Enaminonitriles in heterocyclic synthesis: new routes for the synthesis of some novel azolo[1,5-*a*]pyrimidine, pyrimido[1,2-*a*]benzimidazole, pyrido[1,2-*a*]benimdazole, pyrazolo[3,4-*b*]pyridine, pyrazole and pyrimidine derivatives

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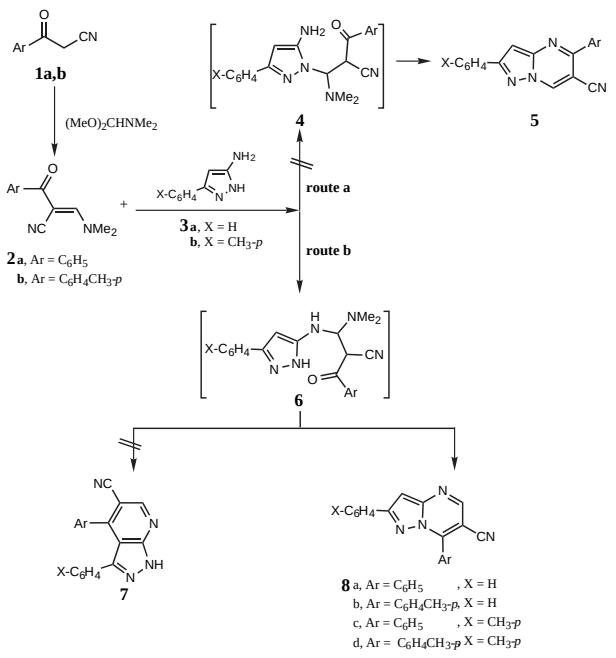
The synthesis of several new azolo[1,5-*a*]pyrimidines, pyrimido[1,2-*a*]benzimidazoles, pyrazolo[3,4-*b*]pyridines, pyrido[1,2-*a*]benzimidazoles, pyrazoles and pyrimidines is reported.

In continuation of our previous interest in the synthesis of variety of heterocycles, from the readily obtainable inexpensive starting materials.[12-14] We report here on the utility of 3-oxopropanenitrile derivatives **2a,b** as building blocks for the synthesis of the otherwise not readily obtainable cyano-1H-pyrazolo[1,5-*a*] pyrimidines, 1,2,4-triazolo[1,5-*a*]pyrimidines, pyrazolo[3,4-*b*]pyridines, pyrazolo [1,2-*a*]benzimidazoles, pyrazoles, and pyrimidines of expected potential biological activity.

We found that treatment of the aroylacetonitriles **1a,b** with dimethylformamide-dimethylacetal (*DMF-DMA*) in dry xylene under reflux for a short time afforded yellowish solid products that were assigned 3-aryl-2-(*N*,*N*-dimethylamino) methylene-3-oxopropanenitriles **2a,b** in almost quantitative yields rather than following recently reported procedures by Kappa *et al.*[3] The behaviour of compounds **2a,b** towards some heterocyclic amines, 1*H*-benz-imidazole-2-acetonitrile, hydrazine, phenyl hydrazine and guanidine is investigated. Thus, compounds **2a,b** reacted with 5-amino-3-arylpyrazoles **3a,b** in ethanol in the presence of a catalytic amount of piperidine to afford products of addition and both dimethylamine and water elimination (Scheme 1).



Scheme 1

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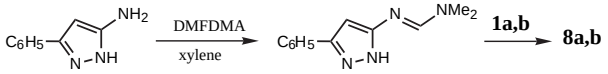
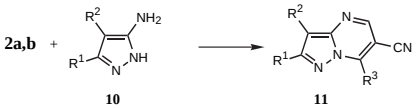
Several structures seemed possible for these products. Thus initial formation of adduct **4** (route a) would lead to **5**, while the formation of adduct **6** can lead to either **7** or **8** (route b). ^{1}H NMR revealed the pyrazole H-4 at δ in the range of 7.20 and absence of any signals corresponding to NH protons; thus structure **7** could be ruled out. Structure **5** was also ruled out on the basis of ^{1}H NMR spectra of the isolated products which revealed a singlet signal in the range of δ 8.90 which was assigned for the pyrimidine CH-2 in structure **8** and not CH-4 in structure **5**.[15] The latter structure was firmly established for the reaction products by the synthesis of the same products *via* condensing **3a** with *DMF-DMA* and subsequent condensation of the so formed amidine 5-*N*-(*N*,*N*-dimethylaminomethylene)amino-3-phenyl-1H-pyrazole (**9**) with aroylacetonitrile **1a,b** to afford products identical in all respects (m.p., mixed m.p. and mass spectra) with those corresponding to compounds **8a,b**.



Similarly, the enaminonitriles **2a**,**b** reacted with 5-amino-3-phenyl-4-bromopyrazole (**10a**) and with 4-(4-chlorophenylazo)-3,5-diaminopyrazole (**10b**) under the same experimental conditions to afford the pyrazolo[1,5-*a*]pyrimidine derivatives **11a-d** in almost quantitative yield.



