HETEROCYCLIC SYNTHESIS FROM 3-AMINO-4-CYANOPYRAZOLE

Ali DEEB*, Medhat EL-MOBAYED, Abdel Naby ESSAWY, Adel Abd EL-HAMID and Atef Mohamid Abd EL-HAMID

Department of Chemistry, Zagazig University, Zagazig, A.R. Egypt

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3-Amino-4-cyanopyrazole *I* reacts with hydroxylamine and with hydrazine to yield *1H,6H*-3--aminopyrazolo[3,4-*c*]pyrazole (*III* and *IV*). Diazotized *IV* couples with 2-naphthol to give the arylazo derivative *VI* which cyclizes to 9*H*-naphthol[2,1-*e*]pyrazolo[3′,4′ : 3,4]pyrazolo[5,1-*c*]-[1,2,4]triazine *VII* by means of acetic acid. The pyrazol-5-ylthiourea obtained from *I* and phenyl isothiocyanate undergoes base-catalyzed cyclization to give pyrazolo[3,4-*d*]pyrimidinethione derivative *IX*. Compound *I* reacts with cyclohexane in the presence of zinc chloride to give the tetrahydropyrazolo[3,4-*b*]quinoline derivative *XI*. The reaction of *I* with pyridine 1-oxide affords 4*H*,5*H*-pyrazolo[5′,1′ : 2,3][1,2,4]triazolo[1,5-*a*]pyridine-3-carbonitrile *XII*.

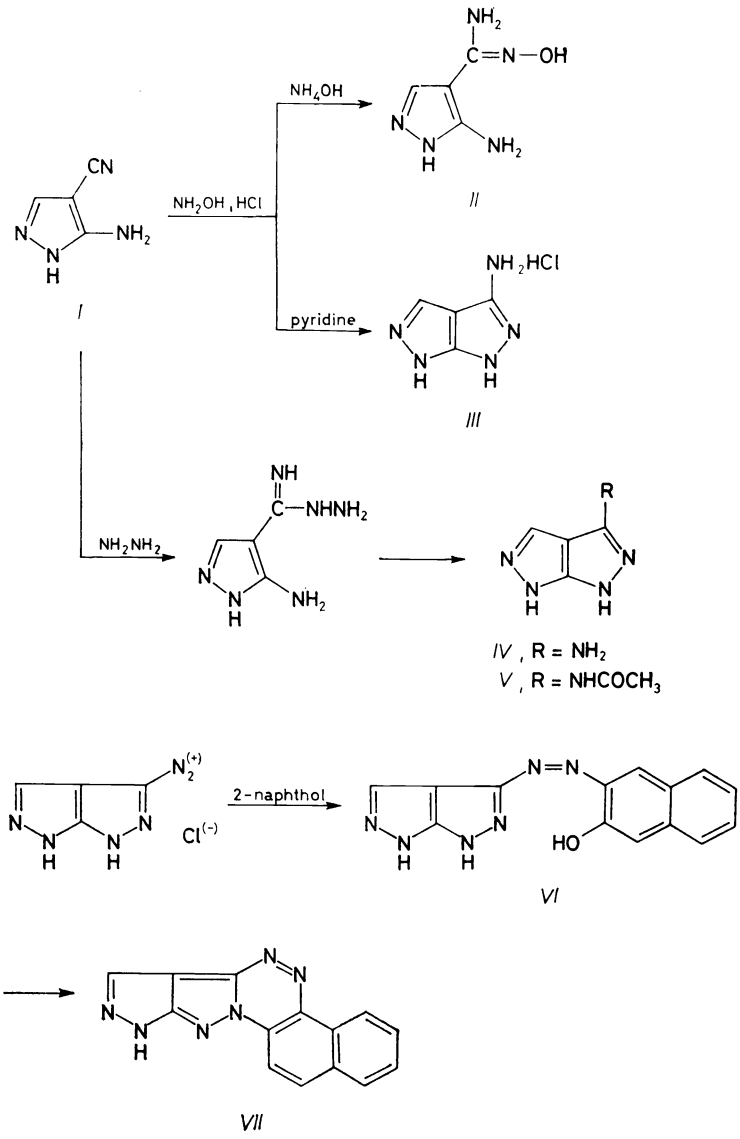
In the course of the programme directed towards the synthesis of fused nitrogen heterocyclic compounds, we have synthesized some pyrazolo[3,4-*c*]pyrazole, pyrazolo[5,1-*c*][1,2,4]triazine, pyrazolo[3,4-*d*]pyrimidine, pyrazolo[3,4-*b*]quinoline and pyrazolo [5′,1′ : 2,3][1,2,4]triazolo[1,5-*a*]pyrimidine derivatives from 3-amino-4--cyanopyrazole. Synthesis of these compounds was of special interest since some pyrazolopyrimidines have been reported to have antipyretic and analgesic activity[1], and pyrazolotriazines act as antitumor agents[2].

