Laterite Catalyzed Ultrasound Assisted Greener Protocol for Synthesis of Pyranopyarazoles

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ABSTRACT *A simple, green protocol developed for synthesis of pyranopyrazoles by a multi component, one pot reaction of various aryl/heteroaryl aldehydes, ethyl acetoacetate, hydrazine hydrate, malononitrile and laterite catalyst in presence of ethanol by means of ultrasonication. Laterite used is heterogeneous catalyst and can be recycled.*

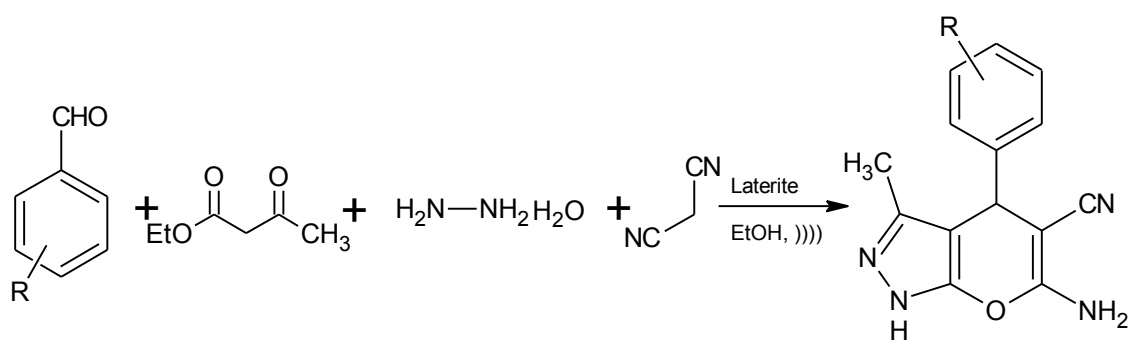
Keywords: *Green, heterogeneous, laterite, ultrasonication*

Introduction:

Pyranopyrazoles are important class of heterocyclic compounds shows significant biological activity [1]. They also have applications as biodegradable agrochemicals [2]. Pyranopyrazoles shows bioactivity that includes antimicrobial, anti-inflammatory, anticancer, insecticidal, molluscidal activities [3]. They also act as chk1kinase inhibitor [4].

By taking into consideration the importance of pyranopyrazoles various efforts have been made till today to synthesize it. Pyranopyrazoles generally synthesized by multicomponent reaction of aryl aldehydes, ethyl acetoacetate, hydrazine hydrate and malononitrile in presence of various catalysts such as triethyl amine [1,7], piperidine[2], 6-amino-β cyclodextrin[5], L-proline and alumina[6],imidazole[8],ammonium chloride[9], citric acid[10], Cetyl trimethyl ammonium bromide[11], silica in water[12] DBSA[13],, $Ba(OH)_2$ in water[14], [BMIM]OH[15], $[(CH_2)_4SO_3HMIM][HSO_4]$[16], lanthanum (III) nitrate[17]etc. Various pyranopyrazoles were also synthesized by performing the reaction using microwave [18], ultrasonication [17] and without solvent [19].

Herein we reported synthesis of various 6-amino-5-cyano-4-aryl-4H-pyrazolo [3, 4-b]pyrans by the reaction of aryl/ heteroaryl aldehyde, ethyl aceto acetate, malononitrile and hydrazine hydrate in presence of laterite catalyst in ethanol under ultrasonication [Scheme1].



Scheme4. Synthesis of Pyrano pyrazoles using laterite catalyst

Experimental:

Material and methods:

All chemicals used in synthesis were of AR grade. Melting points of all synthesized compounds were taken in an open capillary and were uncorrected. IR spectra were recorded on Perkin Elmer spectrophotometer with ATR technology. ^{1}HNMR and ^{13}CMR spectra were recorded on 500 MHz Bruker FT-NMR spectrometer using DMSO-d6 as a solvent. Syntheses were performed in ultrasonicator with 25 KHz frequency.

General procedure:

Synthesis of pyranopyrazoles were done using a mixture of aromatic aldehyde (2.0mmol), EAA (2.0mmol), malononitrile (2.0mmol), hydrazine hydrate (2.5mmol) and laterite (20 wt % w.r.t aldehyde) taken in round bottom flask and kept in sonicator for required time (Table2). The progress of reaction was monitored by TLC using ethyl acetate: hexane solvent system. On completion of reaction, the reaction mass

was filtered and concentrated. Purification of product and isolation of catalyst was done by recrystallisation using ethanol.

Result and Discussion:

In the present work, we wish to report a new synthetic protocol for preparation of pyranopyrazoles in the presence of laterite as a new high efficient and reusable catalyst.

Catalyst- Laterite: The natural laterite was collected, sieved and then subjected to thermal activation. Activated laterite used for catalyzing the reactions. The laterite is naturally available brown colored material may persist as stone or it may occur as soil/ clay [20]. Chemical composition of laterite is silica, alumina and iron. The diameter of laterite used is <60 μm. It acts as heterogeneous acid catalyst.

Optimization of reaction conditions:

To optimize reaction conditions we selected model reaction of 4-chlorobenzaldehyde (2mmol), malononitrile (2mmol), hydrazine hydrate (2.5mmol) and EAA (2mmol) in 5ml ethanol using ultrasound irradiation. Initially reaction was performed at RT in presence of different solvents without catalyst (Table1, entry1 to 4). The reaction in presence of ethanol yields better 41% in 90minutes at RT than the other solvents used. Then the same reaction was tried under sonication yields 46% in 30 minutes. Thereafter reaction was performed in presence of 10wt% catalyst yields 82% in 30 minutes. By increasing the catalyst amount to 20wt%, product yield boost up to 92% in 30 minutes. Further raise in catalyst amount had no impact on reaction time and yield of pyrano pyrazoles.

