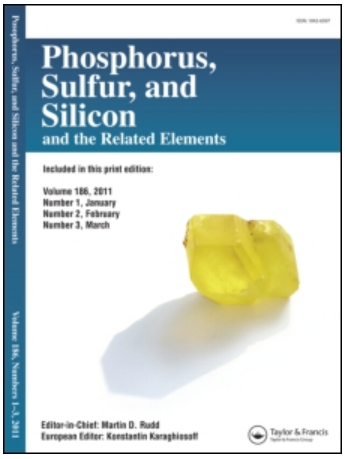

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STUDIES ON PHOSPHONIUM YLIDES-XXII. THE BEHAVIOR OF 3,4-DIPHENYL-5-CYANOPYRIDAZINE-6-THIONE TOWARD PHOSPHORUS YLIDES. NEW SYNTHESIS OF FUROPYRIDAZINE DERIVATIVES

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STUDIES ON PHOSPHONIUM YLIDES-XXII. THE BEHAVIOR OF 3,4-DIPHENYL-5-CYANOPYRIDAZINE-6-THIONE TOWARD PHOSPHORUS YLIDES. NEW SYNTHESIS OF FUROPYRIDAZINE DERIVATIVES

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3,4-Diphenyl-5-cyanopyridazine-6-thione ***(1)*** *reacts with carbethoxymethylene and carbmethoxymethylene-triphenylphosphoranes* ***(2a,b)*** *to give both the olefinic compounds* ***(3a,b)*** *and 3,4-diphenyl-6-alkoxyfuro-[3,2-c]-pyridazines* ***(4a,b)*** *respectively. Treatment of* ***1*** *with phosphorus ylide* ***(2c)*** *afforded only the new furopyridazine* ***(4c)****. On the other hand, when* ***(1)*** *reacts with diphenylmethylenetriphenylphosphorane* ***(2d)****, adduct* ***(5)*** *was obtained together with triphenylphosphine. Moreover, application of reagent (****2e****) on* ***(1)*** *renders the new product 3,4-diphenyl-6-(phenylimino)-5-cyanopyridazine* ***(6)****. Mechanisms accounting for the formation of the new products are discussed and the probable structures of the products are presented based on analytical and spectroscopic data.*

Keywords: 6-Ylidene alkylacetate; furo[3,2-*c*]pyridazines; phosphonium ylides; pyridazines

Pyridazine and its thione derivatives have considerable biological and medicinal activities.[1,2] Some of pyridazine derivatives are also useful as anticancer agents,[3] fungicides,[4] bactericides,[5] and pesticides.[6] This, together with our continuing interest in the reactions of phosphonium ylides for the production of novel synthetically useful ylides and new heterocyclic systems,[7–12] led us to investigate the reaction of carbethoxymethylene- (**2a**), carbmethoxymethylene- (**2b**), tert-butoxycarbonylmethylene- (**2c**); diphenylmethylene- (**2d**) and N-phenylimino- (**2f**)-triphenylphosphoranes with 3,4-diphenyl-5-cyanopyridazine-6-thione (**1**) (Scheme 1).

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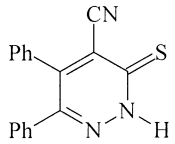


1

$Ph_3P{=}CR_1R_2$

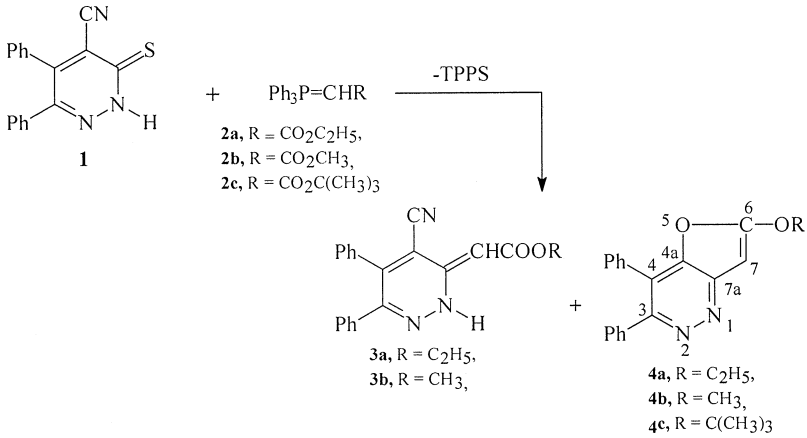
2a, $R_1 = H$; $R_2 = CO_2C_2H_5$,
2b, $R_1 = H$; $R_2 = CO_2CH_3$,
2c, $R_1 = H$; $R_2 = CO_2C(CH_3)_3$
2d, $R_1 = R_2 = Ph$

