

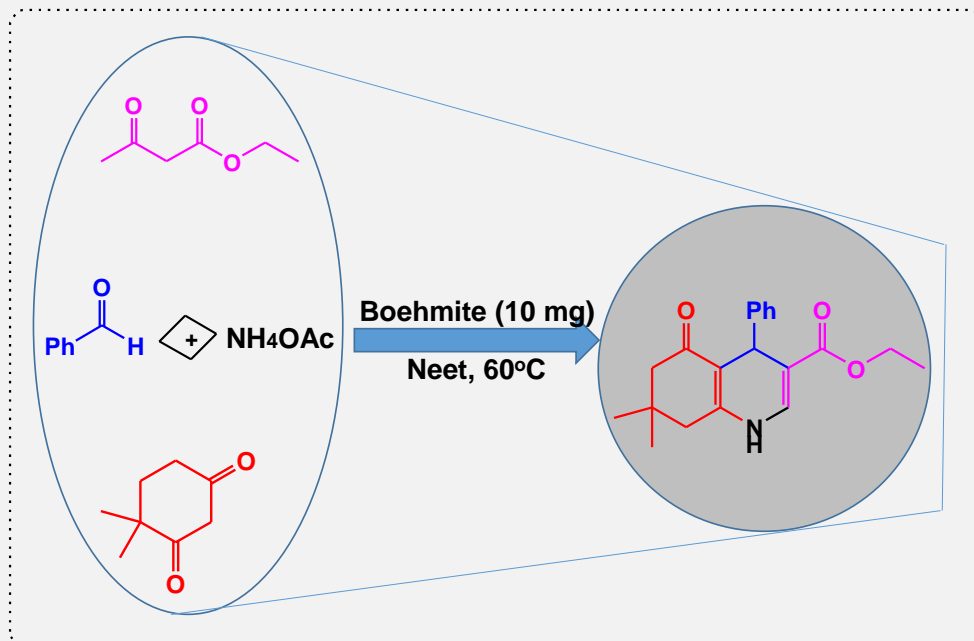
Synthesis of Polyhydroquinoline Derivatives in the Presence of Nanoboehmite by Hantzsch Reaction

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ABSTRACT: Polyhydroquinolines are drugs with various biological properties, including calcium channel blocker, antitumor, antidiabetic, and heart and blood vessel dilator. In this research, various derivatives of polyhydroquinolines were synthesized using nanoboehmite as a catalyst. From the partial reaction of ammonium acetate with aromatic aldehydes, ethyl acetoacetate and dimedone in the presence of nanoboehmite as a catalyst in solvent-free conditions and at temperature of 60 poly derivatives Substituted hydroquinolines were synthesized in short times with excellent yields. The catalyst used is non-toxic and cheap. The structure of the synthesized compounds was confirmed using spectroscopic data. The characteristics of this method are high yield, simple and mild reaction conditions, single container, no need for solvent, use of non-toxic materials, cheap and compatible with the environment and easy separation of the products.



KEYWORDS: Four Component Reaction, Polyhydroquinolines, Antidiabetic, Nanoboehmite, Solvent free.

Introduction

In traditional organic synthesis, bonds are formed step by step [1]. This method often requires the separation and purification of intermediates and changing the reaction conditions for the next step of synthesis [2]. But ideally, a target molecule is prepared from readily available starting materials in a