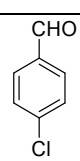
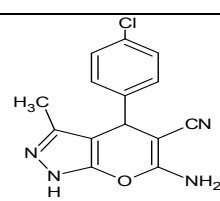
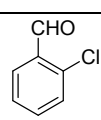
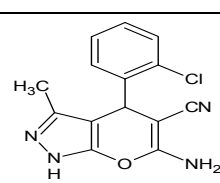
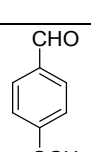
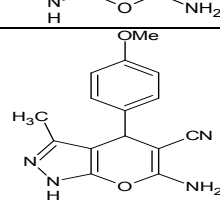
Table1. Optimization of reaction conditions

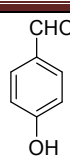
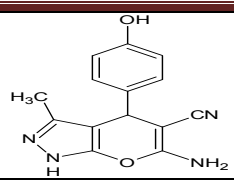
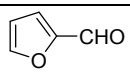
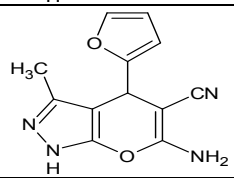
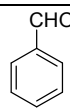
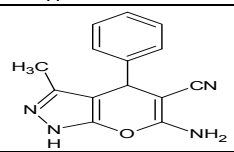
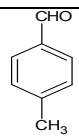
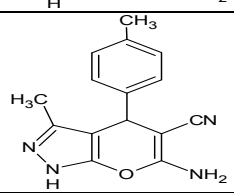
Entry	Catalyst	Solvent/Condition	Time(min)	*Yield (%)
1	**-**	Water/R.T	30	28
2	**-**	THF/RT	120	32
3	**-**	EtOH/RT	90	41
4	**-**	DMF/RT	120	Trace
5	**-**	EtOH/))))	30	46
6	**10 wt%**	EtOH/))))	30	82
7	**20 wt%**	EtOH/))))	30	92

***Isolated yields**

After optimization of reaction conditions the synthesis of pyranopyrazoles was done using aromatic and heteroaromatic aldehydes with electron donating and electron withdrawing groups. (Table2)

Table2. Synthesis of Pyranopyrazoles

Entry	Aldehyde	Product	Reaction time (minutes)	Yield (%)	M.P(^{0}C)	
					Found	Literature
5a			**30**	**92**	**228**	**226-228**
5b			**40**	**90**	**245**	**246-247**
5c			**40**	**86**	**215**	**216-218**

5d			**45**	**88**	**223**	**220-222**
5e			**35**	**87**	**230**	**-**
5f			**35**	**86**	**229**	**228-230**
5g			**30**	**89**	**244**	**245-246**

Reaction Condition: aryl/heteroaryl aldehyde(2.0mmol), EAA(2.0mmol), malononitrile(2.0mmol), hydrazine hydrate(2.5 mmol), laterite(20wt%) in ethanol(5ml)

Selected Spectral Data:

5a: 6-Amino-4-(4-chlorophenyl)-3-methyl-2-4-dihydropyrano [2, 3-c] pyrazole 5-carbonitrile

M.P 228^{0}C, FTIR (cm^{-1}): 3368, 2907, 2528, 2257, 1595, 1524 ^{1}HNMR (500MHz, DMSO-d6, δppm): 1.87 (s, 3H, CH_3), 4.61 (s, 1H, CH), 6.99(s, 2H, NH_2), 7.36 (d, 2H, ArH), 8.09 (d, 2H, ArH), 11.90 (s, 1H, NH)

5C: 6-Amino-4-(4-methoxyphenyl)-3-methyl-2-4-dihydropyrano [2, 3-c] pyrazole 5-carbonitrile

M.P 215^{0}C, FTIR (cm^{-1}): 3389, 2911, 2561, 2262, 1608, 1526 ^{1}HNMR (500MHz, DMSO-d6, δppm): 1.89 (s, 3H, CH_3), 3.9 (s, 3H, CH_3), 4.62 (s, 1H, CH), 6.94(s, 2H, NH_2), 7.40 (d, 2H, ArH), 8.09 (d, 2H, ArH), 11.90 (s, 1H, NH)

5e: 6-Amino-4-(2-furyl)-3-methyl-2-4-dihydropyrano [2, 3-c] pyrazole 5-carbonitrile

M.P 230^{0}C, FTIR (cm^{-1}): 3350, 3170, 2981, 2186, 1740, 1647, 1599, 1492, 1405 ^{1}HNMR (500MHz, DMSO-d6, δppm): 1.98 (s, 3H, CH_3), 4.77 (s, 1H, CH), 6.17 (d, 1H, CH), 6.37(s, 1H, CH), 6.70 (s, 2H, NH2), 7.52 (s, 1H, CH), 12.18 (s, 1H, NH)

5f: 6-Amino-4-phenyl)-3-methyl-2-4-dihydropyrano [2, 3-c] pyrazole 5-carbonitrile

M.P 240^{0}C, FTIR (cm^{-1}): 3368, 2981, 2931, 2531, 2260, 1600, 1520, 1495 ^{1}HNMR (500MHz, DMSO-d6, δppm): 1.78 (s, 3H, CH_3), 4.59 (s, 1H, CH), 6.89(s, 2H, NH_2), 7.15- 7.34 (m, 5H, ArH), 12.11 (s, 1H, NH)

Conclusion:

We have developed greener synthetic protocol for pyranopyrazole synthesis under ultrasound irradiation technique using ecofriendly laterite catalyst with good atom economy.

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