Synthesis of New Azoloazine Derivatives: New Routes to 1,2,4-Triazolo[4,3-*a*]pyrimidines, Pyrazolo[1,5*a*]pyridines and Pyrazolo[3,4-*b*]-pyridinones

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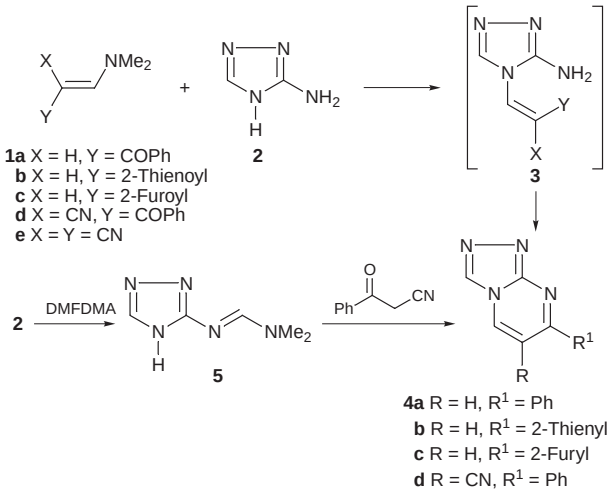
Azoloazines are produced *via* the reaction of aminoazoles with enaminones, enaminonitriles and ethyl alkylidene cyanoacetate.

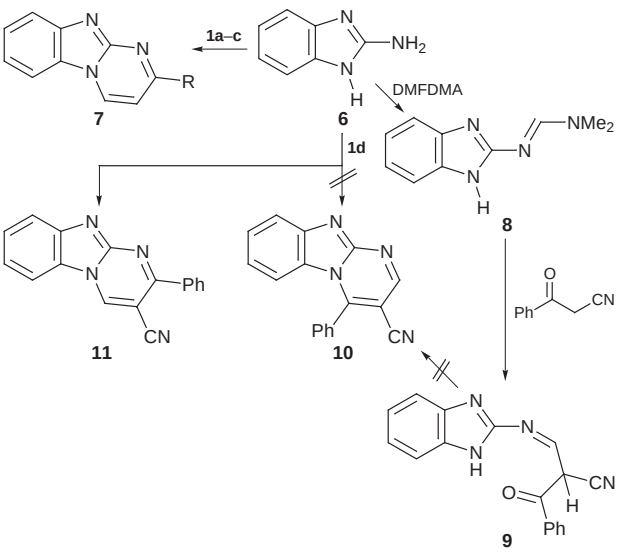
As a part of our program aimed at developing syntheses of new azoloazine derivatives as potential pharmaceuticals and/or agrochemicals, we have recently reported on the utility of the reaction of heterocyclic amines with enaminones as a route to azolopyrimidines and azolopyridines.[7,8] The exact structures of the reaction products have been established based on NOE measurements.[7,8] Here, we report on the reaction of aminoazoles with enaminones, enaminonitriles and α,β-unsaturated esters for the synthesis of azoloazines. We also report approaches for establishing the structures of the reaction products. Thus enaminones **1a**–**c** react with 1*H*-1,2,4-triazole-3-amine **2** to yield addition products which subsequently eliminate dimethylamine and water (Scheme 1). Several isomeric structures appear possible for these products. However ^{1}H NMR spectroscopy established structure **4**. Thus ^{1}H NMR spectra showed the triazole C–H as a singlet at $\delta \approx 9$, low field shifted by *ca.* 1 ppm from its expected position at δ 7.60. This deshielding is attributed to an in space interaction with the substituent in the triazolopyrimidine ring system, as ^{1}H NMR spectroscopy indicated the pyrimidine H-4 as a doublet at $\delta \approx 8.90$. Shifting to such a low field is most likely due to an in space interaction with the triazole 3-H. Conclusive evidence for the proposed structure was obtained from NOE experiments. Thus, for instance, irradiation of the singlet at δ 8.73 (pyrimidine H-4) for **4a** enhanced the signal at δ 8.96 (triazole H-3) and *vice versa*.



