11.5 Hz), 127.4 (d, J = 10.1 Hz), 148.6 (d, J = 10.1 Hz) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 16.9 ppm. IR (neat): $\tilde{\nu}$ = 1475, 1242, 1118, 1050, 1023, 964 cm^{-1}. EIMS (70 eV): m/z (%) = 308 (100) $[M]^+$, 293 (73), 279 (60), 247 (23), 191 (42), 170 (40), 149 (50), 109

(47). HRMS (FAB): calcd. for $C_{12}H_{21}PO_3S_2$ [MH^+] 308.0670; found 308.0675.

Ethyl (*E*)-2-(Diethoxyphosphoryl)-3-(thiophen-2-yl)prop-2-enedithioate (3c): This compound was prepared according to the general procedure (Method B). Purification by flash chromatography on silica gel (AcOEt/heptane, 80:20) gave the product (113 mg, 65%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.2 Hz, 6 H), 1.33 (t, J = 7.2 Hz, 3 H), 3.26 (q, J = 7.5 Hz, 2 H), 4.10 (dq, J = 7.2, 7.2 Hz, 4 H), 6.94 (dd, J = 3.8, 4.9 Hz, 1 H), 7.20 (d, J = 3.8 Hz, 1 H), 7.36 (d, J = 4.9 Hz, 1 H), 7.52 (d, J = 23.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.7, 16.2 (d, J = 7.2 Hz), 31.3, 62.8 (d, J = 5.0 Hz), 127.2, 131.7, 133.6 (d, J = 172.0 Hz), 134.0, 135.5 (d, J = 10.1 Hz), 136.1 (d, J = 22.4 Hz), 227.0 (d, J = 7.9 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 12.3 ppm. IR (neat): $\tilde{\nu}$ = 1585, 1444, 1397, 1372, 1246 cm^{-1}. EIMS (70 eV): *m*/*z* (%) = 350 (40) [$M]^+$, 321 (100), 289 (84), 261 (32), 245 (23), 213 (17). HRMS (FAB): calcd. for $C_{13}H_{19}PO_3S$ [$MH^+]_3$ 350.0234; found 350.0237.

Ethyl (*E*)-2-(Diethoxyphosphoryl)-3-(furan-2-yl)prop-2-enedithioate (3d): This compound was prepared according to the general procedure (Method B). Purification by flash chromatography on silica gel (AcOEt/cyclohexane, 50:50) gave the product (122 mg, 73%) as a dark red solid; m.p. 44–46 °C (AcOEt/cyclohexane, 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.2 Hz, 6 H), 1.37 (t, J = 7.5 Hz, 3 H), 3.32 (q, J = 7.5 Hz, 2 H), 4.16 (dq ≈ q, J = 7.2, 7.2 Hz, 4 H), 6.41 (dd, J = 3.4, 1.9 Hz, 1 H), 6.65 (d, J = 3.4 Hz, 1 H), 7.23 (d, J = 23.0 Hz, 1 H), 7.42–7.43 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2, 16.4 (d, J = 7.2 Hz), 31.2, 63.1 (d, J = 4.9 Hz), 112.7, 116.8, 129.6 (d, J = 9.0 Hz), 133.4 (d, J = 179.7 Hz), 145.5, 149.5 (d, J = 24.6 Hz), 227.7 (d, J = 8.4 Hz) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 13.0 ppm. IR (neat): $\tilde{\nu}$ = 1613, 1537, 1469, 1445, 1391, 1370, 1237, 1014 cm^{-1}. $C_{13}H_{19}O_4PS_2$ (334.4): calcd. C 46.69, H 5.73, S 19.18; found: C 46.79, H 5.76, S 18.96.

Ethyl (*E*)-2-(Diethoxyphosphoryl)-3-(1-tosyl-1*H*-pyrrol-2-yl)prop-2-enedithioate (3e): This compound was prepared according to the general procedure (Method B). Purification by flash chromatography on silica gel (AcOEt/pentane, 30:70) gave the product (165 mg, 78%) as an orange oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.5 Hz, 3 H), 1.35 (dt, J = 7.1, 0.6 Hz, 6 H), 2.41 (s, 3 H), 3.19 (q, J = 7.5 Hz, 2 H), 4.08–4.21 (m, 4 H), 6.22 (t, J = 3.5 Hz 1 H), 6.63 (m, 1 H), 7.32 (d, J = 8.1 Hz, 2 H), 7.45 (m, 1 H), 7.78 (d, J = 8.1 Hz, 2 H), 7.80 (d, J = 23.2 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.0, 16.6 (d, J = 7.1 Hz), 22.0, 31.2, 63.3 (d, J = 5.3 Hz), 113.0, 119.8 (d, J = 1.4 Hz), 125.9, 127.8, 128.1 (d, J = 25.2 Hz), 129.4 (d, J = 10.8 Hz), 130.5, 136.0, 136.3 (d, J = 181.4 Hz), 145.8, 228.6 (d, J = 9.8 Hz) ppm. ^{31}P NMR (101.2 MHz, $CDCl_3$): δ = 12.3 ppm. IR (NaCl): $\tilde{\nu}$ = 1593, 1442, 1367, 1255, 1191, 1175, 1155, 1089, 1022 cm^{-1}.

