Silica-supported Alginic Acid-L-Glutamic Acid: An Efficient Heterogeneous Catalyst for Solvent-free Synthesis of 1,8-Dioxohexahydroacridine and Polyhydroquinoline Derivatives

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Abstract

The classical Hantzsch reaction is one of the simplest and most economical methods for the synthesis of biologically important and pharmacologically useful 1,4-dihydropyridine derivatives. Silica-supported alginic acid-L-glutamic acid (SiO2-AA-L-Glu) under thermal and solvent free conditions is proven to act as a highly efficient catalyst for a one-pot four component reaction of various aldehydes, ammonium acetate, cyclic 1,3-dicarbonyl compounds and ethyl acetoacetate for the synthesis of biologically active substituted Hantzsch 1,8-dioxohexahydroacridine and polyhydroquinoline derivatives in excellent yields. The present environmentally benign procedure for the synthesis of 1,4-dihydropyridines is suitable for library synthesis and it will find application in the synthesis of potent biologically active molecules. The process presented here is operationally simple, environmentally benign and has excellent yield with short reaction time and straightforward workup. Furthermore, the catalyst can be recovered conveniently and reused efficiently.

Keywords: Silica-supported Alginic Acid-L-Glutamic Acid, Heterogeneous Catalyst, 1,8-Dioxohexahydroacridine, Polyhydroquinoline, solvent free

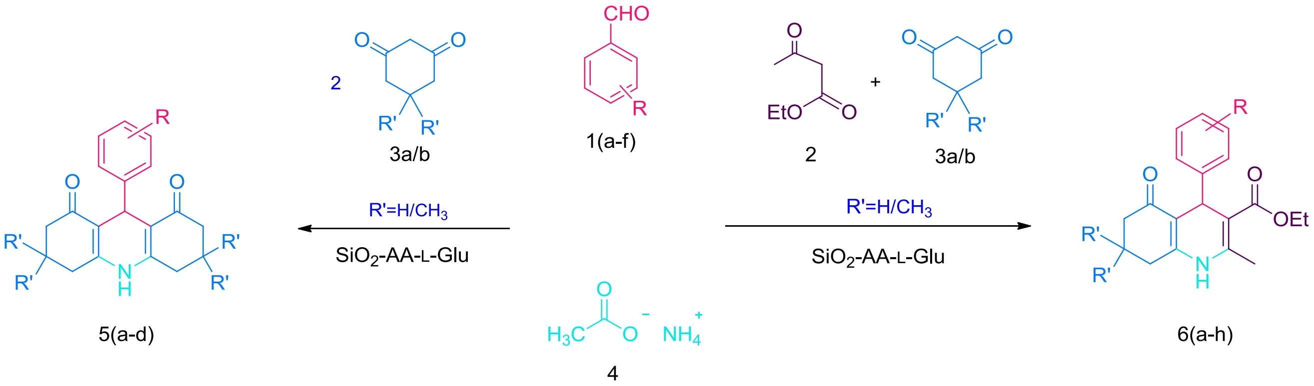
Introduction

4-Substituted 1,4-dihydropyridine (1,4-DHP) nucleus is a fertile source of biologically important molecules possessing various important pharmacological properties such as biological and pharmacological properties such as vasodilator and bronchodilator [1], geroprotective [2], antitumor [3], antihypertensive [4], neuroprotectant [5] and cerebral antischemic activity in the treatment of Alzheimer's disease [6]. Thus, these compounds are analogues of NADH coenzymes, which have been investigated for their calcium channel activity and the heterocyclic rings are found in variety of bioactive compounds [7]. In 1882, Arthur Hantzsch [8] reported the first synthesis of symmetrical substituted 1,4-dihydropyridines via multi-component condensation of aldehyde, ethylacetoacetate and ammonia in acetic acid or refluxing alcohol.

