FULL PAPER

Ceria-Molybdenum Mix Metal Oxide: A Mild and Efficient Recyclable Catalyst for One-Pot Synthesis of Polyhydroquinoline via Hantzsch Reaction

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Abstract:
In laboratory, ceria-molybdenum mix metal oxide catalyst was synthesized by using simple grinding method and characterized by FT-IR, XRD, SEM, and EDX. Catalytic activities of catalyst were testified in Hantzsch condensation reaction for the synthesis of polyhydroquinoline by using dimedone, substituted aryl aldehydes, ethylacetocetate and ammonium acetate with high percent yield. It is an efficient catalyst for 1,4-dihydropyridines synthesis. Cerium molybdenum mix metal oxide catalyst can be re-covered and re-used.

Keywords: ceria-molybdenum (Ce-Mo); 1,4-dihydropyridines; Hantzsch condensation; polyhydroquinoline; synthesis; mix metal oxide catalyst

1. Introduction
Recently from 2-3 decades, 1,4-dihydropyridines/ polyhydroquinoline (PHQ) identified, as a desired structure that is screened synthon / moiety as part of many drug design processes in medicinal chemistry due to their amine group and other functional group increase biological importance of molecules. In between the nitrogen base pair containing heterocyclic designs, small molecule like azoles, imidazoles, 1, 4-dihydropyridines extremely important component due to their presence in a huge number of biological application such as neuroprotectants [1], geroprotective, cerebral antiischemic agents, bronchodilator [2], anti-inflammatory, multidrug resistance (MDR) in cancer [3], antimicrobial [4], antitubercular [5], anti-parkinson, anticancer [6], analgesic and anticonvulsant [7], activities usual products as advantage pharmacophores. Similarly in polyhydroquinoline (PHQ) and its derivatives is impressive significance because of their important roles in biological systems such as anti-malarial activity against plasmodium falciparum, in vitro antibacterial activity against pathogenic strains of bacteria and fungi, moreover their antitubercular activity against Mycobacterium tuberculosis H37Rv strain[8]. Furthermore they have used as calcium channel agonist [9], it is fix the disarranged heart proportion as a chain cutting specialist [10], Cardiovascular agents, nifedipine, nicardipine, hypertension treatment [11], anticancer agents [12], antimicrobial activity [13], antihyperglycemic as well as antidyslipidemic [14], similarly other related derivatives which are effective in the treatment of hypertension [15]. Various methods have been reported for the synthesis of 1,4-Dihydropyridines (DHP) or polyhydroquinoline (PHQ), for the reason lots of biological importance associated with these derivatives. The classical method involves a one pot four-component cyclocondensation of an aryl aldehyde, dimedone, ethylacetocetate and

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ammonia in presence of Lewis acid catalyst or acid / acetic acid or reflux in ethanol or other solvent [16]. However, such methods suffer from quite a few disadvantages such as extensive reaction times, use of harmful and volatile as well as excess organic solvents, low product yields and harsh reaction conditions.

Recently, researcher attract to simplify methods for synthesis of highly active compound of polyhydroquinoline such as using both conventional as well as nonconventional method [17]. Large number of mixed metal oxides catalyst utilized as reusable catalysts. It is an attractive class of materials for sustainable development of pharmaceutical industrial products [18]. So many classical methods, for the synthesis of polyhydroquinoline were reported such as acetic acid, PEG-400 reaction medium [19], ionic liquids [20]. Some reaction used as special technique like microwave irradiation and ultrasound [21]. Many more methods are require prolong heating time [22,16], Similarly, some other reported methods are including TMSCI [23], HClO₄-SiO₂ [24], HY- zeolite [25], Ionic liquids [26], MCM-41[10], Mesoporous vanadium ion doped titanic nanoparticles (V–TiO₂) [27], Yb(OTf)₃, Gadolinium triflate [28], Cu (II) Complex, silica supported sulfuric acid (SSA) [29], this reported method quite efficient for the synthesis of 1,4-dihydropyridines or polyhydroquinolines and the development in this field remarkable as well as needs to improvement of the synthesis process.

