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An efficient one-pot multi component synthesis of pyrimidine derivatives in aqueous media

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ABSTRACT

A simple and efficient synthesis of aryl and heteroaryl substituted pyrimidines has been developed via initial Knoevenagal, subsequent addition and final cyclization of aldehyde, ethylcyanoacetate and guanidine nitrate. Piperidine has been used as a catalyst. Short reaction time, environment friendly procedure and excellent yields are the advantages of this procedure. All synthesized compounds were characterized by IR, NMR and Mass spectral data.

Keywords: One-pot synthesis, Pyrimidine derivatives, Piperidine, Aqueous media.

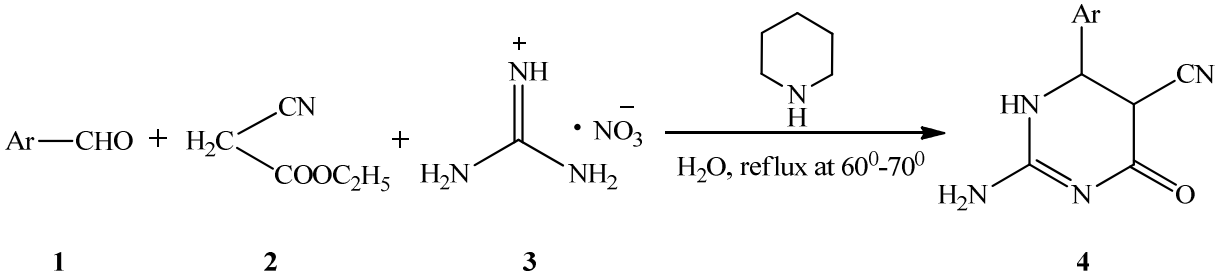
INTRODUCTION

Heterocyclic molecules are of biological interest due to their potential physical and chemical properties [1]. Among these the pyrimidine compounds occupy a unique position in pharmaceutical chemistry, as they are components of nucleic acids. The important pyrimidine compounds have diverse applications as bactericidal [2], fungicidal [3], analgesics [4], anti-inflammatory [5] and antitumor agents [6].

Nowadays, the one-pot methods involving multi component condensation using different reagents and catalysts are popular in synthetic organic chemistry for the synthesis of heterocyclic compounds. These single step methods are more convenient as compared with two step strategies as they require shorter reaction times, simplicity of product isolation and higher yields.

Although a number of papers have been reported concerning the synthesis of pyrimidine derivatives [7, 8], few one pot syntheses [9, 10] have been published using aromatic aldehydes, ethyl cyanoacetate and guanidine nitrate. Peter Russell and George H. Hitchings prepared 2,4,6-triaminopyrimidines by refluxing malononitrile with guanidine in alcohol [11]. Biginelli reported one-step synthesis of 3,4-dihydro pyrimidones by three- component condensation of aldehydes, ethyl acetoacetate and urea [12] in alcoholic medium using strong mineral acid. These compounds possess several pharmaceutical properties like antibacterial, antiviral, anti-inflammatory, antihypertensive and antitumor agents [13, 14]. They also serve as calcium channel blockers, as α-1a-antagonists and neuropeptide antagonists. Several protocols and different reaction condition have been employed to improve the yield of Biginelli reaction product [15-18]. These facts and usefulness of Biginelli reaction inspired us to synthesize such type of new compounds to investigate promising biological activities.

As part of our efforts to design and synthesize new pyrimidine derivatives [19, 20], in this work we would like to report the synthesis of 2-amino-4-oxo-6-aryl-tetrahydropyrimidine-5-carbonitrile and its derivative by three-component condensation of aromatic aldehydes, ethyl cyanoacetate and guanidine nitrate using piperidine as a catalyst in aqueous medium under refluxing condition.



1 **2** **3** **4**

Scheme-1

MATERIALS AND METHODS

The melting points were taken in open capillaries and were found to uncorrected. All products were characterized by IR, NMR and Mass spectral data. The ^{1}H NMR and ^{13}C NMR spectra were recorded by using $CDCl_3$/DMSO-d_6 solvent on Brucker 400 MHz spectrometer with tetra methyl silane as an internal standard. The reaction progress was monitored by TLC on Silica gel 60 F 254 plates. All aldehydes, ethyl cyanoacetate, guanidine nitrate were all commercial products and were used without further purification. Solvents were distilled before use. Yields refer to the isolated yields of the products.

General procedure for the synthesis of 2-amino pyrimidine derivative

A mixture of aldehyde (1mmol), ethyl cyanoacetate (1.2 mmol), guanidine nitrate (1.5 mmol) and catalytic amount of piperidine was taken in a round bottom flask (100mL) with water as a solvent and refluxed at 100^{0}C. The progress of the reaction was monitored by TLC. After the completion of the reaction the solid product was collected by filtration. The product was dried and recrystallised from hot ethanol to obtained pure product.

