Synthesis of Heterocylic Compounds Containing Nitrogen and Sulphur from 3-amino-4-cyanopyrazole

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Summary: Condensation of 3-amino-4-cyanopyrazole (1) with hydroxylamine hydrochloride and hydrazine hydrate afforded -o-amino pyrazolo (3,4:3,4) pyrazole (3) and (4). Treatment of (4) with acetic anhydride gave the acetyl derivative (5). Also the diazonium salt of compound (4) couples with β-naphthol to give (6) which on treatment with acetic acid gave 9H-naphthol [2.1-e] pyrazolo (3,4:3,4) pyrazolo [5,1-c] [1,2,4] triazine (7). Also the reaction of (1) with phenylisothiocyanate and benzoylisothiocyanate gave (9) and (10). The reaction of (1) with cyclohexanone in the presence of $ZnCl_2$ afforded pyrazolo-tetrahydroquinoline derivative (11).

Introduction

Previously, it has been reported that the amino pyrazoles are intermediate for the preparation of the therapeutically interesting pyrazolo [1,5-a] pyrimidines [1-3]. The synthesis of various compounds (2-11) are outlined in Scheme 1.

Thus the condensation of compounds (1) with hydroxylamine hydrochloride in methanol and ammonium hydroxide at room temperature afforded 3-amino-N-hydroxy pyrazolo-3-carboximid amide (2) [4]. The IR spectrum showed a well defined absorption band at 3400-3300 cm^{-1} referred to NH_2, at 3250 cm^{-1} due to OH and no absorption band due to ν_{CN} group.

When the reaction of (1) was carried out with hydroxylamine hydrochloride in refluxing pyridine for 5 hrs, the product was identified as 2-amino pyrazolo (3,4:3,4) pyrazole hydrochloride (3). The IR spectrum of (3) showed absorption band at 3250-3300 cm^{-1} referred to ν_{NH2} and NH groups and at 1625 cm^{-1} due to $\nu_{C=N}$.

When 3-amino-4-cyanopyrazole (1) was treated with hydrazine hydrate at room temperature for 5 days [5], hydrazine attacked the cyano group followed by cyclization to give 2-amino pyrazolo (3,4:3,4) (4). The structure of (4) was confirmed by the IR spectrum which showed absorp-

tion bands between 3300 and 3450 cm^{-1} due to NH, a band at 1630 cm^{-1} due to $\nu_{C=N}$ and no absorption band referred to ν_{CN} group, which indicate that the reaction took place near the amino group. The ^{1}H-NMR spectrum of (4) shows signals at δ8.10 (s,1H,CH=N), at δ6.10 (s,2H,2NH) and at δ5.40 (s,2H, NH_2).

On the other hand, when (4) was treated with acetic anhydride under reflux, acetylation of amino group took place to give the corresponding acetylamino derivative (5). The IR spectrum of (5) showed broad band between 3200 cm^{-1} and 3450 cm^{-1} due to ν_{NH}, a band at 1660 cm^{-1} due to $\nu_{C=O}$ and a band at 1630 cm^{-1} due to $\nu_{C=N}$.

Compound (4) was converted to the diazonium salt [6] which coupled with β-naphthol to yield 1-[2,6-dihydropyrazolo-(3,4:3,4)-pyrazol-3-yl-azo]-2-naphthol (6). The IR spectrum of (6) showed broad band at 3250 cm^{-1} referred to OH and a band at 1620 cm^{-1} due to $\nu_{C=N}$.

The azo compound (6) could be readily cyclized into 9H-naphthol (2,1-e) pyrazolo (3,4:3,4) pyrazolo (5,1-c) (1,2,4) triazine (7) on treatment with acetic acid at reflux temperature (Scheme 1). The IR spectrum of (7) showed bands at 3230 cm^{-1} due to ν_{NH}, a band at 1630 cm^{-1} due to $\nu_{C=C}$, a band at 1570 due to $\nu_{N=N}$ and no absorption bands due to ν_{OH}.

