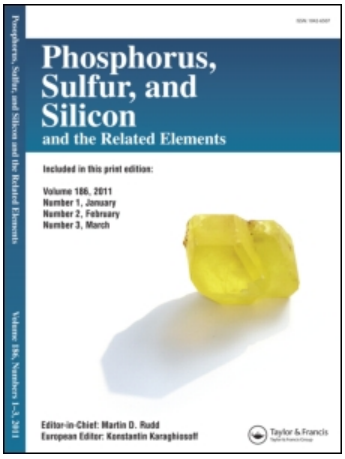

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Khalifa, Fathy A.(1991) 'BENZIL IN HETEROCYCLIC SYNTHESIS: SYNTHESIS AND REACTIONS OF 3, 4-DIPHENYL-5-CYANO-PYRIDAZINE-6-THIONE', Phosphorus, Sulfur, and Silicon and the Related Elements, 56: 1, 81 — 86
To link to this Article: DOI: 10.1080/10426509108038069
URL: http://dx.doi.org/10.1080/10426509108038069

Phosphorus, Sulfur, and Silicon, 1991, Vol. 56, pp. 81–86
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BENZIL IN HETEROCYCLIC SYNTHESIS: SYNTHESIS AND REACTIONS OF 3,4-DIPHENYL-5-CYANO-PYRIDAZINE-6-THIONE

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(Received June 11, 1990; in final form July 19, 1990)

3,4-Diphenyl-5-cyanopyridazine-6-thione (**7**) is prepared via three routes either by the reaction of benzil hydrazone (**1**) and cyanothioacetamide (**2**) or by the reaction of benzil (**3**) with cyanothioacetamide to give (**4**) which reacts with hydrazine hydrate to give the intermediate (**5**) that cyclised to (**7**) by boiling with glacial acetic acid or by the action of P_2S_5 on 3,4-diphenyl-5-cyanopyridazin-6-one[1] (**6**). Methylation of the SH group in (**7**) afforded (**8**) while its reaction with ethyl bromoacetate gave the pyridazine derivative (**9**). Treatment of (**8**) and (**9**) with hydrazine hydrate produced directly the pyrazolopyridazine derivative (**10**).[1] Treatment of (**9**) with NH_3/EtOH afforded the amidic derivative (**11**) while its treatment with dil. HCl gave 3,4-diphenyl-5-cyanopyridazin-6-one (**6**).[1] Treatment of (**9**) with NH_3/heat then acidification gave carboxylic derivative (**12**). Treatment of (**9**) with p-chloroaniline and p-toluidine gave p-chloroanilino and toluidino derivatives (**13 a,b**).

Key words: Pyridazine-6-thiones; synthesis, reactions IR and ^{1}H-NMR.

Pyridazine and its thione derivatives have considerable biological and medicinal activities.[2,3] As a part of a programe[4,5,6] directed to the synthesis of some pyridazine derivatives as anticancer agents,[7] fungicides[8] and bactericides,[9] I report here two novel syntheses of 3,4-diphenyl-5-cyanopyridazine-6-thione **7** together with its substitution reactions. Thus, it has been found that benzilhydrazone **1** reacted with cyanothioacetamide **2** in pyridine to yield 3,4-diphenyl-5-cyanopyridazine-6-thione **7**. The structure of **7** was confirmed by elemental analysis, IR and ^{1}H NMR spectra (cf. Tables I and II). The same compound **7** could be obtained by other two routes.

Compound **7** was obtained also by the action of phosphorus pentasulphide in pyridine on 3,4-diphenyl-5-cyanopyridazin-6-one[1] **6**. On the other hand, compound **7** was again obtained through the reaction of benzil **3** with cyanothioacetamide **2** which gave **4**. This reacted with hydrazine hydrate to give **5**. Compound **5** could then be cyclised using glacial acetic acid to yield **7**. Treatment of **7** with methyl iodide in sodium ethoxide gave the corresponding 3,4-diphenyl-5-cyano-6-S-methylpyridazine **8**. The structure of **8** was confirmed by elemental analysis, I.R. and ^{1}H NMR spectral data (cf. Tables I and II).

