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BENZOIN IN HETEROCYCLIC SYNTHESIS: SYNTHESIS AND REACTIONS OF 4-CYANO-2,3-DIPHENYL-2H-PYRROL-5-THIONE

Fathy A. Khalifa, Nabila A. Ismail[+], Ahmed H.H. Elghandour and Hussein F. Zohdi

Department of Chemistry, Faculty of Science, Cairo University,Giza, A.R. Egypt.
[+]Department of Chemistry, Faculty of Science, Zagazig University,Zagazig,A.R.Egypt.

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Benzoin; cyanothioacetamide; pyrrolethione; hydrazinodihydropyrrole; pyrrolo[2,3-c] pyrazole.

Abstract

Several new pyrrole and pyrazole derivatives were synthesised via the reactions of 4-cyano-2,3-diphenyl-2H-pyrrol-5-thione.

Introduction:

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 report here a novel synthesis of some pyrrole derivatives and their substitution reactions.

Results and Discussion

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 4-cyano-2,3-diphenyl-2H-pyrrol -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. (cf. Tables 1 and 2). Thus, the IR spectrum of **4** showed absorption bands at 3320 cm^{-1} for NH group in addition to 2200 cm^{-1} (CN) group. ^{1}H 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 4-cyano-2,3-diphenyl-5-(methylthio) pyrrole **5**. The structure of **5** was confirmed by elemental analysis. IR and ^{1}H NMR spectral data. (cf. Tables 1 and 2).

On the other hand treatment of **4** with ethyl bromoacetate in the presence of sodium ethoxide gave 4-cyano-2,3-diphenyl-5-(ethoxycarbonylmethylthio)pyrrole **6**. The IR (cm^{-1}) spectrum of

6, showed the ester carbonyl band at 1740 cm^{-1} and the cyano group at 2220 cm^{-1}. The ^1H-NMR (δ ppm) of 6 revealed signals at 1.31 (t, 3H, CH_3), 3.8 (s, 2H, S-$\underline{CH_2}$-), 4.3 (q, 2H, CH_2), 4.5 (s, 1H, CH), 6.8-7.4 (m, 10H, Arom. S) (cf. Tables 1 and 2). Refluxing of **4** with dil. HCl yielded 4-cyano-2,3-diphenylpyrrole-5-one **7**. The IR spectrum of **7** show a peak of NH at 3300 cm^{-1} (CN) group at 2220 cm^{-1} and ring carbonyl peaks at 1690 cm^{-1}. Moreover, treatment of **5** and **6**, with hydrazine hydrate in absolute ethanol gave one and the same product 3-amino-(4,5-diphenylpyrrolo)[2,3-c]pyrazolene **10** which obtained through the nonisolable intermediate **9**. The structure of **10** was confirmed by elemental analysis IR and ^1H NMR (cf. Tables 1 and 2). The IR (cm^{-1}) spectrum of **10** showed appearance of a peak at 3350, 3240, 3180 characteristic for NH_2 group. ^1H NMR (δ ppm) of **10** revealed signals at 7.61, 7.91 (m, 10H, Arom. S.) and 10.1 (s, 2H, disapp. after D_2O exchange, NH_2). Treatment of **6** with excess ammonia in absolute ethanol at 0°C produced 4-cyano-2,3-diphenyl -5-(carboxyamidomethylthio)pyrrole **11**. The IR (cm^{-1}) spectrum of **11** showed the appearance of (C=O) band at 1685, (NH_2 and NH) band at 3350, 3240, 3180 and (CN) band at 2220. ^1H NMR (δ ppm) of **11** revealed signals at 3.80 (s, 2H, S-$\underline{CH_2}$-) 6.50 (s, br, 2H, NH_2) and 6.80, 7.30 (m. 10H, Arom. H), (cf. Tables 1 and 2). Boiling of **6** with hot ammonia then acidification afforded directly the corresponding 4-cyano-2,3-diphenyl-5-(carboxymethylthio)pyrrole **12**. The structure of **12** was confirmed by elemental analysis, IR and ^1H NMR spectra (cf. Tables 1 and 2). Where ^1H NMR (δ ppm) showed a signal at 11.3 (s, 1H, COOH). Treatment of **6** with aniline or phenyl hydrazine in absolute ethanol afforded 4-cyano-2,3-diphenyl-5-anilinopyrrole **8a** and 4-cyano-2,3-diphenyl-5-phenylhydrazinopyrrole **8b**, respectively. The structure of **8a** and **b** were confirmed based on elemental analysis, IR and ^1H NMR (cf. Tables 1 and 2).

