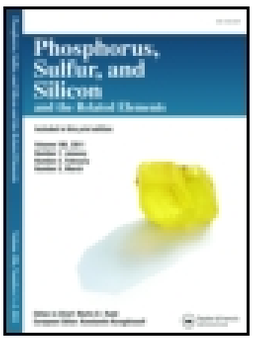

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Chemistry of Phosphorus Ylides: Part 45 Synthesis of Phosphoranylidene Thietane, Azetidine and Thiazinane Derivatives as Potent Chemo Preventative Agents

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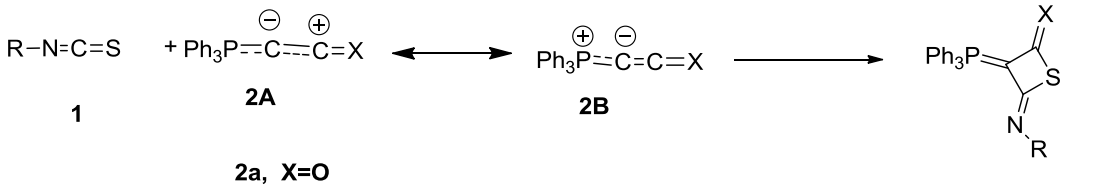
Abstract

Reactions of nucleophilic active phosphacumulenes with iso(thio)cyanate compounds were performed. The reaction products depend on the nature of the reagent, substrate and the condition of the reaction used. New heterocyclic 4-membered or 6-membered sulfur and nitrogen compounds such as phosphoranylidene thietane, azetidine and thiazinane were obtained. On the other hand, the stable phosphonium ylides with the iso(thio)cyanate afforded phosphoranylidene thiocarbamoyl derivatives. Possible reaction mechanisms are considered and the structural assignments are based on compatible analytical and spectroscopic data.



1

2A

2a, X=O
b, X= N-Ph

2B

4a, X= O
b, X= N-Ph

Keywords

Isothiocyanates; isocyanate; ylides; phosphoranylidene; thietane; azetidine; thiazinane; thiocarbamoyls

Introduction

Naturally occurring isothiocyanates are effective chemo protective agents against chemical carcinogenesis in experimental animals.[1-5] These compounds inhibit rat lung, esophagus, mammary gland, liver, small intestine, colon and bladder tumorigeneses.[5,6] They also reduce risk for prostate cancer.[7-9] Moreover, studies have demonstrated that several isothiocyanates inhibit cell growth by inducing apoptosis which is suggested to be potentially involved in the anticarcinogenic action of isothiocyanates.[10-12] On the other hand, methyl isocyanate is an intermediate chemical in the production of carbamate pesticides,[13-15] such as carbaryl, carbofuran, methomyl and aldicarb. It has also been used in the production of rubber coatings and adhesive.[16-18] In summary, isocyanates are very useful and versatile compounds in organic and polymer chemistry and their applications are focused on the production of polyurethanes.[19] The isocyanate group contains cumulated double bond sequence, which in its reactivity is governed by the positive character of the carbon atom, which is susceptible to attack by nucleophiles and oxygen and nitrogen by electrophiles. On the other hand, phosphacumulenes and stabilized phosphonium ylides have numerous industerial applications[20,21]. Moreover, their different pharmacological applications[22] are well known.

Results and Discussion

In our continuing studies on the reactions of active and stabilized phosphonium ylides we have described the isolation and identification of different homocyclic and heterocyclic compounds bearing phosphorus moieties, which have antimutagenic effects.[23-28]

In the present study, we describe the reactions of the active nucleophilic reagents and stabilized phosphonium ylides with isocyanate and isothiocyanate compounds to prepare heterocyclic phosphorus compounds of biological interest.

Phosphacumulene ylides can be represented by the resonance structures **2A** and **2B**. They react with some unsaturated compounds according to the resonance structure **2A** and with carbonyl compounds according to the resonance structure **2B** (Wittig reaction). Thus, the reaction of 4-methoxyphenylisothiocyanate (**1**) with (2-oxovinylidene)-triphenylphosphorane (**2a**) in THF,

afforded firstly the dipolar intermediate **3**.[29] 2,2-Cyclization in the intermediate occurs via the sulfur atom, which is more nucleophilic than the nitrogen atom to give the four-membered heterocyclic thiocarbomyl compounds, 4-((4-methoxyphenyl)imino)-3-(triphenylphosphoranylidene)thietan-2-one (**4a**). The most important features in the spectroscopic data of **4a** are the disappearance of thiocarbonyl group in their ^{13}C NMR and IR spectra and the appearance of the carbonyl group at δ = 189.5 and at ν = 1731 cm^{-1}, respectively. In the ^{31}P NMR spectrum of **4a** a signal is observed at δ = 10.0, which supports the presence of phosphorus in the four membered ring.[30] Moreover, the proposed structure of **4a** was further unequivocally confirmed by X-ray crystallography (Figure 1).

When the isothiocyanate **1** was allowed to react with (*N*-phenyliminovinylidene)-triphenylphosphorane (**2b**), the corresponding 4-methoxy-*N*-4-(phenylimino)-3-(triphenylphosphoranylidene)thietan-2-ylidene)aniline (**4b**) was obtained (Scheme1).

We have found that the reaction of methylisothiocyanate (**5**) with the phosphacumulenes **2a** or **2b** proceeds in THF at room temperature to give the dipolar intermediates **6**, which under our experimental conditions react with another molecule of methyl isothiocyanate **5** to give the corresponding six-membered compounds, namely 3-methyl-6-(methylimino)-2-thioxo-5-(triphenylphosphoranylidene)-1,3-thiazinan-4-one (**7a**) and 3-methyl-6-(methylimino)-4-(phenylimino)-5-(triphenyl-phosphoranylidene)-1,3-thiazinane-2-thione (**7b**), respectively. The structure of the six-membered compounds **7a**,**b** was confirmed by their spectroscopic data. In the ^{13}C NMR spectrum of compound **7b** the signal of the C = S carbon atom appeared at δ = 191.3 and the in the ^{31}P NMR spectrum a signal at δ = 26.2 was observed, which supports the presence of a phosphorus group in the six membered ring.[31,32] In the mass spectrum the M^+ peak appeared at 523 (5%).

Moreover, the reaction of 1,2-dichloro-4-isocyanatobenzene (**8**) with the phospha-cumulene **2a** in THF afforded firstly the dipolar intermediate **9a**. [2+2]-Cycloaddition through the carbon-nitrogen bond, leads to the four-membered hetero iminocarbonyl compound, 1-(3,4-dichlorophenyl)-3-(triphenyl-λ^5-phosphanylidene)azetidine-2,4-dione (**10a**). The most important features in the spectroscopic data of **10a** are, that a signal at δ = 19.0 was observed in the ^{31}P

NMR spectrum and that in its ^{13}C NMR spectrum two signals were observed at δ = 170.0 and 167.8, which are assigned to the two carbonyl groups.

Reaction of phosphacumulene **2b** with the isocyanate **8** afforded 1-(3,4-dichloro-phenyl)-4-phenylimino-3-(triphenyl-λ^5-phosphanylidene)azetidin-2-one (**10b**) (Scheme 3).

The behavior of the stabilized phosphonium ylides **11a-c** towards the isothiocyanates **1**, **5** and the isocyanate **8** was also studied in order to determine the site of attack. It was found that the methylene triphenylphosphoranes **11a-c** react with the isothio-cyanate **1** in THF to give the intermediate betaines **12a-c**, which produce the new ylides **13a-c**. In case of using the phosphorane **11c**, adduct **13c** was isolated together with 1,3-bis(4-methoxyphenyl)thiourea (**14**). Formation of the thiourea derivative **14** is catalyzed by the phosphorane **11c**.[33,34] The elemental analysis, IR, ^1H-, ^{13}C-, ^{31}P NMR and MS data support the structures of the compounds. For example compound **13a** showed bands at 3445 (NH), 1643 C = O, and 1290 cm^{-1} C = S in its IR spectrum. In the ^1H NMR spectrum of **13a**, signals at δ = 11.98 (NH, exchangeable with D_2O), 7.50-7.73 (aromatic protons), 3.67 (phenyl OCH_3) and 2.84 (ester OCH_3) were observed. The ^{13}C NMR spectrum of **13a**, showed signals at δ = 189.5 (C = S), 168.1 (C = O), 133.1-113.9 (aromatic carbon atoms), 55.7 (phenyl OCH_3) and 50.1 (ester OCH_3). The ^{31}P NMR chemical shift observed for **13a** was at δ = 12.4.[35,36] (Scheme 4).

In the same sense, methylisothiocyanate (**5**) and 3,4-dichlorophenylisocyanate (**8**) react with the stabilized phosphonium ylides **11a-c** to give the corresponding thiocarbamoylphosphanylidenes **15a-c** (Scheme 5) and the phosphanylidenes **16a-c** (Scheme 6), respectively. In case of using the phosphorane **11c**, the urea derivative **17** was also isolated. All the spectroscopic data of the above mentioned new compounds are cited in the experimental section. The molecular structure of compound **15a**, determined by single crystal X-ray diffraction, is shown in Figure 2.

Experimental

Melting points were determined with an electrothermal digital melting point apparatus (Electro-Thermal Engineering Ltd., Essex, United Kingdom). The IR spectra were recorded in KBr disks with a Pye Unicam SP 3300 and a Shimadzu FT IR 8101 PC IR spectrophotometer (Pye Unicam

Ltd, Cambridge, UK and Shimadzu, Tokyo, Japan, respectively). ^{1}H and ^{13}C NMR spectra were obtained with a Jeol ECA 500 MHz NMR Spectrometer (Tokyo, Japan) using $CDCl_3$ and d^6-DMSO as solvents and TMS as internal reference at 500 and 125 MHz, respectively. ^{31}P NMR spectra were obtained with a Jeol ECA 500 MHz NMR spectrometer operating at 200 MHz. Mass spectra (EI-MS) were obtained with an ISQ (Single Quadrupole MS, Thermo Scientific) instrument. Elemental analyses (C, H, N, S) were performed with an Elementar Vario EL Analyzer; the phosphorus content was measured by spectrophotometric methods. X-ray crystallography was carried out with a Kappa CCD Enraf Nonius FR 590 diffractometer, National Research Centre, Dokki, Cairo, Egypt. The reported yields are of pure isolated materials obtained by column chromatography using silica gel 60 (Merck) and TLC, which was performed on Merck Kiesel gel F254 precoated plates (Merck, Darmstall, Germany). Solvents were dried / purified according to literature procedures. The starting materials **1, 5** and **8** were obtained from Fluka Chemicals.

Reaction of 4-Methoxyphenylisothiocyanate (1) with (2-Oxovinylidene)- triphenyl-phosphorane (2a) and (N-phenyliminovinylidene)triphenylphosphorane (2b). General Procedure

To a solution of **1** (0.165 g, 0.001 mol) in 20 mL of dry THF was added a solution of **2a**[37] (0.302 g, 0.001 mol), or **2b**[38] (0.377 g, 0.001 mol) in 30 mL of THF. The reaction mixture was stirred for 8 h in case of **2a** or 6 h in case of **2b**; the progress of the reaction was monitored by TLC. The solvent was distilled off under reduced pressure and the residue was crystallized to give **4a** or **4b**.

4-((4-Methoxyphenyl)imino)-3-(triphenylphosphoranylidene)thietan-2-one (4a)

The compound was obtained from petrol ether (60-80 °C) as yellow crystals, yield 85%; m.p. 171--173 °C. IR (KBr, cm^{-1}): ν = 1731 (C = O), 1644 (C = N). ^{1}H NMR (500 MHz, d^6- DMSO): δ = 3.66 (s, 3H, OCH_3), 7.51-7.61 (m, 19H, arom-H). ^{13}C NMR (125 MHz, d^6-DMSO): δ = 189.5 (C = O), 162.2 (C = N), 129.2, 129.3, 129.9, 130.0, 133.4, 134.0, 134.1, 134.7, 134.8, 135.1 (arom-C), 55.5 (OCH_3). ^{31}P NMR (200 MHz, d^6-DMSO): δ = 10.0. MS (EI, 70 eV): m/z

(%) 278 [(TPPO), 5], 262 [(TPP), 55]. Anal. Calcd. for $C_{28}H_{22}NO_2PS$ (467.52): C, 71.93; H, 4.74; N, 3.00; P, 6.63; S, 6.86. Found: C, 71.83; H, 4.60; N, 2.90; P, 6.54; S, 6.74%.

***X-Ray crystallography of* 4a**

Single crystals of compound **4a** were obtained by slow evaporation of the solvent. A suitable crystal was selected, checked and mounted on top of a thin glass fiber. The X-ray single crystal diffraction data were collected at room temperature (298 K) with an Enraf-Nonius 590 diffractometer with a Kappa CCD detector using graphite monochromated Mo-Kα (λ = 0.71073Å) radiation at the National Research Centre of Egypt.[39,40] The structure was solved by direct methods using SHELXS-97[41] and SUPERFLIP[42] implemented in the CRYSTALS program suit.[43] The refinement was carried out by the full-matrix least-squares method on the positional and anisotropic temperature parameters of all non-hydrogen atoms based on F^2 using the CRYSTALS package. The general-purpose crystallographic tool PLATON[44] was used for the structure analysis and presentation of the results. Molecular graphics were generated using ORTEP-3 for Windows[45] and DIAMOND[46] programs. Details of the data collection conditions and the parameters of the refinement process are given in Table 1.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1532652. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax:+44(0)1223 336033 or E-mail: deposit@ccdc.cam.ac.uk].