As a part of this work, we became interested in the synthesis of new heterocyclic system incorporating the pyrimidine thione moiety [4]. Thus, it was found that treatment of 3-amino-4-cyanopyrazole (1) with phenyl isothiocyanate at room temperature in dimethyl formamide containing pyridine lead to the corresponding N,N-disubstituted thiourea (8). The structure of (8) showed the IR absorption bands at 3200 cm^{-1} due to ν_{NH}, at 2220 cm-^{1} for ν_{CN}, at 1610-1500 cm^{-1} due to the aromatic ring and at 1280 cm^{-1} due to $\nu_{C=S}$.

When compound (8) was heated with triethylamine in pyridine, cyclization took place to give, 1,7-dihydro-6-(phenylamino)-4H-pyrazolo (3,4-d) pyrimidine-4-thione (9). All spectral data were in accord with the structure (9). The IR spectrum exhibited the presence of NH at 3200 cm^{-1}, at 1620 cm^{-1} due to $\nu_{C=N}$ and at 1160 cm^{-1} due to $\nu_{C=S}$. The ^{1}H-NMR spectrum in DMSO-d_6 showed the presence of signals at δ10.30 (d,2H,2NH), at δ8.40 (s,1H,CH=N), at δ7.20 (m,5H,Ph) and at δ3.30 (s,1H,NH-Ph).

Similar to the behaviour of (1) with phenylisothiocyanate, the reaction of (1) with benzoylisothiocyanate in acetone at the reflux temperature gave N-(4-cyanopyrazole-3-yl)-N-benzoylthiourea (10) which was identified on the basis of elemental analysis and spectroscopic interpretation. The IR spectrum of (10) showed the absorption bands at 3200 cm^{-1} referred to ν_{NH}, at 2200 cm^{-1} to CN, at 1660 cm^{-1} to $\nu_{C=O}$ and at 1280 cm^{-1} referred to $\nu_{C=S}$. Attempted cyclization of (10) to the corresponding pyrazolo pyrimidine thione derivative was unsuccessful.

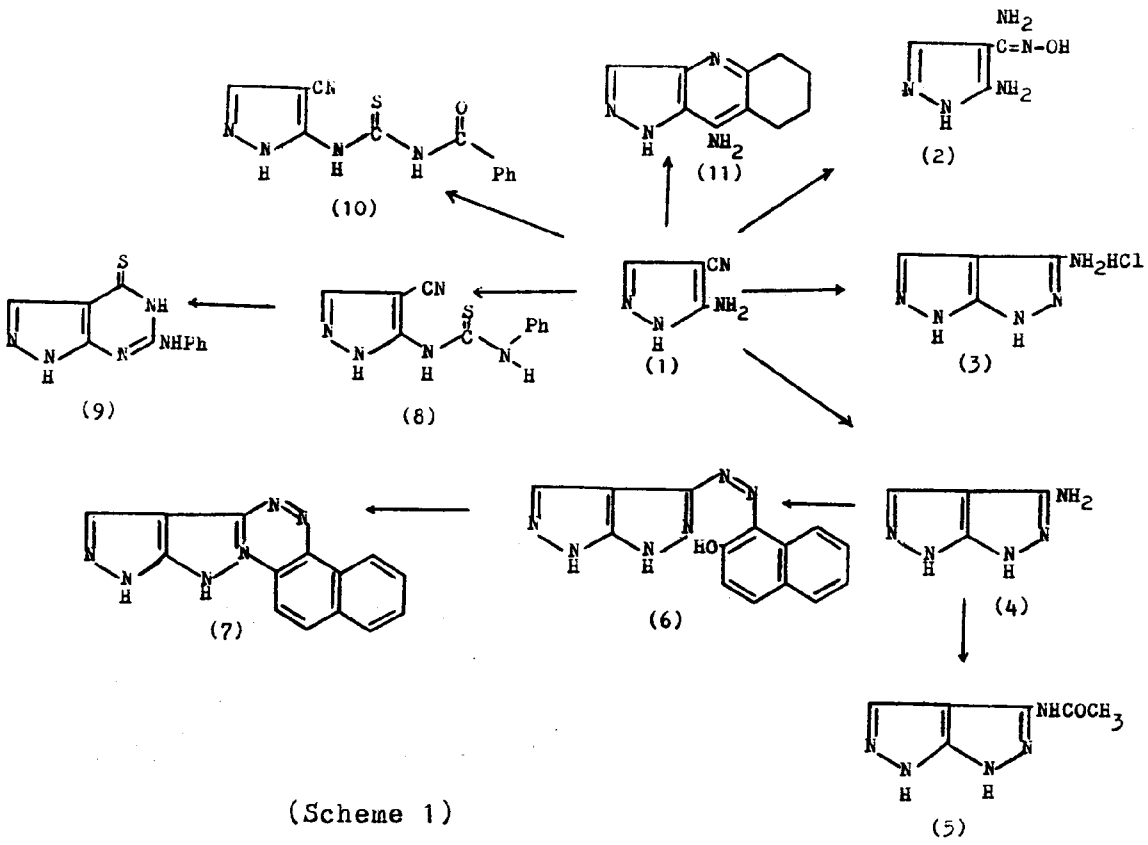
The reaction of (1) with cyclohexanone [7] in the presence of anhydrous zinc chloride lead to the formation of 4-amino pyrazolo (3,4-b) tetrahydroquinoline (11). The IR spectrum showed absorption bands below 3000 cm^{-1} due to ν_{C-H} and broad band at 3220 cm^{-1} due to NH. The ^{1}H-NMR spectrum of (11) in DMSO-d_6 exhibited the signals at δ8.20 (s,1H,CH=N), δ7.50 (m,1H,NH), δ6.00 (s,2H,NH_2), δ2.20 (s,2H,N=CH-CH_2), δ1.90 (s,2H,-CH=CH-CH_2) and at δ1.50 (m,4H,-CH_2-CH_2-).

