Heterocyclic Synthesis *via* Enaminonitriles: One-pot Synthesis of Some New Pyrazole, Isoxazole, Pyrimidine, Pyrazolo[1,5-*a*]pyrimidine, Pyrimido[1,2-*a*]benzimidazole and Pyrido[1,2-*a*]benzimidazole Derivatives

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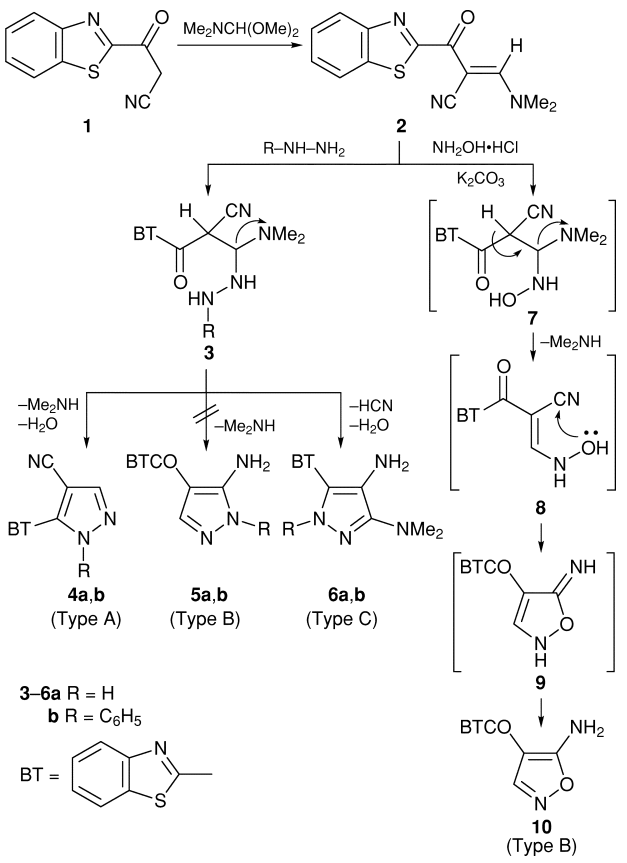
A convenient synthesis of some new pyrazole, isoxazole, pyrimidine, pyrazolo[1,5-*a*]pyrimidine, pyrimido[1,2-*a*]-benzimidazole and pyrido[1,2-*a*]benzimidazole derivatives is reported.

In continuation of our studies on the chemistry of 3-(benzothiazol-2-yl)-3-oxopropanenitrile (**1**)[1,2] and as a part of our program directed towards developing new approaches to a variety of heterocycles incorporating a benzothiazole moiety[1–5] for biological screening, we report here on the synthesis of the multifunctional, *hitherto* unreported 3-(benzothiazol-2-yl)-2-(*N*,*N*-dimethylamino)methylene-3-oxopropanenitrile (**2**) and its utility as a building block for the synthesis of the title compounds.

Thus, treatment of 3-(benzothiazol-2-yl)-3-oxopropanenitrile (**1**) with dimethylformamide dimethylacetal (DMF-DMA) in dry xylene at reflux temperature, afforded a yellow crystalline product identified as 3-(benzothiazol-2-yl)-2-(*N*,*N*-dimethylamino)methylene-3-oxopropanenitrile (**2**) (Scheme 1). The structure of the isolated product was confirmed on the bases of its elemental analysis and spectral data.



Scheme 1

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The reactivity of the enaminonitrile **2** towards some nitrogen nucleophiles was investigated. Thus, treatment of compound **2** with hydrazine hydrate, in refluxing ethanol, afforded a colourless product for which three possible structures **4a**, **5a** or **6a** can be formulated (Scheme 1). The spectral data of the isolated product was in complete agreement with structure **4a**.

