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Highly Efficient Cascade synthesis of Benzopyran

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Introduction:

Benzopyran is a polycyclic organic compound that results from the fusion of a benzene ring to a heterocyclic pyran ring.benzopyrans or chromenes, are key structural units of a variety of biologically important compounds, many of which are pharmaceutically significant unit of heterocyclic compounds.

Multicomponent reactions (MCRs) are highly efficient approaches to access complex structures in a simple synthetic operation from three or more reactants. High atom economy, great efficiency and procedural convenience in the construction of heterocycles are the advantages of MCRs [1-2].

Chemically, chromones (4H-chromen-4-ones) are heterocyclic compounds with the benzopyrone framework. Molecules containing the chromone or benzopyranone ring have a wide range of biological activities [3-6] such as antioxidant [7], anti-HIV [8,9], neuroprotective [10], antiepileptic [11,12], antimicrobial [13], antidiabetic [14], antihypertensive [15], and anticancer agents [16].

These compounds can be prepared by multicomponent condensation of dimedone with aldehyde and malononitrile in the presence of various catalysts including tetra-methyl ammonium hydroxide [17], iodine [18], NaBr [19], solid acids [20] ion-exchange resins [21] and metal complexes [22].Development of a mild, neutral, and reusable catalyst for one-pot synthesis of benzopyrans still remains an attractive goal for researchers [23]. Some natural product that contains benzopyran scaffold were finds the application in drug and medicinal chemistry.

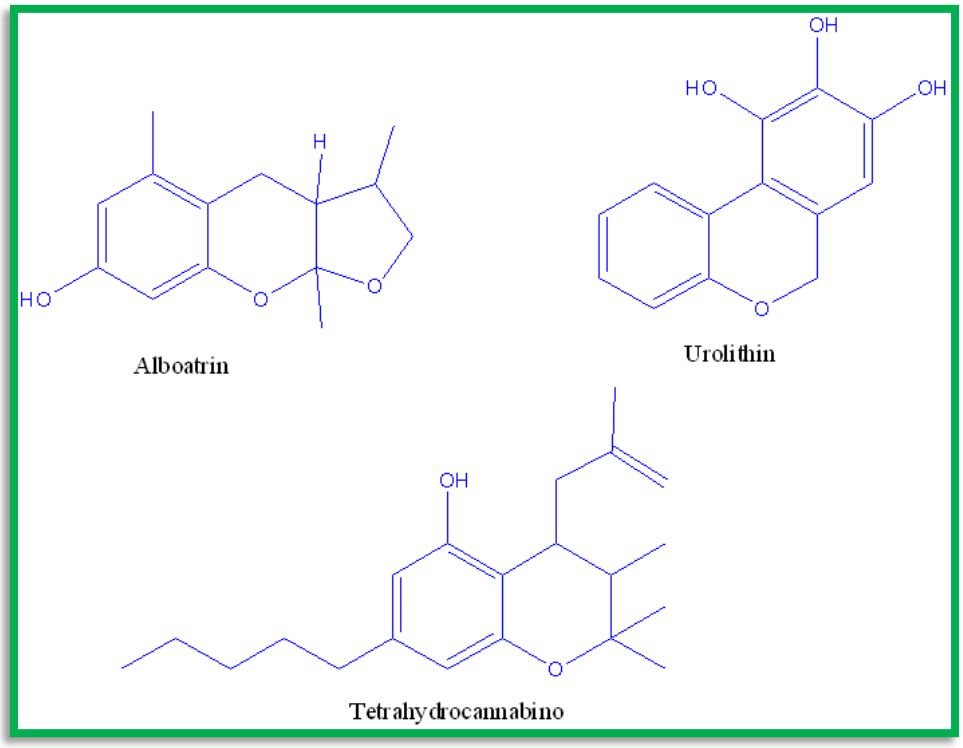


Fig1: Natural Product containing Benzopyran moiety.

Experimental:

All the chemicals were purchased from merck and are used without Melting points were determined in open capillary tubes and were uncorrected. Purity of the compounds was checked by TLC on silica gel plates. Iodine chamber was used as a visualizing agent. IR-spectra were recorded using KBr pellets on a SHEMADZU spectro-photometer. NMR spectra on BRUKER 400 MHz Spectrophotometer using DMSO as solvent and TMS as internal standard. ESI-MS was also done for structural evaluation of the synthesizedcompounds.

