Studies with Heteroaromatic Amines: the Reaction of Some Heteroaromatic Amines with 1-Substituted 3-Dimethylaminopropanones, Enaminones and Cinnamonitriles†

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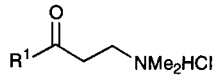
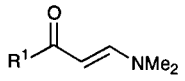
Heteroaromatic amines react with 1-substituted 3-dimethylaminopropanones, with enaminones and with cinnamonitriles to yield azolopyrimidines or azolopyridines.

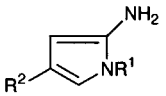
As part of our programme aimed at synthesizing azolopyrimidines as potential antischistosomal agents,[10–12] a route for the synthesis of azoloazines with aryl and heteroaryl substituents was required. Thus, in contrast to the reported formation of the pyrazolo[1,5-*a*]pyrimidine derivative **4a** from the reaction of **1a** with **3b** in refluxing DMF,[10] the reaction of **1a** with **3a** under the same reaction conditions afforded an oily mixture of products. However, when **1a** and **3a** were heated at 120 °C in the absence of solvent, a condensation product of molecular formula $C_{13}H_{11}N_3$ was isolated in 47% yield. The ^{1}H NMR spectrum of the product indicated that the pyrazole C-4 was involved in the reaction, as it showed an absence of any pyrazole 4-H signal at δ 5.0–7.0. Two structures were thus considered for this product (*cf.* structures **5a** and **5b**). Structure **5b** was established for the reaction product based on spectral evidence. Thus, irradiation of the methyl singlet at δ 2.5 enhanced the resonance of the doublet at δ 8.2 observed in the ^{1}H NMR spectrum. Irradiation of the latter doublet enhanced the doublet at δ 7.6 as well as the methyl signal. Similar to the behaviour of **1a** towards **3a**, compound **3a** also reacted with **1b**,**c** to yield the pyrazolo[3,4-*b*]pyridine derivatives **5c**,**d**. Also, the reaction of 5-amino-1,3-diphenylpyrazole **3c** with **1a** gave the pyrazolo[3,4-*b*]pyridine derivative **5e**.



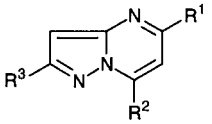
1a R^1 = Ph
b R^1 = 2-naphthyl
c R^1 = 2-thienyl



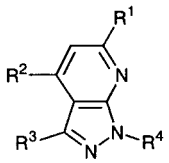
2a R = Ph
b R = 2-furyl
c R = 2-pyridyl



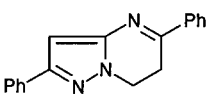
3a R^1 = H, R^2 = Me
b R^1 = H, R^2 = Ph
c R^1 = R^2 = Ph



4a R^1 = R^3 = Ph, R^2 = H
b R^1 = H, R^2 = Ph, R^3 = Me
c R^1 = H, R^2 = 2-pyridyl, R^3 = Me
d R^1 = H, R^2 = 2-furyl, R^3 = Me
e R^1 = Ph, R^2 = H, R^3 = Me
f R^1 = 2-pyridyl, R^2 = H, R^3 = Me
g R^1 = 2-furyl, R^2 = H, R^3 = Me
h R^1 = H, R^2 = R^3 = Ph



5a R^1 = R^4 = H, R^2 = Ph, R^3 = Me
b R^1 = Ph, R^2 = R^4 = H, R^3 = Me
c R^1 = 2-naphthyl, R^2 = R^4 = H, R^3 = Me
d R^1 = 2-thienyl, R^2 = R^4 = H, R^3 = Me
e R^1 = R^3 = R^4 = Ph, R^2 = H
f R^1 = H, R^2 = R^3 = R^4 = Ph



