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Benzoin in Heterocyclic Synthesis: Synthesis and Reactions of 2,3-Diphenyl-4-cyanopyrrole-5-thione

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Abstract□2,3-Diphenyl-4-cyano-pyrrole-5-thione (**4**) was prepared either by the reaction of benzoin (**1**) and cyanothioacetamide (**3**) followed by cyclization using AcOH/sodium acetate or by refluxing a mixture of benzoin (**1**) and cyanothioacetamide in pyridine to afford directly **4**. Several new pyrrole and pyrazole derivatives were synthesised using **4** as synthon. The structure of the newly synthesised derivatives were based on celemental and spectral data studies. Methylation of the SH group in **4** afforded **5**. Reaction of **4** with ethyl bromo acetate afforded (**6**). Treatment of (**5**) and (**6**) with hydrazine hydrate afforded the same pyrazole derivative (**10**) through the intermediate (**9**). Treatment of **6** with aniline and phenylhydrazine afforded the pyrrole derivatives **8a,b** respectively. Treatment of **6** while dil HCl gave 2,3-diphenyl-4-cyano-pyrrole-5-one (**7**). Treatment of **6** with NH_3/EtOH afforded the amidic derivatives (**11**) with treatment of **6** with NH_3/heat then acidification it gave the carboxylic derivatives (**12**).

Keywords□2,3-Diphenyl-4-cyanopyrrole-5-thione, benzoin, cyanothioacetamide.

The reported biological activities[1-3] of pyrrole and its derivatives stimulated our interest for the synthesis of new heterocyclic derivatives of this ring system. As a part of our program[4-8] directed for synthesis of some heterocyclic compounds with considerable biological and medicinal activity. We reported, here, a novel synthesis of some pyrrole derivatives and their substitution reactions.

Thus, it has been found that benzoin **1** reacted with cyanothioacetamide **2** in absolute ethanol in the presence of catalytic amount of piperidine, to afford the intermediate **3** which could be cyclized using acetic acid and sodium acetate to afford 2,3-diphenyl-4-cyano-pyrrole-5-thione **4**. The same compound **4** could also be obtained directly when **1** and **2** were heated under reflux in pyridine. The structure of **4** is confirmed by elemental analysis, IR and ^{1}H-NMR spectral data (Tables I and II). Thus, the IR (cm^{-1}) spectrum of **4** showed absorption bands at 3400, 3320 and 3100 for NH group in addition to 2200 (CN) group. 1H NMR (δ ppm) of **4** revealed signals at 8.60 (s, 1H, NH); and at 7.63, 7.90 (m, 10H, Arom.H). Treatment of **4** with methyl iodide in sodium ethoxide afforded 2,3-diphenyl-4-cyano-5-S-methylpyrrole **5**. The structure of **5** was confirmed by elemental analysis, IR and ^{1}H-NMR spectral data (Tables I and II).

On the other hand treatment of **4** with ethyl bromoacetate in the presence of sodium ethoxide gave 2,3-diphenyl-4-cyano-5-(ethoxycarbonylmethylthio) pyrrole **6**. The IR (cm^{-1}) spectrum of **6**, showed the ester carbonyl band at 1740 and the cyano group at 2220. The ^{1}H-NMR (δ ppm) of **6** revealed signals at 1.31 (t, 3H, CH_3), 3.8 (s, 2H, $5CH_2$), 4.3 (q, 2H, CH_2), 4.5 (s, 1H, CH), 7.4-6.8 (m, 10H, Arom. H) (Tables I and II). Refluxing of **4** with dil-HCl yielded 2,3-diphenyl-4-cyano-pyrrole-5-one **7**. The IR (cm^{-1}) spectrum of **7** show a peak of NH at 3340, 3300, 3120 (CN) group at 2220 and ring carbonyl peaks at 1690. Moreover, treatment of **5** and 6, with hydrazine hydrate in absolute ethanol gave one and the same product 4,5-diphenylpyrrolo[2,3-c]-3-aminopyrazolene **10** which obtained through the nonisolable intermediate **9**. The structure of **10** was confirmed by elemental analysis, IR and ^{1}H-NMR (Tables I and II). The IR (cm^{-1}) spectrum of **10** showed appearance of a peak at 3350, 3240, 3180 characteristic for NH_2 group. ^{1}H-NMR (δ ppm) of **10** revealed signals at 7.61, 7.91 (m, 10H, Arom.H) and 10.1 (s, 2H, disappear after D_2O exchange, NH_2). Compound **10** showed no signals for NH group. Treatment of **6** with excess ammonia in absolute ethanol at 0°C produced 2,3-diphenyl-4-cyano-6-(carboxyamidomehylthio) pyrrole **11**. The IR (cm^{-1}) spectrum of **11**