General procedure for the synthesis of benzopyrans:

A mixture of aldehyde (1 mmol), malononitrile (1.2 mmol) dimedone (1 mmol) and SiO_2-$ZnCl_2$ (12 mol%) was refluxed in ethanol as a solvent for several hours. completion of the reaction was confirmed by TLC analysis (ethyl acetate/n-hexane, 1:3). The catalyst was separated by simple filtration, washed with acetone and dried under reduced pressure. Pure benzopyran product was obtained by concentration of the mixture, followed by crystallization

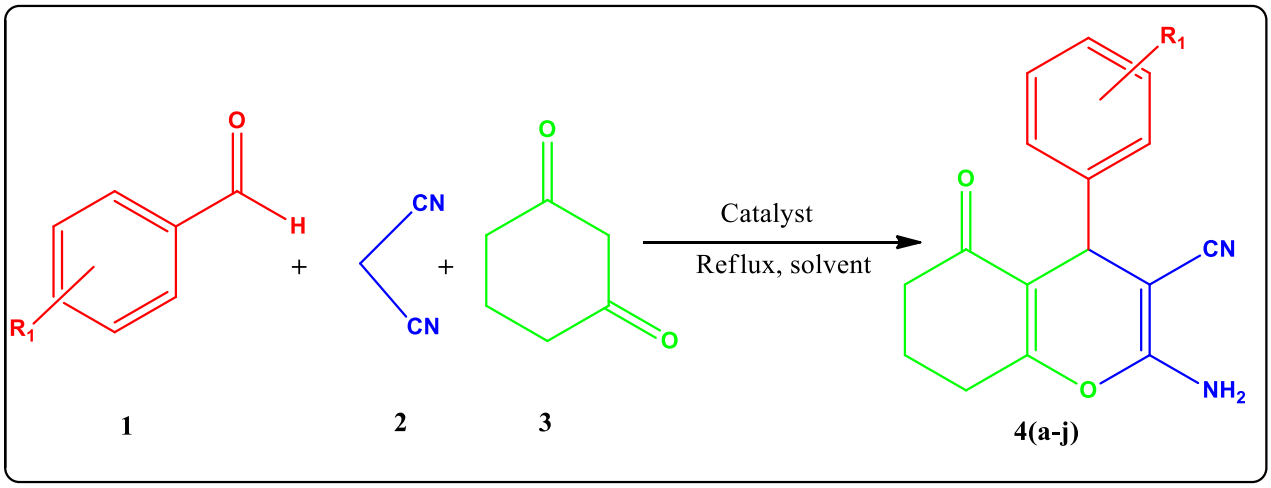
of the residue from absolute ethanol.

Result and Discussion:

Synthesis of benzopran from substituted benzaldehyde, malononitrile and dimedone catalyzed by SiO_2-$ZnCl_2$ in ethanol as a solvent under reflux condition was a fascinating approach in organic synthesis. Before concluding the reaction condition synthesis of benzopyran was passed from several trials.

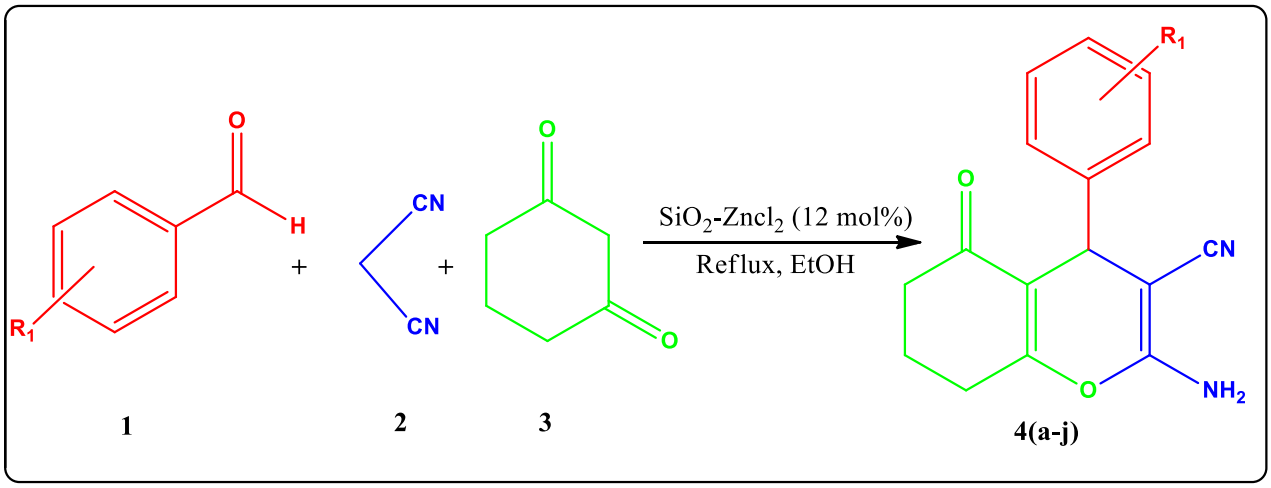
In the very first attempt the synthesis was carried without catalyst at room temperature in solvent free reaction condition made no any impact on reaction condition so didn't generate any yield of the product (Table 1, entry 1). Moving forward for the synthesis of benzopyran from aromatic aldehyde, malononitrile and dimedone under reflux condition in solvent less condition with 5 wt%, 7 wt% and 10 wt% of SiO_2-$ZnCl_2$ as a catalyst in separate attempt of synthesis gives 18%, 28% and 43% of isolated product yield respectively (Table 1, entries 2,3,4). The generated yield was unsatisfactory so these reaction conditions were ruled out. In next trial with similar reaction condition 12 wt% and 15 wt% of catalyst was used to gives 54 and 55% of corresponding bezopyran yield (Table 1, entries 5, 6). So from this result it was seen that 12 mol% provided greater yield while increasing the amount of catalyst to 15% was not made much more impact on respective yield of product. From all above results it was concluded that solvent free reaction unable to contribute towards yield. So in order to study the effect of solvent ethanol was used as solvent for the synthesis of benzopyran was produced surprising result and afford 82% of product (Table1, entry 7). In order to compare solvent effect with several other readily available solvent was not affect much more to reaction condition and provides frustrating results (Table 1, entries 8, 9, 10).

