Studies with Condensed Azines: New Routes to Pyrazolo[3,4-*b*]pyridines and Pyrrolo[3,2-*b*]pyridines

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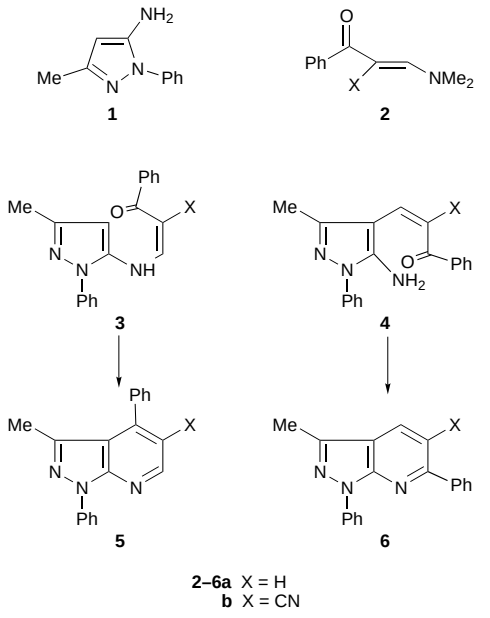
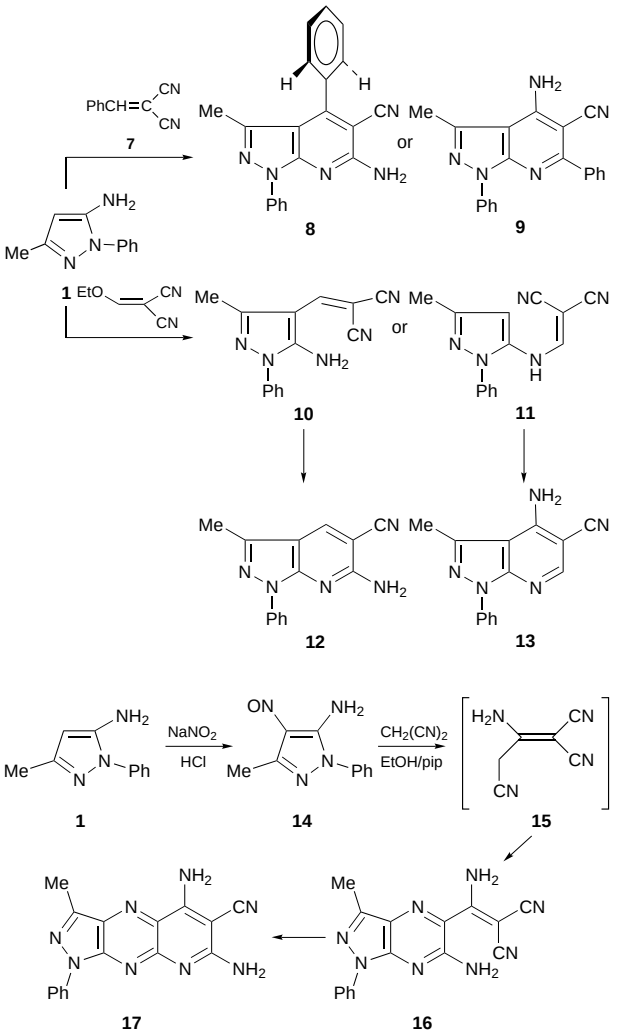
Several condensed pyrazole derivatives are obtained from the reaction of 3-methyl-1-phenylpyrazol-5-amine (**1**) with α,β-unsaturated ketones, α,β-unsaturated nitriles and isothiocyanates.