Experimental

All melting points are uncorrected. IR spectra (KBr) were recorded on a Pye-Unicam SP-1100 spectrophotometer. ^1H 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 Perkin-Elmer 2400-CHN Analyzer.

Preparation of 4-cyano-2,3-diphenyl-2H-pyrrol-5-thione(4):

Route (a)

A mixtrue of benzoin (0.01 mol) and cyanothioacetamide **2** (0.01 mol) in pyridine (50 ml) was heated under reflux for 5h. 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 m.p. > 300°C (cf. Table 1).

Route (b)

(1) A mixture of benzoin **1** (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 3h. The solid obtained after cooling and pouring onto ice-water was crystallized from ethanol to give **3** as pale yellow crystals with m.p. 120°C.

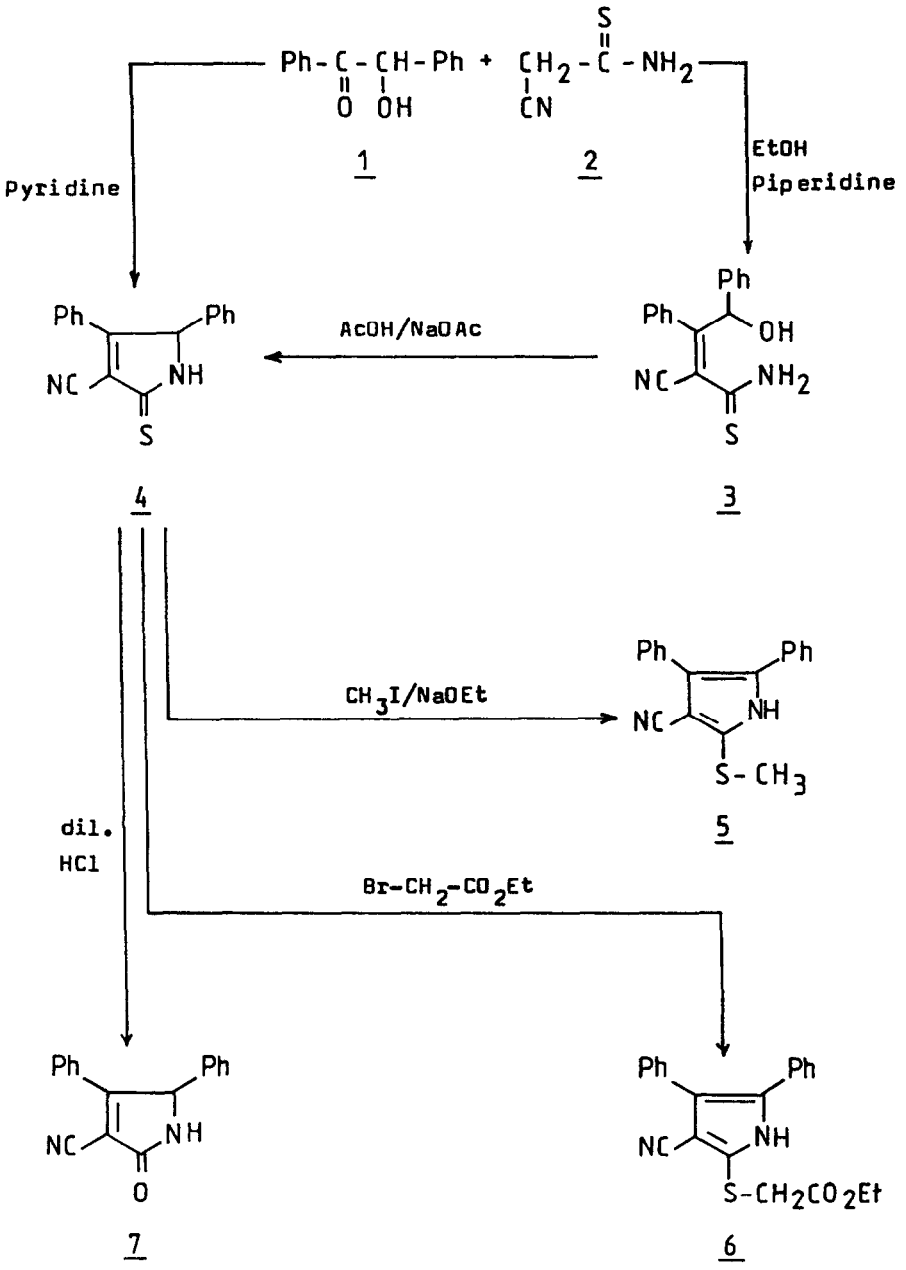
Ph-C(=O)-CH(OH)-Ph + CH2(CN)-C(=S)-NH2
1
2
Pyridine
EtOH
Piperidine
AcOH/NaOAc
4
3
CH3I/NaOEt
5
dil. HCl
Br-CH2-CO2Et
7
6

