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SUBSTITUTED PYRIDINE CATALYSED DOMINO SYNTHESIS OF PYRAZOLINES AND PYRIMIDINES.

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ABSTRACT

A novel and efficient base catalysed domino synthesis of pyrazolines and pyrimidines through chalcones as intermediate compounds were reported. The base employed as catalyst to synthesize above compounds was alkyl substituted pyridines due to more basic strength, low volatility and low toxicity. In order to synthesize chalcones, catalytic amount of Cu^{+} was added to make active methyl group more active. We achieved good yields and products were characterized by IR, ^{1}H NMR and Mass spectral data.

KEY WORDS: alkyl substituted pyridines, Chalcones, Pyrazolines and Pyrimidines.

INTRODUCTION

Chalcones are chemically narrated as α, ß-unsaturated ketones bearing large variable aromatic systems at 1, 3-positions'. These are excellent pre-coursers to synthesize many hetero cyclic compounds [1, 2, 3, 4]. Majorly Pyrazolines and pyrimidines were well pre-coursed by Chalcones and versatile biological activities *viz* anti- cancer[5,6] antimalarial[7, 8], antimicrobial [9, 10, 11],anti-inflammatory [12, 13] activities of chalcones; anti-amoebic [14, 15], anti-microbial[16,17,18], anti-inflammatory[19,20,21,22] activities of pyrazolines and antimalarial [23], anti-microbial[24,25], anti-viral[26] activities of pyrimidines were reported. Literature showed various inorganic and organic acids [27, 28] catalyzed synthesis of pyrazolines and pyrimidines involving two steps. Initially, the base catalyzed preparation of chalcones and then acid catalyzed conversion of chalcones to pyrazoles and pyrimidines. These reaction procedures involve much use of chemicals and loss in the yield of the final product due to work ups at

every step. To overcome these challenges, more environment benign domino reactions were the revolutionary synthetic approach today. Here we report the synthesis of pyrazolines from the domino reaction of substituted acetophenones with aromatic aldehydes forming chalcones and then with hydrazines in the presence of alkyl substituted pyridines such as 2,6-dimethylpyridine (2,6-DMP), 4-methylpyridine (Scheme 1) and the methodology was extended to the synthesis of pyrimidines from the domino reaction of substituted acetophenones with aromatic aldehydes forming chalcones and then with guanidine / thiourea/urea in the presence of alkyl substituted pyridines (Scheme 3). In order to minimize the toxicity of pyridine catalyst, alkyl substituted pyridines were chosen with catalytic amount of Cu^{+} as they posses more basic strength than un-substituted pyridine and we could work in less vaporized atmosphere at high temperatures too due to their high boiling points.

MATERIALS AND METHODS

The chemicals used were commercially obtained from Aldrich. The progress of the reactions was monitored by TLC using silica gel-G (Merck grade) using U.V.light for detection of spots. The structures of compounds were characterized by m.p.s, I.R., ^{1}H NMR, mass spectral data. All the m.p.s were determined in open capillaries using electro thermal m.p. apparatus and uncorrected. IR spectra were recorded in KBr on Shimhadzu FTIR presige-21; ^{1}H NMR spectra were recorded at 400 MHz on Bruker spectrometer using TMS as an internal reference.

EXPERIMENTAL SECTION

Preparation of Pyrazolines (5a-k): Acetophenones **1** (0.01mole), catalytic amount of Cu I were charged in *rbf* containing 10ml of ethanol and stirred well on magnetic stirrer for 15 min. Few drops of 2, 6-dimethyl Pyridine or 4-methyl pyridine was added while stirring. Aromatic aldehydes 2 were added to the above mixture; contents were refluxed in water bath for 1-1.5hrs. The progress of the reaction was monitored by TLC. After complete conversion of reactants, the reaction mixture was cooled to room temperature and then Phenyl hydrazine hydrochloride (0.01mole) 4 was added drop wise and refluxed for 1 hr. The progress of the reaction was monitored by TLC. The reaction mixture was poured in crushed ice, neutralized with 0.01N HCl, the precipitate was filtered out, dried and recrystallized from rectified spirit. The product so obtained was confirmed by m.p.s, I.R., ^{1}H NMR, mass spectral data.

