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Silica-supported molybdenum oxide (MoO$_3$-SiO$_2$): As a heterogeneous and recyclable catalyst for the synthesis of polyhydroquinoline derivatives

Amir Khojastehnezhad [1, *], **Behrooz Maleki** [2], **Akram Vedad Mofrad** [2]

[1] Young Researchers Club and Elites, Mashhad Branch, Islamic Azad University, Mashhad, Iran
[2] Department of Chemistry, Hakim Sabzevari University, Sabzevar, 96179-76487, Iran

*corresponding author e-mail address: *akhojastehnezhad@yahoo.com*

ABSTRACT

A silica-supported molybdenum oxide (MoO$_3$-SiO$_2$) catalyst was prepared and characterized using fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), scanning electron microscopy (SEM) and energy-dispersive X-ray spectroscopy (EDS) analysis. The activity of the prepared catalyst as a hetrogeneous and recyclable catalyst was evaluated in one-pot synthesis of polyhydroquinoline derivatives by reaction of dimedone, an aromatic aldehyde, ethyl acetoacetate and ammonium acetate under solvent-free conditions. The catalyst showed to be highly active under solvent-free conditions giving high yields of the products over short reaction times. Furthermore, the catalyst was recovered by simple filtration and reused several times with no significant loss of its activity.

Keywords: *Polyhydroquinoline, molybdenum oxide, MoO$_3$-SiO$_2$, supported heterogeneous catalyst, solvent-free.*

1. INTRODUCTION

Recently, multicomponent reactions (MCRs) have attracted attention of organic chemists because they improved the efficiency of the reaction and also decrease using of different solvent and materials. The MCRs increase the yield of the reaction and reduce the reaction time compared with traditional multiple-step reactions [1]. Thus, several research groups in the field of medicinal chemistry, drug discovery and organic synthesis have worked on the design of novel MCRs.

In recent decades, heterogeneous catalysts with easy recovery and reusability over homogeneous systems have gained significantly importance in organic reactions due to low prices and environmentally friendly behavior [2-4]. The immobilization of homogeneous reagents on the surface of solid support like silica is one of the suitable routes for developing efficient heterogeneous catalysts. In supported catalysts, the catalytic activity of the catalyst is strongly dependent on support properties. These supported catalysis have other features such as low toxicity, moisture resistance and air tolerance compared to conventional homogeneous catalysis [5-7].

Polyhydroquinoline and 2, 5 – dioxo - 1, 2, 3, 4, 5, 6, 7, 8 - octahydroquinolines derivatives are very well-known molecules that include a six-membered heterocyclic ring, which have been reported to possess a wide range of biological properties and pharmaceutical activities such as vasodilator, antitumor,

bronchodilator, antiartherosclerotic, geroprotective and hepatoprotective activity [8-13]. Thus, the synthesis of these heterocycles has become an area of great interest.

Many classical methods have been reported for synthesis of this molecule in presence of different catalysts such as Co$_3$O$_4$-CNTs [14], Fe$_3$O$_4$@chitosan [15], SBA-15/SO$_3$H [16], molecular iodine [17], hafnium(IV)bis(perfluorooctanesulfonyl)imide [18], carbon based solid acid [19], PPA-SiO$_2$ [20], guanidine hydrochloride [21], trifluoroethanol [22], Pd-nanoparticles [23]. Although all of the mentioned synthetic methods have advantages, but they also have some limitations like low yields, thermal conditions or difficult preparations of catalysts and long reaction time. In order to overcome the mentioned limits and disadvantages of the above methods and also, in continuation of our work on synthesis of new catalysis [24-30], we wish to report an suitable method for the synthesis of polyhydroquinoline derivatives in good to excellent yields with silica-supported molybdenum oxide (MoO$_3$-SiO$_2$) as acidic catalyst under solvent-free conditions (Scheme 1).
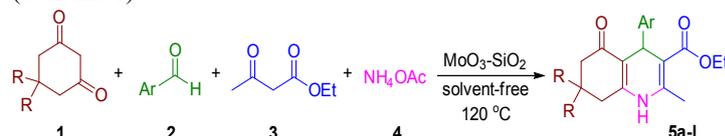
Scheme 1. Synthesis of polyhydroquinoline derivatives (5a-l) using of MoO$_3$-SiO$_2$.

2. EXPERIMENTAL SECTION

General. All chemicals were purchased from Merck, Aldrich and Fluka Chemical Companies and used without further purification.
General procedure for synthesis of Polyhydroquinolines derivatives (5a-l). A mixture of dimedone or 1,3-

cyclohexanedione 1 (1 mmol), aromatic aldehyde 2a-l (1 mmol), ethyl acetoacetate 3 (1.2 mmol), ammonium acetate 4 (3 mmol), and MoO$_3$-SiO$_2$ (20 mol%) was heated on an oil bath at 120°C for 15-45 min. Completion of the reaction was indicated by TLC.

