Studies on Fused Azoles: Synthesis of Several New Polyfunctionally Substituted Fused Pyrazoles

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The synthesis of several new polyfunctionally substituted fused pyrazoles via reaction of 5-amino-3-methylthio-1*H*-pyrazole-4-carbonitrile (**1**) with different reagents is described.

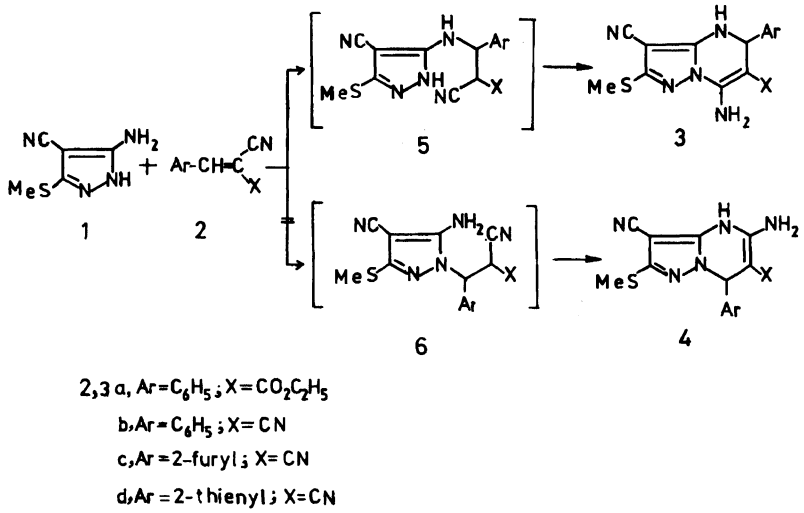
Polyfunctionally substituted heteroaromatics are biologically interesting molecules and their synthesis has recently received considerable attention.[1—3] In previous work we have reported several synthesis of fused azoles,[4] azines,[5] and benzazines,[6,7] which are required as potential biodegradable agrochemicals. In connection with this work, samples of certain polyfunctionally substituted fused pyrazoles were required. Diverse biological activities have been reported for fused pyrazoles. Among these are reports on the activity of certain derivatives as potential antischistosomal reagents.[8] In this article we report on the results of our investigations using 5-amino-3-methylthio-1*H*-pyrazole-4-carbonitrile (**1**) as a starting material.[9]

Thus, it has been found that compound **1** reacts with the ethyl cinnamate derivative **2a** to yield a 1 : 1 adduct. This may be formulated as the 7-aminopyrazolo[1,5-*a*]-pyrimidine (**3a**) or the 5-amino isomer (**4a**). Structure **3a** was considered more likely, based on analogies in the literature.[10,11] Although monoaminopyrazoles are established to react with cinnamonitriles through initial attack by the ring nitrogen, since it is the most basic center in the molecule,[12,13] 3,5-diaminopyrazoles react by initial attack of the exocyclic amino function since this amino is the more basic in these molecules and the least hindered site.[14] Amino functions in 3,5-diaminopyrazoles are situated in such a way that they interfere with the lone pair resonance of each other, which leads to increased basicity of the exocyclic amino group. Similarly, the SCH_3 function in **1** increases the basicity of the exocyclic amino group by sulfur lone pair resonance. We have shown[14] that a delicate balance between steric factors and relative basicities operates in deciding the site at which electrophiles would attack pyrazole nitrogens. Moreover, ^{1}H NMR of the reaction product showed an amino signal at $\delta=7.8$ ppm that is downfield shifted by ring nitrogen anisotropy. It is worth noting that the position of this signal in ^{1}H NMR has been used earlier to differentiate between 7-amino and 5-aminopyrazolo[1,5-*a*]pyrimidines.[14] Although we first observed the –CH signal of C-5 in **3a** as a singlet, high resolution ^{1}H NMR showed this signal as a doublet with a small J value. Similarly, compounds **2b**—**d** reacted with **1** to yield **3b**—**d**. Compounds **3a**—**d** were assumed to be formed via addition of an exocyclic amino function to the activated double bond system in **2a**—**d** to form the Michael adduct **5**, which then cyclizes into **3** (Chart 1). Alternatively, addition of a ring nitrogen to **2a**—**d** to form the Michael adduct **6** will lead to formation of **4a**—**d**.