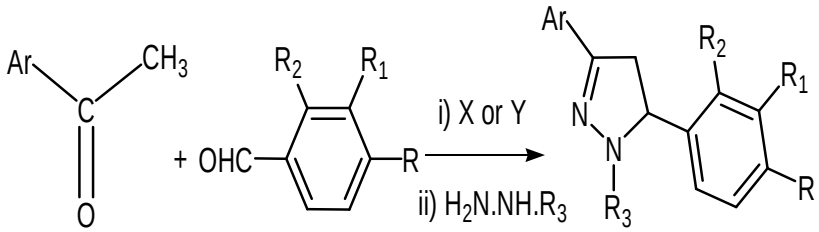
The sequence of the reaction is shown in scheme 2. The intermediate chalcone compounds 3a-k was also isolated and was confirmed by m.p.s, I.R., ^{1}H NMR, mass spectral data and were found to be in concordance with literature [29,30].

Preparation of Pyrimidine: p-aminoacetophenone 6 (0.01mole), catalytic amount of CuI were charged in *rbf* containing 5ml of ethanol and stirred well on magnetic stirrer for 15 min. Few drops of 2,6-dimethyl Pyridine (2,6-DMP) or 4-methyl pyridine was added while stirring. P-nitrobenzaldehyde 7 was added to the above mixture; contents were refluxed in water bath for 1-1.5hrs. The progress of the reaction was monitored by TLC. After complete conversion of reactants, the reaction mixture was cooled to room temperature and then aromatic aldehyde (0.01mole) 9 was added drop wise and refluxed for 1 hr. The progress of the reaction was monitored by TLC. Schiff's base 10a/10b was resulted. To the reaction mixture, guanidine/thiourea/urea (0.01mole) was added portion wise while stirring and refluxed for 2-3 hrs. The reaction mixture was poured in crushed ice, neutralized with 0.01N HCl, the precipitate was filtered out, dried and recrystallized from rectified spirit. The product so obtained was confirmed by m.p.s, I.R., ^{1}H NMR, mass spectral data.

The sequence of the reaction is shown in scheme 4. The intermediate compounds 8, 10a & 10b were also isolated and were confirmed by m.p.s, I.R., ^{1}H NMR spectral data and were found to be in concordance with literature [31].

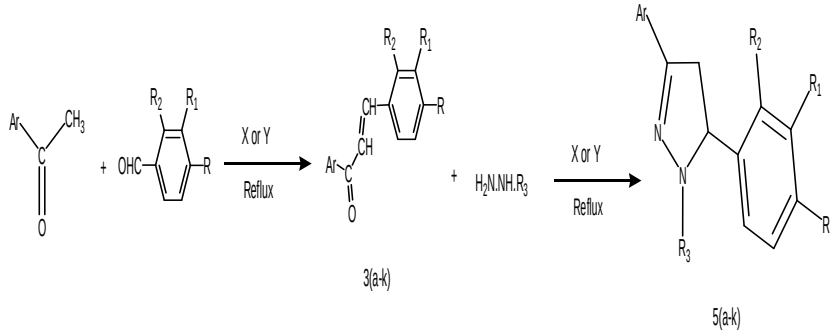
RESULTS AND DISCUSSIONS

In order to synthesis of pyrazolines Acetophenones, Aromatic aldehydes and Phenyl hydrazine hydrochloride were treated with CuI and alkyl substituted pyridine in presence of ethanol. Yields are good i.e. 76-82%, Less are the reaction times and wastage of chemicals too. The product so obtained was confirmed by m.p.s, I.R., ^{1}H NMR, mass spectral data and were found to be in concordance with literature.

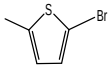


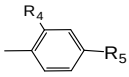
1 2 5(a-k)

Scheme 1



Scheme 2

For Compounds 5a-f, Ar =  ; R_3 = -Ph.

