

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

Abdalla M. Negm, Fathy M. Abdelrazek, Mohamed H. Elnagdi and Lina H. Shaaban

Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt

(Received July 8, 1994)

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: Pyrazolo [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 systems from laboratory available starting 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, ¹H-NMR spectra were measured on an EM-390 90 MHz spectrometer in DMSO-d₆ using TMS as internal standard. Chemical shifts are expressed as δ ppm. Analytical data were obtained from the Microanalytical Center at Cairo University.

Reaction of 1 with malononitrile, ethyl cyanoacetate, phenacyl bromide, malononitrile dimer, 3-methyl-1-

phenyl-2-pyrazolin-5-one and 2-cyano-methylene-5H-thiazolidin-4-one. (General procedure)

Equimolecular 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 filtration and recrystallized from the proper solvent to give **4**, **8**, **11**, **17**, **19** and **23** respectively.

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

Brown crystals m.p. >300°C (DMF/EtOH) 72% IR: 3335 (NH₂), 2204 (CN). ¹H-NMR: 3.7 (br, s, 2H, NH₂), 7.4-7.9 (m, 8H, aromatic+NH+NH₂) C₁₂H₁₀N₆S (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 (NH₂) 2215 (CN) 1670 (CO). ¹H-NMR: 7.15-8.2 (m). C₁₂H₇N₅O (237.2) Calcd. C 60.8, H 3.0, N 29.5. Found:

Correspondence to: Fathy M. Abdelrazek, Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt

C, 60.9, H 3.1, N 30.1.

(Azo-N-phenacyl)-phenylhydrazonocyanothioacetamide, 11

Yellow crystals m.p. 174°C (EtOH/dioxan) 56%. IR: 3462 (NH₂) 2218 (CN), 1680 (CO). ¹H-NMR: 3.2 (s, 2H, CH₂) 4.9 (br, s, 2H, NH₂) 7.1-8 (m, 10H, aromatic). C₁₇H₁₄N₄OS (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°C (DMF) 75%. IR: 3337 (NH₂) 3205 (NH), 2206 (CN). ¹H-NMR: 3.4 (br, s, 4H, 2NH₂) 7.0-7.9 (m, 8H, aromatic+NH+NH₂). C₁₅H₁₂N₈S (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°C (AcOH) 65%. IR: 3119 (NH) 2218 (CN) 1675 (CO). ¹H-NMR 2.0 (s, 3H, CH₃) 3.4 (s, 1H, SH) 7.1-8.0 (m, 10H, aromatic) 14.2 (s, 1H, NH). C₁₉H₁₅N₅OS (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°C (EtOH/dioxan) 69%. IR: 3487-34 (NH₂): 2211 (CN). ¹H-NMR: 4.2 (br, s, 2H, NH₂) 7.1-7.9 (m, 6H, aromatic) 11.1 (br, s, 2H, NH₂). C₁₄H₁₀N₆S₂ (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 cooling 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 crystals, m.p. >300°C, 76%. IR: 3415-3240 (NH₂) 2210 (CN), 1680 (CO), ¹H-NMR: 3.7 (s, 2H, CH₂), 7.1-8.0 (m, 12H, aromatic+NH₂), 10.9 (br, s, 2H, NH₂). C₂₀H₁₆N₆OS (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 crystals m.p. 160°C, 72%. IR: 3240 (NH), 2216 (CN). ¹H-NMR: 7.1-8.0 (m, 11H, aromatic), 14.1 (s, 1H, NH). C₁₇H₁₂N₄S (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 ml 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°C. IR: 3344 (NH₂), 2211 (CN). ¹H-NMR: 3.7 (br, s, 2H, NH₂), 7.1-8.0 (m, 10H, Aromatic), 14.2 (br, s, 2H, NH₂). C₂₀H₁₄N₆S (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

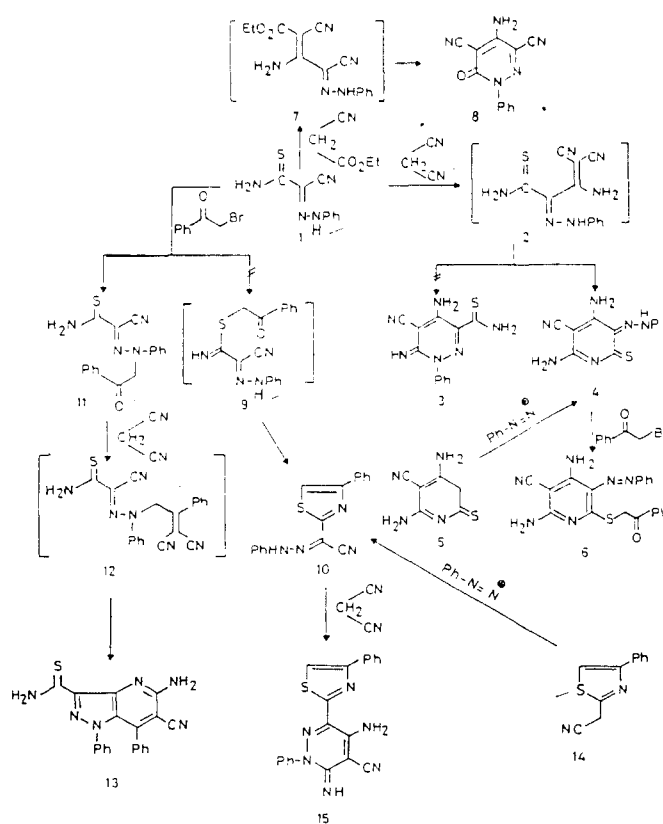
To a solution of **10** (3.0 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) in 30 ml of ethanol was added 0.5 ml of triethylamine as catalyst. The reaction mixture was refluxed for 3 h, left to cool, poured onto ice and neutralized with HCl, then the formed precipitate was filtered off and recrystallised to afford red crystals m.p. 189°C (EtOH), 63%. IR: 3465-3280 (NH₂+NH), 2218 (CN). ¹H-NMR: 7.1-8.0 (m, 13H, Aromatic+NH₂), 14.3 (s, 1H, NH). C₂₀H₁₄N₆S (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-methyl-4-thioxopyrazolo[3,4-c] pyridazine, 20: Cyclisation of 19