Table 1: Optimization of reaction condition for the synthesis of Benzopyran.



Entry	Catalyst amount (wt%)	Temperature (^{0}C)	Solvent	Yield^x
1	-	-	-	0
2	5	Reflux	-	18
3	7	Reflux	-	28
4	10	Reflux	-	43
5	12	Reflux	-	54
6	15	Reflux	-	55
7	12	Reflux	EtOH	82
8	12	Reflux	H_2O	70
9	12	Reflux	C_6H_6	65
10	12	Reflux	CH_2Cl_2	58
Reaction is carried with bezaldehyde (1 mmol), malononitrile (1.2 mmol), dimedone (1mmol) under reflux condition using ethanol as a solvent. ^{x} indicates isolated yield of the product.				

Table 2: Amount of yield of bezopyran derivative under optimized reaction conditions.



Entry	R_1	Product	Time (hr)	Yield (%)[x]
1	C_6H_5	4a	5	82
2	2-Cl	4b	3.5	92
3	4-Cl	4c	4.5	86
4	2,4-Cl	4d	3.5	88
5	4-Br	4e	4.5	86
6	2-NO_2	4f	4.5	89
7	4-NO_2	4g	4	90
8	4-CH_3	4g	6	78
9	2-OCH_3	4h	5.5	74
10	4-OCH_3	4i	6	72

Reaction is carried with bezaldehyde (1mmol), malononitrile (1.2 mmol), dimedone (1mmol) under reflux condition using ethanol as a solvent., [x] indicates yield of isolated solvent

Synthesis of benzopyran under standard reaction condition using ethanol as solvent under reflux with SiO_2-$ZnCl_2$ was confirmed. Bezaldehyde, malononitrile and dimedone were allowed to react in RBF under reflux with ethanol as a solvent using SiO_2-$ZnCl_2$ as a catalyst generates 82% of yield of product (Table 2, entry 1). As seen from the table 2 chloro benzaldehyde offers highest amount of yield of 92 % (Table 2, entry 2) where as the 4-

methoxy benzaldehyde used as a starting material produces minimum of 72% of the product yield (Table 2, entry 10). So from all these summarized results of Table 2 conclude that the aromatic aldehyde with electron withdrawing group gives maximum yield whereas the electron releasing group affords less amount of yield.

Conclusion:

Synthesis of benzopyran by substituted aromatic aldehyde, malononitrile and dimedone catalyzed by SiO_2-$ZnCl_2$ is an efficient pathway for this particular synthesis which is preceded under reflux condition and ethanol as a solvent. e. The catalysts show environmental friendly character, which can be easily prepared, stored, recycled without obvious loss of activity.This protocol proceeds smoothly and provides the product yield from 72% to 92%. The catalyst was easily recovered at the end of the reaction. Therefore, a simple work-up procedure, mild reaction conditions and good to excellent yields are some major benefits of this protocol.

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