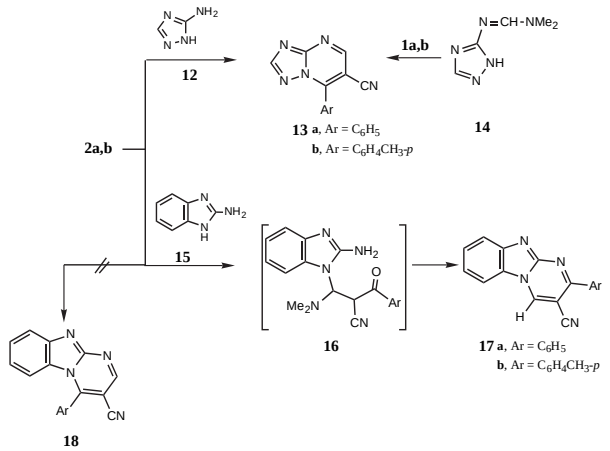
a $R^1 = C_6H_5$; R^2 = Br
b $R^1 = NH_2$; R^2 = N=N-C_6H_4Cl-*p*

a $R^1 = R^3 = C_6H_5$, R^2 = Br
b $R^1 = C_6H_5$; R^2 = Br; $R^3 = C_6H_4CH_3$-p
c $R^1 = NH_2$; R^2 = N=N-C_6H_4Cl-p; $R^3 = C_6H_5$
d $R^1 = NH_2$; R^2 = N=N-C_6H_4Cl-p, $R^3 = C_6H_4CH_3$-p

Formation of compounds **8a-d** and **11a-d** is assumed to take place *via* the addition of the exocyclic amino group in **3a,b** and **10a,b** to the α,β-unsaturated moiety in compounds **2a,b** to yield the corresponding acyclic non-isolable intermediates which cyclize and aromatize into the final products **8a-d** and **11a-d**. It is of importance to report here that whereas ring N is the most nucleophilic centre in compounds **3a,b**,[16-18] however, it is sterically hindered. Our approach for elucidating structure **8** may thus be taken as a basic approach for establishing structure of products formed by reacting functionalized alkenes with the unsubstituted aminoazoles.

In the same manner, the enaminonitriles **2a,b** reacted with 3-amino-1,2,4-triazole (**12**) to afford the 4-aryltriazolo[1,5-*a*]pyrimidine-3-carbonitrile derivatives **13a,b** in moderate yields (Scheme 2). Structure of compounds **13a,b** was established on the basis of their elemental analysis and spectral

data. A final evidence for the proposed structures, comes from synthesizing compounds **13a,b** *via* reaction of 3-*N*-(*N*,*N*-dimethylamino-methylene)amino-1,2,4-triazole (**14**) with aroylacetonitriles **1a,b** to afford products identical in all aspects (mp., TLC, IR, and mass spectra) with those obtained previously from reaction of compounds **2a,b** with 3-amino-1,2,4-triazole (**12**) as described before.



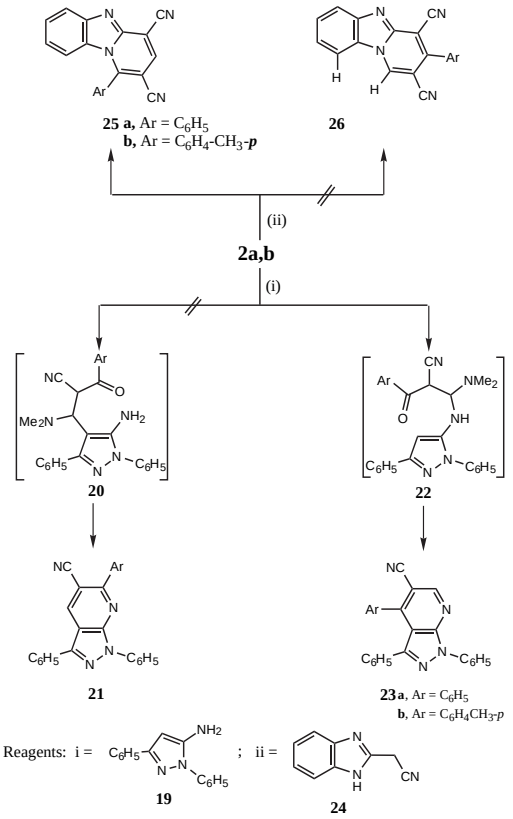
Scheme 2

In contrast to their behaviour towards **3a,b**, **10a,b** and **12**, compounds **2a,b** reacted through the ring nitrogen in 2-aminobenzimidazole (**15**) to afford the pyrimido[1,2-*a*]benzimidazole derivatives **17a,b** *via* the non-isolable intermediate **16** (Scheme 2). Thus, ^{1}H NMR showed a low field singlet at δ ~ 9.2, this is assignable for H-4 in compounds **17a,b** and is being deshielded by van der Waal's deshielding forces, while H-5 appeared at δ = ~ 7.8 which is typical for such proton. If the reaction product is the isomeric **18**, formed *via* initial addition to the exocyclic amino group in compound **15**, this singlet should appear at a higher field.