After completion, appropriate amount of hot ethanol was added and the reaction stirred for 2 min. The catalyst was recovered from the reaction mixture by filtration. The reaction mixture without catalyst was poured into crushed ice, and the obtained product which separated was isolated by filtration to afford polyhydroquinolines 5a-l.

3. RESULTS SECTION

The catalyst was prepared according to the literature [31], and then in order to find the optimum amount of the catalyst (MoO$_3$-SiO$_2$), four-component reaction of dimedone, benzaldehyde, ammonium acetate and ethyl acetoacetate was selected as a model reaction. The reaction was performed in with or without different amount of catalyst (Table 1). The reaction was not carried out in absence of the catalyst (Entry 1). The yield of 5a was improved when we used more amount of catalyst (Entries 2–4), with the use of 20 mol% of catalyst resulted in the highest yield in 20 min (Entry 4). In larger amount of the catalyst, the yield of the reaction was not changed significantly (Entries 5 and 6).

Table 1. Comparison of the amount of MoO3-SiO2 for the synthesis of 5aa.

Entry	Catalyst amount (mol %)	Temperature	Time (min)	Yield (%)[b]
1	None	120 ^{o}C	60	---
2	5	120 ^{o}C	30	44
3	10	120 ^{o}C	20	73
4	**20**	**120 ^{o}C**	**20**	**90**
5	30	120 ^{o}C	20	91
6	50	120 ^{o}C	20	91

[a] Reaction conditions: dimedone (1 mmol), benzaldehyde (1 mmol), ethyl acetoacetate (1.2 mmol) and ammonium acetate (3 mmol) in presence of MoO$_3$-SiO$_2$ at 120 ^{o}C.
[b] Isolated yields.

And then, other conditions such as temperature, use of various solvents and solvent-free conditions (Table 2) were investigated; the yield of the reaction in the absence of the catalyst and under solvent-free conditions was zero (Entry 1). The yields of the reaction were better in solvent-free conditions than solvents (Entries 2-7). Increasing the temperature improve the yields of the reaction (Entries 7-12). The best result was at 120 oC under solvent-free conditions (Entry 11). Moreover, the model reaction was performed in presence of ammonium heptamolybdate ((NH$_4$)$_6$Mo$_7$O$_{24}$) and naked silica (SiO$_2$) in the same time and conditions led to lower yields than MoO$_3$-SiO$_2$ as catalyst (Entries 13 and 14).

Table 2. Comparison of various conditions and temperatures for the synthesis of **5a**[a].

Entry	Catalyst	Conditions	Time (min)	Temperature (°C)	Yield (%)[b]
1	---	Solvent-free	60	120	---
2	MoO$_3$-SiO$_2$	CHCl$_3$	30	reflux	low
3	MoO$_3$-SiO$_2$	CH$_2$Cl$_2$	30	reflux	low
4	MoO$_3$-SiO$_2$	H$_2$O	30	reflux	45
5	MoO$_3$-SiO$_2$	MeOH	30	reflux	54
6	MoO$_3$-SiO$_2$	EtOH	30	reflux	66
7	MoO$_3$-SiO$_2$	Solvent-free	30	rt	48
8	MoO$_3$-SiO$_2$	Solvent-free	15	80	65
9	MoO$_3$-SiO$_2$	Solvent-free	15	100	80
10	MoO$_3$-SiO$_2$	Solvent-free	15	110	84
11	**MoO$_3$-SiO$_2$**	**Solvent-free**	**15**	**120**	**90**
12	MoO$_3$-SiO$_2$	Solvent-free	15	130	90
13	(NH$_4$)$_6$Mo$_7$O$_{24}$	Solvent-free	30	120	76
14	SiO$_2$	Solvent-free	30	120	low

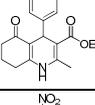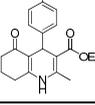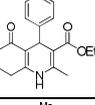[a] Reaction conditions: dimedone (1 mmol), benzaldehyde (1 mmol), ethyl acetoacetate (1.2 mmol) and ammonium acetate (3 mmol) in presence of MoO$_3$-SiO$_2$.
[b] Isolated yields.

Then, the scope and efficiency of the reaction were investigated for the synthesis of a variety of substituted polyhydroquinoline 5a-l in the presence of MoO$_3$-SiO$_2$ using number aromatic aldehydes bearing both electron-donating and electron-withdrawing substitutents. Good to excellent yields were obtained as illustrated in Table 3.

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Table 3. Synthesis of polyhydroquinoline derivatives **5a-l**[a] using MoO₃-SiO₂ as catalyst.