4-Methoxy-N-4-(phenylimino)-3-(triphenylphosphoranylidene)thietan-2-ylidene)aniline (4b)

Isolated from column chromatography using petrol ether (60-80 °C) ethyl acetate (80:20, *v/v*) as an eluent, white crystals, yield 75%, m.p. 103--105 °C. IR (KBr, cm^{-1}): ν = 2928 (arom-CH), 1648, 1618 (2 C = N), 1439 (C = P). ^{1}H NMR (500 MHz, d^6-DMSO): δ = 3.72 (s, 3H, OCH_3) 6.85-7.84 (m, 24H, arom-H).^{13}C NMR (125 MHz, d^6-DMSO): δ = 164.6 (C = N), 155.9 (C = P), 114.2, 114.4, 119.6, 121.2, 123.4, 126.7, 129.1, 129.2, 132.6, 140.0 (arom-C), 55.7 (OCH_3). MS (EI, 70 eV): *m/z (%)* 511 [(M^+ -OCH_3), 5], 294 [(TPPS), 100], 262 [(TPP), 10]. Anal. Calcd. for

$C_{34}H_{27}N_2OPS$ (542.16): C, 75.26; H, 5.02; N, 5.16; P, 5.71; S, 5.91. Found: C, 75.16; H, 4.97; N, 5.10; P, 5.63; S, 5.82%.

Reaction of Methylisothiocyanate (5) with (2-Oxovinylidene)triphenylphosphorane (2a) and (N-Phenyliminovinylidene)triphenylphosphorane (2b). General Procedure

To a solution of **5** (0.073 g, 0.001 mol) in 20 mL of dry THF, was added a solution of **2a** (0.302 g, 0.001 mol) or **2b** (0.377 g, 0.001 mol) in 30 mL of THF. The reaction mixture was stirred for 12 h in case of **2a** or 10 h in case of **2b** (TLC). The solvent was distilled off under reduced pressure and the residue was crystallized, yielding **7a** or **7b**, respectively.

3-methyl-6-(methylimino)-2-thioxo-5-(triphenylphosphoranylidene)-1,3-thiazinan-4-one (7a)

Isolated from column chromatography using petrol ether (60-80 °C)/ethyl acetate (5:95, *v/v*) as an eluent, white crystals, yield 65%, m.p. 114--115 °C. ^{1}H NMR (500 MHz, d^6-DMSO): δ = 1.98 (s, 3H, N-CH_3), 2.00 (s, 3H, N-CH_3), 7.46-7.71 (m, 15H, arom-H), ^{13}C NMR (125 MHz, d^6-DMSO): δ = 197.5 (C = S), 181.3 (C = O), 132.0, 130.8, 130.7, 129.2, 129.1 (arom-C), 16.7, 16.1 (CH_3). ^{31}P NMR (200 MHz, d^6- DMSO): δ = 28.2. MS (EI, 70 eV): *m/z (%)* 433 [(M^+ - CH_3), 19], 418 [(M^+ -2CH_3), 14], 294 [(TPPS), 15], 262 [(TPP), 13]. Anal. Calcd. for $C_{24}H_{21}N_2OPS_2$ (448.08): C, 64.27; H, 4.72; N, 6.25; P, 6.91; S, 14.30. Found: C, 64.16; H, 4.60; N, 6.14; P, 6.79; S, 14.18%.

3-methyl-6-(methylimino)-4-(phenylimino)-5-(triphenylphosphoranylidene)-1,3-thiazinane-2-thione (7b)

Isolated from column chromatography using petrol ether (60-80 °C)/ethyl acetate (75: 25, v/v) as an eluent, yellow crystals, yield 70%, m.p. 125--128 °C. IR (KBr, cm^{-1}): ν = 1640, 1620 (2 C = N), 1560 (C = P), 1249 (C = S). ^{1}H NMR (500 MHz, d^6-DMSO): δ = 2.83 (s, 3H, N-CH_3), 2.89 (s, 3H, N-CH_3), 7.48-7.68 (m, 20H, arom-H), ^{13}C NMR (125 MHz, d^6-DMSO): δ = 191.3 (C = S), 168.6, 168.4 (C = N), 143.5 (C = P), 129.0, 129.1, 133.0, 133.1 (arom-C), 30.0 (CH_3).^{31}P NMR (200 MHz, d^6-DMSO): δ = 26.2. MS (EI, 70 eV): *m/z (%)* 523 [(M^+), 5], 294 [(TPPS),

100] 262 [(TPP), 15], 262 [(M^+-TPP) 5]. Anal. Calcd. for $C_{30}H_{26}N_3PS_2$ (523.13): C, 68.81; H, 5.00; N, 8.02; P, 5.91; S, 12.25. Found: C, 68.68; H, 3.99; N, 7.90; P, 5.88; S, 12.14%.

Reaction of 3,4 Dichlorophenyl Isocyanate (8) with (2-Oxovinylidene) Triphenylphosphorane (2a) and (N-Phenyliminovinylidene)triphenylphosphorane (2b). General Procedure

To a solution of **8** (0.188 g, 0.001 mol) in 20 mL of dry THF was added a solution of **2a** (0.302 g, 0.001 mol) or **2b** (0.377 g, 0.001 mol) in 30 mL of THF. The reaction mixture was stirred for 30 min in case of **2a** or 2 h in case of **2b**. The solvent was distilled off under reduced pressure, and the residue was crystallized to give **10a** or **10b**.

1-(3,4-Dichlorophenyl)-3-(triphenyl-λ^5-phosphanylidene)azetidine-2,4-dione (10a)

Crystallized from petrol ether (60-80 °C) as pale yellow crystals, yield 85%, m.p. 102--105 °C. IR (KBr, *cm*$^{-1}$): ν = 1692 (C = O, ylide), 1590 (C = O). ^{1}H NMR (500 MHz, d^6-DMSO): δ = 7.54-7.63 (18H, arom-H).^{13}C NMR (125 MHz, d^6-DMSO): δ = 170.0 (C = O, ylide), 167.8 (C = O), 140.5 (C = P), 119.1, 120.1, 126.1, 126.2, 126.8, 129.4, 130.9, 132.6, 133.4 (arom-C). ^{31}P NMR (200 MHz, d^6-DMSO): δ = 19.0. MS (EI, 70 eV): *m/z (%)* 278 [(TPPO), 20], 262 [(TPP), 5]. Anal. Calcd. for $C_{27}H_{18}Cl_2NO_2P$ (490.32): C, 66.14; H, 3.70; Cl, 14.46; N, 2.86; P, 6.32. Found: C, 66.03; H, 3.60; Cl, 14.35; N, 2.77; P, 6.21%.

1-(3,4-Dichlorophenyl)-4-phenylimino-3-(triphenyl-λ^5-phosphanylidene)azetidin-2-one (10b)

Isolated from column chromatography using petrol ether (60-80 °C)/ethyl acetate (70:30 *v/v*) as an eluent, white crystals, yield 75%, m.p. 175--177 °C. IR (KBr, cm^{-1}): ν = 1672 (C = O), 1645 (C = N), 1560 (C = P). ^{1}H NMR (500 MHz, d^6-DMSO): δ = 6.94-7.81 (23H, arom-H).^{13}C NMR (125 MHz, d^6-DMSO): δ = 161.8 (C = N), 152.7 (C = O), 140.1 (C = P), 114.0, 114.1, 119.2, 120.1, 124.1, 131.0, 131.1, 131.6, 132.8, 132.9 (arom-C). ^{31}P NMR (200 MHz, d^6-DMSO): δ = 14.2. MS (EI, 70 eV): *m/z (%)* 565 [M^+, 5], 278 [(TPPO), 10] 262 [(TPP), 5]. Anal. Calcd. for $C_{33}H_{23}Cl_2N_2OP$ (565.43): C, 70.10; H, 4.10; Cl, 12.54; N, 4.95; P, 5.48. Found: C, 69.99; H, 4.00; Cl, 12.43; N, 4.82; P, 5.39%.