Treatment of **7** with ethyl bromoacetate in the presence of sodium ethoxide gave 3,4-diphenyl-5-cyano-6-(ethoxycarbonylmethylthio)pyridazine **9**. The IR spectrum of **9** showed the ester (C=O) band at 1740 cm^{-1}. Treatment of **8** and **9** with hydrazine hydrate in absolute ethanol gave one and the same product, the pyrazolopyridazine derivative **10**.

The structure of **10** was confirmed by elemental analysis, IR and ^{1}H NMR spectral data also by the preparation of an authentic sample.[1] However, treatment of **9** in absolute ethanol with an excess of ammonia at 0°C produced 3,4-diphenyl-

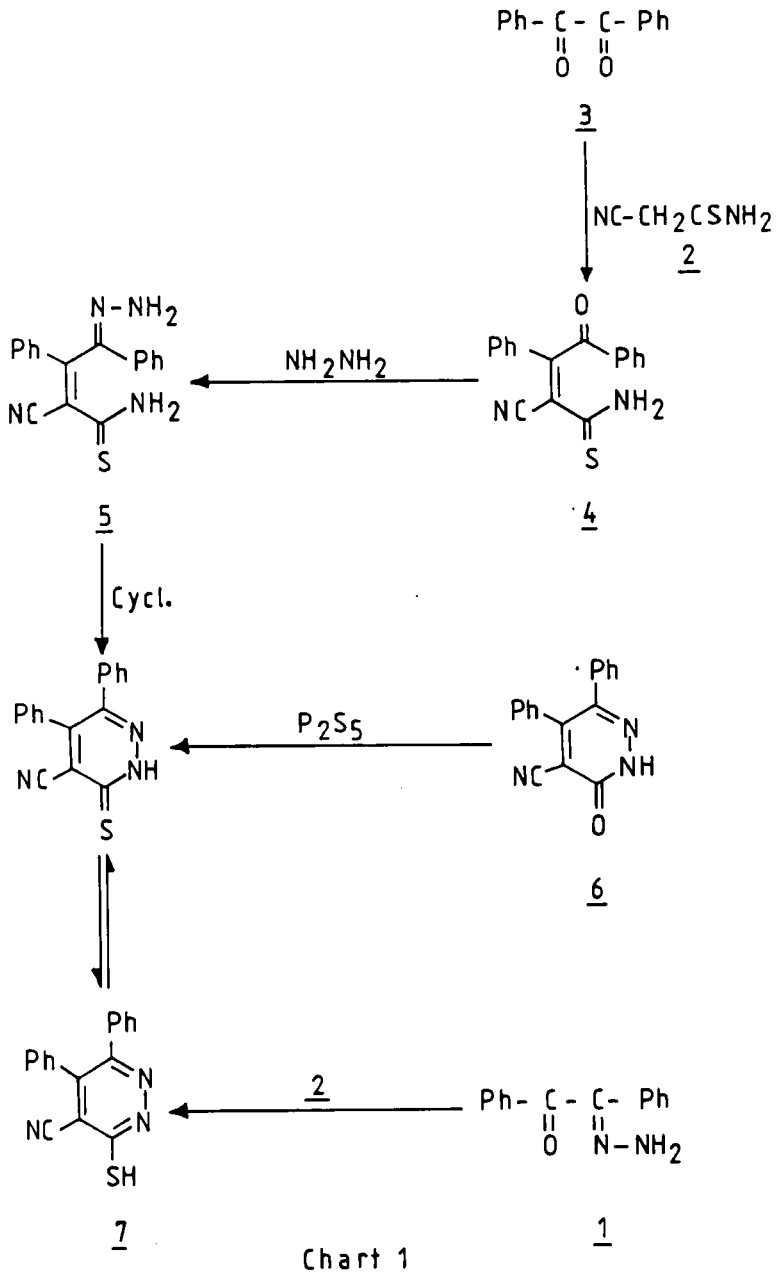

Chart 1

5-cyano-6-(carboxyamidomethylthio)-pyridazine **11**. The IR spectrum of **11** showed the presence of a (C=O) band at 1685 cm^{-1} and NH_2 bands at 3350 and 3180 cm^{-1}. Hydrolysis of **9** with hot ammonia then acidification afforded directly the corresponding 3,4-diphenyl-5-cyano-6-(hydroxycarbonylmethylthio)pyridazine **12**. The structure of **12** was confirmed by elemental analysis, IR and ^1H NMR spectral data (cf. Tables I and II). Treatment of **9** with p-chloroaniline and p-toluidine

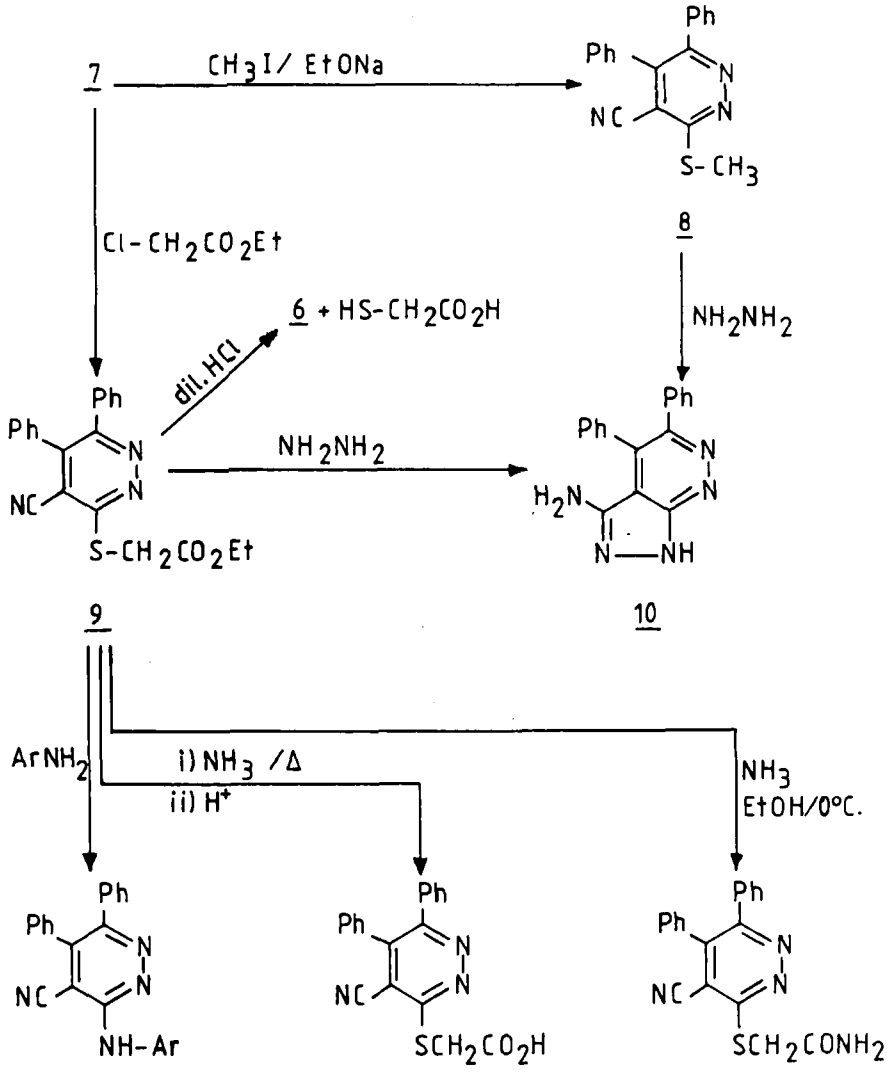

Chart 2

afforded p-chloroanilino and p-toluidino derivatives **13 a,b** respectively. The structure of **13 a,b** was confirmed by elemental analyses, IR and ^{1}H NMR.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a Pye-Unicam SP-1100 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed as (δ ppm). Elementary analyses were performed at the microanalytical centre of Cairo University.

TABLE I

List of compounds **4, 5, 8, 9, 11, 12, 13 a,b**

Compound	Solvent of crystallization	Colour	M.P. (°C)	Yield (%)	Mol. Formula	Analysis, % Calcd./Found C	H	N	S	Cl
4	ethanol	yellow	225	90	$C_{17}H_{12}N_2OS$	69.8	4.1	9.6	11.0	—
						69.8	4.2	9.8	10.8	—
5	ethanol	brown	285	80	$C_{17}H_{14}N_4S$	66.7	4.6	18.3	10.5	—
						66.4	4.5	18.5	10.6	—
8	ethanol	white	161	60	$C_{18}N_{13}N_3S$	71.3	4.3	13.9	10.6	—
						70.9	4.3	13.8	10.6	—
9	acetic acid	colourless	182	60	$C_{21}H_{17}N_3O_2S$	67.2	4.6	11.2	8.1	—
						67.0	4.5	11.4	8.2	—
11	ethanol	white	205	80	$C_{19}H_{14}N_4OS$	65.9	4.1	16.2	9.3	—
						65.8	4.0	16.0	9.4	—
12	acetic acid	white	235	85	$C_{19}H_{13}N_3O_2S$	65.7	3.8	12.1	9.2	—
						65.8	3.7	12.0	9.3	—
13a	benzene	yellow	165	80	$C_{23}H_{15}N_4Cl$	72.1	3.9	14.6	—	9.4
						72.2	4.0	14.3	—	9.2
13b	benzene	yellow	155	75	$C_{24}H_{18}N_4$	79.6	4.9	15.5	—	—
						79.5	4.8	15.3	—	—

Preparation of 3,4-diphenyl-5-cyanopyridazine-6-thione (**7**):

Route (a)

A mixture of benzilhydrazone (0.01 mol) and cyanothioacetamide (0.01 mol) in absolute ethanol (50 ml) was heated under reflux in the presence of two drops of piperidine for 5 h. The solution was cooled and poured onto ice-water. The solid separated was collected, washed with H_2O, dried and then crystallized from ethanol to give **7** as brown powder with m.p. > 300°C (cf. Table I).

Route (b)

(i) A mixture of benzil **3**, (0.01 mol) and cyanothioacetamide **2** (0.01 mol) in ethanol (30 ml) in the presence of piperidine (0.5 ml) was heated under reflux for 3 h. The solid obtained after cooling and pouring into ice-water was crystallized from ethanol to give **4** as pale yellow crystals with m.p. 225°C.

(ii) A solution of **4** (0.01 mol) and hydrazine hydrate (0.01 mol) was heated under reflux in absolute ethanol (30 ml) for 3 h. The reaction mixture was cooled and then poured onto ice-water. The solid so obtained was crystallized from ethanol to give 5 as pale brown crystals with m.p. 285°C.

(iii) A mixture of (0.01 mol) **5** and glacial acetic acid (20 ml) was heated under reflux for 2 h then cooled and poured onto ice-water. The solid obtained was crystallized from ethanol to give **7** as brown crystals with m.p. > 300°C.

Route (c)

3,4-Diphenyl-3-cyanopyridazin-6-one[1] (0.01 mol) was dissolved in xylene (100 ml)[9] and heated at 100°. Then finely powdered P_2S_5 (0.01 mol) was added with stirring, and the mixture was gently boiled under reflux for 4 h. The mixture was filtered while hot, allowed to cool, and filtered. The xylene was treated with sodium carbonate solution, washed with water, dried over sodium sulphate (anhydrous), concentrated and then treated with light petroleum (40–60°). The obtained product was crystallized from ethanol to give **7** as brown crystals with m.p. > 300°C.

Preparation of 3,4-diphenyl-5-cyano-(6-methylthio)pyridazine 8 and 3,4-diphenyl-5-cyano-6-(ethoxycarbonylmethylthio)pyridazine **9**:

General procedure:

A mixture of methyl iodide or ethyl bromoacetate (0.01 mol) was added dropwise to a stirred solution of sodium ethoxide (0.01 atom of sodium metal in 100 ml ethanol) and **7** (0.01 mol). After refluxing

TABLE II

IR and ^{1}H NMR data of compounds **4, 5, 8, 9, 11, 12, 13 a,b**

Compound	IR (KBr), cm^{-1}	^{1}H NMR (δ ppm)
4	3340–3280 (NH_2); 2220 (CN); 1650 (CO); 1540 (C=S).	7.62–7.90 (*m*, 10H, aromat.) 9.30 (*s*, br, 2H, NH_2).
5	3350–3280 (NH_2); 2220 (CN); 1540 (C=S)	7.61–7.91 (*m*, 10H, aromat.) 9.31 (*s*, br, 4H, NH_2).
8	2220 (CN)	2.51 (*s*, 3H, CH_3), 7.10–7.70 (*m*, 10H, aromat.).
9	2220 (CN); 1740 (CO).	1.3 (*t*, 3H, CH_3), 3.8 (*s*, 2H, CH_2), 4.2 (*q*, 2H, CH_2); 6.8–7.3 (*m*, 10H, aromat.)
11	2220 (CN), 1685 (CO); 3350–3180 (NH_2)	3.7 (*s*, 2H, CH_2); 6.5 (*s*, br, 2H, NH_2), 6.8–7.2 (*m*, 10H, aromat.).
12	3500–2900 (OH); 2220 (CN); 1720 (CO)	3.8 (*s*, 2H, CH_2); 7.1–7.6 (*m*, 10H, arom.) 11.3 (*s*, 1H, COOH).
13a	3500, 3350, 3120 (NH); 2220 (CN)	6.81–7.82 (*m*, 14H, aromat.), 9.51 (*s*, br, 1H, NH).
13b	3400, 3300, 3100 (NH); 2220 (CN)	2.2 (*s*, 3H, CH_3) 6.82–7.81 (*m*, br, 14H, aromat.) 9.58 (*s*, 1H, NH).

the reaction mixture for 2 h and cooling, the solid separated was filtered off and recrystallized from ethanol to give **8** and **9** respectively (cf. Table I).

Reaction of 8 and 9 with hydrazine hydrate. A mixture of **8** or **9** (0.01 mol) and hydrazine hydrate (0.01 mol) in glacial acetic acid (60 ml) was heated under reflux for 5 h. The reaction mixture was cooled and poured onto water. The solid separated was collected and crystallized from ethanol to give **10**[1] with m.p. and mixed m.p. 273–274°C.

Preparation of 3,4-diphenyl-5-cyan-6-(carboxyamidomethylthio)pyridazine (**11**). A solution of **9** (0.01 mol) in absolute ethanol (30 ml) and excess ammonia solution (28%) was cooled to 0°C for 48 hr. The solid separated was filtered off and crystallized from ethanol to give **11** as yellow crystals (cf. Table I).

Preparation of 3,4-diphenyl-5-cyanopyridazine-6-one (**6**). A solution of **9** (1 g) in dilute HCl (30 ml) was heated under reflux for 2 h then cooled. The solid obtained was crystallized from ethanol to give **6**[1] with m.p. and mixed m.p. 260°C.

Preparation of 3,4-diphenyl-5-cyano-6-(hydroxycarbonylmethylthio)pyridazine **12**. A solution of **9** (1 g) and aqueous ammonia solution (30 ml) was heated under reflux for 2 h and then acidified with dil. HCl to give a solid. The solid obtained was filtered off and crystallized from methanol to give **12** (cf. Table I).

Preparation of 3,4-diphenyl-5-cyano-6-(4-chloroanilino)pyridazine **13a** *and 3,4-diphenyl-5-cyano-(4-methylanilino)pyridazine* **13b**. A mixture of **9** (0.01 mol) and p-chloraniline (0.01 mol) or p-toluidine (0.01 mole) was refluxed in absolute ethanol (30 ml) for 3 hr. The solid which separated on cooling was filtered and recrystallized from benzene to give **13 a,b** (cf. Table I).

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