Cyclization Reactions of 5-Aminopyrazoles with β-Ketoesters, Enamines and β-Keto Anilides: New Synthetic Routes to Pyrazolo[1,5-a]pyrimidine Derivatives

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The pyrazolo[1,5-a]pyrimidines **4**, **10**, **11** and **14** were synthesized from reaction of 4-aryazo-2,5-diaminopyrazoles **1** with cyclic β-ketoesters **2a,b** or cyclic β-ketoesters **7**, **8** or acetoacetanilide **12**, respectively. The reaction of **1** with the enamines **15**, **16** and **17** yielded also the pyrazolo[1,5-a]pyrimidines **18**, **20** and **21**, respectively.

INTRODUCTION

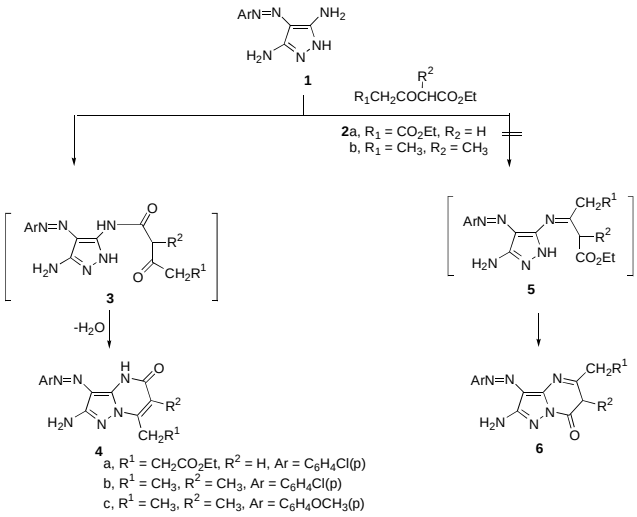
5-Aminopyrazoles are versatile reagents and have been extensively utilized as synthetic starting components for preparation of several polysubstituted fused pyrazoles.[1-3] These fused pyrazoles are interesting as pharmaceuticals[1-3] and biodegradable agrochemicals.[4,5] In conjunction with our interest in this class of compounds, we report here on the synthesis of several new aminopyrazol[1,5-a]pyrimidines and their azo analogues as potential antischistosomal agents. The synthesized compounds possess latent functional substituents and appear promising for utility in further chemical transformations and also for biological studies.

RESULTS AND DISCUSSION

It has been found that compound **1** reacts with diethyl acetonedicarboxylate (**2a**) to yield cyclocondensation product that may be formulated as **4a** and isomeric **6a**. Although structure **6a** seemed more likely based on similarity to the well established behavior of 5-aminopyrazoles **1** towards β-keto esters, an independent structure proof seemed mandatory, as marked increment in reactivity of exocyclic amino nitrogen in **1** compared with other monoaminopyrazoles is to be expected. Such increment results from the opposition of the mesomeric effects of the two amino groups that increase the electron density at each nitrogen atom. Structure **4a** appears more likely based on ^{1}H-NMR spectrum which revealed one proton signal at $\delta = 5.96$ ppm and $\delta = 10.5$ ppm for pyrimidine ring H-6 and NH groups, respectively. Structure **4a** was also preferred following a procedure recently reported.[6]

Similarly, 5-aminopyrazole **1** reacted with α-methylacetoacetate **2b** in refluxing acetic acid to yield also a product *via* ethanol and water elimination. Structure **4b** was established for the reaction product on the basis of ^{1}H-NMR spectrum that clearly indicated the absence of ester group and the presence of signals corresponding to two methyl groups (cf. Scheme I).