Chart 1

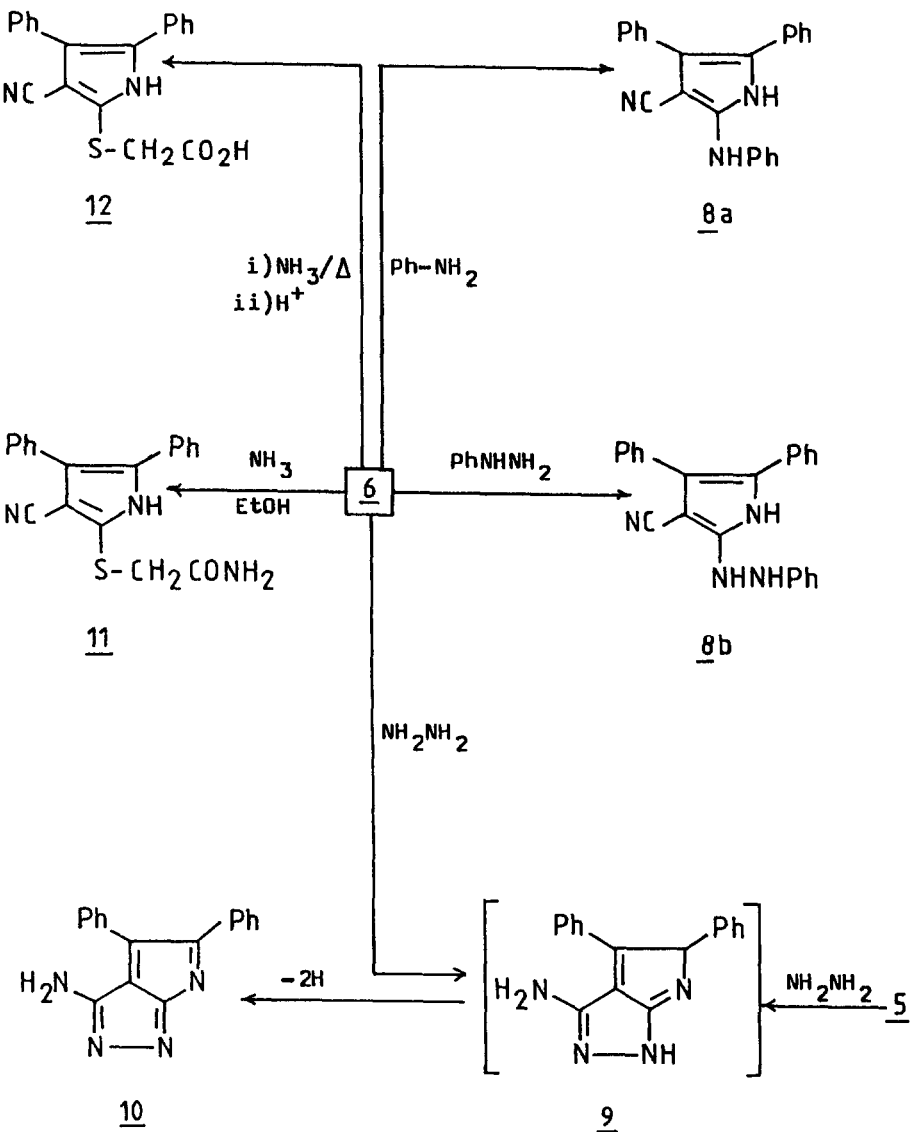
Ph
Ph
NC
NH
S-CH2CO2H
12
i)NH3/Δ
ii)H+
Ph-NH2
NHPh
8a
NH3
EtOH
6
PhNHNH2
S-CH2CONH2
11
NHNHPh
8b
NH2NH2
H2N
N
N—N
10
-2H
9
NH2NH2
5