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simple, safe, rapid, and environmentally friendly operation, quickly and with reasonable yield. In the past decades, many research groups have been looking for new synthetic methods that, along with the complexity of the synthesized compounds, reduce the number of steps and increase the reaction efficiency [3]. One of the most efficient strategies to achieve this goal is the use and development of multicomponent reactions [4]. Multicomponent reactions are a special and very elegant way to access complex structures, which are performed using two or more reactants [5]. High atomic efficiency, high synthetic efficiency, easy methods of creating new multiple bonds in one-pot reactions are the advantages of multicomponent reactions [6]. The multicomponent reaction has attracted the attention of scientists due to its high efficiency, the production of diverse molecules, the production of products with diverse functional groups, and the possibility of producing products with medicinal properties [7]. These reactions satisfy many of the principles of green chemistry, such as performing the reaction in solvent-free conditions or reactions in which water is used as a solvent. So, multicomponent reactions can be introduced as one of the best strategies to achieve ideal synthesis [8]. Nowadays, multi-component reactions occupy a large part of the activities of research units [9]. In the oldest and most extensive multicomponent reactions, amines and carbonyls have been used as two key compounds [10]. In fact, many multicomponent reactions are based on the combination of an amine, a carbonyl compound, and a third nucleophilic component. Strecker reaction can be introduced as the first multicomponent reaction [11]. In this reaction, cyanide ion acts as a nucleophile and leads to the formation of α -aminonitrile. Multicomponent reactions can be based on the formation of enolates as a nucleophile component. Among the multi-component reactions that are performed using different enolate derivatives, we can mention Hantzsch, Biginelli, Mannich and Yogi reactions [12]. Of interest in many of these multicomponent reactions is the ability to undergo irreversible addition of the nucleophile to the carbonyl moiety, producing carbonyl adducts [13]. Among the features that distinguish multicomponent reactions from other reactions, the following can be mentioned:

- 1- In the technique of multicomponent reactions, useful and valuable complex structures are synthesized very quickly, efficiently and effectively, and with little time, without the need to separate intermediates [14].
- 2- By reducing the synthesis steps compared to traditional methods, the reaction is carried out with greater speed and efficiency.
- 3- By changing the components of the old multi-component reactions, new multi-component reactions are designed with various products [15].
- 4- The amount of waste and wastage of products has been minimized and energy, time and raw materials can be saved to achieve the maximum benefit of synthetic products [16].

Polyhydroquinolines, which are structurally related to 1,4-dihydropyridines, are another important group of nitrogen-containing heterocycles that have received attention due to their medicinal activity [17]. These substances have many biological activities that can be mentioned as anti-tumor, vasodilator, anti-fertility, anti-bacterial, anti-allergic, anti-cancer, anti-fungal and anti-hypertensive properties [18]. Today, a number of quinoline antibacterial compounds are widely used to treat infectious diseases. Also, for quinolines with specific functional groups, applications in medicine, agricultural chemistry and also in the

preparation of new alkaloids have been identified [19,20]. Considering the biological importance of polyhydroquinolines, several methods for their synthesis have been reported [21]. The classical method involves the quaternary coupling of an aldehyde with ethyl acetoacetate, dimedone, and ammonia in boiling acetic acid or alcohol [22]. But these methods have drawbacks such as long reaction time, use of excess amount of organic solvent and low yield of products [23]. Recently, many advances have been reported in the field of synthesis of polyhydroquinolines, which include advantages such as solvent-free reaction, high efficiency, and mild reaction conditions [24,25].

A review of scientific literature shows that many catalysts have been used in the Hantzsch reaction for the synthesis of polyhydroquinolines. But each of the above methods has disadvantages. In this project, various derivatives of substituted polyhydroquinolines in positions 2, 3, 4, 5 and 7 of the reaction of aromatic aldehydes, dimedone or cyclohexadione, β -ketoester and ammonium acetate in the presence of a nano-boehmite catalyst were obtained under solvent-free conditions at 60 °C above were synthesized

■ Results and Discussion

Due to their diverse biological properties, polyhydroquinolines are widely used in the pharmaceutical industry and are used in the synthesis of various anti-cancer, anti-diabetic, cardiovascular and blood pressure drugs. Therefore, due to the importance of the use of these compounds, it is necessary to provide new synthetic methods and synthesis of new derivatives from them. The review of scientific literature shows that the most traditional method for the synthesis of polyhydroquinolines is the reaction of β -ketoesters with aldehyde, ammonium acetate, and dimedone or cyclohexadione in the presence of a nanoboehmite catalyst. This method can be used exclusively for the synthesis of polyhydroquinolines with substitutions in positions 2, 3, 4, 5 and 7. Many methods have been reported for the synthesis of these compounds. But due to the widespread use of these compounds, scientists are looking for better, practical and less expensive methods. The FT-IR spectrum of the polyhydroquinoline compound taken as a KBr tablet is shown in **Figure 1**. In the IR spectrum of this compound, which was taken in the form of a KBr tablet, the appearance of the absorption peak of NH group at $3390\text{-}^1\text{cm}$, the absorption peak of C=O groups at $1705\text{-}^1\text{cm}$ corresponding to the ester group and $1650\text{-}^1\text{cm}$ corresponding to the ketone group confirms the reaction.