Scheme I



Similarly, treatment of **1** with cyclic β-ketoesters **7** and **8** in acetic acid afforded the pyrazolo[1,5-a]pyrimidine derivatives **10** and **11**, respectively (cf. Scheme II). The IR and

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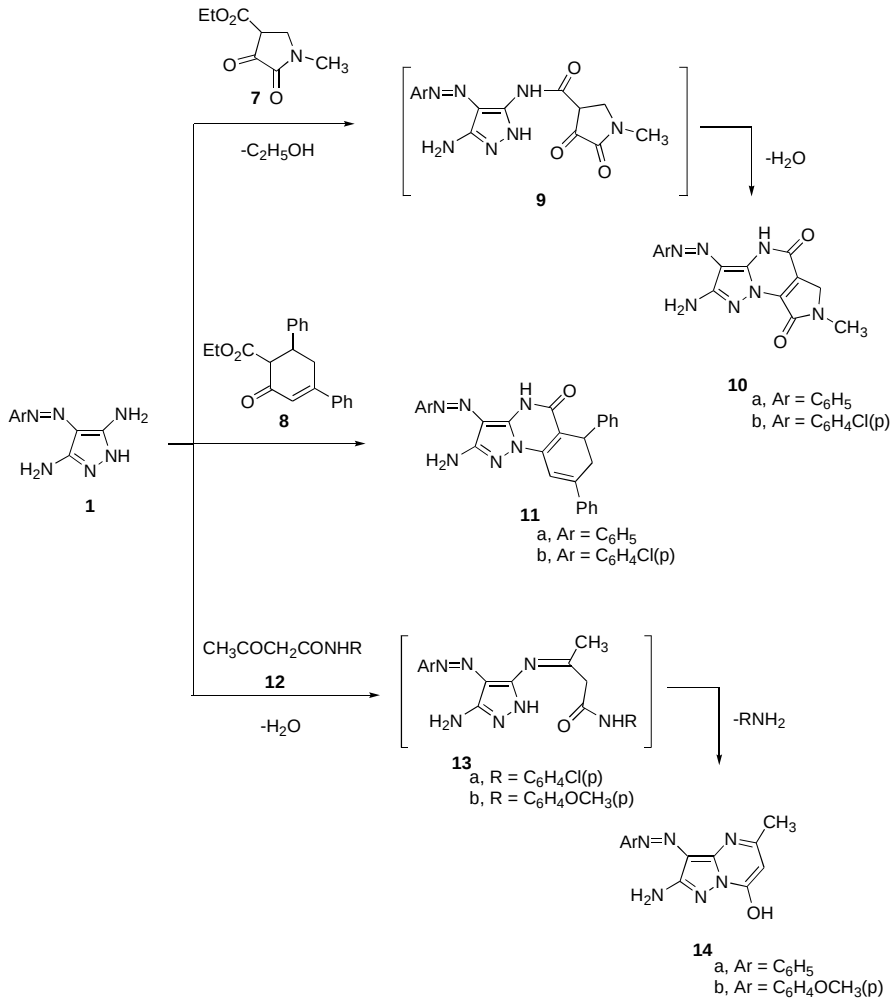
Scheme II



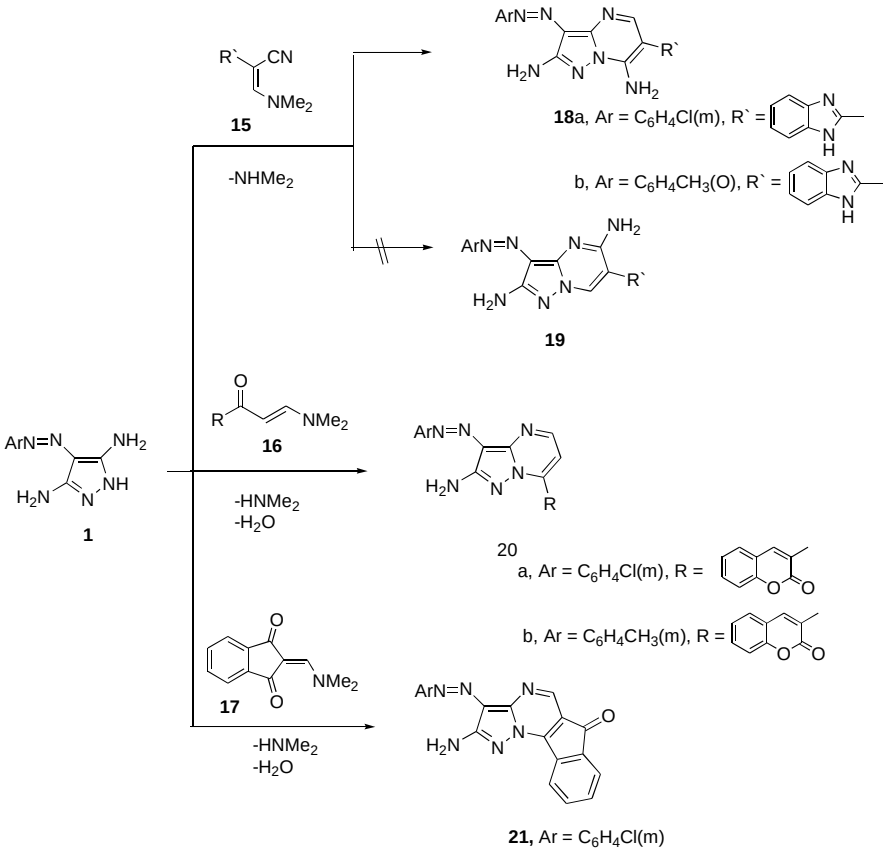
mass spectra were consistent with the proposed structures.