The diazonium salt (**7**) of compound **1** reacted with 2-naphthol gave arylazo derivative **8**. Compound **8** could be cyclized into **9** by refluxing in acetic acid. This is in contrast to the reported direct formation of cyclic pyrazolo[5,1-*c*][1,2,4]triazine on coupling diazotized aminopyrazoles with naphthols.[15] Similarly to 2-naphthol, resorcinol also coupled with diazotized **1** to yield the aryl azo compound **10**, which could be readily cyclized into **11** on reflux in acetic acid.

In contrast to this behavior, diozotized **1** coupled with ethyl cyanoacetate to yield a compound of the molecular formula $C_{10}H_{10}N_6O_2S$ (m/z 278 M^+). This was formulated as the pyrazolo[5,1-*c*][1,2,4]triazine **12** based on spectral data. Thus, IR spectra showed the presence of an amino function at $\nu=3240$ cm^{-1}, only one cyano group at 2200 cm^{-1}, and an ester carbonyl at $\nu=1720$ cm^{-1}. ^{1}H NMR spectra showed an absorption band at $\delta=9.3$ ppm that was integrated for two protons. This was assigned for an amino function. The downfield shift of this amino function could be explained by the anisotropic effect of the ring nitrogen. Also ^{1}H NMR showed as ester and *S*-methyl groups. Similarly, diazotized **1** coupled with ethyl acetoacetate or benzoylacetonitrile to afford the corresponding pyrazolo[5,1-*c*][1,2,4]triazine derivatives **13a,b** (Chart 2). It is assumed that **7** was in equilibrium with its diazoniobetaine. When a usual coupling took place, aryl azo derivatives were formed. However, reaction with the betaine took place via [4+2]cycloaddition leading to the formation of the cyclic product.

When compound **1** was refluxed for a long period with acrylonitrile in pyridine in the presence of a catalytic amount of potassium hydroxide, it afforded a 1 : 1 adduct. This may be formulated as **14**, **15**, or **16**. Structure **16** was readily established based on an IR spectrum that showed an absorption band for a ring carbonyl at $\nu=1690$ cm^{-1}. The behavior of **1** toward acrylonitrile thus parallels that of other 3-amino-1*H*-pyrazoles.[16] Structure **14** was readily eliminated since the same reaction product was also obtained from reac-



2,3 a, Ar=C_6H_5; X=$CO_2C_2H_5$
b, Ar=C_6H_5; X=CN
c, Ar=2-furyl; X=CN
d, Ar=2-thienyl; X=CN

Chart 1.

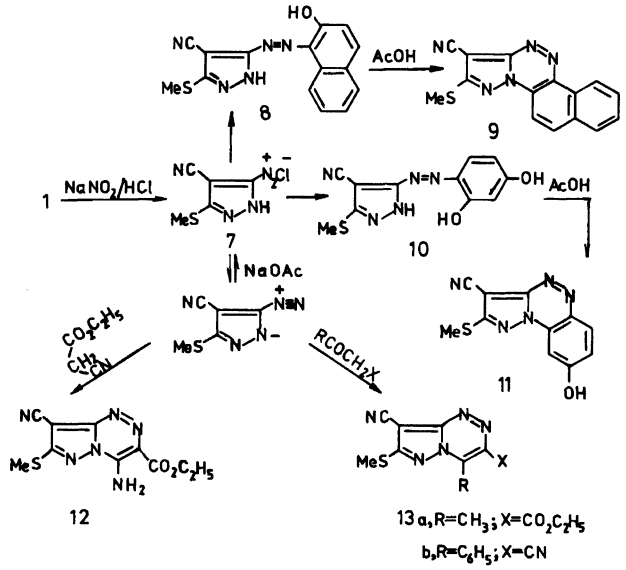


Chart 2.