Entry	Ar	R	Product	Time (min)	Yields (%)[b]
1	C_6H_5	CH_3	**5a**	20	90
2	$4\text{-}ClC_6H_4$	CH_3	**5b**	25	80
3	$4\text{-}NO_2C_6H_5$	CH_3	**5c**	30	86
4	$4\text{-}BrC_6H_5$	CH_3	**5d**	20	88
5	$4\text{-}CH_3C_6H_4$	CH_3	**5e**	20	90
6	$3\text{-}NO_2C_6H_5$	CH_3	**5f**	35	80
7	$2\text{-}ClC_6H_4$	CH_3	**5g**	40	77
8	C_6H_5	CH_3	**5h**	25	82
9	$4\text{-}ClC_6H_4$	H	**5i**	25	85
10	$4\text{-}NO_2C_6H_4$	H	**5j**	20	89
11	C_6H_5	H	**5k**	30	82
12	$4\text{-}ClC_6H_4$	H	**5l**	10	82
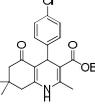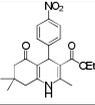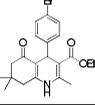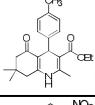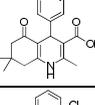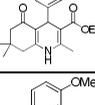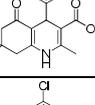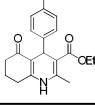
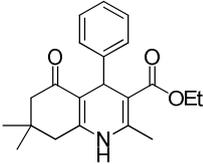[a] Reaction conditions: dimedone or 1,3-cyclohexanedione **1** (1 mmol), aromatic aldehyde **2** (1 mmol), ethyl acetoacetate **3** (1.2 mmol) and ammonium acetate **4** (3 mmol) in presence of 20 mol % of catalyst at 120 ºC under solvent-free conditions.
[b] Isolated Yields.

To show the advantage of the present study, we compared the catalutic activity of MoO₃-SiO₂ in the synthesis of polyhydroquinoline derivative **5a** with other catalysts like Fe₃O₄@chitosan, SBA-15/SO₃H, Bakers' yeast, Yb(OTf)₃ and chiral organocatalysis. As shown in Table 4, MoO₃-SiO₂ is the more efficient catalyst and gives high yields of product in shorter reaction times.

Table 4. Comparison of synthesis of polyhydroquinoline **5a** with other catalysts.

Entry	Catalyst	Conditions	Time (min)	Yield (%)[a]	Ref
	Fe₃O₄@chitosan	EtOH/rt	140	84	15
	SBA-15/SO₃H	Solvent-free/60 ºC	25	90	16
	Bakers' yeast	Solvent-free/rt	1440	79	34
	Yb(OTf)₃	EtOH/rt	300	90	35
	Organocatalysis	ACN/rt	240	82[b]	36
	MoO₃-SiO₂	Solvent-free/120 ºC	20	90	---

[a] Isolated Yield

The reusability of the catalyst in the reaction of dimedone, benzaldehyde, ammonium acetate and ethyl acetoacetate (model reaction) in presence of MoO_3-SiO_2 (20 mol%) was also studied. After completion the reaction, the catalyst was separated by filtration, washed three times with acetone and then dried in vacuum at 100 °C for 2 h. As shown in Fig. 1, this heterogeneous catalysis could be used several times in same model reaction, and its catalytic activity does not noticeably change.
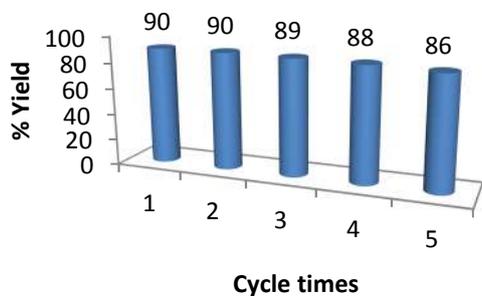
Figure 1. Recycling experiment for MoO_3–SiO_2.

According to proposed mechanism in the literature [37], a plausible mechanism for the preparation of polyhydroquinoline catalyzed by MoO3-SiO2 is shown in Scheme 2.

Scheme 2. Proposed mechanism for the synthesis of polyhydroquinoline derivatives.

4. CONCLUSIONS

In this study, we report a green catalytic method for the synthesis of polyhydroquinoline derivatives by one-pot four-component condensation reaction of dimedone, aromatic aldehydes, ammonium acetate and ethyl acetoacetate using MoO_3–SiO_2 (20 mol %) as an efficient, reusable and heterogeneous catalyst under solvent-free conditions. Good to excellent yields, short reaction times, easy work-up, and using solvent-free conditions are some advantages of this method.

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6. ACKNOWLEDGEMENTS