

Original Research Article

Cu(II)-Schiff base/SBA-15 as an efficient catalyst for synthesis of benzopyrano[3,2-c]chromene-6,8-dione derivatives

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ARTICLE INFORMATION

Received: 29 April 2018

Received in revised: 16 May 2018

Accepted: 20 May 2018

Available online: 8 July 2018

DOI: [10.22034/ajgc.2018.65504](https://doi.org/10.22034/ajgc.2018.65504)

KEYWORDS

Benzopyranchromens

4-Hydroxycoumarin

Cu(II)-Schiff base/SBA-15

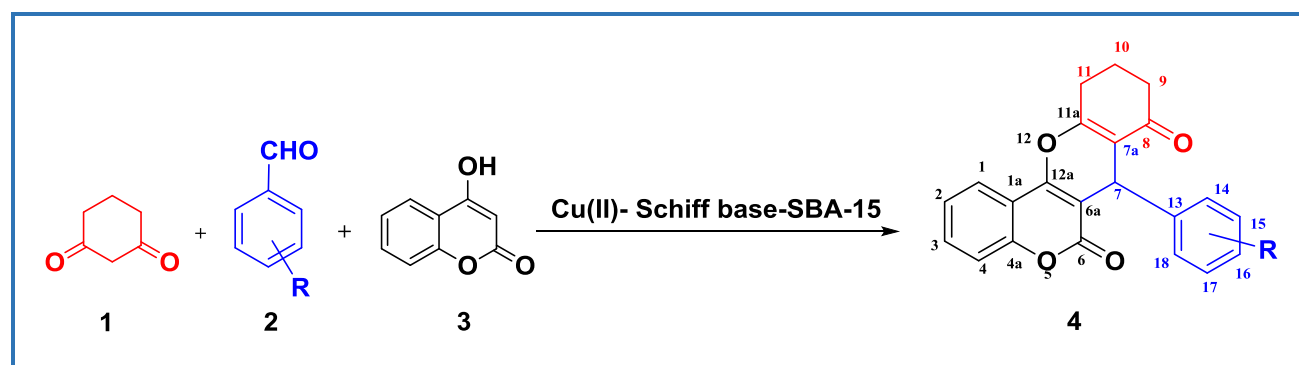
Heterogeneous catalyst

One-pot multi-component reaction

ABSTRACT

In this study, we synthesized the benzopyrano[3,2-c]chromene-6,8-dione derivatives by one-pot multi-component reaction of 1,3-cyclohexanedione, arylaldehydes, and 4-hydroxycoumarin under the solventless condition using Cu(II)-Schiff base/SBA-15 as a reusable heterogeneous catalyst in high yields. These kinds of catalysts are built from mesoporous silica SBA-15 which is covalently anchored with Cu(II)-Schiff base complex. The high yields, simple work-up procedure, reusability of the catalyst, and environmentally friendly conditions are the main advantages of this method compared to the other techniques. The products were identified by using ¹H NMR, mass and IR spectra, which were compared to those reported previously.

Graphical Abstract



Introduction

Coumarin derivatives are found widely in nature and are reported to have various biological activities [1, 2], such as anti-HIV, antibiotic, antifungal, antibacterial, antiviral, and especially anticoagulant [3–7]. In addition, pyran derivatives are well known for their antihistaminic activity and occur in various natural products [8–12]. Various other medical activities have been exhibited by pyran derivatives, including antimicrobial, antitumor, antifungal, antidepressant, and platelet antiaggregating activities [13–16]. Consequently, based on the biological potential of the coumarin and pyran derivatives, development of their synthetic methods will be so beneficial.

We have previously described, synthesis of novel 7-aryl benzopyrano[3,2-c]chromene-6,8-diones derivatives by one-pot three components cyclocondensation of 4-hydroxycoumarin, 1,3-cyclohexadione and aryl aldehyde after 5 hours refluxing in acetic acid in yields of 60-78% (Table 3) [17]. The structures of the compounds were deduced from their IR, Mass, ^1H NMR and C, H, N analysis and their cytotoxic activities were assessed on different human cancer cell lines and the results showed weak-to-moderate antitumoral activities [17]. Recently, we have also described an efficient synthesis of 7-aryl benzopyrano[3,2-c]chromene-6,8-diones derivatives using heteropolyacids catalysts, and among of them, $\text{H}_{14}[\text{NaP}_5\text{W}_{29}\text{MoO}_{110}]$ have exhibited high activity [18]. Despite, high yields and rate of the method, high catalyst loadings (low TOM), use solvent and expensive are major drawbacks of this method. Therefore, research on more effective methods for the synthesis of these compounds is still valuable. In recent years, solid-supported catalysts have gained increased consideration for organic transformations due to their ease of separation from the reaction mixture and the possibility of reuse as well as economical and environmental reasons [19–27].

Among the solid-supported catalysts, silica-based catalysts have attracted a great deal of attention due to their interesting properties including thermal stability and commercial availability for liquid phase reactions. It is believed that mesoporous silica materials such as MCM-41, MCM-48 and SBA-15 with tunable pore sizes are able to facilitate reactions by localizing reactants in their pores and providing a high local concentration of active centers (Typically acidic or basic) [28, 29]. In particular, SBA-15 is better than others because of the properties such as larger pore size and thicker silica walls which result in high hydrothermal stability [30, 31].

Considering the advantages of such material and the transition metal schiff base complexes, many researchers have paid attentions to the incorporation of organometallic complex on mesoporous silica materials [32–34]. Such novel catalyst extremely gathered the features of these two species, which not only maintained the catalytic activity of complexes, but also improved the limitation of both compounds. Thereby, the mesoporous silica materials functionalized by

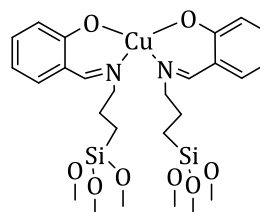
transition metal schiff base complexes showed excellent catalytic ability, and the catalyst could be more widely used in the catalytic reaction process.

The supported Cu(II) catalyst is built up from the direct grafting of mesoporous silica by a silica precursor-schiff base Cu(II) complex according to the known literature procedure (Figure 1) and has also been characterized by DRIFT-IR, atomic absorption spectroscopy (AA), XRD, and TEM [35].

Our experiences on the use of Cu(II)-Schiff base/SBA-15 for synthesis of heterocyclic systems, such as decahydroacridine-1,8-diones, chromeno [4',3'-b]pyrano[6,5-b]quinoline and chromeno[4,3-b] quinoline have shown the significant results [36–38].

Therefore, based on the last results and inherent advantages of the catalyst mentioned, including high activity, stability, low catalyst loading (High TON) in the reactions, we were persuaded to develop the use of Cu(II)-Schiff base/SBA-15 for synthesis of benzopyrano[3,2-c]chromene-6,8-diones derivatives.

Figure 1. Structure of Cu(II)-Schiff base/SBA-15



Experimental

Materials and methods

¹H NMR spectra were taken in CDCl₃ on a Bruker 500 MHz spectrometer (Bruker, Rheinstetten, Germany). The IR spectra were obtained in KBr disks on a Nicolet FT-IR magna 550 instrument (Nicolet, Madison, WI, USA). Electron-impact (70 eV) mass spectra were obtained with a Agilent Technology (HP) spectrometer. The purity of products and the progress of the reactions were confirmed by TLC on silica-gel polygram SILG/UV254 plates.

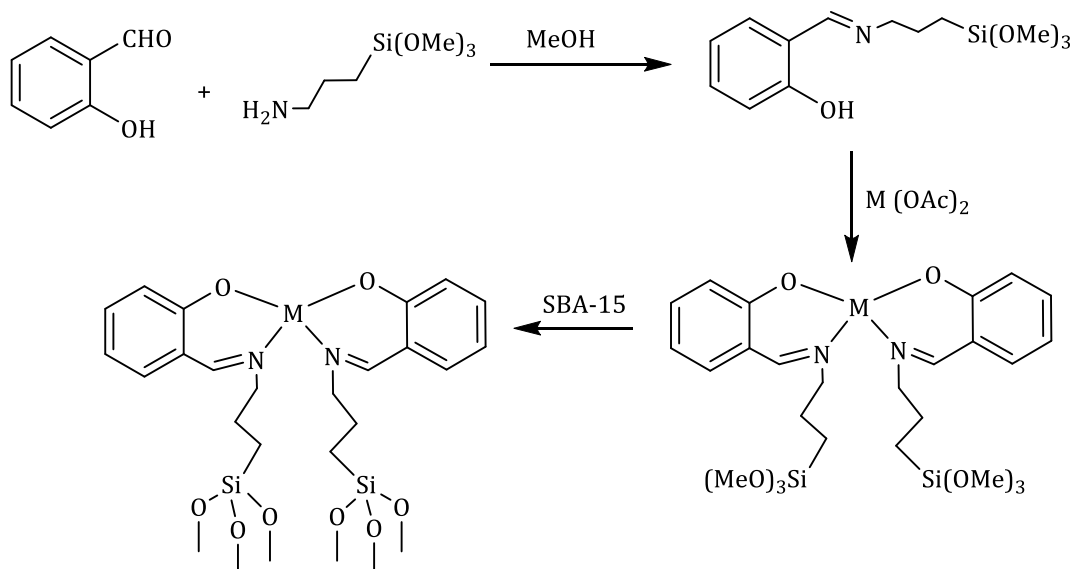
Preparation of the catalyst Cu(II)-Schiff base/SBA-15

The SBA-15 mesoporous material was prepared according to the following procedure as reported by Zhao et al. [31]. The Cu(II)-Schiff base complex was prepared using the pertinent literature procedure with the following modification [35]. Primarily, the thus obtained SBA-15 was ion exchanged with citric acid for 24 h, and then the solid was filtered, washed and dried at 313 K to prepare for using lately. Meanwhile, 2.21 g APTES (10 mmol) was dissolved in 10 mL absolute alcohol, followed by the addition of 1.22 g salicylaldehyde (10 mmol) to get a clear yellow solution

due to imine formation, then the mixture was refluxed for 4 h with stirring. Afterward, the pre-treated SBA-15 powder (500 mg) was added to the solution and another 20 mL absolute alcohol was added as well, then the mixture was refluxed for 12 h to gain the yellow solid, which was filtered, washed with ethanol and diethyl ether for several times till the filtrate became colorless and dried in the oven. Then 0.998 g $\text{Cu}(\text{CH}_3\text{COO})_2$ (5 mmol) was dissolved in 30 mL ethanol to get a dark green solution. Subsequently, the pre-functionalized SBA-15 was added into this solution and the mixture was stirred for 8 h. Eventually, the result product was filtered, washed with water, ethanol for several times when the filtrate was colorless and dried in the vacuum at 333 K overnight. The structure of the functional molecule and the SBA-15 modification procedure was shown in [Scheme 1](#).

General procedure for the synthesis of 7-aryl-9,10-dihydro-7H,11H-benzopyrano[3,2-c]chromene-6,8-dione derivatives 4a-o

1,3-Cyclohexadione **1** (0.03 g, 0.26 mmol), arylaldehydes **2** (1 mmol), 4-hydroxycoumarin **3** (0.042 g, 0.26 mmol) and the catalyst (0.005 g, 0.007 mmol) were thoroughly mixed and placed in the autoclave at 120 °C for the appropriate reaction time ([Table 2](#)) (Monitoring by TLC). After cooling, the mixture was washed with acetone (50 mL) and the catalyst was removed through filtration, rinsed twice with MeOH, and dried at 80 °C for 60 min for subsequent reuse. Analytically, the pure products **4a-o** were obtained by evaporation of the solvent and recrystallization in EtOH. The yields and melting points are shown in [Table 2](#). The products were identified by comparing with the original samples [17].



Scheme 1. Synthesis of the catalyst Cu(II)-Schiff base/SBA-15

9,10-dihydro-7-(4-nitrophenyl)-7H,11H-benzopyrano[3,2-c]chromene-6,8-dione 4c

White powder, 0.09 g (97%), mp 198 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3068 (C-H aromatic), 2914 (C-H aliphatic), 1721 (C=O), 1526, 1362 (NO₂). ¹H NMR (500 MHz, CDCl₃): δ 2.08-2.21 (m, 2H, H₁₀), 2.44-2.47 (m, 2H, H₁₁), 2.79-2.84 (m, 1H, H₉), 2.89-2.90 (m, 1H, H₉), 5.08 (s, 1H, H₇), 7.36 (dd, 1H, $J = 8.0, 1.0$ Hz, H₄), 7.40 (td, 1H, $J = 8.0, 1.0$ Hz, H₂), 7.57 (d, 2H, $J = 8.5$ Hz, H₁₄, H₁₈), 7.62 (td, 1H, $J = 8.0, 1.5$ Hz, H₃), 7.91 (dd, 1H, $J = 8.0, 1.5$ Hz, H₁), 8.13 (d, 2H, $J = 8.5$ Hz, H₁₅, H₁₇). EI-MS, m/z (%): 389 (M⁺, 11), 372 (47), 342 (22), 267 (100), 149 (17), 122 (13), 83 (23), 55 (40). Anal. Calcd for C₂₂H₁₅NO₆: C, 67.86; H, 3.88; N, 3.60; Found: C, 67.69; H, 3.70; N, 3.82.

Results and discussion

Full characterization details of the Cu(II)-Schiff base/SBA-15 have been previously reported [34]. The reaction of 1,3-cyclohexanedione, 4-hydroxycoumarin and 4-nitrobenzaldehyde was chosen as a model reaction to optimize the reaction conditions (Table 1). At first, the model reaction was carried out in the presence of 0.005 g of Cu(II)-schiff base/SBA-15, under neat condition at 110, 120 and 130 °C (Table 1, entry 1–3). Highest yield of the desired product was obtained at 120 °C (Table 1, entry 2).

The effect of catalyst loading was subsequently addressed, with catalyst amounts varied from 0.003, 0.005 and 0.007 g (Table 1, entry 4–7). Reaction yields and times were shown to be very consistent (97%, and 6 min, Table 1, entry 5) even at catalyst loadings up to 0.005 g (0.007 mmol).

The optimization studies provided optimum reaction conditions at 120 °C temperature, using 0.005 g catalyst under neat condition. Such conditions were consequently selected for further experiments in this work (Table 3). To indicated the impact of the catalyst on the progress of the reaction, the model reaction was performed in the presence of different catalysts such as Zr(II)(SBA-15), Pd(II)(SBA-15) and Fe(II)(SBA-15) and in absence of the catalyst in the optimized conditions (Table 2). Subsequently, the activity of desired catalyst was compared with, the only reported catalyst, heteropolyacid H₁₄[NaP₅W₂₉MoO₁₁₀] catalyst [18] in Table 2 (entry 6). As is evident from Table 2, Cu(II)-Schiff base/SBA-15 is the most effective catalyst for the synthesis of the desired product in terms of TON.

After determining the optimum reaction conditions, the scope and efficiency of the proposed protocol was investigated for a series of substituted benzaldehydes with electron donating and electron withdrawing substituents with 1,3-cyclohexadione **1** and 4-hydroxycoumarin **3** under optimum reaction conditions (Table 3). As demonstrated in Table 3, various benzaldehydes provided high yields and short reaction times (Table 3, entries 1–15). The results demonstrate that both the yields and reaction times are relatively independent of electron donating and electron

withdrawing properties of the substituent in aryl aldehyde. However, para-substituted benzaldehydes had relatively better yields (Table 3, entries 3, 6, 9, 12, 15).

Table 1. Screening of reaction conditions in the synthesis of 9,10-dihydro-7-(4-nitrophenyl)-7H,11H-benzopyrano[3,2-c]chromene-6,8-dione **4c**

Entry	T (°C)	T (min)	Yield (%) ^b	Amount of Catalyst (g)	TON ^c	Type of catalyst
1	110	15	76	0.005	108	Cu(II)(SBA-15)
2	120	6	97	0.005	138	Cu(II)(SBA-15)
3	130	-	-	0.005	-	Cu(II)(SBA-15)
4	120	12	56	0.003	133	Cu(II)(SBA-15)
5	120	6	97	0.005	138	Cu(II)(SBA-15)
7	120	6	97	0.007	99	Cu(II)(SBA-15)

^b Isolated yield, Condition: the reaction was run under neat condition

^c TON=turnover number (mol of the product/mol of the catalyst)

Table 2. Comparison of catalytic activity of Cu(II)-Schiff base/SBA-15 with some other heterogeneous catalysts in the synthesis of 9,10-dihydro-7-(4-nitrophenyl)-7H,11H-benzopyrano[3,2-c]chromene-6,8-dione **4c**

Entry	Type of catalyst	Conditions	Amount of Catalyst (g)	T (min)	Yield (%) ^a	TON ^b
1	Cu(II)(SBA-15)	Neat, 120 °C	0.005	6	97	138
2	Fe(II)(SBA-15)	Neat, 120 °C	0.005	25	71	101
3	Pd(II)(SBA-15)	Neat, 120 °C	0.005	19	84	119
4	Zr(II)(SBA-15)	Neat, 120 °C	0.005	26	93	132
5	No catalyst	Neat, 120 °C	-	-	-	-
6	H ₁₄ [NaP ₅ W ₂₉ MoO ₁₁₀] ^c	EtOH, refluxing	0.03	4	90	22.5

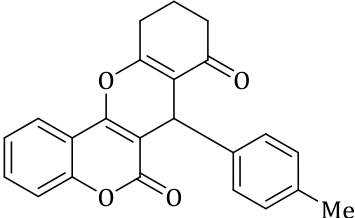
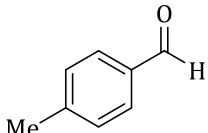
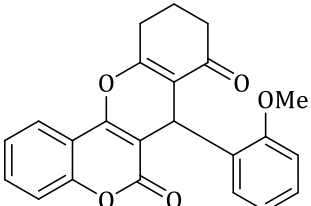
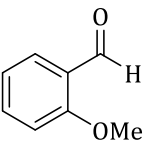
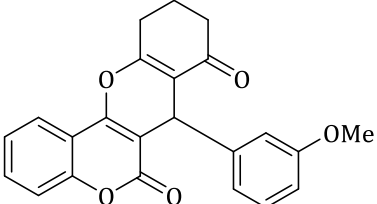
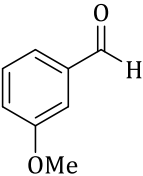
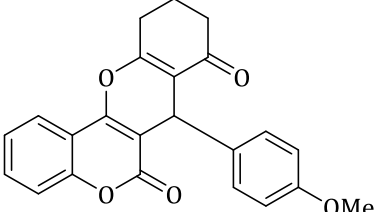
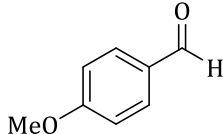
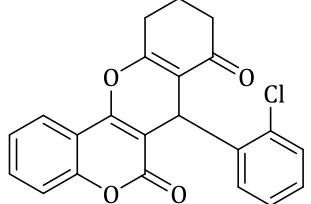
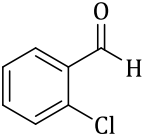
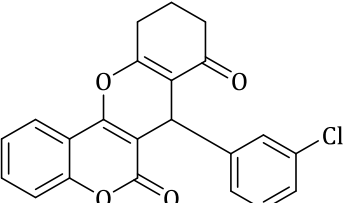
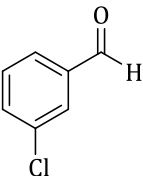
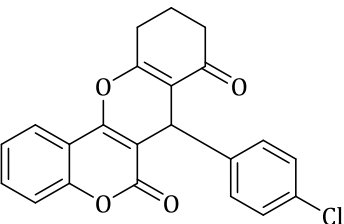
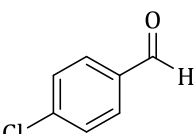
^a Isolated yield

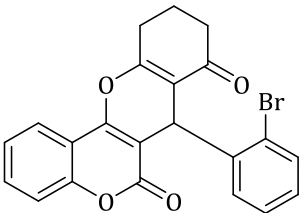
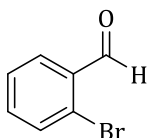
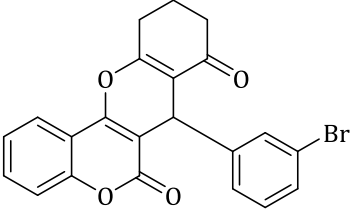
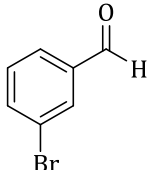
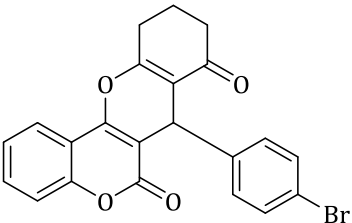
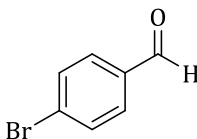
^b TON=turnover number (mol of the product/mol of the catalyst)

^c related to reference [18]

Table 3. Synthesis of benzopyrano[3,2-c]chromene-6,8-diones **4a-o** by Cu(II)-Schiff base/SBA catalyst

Entry	Product	Aldehyde	Time (min)	Yield (%) ^a	m.p. °C [17]
1			7	87	222 [222-223]
2			5	89	218 [218-220]
3			6	97	198 [199-200]
4			15	76	268 [268-269]
5			25	76	218 [218-219]

6			16	94	215 [216-215]
7			25	75	245 [245-246]
8			27	75	188 [188-189]
9			15	90	196 [196-197]
10			25	88	294 [294-295]
11			25	89	247 [247-248]
12			12	96	244 [244-245]

13			25	87	238 [238-239]
14			30	87	265 [265-264]
15			20	90	172 [170-171]

^a Isolated yield

We have also studied the reusability of the catalyst for synthesis of the product **4c** (Table 4). After completion of the reaction, the catalyst was easily separated by adding acetone, followed by filtration and washing with methanol, dried and reused for the next run. The recycled catalyst was successfully reused for six runs in terms of TON and yield (Table 4). However, the yield drops to 70% in the seventh run, which possibly comes from a leakage of Cu²⁺ from SBA-15 channels.

A plausible mechanism for synthesis of the benzopyrano[3,2-c]chromene-6,8-diones **4a-o** in the presence of the catalyst is shown in Scheme 2. Coordination of the carbonyl groups in the intermediate **A** and **C** by the Cu²⁺-cation of the catalyst may increase electrophilicity of the carbonyl groups in both Michael addition and cyclization steps.

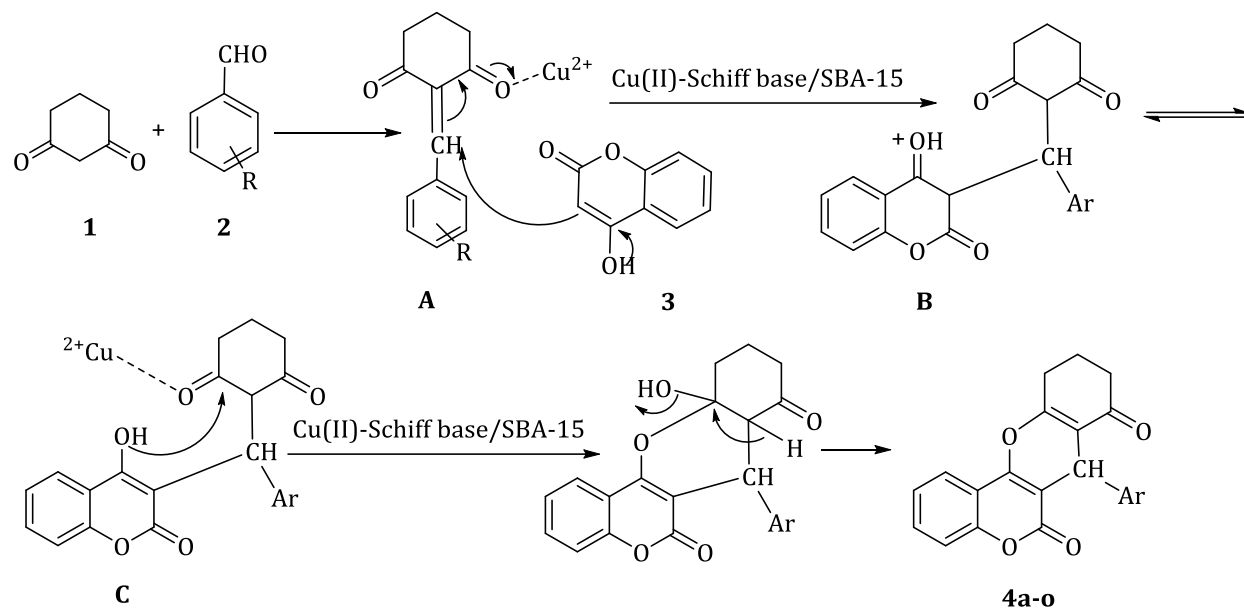
Table 4. Recycle study of the catalyst in the synthesis of the product **4c** under the optimized reaction conditions^a

Run	1	2	3	4	5	6	7
Reaction time (min)	6	6	6	8	8	8	10
Yields (%) ^b	97	97	95	95	95	90	70
TON ^c	138	138	135	135	135	128	100

^a Conditions: 4-hydroxycoumarin (0.05 g, 1 mmol), 1,3-cyclohexadione (0.03 g, 1 mmol) and 4-nitrobenzaldehyde (1 mmol), Cu(II)-Schiff base/SBA-15 (0.005 g, 0.007 mmol), 120 °C

^b Isolated yield

ϵ TON=turnover number (mol of the product/mol of the catalyst)



Scheme 2. A plausible mechanism for the synthesis of benzopyrano[3,2-c]chromene-6,8-diones by Cu(II)-Schiff base/SBA-15

Conclusion

A simple, efficient and environmentally friendly approach for synthesis of the benzopyrano[3,2-c]chromene-6,8-dione derivatives has been developed by a one-pot reaction of 4-hydroxycoumarin, 1,3-cyclohexadiones with aromatic aldehydes using Cu(II)-Schiff base/SBA-15, under neat condition. The short reaction times, high yields, simple workup, using a reusable catalyst, environmentally friendly conditions and avoiding hazardous organic solvents, and toxic catalysts are the main advantages of this method compare to the last reported ones.

Acknowledgments

We would like to appreciate wholeheartedly the Payam-e-Noor University for its support.

Disclosure statement

No potential conflict of interest was reported by the authors.

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How to cite this manuscript: Radineh Motamedi*, Fariba Ebrahimi, Ghasem Rezanejade Bardajee. Cu(II)-Schiff base/SBA-15 as an efficient catalyst for synthesis of benzopyrano[3,2-c]Chromene-6,8-dione derivatives. *Asian Journal of Green Chemistry*, 3 (1) 2019, 22-33. DOI: [10.22034/ajgc.2018.65504](https://doi.org/10.22034/ajgc.2018.65504)