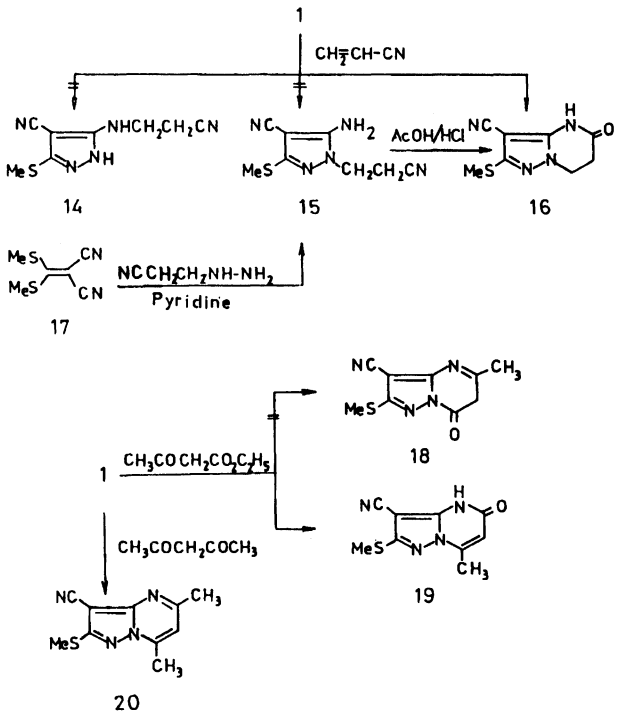


Chart 3.

tion of **17** with 2-cyanoethylhydrazine. Compound **15** once obtained was cyclized to **16** by boiling in an acetic acid-hydrochloric acid mixture.

Compound **1** condensed with ethyl acetoacetate to yield **19** rather than **18** based on IR spectra that showed a keto carbonyl at $\nu=1670$ cm^{-1}. Isomeric **18** would have carbonyl signal at a higher frequency as has been observed earlier.[17] Compound **1** also condensed with acetylacetone to yield the pyrazolo[1,5-*a*]-pyrimidine derivative **20** (Chart 3).

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam spectrophotometer. ^{1}H NMR were measured on Varian EM-390 90 MHz and Varian 200 MHz spectrometers and chemical shifts are expressed in δ ppm. Mass spectra were recorded on a Masspectrometer MS 9(AEI) at 70 eV. Microanalytical data (C,H, N) were obtained from Microanalytical Data Unit at Cairo University.

Reaction of 1 with Ethyl Cinnamate 2a and Cinnamonitrile Derivatives 2b—d. General Procedure: A solution of **1** (0.01 mol) and the appropriate **2a—d** (0.01 mol) in pyridine (30 ml) was heated under reflux for 4 h. The solvent was then evaporated in vacuo, and the remaining solid product was collected by filtration and crystallized from the proper solvent.

Ethyl 5-amino-3-cyano-4,5-dihydro-2-methylthio-5-phenylpyrazolo[1,5-*a*]pyrimidine-6-carboxylate (**3a**) formed yellow crystals from methanol, yield 70%; mp 210 °C. IR $\nu=3480$, 3340—3280 (NH and NH_2), 2210 (CN), and 1690 cm^{-1} (ester CO). ^{1}H NMR $\delta=1.33$ (t, 3H, CH_3), 2.45 (s,

3H, SCH_3), 4.12 (q, 2H, CH_2), 5.42 (d, 1H, C-5 proton, J=3 Hz), 7.22—7.54 (m, 6H, aromatic and NH protons), and 7.83 (br, 2H, NH_2). Found; C, 57.3; H, 4.7; N, 19.9; S, 9.2%. Calcd for $C_{17}H_{17}N_5O_2S$: C, 57.4; H, 4.8; N, 19.7; S, 9.0%.

7-Amino-4,5-dihydro-2-methylthio-5-phenylpyrazolo[1,5-*a*]pyrimidine-3,6-dicarbonitrile (**3b**) formed colorless crystals from DMF/ethanol mixture, yield 73%; mp 240 °C. IR ν=3380, 3340, 3260 (NH and NH_2), 2220, 2200 (CN bands) and 1670 cm^{-1} (C=N). ^1H NMR d=2.45 (s, 3H, SCH_3), 5.35 (d, 1H, C-5 proton, J=3 Hz), 7.25 (s, 2H, NH_2), and 7.45—7.92 (m, 6H, aromatic and NH protons). Found: C, 58.2; H, 3.8; N, 27.4; S, 10.1%. Calcd for $C_{15}H_{12}N_6S$: C, 58.4; H, 3.9; N, 27.3; S, 10.4%.