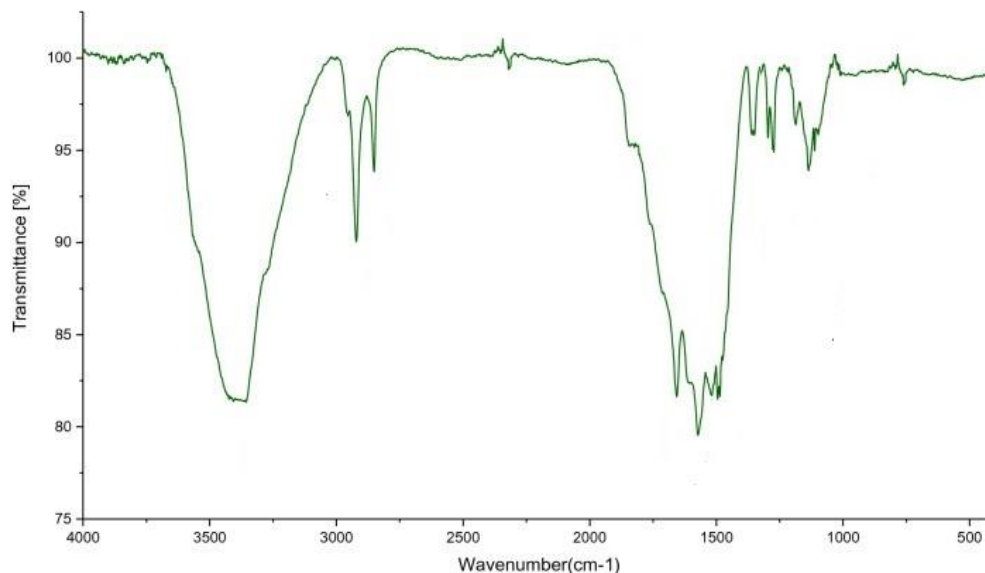


Figure 1. FT-IR spectra for polyhydroquinoline compound.

To optimize the reaction conditions, the reaction of benzaldehyde, ammonium acetate, ethylacetoacetate and dimedone was used as the base reaction. In this reaction, the effects of variables such as the amount of catalyst, temperature, the amount of ammonium acetate and the effect of solvents on the reaction yield were investigated. The results of the reactions are shown in **Table 1**. The best benefit of the reaction is related to the use of 10 mg of Tatu Boehmite at a temperature of 60 °C. **Table 1** shows that 5, 10 and 15 mg of nanobohemite were used. By increasing the amount of catalyst up to 10 mg. The reaction yield increases up to 98%, when the amount of catalyst reaches 15 mg, the reaction yield decreases slightly (93%). The effect of temperature is very important. At room temperature, the reaction time is long (60 min), but at higher temperatures, up to 60 °C, the time decreases drastically (30 min). As can be seen, changing the amount of ammonium acetate has no significant effect on the reaction yield. Also, by examining the effects of the solvent, it was found that the nanobohemite catalyst in the solvent does not work well for this reaction and the reaction time is high and the product efficiency is low.

