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Synthesis of Some New 2-Azolyl- and Azinylthiopyrimidines

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A facile convenient syntheses of the titled compounds, via reacting the precursor 2-amino-2-(pentane-2,4-dion-3-ylthio)-6-phenylpyrimidine-5-carbonitrile (1) with nitrogen nucleophiles and with the carbanions of some active methylene compounds, is reported. Chemical and spectroscopic evidence of the newly synthesised compounds are described.

Key words: 2-Azolyl- and azinylthiopyrimidines

INTRODUCTION

Pyrimidines have remarkably expanded the contribution to biological and medicinal chemistry. Various analogues of thiopyrimidines have been used as effective antimicrobial (Ram *et al.*, 1989), antileishmanial (Garg *et al.*, 1990), and antibacterial (West, 1988) agents. On the other hand, pyrazoles have receive considerable interest due to their potentially biological importance (Elnagdi *et al.*, 1990), (Emmett *et al.*, 1982). Also many pyridine derivatives have been used as antimalarial and antileukemic agents (Scovill *et al.*, 1982). In view of the aforesaid versatile benefits, and in connection with our previous work (Sherif *et al.*, 1993), (Abdel-Fattah *et al.*, 1992), we aimed at incorporating the thioxopyrimidine moiety with either a pyrazole or pyridine moiety to produce some new heterocyclic compounds and determine their biological activities.

MATERIALS AND METHODS

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H-NMR were obtained with a Varian ^{1}H-Gemini 200 spectrometer and chemical shifts are expressed in δ (ppm) using TMS as the internal standard. The elementary analyses were performed by the Microanalytical Data Center, Cairo University, Egypt. Compound **1** was prepared according to our previously reported method (Daboun and El-Reedy, 1983).

Synthesis of 4-amino-2-(3,5-dimethyl-1-thiocarbamoylpyrazol-4-ylthio)-6-phenylpyrimidine-5-carbonitrile (2)

A mixture of **1** (1.63 gm, 5 mmoles) and thiosemicarbazide (0.45 gm, 0.005 mmoles) in ethanol (30 ml) containing a catalytic amount of concentrated hydrochloric acid (3 drops) was heated, under reflux, for 5 h. The reaction mixture was cooled, and poured onto cold water, whereby the solid product precipitated and was collected by filtration, dried and crystallizaed from dilute dioxane. Yield 1 g (55%), m.p. 290℃. IR (cm^{-1}): 3287, 3113 (NH) and 2220 (CN). ^{1}H-NMR (DMSO-d_6): δ 2.16 (s, 6H, $2CH_3$), 7.55 (m, 3H, arom. protons), 7.73 (m, 2H, arom. protons), 7.81 (br, s, 2H, NH_2, D_2O exchangeable) and 12.62 (s, 2H, NH_2, D_2O exchangeable). Anal for $C_{17}H_{15}N_7S_2$ (381.29) Calcd. C, 53.54; H, 3.93; N, 25.70; S, 16.81. Found: C, 53.5; H, 3.7; N, 25.6; S, 16.6.

Synthesis of 3-(4-amino-5-cyano-6-phenylpyrimidin-2-ylthio)-2,4-dimethyl-1H-1,5-benzodiazepine (4)

A mixture of **1** (1.63 gm, 5 mmoles) and o-phenylenediamine (0.54 gm, 5 mmoles) in ethanol (30 ml) containing a catalytic amount of concentrated hydrochloric acid (3 drops) was refluxed for 5 h. The reaction mixture was then poured onto cold water, whereby the solid product so formed was collected, dried and crystallized from acetic acid. Yield 1.39 g (70%), m.p. 190℃. IR (cm^{-1}): 3300, 3120 (NH) and 2215 (CN). Anal for $C_{22}H_{18}N_6S$ (398.28) Cacld. C, 66.34; H, 4.51; N, 21.09; S, 8.04. Found: C, 66.2; H, 4.5; N, 20.7; S, 8.0.