For Compounds 5g-k, Ar=  ; R_3 = -H

X= 2, 6-dimethyl Pyridine; Y= 4-methylpyridine

5a. R, R_2 = -Cl; R_1 = -H

5b. R = -Br, R_1; R_2 = -H

5c. R = -Cl, R_1; R_2 = -H

5d. R = -OCH_3; R_1, R_2= -H

5e. R = -F; R_1, R_2 = -H

5f. R_2= -H; R, R_1= -OCH_3

5g. R= -NO_2, R5= -OH, R_1, R2, R_4= -H

5h. R= -OCH3, R_5= -OH, R_1, R_2, R_4= -H

5i. R= -NMe_2, R_5= -OH, R_1, R_2, R_4= -H

5J. R= -Cl, R_4= -OCH3, R_1, R_2, R_5= -H

5k. R= -NO2, R_4= -OCH3, R_1, R_2, R_5= H

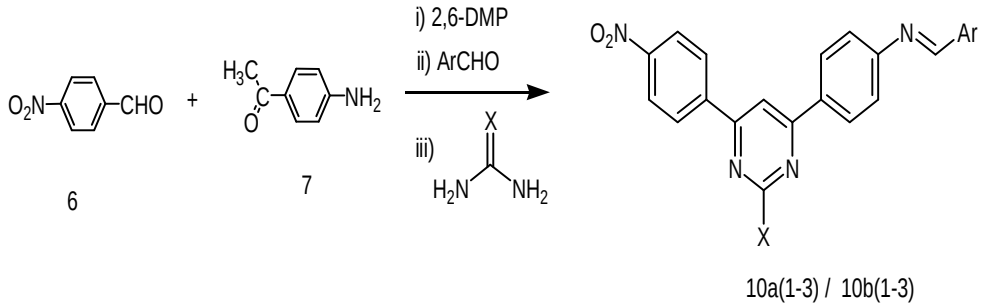
Table1:

Physical Data of Compounds

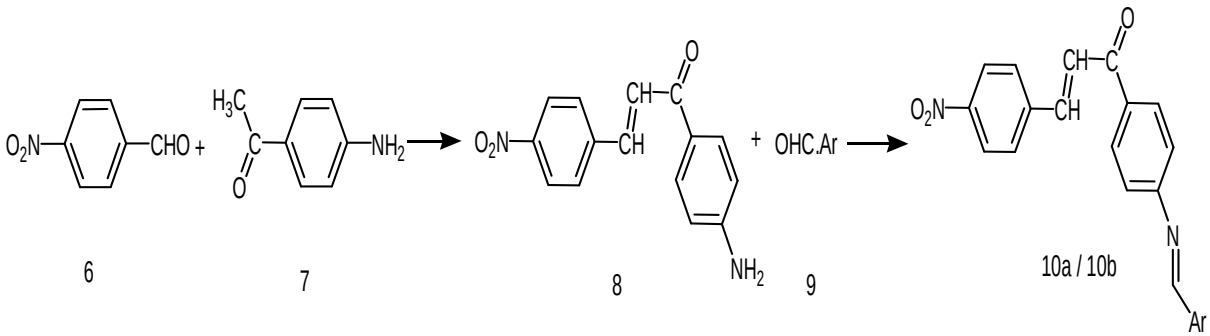
Compound	IUPAC Name of Compound	M.P. in ^{0}C	Yield%
5a	1-(5-bromothien-2-yl)-3-(2,4-dichlorophenyl) 1phenyl-4,5dihydro-1H-pyrazoline	96-98	82
5b	3-(4-bromophenyl)-1-(5-bromothien-2-yl)- 1phenyl-4,5dihydro-1H-pyrazoline	154-156	80
5c	1-(5-bromothien-2-yl)-3-(4-chlorophenyl)- 1phenyl-	138-141	76