2. Results and Discussion

Synthesis of heterogeneous catalyst by using green approach with including percent atom economy is an emerging and challenging area of researchers, considering environmental, eco-friendly catalyst and balance reaction side product. Government apply rules and regulation with alteration legislation on the discharge of waste (contaminated water) and cyanogenic emissions having serious implications for the pharmaceutical industry toward the implementation of innovative “clean technology” together with the utilization of different heterogeneous catalyzed chemical processes [30]. Here, we have minimized the reaction byproduct in chemical reaction as well as catalyst synthesis and balance the atom economy in total synthesis. The recently developed family of mix metal oxide of Ceria-Molybdenum catalyst with their present high Lewis and Bronsted acidic sites.

Characterization of the catalyst

The XRD pattern of the Cerium-Molybdenum (CM) catalyst calcined at 500°C for 2 hrs are shown in Fig. S1. (Supplementary data). The results are in accordance with crystal arrangement with unit cell parameter a= 18.42, b= 19.65, c= 7.42 Å and α = β = γ = 90º and 2θ = 12.9, 22.7, 23.5, 25.8, 27.5 º observed with corresponding to the planes (hkl) 101, 401, 403, 202, 222. In XRD pattern shows highest peak at 2θ = 25.8º and (202) plane correspond to the orthorhombic phase. Empirical formula of catalyst is calculated by EDX data gives Ce1Mo3O9 Fig. S3. SEM image of catalyst are shown in Fig. S2. In FT-IR spectra the bands at 442 cm⁻¹ shows Ce-O tetrahedral bending vibration, 500 cm⁻¹ confirm the ring vibration, 1080- 754 cm⁻¹ indicate the internal assymetric stretch, externl symmetric stretch due to Ce-O-Ce or Mo- O-Mo bending vibration  mode, 1153 cm⁻¹ confirm the Ce-O-Mo streching vib., 3661-3427 cm⁻¹ presence of bridge OH stretching frequency (Ce-OH-Mo) shown in Fig. S4.

In organic synthesis, the catalyst was optimized the reaction conditions to investigate the reaction involving p-hydroxyl benzaldehyde, dimedone, ethyl acetoacetate, and nitrogen source of ammonium acetate in presence of ceria-molybdenum as a heterogeneous catalyst which was prepared by simple grinding method to gives excellent yield.
reported method for the synthesis of 1,4-dihydropyridine shown in Table 3. The data presented the promising features of this method in terms of reaction rate and yield of the product.

Mechanistically representation in synthesis, firstly ammonium acetate dissociates to give NH$_3$ and CH$_3$COOH (Scheme 2). In step (IA) ethylacetoacetate electronically activate in presence of CM mix metal oxide catalyst. Ammonia molecule interacts with electronically activated ethylacetoacetate to form a (IIA) 2°amine molecule. Simultaneously, other hand demidone self enolise in presence of acetic acid. This enolised demidone interact with electronically activated aryl aldehyde to form a(III) allene molecule those are again activating in presence of CM mix metal oxide catalyst. In (IIA) 2°amine molecule interact with electronically activated (III) molecule to form a (IV)$^a$ intermediate. Again (IV)$^a$ intermediate is self cyclization and dehydration to form a target polyhydroquinoline (V) molecules.

The reactions proceed resourcefully and smoothly at 80 ºC (reflux in oil bath) and were completed within 40 min - 60 min. with high percent yield up to 85-94%. Table 2 shows the generality of the present protocol, which is equally effective for various type of aldehydes or

![Scheme 1. Synthesis of polyhydroquinolines (PHQ) derivatives in modal reaction (5e).](image)

