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ORIGINAL PAPER

Silica-supported molybdic acid: preparation, characterization, and its catalytic application in synthesis of pyranocoumarins

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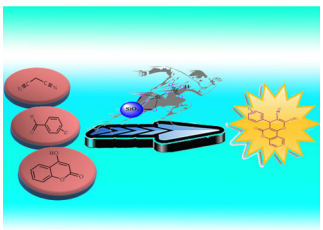
Abstract Silica-supported molybdic acid was employed as novel, recyclable, and safe catalyst in a one-pot three-component condensation of aldehydes, malononitrile, and 4-hydroxycoumarin to produce new and known pyrano[2,3-*c*]chromenes as potent biologically active compounds. This expedient new route has advantages, such as the use of a safe and reusable catalyst, simple operation, short reaction times, and good to excellent yields. The silica-supported molybdic acid as a novel solid acid was characterized by X-ray fluorescence, X-ray diffraction, and Fourier transform infrared spectroscopy.

Graphical abstract



Keywords Silica-supported molybdic acid · Recyclable catalyst · Pyrano[2,3-*c*]chromenes · X-ray fluorescence · X-ray diffraction

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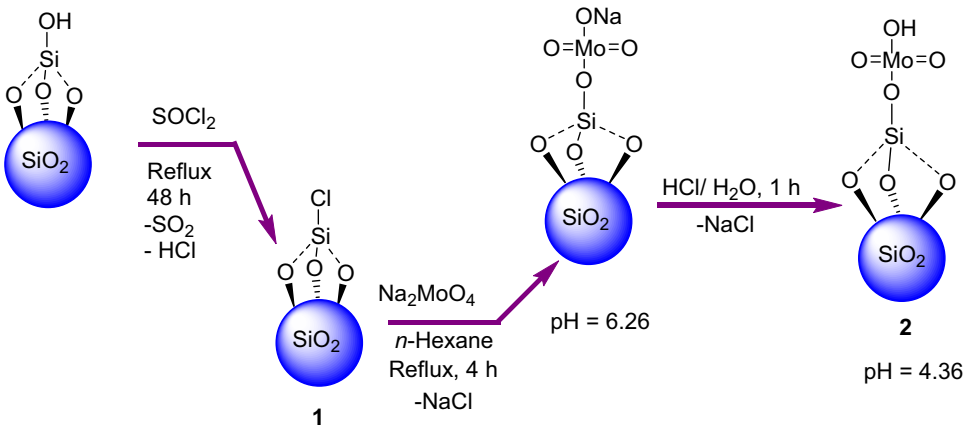
Introduction

Multicomponent reactions are one of the most interesting concepts in modern synthetic chemistry [1]. Multicomponent reactions (MCRs), defined as one-pot reactions in which at least three different substrates join through covalent bonds, have steadily gained importance in synthetic organic chemistry. MCRs allow the creation of several bonds in a single operation and offer remarkable advantages like convergence, operational simplicity, facile automation, reduction in the number of work-up, extraction, and purification processes, and hence minimize waste generation, rendering the transformations green [2]. Development of MCRs can lead to new efficient synthetic methodologies to afford many small organic compounds in the field of modern organic, bioorganic, and medicinal chemistry [3]. Hence, MCRs are considered as a pivotal theme in the synthesis of many important heterocyclic compounds such as chromene derivatives nowadays [4]. Pyrano[3,2-*c*]chromene is a class of vital heterocycles with a wide range of biological effects such as spasmolytic, diuretic, anticoagulant, anticancer, and anti-anaphylactic activity [5]. Compounds having dihydropyran structural motif exhibit a wide range of biological activities, such as diuretic, analgesic, myorelaxant activity [6], anticoagulant [7], anticancer [8], anti-tumoral [9], and anti-HIV [10]. In addition, they are also useful for the treatment of neurodegenerative disorders including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease [11]. Moreover, they are also used as cosmetics, pigments [12], and useful as photoactive materials [13]. A considerable effort has been made for the synthesis of pyran-annulated heterocyclic derivatives due to their wide applications [14].