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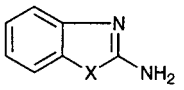
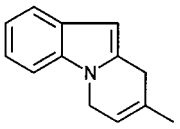
2-Aminobenzimidazole **10a** reacted with **1a** to yield a dihydrobenzimidazo[1,2-*a*]pyrimidine derivative. This was formulated as **11** rather than **12** on the basis of its ^{1}H NMR spectrum, which revealed a doublet for two protons at δ 4.9 and a triplet for one proton at δ 5.3. These are assigned to 4-H and 3-H respectively. If the reaction product were **12**,



10a X = NH
b X = S



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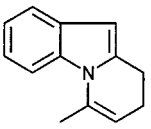

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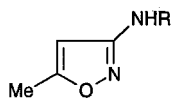
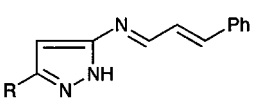
one would expect the doublet at δ 4.9 to appear as a multiplet and the NH signal to appear as a triplet. Moreover, NOE indicated that the doublet at δ 4.9 interacts with aryl protons. If the product were isomeric with **12**, then irradiation of such a doublet would only enhance the other one-proton triplet at δ 5.3.

In contrast to the observed formation of condensed azoles from reaction of **3a–c** or **10a** with **1a–c**, 3-amino-5-methylisoxazole reacted with **1a** to yield the 3-isoxazolylamino ketone **13b**.

The reaction of **3a** with **2a–c** and of **3b** with **2a** afforded products of condensation *via* elimination of water and dimethylamine. ^{1}H NMR spectroscopy of the reaction products



13a R = H
b R = CH_2CH_2COPh



16a R = Me
b R = Ph

indicated that the pyrazole C-4 was not involved in this condensation reaction, as it revealed, in each case, a signal for 4-H at δ 5.8. Two structures seemed to be thus possible (*cf.* **4a**, **4h**). Although structure **4b–d** seemed more likely based on analogy with the reported behaviour of 5-aminopyrazole-4-carbonitrile and 5-aminopyrazole-4-carboxylate towards

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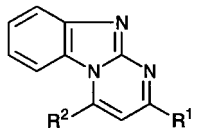
†Dedicated to Professor Dr M. Tisler on the occasion of his 70th birthday.

derivatives of **1**, whose structure has been established by X-ray methods,[13] independent structure elucidation seemed mandatory. Structures **4b–d** were established for the reaction product based on the ^{13}C NMR spectrum of **4b** which showed a low-field doublet at δ 149.04. This is attributed to C-5 which should appear as a doublet at similar field. Attempted preparation of a sample of **4b,h** *via* condensation of **3a**,**b** with cinnamaldehyde failed. Only the cinnamylidene derivatives **16a**,**b** were produced. Trials to effect cyclisation of **16a**,**b** into pyrazolo[1,5-*a*]pyrimidine derivatives failed. We thus believe that these cinnamylidenes are present in the form shown in minor quantities and need to be isomerised prior to cyclisation. All attempted cyclisations of **16a**,**b** into derivatives of **4** failed. It is thus unlikely that **16b** could be cyclised into **4a** as has been reported earlier.[10] The reaction of **3c** with **2a** in refluxing pyridine afforded a pyrazolo[3,4-*b*]pyridine derivative which is formulated as **5f**, as it proved different from **5e** obtained earlier in this work *via* reaction of **3c** with **1a**.