$Ph_3P{=}N{-}Ph$
2e

SCHEME 1

RESULTS AND DISCUSSION

We have found that the reaction of carbethoxymethylenetriphenylphosphorane (**2a**) with 2,3-dihydro-3-thioxo-5,6-diphenyl-4-pyridazinecarbonitrile **(1)** proceeds in refluxing toluene to give two chromatographically pure products assigned structures **3a** and **4a** respectively. Triphenylphosphine sulfide (TPPS) was also isolated from the reaction medium (Scheme 2).



1

$Ph_3P{=}CHR$ -TPPS

2a, $R = CO_2C_2H_5$,
2b, $R = CO_2CH_3$,
2c, $R = CO_2C(CH_3)_3$

3a, $R = C_2H_5$,
3b, $R = CH_3$,

4a, $R = C_2H_5$,
4b, $R = CH_3$,
4c, $R = C(CH_3)_3$

SCHEME 2

Structure elucidation of compound **3a** (20% yield) is based on the following evidence: The IR spectrum of **3a** disclosed the presence of strong absorption bands 1705 cm^{-1} (C=O, ester), 2200 (CN), 3240 (NH).[13] Moreover, the IR spectrum of **3a** lacks the thiocarbonyl absorption band (C=S) at 1175 cm^{-1}. The ^1H NMR spectrum of **3a** in $CDCl_3$ indicated the presence of signals at $\delta = 1.25$ (t, 3H, $COOCH_2C\underline{H}_3$), 4.29 (q, 2H, $COOC\underline{H}_2CH_3$), 5.09 (s, 1H, =C<u>H</u>COOEt), and at 7.19–7.45 (m,

10H, Ar-H). The NH proton gave singlet (exchangeable with D_2O) at $\delta = 7.78$ ppm[14]. The mass spectrum of compound **3a** gives a prominent ion peak at m/z 343 (M^+, 90%).

The second product (60% yield) was assigned as 3,4-diphenyl-6-ethoxyfuro[3,2-*c*]pyridazine (**4a**) based on elemental analysis and spectroscopic evidences: (a) elemental analysis and molecular weight determination (MS) for compound **4a** corresponds to $C_{20}H_{16}N_2O_2$; (b) the main features of the IR spectrum of **4a** (in KBr) reveals the absence of CN, (C=O, ester) and NH absorption bands recorded at 2200, 1705, and at 3240 cm^{-1}, respectively, in the spectrum of the pyridazine **1**. The ^1H NMR spectrum of **4a**, in $CDCl_3$ discloses the presence of signals at $\delta = 1.58$ (t, 3H, ethoxy-CH_3), 4.81 (q, 2H, OCH_2) and at 7.01–7.42 ppm (m, 10H, Ar-H + 1H, =CH). Actually the ^{13}C NMR spectrum afforded strong evidence of the furopyridazine structure **4a**. ^{13}C NMR of compound **4a** (in $CDCl_3$) shows signals at $\delta = 132.82$ (C-3), 143.08 (C-4), 149.18 (C-4a), 150.55 (C-6), 132.41 (C-7), 143.48 (C-7a), 55.52 ($O\underline{C}H_2$), and at 11.26 ppm ($OCH_2\underline{C}H_3$) respectively.[15] The aromatic carbons appeared as six signals at 128.53, 129.09, 129.21, 129.30, 129.78, 130.70 ppm. (cf. Scheme 2). The mass spectrum of **4a** contains a prominent peak for M^+ at 316 (100%) which supports the furopyridazine derivative **4a**.