7-Amino-4,5-dihydro-5-(2-furyl)-2-(methylthio)pyrazolo-[1,5-*a*]pyrimidine-3,6-dicarbonitrile (**3c**) formed red crystals from dioxane, yield 75%; mp 220 °C. IR ν=3400, 3200 (NH and NH_2), 2210 (br, CN band), and 1670 cm^{-1} (C=N). Found: C, 52.5; H, 3.2; N, 28.0; S, 11.0%. Calcd for $C_{13}H_{10}N_6OS$: C, 52.3; H, 3.4; N, 28.2; S, 10.7%.

7-Amino-4,5-dihydro-5-(2-thienyl)-2-(methylthio)pyrazolo[1,5-*a*]pyrimidine-3,6-dicarbonitrile (**3d**) formed orange crystals from dioxane, yield 72%; mp 290 °C. IR ν=3390, 3320, 3200 (NH and NH_2), 2210 (br, CN bonds) and 1650 cm^{-1} (C=N). Found: C, 50.0; H, 3.1; N, 26.7; S, 20.4%. Calcd for $C_{13}H_{10}N_6S_2$: C, 49.7; H, 3.2; N, 26.7; S, 20.4%.

Coupling of Diazotized 1 with 2-Naphthol, Resorcinol and β-Carbonyl Nitriles. General Procedure: A solution of diazotized **1**[18] (0.01 mol) was added to a solution of the appropriate coupling reagent (0.01 mol) in ethanol (50 ml) in the presence of sodium acetate (5 g). The solid product formed on standing was collected by filtration and crystallized from the proper solvent.

Compound **8** formed orange crystals from dioxane, yield 85%; mp 239 °C. IR ν=3480—3200 (NH and OH), 2220 (CN), and 1670 cm^{-1} (C=N). ^1H NMR δ=2.7 (s, 3H, SCH_3), 7.15—8.9 (m, 7H, aromatic and NH protons), 10.9 (br, 1H, OH). Found: C, 58.4; H, 3.5; N, 22.8; S, 10.5%. Calcd for $C_{15}H_{11}N_5OS$: C, 58.2; H, 3.6; N, 22.6; S, 10.4%.

Compound **10** formed orange crystals from dioxane, yield 83% mp 242 °C. IR ν=3500—3100 (br, NH and OH), 2220 (CN), and 1640 cm^{-1} (C=N). Found: C, 48.0; H, 3.5; N, 25.2; S, 11.8%. Calcd for $C_{11}H_9N_5O_2S$: C, 48.0; H, 3.3; N, 25.4; S, 11.6%.

Ethyl 7-animo-3-cyano-2-(methylthio)pyrazolo[5,1-*c*][1,2,4]triazine-6-carboxylate (**12**) formed yellow crystals from dioxane, yield 80%; mp 290 °C. IR ν=3390, 3240 (NH_2), 2200 (CN), 1720 (ester CO), and 1640 cm^{-1} (C=N). ^1H NMR δ=1.3 (t, 3H, CH_3), 2.7 (s, 3H, SCH_3), 4.4 (q, 2H, CH_2), and 9.3 (br, 2H, NH_2). MS m/z 278.1 (M^+). Found: C, 43.3; H, 3.7; N, 30.5; S, 11.2%. Calcd for $C_{10}H_{10}N_6O_2S$: C, 43.2; H, 3.6; N, 30.2; S, 11.5%.

Ethyl 3-cyano-2-methylthio-7-methylpyrazolo[5,1-*c*][1,2,4]triazine-6-carboxylate (**13a**) formed yellow crystals from ethanol, yield 82%; mp 280 °C. IR ν=2920 (CH_3), 2220 (CN), and 1700 cm^{-1} (ester CO). ^1H NMR δ=1.3 (t, 3H, CH_3), 2.3 (s, 3H, CH_3), 2.7 (s, 3H, SCH_3), 4.2 (q, 2H, CH_2). Found: C, 47.5; H, 3.9; N, 25.5; S, 11.3%. Calcd for $C_{11}H_{11}N_5O_2S$: C, 47.6; H, 4.0; N, 25.3; S, 11.6%.