2-amino-4-oxo-6-phenyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (4a): White crystal; Mp: 218-220^{0}C; IR (KBr ν_{max}/cm^{-1}): 3478(NH), 3090(C-H), 2260(CN), 1690(C=O), 1617(C=N), 1567(C=C). ^{1}H NMR (300MHz, $CDCl_3$) δ 8.56 , 2.0 (s,2H NH), 7.27-7.40 (m,5H,Ar), 4.1(d,CH), 3.97(d, CH). ^{13}C NMR ($CDCl_3$) δ: 168.4 ,153.3, 143.5, 128.5, 126.9, 126.7, 116.8(CN), 43.2, 42.4. Molecular weight: 214.22; Mass (m/z): 214 (M$^+$).

2-amino-6-(3,4-dimethoxyphenyl)-4-oxo-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (4c): Yellow crystal; Mp: 127-128^{0}C; IR (KBr ν_{max}/cm^{-1}): 3460 (NH), 3080 (Ar C-H), 2943 (Methyl C-H), 1590 (C=C), 1290 (Aryl-OCH_3), 1670 (C=O), 1567 (C=N), 2310 (CN). ^{1}H NMR (300MHz, $CDCl_3$) δ: 6.74-6.96 (m, 3H, Ar), 2.0, 8.56 (s, 2H, NH), 3.97, 4.1(d, 2H,CH), 3.83 (s, 2H, Methyl proton). ^{13}C NMR ($CDCl_3$) δ: 168.4, 153.3, 149.6, 147.8, 136.8, 121.9, 118.9, 116.8, 109.8, 43.2, 42.7, 56.1. Molecular weight: 274.28; Mass(m/z) : 248(M$^+$).

2-amino-6-(4-nitrophenyl)-4-oxo-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (4d): Yellow crystal; Mp 162-164; IR (KBr ν_{max}/cm^{-1}): 3440 (NH), 3080 (C-H), 2327 (CN), 1640 (C=O), 1560 (C=N), 1567 (C=C), 1523 (N=O). ^{1}H NMR (300MHz, $CDCl_3$) δ: 7.55-8.21 (m, 4H, Ar), 2.0, 8.56 (s, 2H, NH), 3.97, 4.1(d, 2H, CH). ^{13}C NMR ($CDCl_3$) δ: 168.4, 153.3, 149.6, 145.9, 123.7, 123.4, 116.8, 43.2, 42.4. Molecular weight: 259.22; Mass m/z): 259(M$^+$).

2-amino-4-oxo-6-(1*H*-pyrrol-2-yl)-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (4e): Yellow crystal; Mp: 93-95^{0}C; IR(KBr ν_{max}/cm^{-1}): 3420 (NH), 3111(Ar C-H), 2360 (CN), 1720 (C=O), 1593 (C=N). ^{1}H NMR (300MHz, $CDCl_3$) δ: 5.72-6.69(m, 3H, Ar proton), 2.0, 8.56 (s, 2H, NH), 3.02 (m, 1H, CH), 3.9 (m,1H,CH). ^{13}C NMR ($CDCl_3$) δ: 168.4, 153.3, 130.5, 118.0, 116.8, 108.5, 107.7, 43.9, 42.8. Molecular weight: 203.20; Mass(m/z) : 203 (M$^+$).

2-amino-4-oxo-6-(1-methyl-1*H*-pyrrol-2-yl)-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (4h): Yellow crystal; Mp: 148-150^{0}C; IR (KBr ν_{max}/cm^{-1}): 3470 (NH), 3111 (Ar C-H), 2360 (CN), 1720 (C=O), 1542 (C=C), 1593 (C=N),

2953 (Methyl C-H). ^{1}H NMR (300MHz, $CDCl_3$) δ: 5.72-6.69 (m, 3H, Ar proton), 2.0, 8.56(s, 2H, NH), 3.90 (s, 1H, Methyl proton), 3.97, 4.1 (d,2H,CH). ^{13}C NMR ($CDCl_3$) δ: 168.4, 153.3, 132.1, 122.5, 116.8, 108.6, 108.4, 44.2, 40.3, 35.2. Molecular weight: 217.23; Mass(m/z) : 217(M^+).

RESULTS AND DISCUSSION

To evaluate the catalytic effect of various catalysts we started with the model reaction of ethylcyanoacetate (1.2 mmol) with 4-methoxy benzaldehyde (1.0 mmol) and guanidine nitrate (1.5 mmol) in water with use of various catalysts to afford pyrimidine derivatives **4b** in various yields (Table 1). It can be seen from Table 1 that piperidine was the most efficient (Table 1, entry 3) among the all catalysts studied.