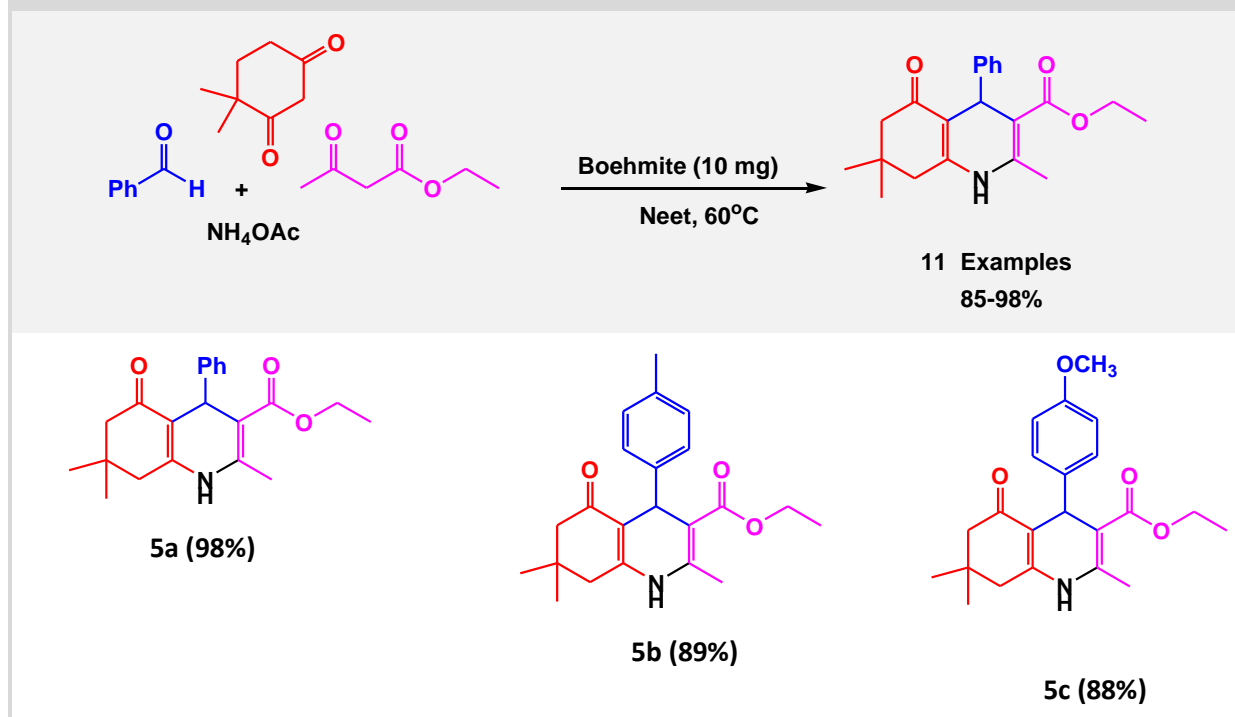
Table 1. Optimizing reaction conditions for polyhydroquinoline synthesis^a