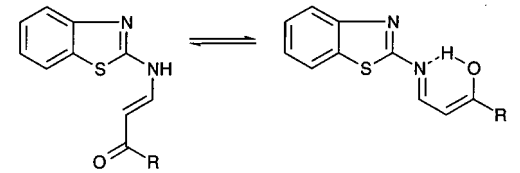
It has been recently reported that 2-aminobenzimidazole **10a** reacts with **2a** in acetic acid to yield a mixture of **17a** and **17c**.[14] In our laboratories, refluxing **10a** with **2a** in pyridine solution afforded only one insoluble product **17c** in 71% yield. Although the melting point of this product is very close to that of **17c** reported in the literature, the ^1H NMR spectrum of the product was somewhat different than that reported[14] for **17c**. We identified the reaction product as **17c** on the basis of elemental analysis and ^1H NMR, COSY and NOESY spectra. A positive NOE was observed between the doublet at δ 9.61 and the ^1H NMR spectrum (which is due to 1-H) with the multiplet at δ 8.32, which the COSY spectrum showed to be coupled to the triplet at δ 7.4 for the 1,2-disubstituted aromatic ring. Thus, it is concluded that 1-H and 9-H interact in space. Thus, structure **17c** is assigned for this reaction product. Compound **17c** is thus formed *via* addition of the ring nitrogen to the activated double bond in **2a**, yielding a Michael adduct which then cyclises by loss of water and aromatises *via* loss of dimethylamine, affording **17c**. Similarly, **17b** was obtained from the reaction of **2c** with **10a**. In contrast to the behaviour of **1a** and **10a**, the aminoazoles **10b** and **13a** reacted with **2a–c** to yield only the heteroaromatic aminoenones **18a**,**b** and **20a–c**. These products are believed to exist in equilibrium with enols **19a,b** and **21a–c** which are stabilized through hydrogen bonding. ^1H NMR showed complex spectra containing signals for each tautomeric form.



17a R^1 = H, R^2 = Ph
b R^1 = 2-pyridyl, R^2 = H
c R^1 = Ph, R^2 = H

We have also found that the reaction of **3a**,**b** with arylmethylidenemalononitriles **22a–c** yields the pyrazolo[1,5-*a*]-pyrimidines **23a–d**. The structure of these products was confirmed by ^1H NMR spectroscopy. Thus, the spectrum of **23a–d** indicated the amino function at $\delta > 7.0$. This is in accordance with previous reports that 7-aminopyrazolo[1,5-*a*]-pyrimidines should show their NH_2 signal at such field.[11] However, it is difficult to exclude completely a possible isomeric 5-amino structure.

In contrast to the reported formation of pyrazolo[1,5-*a*]-pyrimidines on reaction of **3a** with ethyl benzylidenecyanoacetate,[7] the reaction of **22d**,**e** with **3a** afforded a product of condensation at both C-4 and the exocyclic amino group. This product can thus be formulated as **24** or its isomer **25**. Structure **24** (or possible tautomers) could be established for the reaction product based on the ^{13}C NMR spectrum which revealed the ring CO at δ 160. If this product were **25** then the carbonyl carbon would have appeared at higher field. Also, NOE revealed that the aryl and methyl groups are proximal in this product.



18a R^1 = Ph
b R^1 = 2-furyl

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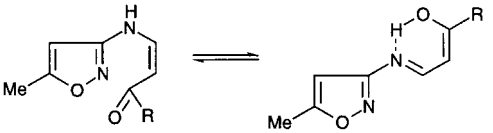
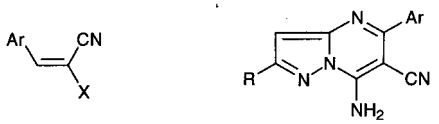


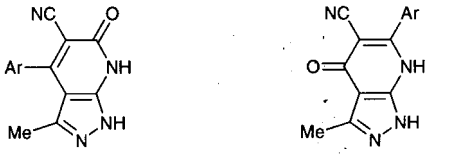
20a R = Ph
b R = 2-pyridyl
c R = 2-furyl

21



22a Ar = Ph, X = CN
b Ar = 4-MeC_6H_4, X = CN
c Ar = 4-$MeOC_6H_4$, X = CN
d Ar = Ph, X = CO_2Et
e Ar = 3-ClC_6H_4, X = CO_2Et

23a Ar = Ph, R = Me
b Ar = 4-MeC_6H_4, R = Me
c Ar = 4-$MeOC_6H_4$, R = Ph
d Ar = R = Ph



24a Ar = Ph
b Ar = 3-ClC_6H_4

25a Ar = Ph
b Ar = 3-ClC_6H_4

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Techniques used: ^1H and ^{13}C NMR, NOE

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