

Molecular Sieve Supported Lanthanum Catalyst for the Efficient Synthesis of Polyhydroquinolines via Hantzsch Synthesis

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RESEARCH ARTICLE

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Abstract

Molecular sieve supported lanthanum catalyst proved to be an efficient heterogeneous catalyst for the one-pot, four-component synthesis of polyhydroquinoline derivatives from aromatic aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in ethanol via Hantzsch reaction. The method has several advantages such as simple reaction conditions, short reaction time, high yields and simple workup procedure, which make it an attractive route for the synthesis of polyhydroquinolines. The catalyst could be reused several times without the loss of its initial activity.

Keywords

Lanthanum, polyhydroquinolines, Hantzsch reaction, multicomponent reaction, 4 Å molecular sieve, heterogeneous catalysis

1 Introduction

The synthesis of polyhydroquinolines (PHQ) is of considerable interest due to their significant pharmacological and biological properties. These heterocycles form important classes of Ca²⁺ channel blockers and constitute the skeleton of drugs used in the treatment of hypertension and cardiovascular diseases [1]. They also possess a wide range of biological activities including antibacterial, antifungal, antitubercular, antimalarial [2] and antitumor properties [3, 4]. These facts clearly reflect the remarkable pharmacological and medicinal potential of PHQs as drug candidates of therapeutic significance and as intermediates in organic synthesis.

During the past decades, multicomponent reactions (MCRs) became a valuable tool in synthetic organic chemistry because of their simplicity, efficiency, and high selectivity. These processes provide complex molecules in a single step and present several advantages, shorter reaction times, less side products, the simple technology results in lower energy consumption as well as waste production, thus leading to environmentally more friendly processes.

Hantzsch described the first method for the preparation of 1,4-dihydropyrimidines via the reaction of aldehydes with ethyl acetoacetate and ammonia in acetic acid or in refluxing alcohols [5]. However, the classical method suffers from disadvantages, such as high temperatures, long reaction times, harsh reaction conditions, and lower yields. Thus, chemists have been working on the elaboration of more efficient procedures for the synthesis of these valuable heterocycles.

In recent years, a number of modified methods have been developed and different catalysts have been explored among others bismuth(III) bromide [6], silicagel-supported polyphosphoric acid [7], nano-zirconia-supported sulfonic acid [8], boehmite silica sulfuric acid [9], organocatalysts [10, 11], ceric ammonium nitrate [12], La₂O₃/TFE [13], TiO₂ nanoparticles [14], Co₃O₄-CNT nano-composite [15], Fe₃O₄ nanoparticles [16, 17], Ni(0) nanoparticles [18], hafnium(IV) bis(perfluorooctanesulfonyl)imide complex [19], heteropolyacid [20], K10 montmorillonite [21], and MCM-41 [22]. Syntheses of PHQs have also been carried out in the presence of various

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ionic liquids as catalysts [23]. Their syntheses have also been reported under catalyst-free conditions, in refluxing water, but this method suffered from longer reaction times [24]. PHQs have also been synthesized under microwave irradiation conditions [25, 26]. However, many of the described methods suffer from disadvantages such as long and tedious preparation of the catalyst [17, 18], use of toxic and corrosive reagents [8, 9, 15, 19, 20], and the use of expensive materials as catalyst [10]. Thus, the development of a simple and efficient method for the preparation of polyhydroquinoline derivatives is still has a synthetic importance.

Heterogeneous catalysts offer several advantages over the homogeneous ones; they are easily separable from the reaction mixture by filtration, often reusable, more selective, non-toxic, non-corrosive, easy to handle, thus their use is more preferable from environmental point of view. As they are easily separable, the contamination of the product either by the catalyst (metal) or by the ligand usually necessary for the homogeneous catalysis can be avoided [27].

Our research group works on the development of new heterogeneous catalytic methods for the preparation of organic compounds using supported metal catalysts. During this work several metals, such as palladium, nickel, copper [28, 29], titanium [30] or lanthanum [31] on different supports (Mg:La 3:1 mixed oxide, 4 Å molecular sieve) were used successfully in different organic syntheses [32]. As the 4 Å molecular sieves are readily available [33] and beside of their good water binding ability, their slightly basic property might accelerate organic reactions, we developed several metal catalysts on 4 Å molecular sieve support.

In this paper we report a method for the one-pot four-component synthesis of polyhydroquinolines promoted by a heterogeneous, 4 Å molecular sieve supported lanthanum catalyst under mild basic conditions.