Reaction of 4-Methoxyphenyl isothiocyanate (1) with Methoxycarbonyl- (11a), Ethoxycarbonyl- (11b) and Acetyl-methylenetriphenylphosphorane (11c). General Procedure

To a solution of **1** (0.33 g, 0.002 mol) in 20 mL of dry THF was added a solution of **11a-c**,[47,48] **11a** (1.002 g, 0.003 mol) or **11b** (1.044 g, 0.003 mol) or **11c** (0.954 g, 0.003 mol) in 30 mL of dry THF. The reaction mixture was refluxed for 20 h in case of **11a** or **11b** and stirred for 6 h in case of **11c**. The solvent was distilled off under reduced pressure and the residue was crystallized to give compounds **13a-c** and **14**.

(4-Methoxyphenylthiocarbamoyl)(triphenyl-λ^5-phosphanylidene)acetic Acid Methyl Ester (13a)

Crystallized from ethanol as white crystals, yield 75%, m.p. 170--172 °C. IR (KBr, cm^{-1}): ν = 3445 (NH), 1643 (C = O, ester), 1290 (C = S). ^{1}H NMR (500 MHz, d^6- DMSO): δ = 2.84 (s, 3H, OCH_3 ester), 3.67 (s, 3H, OCH_3-phenyl), 7.50-7.73 (m, 19H, arom-H), 11.98 (s, NH, exchangeable with D_2O). ^{13}C NMR (125 MHz, d^6-DMSO): δ = 189.5 (C = S), 168.1 (C = O), 156.5 (C = P), 113.9, 125.6, 127.8, 128.5, 129.1, 129.2, 131.9, 132.3, 133.0, 133.1 (arom-C), 55.7 (OCH_3-phenyl), 50.1 (OCH_3, ester). ^{31}P NMR (200 MHz, d^6-DMSO): δ = 12.4. MS (EI, 70 eV): *m/z (%)* 333 [M^+-($CSNHC_6H_4OOCH_3$), 28], 294 [(TPPS), 17], 278 [(TPPO), 32], 262 [(TPP), 10]. Anal. Calcd. for $C_{29}H_{26}NO_3PS$ (499.56): C, 69.72; H, 5.25; N, 2.80; P, 6.20; S, 6.42. Found: C, 69.61; H, 5.13; N, 2.69; P, 6.11; S, 6.36%.

(4-Methoxyphenylthiocarbamoyl)-(triphenyl-λ^5-phosphanylidene)acetic Acid Ethyl Ester (13b)

Isolated from column chromatography using petrol ether (60-80 °C)/ethyl acetate (80:20, v/v) as an eluent, white crystals, yield 70%, m.p. 159--161 °C. IR (KBr, cm^{-1}): ν =3480 (NH), 1630 (C = O, ester), 1242 (C = S). ^{1}H NMR (500 MHz, d^6-DMSO): δ = 0.38 (m, 3H, $\underline{CH_3}$-CH_2), 3.66 (s, 3H, OCH_3), 4.06 (m, 2H, CH_3-$\underline{CH_2}$), 6.78-7.51 (19H, arom-H), 12.07 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (125 MHz, d^6-DMSO): δ = 189.5 (C = S), 168.1 (C = O), 156.6 (C = P), 113.9, 125.6, 129.1, 129.2, 132.8, 132.9 (arom-C), 59.0 (CH_3-$\underline{CH_2}$), 55.7 (OCH_3), 13.7 ($\underline{CH_3}$-CH_2).^{31}P NMR (200 MHz, d^6-DMSO): δ = 11.8. MS (EI, 70 eV): *m/z (%)* 511 [M^{-2}, 5], 294 [(TPPS), 100], 278 [(TPPO), 10], 262 [(TPP), 20], 165 [M^+-Ph_3P = $CHCOOC_2H_5$, 45]. Anal.

Calcd. for $C_{30}H_{28}NO_3PS$ (513.59): C, 70.16; H, 5.50; N, 2.73; P, 6.03; S, 6.24. Found: C, 70.05; H, 5.40; N, 2.64; P, 5.97; S, 6.13%.

N-(4-Methoxyphenyl)-3-oxo-2-(triphenyl-λ^5-phosphanylidene)thiobutyramide (13c)

Isolated from column chromatography using petrol ether (60-80 °C)/ethyl acetate (58:42, *v/v*) as an eluent, white crystals, yield 75%, m.p. 140--142 °C. IR (KBr, cm^{-1}): ν =3480 (NH), 1638 (C = O), 1248 (C = S). ^{1}H NMR (500 MHz, d^6-DMSO): δ = 1.38 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3-Ph), 6.78-7.85 (19H, arom-H), 13.75 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (125 MHz, d^6-DMSO): δ = 191.6 (C = S), 168.1 (C = O), 156.8 (C = P), 113.6, 128.9, 129.0, 131.7, 133.1, 133.2 (arom-C), 55.5 (OCH_3-Ph), 31.0 (OCH_3). MS (EI, 70 eV): *m/z (%)* 294 [(TPPS), 51], 278 [(TPPO), 41], 262 [(TPP), 8]. Anal. Calcd. for $C_{29}H_{26}NO_2PS$ (483.56): C, 72.03; H, 5.42; N, 2.90; P, 6.41; S, 6.63. Found: C, 71.94; H, 5.30; N, 2.81; P, 6.32; S, 6.53%.

Reaction of Methylisothiocyanate (5) with Methoxycarbonyl- (11a), Ethoxy-carbonyl-(11b) and Acetyl-methylenetriphenylphosphorane (11c). General Procedure.

To a solution of **5** (0.146 g,0.002 mol) in 20 mL of dry THF was added a solution of **11a** (1.002 g, 0.003 mol) or **11b** (1.044 g, 0.03 mol) or **11c** (0.954 g, 0.003 mol) in 30 mL of dry THF. The reaction mixture was refluxed for 24 h in case of **11a** or **11b** and stirred for 6 h in case of **11c**. The solvent was distilled off under reduced pressure, and the residue was crystallized to give **15a, b** and **15c**, respectively.

Methyl Thiocarbamoyl)-(triphenyl-λ^5-phosphanylidene)acetic Acid Methyl Ester (15a)

Isolated from column chromatography using petrol ether (60-80 °C)/ethyl acetate (85:15, *v/v*) as an eluent, white crystals, yield 85%, m.p. 181--183 °C. IR (KBr, cm^{-1}): ν =3480 (NH), 1636 (C = O, ester), 1294 (C = S). ^{1}H NMR (500 MHz, d^6-DMSO): δ = 2.59 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 7.25-8.55 (15H, arom-H),12.06 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (125 MHz, d^6-DMSO): δ = 191.5 (C = S), 169.3 (C = O), 128.3, 128.4, 133.0, 133.1 (arom-C), 49.5 (OCH_3), 31.5 (CH_3). ^{31}P NMR (200 MHz, d^6-DMSO): δ = 12.3. MS (EI, 70 eV): *m/z (%)* 407 [M^+, 37], 374 [M^{-2}-(OCH_3), 100], 348 [M^{-2}-$COOCH_3$, 6], 294 [TPPS, 26], 262 [TPP, 22]. Anal.

