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Heterocyclic Synthesis via Enaminonitriles: an Efficient, One Step Synthesis of Some Novel Azolo[1,5-α]Pyrimidine, Pyrimido[1,2-α]-Benzimidazole, Pyrido[1,2-α]Benzimidazole Pyrimidine and Pyrazole Derivatives

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HETEROCYCLIC SYNTHESIS *VIA* ENAMINONITRILES: AN EFFICIENT, ONE STEP SYNTHESIS OF SOME NOVEL AZOLO[1,5-*a*]PYRIMIDINE, PYRIMIDO[1,2-*a*]-BENZIMIDAZOLE, PYRIDO[1,2-*a*]BENZIMIDAZOLE PYRIMIDINE AND PYRAZOLE DERIVATIVES

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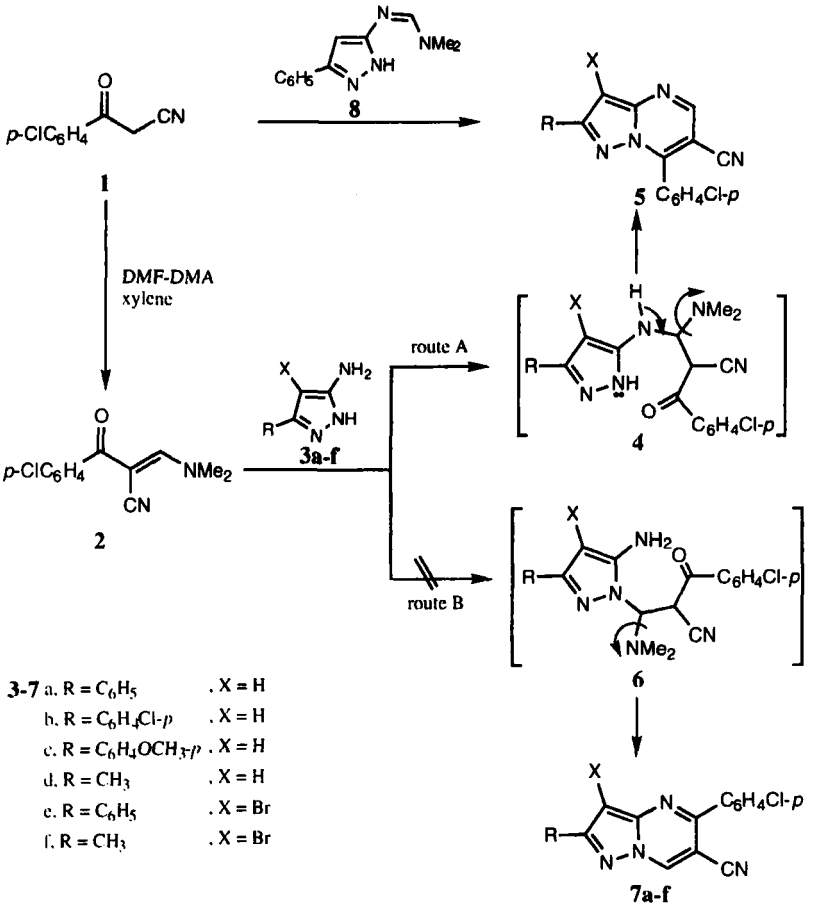
ABSTRACT. Some novel pyrazolo[1,5-*a*]pyrimidines **5a-f**, **10a,b**, 1,2,4-triazolo[1,5-*a*]-pyrimidine (**12**), and pyrimido[1,2-*a*]benzimidazole **18** could be synthesized by reacting 3-(4-chlorophenyl)-2-(*N,N*-dimethylamino)methylene-3-oxopropanenitrile (**2**) with 5-amino-3- and/or 4-substituted-1H-pyrazoles **3a-f** and **9a,b**, 3-amino-1,2,4-triazole (**11**) and 2-aminobenzimidazole (**14**), respectively. The reaction of **2** with 1H-benzimidazol-2-ylacetonitrile (**19**) afforded the pyrido[1,2-*a*]benzimidazole **20**. On the other hand, the reaction of **2** with guanidine, hydrazine, and phenyl hydrazine afforded the pyrimidine **24**, and the pyrazoles **27**, **28**, respectively. However, the reaction of **2** with hydroxyl amine did not afford the isoxazole **32**.