2-Methylthio-7-phenylpyrazolo[5,1-*c*][1,2,4]triazine-3,6-dicarbonitrile (**13b**) formed yellow crystals from dioxane, yield 75%; mp 260 °C. IR ν=2220 (CN) and 1640 cm^{-1} (C=N). ^1H NMR δ=2.65 (s, 3H, SCH_3), 7.2—8.2 (m, 5H, C_6H_5). Found: C, 57.0; H, 3.0; N, 29.0; S, 11.0%. Calcd for $C_{14}H_8N_6S$: C, 57.5; H, 2.8; N, 28.8; S, 11.0%.

Cyclization of Compounds 8 and 10: A solution of either **8** or **10** (2 g) in acetic acid (30 ml) was heated under reflux for 3 h. The solvent was then evaporated in vacuo and the remaining product was collected by filtration and crystallized from the proper solvent.

Compound **9** formed red crystals from acetic acid, yield 82%; mp 288 °C. IR ν=2210 (CN) and 1590 cm^{-1} (C=N). ^1H NMR δ=2.6 (s, 3H, SCH_3), 7.1—8.2 (m, 6H, aromatic protons). Found: C, 61.5; H, 3.4; N, 24.3; S, 10.9%. Calcd for $C_{15}H_9N_5S$: C, 61.8; H, 3.1; N, 24.0; S, 11.0%.

Compound **11** formed yellow crystals from DMF, yield 73%, mp 270 °C. IR ν=3490 (OH), 2220 (CN), and 1620 cm^{-1} (C=N). Found: C, 51.2; H, 2.5; N, 27.4; S, 12.6%. Calcd for $C_{11}H_7N_5OS$: C, 51.4; H, 2.7; N, 27.2; S, 12.5%.

Reaction of 1 with Acrylonitrile: A solution of **1** (0.01 mol) in pyridine (50 ml) and water (10 ml) was treated with acrylonitrile (0.015 mol) and potassium hydroxide (two pellets). The reaction mixture was heated under reflux for 12 h and the solvent was then evaporated in vacuo. The residue was triturated with water and treated with little acetic acid. The solid product, so formed, was collected by filtration and crystallized from DMF.

Compound **16** formed yellow crystals, yield 75%; mp 275 °C. IR ν=3170, 3100 (NH), 2220 (CN), and 1670 cm^{-1} (ring CO). MS m/z 208 (M^+). Found: C, 46.3; H, 3.9; N, 27.1; S, 15.5%. Calcd for $C_8H_8N_4OS$: C, 46.1; H, 3.9; N, 26.9; S, 15.4%.

Condensation of 1 with Ethyl Acetoacetate and Acetylacetone. General Procedure: A solution of **1** (0.01 mol) in ethanol (50 ml) was treated with ethyl acetoacetate or acetylacetone (0.01 mol) in the presence of piperidine (2 ml). The reaction mixture was heated under reflux for 5 h. The solvent was then evaporated in vacuo and the remaining solid product was collected by filtration and crystallized from the proper solvent.

4,5-Dihydro-2-methylthio-7-methyl-5-oxopyrazolo[1,5-*a*]-pyrimidine-3-carbonitrile (**19**) formed brown crystals from DMF, yield 73%; mp 300 °C. IR ν=3260, 3200 (NH), 2215 (CN), and 1670 cm^{-1} (CO). Found: C, 49.4; H, 3.5; N, 25.3; S, 14.3%. Calcd for $C_9H_8N_4OS$: C, 49.1; H, 3.7; N, 25.4; S, 14.6%.

5,7-Dimethyl-2-(methylthio)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**20**) formed brownish yellow crystals from DMF, yield 72%. mp 222 °C. IR ν=2210 (CN) and 1620 cm^{-1} (C=N). ^1H NMR δ=2.4, 2.5 (two singlets, $2CH_3$), 2.7 (s, 3H, SCH_3), 7.1 (s, 1H, pyrimidine H). Found: C, 55.2; H, 4.7; N, 25.4; S, 14.6%. Calcd for $C_{10}H_{10}N_4S$: C, 55.0; H; 4.6; N, 25.7; S, 14.7%.

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