Chart 2

(ii) A mixture of **3** and glacial acetic acid (20 ml) was heated under reflux for 2h 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 4-cyano-5-(methylthio)-1,2-diphenyl-pyrrole 5 and 4-cyano-5-(ethoxycarbonyl-methylthio)-2,3-diphenyl-pyrrole 6

General procedure:

A mixture of methyl iodide or ethylbromoacetate (0.01 mol) was added dropwise to a stirred solution of sodium ethoxide (0.01 atom of sodium metal in 100 ml ethanol) and **4** (0.01 mol). After refluxing the reaction mixture for 2 hr and cooling, the solid that separated was filtered off and recrystallized from ethanol to give **5** and **6** respectively (cf. Table 1).

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 ml) was heated under reflux for 5 hr. The reaction mixture was cooled and poured onto water. The solid separated was collected and crystallized from ethanol to give **10** (cf. Table 1).

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

A mixture of **6** (0.01 mol) and aniline (or phenylhydrazine) (o.01 mol) in absolute ethanol (30 ml) was heated under reflux for 2h. The solid, which separated on cooling, was filtered and recrystallized from ethanol to give **8a** and **8b** respectively (cf. Table 1).

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

A solution of **6** (0.01 mol) in absolute ethanol (30 ml) and excess ammonia solution (28%) was cooled to 0°C for 48 hr. The solid, which separated, was collected and crystallized from ethanol to give **10** as yellow crystals (cf. Table 1).

Preparation of 4-cyano-2,3-diphenyl-2H-pyrrol-6-one 7

A solution of **4** (1 g) in dilute HCl (30 ml) was heated under reflux for 2 hr then cooled. The solid obtained was crystallized from ethanol to give **7** (cf. Table 1).

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

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

Table 1: *List of compound 3, 4, 5, 6, 7, 8a, 8b, 10, 11 and 12*

Compound	Solvent of Crystallization	Colour	M.p. °C	Yield (%)	Mol. Formula	Analysis % Calcd./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 2: IR and ^{1}H NMR data of compounds 3,4,5,6,7,8a,8b,10,11 and 12.

Compound	IR (KBr) cm^{-1}	1H NMR (δppm)
3	3340, 3280 (NH_2); 2220 (CN); 1540 (C=S)	4.50 (s, 1H, CH); 7.61-7.90 (m, 10 H, Arom.); 9.30 (s, br, 2H, NH_2); 10.51 (s, 1H, OH).
4	3320 (NH), 2220 (CN)	4.50 (s, 1H, CH); 7.63-7.90 (m, 10 H, Arom.); 8.60 (s, 1H, NH).
5	3300 (NH); 2220 (CN)	2.51 (s, 3H, S-CH_3); 7.10-7.70 (m, 10H, Arom.); 9.8 (s, br, 1H, NH).
6	3250 (NH); 2220 (CN), 1740 (CO)	1.31 (t, 3H, CH_3); 3.80 (s, 2H, S-CH_2); 4.30 (q, 2H, CH_2); 6.80-7.40 (m- 10H, Arom.); 9.7 (s, br, 1H, NH).
7.	3300 (NH), 1670 (CO).	5.4(s, 1H, pyrrole H-5); 7.61-7.91 (m, 10H, Arom.); 8.80 (s, 1H, NH).
8a	3400, 3250 (NH); 2220(CH)	7.60-7.90 (m, 15H, Arom.); 9.58 (s, br, 2H, two NH).
8b	3450, 3300, 3200 (NH groups), 2220 (CN).	
10	3350, 3240 (NH_2)	7.61-7.91 (m, 10H, Arom.) 10.1 (s, br, 2H, NH_2, lost after D_2O exchange)
11	3350, 3240, 3200 (NH_2 and NH); 2220 (CN), 1685 (CO).	3.8 (s, 2H, S-CH_2); 6.50 (s, br, 3H, NH_2 and NH); 7.10-7.70 (m, 10H, Arom).
12	3200 (NH), 2220 (CN), 1720 (COOH)	3.7 (s, 2H, S-CH_2); 7.10-7.60 (m, 10H, Arom.) 9.7 (s, br, 1H, NH); 11.3 (s, 1H, COOH).

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