In conjunction with our previous interest in the chemistry of azoloazines,[5,6,7] we report here the novel syntheses of pyrazolo[3,4-*b*]pyridines and pyrrolo[3,2-*b*]pyridines. We found that 3-methyl-1-phenylpyrazol-5-amine (**1**) reacts with 1-phenyl-3-dimethylaminoprop-2-en-1-ones **2a**,**b** in the presence of zinc chloride and pyridine, respectively, to yield addition products with the elimination of dimethylamine and water. The products can thus be formulated as **5** or the isomeric structure **6**. Structure **6** was established based on ^{1}H NMR data and NOE experiments. NOE difference experiments showed that the methyl group and pyridine H-4 interact through space. Thus, irradiating the methyl signal at δ 2.62 and 2.68 enhanced the pyridine H-4 signal at δ 8.45 and 9.07 in **6a** and **6b** respectively. Moreover, when **1** and **2a** were refluxed in ethanol, compound **4a** was isolated in good yield. It could then be cyclised to **6a** on fusion with $ZnCl_2$. Compound **1** also reacted with benzylidenemalononitrile (**7**) in refluxing pyridine to yield an addition product which then underwent auto-oxidation to give **8** or the isomeric structure **9**. Again, structure **8** was established based on the shielding effect of the methyl signal by the aromatic ring current and by NOE experiments. Thus irradiating the methyl signal at δ 1.86 little enhanced the phenyl protons at δ 7.21 while no enhancement of the NH_2 protons was observed. The observed small effect is perhaps due to the existence of phenyl *o*-H's out of plane as shown in structure (**8**). The observation that the methyl protons are shifted upfield to δ 1.86 (expected position is *ca.* δ 2.45) further supports this conclusion.

Compound **1** also reacted with ethoxymethylidenemalononitrile to yield a product that may be formulated as acyclic **10** and **11** or cyclic **12** and **13**. ^{1}H NMR revealed an absence of any signal for a pyrazole H-4 and thus the acyclic form **11** was excluded. ^{13}C NMR indicated the presence of only one CN carbon at δ 109.85 and thus the acyclic form **10** could also be excluded. NOE difference experiments showed no interaction between the methyl protons at δ 2.45 and the 6-H pyridine proton at δ 8.48. It showed in contrast that the methyl protons and amino protons are proximal. Thus irradiating the methyl signal at δ 2.45 enhanced the amino proton signal at δ 5.8 and *vice versa.* Hence structure **12** was excluded and structure **13** was established. When the same reaction was carried out in refluxing ethanol for 2 h, compound **11** was formed instead of **13**. ^{1}H NMR revealed the presence of the pyrazole H-4 signal at δ 6.33. Compound **11** was cyclised to give **13** on refluxing in ethanol for a few more hours. Thus structure **13** was further established.





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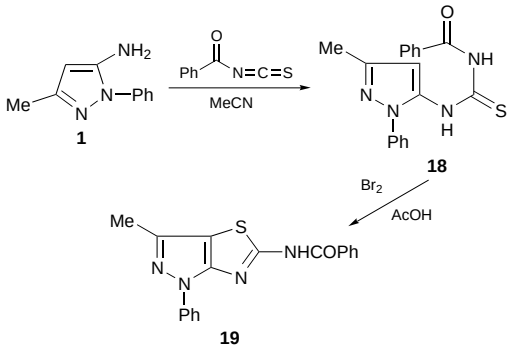
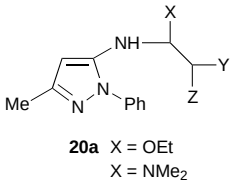
Attempted diazotisation of **1** gave the nitroso derivative **14** which reacted with malononitrile to yield a product of molecular formula $C_{16}H_{12}N_8$. The same product was also obtained by reacting **14** with the malononitrile dimer **15**. It was thus assumed that malononitrile first dimerises under the reaction conditions, which then condenses with **14** to yield a product that can be formulated as **16** or isomeric **17**. Structure **17** was established on the basis of ^{13}C NMR which revealed the presence of only one CN signal. Moreover, compound **17** was recovered almost unreacted when boiled in acetic acid: a condition expected to effect cyclisation of **16** into **17**.

Compound **1** also reacted with benzoyl isothiocyanate (prepared *in situ*) in acetonitrile to give the thiourea derivative **18**. Compound **18** on treatment with bromine in acetic acid gave pyrazolo[3,4-*d*]thiazole **19**.