The interesting biological activities reported for pyrazolo[1,5-*a*]-pyrimidines have stimulated chemists to develop the chemistry of this class of compounds.[1-4] In the last 20 years, an enormous number of papers and patents dealing with the chemistry or biological activities of such compounds have been reported.[5-10] Enaminonitriles have recently been reported as useful precursors for the synthesis of pyrazolo[1,5-*a*]pyrimidines,[11-13] however, the use of 3-(4-chlorophenyl)-2-(*N,N*-dimethylamino)methylene-3-oxo-

propenenitrile (**2**) has not been reported. Since chloro substituted pyrazolo[1,5-*a*]pyrimidine have proved to be of potential biological activities[14,15] and in continuation of our previous interest[16,17] in the synthesis of a variety of heterocyclic systems from the readily obtainable inexpensive starting materials for biological screening program in our laboratory, we report here on the behaviour of the hitherto unreported 3-(4-chlorophenyl)-2-(*N,N*-dimethylamino)-methylene-3-oxopropenenitrile (**2**) towards some nitrogen nucleophiles. The work has resulted in the formation of several new pyrazolo[1,5-*a*]pyrimidines, 1,2,4-triazolo[1,5-*a*]pyrimidines, pyrimido[1,2-*a*]benzimidazoles, pyrimidine, pyrido[1,2-*a*]benzimidazole, and pyrazoles derivatives of expected biological activities.

Thus, it was found that, it is better to prepare compound **2** by heating an equimolar amounts of 4-chlorobenzoylacetonitrile (**1**) and *N,N*-dimethylformamide dimethylacetal (*DMF-DMA*) in dry xylene under gentle reflux for a short time rather than following a recent reported procedures by Kappe *et al.*[18] The structure of compound **2** was confirmed on the basis of its elemental analysis and spectral data (Scheme 1).

Compound **2** reacted with some substituted 5-amino-1H-pyrazole derivatives **3a-f** in ethanol in the presence of piperidine as a catalyst, under reflux, to afford in almost quantitative yield and only after 10 min., the substituted pyrazolo[1,5-*a*]pyrimidine derivatives **5a-f**. Structure of the latter products was confirmed based on their elemental analysis and spectral data. For example, the mass spectrum of compound **5a**, formed from **2** and 5-amino-3-phenyl-1H-pyrazole (**3a**), revealed a molecular ion peak *m/z* 330 and 331 (M^+) and (M^++1), respectively. Its ^{1}H NMR spectrum revealed a singlet signal at δ 7.12 (CH-3) and at δ 8.56 (CH-5) in addition to aromatic protons as a multiplet at δ 7.95-7.38. The singlet signals at δ 7.12 disappeared when the 4-bromo derivative **3e** was used instead of **3a**. The IR spectrum of the same compound revealed a strong absorption peak at 2220 cm^{-1} for cyano group and absence of any peaks due to carbonyl absorption.