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Table I. List of compounds 3, 4, 5, 6, 7, 8a, 8b, 10, 11 and 12

Compound	Solvent of Crystallization	Colour	M.p. °C	Yield (%)	Mol. Formula	Analysis % Calc./Found C	H	N	S
3	ethanol	pale yellow	120	85	$C_{17}H_{14}N_2SO$	69.4 69.1	4.8 4.4	9.5 9.4	10.9 10.7
4	ethanol	brown	>300	73	$C_{17}H_{12}N_2S$	73.9 74.0	4.3 4.1	10.1 10.0	11.6 11.8
5	ethanol	yellow	188	70	$C_{18}H_{14}N_2S$	75.2 75.0	3.8 3.5	9.6 9.4	11.1 11.0
6	ethanol	white	210	75	$C_{21}H_{18}N_2SO_2$	69.6 69.4	4.9 5.0	7.7 7.9	8.8 8.5
7	ethanol	white	244	82	$C_{17}H_{12}N_2O$	78.5 78.4	4.6 4.6	10.7 10.9	– –
8a	ethanol	yellow	185	81	$C_{23}H_{17}N_3$	82.4 82.0	5.1 5.0	12.5 12.3	– –
8b	ethanol	yellow	195	75	$C_{23}H_{18}N_4$	78.9 78.6	5.1 5.1	15.9 16.0	– –
10	ethanol	brown	250	65	$C_{17}H_{12}N_4$	74.9 74.7	4.4 4.2	20.6 20.5	– –
11	ethanol	yellow	254	74	$C_{19}H_{15}N_3OS$	68.5 68.7	4.5 4.4	12.6 12.5	9.7 10.0
12	ethanol	yellow	265	87	$C_{19}H_{14}N_2O_2S$	68.2 67.0	4.2 4.0	8.4 8.1	9.6 10.0

Table II. IR and ^{1}H-NMR data of compounds 3, 4, 5, 6, 7, 8a, 8b, 10, 11, and 12

Compound	IR (KBr) cm^{-1}	^{1}H-NMR (δ ppm)
3	3340,3280, 3120 (NH_2); 2220 (CN), 1540 (C=S)	4.50 (s, 1H, CH); 8.51 (s, br, OH); 7.61-7.90 (m, 10H, Arom); 9.30(s, br, 2H, NH_2)
4	3400, 3320, 3100 (NH), 2220 (CN)	4.50 (s, 1H, CH); 7.63-7.90 (m, 10H, Arom.); 8.60 (s, 1H, NH)
5	2220 (CN)	2.51 (s, 3H, $5CH_3$); 4.51 (s, 1H, CH); 7.10-7.70 (m, 10H, Arom.)
6	2220 (CN), 1740 (CO)	1.31 (t, 3H, CH_3); 3.80 (s, 2H, $5CH_2$); 4.30 (q, 2H, CH_2); 6.80-7.40 (m, 10H, Arom.)
7	3340, 3300, 3120 (NH), 1670 (CO).	4.50 (s, 1H, CH); 7.61-7.91 (m, 10H, Arom.); 8.80 (s, 1H, NH)
8a	3500, 3250, 3120 (NH), 2220 (CN)	4.50 (s, 1H, CH); 7.60-7.90 (m, 15H, Arom.); 9.58 (s, 1H, NH)
8b	3450, 3300, 3120 (NH), 2220 (CN)	
10	3350, 3240, 3180 (NH_2)	7.61-7.91 (m, 10H, Arom.), 10.1 (s, br, 2H, NH_2)
11	3350, 3240, 3180 (NH_2); 2220 (CN), 1685 (CO).	3.8 (s, 2H, $5CH_2$); 4.50 (s, 1H, CH); 6.50 (s, br, 2H, NH_2); 7.10-7.70 (m, 10H, Arom. H)
12	2220 (CN), 1720 (COOH)	3.7 (s, 2H, $5CH_2$); 4.50 (s, 1H, CH); 7.10-7.60 (m, 10H, Arom.); 11.3 (s, 1H, COOH)