Synthesis of 4-amino-2-(o-aminoanilino)-6-phenylpyrimidine-5-carbonitrile (5)

Method (A): The same experimental procedure described above for the synthesis of **4** has been followed up using ammonium acetate (0.64 gm, 6 mmoles) as

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a catalyst instead of concentrated hydrochloric acid. Yield 1 gm (70%), m.p. 285°C (dilute acetic acid). IR (cm^{-1}): 3436, 3399 (NH) and 2203 (CN). ^{1}H-NMR (DMSO-d_6): δ 4.85(br, s, 2H, NH_2, D_2O exchangeable), 6.92 (s, 2H, NH_2, D_2O-exchangeable), 7.27-7.92 (m, 9H, arom. protons) and 8.80 (s, 1H, NH, D_2O exchangeable). Anal for $C_{17}H_{14}N_6$ (302.17), (M^+=302, 100%) Calcd. C, 67.56; H, 4.63; N, 27.79. Found: C, 67.4; H, 4.6; N, 27.6.

Method (B): A mixture of **6** (1.21 gm, 5 mmoles) and o-phenylenediamine (0.054 gm, 5 mmoles) in ethanol (30 ml) was heated, under reflux, for 3 h. The reaction mixture was cooled, poured onto cold water, whereby the solid product that precipitated was filtered off, dried and crystallized from dilute acetic acid. Yield 0.9 gm (60%), identical in all aspects with an authentic sample prepared according to method A (m. p., mixed m.p. and IR spectrum).

Synthesis of 4-amino-2-(3,5-dimethyl-1H-pyrazol-4-ylthio)-6-phenylpyrimidine-5-carbonitrile. acetate (7)

A mixture of **1** (1.63 gm, 3 mmoles) and hydrazine hydrate (1.5 ml, 3 mmoles) in ethanol (30 ml) containing ammonium acetate (0.46 gm, 6 mmoles) was heated, under reflux, for 3 h. The reaction mixture was then poured onto cold water, whereby the solid product so precipitated was filtered off, dried and crystallized from dilute acetic acid. Yield 1.3 gm (70%), m.p. 275°C. IR (cm^{-1}): 3302, 3125 (NH) and 2221 (CN). ^{1}H-NMR (DMSO-d_6): δ 2.06 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 7.51-7.67 (m, 5H, arom. protons), 7.77 (br, s, 2H, NH_2, D_2O exchangeable) and 12.71 (s, 1H, COOH, D_2O exchangeable). Anal for $C_{18}H_{18}N_6O_2S$ (382.22) Calcd. C, 56.56; H, 4.70; N, 21.97; S, 8.38. Found: C, 56.4; H, 4.5; N, 21.9; S, 8.2.

Synthesis of 4-amino-2-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-ylthio)-6-phenylpyrimidine-5-carbonitrile (8)

The same experimental procedure described above for the synthesis of 7 has been followed up using phenylhydrazine (0.64 gm, 6 mmoles) instead of hydrazine hydrate. Yield 0.99 gm (50%), m.p. 230°C (dilute ethanol). IR (cm^{-1}): 3305, 3144 (NH) and 2210 (CN). Anal for $C_{22}H_{18}N_6S$ (398.22) Calcd. C, 66.35; H, 4.52; N, 21.09; S, 8.03. Found: C, 66.3; H, 4.5; N, 20.9; S, 7.9.

Synthesis of 9-11, 15 and 17: General procedure

Equimolecular amounts of **1** (5 mmoles) and each of the appropriate active methylene compound (in case of each of malononitrile and monothiomalonamide, 1 mmoles was used) in ethanol (30 ml) containing ammonium acetate (0.46 gm, 6 mmoles) was refluxed for 5 h. The reaction mixture was cooled, poured onto cold water and the precipitate was filtered off, dried and crystallized from the proper solvent.