**Table 1. Optimization reaction condition in modal reaction 5e.**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Solvent</th>
<th>Amount of catalyst (mg)</th>
<th>Reaction time</th>
<th>Yield (%)</th>
<th>a Isolated yield. b Catalyst reusability three times consecutive reuse.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td></td>
<td>5 hr</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Water</td>
<td>100</td>
<td>5 hr</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Water : Ethanol (1:1)</td>
<td>100</td>
<td>2hr</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ethanol</td>
<td>100</td>
<td>40 min</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Acetonitrile</td>
<td>100</td>
<td>2 hr</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Acetonitrile: Water (1:1)</td>
<td>100</td>
<td>2 hr</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Ethanol</td>
<td>50</td>
<td>40 min</td>
<td>94$^b$ (93.8, 93.5, 93.2)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Ethanol</td>
<td>25</td>
<td>40 min</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Synthesis of polyhydroquinolines (PHQ) using CM catalyst under modal reaction 5e.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Entry</th>
<th>R</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Melting point (°C)</th>
<th>a Isolated yield.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>H</td>
<td>40</td>
<td>93</td>
<td>204-206</td>
<td>203-204 [31]</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>4-Cl</td>
<td>42</td>
<td>92</td>
<td>230-232</td>
<td>243-245 [31]</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>4-CH$_3$</td>
<td>45</td>
<td>85</td>
<td>255-258</td>
<td>258-260 [32]</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>4-NO$_2$</td>
<td>60</td>
<td>90</td>
<td>241-244</td>
<td>244-246 [32]</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>4-OH</td>
<td>45</td>
<td>94</td>
<td>232-235</td>
<td>228-230 [32]</td>
</tr>
<tr>
<td>6</td>
<td>5f</td>
<td>2-Cl</td>
<td>45</td>
<td>85</td>
<td>205-207</td>
<td>209-210 [33]</td>
</tr>
<tr>
<td>7</td>
<td>5g</td>
<td>4-OMe</td>
<td>40</td>
<td>90</td>
<td>253-255</td>
<td>252-254 [34]</td>
</tr>
<tr>
<td>8</td>
<td>5h</td>
<td>3-NO$_2$</td>
<td>55</td>
<td>91</td>
<td>176-178</td>
<td>177-178 [35]</td>
</tr>
<tr>
<td>9</td>
<td>5i</td>
<td>3-OH</td>
<td>40</td>
<td>86</td>
<td>283-285</td>
<td>284-286 [36]</td>
</tr>
<tr>
<td>10</td>
<td>5j</td>
<td>2-NO$_2$</td>
<td>60</td>
<td>90</td>
<td>207-208</td>
<td>208-210 [34]</td>
</tr>
</tbody>
</table>

aIsolated yield.
ethy lacetoacetate. Moreover, the experimental method is so simple and there was no undesirable side product considering green approach.

**Scheme 2.**

**Table 3.** Comparisons of results of other reported procedures with the present method^a^.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/conditions</th>
<th>Catalyst (mg)</th>
<th>Time (min) / yield^b^</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I_2/EtOH, r.t.</td>
<td>76</td>
<td>120/93</td>
<td>[37]</td>
</tr>
<tr>
<td>2</td>
<td>HY-Zeolite/CH_3CN, r.t.</td>
<td>100</td>
<td>120/90</td>
<td>[24]</td>
</tr>
<tr>
<td>3</td>
<td>[TBA]_2[W_6O_19]/110ºC</td>
<td>132</td>
<td>20/82</td>
<td>[38]</td>
</tr>
<tr>
<td>4</td>
<td>Nano-γ-Fe_2O_3·SO_3H/</td>
<td>31</td>
<td>90/93</td>
<td>[39]</td>
</tr>
<tr>
<td>5</td>
<td>SO_4^2-/TiO_2 NPs/Et-OH, reflux</td>
<td>20</td>
<td>60/93</td>
<td>[40]</td>
</tr>
<tr>
<td>6</td>
<td>Scolecite, Ethanol, Reflux</td>
<td>200</td>
<td>45/93</td>
<td>[33]</td>
</tr>
<tr>
<td>7</td>
<td>Ceria-Molybdenum, Ethanol, Reflux/ 80°C</td>
<td>50</td>
<td>40/94</td>
<td>Our result</td>
</tr>
</tbody>
</table>

^aSynthesis of polyhydroquinoline, ^bPercent isolated yield.

3. Material and Methods

Experimental

**General procedure for the synthesis of Catalyst**

The ceria-molybdenum (CM) metal oxide catalyst where prepared by simple grinding method, 0.33 gm of ammonium Ceríc nitrate salt (as a source of Ce) and 0.49 gm of ammonium heptamolybdate salt (as a source of Mo) are well mix with mortal and piston for 20 min to change a colure of mixture to form a catalyst, then mixture was calcined at 500ºC for 02 hr. Prepared ceria-molybdenum (CM) mix metal oxide used as a catalyst in organic transformation such as, in synthesis of polyhydroquinolines (PHQ).