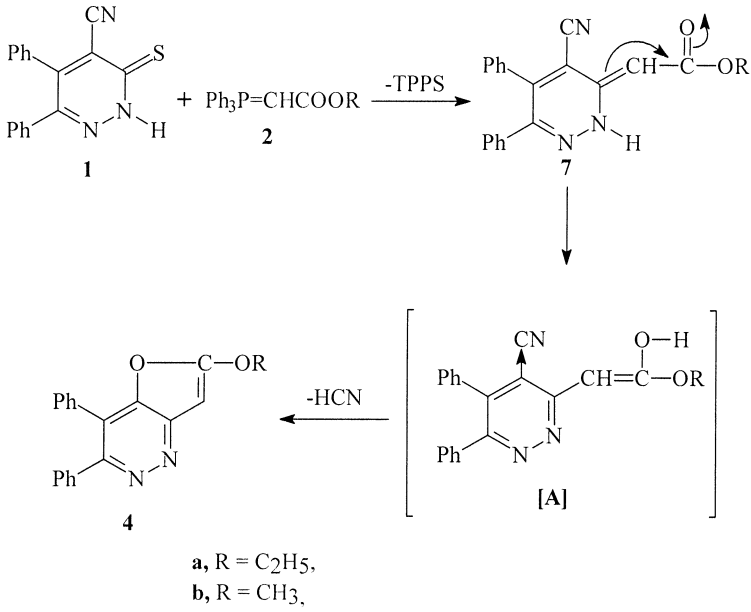
Similary carbmethoxymethylenetriphenylphosphorane **2b** reacts with pyridazine **1**, in refluxing toluene, to give 3,4-diphenyl-6-ylidenemethyl acetate (**3b**) (15% yield) and 3,4-diphenyl-6-methoxy-furo[3,2-*c*]pyridazine **4b** (65% yield). Triphenylphosphine sulfide was also isolated from the reaction mixture.

Structures **3b** and **4b** were deduced from correct microanalysis, IR, ^1H NMR, and mass spectral data. (cf. Experimental, Scheme 2).

A possible explanation of the course of the reaction of phosphonium ylides **2a-b** with pyridazine derivative **1** is shown in Scheme 3. Stabilized ylides **2a-b** react with 5,6-diphenyl-4-cyanopyridazine-3(2H)-thione **(1)** according to the Wittig mechanism, [16,17] yielding the respective ethylene products **3** and triphenylphosphine sulfide.

The mechanism for the formation of adducts **4a,b** is most likely takes place by an addition (to the double bond)-elimination (of the cyanide ion) sequence followed by intramolecular cyclization to afford the fused furopyridazine derivatives (Scheme 3).

We have found that 5,6-diphenyl-4-cyanopyridazine-3(2H)-thione **(1)** reacts with an equimolar amount of tert-butoxycarbonylmethylenetriphenylphosphorane (**2c**) to give compound **4c** in 85% yield along with triphenylphosphine sulfide. Structure elucidation of product **4c** has been determined on the basis of IR, ^1H NMR, MS and elemental analyses (cf. Experimental, Scheme 2).



a, R = C_2H_5,
b, R = CH_3,

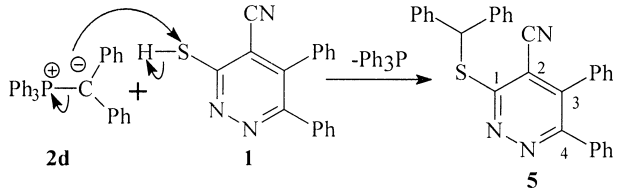
SCHEME 3

5,6-Diphenyl-4-cyanopyridazine-3(2H)-thione**(1)** was found to react with 1 mmol equivalent of freshly prepared diphenylmethylenetriphenylphosphorane (**2d**) in refluxing toluene, yielding a colored product assigned structure **5**. Triphenylphosphine was also isolated from the reaction in quantitative yield. Compound **5** is a chromatographically pure yellow crystalline material with a sharp melting point.