Calcd. for $C_{23}H_{22}NO_2PS$ (407.47): C, 67.80; H, 5.44; N, 3.44; P, 7.60; S, 7.87. Found: C, 67.71; H, 5.32; N, 3.33; P, 7.51; S, 7.75%.

***X-Ray crystallography analysis of* 15a**

Single crystals of compound **15a** were grown by slow solvent evaporation of the solvent. A suitable crystal was selected, checked and mounted on top of a thin glass fiber. The X-ray single crystal diffraction data were collected at room temperature (298 K) with an Enraf-Nonius 590 diffractometer with a Kappa CCD detector using graphite monochromated Mo-Kα (λ = 0.71073Å) radiation, at the National Research Centre of Egypt (Table 2). Crystallographic data (excluding structure factors) for the structure of **15a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1532653.

(Methythiocarbamoyl)-(triphenyl-λ^5-phosphanylidene)acetic Acid Ethyl Ester (15b).

Isolated from column chromatography using petrol ether (60-80 °C)/ethyl acetate (88:12, *v/v*) as an eluent, white crystals, yield 60%, m.p. 159--161 °C. ^{1}H NMR (500 MHz, d^6-DMSO): δ = 1.16 (s, 3H, CH_3), 2.59 (m, 3H, $\underline{CH_3}$-CH_2), 4.10 (m, 2H, CH_3-$\underline{CH_2}$), 7.60-8.47 (m, 15H, arom-H),12.05 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (125 MHz, d^6-DMSO): δ = 191.6 (C = S), 169.1 (C = O), 128.3, 128.4, 132.9, 133.0 (arom-C), 58.6 (CH_3-$\underline{CH_2}$), 31.4 ($\underline{CH_3}$-CH_2), 13.6 (CH_3). MS (EI, 70 eV): *m/z (%)* 421 [M^+, 45], 376 [M^+-(OC_2H_5), 35], 294 [(TPPS), 20], 262 [(TPP), 11]. Anal. Calcd. for $C_{24}H_{24}NO_2PS$ (421.49): C, 68.39; H, 5.74; N, 3.32; P, 7.35; S, 7.61. Found: C, 68.30; H, 5.65; N, 3.24; P, 7.26; S, 7.52%.

N-Methyl-3-oxo-2-(triphenyl-λ^5-phosphanylidene)thiobutyramide (15c)

Isolated from column chromatography using petrol ether 60--80 °C/ethyl acetate (65:35, *v/v*) as an eluent, yellow crystals, yield 75%, m.p. 40--42 °C. IR (KBr, cm^{-1}): ν =3480 (NH), 1670 (C = O, ester). ^{1}H NMR (500 MHz, d^6-DMSO): δ = 1.27 (s, 3H, CH_3), 2.80 (s, 3H, OCH_3), 5.00 (s, 1H, NH, exchangeable with D_2O), 7.41-7.61 (m, 15H, arom-H), ^{13}C NMR (125 MHz, d^6-DMSO): δ = 174.0 (C = S), 167.9 (C = O), 128.6, 128.7, 132.1, 132.2 (arom-C), 38.8 (OCH_3), 14.1 (CH_3). MS (EI, 70 eV): *m/z (%)* 374 [M^{-2}-CH_3, 13], 294 [(TPPS), 10], 278 [(TPPO), 100],

262 [(TPP), 30]. Anal. Calcd. for $C_{23}H_{22}NOPS$ (391.47): C, 70.57; H, 5.66; N, 3.58; P, 7.91; S, 8.19. Found: C, 70.46; H, 5.56; N, 3.50; P, 7.81; S, 8.10%.

Reaction of 3,4 Dichlorophenylisocyanate (8) with Methoxycarbonyl- (11a), Ethoxycarbonyl- (11b), and Acetyl-methylenetriphenylphosphorane (11c). General Procedure

To a solution of **8** (0.73 g, 0.002 mol) in 20 mL of dry THF was added a solution of **11a** (1.002 g, 0.003 mol) or **11b** (1.044 g, 0.003 mol) or **11c** (0.954 g, 0.003 mol) in 30 mL of dry THF. The reaction mixture was refluxed for 9 h in case of **11a** or **11b** and for 20 h in case of **11c** (TLC). The solvent was distilled off under reduced pressure and the residue was crystallized to give compounds **16a-c**. In case of using the phosphorane **11c** the urea derivative **17** was isolated together with **16c** (m.p. and mixed m.p. 277--279 °C).

N-(3,4-Dichlorophenyl)-2-(triphenyl-λ^5-phosphanylidene)malonamic Acid Methyl Ester (16a)

Crystallized from petrol ether (60-80 °C), white crystals, yield 90%, m.p. 192--194 °C. IR (KBr, cm^{-1}): ν = 3435 (NH), 1642 (C = O, ester), 1613 (C = O, amide). ^{1}H NMR (500 MHz, d^6-DMSO): δ = 3.03 (s, 3H, OCH_3), 7.47-7.76 (m, 18H, arom-H), 11.06 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (125 MHz, d^6-DMSO): δ = 170.6 (C = O, ester), 168.1 (C = O, amide), 140.0 (C = P), 118.7, 120.8, 127.1, 128.6, 128.7, 130.0, 132.0, 132.2, 133.4, 133.5 (arom- C), 49.7 (CH_3). MS (EI, 70 eV): *m/z (%)* 524 [M^{+2}, 5], 278 [(TPPO), 40], 262 [(TPP), 15]. Anal. Calcd. for $C_{28}H_{22}Cl_2NO_3P$ (522.36): C, 64.38; H, 4.25; Cl, 13.57; N, 2.68; P, 5.93. Found: C, 64.30; H, 4.16; Cl, 13.50; N, 2.57; P, 5.83%.

N-(3,4-Dichlorophenyl)-2-(triphenyl-λ^5-phosphanylidene)malonamic acid ethyl ester (16b)

Crystallized from petrol ether (60-80 °C), white crystals, yield 80%, m.p. 131--133 °C. IR (KBr, cm^{-1}): ν = 3449 (NH), 1639 (C = O, ester), 1605 (C = O, amide). ^{1}H NMR (500 MHz, d^6-DMSO): δ = 0.38 (m, 3H, $\underline{CH_3}$-CH_2), 3.56 (m, 2H, CH_3-$\underline{CH_2}$), 7.36-7.65 (m, 18H, arom-H), 11.13 (s, 1H, NH, exchangeable with D_2O), ^{13}C NMR (125 MHz, d^6-DMSO): δ = 170.0 (C = O, ester), 167.8 (C = O, amide), 140.5 (C = P), 119.1, 119.6, 120.1, 123.2, 126.4, 127.1, 128.5, 129.3, 130.9, 131.4, 132.0, 132.6, 133.4 (arom-C), 58.6 (CH_3-$\underline{CH_2}$), 13.8 ($\underline{CH_3}$-CH_2). MS (EI, 70

eV): *m/z (%)* 538 [M^{+2}, 5], 278 [(TPPO), 85], 262 [(TPP), 10]. Anal. Calcd. for $C_{29}H_{24}Cl_2NO_3P$ (536.39): C, 64.94; H, 4.51; Cl, 13.22; N, 2.61; P, 5.77. Found: C, 64.83; H, 4.42; Cl, 13.13; N, 2.50; P, 5.64%.