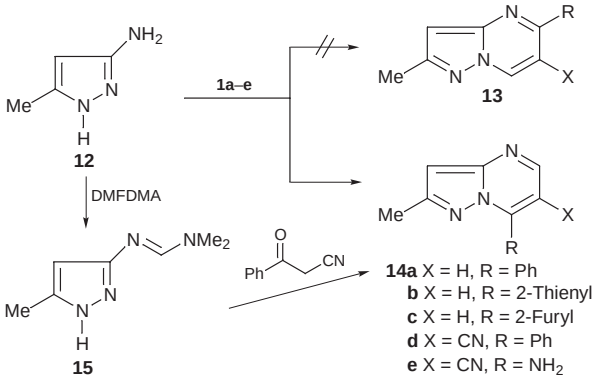
Scheme 1

Similarly, 1,2,4-triazole 3-amine **2** reacted with **1d** to yield 1,2,4-triazolo[4,3-*a*]pyrimidine **4d** which was also obtained from the reaction of **5** with benzoylacetonitrile in pyridine.

2-Aminobenzimidazole **6** has been reported to react with enaminones **1a**–**c** to yield **7** the structure of which was established based on NOESY experiments.[9] Now, we report that condensing **6** with dimethylformamide dimethyl acetal DMFDMA affords **8** (Scheme 2). This, when reacted with benzoylacetonitrile led to **9**, which could not be further cyclized into a benzimidazopyrimidine derivative **10**.

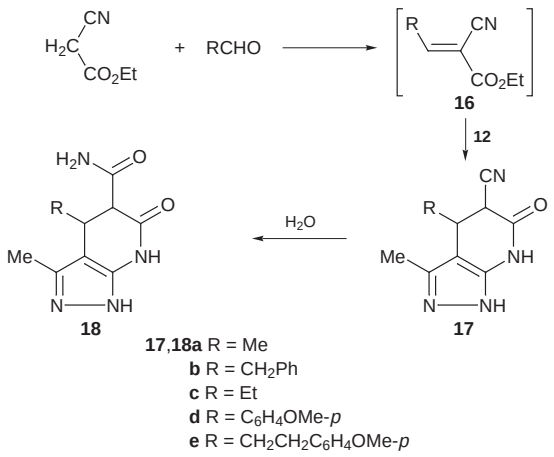


Scheme 2



Scheme 3

* To receive any correspondence.



17,**18a** R = Me
b R = CH_2Ph
c R = Et
d R = C_6H_4OMe-*p*
e R = $CH_2CH_2C_6H_4OMe$-*p*

Scheme 4

However, 2-aminobenzimidazole **6** reacted with **1d** to afford the benzimidazo[3,2-*a*]pyrimidine **11** (Scheme 2). Failure to effect cyclization of **9** into **10** may be due to the steric strain in the latter as a result of steric interaction between aryl moieties.

In previous work[7] it has been shown that 3-methyl-5-aminopyrazole **12** reacts with enaminones **1a**–**c** to yield the 7-substituted pyrazolo[1,5-*a*]pyrimidines **14a**–**c** (Scheme 3). The isomeric structure **13** was ruled out based on analogy to previous reports on the structure of the product reaction **12** with **1a**–**c**.[10] Now we report conclusive evidence for structure proposed for these compounds, as well as the synthesis of further pyrazolo[1,5-*a*]pyrimidine derivatives utilizing the same synthetic approach. Thus pyrazoleamine **12** condensed with DMFDMA to yield formamidine **15** which reacted with benzoylacetonitrile to give **14d**. The same product **14d** was obtained *via* the reaction of **12** with **1d**. In addition reacting compound **12** with **1e** afforded **14e** (Scheme 3).

In a previous report we have shown that the reaction of **12** with ethyl benzylidene cyanoacetate affords pyrazolo-[3,4-*b*]pyridine.[7] Now we report that reacting **16a**,**b** (generated *in situ via* aldehydes and ethyl cyanoacetate), with **12** gives the pyrazolo[3,4-*b*]pyridine derivatives **17a**,**b** (Scheme 4). A similar reaction of **16c**–**e** with **12** afforded **18c**,**d** *via* hydrolysis of **17c**,**d**. The structures of these derivatives are assigned based on NOE measurements: for compound **17a** for example, NOE indicated the close proximity of alkyl substituents at C-3 and C-4.

Techniques used: IR, ^1H and ^{13}C NMR, elemental analysis and NOE measurements

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