Also, the reaction of **1** with acetoacetanilides **12** in benzene containing a few drops of HCl afforded products *via* water and primary aromatic amine elimination. The pyrazolopyrimidines **14** were established as reaction products based on their correct elemental analysis and spectral data (cf. Scheme II). Compounds **14** are assumed to be formed *via* initial condensation of the exocyclic amino function in **1** with the carbonyl group in **12** to give the intermediate **13** which readily cyclized to the final isolable product **14**.

Enamines are versatile reagents and their utilization in synthesis of heterocycles has received considerable interest.[6-11] In continuation of our interest in synthesis of fused azoles, we report here on the reactivity of 5-aminopyrazoles **1** towards enaminonitrile **15** and the enaminones **16** and **17**. Thus, reaction of **1** with the enaminonitrile **15** in ethanol containing a few drops of acetic acid afforded a product with dimethylamine elimination. The 7-aminopyrazolo[1,5-a]-pyrimidine **18** and 4-aminopyrazolo[1,5-a]pyrimidine **19** seemed possible products for such reaction; however, the 7-aminopyrazolo[1,5-a]pyrimidine **18** was established as a reaction product based on ^{1}H NMR spectra which revealed a signal corresponding to the amino group at $\delta > 7.00$ ppm. If 4-aminopyrazolo[1,5-a]pyrimidine **19** is the reaction product, one would expect a signal at $\delta = 4$-6 ppm for the amino group. Deshielding of 7-aminopyrazolopyrimidine protons by ring nitrogen anisotropy has been previously observed.[12] Compound **18** proposed to form *via* initial addition of the exocyclic amino group in **1** to the activated double bond in **15** by elimination of dimethylamine and cyclization through addition of the pyrazole NH to the cyano group.

In a similar way, compound **1** reacted with 1-(3-coumarinyl)-3-(N,N-dimethylamino)-2-propen-1-one (**16**) and 2-(N,N-dimethylaminomethylene)indane-1,3-dion (**17**) to afford the pyrazolo[1,5-a]pyrimidines **20** and **21**, respectively (cf. Scheme III).

Scheme III



EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Shimadzu IR-740 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Ac-80 spectrometer with [$^2H_6$] DMSO as solvent and TMS as internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured on Gs/MS INCOS XL Finnigan MAT. Microanalysis was performed on LECOCHNS-932.

Preparation of pyrazolo[1,5-a]pyrimidines (4)

A solution of **1** (0.01 mol) and (0.01 mol) of **2a** or **2b** in acetic acid (20 mL) was heated under reflux for 4 hours. The reaction mixture was cooled and the solid products so formed were collected by filtration and recrystallized from the proper solvent and then identified as **4a,b**.

