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# Synthesis of 2-Amino-4*H*-chromene Derivatives under Solvent-Free Condition Using MOF-5

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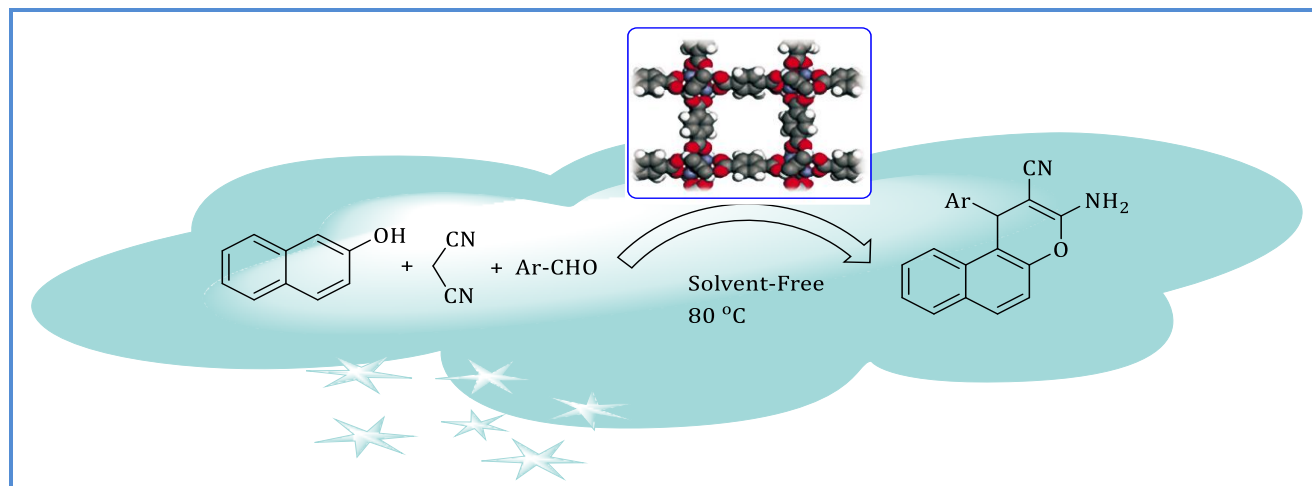
### ABSTRACT

MOF-5 has been employed as a powerful catalyst for the preparation of 2-amino-4*H*-chromene. A wide variety of aromatic aldehydes was condensed with malononitrile and 2-naphthol under mild and solvent-free conditions in the presence of the trace amount of catalyst. A variety of 2-amino-4*H*-chromene can be obtained in good to excellent yield up to 95% in relatively short time reaction and easy workup.

### Graphical Abstract

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## Introduction

Chromene analogues derivatives are an important class of heterocyclic compounds. 2-Amino-4H-chromene are an important class of heterocyclic compounds having important biological activities such as antiviral [1], antimicrobial [2], antiproliferative [3], mutagenic [4], antitumor [5], pheromonal [6], and central nervous system activity [7]. Several protocols have been reported for the synthesis of 2-amino-4H-chromenes and their derivatives using malononitrile, 2-naphthol and aldehyde. Various catalysts such as tetramethylguanidine [8], Fe<sub>3</sub>O<sub>4</sub> nanoparticles [9], TiCl<sub>4</sub> [10], InCl<sub>3</sub> [11], Mg/Al-HT [12], potassium phthalimide-*N*-oxyl [13], bifunctional nanostructured molten salt [4,4-bipyridine]-1,1-dium tricyanomethanide [14], methane sulfonic acid [15], and etc., have been used for these reactions. Most of these reported protocols require a long reaction time, high temperature, and use of organic solvents, and have problems associated with the reusability of catalysts. In order to make the reaction simple and green, it is important to use environmentally friendly medium for the organic reactions, and combination of heterogeneous catalysts and water is the most demanding combination for catalytic reactions.