Scheme 1



A literature survey shows that several modified methods have been reported using different homogeneous or heterogeneous catalysts such as cetyltrimethylammonium chloride/bromide [15, 16], tetrabutylammonium bromide (TBAB) [17], triethylbenzylammonium chloride (TEBA) [18], chitosan [19], K_3PO_4 [20], Na_2CO_3 under grinding [21], Mg/Al hydrotalcite [22], $[BMIm]BF_4$ [23], [2-aemim][PF_6] [24], DBU [25], and piperidine under microwave irradiation [26]. However, many proposed methods for the synthesis of these compounds suffer from disadvantages including relying on multi-step conditions, the use of toxic organic solvents or catalysts containing transition metals, tedious work-up procedure, troublesome waste discarding, high reaction time, and low yields [27]. Thus, obviation of these limitations is necessary to develop a simple and green synthesis of 2-amino-4*H*-chromenes.

In this work, a new methodology to obtain novel and known pyrano[2,3-*c*]chromenes, via a one-pot three-component condensation, is reported. In this paper, we introduce silica-supported molybdic acid (SSMA) as a novel and safe catalyst for the synthesis of novel and known pyranocoumarin derivatives.

Results and discussion

In continuation of our previous studies on the development of various catalysts in synthesis of organic compounds [29–31], as can be seen in Scheme 1, from the reaction of readily available materials such as silicagel and thionyl chloride, silica chloride **1** has been prepared [32]. Accordingly, we found that anhydrous sodium molybdate can react with **1** to give silica-supported molybdic acid (SSMA, **2**). This reaction is clean and easy. From the synthetic point of view, the nucleophilic substitution at silicon is also attractive.