Ethyl 2-amino-3-(4-chlorophenylazo)-4,5-dihydro5-oxo-pyrazolo[1,5-a]pyrimidine-7-yl]ethanoate (4a)

Red crystals from ethanol/dioxane, m.p. 162-164 °C, yield 65%. IR (υ_{max}/cm^{-1}): 3473, 3294 (NH_2, NH), 1726 (CO), 1660 (CO), 1600 (N=N). ^{1}H-NMR [$^2H_6$] DMSO (δ, ppm): 1.21-1.28 (t, *J* = 7 Hz, 3H, CH_3), 3.86 (s, 2H, CH_2), 4.16-4.23 (q, *J* = 7 Hz, 2H, CH_2), 5.96 (s, 1H, pyrimidine H-6), 6.74 (s, 2H, NH_2), 7.56-7.60 (d, *J* = 8.8 Hz, 2H, aromatic protons), 7.85-7.90 (d, *J* = 8.8 Hz, 2H, aromatic protons), 10.5 (s, 1H, NH). $C_{16}H_{15}ClN_6O_3$ (374.74). MS *m/z* 374 (M^+). Calcd. C, 51.28, H, 4.03, N, 22.42. Found C, 51.23, H, 4.11, N, 22.12%.

2-Amino-3-(4-chlorophenylazo)-6,7-dimethyl-4,5-dihydro-5-oxo-pyrazolo[1,5-a]pyrimidine (4b)

Red crystals from DMF, m.p. 294-296 °C, yield 70%. IR (υ_{max}/cm^{-1}): 3443, 3254 (NH_2, NH), 1660 (CO), 1640 (C=N). ^{1}H-NMR [$^2H_6$] DMSO (δ, ppm): 1.9 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 6.65 (s, 2H, NH_2), 7.40-7.60 (d, *J* = 8.8 Hz, 2H, aromatic protons), 7.75-7.92 (d, *J* = 8.8 Hz, 2H, aromatic protons), 8.10 (s, 1H, NH). $C_{14}H_{13}ClN_6O$ (316.75). Calcd. C, 53.09, H, 4.16, N, 26.53. MS *m/z* 316 (M^+). Found C, 53.23, H, 4.11, N, 26.12%.

2-Amino-6,7-dimethyl-4,5-dihydro-5-oxo-3-(4-methoxy-phenylazo)pyrazolo[1,5-a]pyrimidine (4c)

Orange crystals from ethanol/dioxane, m.p. 286-288

°C, yield 65%. IR (υ_{max}/cm^{-1}): 3500, 3340 (NH, NH_2), 1680 (CO), 1630 (C=N), 1610 (N=N). ^{1}H-NMR [$^2H_6$] DMSO (δ, ppm): 1.93 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 6.80 (s, 2H, NH_2), 7.10-7.30 (d, *J* = 8.8 Hz, 2H, aromatic protons), 7.66-7.80 (d, *J* = 8.8 Hz, 2H, aromatic protons), 8.10 (s, 1H, NH). $C_{15}H_{16}N_6O_2$ (312.33). Calcd. C, 57.67, H, 5.16, N, 26.91. MS *m/z* 312 (M^+). Found C, 57.11, H, 5.34, N, 26.84%.

Reaction of 1 with β-ketoesters 7, 8, acetoacetanilide derivatives 12: Formation of compounds 10, 11 & 14

A mixture of **1** (0.01 mol) and (0.01 mol) of each of cyclic β-ketoesters **7**, **8** or acetoacetanilide derivatives **12** in acetic acid (30 mL) was heated under reflux for 3 hours. The solvent was then evaporated under *vacuo* and the resulting solid products were filtered off and recrystallized from the suitable solvent.

2-Amino-3-phenylazo-7,12-dihydro-6-methylpyrazolo[3,4-d]pyrimidine-5,8-dione (10a)

Brown crystals from DMF, m.p. > 300 °C, yield 65%. IR (υ_{max}/cm^{-1}): 3350, 3300 (NH_2, NH), 1715, 1700 (CO), 1600 (N=N). $C_{15}H_{13}N_7O_2$ (323.3). MS *m/z* 323 (M^+) Calcd. C, 55.72, H, 4.05, N, 30.32. Found C, 55.63, H, 4.32, N, 30.11%.