In recent years, much attention has been focused on reaction *via* catalyst and nano catalyst [16-29]. Metal organic frameworks are important crystalline material in the field of heterogeneous catalysts or catalyst supports for a variety of organic transformations [30]. Metal organic frameworks (MOFs) open the possibility to design and synthesize variety of new porous materials. Some of the features of MOFs for their use as heterogeneous catalysts are high internal surface area, microporosity, ease of the separation of the product, acid sites, base sites, stability, diffusion, and high metal content [31]. MOFs catalyst can be used in many reactions such as oxidation of organosulfide, cyclopropanation of alkene, *N*-methylation of aromatic primary amines, Sonogashira reaction, Suzuki cross-coupling, Friedel-Crafts alkylation and acylation, three-component coupling reaction

of aldehyde, alkyne, and amine, the Biginelli reaction, Knoevenagel condensation, cycloaddition of CO<sub>2</sub> with epoxides, alkene epoxidation, oxidation of homocoupling of phenylboronic acid, trans esterification reaction, hydrolysis of ammonia borane, aza Michael condensation and 1,3-dipolar cycloaddition reactions [31].

Herein, in an extension of our previous studies on the catalyst reactions *via* MOF [32-35], we wish to present a versatile and new method for the synthesis of 2-amino-4*H*-chromene.

## Experimental

### General procedure for the synthesis of MOF-5

Li et al. [36] have synthesized MOF-5 by three approaches: direct mixing of the reactants with Et<sub>3</sub>N, slow addition of Et<sub>3</sub>N and solvothermal synthesis. we synthesized MOF-5 nanoporous with solvothermal method. Zn(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O and H<sub>2</sub>BDC were dissolved in DMF. Then, the solution was transferred into a teflon-lined autoclave, which was then heated at 373 °K for 24 h. The reaction products were cooled to room temperature, and the solids were collected by centrifugation, washed with ethanol, and dried at room temperature.

### General procedure for the preparation of 2-amino-4*H*-chromene

In the 50 mL flask mixture of malononitrile (1.0 mmol), aldehyde (1 mmol), and 2-naphthol (1.0 mmol) in the presence of a catalytic added and the mixture was stirred at 80 °C. After completion of the reaction as indicated by TLC, (*n*-hexane/ethyl acetate, 2:1), ethyl acetate (10 mL) was added and the reaction mixture was stirred and heated to reflux for 10 min. The resulting mixture was then filtered to separate catalyst from the other materials. The resulting mixture was then washed with water (10 mL) and decanted. Then organic layer was dried, filtered, the solvent was removed, and the crude product was purified by recrystallization from ethanol (95%) to give the pure product with high to excellent yields.

## Results and Discussion

In a pilot experiment and to achieve suitable conditions for the synthesis of 2-amino-4*H*-chromene, various reaction conditions have been investigated in the reaction of malononitrile, 4-chlorobenzaldehyde and 2-naphthol in the presence of a catalytic amount of MOF-5 as a model reaction. After that, in order to explore the scope and limitations of the reaction, various aryl aldehydes were used.

Initially, the catalytic applicability of the resulting MOF-5 was investigated for the preparation of 2-amino-4*H*-chromene derivatives. The reaction was performed with different amounts of MOF-5 under solvent-free conditions (Table 1). The best results were obtained by using 10 mg

nanostructured under solvent-free conditions at 80 °C (entry 3). No improvement in yield was observed on increasing either the amount of catalyst. The reaction did not proceed in the absence of nanocatalyst.