4-Amino-2-[6-amino-2,4-dimethyl-5-(p-chlorophenylcarbamoly)pyridin-3-ylthio]-6-phenylpyrimidine-5-carbonitrile (9)

Yield 1.75 gm (70%), m.p. 165°C (acetic acid). IR (cm^{-1}): 3380, 3200 (NH), 2220 (CN) and 1670 (CO). ^{1}H-NMR (DMSO-d_6): δ 2.26 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.93 (s, 2H, NH_2, D_2O exchangeable), 4.09(s, 2H, NH_2, D_2O exchangeable), 7.36-7.86 (m, 9H, arom. protons) and 10.45 (s, 1H, NH, D_2O exchangeable). Anal for $C_{25}H_{20}ClN_7OS$(503.44) Calcd. C, 59.64; H, 3.98; Cl, 7.06, N, 19.53; S, 6.38. Found: C, 59.7; H, 3.8; Cl, 7.0; N, 19.5; S, 6.4.

4-Amino-2-(3-cyano-4,6-dimethyl-2-thioxopyridin-5-ylthio)-6-phenylpyrimidine-5-carbonitrile (10)

Yield 1 gm (60%), m.p. 310°C (dilute dimethylformamide). IR (cm^{-1}): 3400-3350 (NH) and 2217, 2210 (2 CN). Anal for $C_{19}H_{14}N_6S_2$ (390.31) (M^+=390, 100%) Calcd. C, 58.46; H, 3.58; N, 21.52; S, 16.42. Found: C, 58.3; H, 3.5; N, 21.4; S, 16.4.

3-(4-Amino-5-cyano-6-phenylpyrimidin-2-ylthio)-5,7-diamino-2,4-dimethyl-1,8-naphthyridine-6-carbonitrile (11)

Yield 1.5 gm (70%), m.p. 250°C (acetic acid). IR (cm^{-1}): 3380-3320 (NH) and 2218, 2220 (2CN). ^{1}H-NMR ($CDCl_3$): δ 2.32 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.51-7.54 (m, 3H, arom. protons) and 7.69-8.01 (d, 2H, arom. protons). Anal for $C_{22}H_{17}N_9S$ (439.34); (M^+=439, 24%) Calcd. C, 60.14; H, 3.86; N, 28.69; S, 7.83. Found: C, 60.0; H, 3.6; N, 28.6; S, 7.7.

4-Amino-2(3-cyano-2-dicyanomethylene-4,6-dimethyl-1H-pyridin-5-ylthio)-6-phenylpyrimidine-5-carbonitrile (15)

Yield 1.68 gm (80%), m.p. 295°C (dilute dimethylformamide). IR (cm^{-1}): 3300, 3235 (NH) and 2212, 2190 (CN groups). Anal for $C_{22}H_{14}N_8S$ (422.28); (M^+=422, 13.8%) Calcd. C, 62.57; H, 3.31; N, 26.52; S, 7.59. Found: C, 62.4; H, 3.3; N, 26.5; S, 7.3.

4-Amino-6-(4-amino-5-cyano-6-phenylpyrimidin-2-ylthio)-5,7-dimethylpyrido[2,3-d]pyrimidine-2-acetamide (17)

Yield 1.5 gm (70%), m.p. 190°C (dilute acetic acid). IR (cm^{-1}): 3463, 3365 (NH), 2215 (CN) and 1647 (2 CO). ^{1}H-NMR ($CDCl_3$): δ 2.33 (s, 6H, $2CH_3$), 3.95 (s, 2H, CH_2), 5.74 (br, s, 2H, NH_2, D_2O exchangeable), 7.54 (m, 3H, arom. protons) and 7.94 (m, 2H, arom. protons). Anal for $C_{22}H_{19}N_9OS$ (457.27); (M^+=457, 20.3

