Synthesis of New Pyrazolo[1,5-*a*]pyrimidines And Pyrazolo[3,4-*b*]pyridines

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While 3(5)-aminopyrazole reacts with enaminonitrile to yield pyrazolo[1,5-*a*]pyrimidines, 3-amino-5-pyrazolone reacts with the same reagents to yields pyrazolo[3,4-*b*]pyridines.

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Azoloazines are biologically interesting molecules and their chemistry is now receiving considerable attention [1-3]. One of the major routes to azoloazines is the reaction of α,β-unsaturated ketones, and/or nitriles with azolylamine derivatives [4,5]. However, in many cases the exact structure of the reaction products is difficult to identify as a result of the close similarities between possible reaction products. Previous publications, from our laboratories recently described the synthesis of a variety of new azoloazines whose structure was established by NOE experiments [6,7] In conjunction with this work, we report here the synthesis of a variety of new pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyridines *via* reaction of 3-aminopyrazole **1** and 3-amino-1-phenyl-1*H*-pyrazole-5-one **8** with enaminones and with enaminonitriles.

Thus, we found that **1** reacts with the enamines **7a,b** to yield products of condensation by elimination of dimethylamine and water. The ^{1}H NMR spectra clearly indicated that the pyrazole 4-H were not involved in the reactions. Structure **2** was established through authentic synthesis by condensation of **1** with dimethylformamide-dimethylacetal (DMFDMA) and subsequent treatment of the amidine **3** with benzoylacetonitrile and malononitrile to give **2a,b** respectively (Figure 1).

The product of the reaction of **1** with **7c** depended on the reaction conditions. Thus refluxing **1** and **7c** in pyridine for 3 hours afforded the pyrazolylaminoacrylate derivative **4**, in analogy with the reported formation of pyrazolylaminoacrylate on reaction of 3-amino-5-phenylpyrazole with the same reagent in refluxing ethanol [8]. However, when a mixture of **1** and **7c** was heated at reflux in xylene in the presence of sodium hydride, a mixture of **5** and **6** in a 2:3 ratio was formed. Compound **5** could also be formed by cyclization of **4** in refluxing acetic acid, while long reflux of **4** in xylene afforded again **5** and **6** in the same ratio (2:3).

Compound **8** also reacted with **7a,d** to yield products of condensation by elimination of water and dimethylamine. The ^{1}H NMR of the product indicated disappearance of both amino and methylene signals. Structure **9** was established by authentic synthesis. The condensation of **8** with DMFDMA gave the dimethylaminomethylene derivative **10** which was then treated with

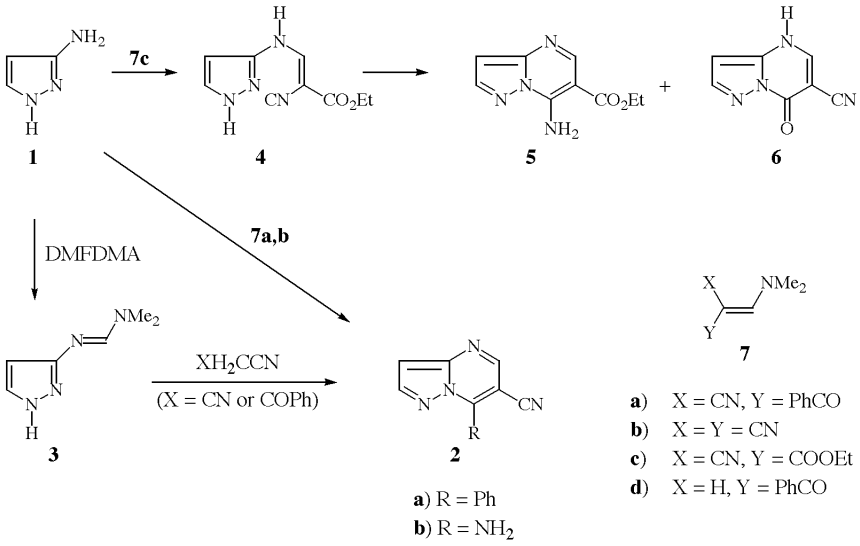

Figure 1

benzoylacetonitrile to give **11**. Reaction of **11** with ethanolic sodium ethoxide at reflux yielded **9a** identical in all respects with the product obtained from treatment of **8** with **7a** (Figure 2).