N-(3,4-Dichlorophenyl)-3-oxo-3-phenyl-2-(triphenyl-λ^5-phosphanylidene) butyramide (16c)

Isolated from column chromatography using petrol ether (60-80 °C)/ethyl acetate (75:25, *v/v*) as eluent, white crystals, yield 80%, m.p. 146--148 °C. ^{1}H NMR (500 MHz, d^6-DMSO): δ = 1.41 (s, 3H, OCH_3),7.16-7.75 (m, 18H, arom-H), 12.65 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (125 MHz, d^6-DMSO): δ = 192.1 (C = O, ester), 168.5 (C = O, amide), 140.0 (C = P), 129.0, 129.1, 129.2, 129.3, 132.1, 132.5, 133.4, 133.5, 133.6 (arom-C), 29.8 (CH_3). MS (EI, 70 eV): *m/z (%)* 504 [M^{-2}, 5], 278 [(TPPO), 85], 262 [(TPP), 5]. Anal. Calcd. for $C_{28}H_{22}Cl_2NO_2P$ (506.36): C, 66.42; H, 4.38; Cl, 14.00; N, 2.77; P, 6.12. Found: C, 66.31; H, 4.29; Cl, 13.91; N, 2.65; P, 6.00%.

Conclusion

The synthesis of new heterocyclic compounds containing sulfur, nitrogen and thiocarbamoyl moieties exemplify an interesting method for the reaction of isothiocyanate and isocyanate compounds with active phosphacumulenes and stable phosphonium ylides. In case of using active phosphacumulenes cycloaddition reactions took place and the reaction products depend on the type of the reagent, substrate and the conditions of the reaction used. If the reaction is performed between the isothiocyanate **1** or isocyanate **8** and the phosphacumulenes **2a**,**b**, then 1,4-cyclization of the intermediates **3**,**9** proceeds quickly with the formation of the four membered ring compounds **4a**,**b** and **10a**,**b** respectively. On the other hand, the isothiocyanate **5** reacts with **2a**,**b** to give the dipolar intermediates **6a**,**b** and by [4+2]-cycloaddition with a second molecule of the isothiocyanate **5** to form the six membered compounds **7a**,**b**. Moreover, a difference in the nucleophilic character of phosphorus reagents was observed: phosphacumulenes > phosphonium ylides. While the phosphacumulenes react smoothly with the reactants, the stable phosphonium ylides react less rapidly to give the phosphoranylidene thiocarbamoyl derivatives

13, **15** and **16**. This process can be considered as a simple and efficient route for the formation of new phosphanylidene-thietane, -azetidine, -thiazinanes and thiocarbamoyl compounds.

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Table 1. Details of data collection and structure refinement of compound **4a**.

Chemical formula	$C_{28}H_{22}NO_2PS$
Molecular mass	467.53
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	298
a, b, c (Å)	8.7939 (5), 15.0079 (9), 17.571 (2)
β (°)	93.709 (2)
V (Å^3)	2314.1 (3)
Z	4
Radiation type	Mo-$K\alpha$
μ (mm^{-1})	0.24
Data collection	
Diffractometer	Nonius Kappa CCD
T_{min}, T_{max}	0.824, 0.990
No. of measured, independent and observed [$I \geq 2\sigma(I)$] reflections	6691, 6472, 1200
R_{int}	0.183
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.704
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.155, 0.396, 0.96
No. of reflections	6472
No. of parameters	298
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	1.03, −0.42

Table 2. Details for data collection and structure refinement of compound **15a**.

Chemical formula	$C_{46}H_{44}N_2O_4P_2S_2$
Molecular mass	814.95
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	298
a, *b*, *c* (Å)	10.0747 (2), 12.6518 (2), 17.7068 (4)
α, β, γ (°)	106.0305 (10), 95.7145 (11), 101.8313 (7)
V (Å^3)	2093.65 (5)
Z	2
Radiation type	Mo-*K*α
μ (mm^{-1})	0.25
Data collection	
Diffractometer	Nonius Kappa-CCD
T_{min}, T_{max}	1.00, 1.00
No. of measured, independent and observed [$I \geq 2.0\sigma(I)$] reflections	35969, 18117, 6678
R_{int}	0.065
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.807
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.060, 0.115, 0.90
No. of reflections	6678
No. of parameters	511
No. of restraints	6
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.51, −0.39

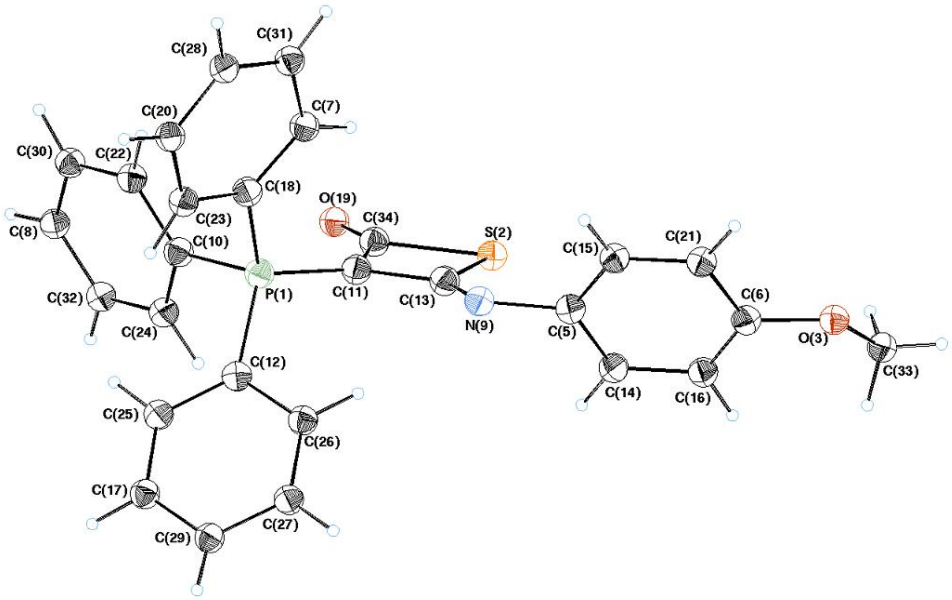


Figure 1. ORTEP view of the molecular structure of **4a** in the crystal showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