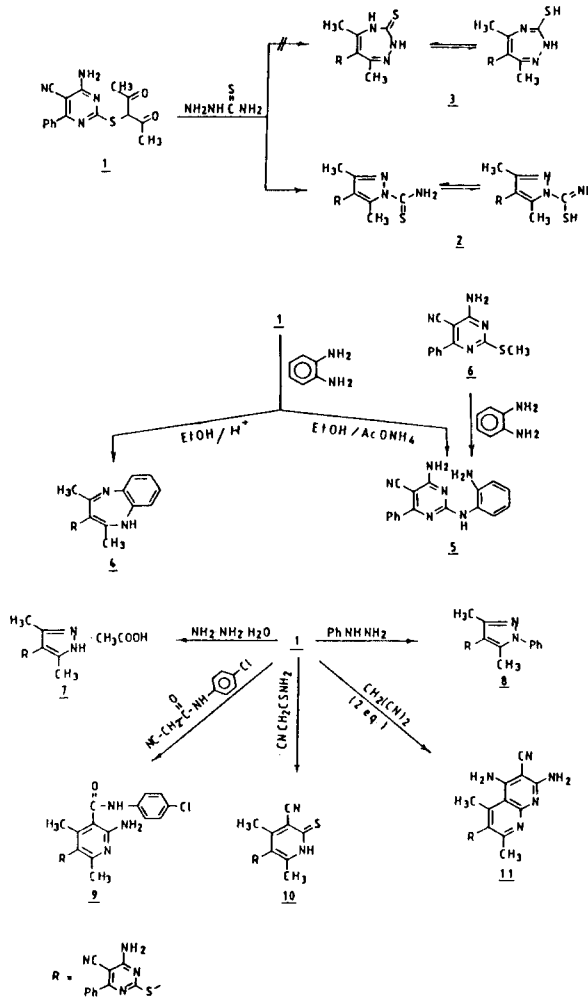
%) Calcd. C, 57.78; H, 4.15; N, 27.55; S, 7.01. Found: C, 57.6; H, 4.0; N, 27.3; S, 6.8.

RESULTS AND DISCUSSION

Our approach to the synthesis of the desired compounds started with 4-amino-2-(pentane-2,4-dion-3-ylthio)-6-phenylpyrimidine-5-carbonitrile (**1**) (Daboun and El-Reedy, 1983). Condensation of equimolecular amounts of **1** with thiosemicarbazide in refluxing ethanol in the presence of few drops of hydrochloric acid yielded a product that could be formulated as the 4-amino-2-(3,5-dimethyl-1-thiocarbamoylpyrazol-4-ylthio)-6-phenylpyrimidine-5-carbonitrile (**2**) or the isomeric structure **3**. The tautomeric forms of **2** or **3** could not be ruled out (cf. Scheme 1). ^{1}H-NMR spectrum (DMSO-d_6) of the reaction product showed signals at δ 2.16 (s, 6H, $2CH_3$), 7.55 (m, 3H, arom. protons), 7.73 (m, 2H, arom. protons), 7.81 (s, br, 2H, NH_2, D_2O-exchangeable) and 12.62 (s, 2H, NH_2, D_2O-exchangeable). ^{1}H-NMR data could not differentiate sharply between **2** and **3**. Analysis of the mass spectra of **2** and **3** proved helpful for differentiating the two structures. Thus, the MS of the reaction product showed a distinct peak at m/z 289 (18.3%) which could only be obtained by the loss of a $CSNH_2$ moiety from **2**, and since structure **3** could never loss $CSNH_2$, it was excluded and structure **2** was assigned to the reaction product.

The reaction of **1** with o-phenylenediamine proved to be dependent upon the reaction conditions. Thus, when **1** and o-phenylenediamine were heated under reflux in ethanol in presence of few drops of hydrochloric acid, the condensation product that could be formulated as the 3-(4-amino-5-cyano-5-phenylpyrimidin-2-ylthio)-2,4-dimethyl-1H-1,5-benzodiazepine (**4**) was obtained. Both elemental analyses and spectral data of **4** were in agreement with its assigned structure. Thus, the IR spectrum of **4** displayed an NH absorption band near 3436 cm^{-1} and no carbonyl band was observed.