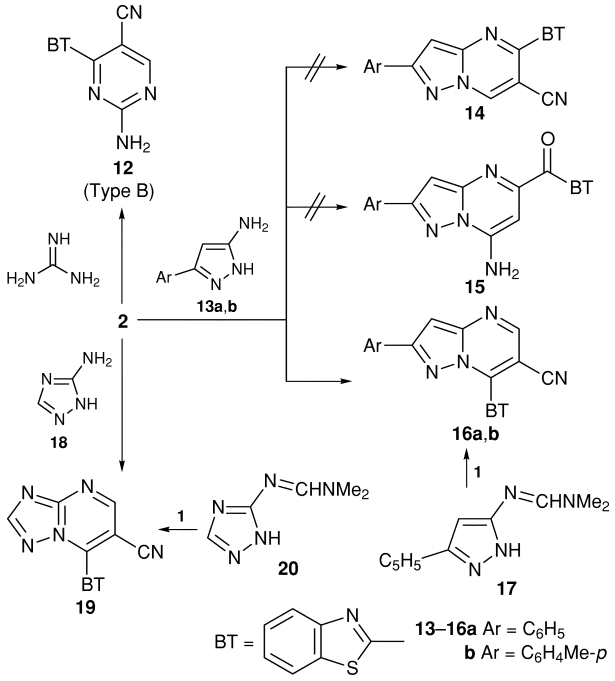
Similarly, compound **2** reacted with phenylhydrazine in ethanol at reflux temperature to afford a yellow product which was identified as 5-(benzothiazol-2-yl)-1-phenylpyrazole-4-carbonitrile (**4b**) (Scheme 1). The other possible structures **5b** and **6b** were easily excluded on the basis of spectral data.

The formation of compounds **4a** and **4b** is assumed to take place *via* a *Michael* type addition of the amino group of hydrazines to the enamine double bond in **2** to form the non-isolable acyclic intermediate **3** which readily undergoes intramolecular cyclization into the pyrazole derivatives **4a** and **4b** *via* the loss of dimethylamine and water molecules, (Scheme 1, type A).

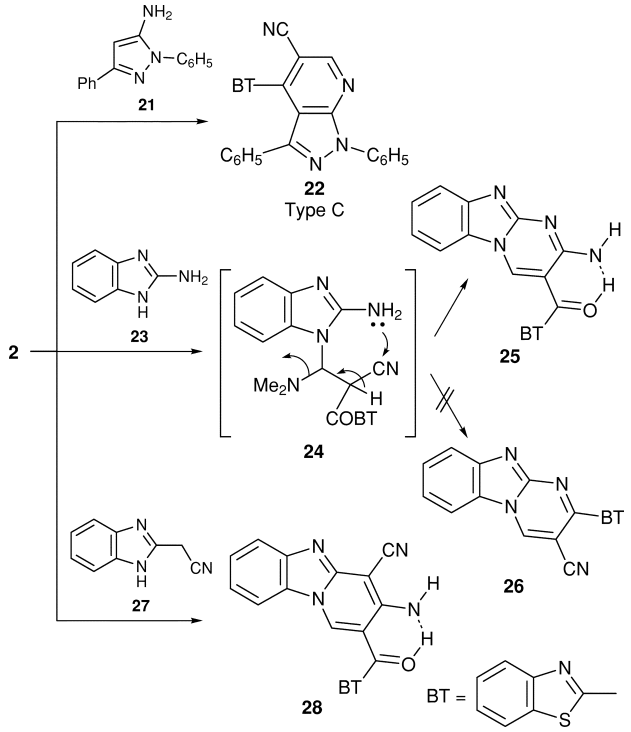
In contrast to its behaviour towards hydrazines, compound **2** reacted with hydroxylamine hydrochloride in ethanol, in the presence of potassium carbonate anhydrous, and afforded the aminoisoxazole derivative **10** (Scheme 1). The structure of the latter product was established on the basis of its elemental analysis and spectral data. For example, its IR spectrum revealed the lack of absorption band corresponding to a nitrile function and showed bands at 3391 and 3132 cm^{-1} corresponding to amino group in addition to a strong carbonyl band at 1665 cm^{-1}. Its mass spectrum revealed molecular ion peak at *m*/*z* 245 (M^+). Compound **10** is assumed to be formed *via* the addition of the NH_2 group of hydroxylamine to the activated double bond in compound **2** to form the non-isolable intermediate **7** which loses a molecule of dimethylamine affording **8** which underwent an intramolecular cyclization to afford the isoxazole derivative **10** (Scheme 1, type B).