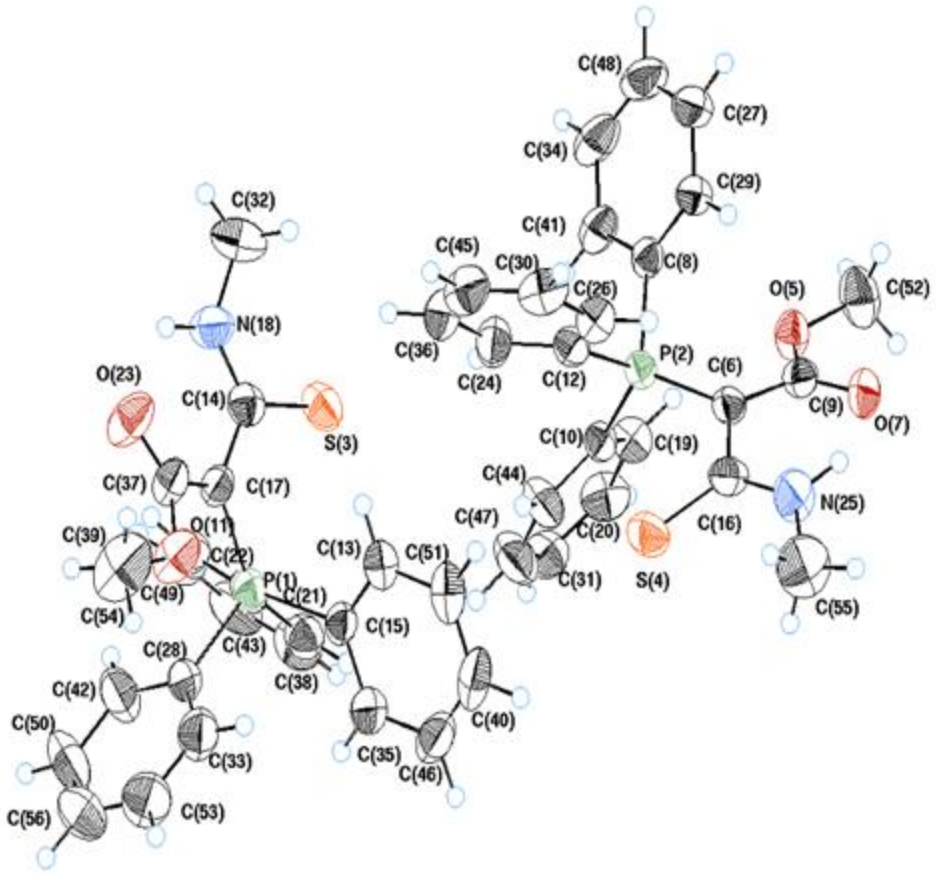
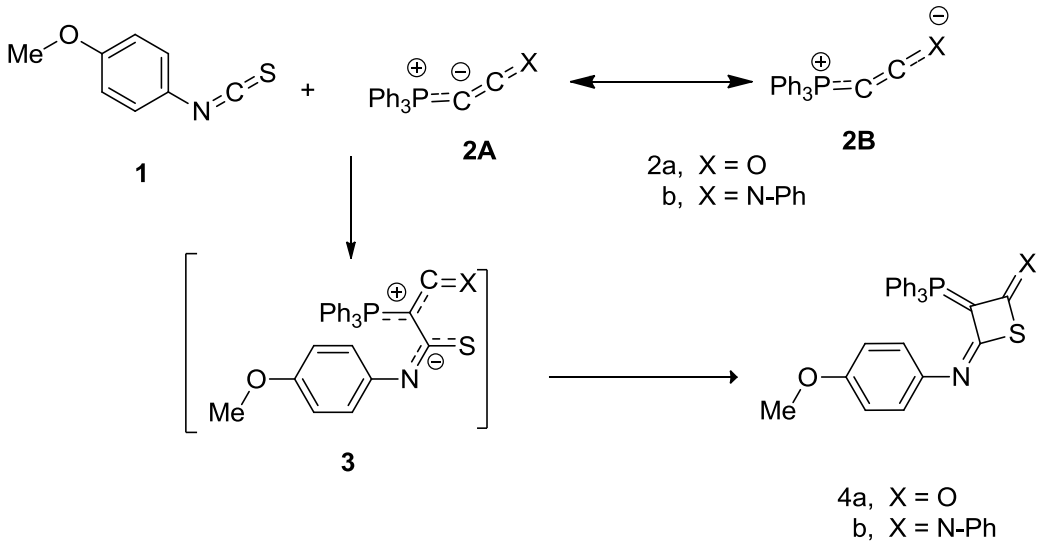
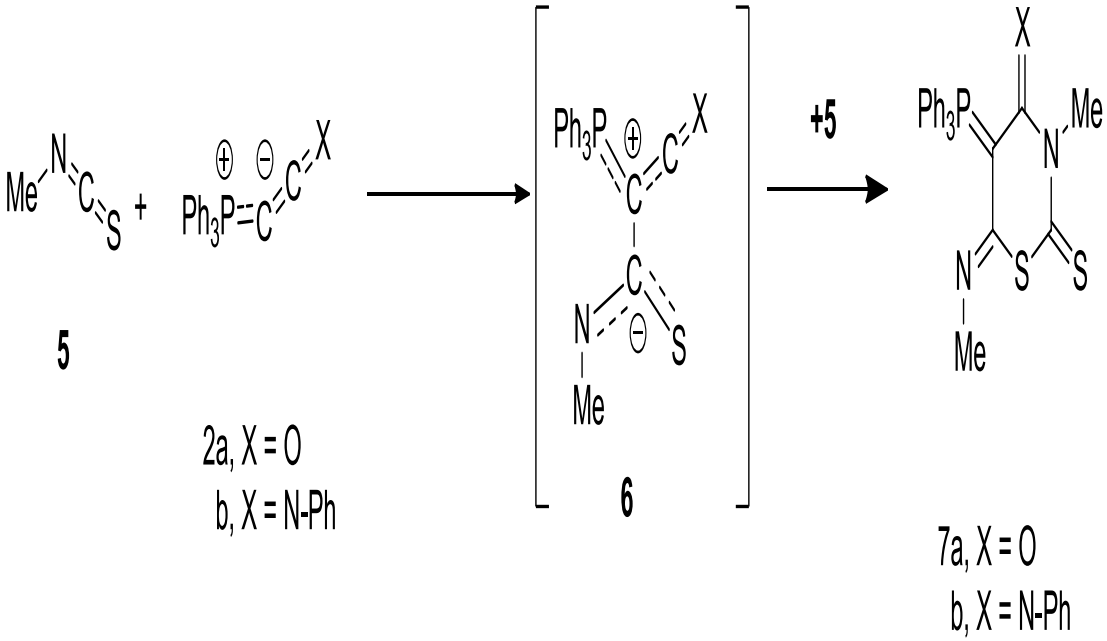