Surprisingly, the reaction of **1** with o-phenylenediamine in refluxing ethanolic ammonium acetate led to an unexpected reaction product. The structure of such product could be deduced as 4-amino-2-(o-aminoanilino)-6-phenylpyrimidine-5-carbonitrile (**5**) on the following basis: (a) It was found to be a sulphur free compound. (b) Its IR spectrum showed no absorption in the carbonyl region. (c) ^{1}H-NMR (DMSO-d_6) showed no chemical shifts up to δ 4.8 ppm, indicating no methyl protons. (d) Its MS spectrum showed a molecurlar ion peak at m/z 302 (100%) corresponding to the molecular formula $C_{17}H_{14}N_6$. (e) Compound **5** could be independently prepared by refluxing the 2-methylthiopyrimidine derivative **6** with o-phenylenediamine in ethanol.



Scheme 1

Compound **1**, as a typical 1,3-diketones, reacted with equimolecular amount of hydrazine hydrate, in refluxing ethanol containing ammonium acetate, to afford the condensation product, 4-amino-2-(3,5-dimethyl-1H-pyrazol-4-ylthio)-6-phenylpyrimidine-5-carbonnitrile (**7**) as acetate salt (Scheme I). The structure of **7** was confirmed by elemental and spectral data. Thus, its ^{1}H-NMR spectrum (DMSO-d_6) revealed signals at δ (ppm): 2.06 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 7.51-7.67 (m, 5H, aromatic protons), 7.77 (br, s, 2H, NH_2, D_2O exchangeable) and 12.71 (s, 1H, COOH, D_2O exchangeable). Similarly, compound **1** reacted with phenylhydrazine under the same experimental condition to afford 4-amino-2-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-ylthio)-6-phenylpyrimidine-5-carbanitrile (**8**) with agreeable values in elemental analyses and compatible IR data.

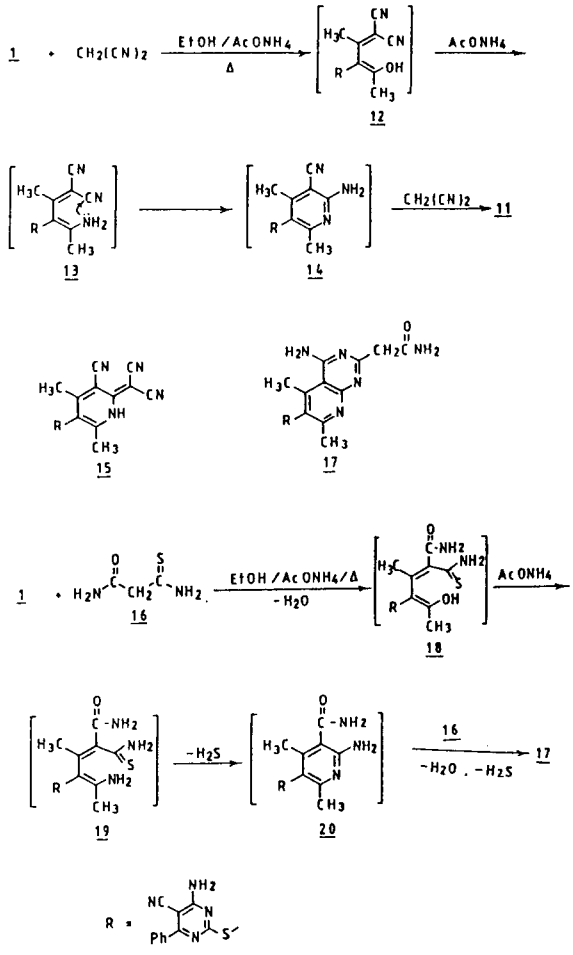
Next, it was of interest to investigate the reactivity of **1** towards carbanions of activated methylene compounds aiming at a facile synthesis of heterocycles

of expected biological activities. Thus, compound **1** reacted with p-chlorocyanoacetanilide in refluxing ethanol, containing ammonium acetate, to produce a product which could be analyzed for $C_{25}H_{20}ClN_7OS$. Based on spectral data, the 4-amino-6-phenyl-2-(pyridin-5-ylthio)pyrimidine-5-carbonitrile (**9**) was established for such a product. Thus, its ^{1}H-NMR spectrum (DMSO-d_6) revealed signals at δ (ppm): 2.26 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.93 (s, 2H, NH_2, D_2O exchangeable), 4.09 (s, 2H, NH_2, D_2O ex-changeable), 7.36-7.86 (m, 9H, aromatic protons) and 10.45 (s, 1H, NH, D_2O exchangeable).