Table-1: Catalytic activity of different catalysts to synthesize compound 4b

Entry	Catalyst	Time (h)	Yield[b] (%)
1	NaOH	5	86
2	P_2O_5	4	82
3	Piperidine [a]	3	93
4	C_2H_5ONa	5	78
5	K_2CO_3/TBAB	4	80
6	$(C_2H_5)_2NH$	6	84

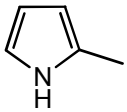
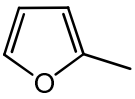
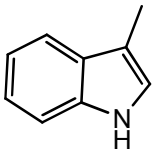
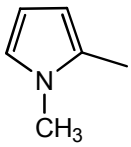
[a] *Reaction conditions: Ethylcyanoacetate (1.2 mmol), 4-methoxy benzaldehyde (1.0 mmol), guanidine nitrate (1.5 mmol) in water at reflux temperature.* [b] *Isolated Yields*

Table-2: Synthesis of pyrimidines in the presence of piperidine in different solvents [a]

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	Piperidine	Ethanol	4	87
2	Piperidine	Methanol	5	82
3	Piperidine	Water	3	95
4	Piperidine	CH_3CN	6	73
5	Piperidine	DMF	7	67

[a] *All reactions were carried out in reflux temperature*

Table-3: Piperidine catalyzed synthesis of 2-amino pyrimidines

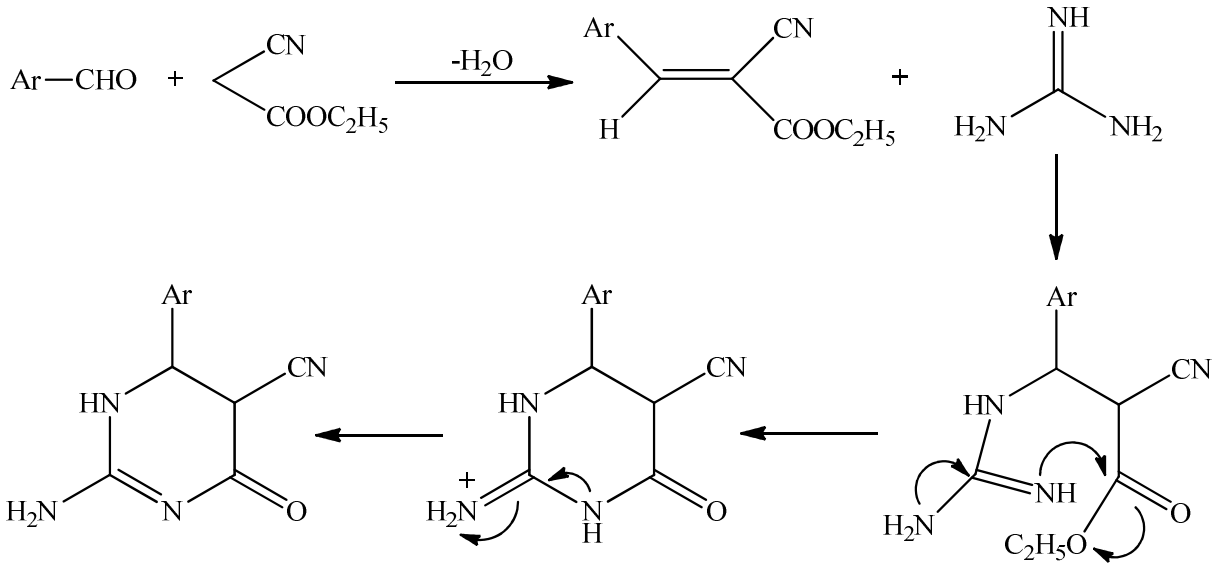
Entry	Ar	Product [a]	Yield [b] (%)	M.P (°C)
1	C_6H_5	**4a**	95	218-220
2	4-(CH_3O)-C_6H_4	**4b**	93	110-112
3	3,4-(CH_3O)-C_6H_3	**4c**	90	127-128
4	4-NO_2-C_6H_4	**4d**	91	162-164
5		**4e**	83	93-95
6		**4f**	92	76-78
7		**4g**	94	190-192
8		**4h**	87	148-150

[a] *All compounds thus obtained were characterized by physical and spectral data.*
[b] *Isolated Yields*

This work has also been extended to observe the effect of solvent on the reaction (Table 2, entries 1-5) and aqueous condition was found to be the best condition when considering the reaction yields and environmental damage (Table-2, entry 3).

In order to evaluate the generality of this model reaction we then prepared a range of 2-amino pyrimidine derivatives under the optimized reaction conditions. In all cases, aryl aldehydes and heteroaryl aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the expected products in good to excellent yields in relatively short reaction times. The kind of aldehyde has no significant effect on the reaction. The results are shown in Table 3.

In the presence of piperidine, reaction proceeds smoothly giving desired products in short time and in a quantitative yield. The formation of the product takes place when aryl aldehydes were reacted with ethylcyanoacetate to form arylmethylene ethylcyanoacetate, which subsequently added with guanidine fallowed by cyclization and tautomarisation to form desired product (Scheme-2).



Scheme-2: Plausible mechanism for the formation of pyrimidine derivative

CONCLUSION

In conclusion, we have developed a simple, quick and efficient method for the synthesis of 2-amino-4-oxo-6-aryl-tetrahydropyrimidine-5-carbonitrile using piperidine. This new procedure is much more efficient, apart from its simplicity, the important advantage of the present procedure is the ability to tolerate variations in all aldehydes of the reaction. To the best of our knowledge, this is one of the quickest, economical and simple alternatives towards the synthesis of 2-amino-4-oxo-6-aryl-tetrahydropyrimidine-5-carbonitrile. Ease of separation of pure product, selectively and in high yields in comparison to the two-step strategies, are a few of the unique features of this method.

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