**Table 1.** optimization of amount of catalyst in synthesis of 2-amino-4H-chromene

Entry	Amount of catalyst (mg)	Time (min)	Yield (%) <sup>a</sup>
1	-	120	Trace
2	4	50	61
3	6	40	78
4	8	25	85
5	10	20	95
6	12	20	95

<sup>a</sup>Yield of isolated products

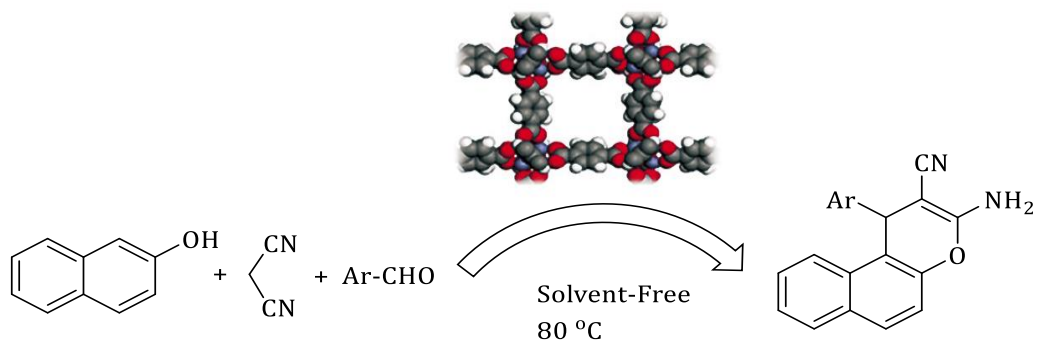
We examined the effect of various solvents on a model reaction (Table 2). We did this experiment at ethanol, H<sub>2</sub>O and CH<sub>3</sub>CN but the reaction did not take place even after prolonged reaction time (Table 1, entries 1-3). As could be seen in Table 2, in solvent-free condition the yield of the reaction was found to be very good (95 %).

**Table 2.** optimization of solvent in synthesis of 2-amino-4H-chromene

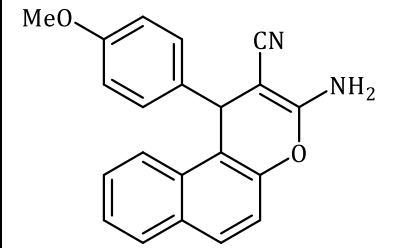
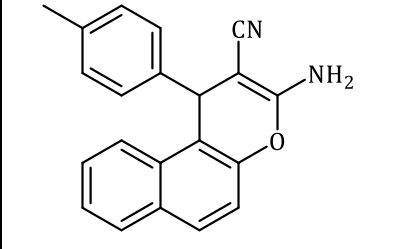
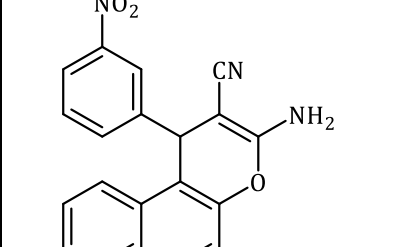
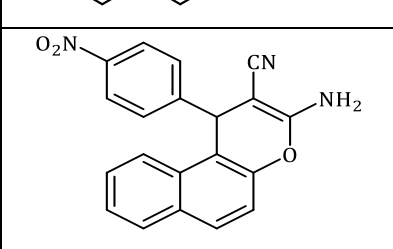
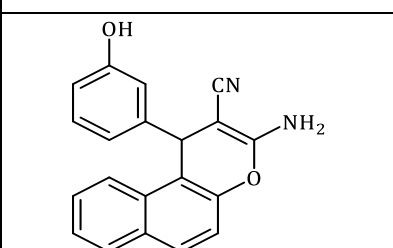
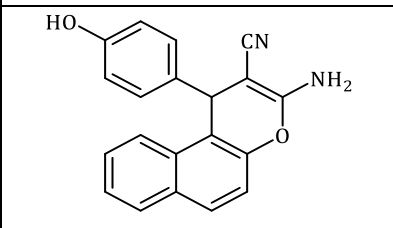
Entry	Solvent	Time (min)	Yield (%) <sup>a</sup>
1	-	20	95
2	EtOH	60	79
3	H <sub>2</sub> O	60	67
4	CH <sub>3</sub> CN	60	Trace
5	CH <sub>2</sub> Cl <sub>2</sub>	55	Trace
6	CHCl <sub>3</sub>	50	84
7	<i>n</i> -hexane	70	trace