Enaminonitrile **2** reacts also with guanidine in refluxing ethanol to give a high yield of a crystalline product for which structure **12** was assigned on the basis of its spectral data (IR and mass spectra). Thus, the IR spectrum of the reaction product, showed an amino and nitrile absorptions at 3375, 3325 and 2212 cm^{-1}, respectively, which are compatible with the assigned structure which seemed to be formed *via* the cyclization mode of type B (Scheme 2).

The foregoing results prompted us to investigate the behaviour of **2** towards some heterocyclic amines as potential precursors for fused heterocyclic systems.[6] Thus, treatment of compound **2** with 5-amino-3-aryl-1*H*-pyrazoles **13a**,**b** in refluxing ethanol, in the presence of a catalytic amount of piperidine, furnished in each case a single product identified as pyrazolo[1,5-*a*]pyrimidine derivatives **16a**,**b**



Scheme 2



Scheme 3

(Scheme 2). A further evidence for the proposed structure **16** was obtained by an independent synthesis of compound **16a** *via* treatment of 5-*N*-(*N*,*N*-dimethylaminomethylene)-imino-3-phenyl-1*H*-pyrazole (**17**) with 3-(benzothiazol-2-yl)-3-oxopropanenitrile (**1**) in ethanol in the presence of a catalytic amount of piperidine to afford a product identical in all respects (mp., TLC and spectra) with that obtained previously from reaction of **2** with **13a**.

In a similar manner, compound **2** reacted with 3-amino-1,2,4-triazole (**18**) and afforded the triazolo[1,5-*a*]pyrimidine derivative **19** (Scheme 2). The structure of compound **19** was established on the basis of its elemental analysis and spectral data besides an independent synthesis from 3-*N*-(*N*,*N*-dimethylaminomethylene)imino-1,2,4-triazole (**20**) and **1** to afford a product identical in all respects with that obtained previously from reaction of **2** with **18**.

On the other hand, compound **2** reacted with 5-amino-1,3-diphenylpyrazole (**21**) and afforded the pyrazolo[3,4-*b*]-pyridine derivative **22**. The structure of compound **22** was established on the basis of its elemental and spectral data (see Experimental).

In contrast to the behaviour of **2** towards 5-amino-3-arylpyrazoles **13a**,**b**, and 3-amino-1,2,4-triazole (**18**), 2-aminobenzimidazole (**23**) reacted with **2** under the same experimental conditions and afforded the pyrimido[1,2-*a*]-benzimidazole derivative **25** (Scheme 3). Structure of compound **25** was confirmed on the basis of its elemental analysis and spectral data. The formation of compound **25** can be explained on the basis of an initial *Michael* addition of the endocyclic NH in **23** to the double bond in **2** to afford the non-isolable intermediate **24** which may cyclize into **25** or **26**. However, structure **26** was easily excluded.

Although the endocyclic NH in compounds **13a**,**b** is the most nucleophilic center[9,10] it is also the most sterically hindered site. Therefore, addition takes place at the exocyclic NH_2 to afford the pyrazolopyrimidine derivatives **16a**,**b** which is in contrast to a recent report.[11] However, in case of the reaction of **2** with 2-aminobenzimidazole (**23**), the formation of the adduct **24** takes place *via* the attack of the endocyclic NH of the imidazole ring into the activated double bond of the enaminonitrile **2**, followed by an intramolecular cyclization to afford the pyrimido[1,2-*a*]-benzimidazole derivative **25** (Scheme 3).

The reaction of enaminonitrile **2** with 1*H*-benzimidazole-2-acetonitrile (**27**) was also conducted in refluxing ethanol, in the presence of a catalytic amount of piperidine to afford 3-amino-2-(benzothiazol-2-yl)carbonylpyrido[1,2-*a*]-benzimidazole-4-carbonitrile (**28**).

Techniques used: IR, ^1H, ^{13}C NMR, and mass spectrometry

References: 14

Schemes: 3

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