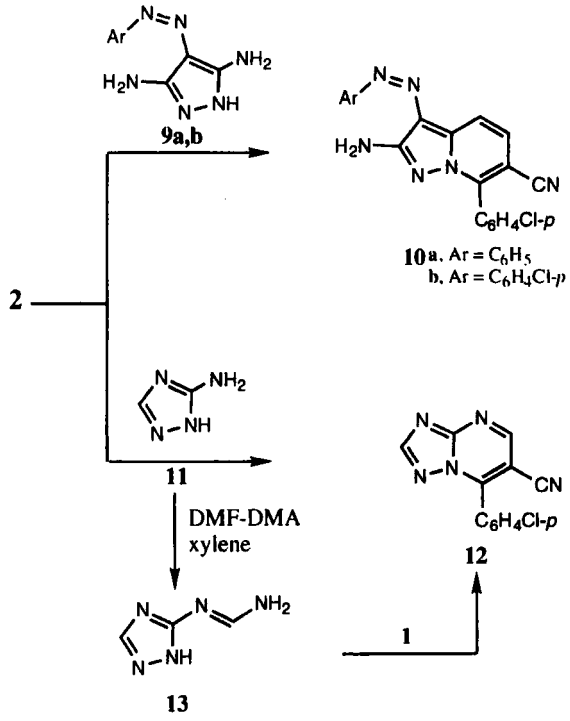
Scheme 1

The formation of compounds **5a-f** is assumed to take place *via* an initial *Michael* addition of the exocyclic amino group in compounds **3a-f** to the activated double bond in **2** to form the acyclic- nonisolable- intermediates **4a-f** (route A), which undergo cyclization and aromatization via loss of both water and dimethyl amine molecules affording the final isolable products **5a-f**. Although the endocyclic imino group in compounds **3a-f** is the most nucleophilic center,[19-21] however, it is the most sterically hindered site,[22] therefore, the reaction is assumed to take place *via*

route A rather than route B is shown in Scheme 1. Structure **5** was further confirmed *via* an independent synthesis of compound **5a** by reacting an equimolar amounts of 5-*N,N*-dimethylamino-methylene-3-phenylpyrazole (**8**) with **1** in ethanol under reflux to afford a product identical in all respects (m.p., mixed m.p., TLC and spectra), with those of compound **5a**.

Similarly, compound **2** reacted with 4-arylazo-3,5-diamino-pyrazoles **9a,b** under the same experimental conditions to afford the polysubstituted pyrazolo[1,5-*a*]pyrimidines **10a,b** and with 3-amino-1,2,4-triazole (**11**) to yield the 7-(4-chlorophenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carbonitrile (**12**) in almost quantitative yield (Scheme 2). The structure of each of compounds **10a,b** and **12** was established on the basis of its elemental analysis and spectral data. Furthermore, the structure of compound **12** was confirmed by an independent synthesis of the same compound *via* reacting an equimolar amounts of compound **1** with 3-*N,N*-dimethylaminomethylene-1,2,4-triazole (**13**) in ethanol in the presence of a catalytic amount of piperidine under reflux to afford a product identical in all respects with those of compound **12** (Scheme 2).

In contrast to its behaviour towards compounds **3a-f**, **9a,b** and **11**, compound **2** reacted with 2-aminobenzimidazole (**14**) under the same experimental conditions to afford the pyrimido[1,2-*a*]benzimidazole derivative **18** (Scheme 3). The structure of compound **18** was established based the elemental analysis and spectral data of
the isolated reaction product. Formation of compound **18** is assumed to take place *via* an initial *Michael*-type addition of the imino function in compound **14** to the activated double bond in **2** to form the non-isolable acyclic intermediate **17** (route B) which undergoes cyclization and aromatization affording **18**. The discrepancy in the behaviour of compounds **3a-f**, **9a,b**, **11** and **14** can be explained on the basis of steric factors. Thus, if the reaction proceeds according to route A, compound **16** is difficult to



Scheme 2

be formed due steric interaction of the 4-chlorophenyl moiety and the benzene ring of the benzimidazole nucleus.

In a similar manner, compound **2** reacted with 1H-benzimidazole-2-ylacetonitrile (**19**), under the same experimental condition and afforded a yellow crystalline product which was identified as 8-(4-chlorophenyl)pyrido[1,2-a]benzimidazole-7,9-dicarbonitrile (**20**) on the basis of its elemental analysis and spectral data (Scheme 3).

Compound **2** reacted with guanidine (**21**), liberated *in situ* from guanidine nitrate and potassium carbonate in ethanol under reflux and afforded a colorless crystalline product which was identified as 2-amino-4-(4-chlorophenyl)pyrimidine-5-carbonitrile