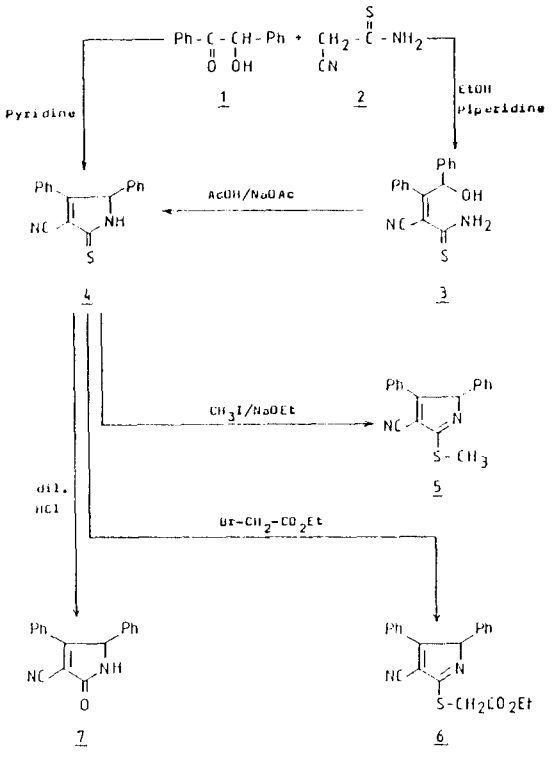

Chart 1

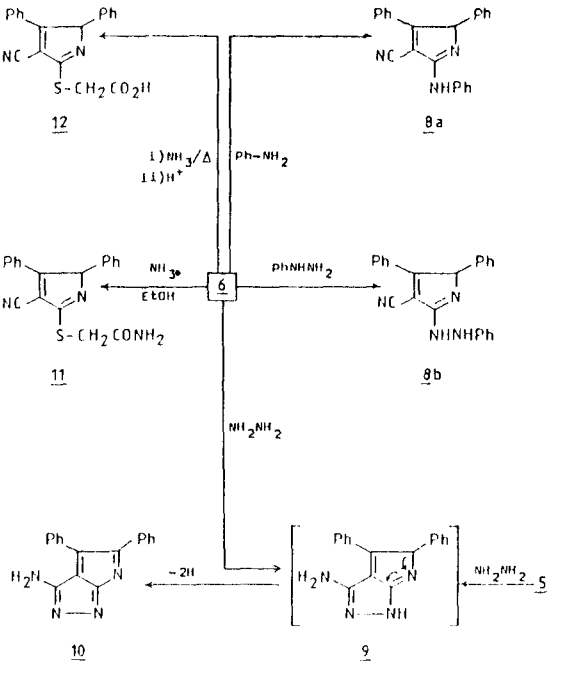

Chart 2

showed the appearance of (C=O) band at 1685, (NH_2) band at 3350, 3240, 3180 and (CN) band at 2220. ^{1}H-NMR (δppm) of **1** revealed signals at 3.80 (s, 2H, $5CH_2$) 6.50 (s, br, 2H, NH_2) and 6.80~7.30 (m, 10H Arom. H) (Tables I and II). Boiling of **6** with hot ammonia then acidification afforded directly the corresponding 2,3-diphenyl-4-cyano-5-(hydroxycarbonylmethylthio) pyrrole **12.** The structure of **12** was confirmed by elemental analysis, IR and ^{1}H-NMR spectra (Tables I and II). Where ^{1}H-NMR (δ ppm) showed a signal at 11.3 (s. 1H, COOH). Treatment of **6** with aniline or phenylhydrazine in absolute ethanol afforded 2,3-diphenyl-4-cyano-5-anilinopyrrole **8a** and 2,3-diphenyl-4-cyano-5-phenylhydrazino pyrrole **8b** respectively. The structure of **8a** and **b** were confirmed based on elemental analysis, IR and ^{1}H-NMR (Tables I and II).