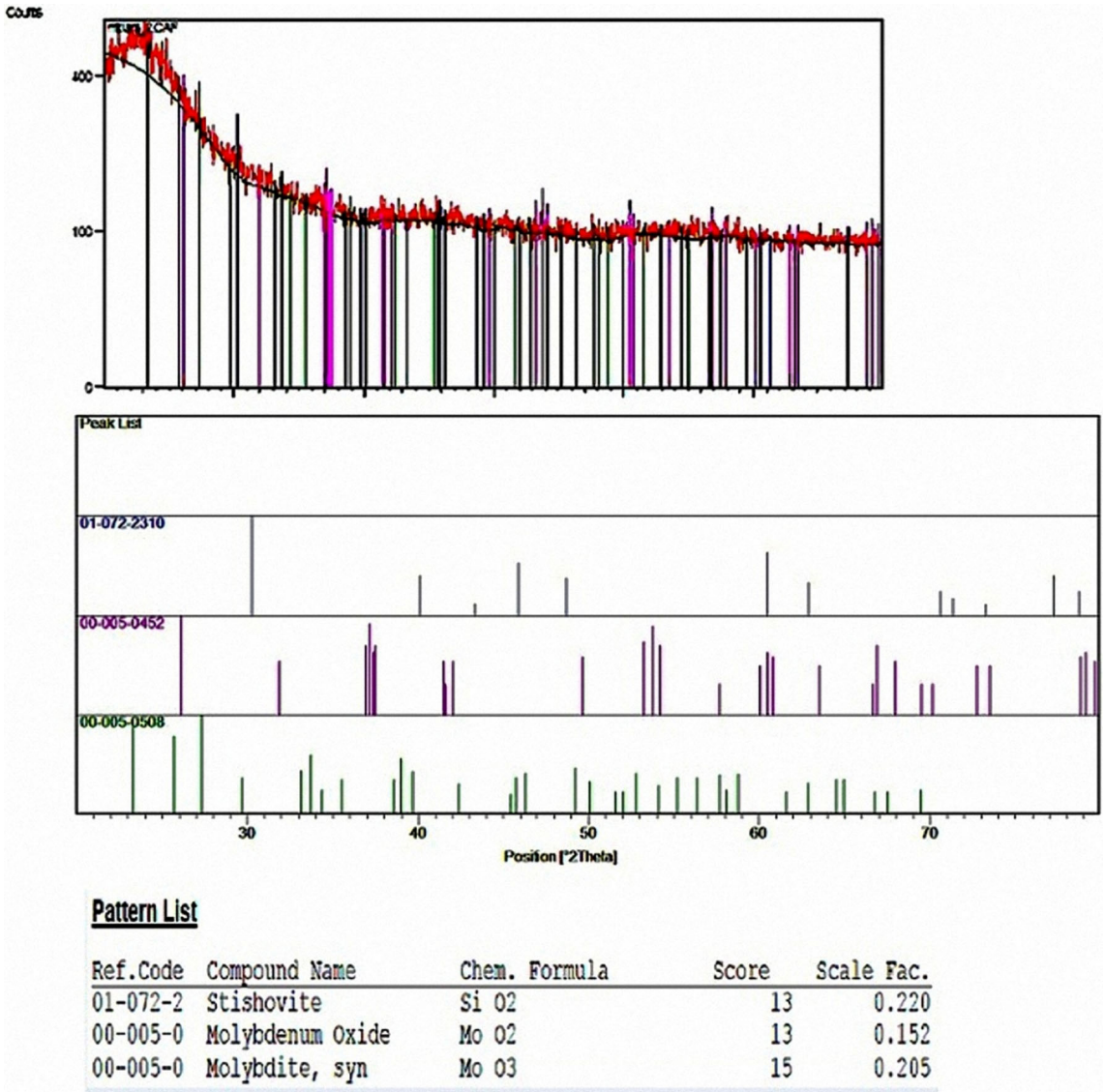
Table 1 XRF data of SSMA **2**

Compounds	Concentration/%
SiO_2	71.14
MoO_4	25.62
Na_2O	1.90
Cl	0.460
ZnO	0.355
CaO	0.289
Fe_2O_3	0.046
Al_2O_3	0.045
CuO	0.027
GeO_2	0.023
MnO	0.022
TiO_2	0.022
Total	99.95

SSMA was characterized by X-ray fluorescence (XRF), X-ray diffraction (XRD), and FT-IR spectra. As can be seen in Table 1, XRF data for the SSMA show the composition of the catalyst as 71.14 (%W/W) SiO_2 and 25.62 (%W/W) MoO_4.

Figure 1 shows the XRD patterns for the silica molybdic acid which exhibits the presence of molybdic acid crystalline phase supported on amorphous silica as a broad peak around 23° (2θ). The three peaks in the 35–40° region of the XRD spectrum could be attributed to the presence and linking of MoO_3 to the silicagel [33].

The FT-IR spectra for the anhydrous sodium molybdate, silica chloride, and silica-supported molybdic acid are shown in Fig. 2. This spectrum shows the characteristic bonds of anhydrous sodium molybdate and silica chloride.



Pattern List

Ref.Code	Compound Name	Chem. Formula	Score	Scale Fac.
01-072-2	Stishovite	Si O2	13	0.220
00-005-0	Molybdenum Oxide	Mo O2	13	0.152
00-005-0	Molybdite, syn	Mo O3	15	0.205

Fig. 1 XRD pattern for the SSMA (**2**)

The adsorption in 3452, 1634, 1086, 800 cm^{-1} in the catalyst spectrum reveals both bonds in SiO_2–Cl and MoO_4 groups.

The successful incorporation of molybdate groups was also confirmed by EDX analysis (Fig. 3), which showed the presence of Mo in addition to Si and O elements.

We evaluated the amounts of molybdic acid supported on SiO_2 using two methods, including (a) titration with 0.1 N NaOH (neutralization reaction) and (b) calculating the weight difference between primary solid acid loosed chloride and new silica-supported molybdic acid. After these experiments, we found that 1 g catalyst includes 0.04 g –$OMoO_3H$. Regarding to the molecular weight of MoO_4H (161 g), therefore, 1 g of catalyst is equal to 0.25 mmol.