When **1** was heated under reflux with 2-cyanothioacetamide, in ethanol containing ammonium acetate, the condensation product having the molecular formula $C_{19}H_{14}N_6S_2$ (m/z=390, 100%) was formed. The 4-amino-2-(3-cyano-4,6-dimethyl-2-thioxopyridin-5-ylthio)-6-phenylpyrimidine-5-carbonitrile (**10**) was assigned for this product based on correct elemental analyses and spectral data. Thus, its IR spectrum displayed absorption bands near 3400 and 3350 cm^{-1} (NH & NH_2) and 2217 cm^{-1} (CN).

Trials to react equimolecular amounts of **1** and malononitrile in refluxing ethanolic-ammonium acetate solution led to the formation of poor yield of a product analyzed for $C_{22}H_{17}N_9S$ (m/z=439, 24%). The same product was obtained in good yield on reacting compound **1** with two equivalents of malononitrile. The elemental analyses and spectral data of both products could be rationalized in terms of the 3-(4-amino-5-cyano-6-phenylpyrimidin-2-ylthio)-5,7-diamino-2,4-dimethyl-1,8-naphthyridine-6-carbonitrile (**11**). Thus, the IR spectrum displayed absorption bands at 3380-3320 (NH_2) and 2218, 2220 cm^{-1} (2CN). Its ^{1}H-NMR spectrum ($CDCl_3$) showed signals at δ (ppm) 2.32 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.51-7.54 (m, 3H, aromatic protons) and 7.96-8.01 (d, 2H, aromatic protons). Formation of **11** was assumed to be proceeded via intermediacy of the condensation product **12** which reacted with ammonium acetate to give the amino intermediate **13**, followed by spontaneous cyclization to give **14**. The enamino nitrile moiety in **14** added to another molecular of malononitrile to give the final isolable product **11** (Scheme 2).

On the other hand, the reaction of **1** with malononitrile dimer (Taylor and Hartke, 1959) in refluxing ethanol, in presence of ammonium acetate, was investigated and resulted in the formation of the condensation product **15**, which was found to be completely different from **11**. On the basis of elemental analyses, IR and mass spectral data, such a reaction product could be formulated as 4-amino-2-(3-cyano-2-dicyanomethylene-4,6-dimethyl-1H-pyridin-5-ylthio)-6-phenylpyrimidine-5-carbonitrile (**15**). Thus, the MS spectrum of **15** showed a molecular ion peak at m/z 422 (13.8



Scheme 2

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Compound **1** reacted with monothiomalonamide (**16**) (Schaper, 1985) in ethanolic ammonium acetate solution, under reflux, to afford a product analyzed for $C_{22}H_{19}N_9OS$ (m/z=457,24.5%). The 4-amino-6-(4-amino-5-cyano-6-phenylpyrimidin-2-ylthio)-5,7-dimethylpyrido[2,3-d]pyrimidine-2-acetamide (**17**) was established for the reaction product based on its correct elemental analyses and compatible spectroscopic data. Thus, its ^{1}H-NMR spectrum ($CDCl_3$) revealed signals at δ (ppm): 2.33 (s, 6H, $2CH_3$), 3.95 (s, 2H, CH_2), 5.74 (br, s, 2H, NH_2, D_2O exchangeable), 7.54 (m, 3H, aromatic protons) and 7.94 (m, 2H, aromatic protons). Formation of **17** was assumed to proceed via initial formation of the condensation product **18**, which in the presence of ammonium acetate was converted to the amino derivative **19**, followed by spontaneous cyclization, via loss of a H_2S molecule, into **20**. The latter condensed with another molecule of monothiomalonamide to afford the final isolable product **17** (Scheme 2).

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