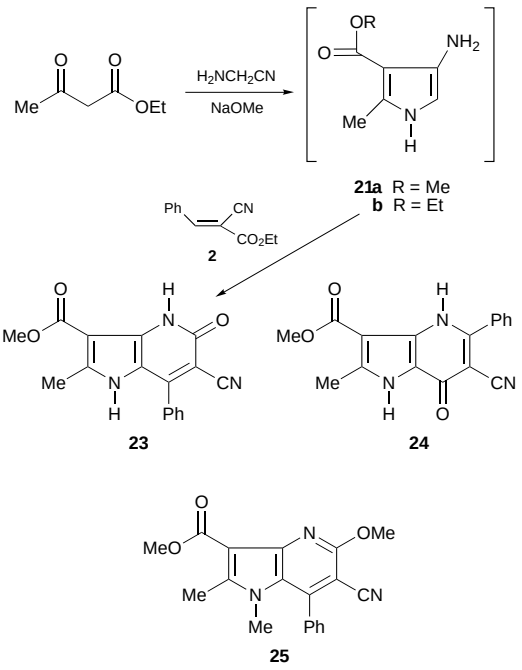




20a X = OEt
X = NMe_2

The fact that **1** reacted with **2a**,**b**, **7** and nitrous acid at C-4 while reaction with benzoyl isothiocyanate and ethoxymethylidenemalononitrile occurred preferentially at the exocyclic amino group can be interpreted as follows. Firstly reaction with nitrous acid was conducted in acid solution. Under such conditions, the exocyclic amino group is protonated and the attacking reagent is thus directed to C-4. For the reactions with **2a**,**b**, ethoxymethylidenemalononitrile and benzoyl isothiocyanate, we believe that both the exocyclic amino and C-4 are potential sites for attack, with the former being more reactive. Thus in reaction with benzoyl isothiocyanate, the addition at the exocyclic amino is irreversible, and thus the reaction product with the amino function was isolated. In reactions with **2a**,**b** and **7**, the reaction at the exocyclic amino group is reversible while the one at C-4 is irreversible. Thus the reaction is thermodynamically controlled and the products are exclusively those of addition at C-4. Although adducts **20a**,**b** seem to be structurally related, the fact that EtO^- is a better leaving group than NMe_2 has resulted in ready elimination of EtO^- from the adduct **20a**, leading to the formation of **11**, while reaction leading to **3** will revert to the starting material.

Methyl 4-amino-2-methyl-1*H*-pyrrole-3-carboxylate (**21a**) was generated *in situ via* reacting ethyl acetoacetate with



aminoacetonitrile in sodium methoxide solution as has been described earlier[8] (**21a** was formed instead of **21b** due to transesterification in methanol). The pyrroleamine **21a** reacted with ethyl benzylidenecyanoacetate **22** to yield a product that may be formulated as **23** or the isomeric **24**. This compound underwent methylation with methyl iodide to give the dimethyl derivative **25**, the structure being confirmed by NOE which revealed steric interaction between the methyl signal at δ 2.66 and the *N*-methyl signal at δ 3.08 and the phenyl protons at δ 7.53.

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Techniques used: IR, NMR, (^1H, ^{13}C, NOE) and microanalysis

References: 8

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References cited in this synopsis

5 M. H. Elnagdi, M. R. H. Elmoghayer and K. U. Sadek, *Adv. Heterocycl. Chem*., 1990, **48**, 223.
6 M. H. Elnagdi, N. Al-Awadi and A. W. Erian, *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky and C. W. Rees, Elsevier, Amsterdam, 1996, volume 7, p. 431 and references cited therein.
7 A. El-Enzy, B. Al-Saleh and M. H. Elnagdi, *J. Chem. Res*., 1997, (*S*) 4; (*M*) 0110.
8 G. H. Birnberg, W. J. Fanshawe, G. D. Francisco and J. W. Epstein, *J. Heterocycl. Chem*., 1995, **32**, 1293.