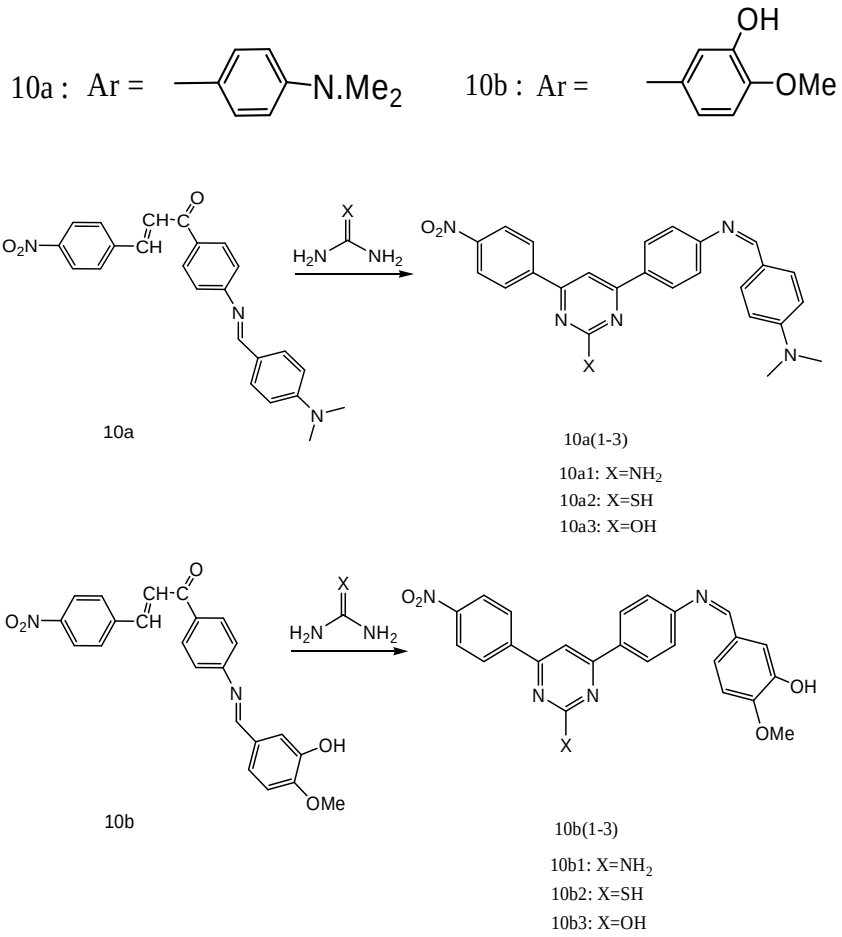
	4,5dihydro-1H-pyrazoline		
5d	1-(5-bromothien-2-yl)-3-[4-methoxy phenyl]-1phenyl-4,5dihydro-1H-pyrazoline	101-103	80
5e	1-(5-bromothien-2-yl)-3-(4-fluorophenyl)- 1phenyl-4,5dihydro-1H-pyrazoline	104-106	72
5f	1-(5-bromothien-2-yl)-3-(2,4-dimethoxy)-1phenyl-4,5dihydro-1H-pyrazoline	115-117	81
5g	3-(2-hydroxyphenyl)- 5-(4-nitrophenyl)- pyrazoline	220-224	78
5h	3-(2-hydroxyphenyl)- 5-(4-methoxyphenyl)- pyrazoline	132-134	82
5i	5-(4-dimethylaminophenyl)-3-(2-hydroxyphenyl)-pyrazoline	234-236	80
5j	3-(2-hydroxyphenyl) 5-(4-chlorophenyl)- pyrazoline	130-133	75
5k	3-(4-methoxyphenyl) 5- (4-nitrophenyl)- pyrazoline	150-152	78

We synthesized pyrimidines also by adopting similar domino synthetic method and achieved very good yields with in short times and with less wastage of chemicals. M.p.s, I.R., ^{1}H NMR spectral data and were found to be in concordance with literature.



Scheme 3





Scheme 4

Table 2:

Physical Data of Compounds

10a1	4-(4-(4-(dimethyl amino) benzylideneamino) phenyl)-6-(4-nitrophenyl)pyrimidine-2-amino	104-106	82
10a2	3-(4-(2-amino-6-(4-nitrophenyl) pyrimidine-4-yl) phenyl imino)isoindolin-1-one	132-134	80
10a3	5-((4-(2-amino-6-(4nitrophenyl) pyrimidine-4-yl) phenyl imino)methyl-2-methoxy phenol	148-151	76
10b1	4-(4-(4-(dimethyl amino) benzylideneamino)phenyl)-6-(4-nitrophenyl)pyrimidine-2-thiol	128-133	81
10b2	3-(4-(2-mercapto-6-(4-nitrophenyl) pyrimidine-4-yl) phenyl imino) isoindolin-1-one	164-167	73
10b3	5-((4-(2-mercapto-6-(4nitrophenyl) pyrimidine-4-yl)phenyl imino)methyl-2-methoxyphenol	181-184	78

CONCLUSION

Domino synthesis of pyrazolines and pyrimidines under alkyl substituted pyridines as catalyst with high yields within the range of 70% - 82% conclude that alkyl substituted pyridines are efficient catalysts due to their more basic strength and low evaporation due to their high boiling points and thereby one can work under low toxic atmosphere. On addition of Cu^{+}, active methyl group becomes more active and completion of reaction becomes more effective. In addition work up procedures was reduced facilitating more environment benign reaction procedures.

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