On the other hand, the enaminonitriles **2a,b** reacted with 5-amino-1,3-diphenylpyrazole (**19**) in pyridine under reflux and afforded products that may be formulated as the pyrazolo[3,4-*b*]pyridine derivatives **21** or its isomer **23** *via* the non-isolable intermediates **20** or isomeric **22**, respectively (Scheme 3). Again, ^{1}H NMR spectra of the isolated reaction products, supported structure **23** as it revealed the pyridine ring CH-2 at δ in the range of 8.8 which is in accordance with structure **23**.[21] If the reaction product is the isomeric **21**, one would expect this proton (now H-4) to appear at higher field as it is shielded by phenyl moiety ring current.

Also, compounds **2a,b** reacted with 1*H*-benzimidazole-2-acetonitrile (**24**) in ethanol in the presence of a catalytic amount of piperidine and afforded in each case a single product for which structure **25a**, or **25b** was assigned on the basis of their elemental analysis and spectral data (Scheme 3). Thus, ^{1}H NMR spectrum of the isolated reaction product revealed one proton at high field as a doublet at δ = 6.13 (*J* = 11) which is assigned for H-9 in structure **25a**. This is highly shielded by lying over the benzene ring at C-1 which is perpendicular to the ring plane. A singlet at δ = 7.91 was observed and is attributed to H-3 in the benzimidazopyridine ring system. This is a typical value for pyridine H-4. If the reaction product was **26**, it would be difficult to assign the high field signal at δ = 6.13, moreover, the singlet due to pyridine H-2 in this case should appear at a lower field.

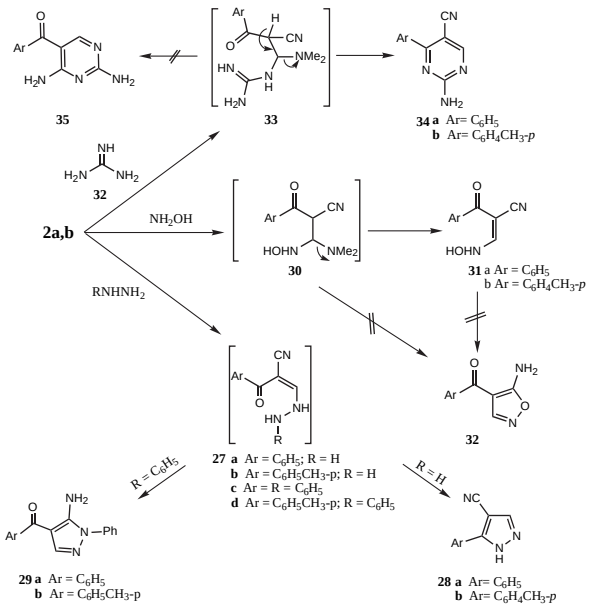
Compounds **2a,b** reacted with hydrazine hydrate in ethanol to yield the 4-cyanopyrazole derivatives **28a,b**. On the other hand, compounds **2a,b** reacted with phenyl hydrazine under the same experimental conditions to yield the aminopyrazoles **29a,b**. It was believed that **2a,b** reacted initially with both



Scheme 3

hydrazine and phenylhydrazine to yield the nonisolable acyclic hydrazino derivatives **27a-d**. The intermediates **27a,b** cyclized readily *via* water elimination leading to pyrazoles **28a,b**. Similar cyclization of **27c,d** into **28** is sterically hindered as it could produce pyrazoles with two adjacent bulky substituents, consequently, **27c,d** cyclizes *via* addition to cyano group yielding the amino pyrazole derivatives **29a,b** as confirmed by elemental analyses and spectral data (Scheme 4).

In contrast to its behaviour towards hydrazines, compounds **2a,b** reacted with hydroxyl amine in ethanol under reflux and afford in an excellent yield the hydroxylaminopropenonitrile



Scheme 4

derivatives **31a,b** based on elemental analysis and spectral data of the isolated reaction products. It is of value to report here that all trials to convert compounds **31a,b** into the corresponding isoxazole derivatives **32a,b** were unsuccessful, which is in contrast to a recent report.[22] This can be attributed to the fact that compounds **31a,b** is mainly existing in the *anti*-form as indicated from its ^{1}H NMR spectra.

The reaction of enaminonitriles **2a,b** with guanidine in ethanol under reflux has afforded the aminopyrimidines **34a,b** *via* the acyclic non-isolable intermediates **33a,b**. Structure **35** was readily ruled out on the basis of spectral data (IR and MS) of the isolated products. For example, the IR spectrum of the reaction products revealed absorption peaks for the nitrile and amino functions at 2220 and 3310 cm^{-1}, respectively, which are compatible with structure **34**. Besides the IR spectra, the mass spectra revealed molecular ion peaks at *m/z* 196 (M^{+}) and 210 (M^{+}) for compounds **34a** and **34b**, respectively. ^{13}C NMR spectrum of compound **34b** is also in full agreement with that proposed structure (*cf.* Experimental). A plausible mechanism for the formation of compounds **34a,b** is depicted in Scheme 4.

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

References: 24

Schemes: 4

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