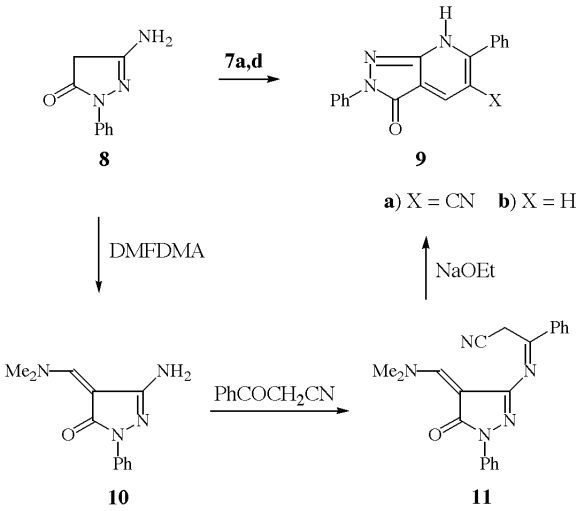

Figure 2

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR 2000 spectrometer. ^{1}H NMR spectra were obtained on a Bruker AC-80 spectrometer with DMSO-d_6 as solvent and TMS as internal standard. Elemental analysis were performed on a LECO CHNS-932 analyzer.

7-Phenylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile (**2a,b**).

Method A.

A mixture of **1** (0.01 mol) and **7a,b** (0.01 mol) was refluxed in ethanol (30 ml) in the presence of piperidine for 3hrs. The reaction mixture was then allowed to cool to room temperature and the product, was collected and recrystallized.

Method B.

A mixture of **6** (0.01 mol) and benzoylacetonitrile (or malononitrile) (0.01 mol) was refluxed in ethanol (30 ml) in the presence of piperidine for 3 hours. The reaction mixture was then allowed to cool to room temperature and the solid product formed, was collected and crystallized. Compound **2a** formed yellow crystals from ethanol, mp 220-221°, yield 25%; ir: ν (cm^{-1}) 3045 (CH arom.), 2230 (CN); ^{1}H-nmr (DMSO-d_6): δ 6.89 (d; 1H, H-3), 7.60-7.96 (m ; 5H, aromatic.), 8.28 (d; 1H, H-2),8.64 (s; 1H, H-5).

Anal. Calcd. for $C_{13}H_8N_4$: C, 70.90; H, 3.64; N, 25.45. Found: C, 70.67; H, 3.58; N, 25.23.

Compound **2b** formed yellow crystals from ethanol/DMF, mp 309-311°, yield 36%; ir: ν (cm^{-1}) 3350-3306 (NH_2),2216 (CN); ^{1}H-nmr (DMSO-d_6): δ 6.55 (d; 1H, H-3), 8.18 (d; 1H, H-2), 8.28 (s; 1H, H-5), 8.69 (bs; 2H, NH_2).

Anal. Calcd. for $C_7H_5N_5$: C, 52.83; H, 3.14; N, 44.00. Found: C, 752.75; H, 3.14; N, 43.70.

N,*N*-Dimethyl-*N*-(1*H*-pyrazol-3-yl)-formamidine (**3**).

A mixture of **1** (0.01 mol) and DMFDMA (0.01mol) was refluxed in xylene (25 ml) for 3 hours. The reaction mixture was then allowed to cool to room temperature and the product was collected and crystallized. Compound **3** formed colorless crystals from toluene, mp 115-117°, yield 95 %; ir: ν (cm^{-1}) : 3149 (NH), 2919 and 2830 (CH aliph.); ^{1}H-nmr (DMSO-d_6): δ 3.00 (s; 6H, $2CH_3$), 3.15 (s; NH + DMSO), 5.83 (d; 1H, H-4), 7.33 (d; 1H, H-5), 7.89 (s; 1H,aminomethylene CH).

Anal. Calcd. for $C_6H_{10}N_4$: C, 52.17; H, 7.25; N, 40.58. Found: C, 51.98; H, 7.09; N, 40.39.

Ethyl 2-Cyano-3-(pyrazol-3-yl)aminoacrylate (**4**).

A mixture of **1** (0.01 mol) and **7c** (0.01 mol) was refluxed in pyridine (25 ml) for 3 hours. The reaction mixture was then poured on water. The product was collected and crystallized. Compound **4** formed colorless crystals from methanol, mp 185-186°, yield 32 %; ir: ν (cm^{-1}) 3290 and 3115 (2NH's), 2945 (CH aliph.), 2195 (CN), 1706 (CO); ^{1}H-nmr (DMSO-d_6): δ 1.18-1.38 (t; 3H, CH_3), 4.07-4.30 (q; 2H, CH_2), 6.11(d; 1H, H-4), 7.67 (d; 1H, H-3'), 8.19-8.51 (m; 1H, H-5), 10.82 (bd; 1H, 3-NH), 12.53 (bd; 1H, 1-NH).

Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.85; N, 27.18. Found: C, 52.58; H, 4.78; N, 26.97.

Ethyl 7-Aminopyrazolo[1,5-*a*]pyrimidine-6-carboxylate (**5**).