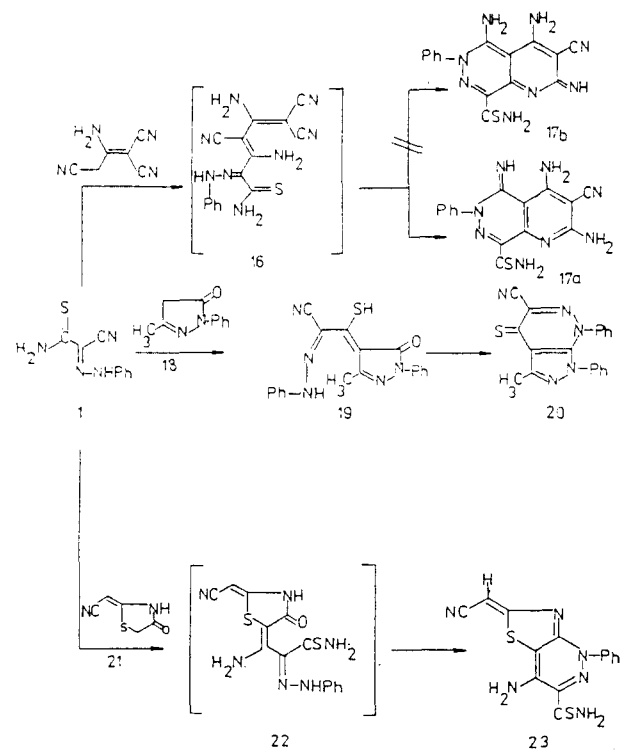
A solution of **19** (3.6 g, 0.01 mol) in acetic acid/ acetic anhydride mixture (30 ml. 1:1) was refluxed for 2 h. After cooling to room temperature and dilution with water, a solid precipitate appeared which was filtered off and recrystallized from dil. acetic acid to afford 2.6 g (76%) of **20**, m.p. 265°C. IR: 2211 (CN). ¹H-NMR 1.85 (s, 3H, CH₃), 7.15-7.85 (m, 10H, aromatic). C₁₉H₁₃N₅S (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 derivative 6. $^1\text{H-NMR}$ 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 ν 2217 and 2205 cm^{-1} and a carbonyl absorption at ν 1670 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 paths, 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 $\text{C}=\text{S}$ function forming the condensation intermediate 7. The methylene func-

tion 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, compound 1 was allowed to react with phenacyl bromide in refluxing pyridine aiming to obtain 10 via the S-phenacyl intermediate 9. However, $^1\text{H-NMR}$ 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 reaction 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. Experm. 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 aniline. 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. $^1\text{H-NMR}$ 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 benzenoid 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. Experiments). Compound **19** could be cyclised into the pyrazolo pyridazine derivative **20** on reflux in acetic acid/acetic anhydride mixture. The IR-spectrum of **20** showed the disappearance of the carbonyl absorption band compared with that of **19**. $^1\text{H-NMR}$ 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.

REFERENCES CITED

- Abdelrazek, F. M., Salah, A. M., Elbazza, Z. E., Synthesis of novel thieno-[2,3-d] pyrimidine, thieno[2,3-b]pyridine and thiazolo[3-2,a]thieno[2,3-d]-pyrimidine derivatives and their effect of the production of Mycotoxin. *Arch Pharm. (Weinheim)*, 325, 301-305 (1992).
- Elnagdi, M. H., Abdelrazek, F. M., Ibrahim, N. S., Erian, A. W., Studies on alkylheteroaromatic compounds. The reactivity of polyfunctionally substituted azines towards electrophilic reagents. *Tetrahedron*, 45(11), 3597-3604 (1989).
- Elnagdi, M. H., Ghozlan, S. A. S.M Abdelrazek, F. M., Seliem, M A., Studies with polyfunctionally substituted heterocycles., Synthesis of new thiopyrans, pyridines, pyrans and their fused derivatives with other ring systems. *J. Chem. Res.(s)*, 116-117 (1991).
- Fanmy, S. M., Mohareb, R. M., Cyanothioacetamide in heterocyclic synthesis., A novel synthesis of 2-pyridothione derivatives. *Tetrahedron*, 42, 687-690 (1986).
- Kandeel, Z. E., Abdelrazek, F. M., Elnagdi, M. H., Torgoman, A. M., Nitriles in heterocyclic synthesis., New route for the synthesis of pyridine and pyrido[2,3-d] pyridazine derivatives. *Heterocycles*, 24(9), 2455-2461 (1986).
- Schafer, H., Gewald, K., Zur chemie des 4-phenylthiazolyl-(2)-acetonitrils. *J. Prakt. Chem.*, 316, 684-692 (1974).