It has been reported[3] that 2-amino-3-cyano-5,7-diphenylpyrazolo[1,5-*a*]pyridine reacts with hydroxylamine in boiling sodium methoxide/methanol to give the corresponding amidoxime. We carried out the reaction of 3-amino-4-cyanopyrazole *I* with hydroxylamine hydrochloride in methanol containing ammonium hydroxide at room temperature and obtained the corresponding amidoxime *II* in 70% yield. The further attempted reaction in boiling pyridine for 5 h afforded 1*H*,6*H*-3-amino-pyrazolo[3,4-*c*]pyrazole hydrochloride *III*, via the initial addition to cyano group followed by nucleophilic cyclization. Similarly, compound *I* reacted with hydrazine hydrate at room temperature to yield 1*H*,6*H*-3-aminopyrazolo[3,4-*c*]pyrazole *IV* in 50% yield. Treatment of *IV* with acetic anhydride resulted in the corresponding acetamido-derivative *V*. The diazotized compound *IV* coupled with 2-naphthol to yield the arylazo derivative *VI*. This compound could be readily cyclized into *VII*

* To whom correspondence should be addressed.

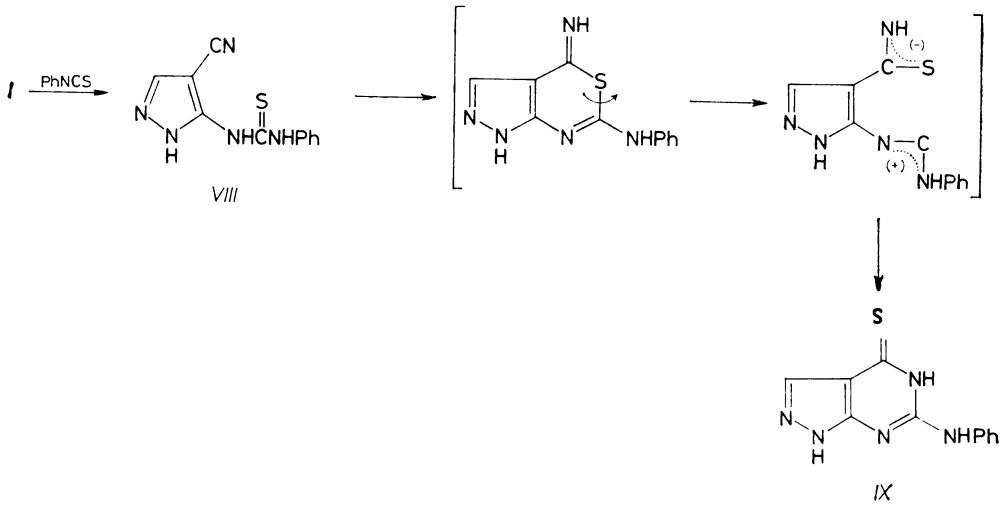
by treatment with acetic acid (Scheme 1). This is in contrast to the reported direct formation of pyrazolo[5,1-*c*]-*as*-triazines after treating the diazotized aminopyrazoles with 2-naphthol, via a dipolar cycloaddition sequence[4].