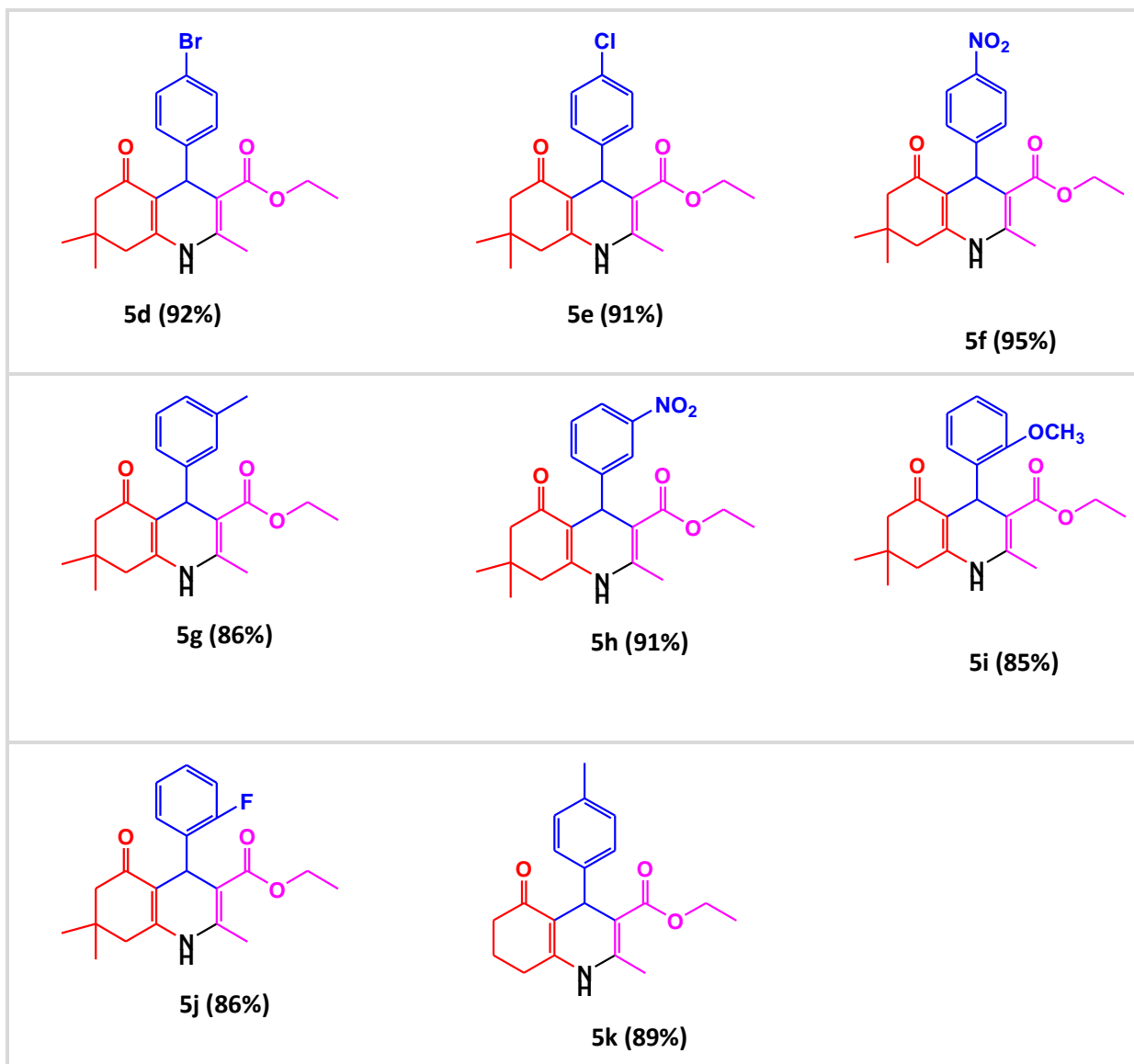
Entry	Catalyst (mg%)	Solvent	Temp (°C)	Yield (%) ^a

1	--	Neat	80	No
2	5	Neat	60	69
3	10	Neat	60	98
4	15	Neat	60	93
5	10	Neat	80	97
6	10	DMF	60	67
7	10	H ₂ O	60	71
8	10	THF	60	52
9	10	MeOH/H ₂ O	60	37
10	10	CHCl ₃	60	49
11	10	MeOH	60	80
12	10	DMSO	60	61
13	10	Neat	----	29
14	10	Neat	40	62