Structure elucidation of the new product is based on the following evidence. The IR spectrum of compound **5** lacks both the NH and C=S absorption bands appearing in the spectrum of **1** at 3240, 1175 cm^{-1}, respectively. Moreover, the IR spectrum of **5** disclosed the presence of strong absorption band at 2200 cm^{-1} (CN) and at 1640 cm^{-1} (C=N). The ^1H NMR spectrum of **5** shows signals at $\delta = 6.87$ (1H, s, S-C<u>H</u>$(Ph)_2$), and at 7.18-7.58 (20H, m, four phenyl groups).

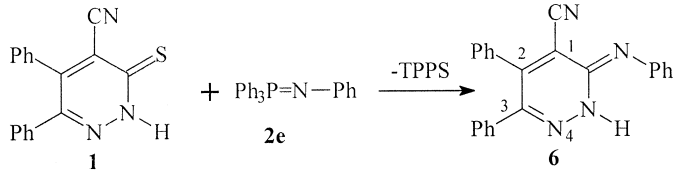
The structure assigned for compound **5** was based on the ^{13}C NMR spectrum which has signals at $\delta = 53.25$ corresponding to the S-<u>C</u>H$(Ph)_2$ group, 113.38 (C≡N), 160.48 (C-1), 111.38 (C-2), 141.40 (C-3), 157.02 (C-4), 127.87, 128.42, 128.85, 128.86, 128.91, 129.14, 129.40, 129.50, 129.97, 130.35, 132.56, 132.36, 140.40 (aromatic carbons). The mass spectrum of **5** showed ion peak at m/z = 455 [M^+, 60%], 167 [CH$(Ph)_2$, 100%].

A possible explanation for the formation of product **5** illustrated in Scheme 4. The mechanism likely occurs via protonation of the ylide (by the S-H proton), followed by reaction of the nucleophilic sulfur center at the electrophilic carbon of the phosphonium salt.



SCHEME 4

In addition, this study has been extended to include the reaction of **1** with N-phenyliminotriphenylphosphorane (**2e**). When 5,6-diphenyl-4-cyanopyridazine-3(2H)-thione **1** was treated with one equivalent of N-phenyliminotriphenylphosphorane (**2e**) in refluxing toluene for 6 h, 3,4-diphenyl-6-(phenylimino)-5-cyanopyridazine **(6)** and triphenylphosphine sulfide were isolated (Scheme 5).



SCHEME 5

Compound **6** (85%) is chromatographically pure colored crystals and possesses a sharp melting point. The identity of product **6** was supported by compatible analytical and mass spectroscopic results (cf. Experimental). Adduct **6** can be possibly obtained via addition of phosphinimine **2e** to the pyridazine **(1)** followed by loss of triphenylphosphine sulfide (Scheme 5).

CONCLUSION

The findings of the present investigation are of particular interest since they represent a novel application of the Wittig reaction. Moreover, a new method for the preparation of 3,4-diphenyl-6-alkoxyfuro[3,2-*c*]-pyridazine **(4a–c)** by the utilization of Wittig reagent **2a–c** is developed.

EXPERIMENTAL

All melting points are uncorrected. Pyridazine derivative **1**, and phosphorane compounds **2a–e** were prepared according to established procedures. The IR spectra were measured in KBr pellets with Perkin-Elmer Infrared Spectrophotometer Model 157 (Gerating). The ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ with a Varian Spectrometer at 270 and 67.5 MHz, respectively using TMS as internal references. The mass spectra were performed at 70 eV with a Kratos MS equipement and/or Varian MAT 311 A spectrometer.

Reaction of 2,3-Dihydro-5,6-diphenyl-3-thioxo-4-pyridazinecarbonitrile (1) with Carbethoxymethylenetriphenylphosphorane 2a

A mixture of pyridazine **1** (0.28 g, 0.001 mmol) and ylide **2a** (0.34 g, 0.001 mmol) in dry toluene (30 ml) was refluxed for 6 h. The volatile materials were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give two products, formulated as **3a** and **4a** respectively.