Experimental

Melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 257 spectrometer using KBr discs. Nuclear magnetic resonance were recorded on a Hitachi Perkin-Elmer VA60 spectrometer. Chemical shifts were expressed in δ values (ppm) using tetramethyl silane as internal standard.

Preparation of 4-amino-N-hydroxypyrazolo-3-carboximidamide (2):

To a solution of (1) (1.08 g, 0.01 mole) in aqueous methanol (50 ml) was added hydroxylamine hydrochloride (0.69 g, 0.01 mole) and the reaction mixture was stirred at room temperature with dil. ammonia for 24 hrs. The solid



(Scheme 1)

crystalline was filtered off, dried and crystallized from aqueous ethanol to give (2) in 70% yield, m.p. 210°C (found: C,34.20; H,4.70; N,49.32). $C_4H_7N_5O$ (141) (requires: C,34.04; H,4.95; N,49.64).

Preparation of 2-aminopyrazolo-[3,4:3,4] pyrazole hydrochloride (3)

To a solution of 3-amino-4-cyanopyrazole (1.08 g, 0.01 mole) in pyridine (15 ml) was added hydroxylamine hydrochloride (0.69 g, 0.01 mole) and the reaction mixture was heated at reflux temperature for 5 hrs. Excess pyridine was removed under vacuum and the residue was crystallized from ethanol to give (3) in 15% yield, m.p. 250°C (found: C,30.40; H,3.40; N,43.89). $C_4H_6N_5Cl$ (159.5) (requires: C,30.09; H,3.76; N,43.53).

Preparation of 2-aminopyrazolo-[3,4:3,4] pyrazole (4):

A mixture of 3-amino-4-cyanopyrazole (1.08 g, 0.01 mole) in hydrazine hydrate (3 ml, 99%) was kept at room temperature for 5 days. The solid product was filtered off and crystallized from acetic acid to give (4) as red crystals in 50% yield, m.p.280°C. (found: C,38.90; H,4.20; N,56.61). $C_4H_5N_5$ (123) (requires: C,39.02; H,4.07; N,56.41).

Preparation of 2-acetyl-aminopyrazolo [3,4:3,4] pyrazole (5):

A solution of (4) (1.25 g, 0.01 mole) in acetic anhydride (10 ml) was refluxed for 5 hrs. The solvent was evaporated in vacuum and the solid crystallized from ethanol to give (5) in 56% yield. m.p. 230°C. (found: C,43.40; H,4.50; N,42.08) $C_6H_7N_5O$ (165) (requires: C,43.63; H,4.24; N,42.42).