A mixture of **1** (0.01 mol) and **7c** (0.01 mol) was refluxed in xylene (25 ml) in the presence of sodium hydride (0.01 mol) for 3hours. The solid product which precipitated during reflux was collected while hot. The product separated was crystallized and identified as **6**. The filtrate was then allowed to cool to room temperature and the product (compound **5**) was then collected and crystallized. Compound **5** formed colorless crystals from methanol, mp 136-138°, yield 25 %; ir: ν (cm^{-1}) 3345 (NH_2), 2950 (CH aliph.), 1683 (CO); ^{1}H-nmr (DMSO-d_6): δ 1.26-1.44(t; 3H, CH_3), 4.22-4.48(q; 2H, CH_2), 6.53 (d; 1H, H-3), 8.18 (d; 1H, H-2), 8.42 (bs; 2H, NH_2), 8.62 (s; 1H, H-5).

Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.43; H, 4.85; N, 27.10. Found: C, 52.29; H, 4.95; N, 26.87.

7-Oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carbonitrile (**6**).

Compound **6** formed red crystals from ethanol/DMF, mp >300°, yield 36 %; ir: ν (cm^{-1}): 3390 (NH), 2205 (CN), 1663 (CO), ^{1}H-nmr (DMSO-d_6): δ 3.22 (s; NH + DMSO), 6.37 (d; 1H, H-3), 7.99 (d; 1H, H-2), 8.64 (s; 1H, H-5).

Anal. Calcd. for $C_7H_4N_4O$: C, 52.50; H, 2.50; N, 35.00. Found: C, 52.34; H, 2.60; N, 34.88.

3-Oxo-2,6-diphenyl-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**9a**).

Method A.

A mixture of **8** (0.01 mol) and **7a** (0.01 mol) was refluxed in pyridine (20 ml) for 3 hours. The reaction mixture was then poured on water. The product was collected and crystallized.

Method B.

A mixture of **11** (0.01 mol) and a solution of sodium ethoxide (prepared from 0.01 mol sodium in 25 ml of ethanol) was refluxed for 3 hours. The reaction mixture was then allowed to cool to room temperature and neutralized with hydrochloric acid

(HCl). The product, was collected and crystallized. Compound **9a** formed pale yellow crystals from ethanol, mp 259-261°, yield 32 %; ir: ν (cm^{-1}): 3428 (NH), 3071 (CH arom.) 2223 (CN), 1663 (CO), ^{1}H-nmr (DMSO-d_6): δ 7.22-7.94 (m; 11H, NH + arom.), 8.80 (s; 1H, H-4).

Anal. Calcd. for $C_{19}H_{12}N_4O$: C, 73.07; H, 3.85; N, 17.95. Found: C, 73.11; H, 3.90; N, 18.0.

3-Oxo-2,6-diphenyl-2*H*-pyrazolo[3,4-*b*]pyridine (**9b**).

A mixture of **8** (0.01 mol) and **7d** (0.01 mol) was refluxed in pyridine (20 ml) for 3 hours. The reaction mixture was then poured on water. The product, was collected and crystallized. Compound **9b** formed buff crystals from ethanol, mp 261-263°, yield 58 %; ir: ν (cm^{-1}) 3445 (NH), 3030 (CH arom.), 1640 (CO), ^{1}H-nmr (DMSO-d_6): δ 7.16-8.34 (m; 13H, all H's).

Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.26; H, 4.52; N, 14.63. Found: C, 75.15; H, 4.59; N, 14.51.

5-Amino-4-dimethylaminomethylene-2-phenyl-2,4-dihydro-pyrazol-3-one (**10**).

A mixture of **8** (0.01 mol) and DMFDMA (0.01 mol) was fused at room temperature for 3 minutes and the reddish orange paste, so formed, was washed with acetone and then filtered. The residual yellow solid, which is compound **10**, was then crystallized. Compound **10** formed bright yellow crystals from ethanol, mp 167-169°, yield 45 %; ir: ν (cm^{-1}) 3352 and 3208 (NH_2), 3027 (CH arom.), 1663 (CO), ^{1}H-nmr (DMSO-d_6): δ 3.74 (s; 6H, $2CH_3$), 5.35 (bs; 2H, NH_2), 6.94-7.98 (m; 6H,CH olefinic + arom.).

Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.61; H, 6.09; N, 24.35. Found: C, 62.48; H, 6.17; N, 24.16.

3-(4-Dimethylaminomethylene-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-ylimino)-3-phenylpropionitrile (**11**).

A mixture of **10** (0.01 mol) and benzoylacetonitrile (0.01 mol) was refluxed in ethanol (25 ml) in the presence of piperidine for 4 hours. The reaction mixture was then allowed to cool to room temperature and the solid product was collected and crystallized. Compound **11** formed orange crystals from ethanol, mp 239-241°, yield 35 %; ir: ν (cm^{-1}) 3434 (NH), 3029 (CH arom.), 2210 (CN), 1607 (CO); ^{1}H-nmr (DMSO-d_6): δ 2.55 (s; 7H, NH + $2CH_3$), 6.98-8.34 (m; 12H, 2CH + arom.).

Anal. Calcd. for $C_{21}H_{19}N_5O$: C, 70.58; H, 5.32; N, 19.60. Found: C,70.72; H, 5.49; N, 19.42.

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