2-Amino-3-(4-chlorophenylazo)-7,12-dihydro-6-methylpyrazolo[3,4-d]pyrimidine-5,8-dione (10b)

Brown crystals from DMF, m.p. > 300 °C, yield 70%. IR (υ_{max}/cm^{-1}): 3350, 3300 (NH_2, NH), 1715, 1700 (CO), 1600 (N=N). $C_{15}H_{12}ClN_7O_2$ (357.75). MS *m/z* 357 (M^+). Calcd. C, 50.36, H, 3.38, N, 27.41. Found C, 50.23, H, 3.11, N, 27.12%.

2-Amino-3-phenylazo-6,8-diphenyl-6,7-dihydro-4H-pyrazolo[1,5-a]quinazoline-5-one (11a)

Brown crystals from DMF, m.p. 292 °C, yield 63%. IR (υ_{max}/cm^{-1}): 3340, 3300 (NH_2), 1700 (CO), 1605 (N=N). $C_{28}H_{20}N_6O$ (456.49). MS *m/z* 456 (M^+). Calcd. C, 73.66, H, 4.41, N, 18.41. Found C, 73.34, H, 4.20, N, 18.23%.

2-Amino-3-(4-chlorophenylazo)-6,8-diphenyl-6,7-dihydro-4H-pyrazolo[1,5-a]quinazoline-5-one (11b)

Brown crystals from DMF, m.p. 290 °C, yield 63%. IR (υ_{max}/cm^{-1}): 3340, 3300 (NH_2, NH), 1700 (CO), 1605 (N=N). $C_{28}H_{21}ClN_6O$ (492.96). MS *m/z* 492 (M^+). Calcd. C, 68.22, H, 4.29, N, 17.05. Found C, 68.23, H, 4.11, N, 17.12%.

2-Amino-3-phenylazo-5-methyl-7-hydroxypyrazolo[1,5-a]-pyrimidine (14a)

Scarlet red crystals from ethanol/DMF, m.p. 250-252 °C, yield 73%. IR (υ_{max}/cm^{-1}): 3490, 3433, 3278 (OH, NH_2), 1640 (C=N), 1610 (N=N). ^{1}H-NMR [$^2H_6$] DMSO (δ, ppm): 2.3 (s, 3H, CH_3), 5.83 (s, 1H, CH), 6.65 (s, 2H, NH_2), 7.36-7.80 (m, 5H, aromatic H), 10.2 (s, 1H, OH). $C_{13}H_{12}N_6O$ (268.27). MS *m/z* 268 (M^+). Calcd. C, 58.20, H, 4.51, N, 31.33. Found C, 58.00, H, 4.70, N, 31.22%.

2-Amino-3-(4-methoxyphenylazo)-5-methyl-7-hydroxy-pyrazolo[1,5-a]pyrimidine (14b)

Red crystals from DMF, m.p. 260-263 °C, yield 75%. IR (υ_{max}/cm^{-1}): 3480, 3433, 3278 (OH, NH_2), 1635 (C=N), 1615 (N=N). ^{1}H-NMR [$^2H_6$] DMSO (δ, ppm): 2.2 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 5.65 (s, 1H, CH), 6.60 (s, 2H, NH_2), 6.95-7.15 (d, *J* = 8 Hz, 2H, aromatic H), 7.80-7.95 (d, *J* = 8 Hz, 2H, aromatic H), 10.10 (s, 1H, OH). $C_{14}H_{14}N_6O_2$ (298.30). MS *m/z* 298 (M^+). Calcd. C, 56.37, H, 4.73, N, 28.17. Found C, 56.30, H, 4.74, N, 28.12%.

Preparation of pyrazolopyrimidines 18, 20 and 21

A solution of **1** (0.01 mol) in acetic acid (30 mL) which treated with (0.01 mol) of **15**, **16** or **17** was heated under reflux for 2 hours. The solvent was then evaporated under *vacuo* and triturated with ethanol. The solid deposited was collected by filtration and recrystallized from the suitable solvent to give **18**, **20** and **21** respectively.