3,4-Diphenyl-6-carbethoxymethylene-5-cyanopyridazine (3a)

Eluent: acetone/petroleum ether (5:95, v:v). Product **(3a)** was separated as yellow crystals, yield (20%), m.p. 149–150°C. Anal. Calcd. for $C_{21}H_{17}N_3O_2$ (343.38): C, 73.45; H, 4.99; N, 12.23. Found: C, 73.40; H, 4.92; N, 12.20%. IR (KBr): 1705 (C=O, ester), 2200 (CN), 3240 cm^{-1} (NH) and lack the (C=S) band at 1175 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 1.25$ (t, 3H, $COOCH_2\underline{C}H_3$), 4.29 (q, 2H, $COO\underline{C}H_2CH_3$), 5.09 (s, 1H, $=\underline{C}HCOOEt$), 7.19–7.45 (m, 10H, Ar-H), 7.78 ppm (s, NH, exchangeable with D_2O). MS: m/z (%) 343 (90) [M^+].

3,4-Diphenyl-6-ethoxyfuro[3,2-c]pyridazine (4a)

Eluent: acetone/petroleum ether (7:93, v:v). **4a** was isolated as orange crystals, yield (60%), m.p. 184–185°C. Anal. Calcd. for $C_{20}H_{16}N_2O_2$ (316.36): C, 75.93; H, 5.09; N, 8.85. Found: C, 75.90; H, 5.12; N, 8.89%. IR (KBr): lack the bands of (C=O) at 1705 cm^{-1}, (CN) at 2200 cm^{-1} and (NH) at 3240 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 1.58$ (t, 3H, ethoxy-CH_3), 4.81 (q, 2H, OCH_2), 7.01–7.42 ppm (m, 10H, Ar-H, 1H =CH). ^{13}C-NMR ($CDCl_3$): 133.82 (C-3), 143.08 (C-4), 149.18 (C-4a), 150.55 (C-6), 132.41 (C-7), 143.48 (C-7a), 55.52 (OCH_2), 11.26 ($OCH_2\underline{C}H_3$), 128.53, 129.09, 129.21, 129.30, 129.78, 130.70 ppm (Ar-C). MS: m/z (%) 316 (100) [M^+].

Triphenylphosphine sulfide was also isolated and identified (mixed m.p. and comparative IR spectra).

Reaction of Pyridazine 1 and Carbmethoxymethylenetriphenylphosphorane (2b)

A mixture of pyridazine **1** (0.28 g, 0.001 mmol) and phosphorane **2b** (0.33 g, 0.001 mmol) in dry toluene (30 ml) was refluxed for 6 h. The volatile materials were evaporated under reduced pressure, and the residual substance was chromatographed on a silica gel column to give two products **3b** and **4b** respectively.

Product 3b

Eluent: acetone/petroleum ether (5:95, v:v). **3b** was isolated as yellow crystals, yield (15%), m.p. 171–172°C. Anal. Calcd. for $C_{20}H_{15}N_3O_2$ (329.35): C, 72.93; H, 4.59; N, 12.75. Found: C, 72.89; H, 4.64; N, 12.71%. IR (KBr): 1710 (C=O, ester), 2200 (CN), 3235 cm^{-1} (NH). ^1H NMR ($CDCl_3$): $\delta = 4.29$ (s, 3H, $COOCH_3$), 4.95 (s, 1H, =$CHCOOCH_3$), 7.79 (s, 1H, NH, exchangeable with D_2O), 7.13–7.42 ppm (m, 10H, Ar-H). MS: m/z (%) 329 (95) [M^+].