The reaction of 3-aminopyrazoles with phenyl isothiocyanate is straightforward and affords the expected pyrazol-3-ylthiourea derivative[5]. We have found that com-



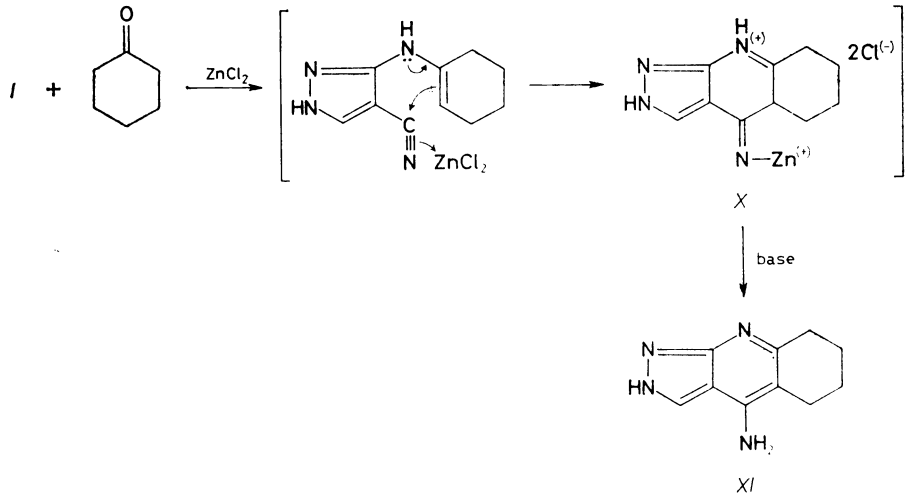
SCHEME 1

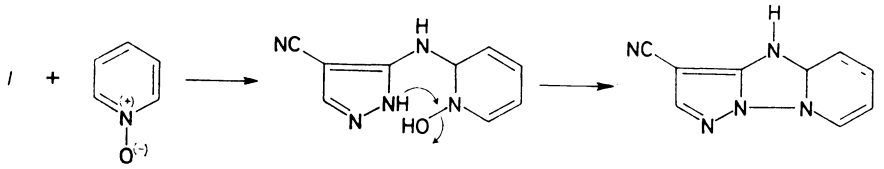
pound *I* reacted with phenyl isothiocyanate in dimethyl formamide to give N-(4--cyanopyrazol-3-yl)-N'-phenylthiourea *VIII* as the only product which was transformed into 1,5-dihydro-6-phenylamino-4*H*-pyrazolo[3,4-*d*]pyrimidine-4-thione *IX* after the treatment with triethylamine in boiling pyridine (Scheme 2).



SCHEME 2

It has been described that anthranilonitrile reacts with cyclohexane to give a cyclocondensation product, an aminoquinoline[6]. The reaction of *I* with cyclohexane in the presence of one molar equivalent of zinc chloride led to separation of a 1 : 1 complex of the expected amino derivative and zinc chloride *X*. 4-Amino-5,6,7,8-tetrahydro-2*H*-





SCHEME 3

-pyrazolo[3,4-*b*]quinoline *XI* was liberated by treatment of this complex with alkaline solution (Scheme 3).

Interest was paid also to study of the reaction of aminopyrazole with pyridine 1-oxide to elucidate if cyclization could be carried out. When compound *I* was treated with pyridine 1-oxide in refluxing dioxane 4*H*,5*H*-pyrazolo[5′,1′ : 2,3]-[1, 2, 4]triazolo[1,5-*a*]pyridine-3-carbonitrile, *XII* was obtained. A mechanism was proposed for the formation of the product. The first step would involve a nucleophilic attack of NH_2 on the pyridine 1-oxide ring, followed by cyclization with the elimination of water molecule to give *XII* (Scheme 3).

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Hitachi Perkin Elmer Va 60 spectrometer with TMS as an internal standard and chemical shifts are expressed as δ(ppm). IR spectra were obtained with a Perkin–Elmer 257 spectrometer (KBr). Analytical data were obtained from the Micro analytical centre, Cairo University.

3-Aminopyrazolo-4-carboxamidoxime *II*

To a solution of 3-amino-4-cyanopyrazole *I* (1·8 g, 0·01 mol) in methanol (50 ml), hydroxylamine hydrochloride (0·69 g, 0·01 mol) was added and the mixture was stirred at room temperature in the presence of NH_4OH (1 ml) for 24 h, the solid product formed was filtered off, dried and crystallized from water to give *II* (yield 70%) with m.p. 210–211°C. For $C_4H_7N_5O$ (141·1) calculated: 34·04% C, 4·99% H; found: 34·20% C, 4·70% H. IR spectrum (cm^{-1}): 3 400–3 300 (NH_2), 3 250 (OH). ^{1}H NMR ($CDCl_3$): 4·25 br, s, 2 H (3-NH_2); 6·0 br, s, 2 H (NH_2); 6·2 s, 1 H (H-4); 9·77 br, s, 1 H (NH); 9·83 s, 1 H (NOH).

1*H*,6*H*-3-Aminopyrazolo[3,4-*c*]pyrazole Hydrochloride *III*

To a solution of 3-amino-4-cyanopyrazole *I* (1·08 g, 0·01 mol) in pyridine (15 ml) hydroxylamine hydrochloride (0·69 g, 0·01 mol) was added, and the reaction mixture was heated under reflux for 5 h. The solvent was then evaporated under reduced pressure and the residue was crystallized from ethanol to give *III* in 15% yield, m.p. 250–251°C. For $C_4H_6N_5Cl$ (159·6) calculated: 30·10% C, 3·79% H; found: 30·40% C, 3·50% H. IR spectrum (cm^{-1}): 3 300–3 250 br (NH_2).

1*H*,6*H*-3-Aminopyrazolo[3,4-*c*]pyrazole *IV*

A suspension of 3-amino-4-cyanopyrazole *I* (1·08 g, 0·01 mol) in hydrazine hydrate (3 ml, 99%) was kept at room temperature for 5 days. The solid product obtained was filtered off and crystallized from acetic acid to give *IV* in 50% yield, m.p. 290–291°C. For $C_4H_5N_5$ (123·1) calculated: 39·02% C, 4·09% H; found: 38·90% C, 4·20% H. IR spectrum (cm^{-1}): 3 400–3 350 (NH_2). ^{1}H NMR ($CDCl_3$): 5·4 br, s, 2 H (NH_2); 6·2 s, 1 H (H-4); 8·1 br, s, 2 H (2 × NH).

3-Acetamidopyrazolo[3,4-*c*]pyrazole *V*

A solution of *IV* (1·23 g, 0·01 mol) in acetic anhydride (10 ml) was refluxed for 5 h. The solvent was then evaporated under reduced pressure and the solid residue was crystallized from ethanol to give *V* in 56% yield, m.p. 230–231°C. For $C_6H_7N_5O$ (165·2) calculated: 43·63% C, 4·27% H; found: 43·40% C, 4·50% H. IR spectrum (cm^{-1}): 3 300 br (NH), 1 670–1 640 (C=O). ^{1}H NMR ($CDCl_3$): 1·9 s, 3 H (CH_3); 6·2 s, 1 H (H-4); 6·5 br, s, 1 H (NHCO); 9·6 br, s, 2 H (2 × NH).

1-[(2,6-Dihydropyrazolo[3,4-*c*]pyrazole-3-yl)azo]-2-naphthol *VI*

To a solution of 2-naphthol (1·4 g, 0·01 mol) in ethanol (40 ml) and water (20 ml) containing sodium acetate (5 g) a solution of diazotized *IV* (0·01 mol) [prepared from *IV* (1·23 g, 0·01 mol) in 50% HCl (3 ml) together with sodium nitrite (0·7 g) in water (2 ml) at 0°C] was added under continuous stirring. The solid product obtained after standing was washed repeatedly with hot water and recrystallized from ethanol to give *VI* in 60% yield, m.p. 270–271°C. For $C_{14}H_{10}N_6O$ (278·3) calculated: 60·42% C, 3·62% H; found: 60·20% C, 3·82% H. IR spectrum (cm^{-1}): 3 250 (OH). ^{1}H NMR ($(CD_3)_2SO$): 6·2 s, 1 H (H-4); 7·8–7·6 m, 6 H (arom); 8·4 br, s, 2 H (2× NH); 9·6 s, 1 H (OH).

Cyclization of *VI*

A solution of *VI* (2·76 g, 0·01 mol) in acetic acid (20 ml) was heated under reflux for 3 h. The solvent was then evaporated under reduced pressure and the solid residue was crystallized from acetic acid to give 9*H*-naphthol[2,1-*e*]pyrazolo[3′,4′ : 3,4]pyrazolo[5,1-*c*][1,2,4]-triazine *VII* in 73% yield, m.p. 300°C. For $C_{14}H_8N_6$ (260·2) calculated: 64·61% C, 3·10% H; found: 64·90% C, 3·30% H. IR spectrum (cm^{-1}): 1 600–1 500 (aromatic rings), no absorption bands referred to the OH group. Owing to the high insolubility of this compound in usual NMR solvents, its NMR spectrum was not recorded.