6-(1H-Benzimidazol-2-yl)-3-(3-chlorophenylazo)-pyrazolo-[1,5-a]pyrimidine-2,7-diamine (18a)

Red crystals from acetic acid, m.p. > 300 °C, yield 75%. IR (υ_{max}/cm^{-1}): 3490, 3395 (NH_2, NH), 1605 (N=N). ^{1}H-NMR [$^2H_6$] DMSO (δ, ppm): 7.40 (s, 2H, NH_2), 7.45-7.70 (m, 8H, aromatic H), 8.32 (s, 1H, pyrimidine H-5), 8.99 (s, 2H, NH_2), 9.60 (s, 1H, NH). $C_{19}H_{14}ClN_4$ (403.83). MS *m/z* 403 (M^+). Calcd. C, 56.51, H, 3.49, N, 31.22. Found C, 56.50, H, 3.80, N, 31.34%.

6-(1H-Benzimidazol-2-yl)-3-(2-methylphenylazo)pyrazolo-[1,5-a]pyrimidine-2,7-diamine (18b)

Brown powder from ethanol/DMF, m.p. 280-282 °C, yield 70%. IR (υ_{max}/cm^{-1}): 3460, 3356 (NH_2, NH), 1620 (N=N). ^{1}H-NMR [$^2H_6$] DMSO (δ, ppm): 2.00 (s, 3H, CH_3), 7.43 (s, 2H, NH_2), 7.50-7.80 (m, 8H, aromatic H), 8.40 (s, 1H, pyrimidine H-5), 8.90 (s, 2H, NH_2), 9.70 (s, 1H, NH). $C_{20}H_{17}N_9$ (383.42). MS *m/z* 383 (M^+). Calcd. C, 62.65, H, 4.47, N, 32.88. Found C, 62.32, H,4.11, N, 32.64%.

2-Amino-2-(3-chlorophenylazo)-4-(coumarin-3-yl)pyrazolo-[1,5-a]pyrimidine (20a)

Red crystals from methanol/DMF, m.p. 276-278 °C,

yield 70%. IR (υ_{max}/cm^{-1}): 3433, 3278 (NH_2), 1725 (CO), 1620 (N=N). ^{1}H-NMR [$^2H_6$] DMSO (δ, ppm): 7.36-7.92 (m, 10H, aromatic H), 8.70 (s, 2H, NH_2), 9.10 (s, 1H, coumarin H-4). MS *m/z* 416 (M^+) $C_{21}H_{13}ClN_6O_2$ (416.82). Calcd. C, 60.51, H, 3.14, N, 20.16. Found C, 60.00, H, 3.70, N, 20.22%.

2-Amino-4-(coumarin-3-yl)-2-(3-methylphenylazo)pyrazolo-[1,5-a]pyrimidine (20b)

Red crystals from dioxan, m.p. 198-200 ℃, yield 75%. IR (υ_{max}/cm^{-1}): 3370, 3280 (NH_2), 1718 (CO), 1606 (N=N). ^{1}H-NMR [$^2H_6$] DMSO (δ, ppm): 2.20 (s, 3H,CH_3), 7.30-7.81 (m, 10H, aromatic H), 8.80 (s, 2H, NH_2), 9.10 (s, 1H, coumarin H-4). $C_{22}H_{16}N_6O_2$ (396.41). MS *m/z* 396 (M^+) Calcd. C, 66.66, H, 4.07, N, 21.20. Found C, 66.60, H,4.40, N, 21.21%.

2-Amino-3-(3-chlorophenylazo)-1,4-10c-triazacyclopenta-[c]fluoren-6-one (21)

Red crystals from DMF, m.p. > 300 ℃, yield 75%. IR (υ_{max}/cm^{-1}): 3410, 3294 (NH_2), 1708 (CO), 1620 (N=N). MS *m/z* 374 (M^+) $C_{19}H_{11}ClN_6O$ (374.78). Calcd. C, 60.89, H, 2.96, N, 22.42. Found C, 60.60, H, 2.40, N, 22.21%.

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Key Words

2,5-Diaminopyrazoles; Pyrazolo[1,5-a]pyrimidines.

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