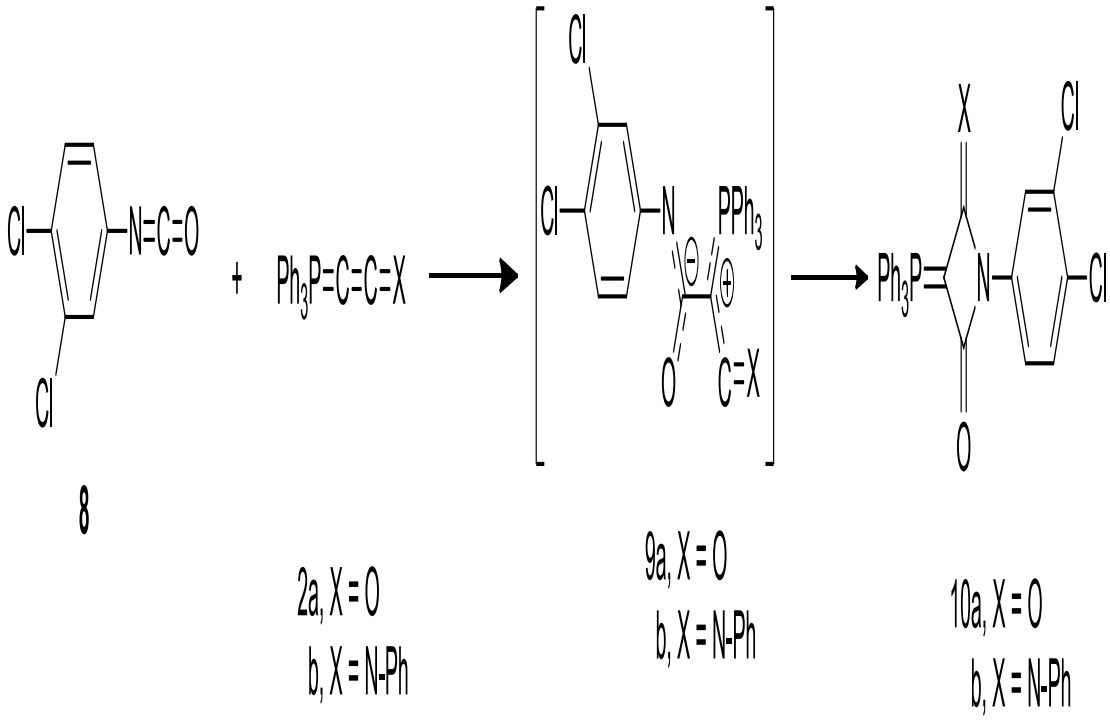
Figure 2. ORTEP view of the molecular structure of **15a** in the crystal, showing the atom numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.



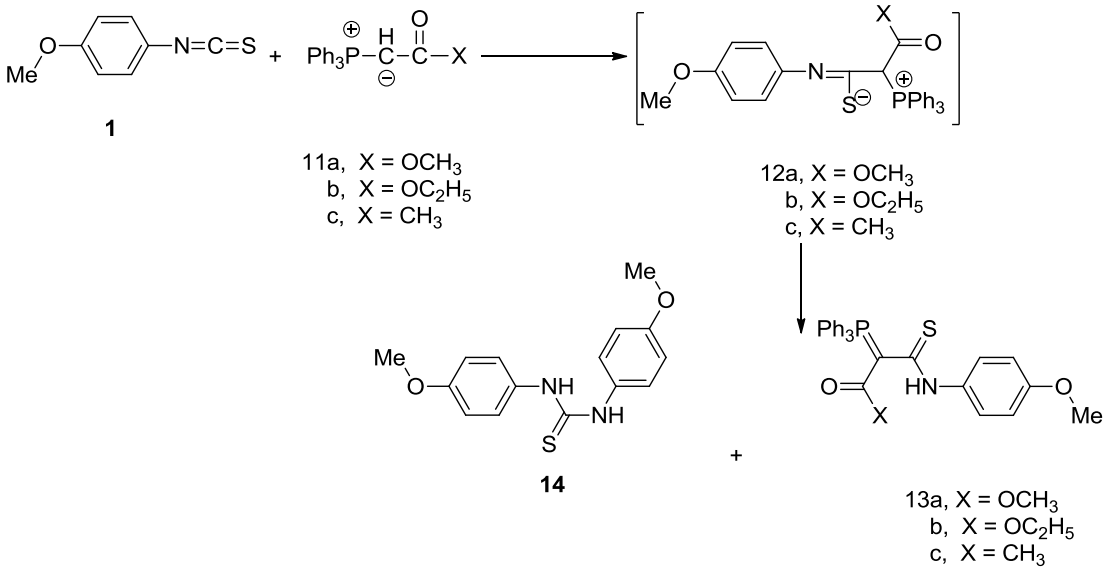
Scheme 1. Synthesis of compounds **4**.



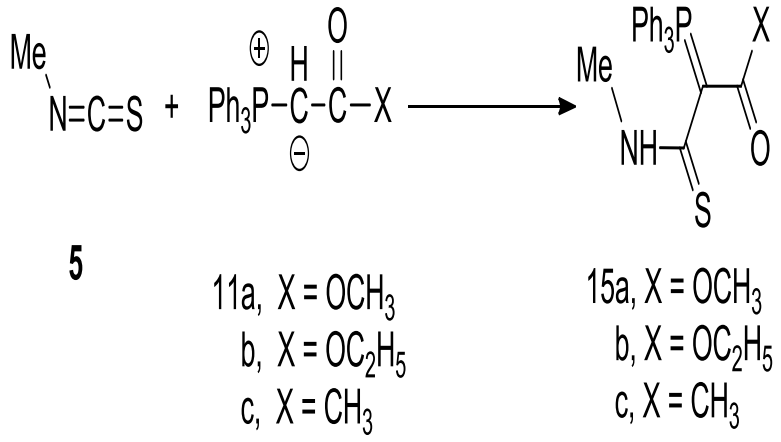
Scheme 2. Synthesis of compounds **7**.



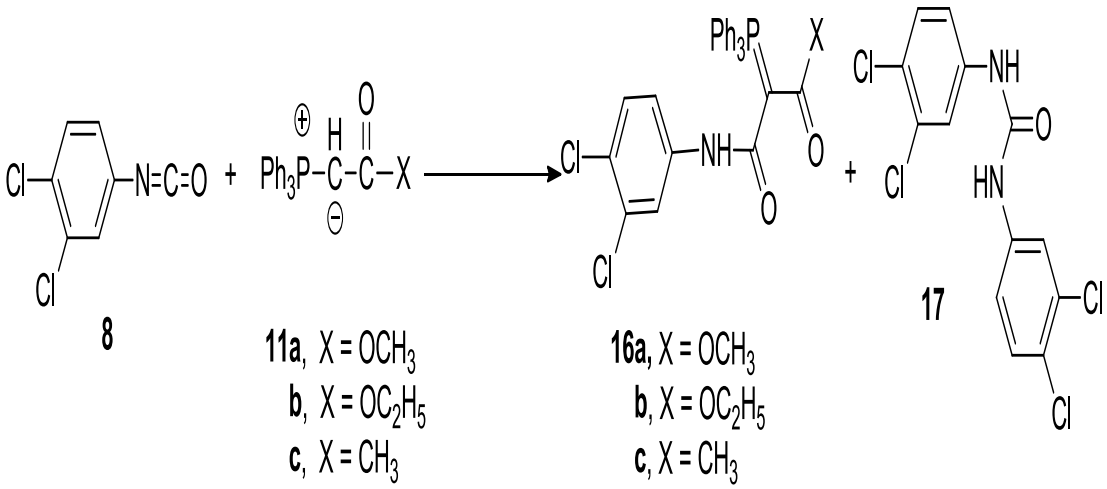
Scheme 3. Synthesis of compounds **10**.



Scheme 4. Synthesis of compounds **13**.



Scheme 5. Synthesis of compounds **15**.



Scheme 6. Synthesis of compounds **16**.