Furopyridazine Derivative (4b)

Eluent: acetone/petroleum ether (7:93, v:v). **4b** was separated as orange crystals, yield (65%), m.p. 232–233°C. Anal. Calcd. for $C_{19}H_{14}N_2O_2$ (302.33): C, 75.48; H, 4.66; N, 9.26. Found: C, 75.43; H, 4.70; N, 9.22%. IR (KBr): lack the bands of (C=O) at 1710 cm^{-1}, (CN) at 2200 cm^{-1} and (NH) at 3235 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 3.96$ (s, 3H, OCH_3), 7.1–7.53 ppm (m, 10H, Ar-H, 1H =CH). MS: m/z (%) 302 (95) [M^+].

Triphenylphosphine sulfide was also isolated and identified.

Similarly, the reaction of pyridazine **1** with tert-butoxycarbonylmethylenetriphenylphosphorane **(2c)** was performed with an equimolar ratio in a boiling toluene for 10 h to give product **4c** as orange crystals m.p., 98-99°C, yield (85%). Anal. Calcd. for $C_{22}H_{20}N_2O_2$ (344.41): C, 76.72; H, 5.85; N, 8.13. Found: C, 76.76; H, 5.87; N, 8.17%. IR (KBr): lack the bands of (C=O) at 1705 cm^{-1}, (CN) at 2200 cm^{-1} and (NH) at 3240 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.25$ (s, 9H, —$O(C\underline{H}_3)_3$), 7.14–7.81 ppm (m, 10H, Ar-H, 1H =CH). MS: m/z (%) 344 (95) [M^+].

Triphenylphosphine sulfide was also isolated and identified.

Reaction of Pyridazine 1 with Diphenylmethylenetriphenylphosphorane (2d)

To a solution of **1** (0.28 g, 0.001 mmol) in dry toluene (30 ml) was added (0.43 g, 0.001 mmol) of freshly prepared of ylide **2d**. The reaction was

refluxed for 10 h and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography using acetone/petroleum ether (10:90, v:v) as eluent to give adduct **5** as yellow crystals, yield (75%), m.p. 161–162°C. Anal. Calcd. for $C_{30}H_{21}N_3S$ (455.58): C, 79.09; H, 4.64; N, 9.22; S, 7.03. Found: C, 79.14; H, 4.67; N, 9.25; S, 7.07%. IR (KBr): 2200 cm^{-1} (CN), 1640 (C=N). ^1H NMR ($CDCl_3$): $\delta = 6.78$ (1H, s, S-C<u>H</u>(Ph_2), 7.18–7.58 ppm (m, 20H, four phenyl groups). ^{13}C-NMR ($CDCl_3$): 53.25 [S-<u>C</u>H($Ph)_2$], 113.38 (<u>C</u>N), 160.48, 157.02 [C-S-C], 141.40 ppm (C=N). MS: m/z (%) 455 (60) [M^+], 167 (100) [CH(Ph_2)].

Triphenylphosphine was also isolated and identified (mixed m.p. and comparative IR spectra).

Reaction of Pyridazine 1 with N-phenyliminophosphorane (2e)

A mixture of **1** (0.28 g, 0.001 mmol) and (0.35 g, 0.001 mmol) was refluxed in dry toluene (30 ml) for 6 h and the volatile materials were evaporated under reduced pressure. The residual substance was chromatographed on a silica gel using acetone/petroleum ether (10:90, v:v) as eluent to give adduct **6** as orange crystals, m.p. 175–176°C, yield (85%), Anal. Calcd. for $C_{23}H_{16}N_4$ (348.40): C, 79.28; H, 4.62; N, 16.08. Found: C, 79.24; H, 4.61; N, 16.11%. IR (KBr): 1590 cm^{-1} (C=N), 2200 (CN), 3342 cm^{-1} (NH). ^1H NMR ($CDCl_3$): $\delta = 7.07$–7.94 (m, 15H, Ar-H), 7.83 ppm (s, 1H, NH, exchangeable with D_2O). ^{13}C-NMR ($CDCl_3$): 154.60 (C-1), 108.53 (C-2), 141.80 (C-3), 166.30 (C-4), 114.5 ppm (CN).

Triphenylphosphine sulfide was also isolated and identified.

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