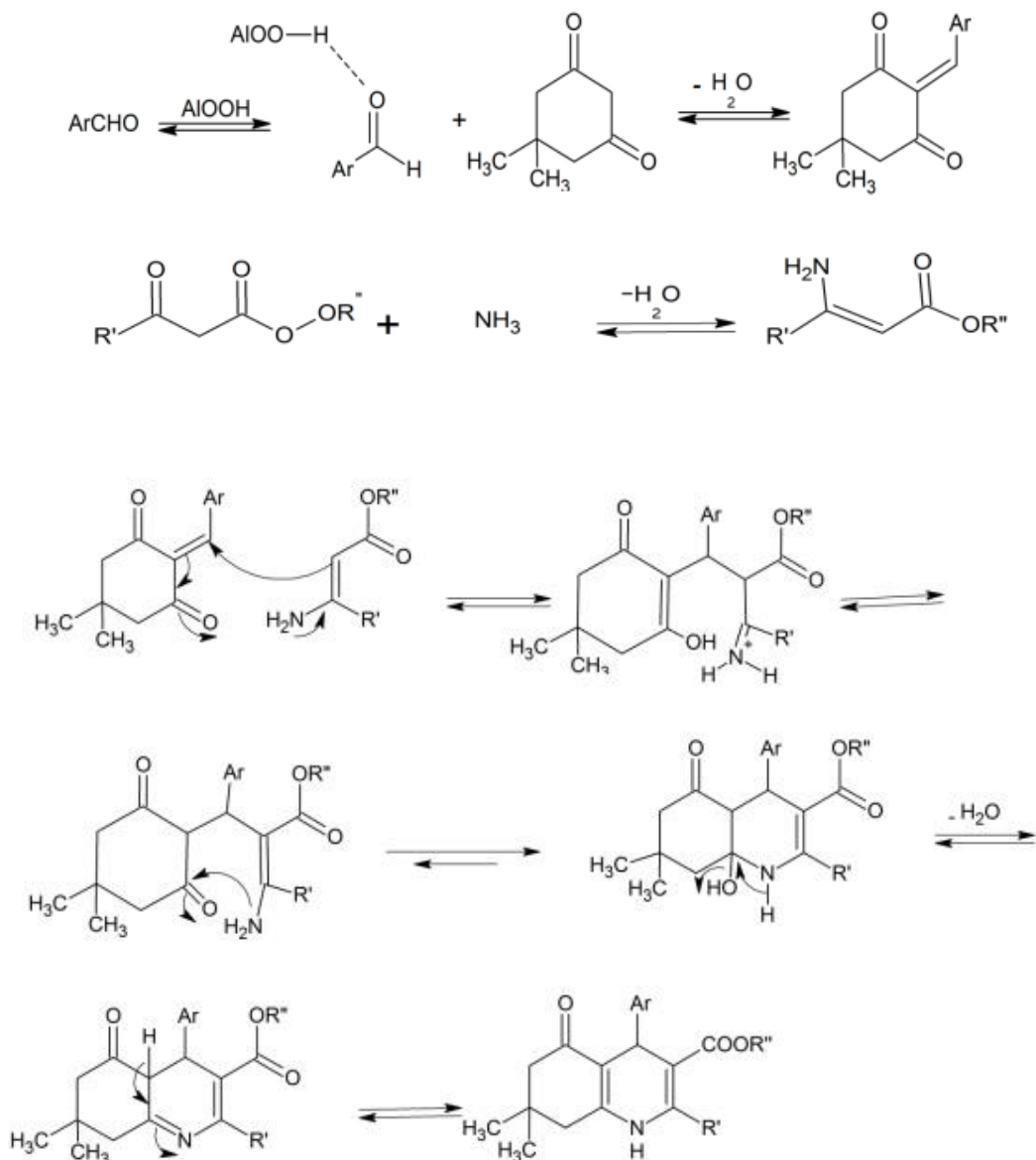
The reaction of various benzaldehydes with dimedone, 3,1-cyclohexadione, ethylacetate and ammoniumacetate in solvent-free conditions and the amount of 10 mg catalyst at 60 °C was carried out and various derivatives of substituted polyhydroquinolines were obtained in different positions. The above was synthesized. The results are shown in **Table 2**. As can be seen in the table, both aldehydes with electron-withdrawing groups such as: Cl, Br, F and aldehydes with electron-donating groups such as: CH₃ and OCH₃ react well, but when the electron-withdrawing group in There is a para-aldehyde position, the yield of the reaction is higher.

Table 2. Reaction yield of substituted polyhydroquinoline derivatives ^a





The proposed mechanism of this reaction is a two-step mechanism in which nanoboehmite plays the role of Brønsted acid due to having a large number of OH groups on its surface. The first intermediate of this reaction is the Konevonagel condensation product, which is formed from the reaction of aldehyde with dimedone. The second intermediate of this reaction is the enamine ester, which is formed by condensation of β -ketoester with ammonia. Further condensation of these two intermediates leads to the preparation of polyquinolines as shown in **scheme 1**.



Scheme 1. Plausible mechanism.

Conclusion

In this research work, we succeeded in synthesizing different derivatives of polyhydroquinoline from the reaction of aromatic aldehydes with dimedone or cyclohexadione, ammonium acetate, ethyl acetoacetate using nanoboehmite catalyst. Among the features of this method, the following can be mentioned:

1- The one-pot reaction, in which there is no need to separate intermediates and carry out the reaction in the next stages, which leads to a decrease in the yield of the reaction.

2- Performing the reaction in solvent-free conditions, organic solvents are toxic and destructive to the environment.

3- Due to the simplicity and mildness of the reaction conditions, there is no need to use destructive acid catalysts.

4- Use of nano boehmite catalyst, which is non-toxic and environmentally friendly.