**Typical procedure for the synthesis of polyhydroquinoline derivatives 5e:**

A mixture of p-hydroxy aldehyde 0.122 mg(1 mmol), dimedone 0.140 mg (1mmol), ethy lacetoacetate 0.130 mg (1 mmol), ammonium acetate 0.170 mg (1.5 mmol) and 50 mg ceria-molybdenum (CM) as a catalyst, were the mixture was refluxed up to completion of reaction in presence of ethanol. Reaction was monitored by using TLC (pet ether: ethyl acetate 6: 4, as an eluent). After completions of reaction then add 5ml excess ethanol to reactant disappeared and
filtered to separate a catalyst. Then few mL of child water was added drop wise with continuous stirring in the filtrate to obtained crud product of polyhydroquinolines (PHQ) (5e), solid crude product was filtered and recrystallized from ethanol to get a pure product.

**Reusability and recycling test**

Subsequent to completion of the catalytic reactions, the Lewis acid catalyst ceria-molybdenum (CM) was recollect through filtration for further reuse of next batch reaction. Then they are carefully washed consecutively with acetone or ethyl acetate (2-3 times). Then the recollected catalyst was dried in a furnace at 110ºC for 10 min. The recycling effectiveness of the CM catalyst was tested up to four time reused without loose of catalytic activity. In the synthesis of polyhydroquinoline from dimedone, substituted aryl aldehydes, ethylacetoacetate and ammonium acetateas reactants, subsequent this recycling process, CM catalyst was reused for three consecutive cycles.

**Spectroscopic data of synthesized some principal compounds**

**Ethyl-4-phenyl-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 1, 5a):** ^1^H NMR (400 MHz, DMSO, δ ppm): 0.91-1.04 (S, 6H, CH₃), 1.18 (t, 3H, CH₃), 1.99-2.54 (m, 4H, CH₂), 3.97-4.02 (m, 2H, CH₂), 4.78 (s, 1H, CH), 6.54-6.99 (dd, 4H, Ar-H), 8.73 (s, 1H, OH), 8.79 (broad, 1H, NH); ^1^C NMR (400 MHz, DMSO): δ 14.12, 18.22, 26.60, 29.17, 32.02, 34.86, 50.43, 58.75, 104.46, 110.56, 114.23, 128.30, 138.42, 144.01, 148.93, 155.02, 166.99, 194.30.; FT-IR (cm⁻¹): 3451, 3190, 2948, 2313, 1677, 1478, 1373, 1211, 1153, 1016, 839, 796; Mass (GC-MS): (m/z) M⁺ = 338.14

**Ethyl-4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 1, 5e):** ^1^H NMR (400 MHz, CDCl₃) = δ 0.94-1.04 (s, 6H, 2 CH₃), 1.18 (t, 3H, CH₃), 1.99-2.54 (m, 4H, 2 CH₂), 3.97-4.02 (m, 2H, CH₂), 4.78 (s, 1H, CH), 6.54-6.99 (dd, 4H, Ar-H), 8.73 (s, 1H, OH), 8.79 (broad, 1H, NH); ^1^C NMR (400 MHz, CDCl₃): δ 14.12, 18.22, 26.60, 29.17, 32.02, 34.86, 50.43, 58.75, 104.46, 110.56, 114.23, 128.30, 138.42, 144.01, 148.93, 155.02, 166.99, 194.30.; FT-IR (cm⁻¹): 3451, 3190, 2948, 2313, 1677, 1478, 1373, 1211, 1153, 1016, 839, 796; Mass (GC-MS): (m/z) M⁺ = 338.14

**Conclusions**

In summary, we have developed new methods of one-pot synthesis of polyhydroquinolines(PhQ) using ceria-molybdenum mix metal oxide catalyst to gives excellent yields. Ceria-molybdenum (CM) as a heterogeneous Lewis acid catalyst offers several advantages such as reusability without loss of catalytic activity up to three cycles, easy to separate, easy to handling. In the synthesis of catalyst and organic synthesis milder reaction condition, better yield, simple experimental procedure and easier work-up, is an environmental binge process, eco-friendly, less toxic catalyst as well as less corrosive, over all synthesis become a green synthesis.

**Supporting Information**

Full experimental detail, ^1^H and ^1^C NMR, Mass spectra and other information of this material can be found via the "Supplementary Content" section of this article’s webpage.

**Acknowledgments**

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