EXPERIMENTAL

All melting point 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) units. Elementary analyses were performed at the Microanalytical Centre of Cairo University.

Preparation of 2,3-diphenyl-4-cyano-5-thione (4)
Route (a): A mixture of benzoin (0.01 mol) and cyanthioacetamide **2** (0.01 mol) pyridine (50 m*l*) was heated under reflux for 5 h. The solution was cooled and poured onto ice-water. The solid separated after acidification was collected, washed with H_2O, dried and then crystallized from ethanol to give **4** as brown powder with mp. >300°C (Table I).
Route (b): i) A mixture of benzoin **1** (0.01 mol) and cyanothioacetamide **2**(0.01 mol) in ethanol (30 m*l*) in the presence of piperidine (0.5 m*l*) was heated under reflux for 3 h. The solid obtained after cooling and pouring onto ice-water crystallized from ethanol to give **2** as pale yellow crystals with mp. 120°C.

ii) A mixture of **3** and glacial acetic acid (20 m*l*) was heated under reflux for 2 h then cooled and poured onto ice-water. The solid obtained was crystallized from ethanol to give **4** as brown crystals with m.p. >300°C.

Preparation of 2,3-diphenyl-4-cyano-(6-methylthio)pyrrole 5 and 3,4-diphenyl-5-cyano-6-(eth-

oxycarbonylmethylthio)pyrrole 6

General procedure: A mixture of methyl iodide, ethylbromoacetate (0.01 mol) was added dropwise to a stirred solution of sodium ethoxide (0.01 atom of sodium metal in 100 m*l* ethanol) and **4** (0.01 mol). After refluxing the reaction mixture for 2 h and cooling, the solid separated was filtered off and recrystallized from ethanol to give **5** and **6** respectively (Table I).

Reaction of 5 and 6 with hydrazine hydrate

A mixture of **5** or **6** (0.01 mol) and hydrazine hydrate (0.01 mol) in glacial acetic acid (60 m*l*) 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** (Table I).

Preparation of 2,3-diphenyl-4-cyano-5-anilino pyrrole 8a and 2,3-diphenyl-4-cyano-5-phenylhydrazino pyrrole 8b

A mixture of **6** (0.01 mol) and aniline or phenylhydrazine (0.01 mol) in absolute ethanol (30 m*l*) was heated under reflux for 2 h. The solid separated on cooling was heated under reflux for 2 h. The solid separated on cooling was filtered and recrystallized from ethanol to give **8a** and **b** respectively (Table I).

Preparation of 2,3-diphenyl-4-cyano-5-(carboxyamidomethylthio)pyrrole 11

A solution of **6** (0.01 mol) in absolute ethanol (30 m*l*) and excess ammonia solution (28%) was cooled to 0°C for 48 h. The solid separated was filtered off and crystallized from ethanol to give **10** as yellow crystals (Table I).

Preparation of 2,3-diphenyl-4-cyanopyrrole-6-one 7

A solution of **4** (1g) in dilute HCl (30 m*l*) was heated under reflux for 2 h than cooled. The solid obtained was crystallized from ethanol to give **7** (Table II).

Preparation of 2,3-diphenyl-4-cyano-5-(hydroxycarbonylmethylthio)pyrrole 12

A solution of **6** (1g) and aqueous ammonia solution (30 m*l*) was heated under reflux for 2 h and then acidified with dil-HCl. The solid obtained was filtered off and crystallized from ethanol to give **11** (Table I).

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