5- High gain of reaction

6- Short reaction time

■ Experimental

Chemical raw materials were purchased from Akros and Merck commercial companies and were used without purification. Nuclear Magnetic Resonance (NMR) ^1H (80) was performed by Bruker spectrophotometer. The nuclear magnetic resonance multiplicity is specified as single (s), multiple (m). From (TMS) has been used as an internal standard. Infrared (IR) spectra were recorded using a Shimadzu 470 IR spectrometer. The spectra of the compounds were taken in the form of KBr tablets. The melting points of the compounds were measured using the Bamstead/Electrothermal device.

Conventional sol-gel processing

0.25 M solution of metal alkoxide in parent alcohol was prepared and then hydrolyzed with a 10% solution of deionized water in parent alcohol under vigorous stirring at ambient temperature. The product was filtered off and dried overnight at 100°C and stored for analysis.

Hydrothermally assisted sol-gel processing

For the hydrothermally assisted sol-gel processing, metal alkoxides were diluted to various concentrations with parent alcohol, the mixture was loaded into a glass container and transferred into a 300 ml stainless steel autoclave. Dilution of metal alkoxides was carried out in Schlenk line, and their transfer into autoclave was performed in moisture-free atmosphere to prevent their hydrolysis before introducing into a hydrothermal chamber. The gap between glass container and chamber was filled with 50 ml of distilled water and then the autoclave was tightly closed. The chamber was heated at various temperatures. After five to twenty four hours, the autoclave was cooled and the product was filtered off and dried overnight at 100°C.

Synthesis of nanoboehmite

The nanoboehmite used in the synthesis of polyhydroquinolines was prepared by the cell-gel method from the hydrolysis of aluminum-2-butoxide. The size of the obtained particles was 5-10 nm and its specific surface area was 326 m²/g.

General method for the synthesis of polyhydroquinolines in the presence of nanoboehmite

10 mg of catalyst was added to a mixture of aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (2.1 mmol), and the reaction mixture was heated at 60 °C for a certain

period of time in the absence of the solvent was stirred. The progress of the reaction was checked by thin layer chromatography. After the end of the reaction, the catalyst was separated from the reaction mixture and washed with ethanol. Then the solvent was evaporated and the pure product was obtained with a good yield.

Supporting Information

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

Pale yellow solid, mp = 245 – 247 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.24 (dd, J = 7.0, 3.2 Hz, 2H), 7.16 (dd, J = 4.5, 3.0 Hz, 2H), 6.20 (br, 1H), 5.02 (s, 1H), 4.07–4.03 (m, 2H), 2.36 (s, 3H), 2.33–2.16 (m, 4H), 1.20–1.16 (t, J = 7.0 Hz, 14.0 Hz, 3H), 1.06 (s, 3H), 0.92 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 195.7, 167.1, 148.9, 145.3, 143.6, 131.2, 129.8, 128.3, 110.9, 105.5, 59.7, 51.0, 41.3, 36.4, 32.1, 29.5, 27.8, 19.6, 14.4.

Ethyl 4-(2-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-3-carboxylate (5j):

White solid, mp = 209 – 211 °C ¹H NMR (500 MHz, CDCl₃) δ 7.39 (dd, J = 8.0, 4.1 Hz, 1H), 7.24 (dd, J = 8.0, 2.0 Hz, 1H), 7.13–7.10 (m, 1H), 7.03–7.00 (m, 1H), 6.58 (br, 1H), 5.38 (s, 1H), 4.07–4.00 (m, 2H), 2.26 (s, 3H), 2.21–2.12 (m, 3H), 1.18–1.15 (t, J = 7.0 Hz, 14.0 Hz, 3H), 1.05 (s, 3H), 0.93 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 196.3, 195.4, 167.9, 167.4, 163.2, 159.2, 136.7, 133.5, 132.4, 132.1, 129.6, 129.3, 128.2, 128.0, 127.6, 126.3, 111.2, 105.7, 61.0, 59.7, 41.3, 36.4, 32.1, 32.0, 29.8, 29.4, 28.5, 27.4, 27.1, 19.2, 14.6, 13.2.

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Copies of NMR spectra of synthesized compounds:

