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Heterocyclic Synthesis with Nitriles: New Routes for Synthesis of Pyridazines, Pyridines and their Fused Derivatives

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Phenylazocyanothioacetamide **1** reacts with malononitrile to afford the pyridinethione **4** which reacts with phenacylbromide to yield the pyridine-S-phenacyl derivative **6**. **1** reacts with ethyl cyanoacetate to yield the pyridazine derivative, **8**, and with phenacyl bromide to afford the N-phenacyl derivative **11**, instead of the thiazole **10**. Compound **11** afforded the pyrazolopyridine **13** on reaction with malononitrile while **10** was obtained on coupling of the thiazole **14** with diazotised aniline. Compound **10** reacts with malononitrile to afford the thiazolyl pyridazine **15**. Compound **1** reacts with malononitrile dimer to afford the pyridopyridazine derivative **17a**. **1** reacts also with active methylene heterocycles to afford the pyrazolo and thiazolo-fused pyridazines **20** and **23** respectively.

Key words: Pryazolo [4,3-b] pyridine, Pyrido [2,3-d] pyridazine, Thiazolo [4,5-c]-pyridazine

INTRODUCTION

Recently we have been involved in a program aiming to develop new simple procedures for synthesis of biodegradable heterocyclic sustems from laboratory available srarting materials (Kandeel *et al.*, 1986, Elnagdi *et al.*, 1989, 1991, Abdelrazek *et al.*, 1992). In continuation of this work, we report here the synthesis of the title compounds starting from the readily obtainable phenylazocyanothioacetamide **1**.

MATERIALS AND METHODS

All melting points are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer, ^{1}H-NMR spectra were measured on an EM-390 90 MHz spectrometer in DMSO-d_6 using TMS as internal standard. Chemical shifts are expressed as δ ppm. Analytical data were obtained from the Microanalytical Center at Cairo University.

Recation of 1 with malononitrile, ethyl cyanoacetate, phenacyl bromide, malononitrile dimer, 3-methyl-1-phenyl-2-pyrazolin-5-one and 2-cyand-methylene-5H-thiazolidin-4-one. (General procedure)

Equimolecualr amounts of **1** (2 g, 0.01 mol) and the corresponding active methylene compound (0.01 mol) were refluxed in pyridine (30 ml) for three hours. The reaction mixture was poured after cooling to room temperature onto cold water and neutralized by hydrochloric acid to yield solid products, which were collected by filteration and recrystallized from the proper solvent to give **4**, **8**, **11**, **17**, **19** and **23** respecively.

2,4-Diamino-5,6-dihydro-5-phenylhydrazone-6-thioxopyridin-3-carbo-nitrile, 4

Brown crystals m.p. >300°C (DMF/EtOH) 72% IR: 3335 (NH_2), 2204 (CN). ^{1}H-NMR: 3.7 (br, s, 2H, NH_2), 7.4-7.9 (m, 8H, aromatic+NH+NH_2) $C_{12}H_{10}N_6S$ (270.3). Calcd. C 53.3, H 3.7, N 31.1. Found: C 53.3, H 3.8, N 31.6.

4-Amino-1,6-dihydro-1-phenyl-6-oxopyridazin-3,5-dicarbonitrile, 8

Brown crystals m.p. 165°C (EtOH) 63% IR: 3447 (NH_2) 2215 (CN) 1670 (CO). ^{1}H-NMR: 7.15-8.2 (m). $C_{12}H_7N_5O$ (237.2) Calcd. C 60.8, H 3.0, N 29.5. Found:

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C, 60.9, H 3.1, N 30.1.

(Azo-N-phenacyl)-phenylhydrazonocyanothioacetamide, 11

Yellow crystals m.p. 174℃ (EtOH/dioxan) 56%. IR: 3462 (NH_2) 2218 (CN), 1680 (CO). ^{1}H-NMR: 3.2 (s, 2H, CH_2) 4.9 (br, s, 2H, NH_2) 7.1-8 (m, 10H, aromatic). $C_{17}H_{14}N_4OS$ (322.4) Calcd. C 63.3, H 4.4, N 17.4. Found: C 63.2, H 4.4, N 17.9.

6,8-Diamino-1,2-dihydro-1-imino-2-phenyl-7-cyanopyrido[2,3-d]pyridazine-4-thioamide, 17a

Dark brown crystals m.p. >300℃ (DMF) 75%. IR: 3337 (NH_2) 3205 (NH), 2206 (CN). ^{1}H-NMR: 3.4 (br, s, 4H, $2NH_2$) 7.0-7.9 (m, 8H, aromatic+NH+NH_2). $C_{15}H_{12}N_8S$ (336.4) Calcd. C 53.6, H 3.6, N 33.3. Found: C 53.5, H 3.7, N 33.5.

1-Cyano-1-phenylhydrazono-2-thiolo-2-(1-phenyl-3-methyl-5-oxopyrazolin-4-ylidene) glyoxal, 19

Yellow crystals m.p. 219℃ (AcOH) 65%. IR: 3119 (NH) 2218 (CN) 1675 (CO). ^{1}H-NMR 2.0 (s, 3H, CH_3) 3.4 (s, 1H, SH) 7.1-8.0 (m, 10H, aromatic) 14.2 (s, 1H, NH). $C_{19}H_{15}N_5OS$ (361.4) Calcd. C 63.1, H 4.2, N 19.4. Found: C 63.1, H 4.2, N 19.6.

4-Amino-6-cyanomethylene-1-phenyl-6H-thiazolo[4,5-c] pyridazine-3-thioamide, 23

Brown crystals m.p. 165℃ (EtOH/dioxan) 69%. IR: 3487-34 (NH_2): 2211 (CN). ^{1}H-NMR: 4.2 (br, s, 2H, NH_2) 7.1-7.9 (m, 6H, aromatic) 11.1 (br, s, 2H, NH_2). $C_{14}H_{10}N_6S_2$ (326.4). Calcd. C 51.5, H 3.1, N 25.8. Found: C 51.3, H 3.2, N 26.2.

2,4-Diamino-6-phenacylmercapto-5-phenylazopyridin-3-carbonitrile, 6

To a solution of **4** (2.7 g, 0.01 mol) in 30 ml of pyridine was added phenacylbromide (1.99 g, 0.01 mol) and the reaction mixture was refluxed in pyridine. After cooliong down, the reaction mixture was poured on cold water. The solid product so formed was collected by filtration and recrystallised from dioxan/ethanol to give brown crysrals, m.p. >300℃, 76%. IR: 3415-3240 (NH_2) 2210 (CN), 1680 (CO), ^{1}H-NMR: 3.7 (s, 2H, CH_2), 7.1-8.0 (m, 12H, aromatic+NH_2), 10.9 (br, s, 2H, NH_2). $C_{20}H_{16}N_6OS$ (388.5). Calcd. C 61.8, H 4.2, N 21.6. Found: C 61.8, H 4.1, N 21.5.

1-(4-Phenylthiazol-2-yl)-1-phenylhydrazonoglyoxalonitrile, 10

To a cold solution of the thiazole **14** (2 g, 0.01 mol) in ethanol was added 2.0 g of sodium acetate. To this was added dropwise while cooling and stirring a cold solution of diazotised aniline (0.01 mol). The addition took 30 min, after which stirring at room temperature was continued for 2 h. The solid precipitate so formed was filtered off and recrystallized from ethanol to afford reddish drystals m.p. 160℃, 72%. IR: 3240 (NH), 2216 (CN). ^{1}H-NMR: 7.1-8.0 (m, 11H, aromatic), 14.1 (s, 1H, NH). $C_{17}H_{12}N_4S$ (304.4) Calcd. 67.1, H 4.0, N 18.4. Found: C 67.1, H 3.9, N 18.4.

5-Amino-1,7-diphenylpyrazolo[4,3-b] pyridin-3-thioamide, 13

A mixture of **11** (3.2 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) was refluxed in 30 mol of pyridine for 3 h. After cooling down, the reaction mixture was poured onto cold water and acidified with HCl. The solid product so formed was filtered off and recrystallized from DMF/EtOH to give 2.6 g (70%) of **13** m.p. 150℃. IR: 3344 (NH_2), 2211 (CN). ^{1}H-NMR: 3.7 (br, s, 2H, NH_2), 7.1-8.0 (m, 10H, Aromatic), 14.2 (br, s, 2H, NH_2). $C_{20}H_{14}N_6S$ (370.4) Calcd. C 64.9, H 3.8, N 22.7. Found: C 64.7, H 3.8, N 22.6.

4-Amino-1,6-dihydro-6-imino-3-(4-phenylthiazol-2-yl) pyridazin-5-carbo-nitrile, 15

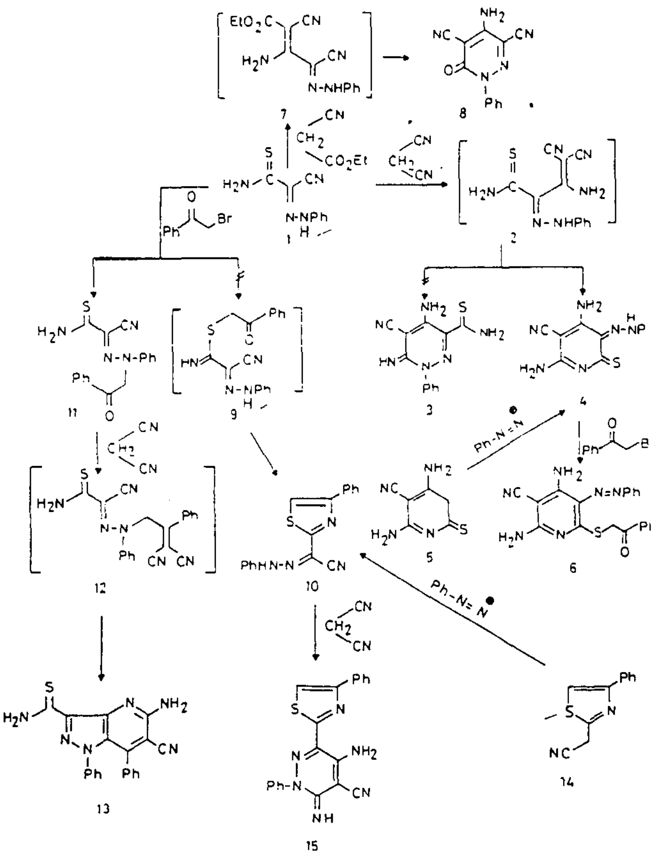
To a solution of **10** (3.0 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) in 30 ml of ethanol was added 0.5 ml of triethylamine as catalyst. The recation mixture was refluxed for 3 h, left to cool, poured onto ice and neutralized with HCl, then the formed precipitate was filtered off and recrystallised to afford red crystals m.p. 189℃ (EtOH), 63%. IR: 3465-3280 (NH_2 +NH), 2218 (CN). ^{1}H-NMR: 7.1-8.0 (m, 13H, Aromatic+NH_2), 14.3 (s, 1H, NH). $C_{20}H_{14}N_6S$ (370.4) Calcd. C 64.9, H 3,8, N 22.7. Found: C 64.8, H 3.8, N 22.8.

3-Cyano-1,7-diphenyl-5-metyl-4-thioxopyrazolo[3,4-c] pyridazine, 20: Cyclisation of 19

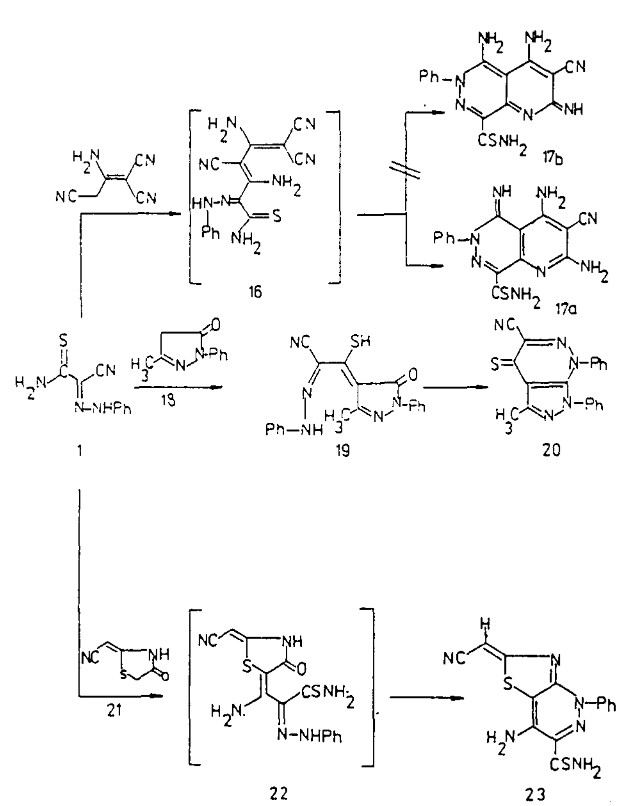
A solution of **19** (3.6 g, 0.01 mol) in acetic acid/acetic anhydride mixture (30 ml. 1:1) was refluxed for 2 h. After cooling to room temperature and dilution with water, a solid precipitate appeared which was filtered off and recrystallized from dil. acetic acid to afford 2.6 g (76%) of 20, m.p. 265℃. IR: 2211 (CN). ^{1}H-NMR 1.85 (s, 3H, CH_3), 7.15-7.85 (m, 10H, aromatic). $C_{19}H_{13}N_5S$ (343.4), Calcd. C 66.5, H 3.8, N 20.4. Found: C 66.5, H 3.9, N 20.7.