<sup>a</sup>Yield of isolated products

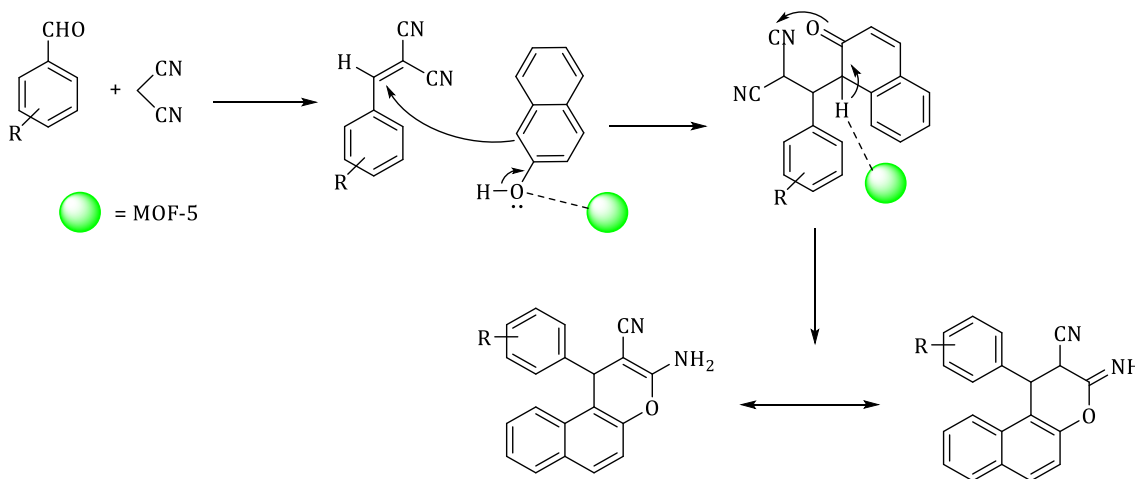
To demonstrate the generality of this methodology and for the synthesis of 2-amino-4H-chromenes, a range of aromatic aldehydes was condensed with malonitrile and 2-naphthol under solvent-free conditions (Table 3). For aromatic aldehydes bearing electron withdrawing groups, the reaction reached completion relatively rapidly, but for benzaldehyde and aromatic aldehydes, with electron-releasing groups, it was found that the reaction did not proceed at 80 °C.

**Table 3.** synthesis of 2-amino-4*H*-chromene using MOF-5 as catalyst

Entry	Aldehyde	Product	Time (min)	Yield (%)
1	benzaldehyde		40	80
2	2-Cl		20	94
3	4-Cl		20	95
4	4-Br		20	93

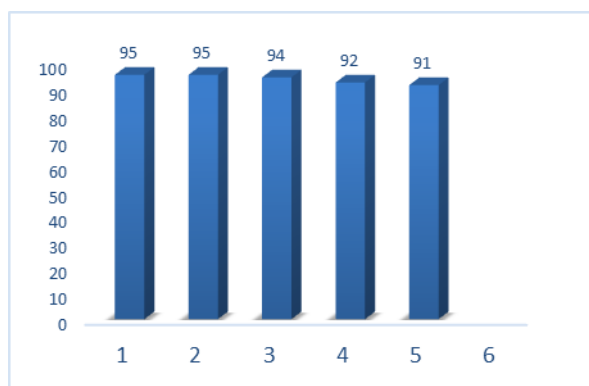
5	4-OMe	 <p>Chemical structure of 2-amino-4-(4-methoxyphenyl)-4H-chromene. The structure features a chromene core with a cyano group (CN) and an amino group (NH<sub>2</sub>) at the 2-position, and a 4-methoxyphenyl group at the 4-position.</p>	45	80
6	4-Me	 <p>Chemical structure of 2-amino-4-(4-methylphenyl)-4H-chromene. The structure features a chromene core with a cyano group (CN) and an amino group (NH<sub>2</sub>) at the 2-position, and a 4-methylphenyl group at the 4-position.</p>	42	78
7	3-NO <sub>2</sub>	 <p>Chemical structure of 2-amino-4-(3-nitrophenyl)-4H-chromene. The structure features a chromene core with a cyano group (CN) and an amino group (NH<sub>2</sub>) at the 2-position, and a 3-nitrophenyl group at the 4-position.</p>	25	90
8	4-NO <sub>2</sub>	 <p>Chemical structure of 2-amino-4-(4-nitrophenyl)-4H-chromene. The structure features a chromene core with a cyano group (CN) and an amino group (NH<sub>2</sub>) at the 2-position, and a 4-nitrophenyl group at the 4-position.</p>	24	91
9	3-OH	 <p>Chemical structure of 2-amino-4-(3-hydroxyphenyl)-4H-chromene. The structure features a chromene core with a cyano group (CN) and an amino group (NH<sub>2</sub>) at the 2-position, and a 3-hydroxyphenyl group at the 4-position.</p>	45	78
10	4-OH	 <p>Chemical structure of 2-amino-4-(4-hydroxyphenyl)-4H-chromene. The structure features a chromene core with a cyano group (CN) and an amino group (NH<sub>2</sub>) at the 2-position, and a 4-hydroxyphenyl group at the 4-position.</p>	45	77