2 Results and Discussion

The structure of the La³⁺/4A catalyst was investigated by scanning electron microscopy (SEM). The characteristic cuboctahedron shape of the molecular sieve support can be seen on Fig. 1. The particles are well defined both in shape and size. The lanthanum is evenly distributed on the surface of the support [31]. EDS showed 3.65 w/w% lanthanum on the surface (Fig. 2). The lanthanum content determined by ICP-OES was 3.88 w/w%. The catalyst has slightly basic properties, its pH value is 8.40, while the pH value of the unmodified support is 10.42 (see Experimental). From the nitrogen adsorption/desorption measurements the specific surface of the catalyst is 35 m²/g.

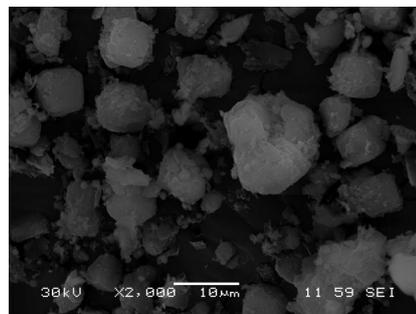
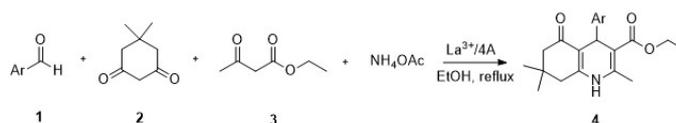


Fig. 1 SEM image of the catalyst

Thin Film Standardless Standard Quantitative Analysis					
Fitting Coefficient: 0.4815					
Element	(keV)	mass%	Counts	Error%	At%
Al K	1.486	27.16	5741.73	0.02	32.39
Si K (Ref.)	1.739	55.60	11717.19	0.01	63.71
La L	4.650	15.75	622.95	0.17	3.65
Au M	2.120	1.49	75.70	1.86	0.24
Total		100.00			100.00

Fig. 2 EDS analysis of the catalyst

We have developed a facile unsymmetric Hantzsch condensation in the presence of this heterogeneous lanthanum catalyst in refluxing ethanol using substituted aldehydes (**1**), dimedone (**2**), ethyl acetoacetate (**3**), and ammonium acetate to produce polyhydroquinoline derivatives (**4**) in high yields (Scheme 1).



Scheme 1 One-pot synthesis of polyhydroquinoline derivatives

The results are summarized in Table 1. As shown, a variety of benzaldehydes were successfully applied to prepare the corresponding polyhydroquinoline derivatives in high yields. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as alkoxy group) were tested in the reaction and gave the desired product in good to excellent yields. The lower yield in the case of **4b** may be explained by solubility problems. There was no significant steric effect observed, as *ortho*-, *meta*-, and *para*-derivatives gave results of the same order (see Table 1 entries 10-12). There is a difference between the observed melting point and the data found in the literature in the case of 2-fluorophenyl-derivative (**4f**), however the ¹H and ¹³C NMR spectra of the compound corresponds to the literary spectra and DSC showed only one sharp melting point.

The workup of the reaction mixtures was simple, the catalyst was filtered, washed with ethanol, then the filtrate was evaporated. The residue was diluted with diethyl ether; the precipitated solid was filtered and subjected to ¹H and ¹³C NMR spectroscopy. No side product was observed.

Although the reaction has been described generally with acidic catalysts, in our case the slightly basic heterogeneous catalyst gave good results. As the EDS measurement showed, the lanthanum is located on the surface of the support, forming potentially acidic sites. The reaction may happen on these parts of the catalysts. Meanwhile the bulk basic phase may help to avoid the potential disadvantageous, acid-catalysed side reactions or a possible decomposition if an acid-sensitive compound or functional group is present (e.g. 4-methoxybenzaldehyde [21]).

The reusability of the lanthanum catalyst was studied in the model reaction of 4-chloro-benzaldehyde (**1e**), dimedone (**2**), ethyl acetoacetate (**3**) and ammonium acetate in refluxing ethanol. After the reaction the solid was filtered and washed with ethanol, then heated at ca. 150 °C for 1 h. The catalyst has been reused in 2 more runs without considerable decrease in its activity; the isolated yields for the three successive runs were 96% each time, which clearly demonstrates the practical recyclability of this catalyst. Taking into account the same results obtained, we did not consider necessary to examine the reusability further.

In the literature we can find titanium catalysed examples for this synthesis (see e.g. Ref. 14), hence we tested our 4 Å molecular sieve supported titanium catalyst [30] in the model reaction of 4-chloro-benzaldehyde (**1e**), dimedone (**2**), ethyl acetoacetate (**3**) and ammonium acetate. The yield of the desired product **4e** was lower (80%) than using the lanthanum catalyst (96%; Table 1, entry 3).

Table 1 Synthesis of polyhydroquinolines catalysed by La³⁺/4A^a

Entry	Ar	Product	Yield (%) ^b	Mp (°C)
1	C ₆ H ₅	4a	99	216-217 (216-217 [34])
2	3-Br-C ₆ H ₄	4b	77	204.8° (202-204 [35])
3	4-Br-C ₆ H ₄	4c	93	255.1° (253-255 [19])
4	2-Cl-C ₆ H ₄	4d	85	212-214 (210-212 [22])
5	4-Cl-C ₆ H ₄	4e	96	241.7° (242-244 [36])
6	2-F-C ₆ H ₄	4f	95	228.3° (108-110 [24])
7	4-(CH ₃) ₂ N-C ₆ H ₄	4g	94	228.8° (229-232 [15])
8	3-CH ₃ O-C ₆ H ₄	4h	92	202-203 (202-204 [22])
9	4-CH ₃ O-C ₆ H ₄	4i	87	257.3° (258-260 [21])
10	2-NO ₂ -C ₆ H ₄	4j	86	204.2° (203-206 [36])
11	3-NO ₂ -C ₆ H ₄	4k	86	178-180 (179-181 [15])
12	4-NO ₂ -C ₆ H ₄	4l	83	186.9° (181-182 [26])

^a Reaction conditions: 1 mmol aldehyde, 1 mmol dimedone, 1 mmol ethyl acetoacetate, 1.5 mmol ammonium acetate, 0.1 g catalyst, 3 mL ethanol, reflux temperature, 4 h. ^b Isolated yields. ^c Determined by DSC.

3 Experimental Section

Morphology of the catalyst samples was investigated by a JEOL 6380LVa (JEOL, Tokyo, Japan) type scanning electron microscope and elemental mapping was also accomplished using the energy-dispersive X-ray detector of the equipment.

Each specimen was fixed by conductive double-sided carbon adhesive tape (using a JEOL 1200 instrument). Applied accelerating voltage and working distance were between 15 and 30 kV and 10 and 12 mm, respectively.

Nitrogen adsorption/desorption isotherms were measured at -196 °C with a computer controlled Nova 200e (Quantachrome) instrument. Transformation of the primary adsorption data was performed with the Quantachrome software. The apparent surface area (S_{BET}) was calculated using the Brunauer-Emmett-Teller (BET) model. Samples were evacuated for 24 h at 110 °C prior to the adsorption measurement.

GC-MS measurements were performed on an Agilent 6890 N-GC-5973 N-MSD chromatograph, using a 30 m x 0.25 mm Restek, Rtx-5SILMS column with a film layer of 0.25 µm. The initial temperature of column was 45 °C for 1 min, followed by programming at 10 °C/min up to 310 °C and a final period at 310 °C (isothermal) for 17 min. The temperature of the injector was 250 °C. The carrier gas was He and the operation mode was splitless.

¹H and ¹³C NMR spectra were made on BRUKER Avance-500 instrument using TMS as internal standard, in CDCl₃.

Melting points were determined on Gallenkamp apparatus and were uncorrected, or on SETARAM DSC 92 apparatus, where the initial temperature was 25 °C, followed by programming at 10 °C/min up to 300 °C under nitrogen atmosphere.

3.1 Preparation of the catalyst

4 Å molecular sieve (4A) was impregnated with La(NO₃)₃ x 6H₂O as follows: 1 mmol of the metal salt was dissolved in 100 mL of deionised water and stirred with 1 g 4A at room temperature for 24 h. The solid was filtered, washed with deionised water and with acetone, then dried in an oven at 150 °C for 1 h.

3.2 Determination of the pH of the catalyst

The catalyst (1 g) was stirred in 30 mL deionised water under continuous measuring of the pH. The values were accepted after reaching a constant value at least during 10 min.

3.3 Typical reaction conditions

A typical reaction was carried out in a 10 mL flask. Aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1.5 mmol), La³⁺/4A (0.1 g) and ethanol (3 mL) were stirred at reflux temperature for 4 h. The progression of the reaction was monitored by TLC. After completion, the solid was filtered, and washed with ethanol, then the filtrate was evaporated. The residue was suspended in diethyl ether, the precipitated solid was filtered and subjected to ¹H and ¹³C NMR spectroscopy.

All products have satisfactory spectral data (¹H and ¹³C NMR). The spectral data of the known compounds were identical with those reported in the literature. Representative physical and spectroscopic data of the products:

Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4a):

Yellow solid, Mp.: 216-217 °C, ¹H NMR (500 MHz, CDCl₃) δ (ppm): 0.93 (s, 3H), 1.06 (s, 3H), 1.20 (t, 3H), 2.17–2.28 (m, 4H), 2.35 (s, 3H), 4.05 (q, 2H), 5.05 (s, 1H), 6.37–6.43 (d, 1H), 7.19–7.29 (m, 5H). ¹³C NMR (500 MHz, CDCl₃) δ (ppm): 14.32, 19.43, 27.25, 29.55, 32.79, 36.71, 41.12, 50.85, 59.93, 106.17, 112.20, 126.13, 127.98, 128.12, 143.67, 147.16, 167.59, 195.77.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4e):

Yellow solid, Mp.: 241.70 °C, ¹H NMR (500 MHz, CDCl₃) δ (ppm): 0.92 (s, 3H), 1.07 (s, 3H), 1.19 (t, 3H), 2.13–2.34 (m, 4H), 2.37 (s, 3H), 4.05 (q, 2H), 5.02 (s, 1H), 6.16 (brs, 1H, NH), 7.16 (d, 2H), 7.24 (d, 2H). ¹³C NMR (500 MHz, CDCl₃) δ (ppm): 14.30, 19.51, 27.20, 29.52, 32.80, 36.33, 41.16, 50.78, 60.00, 105.84, 111.96, 128.08, 129.53, 131.69, 143.72, 145.66, 148.28, 167.29, 195.57. GC: t_r = 28.15 min; MS: m/z (%) = 373(M⁺-1), 344, 328, 300, 262 (100), 234, 178, 150, 77, 42.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(2-fluorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4f):

Yellow solid, Mp.: 228.29 °C, ¹H NMR (500 MHz, CDCl₃) δ (ppm): 0.93 (s, 3H), 1.06 (s, 3H), 1.19 (t, 3H), 2.12–2.14 (m, 4H), 2.29 (s, 3H), 4.03 (q, 2H), 5.23 (s, 1H), 6.53 (s, 1H), 6.89 (t, 1H), 6.98 (t, 1H), 7.07 (d, 1H), 7.35 (t, 1H). ¹³C NMR (500 MHz, CDCl₃) δ (ppm): 13.98, 19.16, 26.86, 29.39, 32.44, 32.54, 40.85, 50.57, 59.74, 104.42, 110.43, 115.09, 115.27, 123.33, 123.36, 127.60, 127.67, 131.35, 131.39, 144.01, 148.96, 167.39, 195.44. GC: t_r = 26.32 min; MS: m/z (%) = 357(M⁺-1), 328, 312, 284, 262 (100), 234, 178, 150, 133, 105, 77, 42.

Ethyl 2,7,7-Trimethyl-5-oxo-4-(3-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4k):

Yellow solid, Mp.: 178-180 °C, ¹H NMR (500 MHz, CDCl₃) δ (ppm): 0.93 (s, 3H), 1.08 (s, 3H), 1.20 (t, 3H), 2.08–2.28 (m, 4H), 2.38 (s, 3H), 4.06 (q, 2H), 5.16 (s, 1H), 6.63 (s, 1H), 7.38 (t, 1H), 7.72 (d, 1H), 7.98 (t, 1H), 8.12 (d, 1H). ¹³C NMR (500 MHz, CDCl₃) δ (ppm): 14.19, 19.40, 27.08, 29.37, 32.76, 37.00, 40.92, 50.58, 60.08, 105.08, 111.17, 121.28, 122.86, 128.59, 134.79, 144.54, 148.27, 149.08, 149.24, 166.94, 195.57.

4 Conclusions

In conclusion, lanthanum on 4 Å molecular sieve support proved to be useful catalyst for the one-pot, four-component synthesis of polyhydroquinolines under mild conditions, using slightly basic heterogeneous catalyst, which is almost unprecedented in the literature. The catalyst could be prepared simply and can be reused with good result without the loss of activity.

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