RESULTS AND DISCUSSION

Compound **1** reacts with malononitrile in refluxing pyridine to afford a 1:1 adduct. Structures **3** and **4** can be suggested for this product. Analytical and spectral data seem to be of no help to discriminate structures **3** and **4**, however structure **4** was preferred on the



Scheme 1



Scheme 2

basis that this product was found to be identical with an authentic sample obtained from coupling of the previously described pyridine thione **5** (Fahmy *et al.*, 1986) with diazotized aniline.

Compound **4** is assumed to be formed via 1, 2-addition of malononitrile to the CN group in **1** to afford the intermediate **2** which cyclizes into **4** (Scheme 1).

Compound **4** reacts with phenacyl bromide to afford the S-phenacyl deruivative **6**. ^{1}H-NMR spectrum of **6** revealed the presence of a CH_2 singlet at δ 3.7 ppm beside the aromatic and NH_2 protons.

Under similar conditions compound **1** reacts with ethyl cyanoacetate to afford a product, analytical data of which revealed no sulphur. IR-spectrum of this product showed two cyano absorption bands at ν2217 and 2205 cm^{-1} and a carbonyl absorption at ν1670 cm^{-1}. The pyridazine structure **8** was assigned to this product, which is assumed to be formed via cyclization of **1** with ethyl cyanoacetate through elimination of H_2S (Scheme 1). The difference in the behaviour of **1** toward malononitrile and ethyl cyanoacetate is rationalised by acknowledging the existence of two operating reaction pathes, the addition to cyano group and condensation with the thioamide moiety. In case of ethyl cyanoacetate the methylene group is sufficiently acidic to condense with the C=S function forming the condensation intermediate **7**. The merhylene function of malononitrile is not equally active and thus such condensation, if occurs at all, is very slow. Alternate **1**, **2**-addition to the CN function of **1** is much faster and thus the intermediate **2** is formed.

As the thiazole derivative **10** was required for biological evaluation as well as for further transformation, compuund **1** was allowed to react with phenacyl bromide in refluxing pyridine aiming to obtain **10** via the S-phenanyl intemediate **9**. However, ^{1}H-NMR of this product revealed the presence of a CH_2 singlet at δ 3.2 ppm and a broad NH_2 singlet at δ 4.9 ppm. Furthermore, the product proved to be stable under condition expected to effect cyclization of **9**, which eliminates its possibility. Thus structure **11** was assigned to this product.

It is believed that the CH_2 group in **11** is not sufficiently acidic to sharte in cyclization under the applied recation conditions, however, when refluxed with malononitrile in pyridine, the pyrazolopyridine derivative **13** was directly obtained presumably via activated intermediate **12**, which readily undergoes cyclization enhanced by the aromaticity of the formed product **13**. Structure **13** is in complete agreement with analytical and spectral data (cf. Experim. Part). On the other hand the desired thiazole derivative **10** could be obtained via coupling of the thiazole derivative **14** (Schafer *et al.*, 1974) with diazotised anline. Compound **10** reacts with malononitrile in ethanolic triethylamine to afford the thiazolyl pyridazine derivative **15**. Analytical and spectral evidence are in favour of this structure.

Compound **1** reacts with malononitrile dimer in refluxing pyridine to afford a 1 : 1 adduct. IR-spectrum of this product showed a broad absorption band at ν 3337 and 3205 cm^{-1} assignable to the NH_2 and NH groups, and at ν 2206 for a one CN group. ^{1}H-NMR revealed a 4H broad singlet at δ 3.4 ppm and an aromatic multiplet of 8H at δ 7.0-7.9 ppm. The pyridopyridazine structure **17a** was thus assigned to this reaction product, and is assumed to originate from the cyclization of the acyclic intermediate **16** (Scheme 2). Structure **17a** was preferred over possible tautomeric **17b**, since **17a** represents the aromatic benzenonid structure which is more stable than the quinonoid structure **17b**.

The reaction of **1** with active methylene heterocycles has also been investigated. Compound **1** reacts with 3-methyl-1-phenyl-2-pyrazolin-5-one **18** to yield a condensation product via loss of ammonia. Structure **19** was given to this product on the basis of its elemental analysis and spectral data (cf. Experim. Part). Compuond **19** could be cyclised into the pyrazolo pyridazine derivative **20** on reflux in acetic acid/aceticanhydride mixture. The IR-spectrum of **20** showed the disappearance of the carbonyl absorption band compared with that of **19**. ^{1}H-NMR spectrum showed the methyl singlet at δ 1.75 ppm and a **10** H aromatic multiplet at 7.2-8.1 ppm.

Compound **1** also reacts with 2-cyanomethylene-5H-thiazolidin-4-one (Scheme 2) to yield an addition product, which was formulated as **23** presumably obtained through the intermediate **22** via loss of water.

Finally, the obtained heterocyclic systems enriched with functional substituents seem to be interesting for biological investigations as well as for further chemical transformations.

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