Ethyl (*E*)-2-(Diethoxyphosphoryl)-3-[1-(trifluoromethylsulfonyl)-1*H*-pyrrol-2-yl]prop-2-enedithioate (3f): This compound was prepared according to the general procedure (Method B). Purification by flash chromatography on silica gel (AcOEt/pentane, 30:70) gave the product (137 mg, 59%) as an orange oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31–1.38 (m, 9 H), 3.30 (q, J = 7.5 Hz, 2 H), 4.07–4.25 (m, 4 H), 6.42 (dd ≈ t, J = 3.6, 3.6 Hz, 1 H), 6.88 (m, 1 H), 7.26 (d, J = 3.2 Hz, 1 H), 7.60 (d, J = 22.8 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.0, 16.4 (d, J = 7.1 Hz), 31.2, 63.6 (d, J = 5.4 Hz), 115.3, 119.5 (q, J = 323.0 Hz), 121.3 (d, J = 1.6 Hz), 126.7, 127.1 (d, J = 11.0 Hz), 130.4 (d, J = 15.9 Hz), 139.5 (d, J = 179.4 Hz), 227.6 (d, J = 9.4 Hz) ppm. ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –75.8 ppm. ^{31}P NMR (101.2 MHz, $CDCl_3$): δ = 11.2 ppm. IR (NaCl): $\tilde{\nu}$ = 1590, 1458, 1420, 1390, 1233, 1174, 1110, 1025 cm^{-1}. CEMS (12 eV): *m*/*z* (%) = 466 (7) [$M]^+$, 404 (100). HRMS (FAB): calcd. for $C_{14}H_{20}F_3NPO_5S_3$ [MH^+] 466.0193; found 466.0208.

Ethyl (*E*)-2-(Diethoxyphosphoryl)-3-(1-tosyl-1*H*-indol-2-yl)prop-2-enedithioate (3g) and Diethyl [6-(Ethylthio)-5-tosyl-5,9b-dihydrothiopyrano[3,2-*b*]indol-5-yl]phosphonate (4g): These compounds were prepared according to the general procedure (Method B). Purification of the crude product by flash chromatography on silica gel (AcOEt/pentane, 30:70–70:30) gave 193 mg (72%) of an inseparable mixture of **3g** and **4g** (24:76 ratio) as a pale orange oil. **3g** (minor): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.09–1.34 (m, 9 H), 2.20 (br. s, 3 H), 2.75–2.88 (m, 1 H), 3.06–3.20 (m, 1 H), 4.07–4.23 (m, 4 H), 6.81–7.95 (m, 9 H), 8.06 (d, J = 8.4 Hz, 1 H) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 10.7 ppm. **4g** (major): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.09–1.34 (m, 9 H), 2.20 (br. s, 3 H), 2.75–2.88 (m, 1 H), 3.06–3.20 (m, 1 H), 4.07–4.23 (m, 4 H), 4.54 (br. s, 1 H), 6.81–7.95 (m, 9 H) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 14.8 ppm. IR (NaCl): $\tilde{\nu}$ = 1712, 1639, 1596, 1510, 1446, 1372, 1246, 1173, 1090, 1022 cm^{-1}. EIMS (70 eV): *m*/*z* (%) = 537 (<1) [$M]^+$, 491 (92), 463 (77), 382 (35), 336 (78), 308 (100).

Ethyl (*E*)-2-(Diethoxyphosphoryl)-3-[1-(trifluoromethylsulfonyl)-1*H*-indol-2-yl]prop-2-enedithioate (3h) and Diethyl [6-(Ethylthio)-5-(trifluoromethylsulfonyl)-5,9b-dihydrothiopyrano[3,2-*b*]indol-5-yl]phosphonate (4h): These compounds were prepared according to the general procedure (Method B). Purification of the crude product by flash chromatography on silica gel (AcOEt/pentane, 30:70–70:30) gave 124 mg (55%) of an inseparable mixture of **3h** and **4h** (13:87 ratio) as a pale orange oil (degradation occurred in solution during ^{13}C NMR analysis). **3h** (minor): ^{31}P NMR (101.2 MHz, $CDCl_3$): δ = 9.7 ppm. **4h** (major): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26–1.42 (m, 9 H), 3.05 (m, 1 H), 3.30 (m, 1 H), 4.11–4.25 (m, 4 H), 5.30 (br. s, 1 H), 6.78 (dd, J = 2.5 and 9.4 Hz, 1 H), 7.27–7.29 (m, 1 H), 7.41–7.47 (m, 2 H), 7.67–7.69 (m, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 15.5, 16.6 (d, J = 6.5 Hz), 16.7 (d, J = 5.1 Hz), 30.9, 45.0, 62.2 (d, J = 6.2 Hz), 62.9 (d, J = 5.8 Hz), 116.0, 120.5 (q, J = 328.0 Hz), 125.9, 126.0, 126.8, 127.7, 130.7, 133.8 (d, J = 26.0 Hz), 137.3, 141.4, 141.6 (d, J = 178.0 Hz) ppm. ^{31}P NMR (101.2 MHz, $CDCl_3$): δ = 13.6 ppm. ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –74.9 ppm. IR (NaCl): $\tilde{\nu}$ = 1464, 1414, 1211, 1175, 1170, 1134, 1024 cm^{-1}. CEMS (14 eV): *m*/*z* (%) = 516 (17) [$M]^+$, 454 (18). HRMS (FAB) calcd. for $C_{18}H_{22}F_3NPO_5S_3$ [MH^+] 516.0350; found 516.0367.

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