The proposed mechanism for the synthesis of 2-amino-4*H*-chromene in the presence of MOF-5 is shown in Scheme 1. Firstly, MOF-5 binds with the oxygen of the carbonyl group making the alpha hydrogen very acidic, thereby involving the Knoevenagel condensation reaction between aromatic aldehyde and malononitrile. In the second step, Knoevenagel product was reacted in a Michael addition with 2-naphthol to produce desired product after rearomatization and intramolecular cyclization with the help of MOF-5 as a catalyst.



**Scheme 1.** Proposed mechanism pathway for the synthesis of 2-amino-4*H*-chromene derivatives using MOF-5 as a catalyst

The reusability of the MOF-5 as heterogeneous catalyst was tested as shown in (Figure 1) using the model reaction under the optimized reaction conditions. After completion of the reaction, the catalyst was easily removed from the reaction medium using centrifugation. Then, it was washed several times with ethanol, water and dried under vacuum and reused again. MOF-5 can be reused more than five times without any significant decrease about catalytic function. It looks like highly stable and reusable catalyst.



**Figure 1.** Reusability of the MOF-5 catalyst

A comparison of the catalytic activities of the different heterogeneous catalysts which was reported in the literature with that of prepared MOF-5 to synthesize the compound of the model reaction is indicated in Table 4. The MOF-5 catalyst method offers several advantageous over most of the literature methods such as, a short reaction time, simple work-up procedure, high reusability of catalyst, high yields [37-43].

**Table 4.** Comparison of MOF-5 with other catalysts

Entry	Catalyst (mg)	Amount; conditions	Yield (%)	Time	Ref.
1	Mg/Al-HT	15 wt%; H <sub>2</sub> O, 60°C	95	2 h	[37]
2	MNPs-NH <sub>2</sub>	0.04 g; EtOH:H <sub>2</sub> O (5:2), 30°C	95	10 min	[38]
3	Tungstic acid-SBA-15	30 mg; H <sub>2</sub> O, 100 °C	86	12 h	[39]
4	Pd@GO	10 mg; EtOH, 80 °C	92	15 min	[40]
5	Fe(HSO <sub>4</sub> ) <sub>3</sub>	0.1 mmol; refluxed in MeCN	83	4 h	[41]
6	TPOP-2	40 mg; solvent-free, 80 °C	87	5 h	[42]
8	MOF-5	10 mg	95	20 min	This work

## Conclusion

In summary, 2-amino-4H-chromenes has been synthesized through addition–cyclization process catalysed by MOF-5 under sonication at 80 °C. The corresponding products can be obtained in moderate to good yields. MOF-5 has been employed as a highly efficient and powerful nanocatalyst for the preparation of 2-amino-4H-chromenes.

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