N-(4-Cyanopyrazol-3-yl)-N′-phenylthiourea *VIII*

To a solution of *I* (1·08 g, 0·01 mol) in dimethyl formamide (20 ml), triethylamine (1·5 ml) and phenyl isothiocyanate (1·6 ml, 0·012 mol) were added, and the reaction mixture was stirred at room temperature for 18 h. The solvent was then evaporated under reduced pressure and the residue was washed repeatedly with water and recrystallized from acetic acid to give *VIII* in 70% yield, m.p. 120–121°C. For $C_{11}H_9N_5S$ (243·3) calculated: 54·30% C, 3·72% H; found: 54·10% C, 3·90% H. IR spectrum (cm^{-1}): 3 200 br (NH), 2 220 (CN). ^{1}H NMR ($CDCl_3$): 6·2 s, 1 H (H-4); 7·3 s, 5 H (C_6H_5); 8·9–8·6 m, 3 H (3 × NH).

1,5-Dihydro-6-(phenylamino)-4*H*-pyrazolo[3,4-*d*]pyrimidine-4-thione *IX*

To a solution of *VIII* (1·8 g, 0·01 mol) in pyridine (20 ml), triethylamine (2 ml) was added and the mixture was refluxed for 10 h. After cooling, the reaction mixture was poured into water.

The solid product obtained was filtered off and crystallized from ethanol to give *IX*, in 35% yield, m.p. 243–244°C. For $C_{11}H_9N_5S$ (243·3) calculated: 54·30% C, 3·72% H; found: 54·00% C, 3·90% H. IR spectrum (cm^{-1}): 3 200 (NH), and no absorption due to cyano group. ^1H NMR ($(CD_3)_2SO$): 3·3 s, 1 H (NHC_6H_5); 6·4 s, 1 H (H-3); 7·2 m, 5 H (C_6H_5); 8·4 s, 1 H (NH); 10·3 s, 1 H (C–NH–C).

4-Amino-5,6,7,8-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinoline *XI*

To a solution of *I* (1·08 g, 0·01 mol) in cyclohexanone (15 ml) anhydrous zinc chloride (0·25 g, 0·01 mol) was added, and the reaction mixture was refluxed for 20 min. The complex with zinc chloride *X* was separated from the solution, the mixture was dissolved in 40% sodium hydroxide (20 ml), and extracted with benzene. The benzene layer was dried (Na_2SO_4) and evaporated to give *XI* in 82% yield, m.p. 200–201°C. For $C_{10}H_{12}N_4$ (188·2) calculated: 63·80% C, 6·43% H; found: 63·55% C, 6·60% H. IR spectrum (cm^{-1}): 3 420–3 320 (NH_2), and no absorption due to cyano group. ^1H NMR ($(CD_3)_2SO$): 1·5 s, br, 4 H (2 × H-6, 2 × H-7); 1·9 s, br, 2 H (2 × H-5); 2·2 s, br, 2 H (2 × H-8); 6·0 s, 2 H (NH_2); 7·5 s, 1 H (H-3); 8·2 s, 1 H (NH).

4*H*,5*H*-Pyrazolo[5′,1′,2,3][1,2,4]-triazolo[1,5-*a*]pyridine-3-carbonitrile *XII*

To a solution of *I* (1·08 g, 0·01 mol) in dioxane (20 ml) pyridine-1-oxide (0·95 g, 0·01 mol) was added, and the mixture was refluxed for 18 h. The solvent was then evaporated under reduced pressure and the obtained oily residue was washed repeatedly with water and recrystallized from acetic acid to give *XII* in 15% yield, m.p. 230–231°C. For $C_9H_7N_5$ (185·2) calculated: 58·37% C, 3·81% H; found: 58·60% C, 3·90% H. IR spectrum (cm^{-1}): 3 200 br (NH), 2 215 (CN). ^1H NMR ($(CD_3)_2SO$): 2·4 s, 1 H (H-4); 6·4 s, 1 H (H-2); 7·4–7·2 m, 4 H (H-5, H-6, H-7, H-8); 8·1 s, 1 H (NH).

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