Preparation of 1-[2,6-dihydropyrazolo-[3,4-c] pyrazole-3-yl) azo] 2-naphthalenol (6):

A solution of (4) (1.23 g, 0.01 mole) in 50% HCl (3 ml) was diazotized with a solution of sodium nitrite (0.7 g) in water (2 ml) at 0°C. The cold solution was added in small portions to a solution of β-napthol (1.4 g, 0.01 mole) and sodium acetate (5 g) in ethanol (40 ml) with stirring to give a precipitate

which was filtered, washed several times with hot water, dried and crystallized from ethanol to give red crystals of compound (6) in 60% yield. m.p. 270°C. (found: C,60.28; H,4.00; N,29.92) $C_{14}H_{10}N_6O$ (278) (requires: C,60.43; H,3.60; N,30.22).

Preparation of 9H-naphthol [2,1-e] pyrazolo [3,4:3,4] pyrazolo [5,1-c] [1,24] triazine (7):

A solution of (6) (2.78 g, 0.01 mole) in acetic acid (20 ml) was heated under reflux for 3 hrs. The reaction mixture was concentrated. Red crystals separated and recrystallized from acetic acid to give (7) in 73% yield. m.p.300°C (found: C,64.40; H,3.30; N,31.93) $C_{14}H_8N_6$ (260) (requires: C,64.62; H,3.08; N,32.31).

Preparation of N-(4-cyano-pyrazol-3-yl)-N-phenyl-thiourea (8):

To a solution of (1) (1.8 g, 0.01 mole) in dry dimethylformamide (20 ml), triethylamine (.01 mole) and phenylisocyanate (0.012 mole) were added and the resultant solution was stirred at room temperature for 18 hrs, before pouring into water (20 ml). The precipitated solid was crystallized from acetic acid to give (8) in 70% yield. m.p. 120°C. (found: C,54.10; H,4.00; N,28.61) $C_{11}H_9N_5S$ (243) (requires: C,54.32; H,3.70; N,28.81).

Preparation of 1,7-dihydro-6-(phenylamino)-4H-pyrazolo[3,4-d] pyrimidine-4-thione (9):

To a solution of (8) (1.8 g, 0.01 mole) in pyridine, triethylamine (0.01 mole) was added and the resultant solution was heated at reflux temperature for 10 hrs. After cooling, the solution was poured into water (40 ml) and the precipitated solid was separated by filtration and recrystallization from ethanol to give (9) in 35% yield, m.p. 243°C. (found: C,54.00; H,4.90; N,28.60) $C_{11}H_9N_5S$ (243) (requires: C,54.32; H,3.70; N,28.81).

Preparation of N-(4-cyanopyrazol-3-yl)-N-benzoyl-thiourea (10):

To a solution of benzoyl isothiocyanate [8] in acetone (50 ml), a suspension of (1) (1.08 g, 0.01 mole) in acetone (30 ml) was added. The reaction mixture was refluxed for two hours and then evaporated in vacuum. The remaining product was washed several times with water and then boiled with ethanol (50 ml). The solid product were collected by filtration and recrystallized from water to give (10) in 50% yield, m.p. 140°C. (found: C,52.80; H,3.50; N,25.38) $C_{12}H_9N_5OS$ (271) (requires: C,53.13; H,3.32; N,25.83).

Preparation of 4-aminopyrazolo [3,4-b] tetrahydro-quinoline (11):

To a solution of (1) (1.08 g, 0.01 mole) in cyclohexanone (15 ml) was added anhydrous zinc chloride (0.25 g, 0.01 mole). The reaction mixture was refluxed for 20 minutes. A complex with zinc chloride was separated from the solution. Treatment of this complex with NaOH (40%) and extraction with benzene, evaporation of the solvent and crystallization from ethanol gave (11) in 82% yield. m.p. 200°C. (found: C,61.50; H,6.60; N,29.54) $C_{10}H_{12}N_4$ (188) (requires: C,61.82; H,6.38; N,29.79).

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