In continuation of our efforts toward the development of novel, efficient, and green procedures for the synthesis of organic compounds [34–36] using safe catalysts [37–39], we turned our attention toward the three-component condensation of malononitrile (**3**), aromatic aldehydes **4**, and 4-hydroxycoumarin (**5**) to produce pyrano[2,3-*c*]coumarins **6** in the presence of SSMA (Scheme 2).

In order to optimize the reaction conditions, we used both protic and aprotic solvents in the presence of various amounts of the SSMA in the reaction of benzaldehyde, **3**, and **5** as a model to investigate the effects of the solvent and the catalyst for preparing compounds **6a**. In this case, the substrates were mixed together in 10 cm^3 of the solvent.

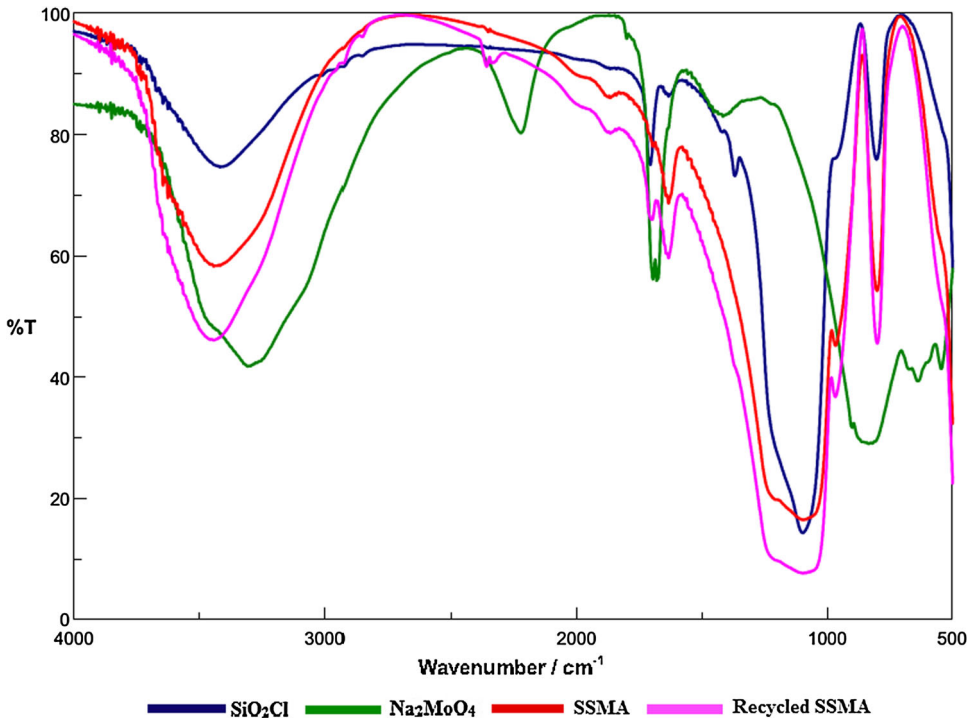


Fig. 2 FT-IR spectra for the comparison of SiO_2Cl, Na_2MoO_4, SSMA, and recycled SSMA

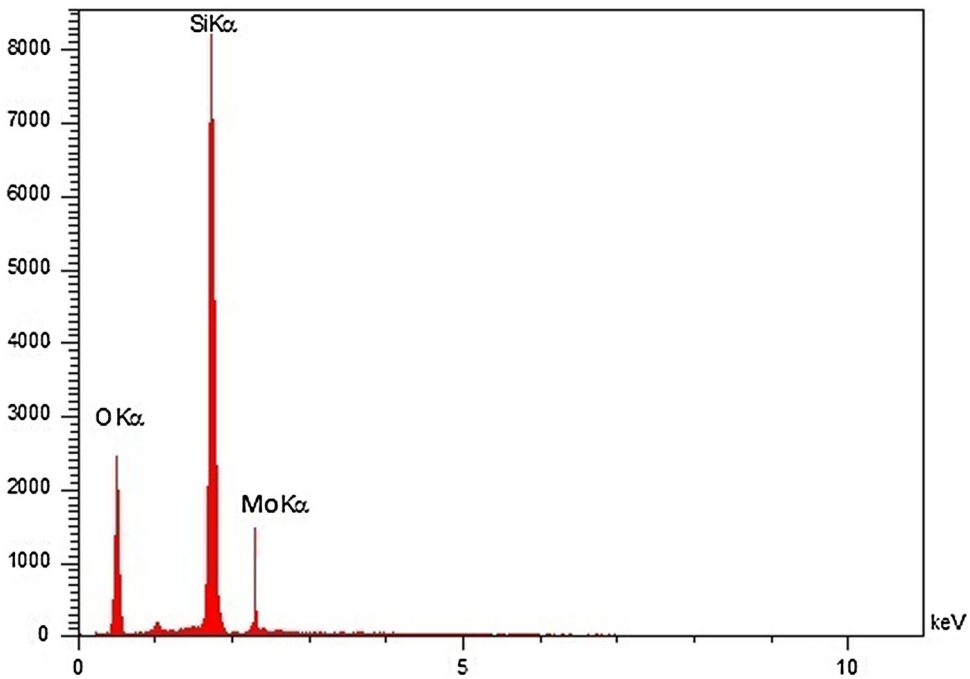


Fig. 3 Energy dispersive spectroscopy (EDAX) pattern of SSMA

As shown in Table 2, we found that polar and protic solvents, such as H_2O and EtOH or MeOH, afford better yields than aprotic ones and also an equal mixture of H_2O and EtOH is the most effective solvent. The effect of temperature was also studied for this reaction and it was found that the reaction would be completed after 360 min at room temperature. However, the thermal-assisted model reaction is efficiently carried out by adding catalytic amounts of SSMA (5 mol%) in a mixture of EtOH and H_2O (50/50).

After optimization of the reaction conditions, in order to extend the scope of this reaction, a wide range of aromatic

Scheme 2

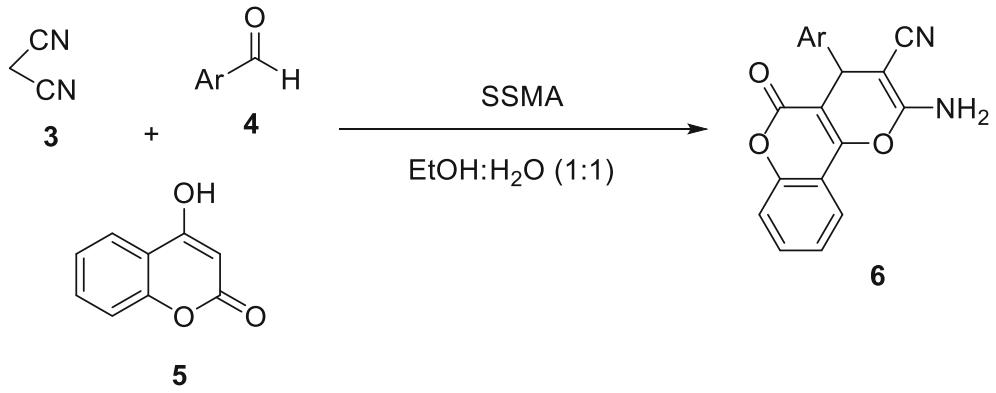


Table 2 Effect of solvent and catalyst on the synthesis of **6a** under refluxing conditions (90 °C); reaction time 40 min

Entry	Catalyst/mol%	Solvent	Yield/%
1	5	CH_2Cl_2	55
2	5	CH_3Cl	60
3	5	EtOH	80
4	5	MeOH	83
5	5	H_2O	67
6	–	H_2O/EtOH	Trace
7	1	H_2O/EtOH	65
8	3	H_2O/EtOH	89
9	5	H_2O/EtOH	94
10	10	H_2O/EtOH	90

Table 3 Synthesis of pyrano[2,3-*c*]coumarin derivatives using SSMA

Entry	Ar	Time/min	Yield[a]/%	M.p./°C
6a	C_6H_5	40	94	260–262 [40]
6b	4-MeO–C_6H_4	25	90	232–234 [40]
6c	2-Cl–C_6H_4	35	80	260–262 [40]
6d	3-NO_2–C_6H_4	40	75	263–265 [40]
6e	4-NO_2–C_6H_4	80	70	232–233 [40]
6f	4-Me–C_6H_4	70	83	254–256 [40]
6g	4-Cl–C_6H_4	55	89	263–265 [40]
6h	2-Thienyl	80	75	263–265 [40]
6i	3-Br–C_6H_4	25	87	274–276 [41]
6j	2-Cl–6-F-C_6H_3	35	93	287–289 [37]
6k	4-Benzyloxy-C_6H_4	50	88	275–277 [37]
6l	1-Naphthyl	90	90	266–268 [42]
6m	4-Isopropyl-C_6H_4	45	94	243–245
6n	Cyclohexyl	25	86	267–270

[a] Isolated yield

aldehydes were used with **3** and **5** (Table 3). All the products were characterized by comparison of their spectra and physical data with those reported in the literature [37, 40–42].

Table 4 demonstrates the merit of this method for the synthesis of pyrano[2,3-*c*]coumarins in comparison with previously reported results. As it can be seen from Table 4, piperidine was employed as a basic catalyst under refluxing EtOH, but this method could not afford good yields (entry 1). In the case of (*S*)-proline (entry 4), the product was obtained in low yield in a long time. In other variations, such as DAHP (entry 3), KF-Al_2O_3 (entry 5), and TEBA (entry 6), the methods need too long reaction times. We believe that these reactions can be efficiently carried out under our suggested conditions with respect to reaction times and product yield.

A mechanistic rationale for the formation of pyranocoumarins **6** is suggested in Scheme 3. It seems that the reaction takes place in three steps. It is reasonable to assume that the initial event involves the generation of the arylmethylene via a Knoevenagel condensation of the aldehyde and malononitrile catalyzed by SSMA **2**. In the next steps, a Michael-type addition to the arylmethylene and subsequent heterocyclization promoted by SSMA give the corresponding products **6**.

The main disadvantage of many reported methods for these reactions is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. In these processes, as outlined in Fig. 4, the SSMA showed recyclability up to six runs without any considerable loss in the product yield and its catalytic activity. The FT-IR spectra of the catalyst after six runs (Fig. 2) showed the same spectral fingerprint of the freshly prepared catalyst indicating the stability of the catalyst throughout the recycling experiment.

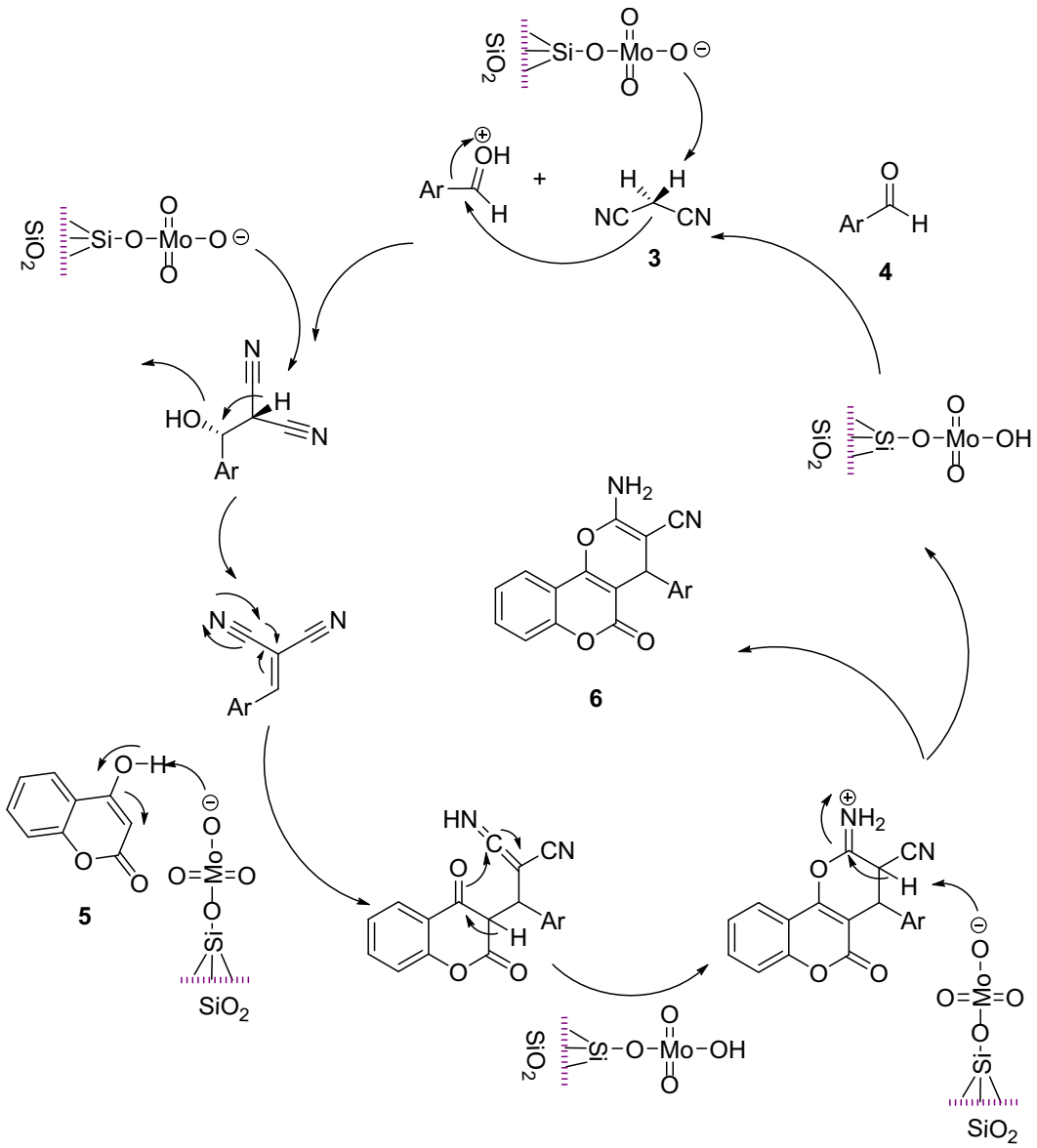
Table 4 Comparison of present work with other methods reported in the literature

Entry	Conditions	Time/ min	Yield/ %
1	Piperidine (0.5 cm^3), EtOH, reflux	30	70 [43]
2	SDS (20 mol%), H_2O, 60 °C	120	85 [44]
3	DAHP (10 mol%), H_2O:EtOH (1:1), r.t.	180	81 [45]
4	(*S*)-Proline (10 mol%), H_2O:EtOH (1:1), reflux	240	72 [45]
5	KF-Al_2O_3 (0.125 g), EtOH, reflux	240	90 [46]
6	TEBA (0.07 g), H_2O, 90 °C	420	96 [18]
7	SSMA (5 mol%), H_2O:EtOH (1:1), reflux	40	94[a]

Synthesis of **6a**

[a] Present work

Scheme 3



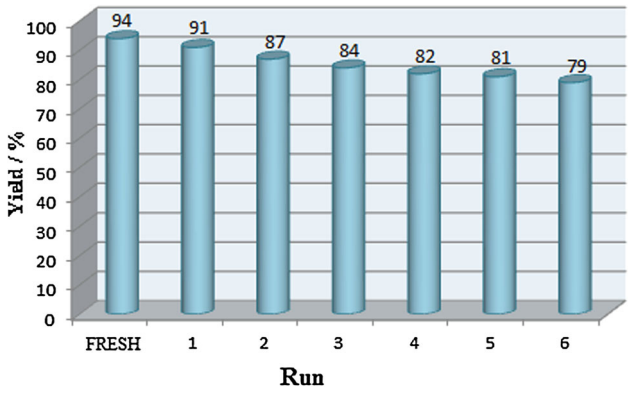


Fig. 4 Recyclability of SSMA for synthesis of **6a**. Reaction time 40 min

Experimental

The chemicals were purchased from Merck and Aldrich chemical companies. The silica chloride **1** was synthesized according to the published procedure [28]. The reactions were monitored by TLC (silicagel 60 F_{254}, hexane : EtOAc). Fourier transform infrared (FT-IR) spectroscopy spectra were recorded on a Shimadzu-470 spectrometer, using KBr pellets and the melting points were determined on a KRUSS model instrument. ^{1}H NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer at 400 MHz, in which DMSO-d_6 was used as solvent and TMS as the internal standard. X-ray diffraction (XRD) pattern was obtained by Philips X Pert Pro X diffractometer operated with a Ni filtered Cu Kα radiation source. X-ray fluorescence (XRF) spectroscopy was recorded by X-Ray Fluorescence Analyzer, Bruker, S_4 Pioneer, Germany. The varioEl CHNS Isfahan Industrial University was used for elemental analysis.

Preparation of silica chloride 1

To an oven-dried (125 °C, vacuum) sample of silicagel 60 (10 g) in a round bottomed flask (250 cm^3) equipped with a condenser and a drying tube, thionyl chloride (40 cm^3) was added and the mixture in the presence of $CaCl_2$ as a drying agent was refluxed for 48 h. The resulting white-grayish powder was filtered and stored in a tightly capped bottle [28].

Preparation of silica-supported molybdic acid (2)

To a mixture of 6.00 g silica chloride and 3.7 g sodium molybdate, 10 cm^3 *n*-hexane was added. The reaction mixture was stirred under refluxing conditions (70 °C) for 4 h. After completion of the reaction, the reaction mixture was filtered and washed with distilled water, and dried and then stirred in the presence of 40 cm^3 0.1 N HCl for 1 h. Finally, the mixture was filtered, washed with distilled water, and dried to afford SSMA.

Preparation of pyrano[2,3-c]coumarin derivatives 5 using SSMA

Malononitrile (**3**, 1.1 mmol), aromatic aldehyde **4** (1 mmol), 4-hydroxycoumarin (**5**, 1 mmol), and SSMA (**2**, 5 mol%) were added to a 10-cm^3 mixture EtOH/H_2O (50/50) in a 25-cm^3 Pyrex flask and refluxed for an appropriate time (Table 3). The reaction progress was controlled by thin layer chromatography (TLC) using hexane/EtOAc (1:1). After completion of the reaction, the solvent was removed under vacuum, the crude products **6** were obtained after recrystallization from EtOH.

2-Amino-4-(4-isopropylphenyl)-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (**6m**, $C_{22}H_{18}N_2O_3$)
IR (KBr): $\bar{\nu}$ = 3389, 3310, 2201, 1713, 1671, 1606, 1374, 1049 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.90 (dd, J = 6.5, 1.3 Hz, 1H), 7.73–7.69 (m, 1H), 7.51–7.44 (m, 2H), 7.38 (s, 2H), 7.19–7.15 (m, 4H), 4.41 (s, 1H), 2.84 (m, 1H), 1.17 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 159.54, 158.00, 157.95, 153.28, 152.08, 147.11, 140.70, 132.88, 127.45, 126.42, 124.65, 122.41, 119.29, 116.54, 112.95, 104.18, 58.03, 38.85, 36.50, 33.23, 23.79 ppm.

2-Amino-4-cyclohexyl-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (**6n**, $C_{19}H_{18}N_2O_3$)
IR (KBr): $\bar{\nu}$ = 3427, 3280, 2188, 1720, 1669, 1594, 1389, 1048 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.82 (dd, J = 6.4, 1.4 Hz, 1H), 7.72–7.67 (m, 1H), 7.48–7.43 (m, 2H), 7.35 (s, 2H), 4.43 (s, 1H), 1.74 (m, 1H), 1.63–1.57 (m, 4H), 1.38–1.32 (m, 2H), 1.18–0.94 (m, 4H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 160.64, 160.06, 154.63, 152.02, 132.67, 124.56, 122.05, 116.53, 116.00, 113.00, 104.60, 52.48, 43.18, 36.66, 30.51, 27.52, 26.11, 25.85, 25.52 ppm.

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