The utilization of cyclic 1,3-diketone in Hantzsch reaction for the synthesis of polyhydroquinoline and 1,8-dioxohexahydroacridine was recently demonstrated by using molecular iodine [9], ionic liquids [10,11], iodotrimethylsilane (TMSI) [12], organocatalysts [13-15], microwave irradiation [16], HY-zeolite [17], p-TSA [18], montmorillonite K10 clay [19], hafnium (IV) bis(perfluorooctanesulfonyl)imide complex $[Hf(NPf_2)_4]$ [20], scolecite [21], 5-pyrrolidine-2-yltetrazole [22], ceric ammonium nitrate (CAN) [23,24], and silica sulfuric acid [25]. However, many of these methodologies have been associated with several shortcomings such as requirement of long reaction times, use of expensive reagents and harsh reaction conditions. Similarly, the difficulties such as low product yields, occurrence of several by-products and recovery of the catalyst are encountered. Therefore, it was thought that there is room for improvement especially towards developing a green protocol for synthesis of 1,8-dioxohexahydroacridine and polyhydroquinolines at ambient temperature.

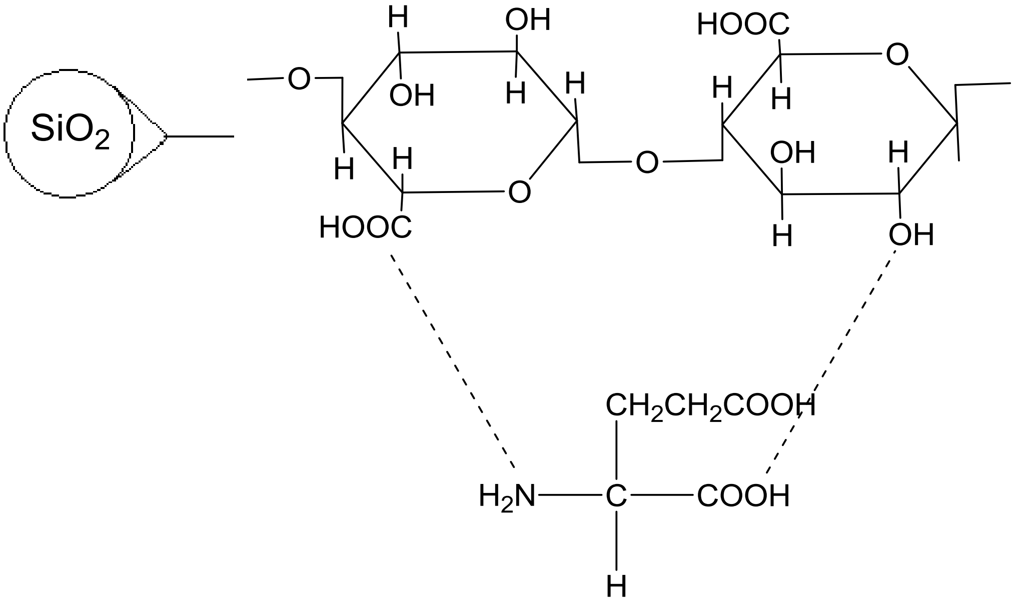
Result and discussion

In continuation with our research devoted to the development of green organic chemistry herein, we report herein a facile and efficient synthesis of this derivatives via a one-pot, four-component Hantszch condensation of 1,3-dicarbonyl compound, aldehydes, ethyl acetoacetate and ammonium acetate using a catalytic amount of SiO2-AA-L-Glu as a new, heterogeneous and essential catalyst under solvent-free conditions at 100 °C (scheme 1).



Scheme 1. Hantzsch synthesis of polyhydroquinoline and 1,8-dioxohexahy droacridine derivatives catalyzed by SiO_2-AA-L-Glu under solvent-free conditions

In recent years heterogeneous catalysts have attracted a great attention due to efficiency, and for economic and environmental reasons. In the green chemistry context, replacement of homogeneous catalysts with heterogeneous ones for the productions of fine chemicals in industrial processes appears as expansive research area [26-28]. Silica-supported Alginic Acid-L-Glutamic Acid (scheme 2) has been prepared by a simple method to act as a very efficient and reusable catalyst for the synthesis of biologically active substituted Hantzsch derivatives. The IR spectrum of the catalyst showed the characteristic absorption of acid (O–H) groups at 3445 cm^{-1}, carbonyl groups at 1627 cm^{-1} and Si-O-Si at 1097 cm^{-1} (Figure 1).



Scheme 2. Structure of Silica-supported Alginic Acid-L-Glutamic Acid

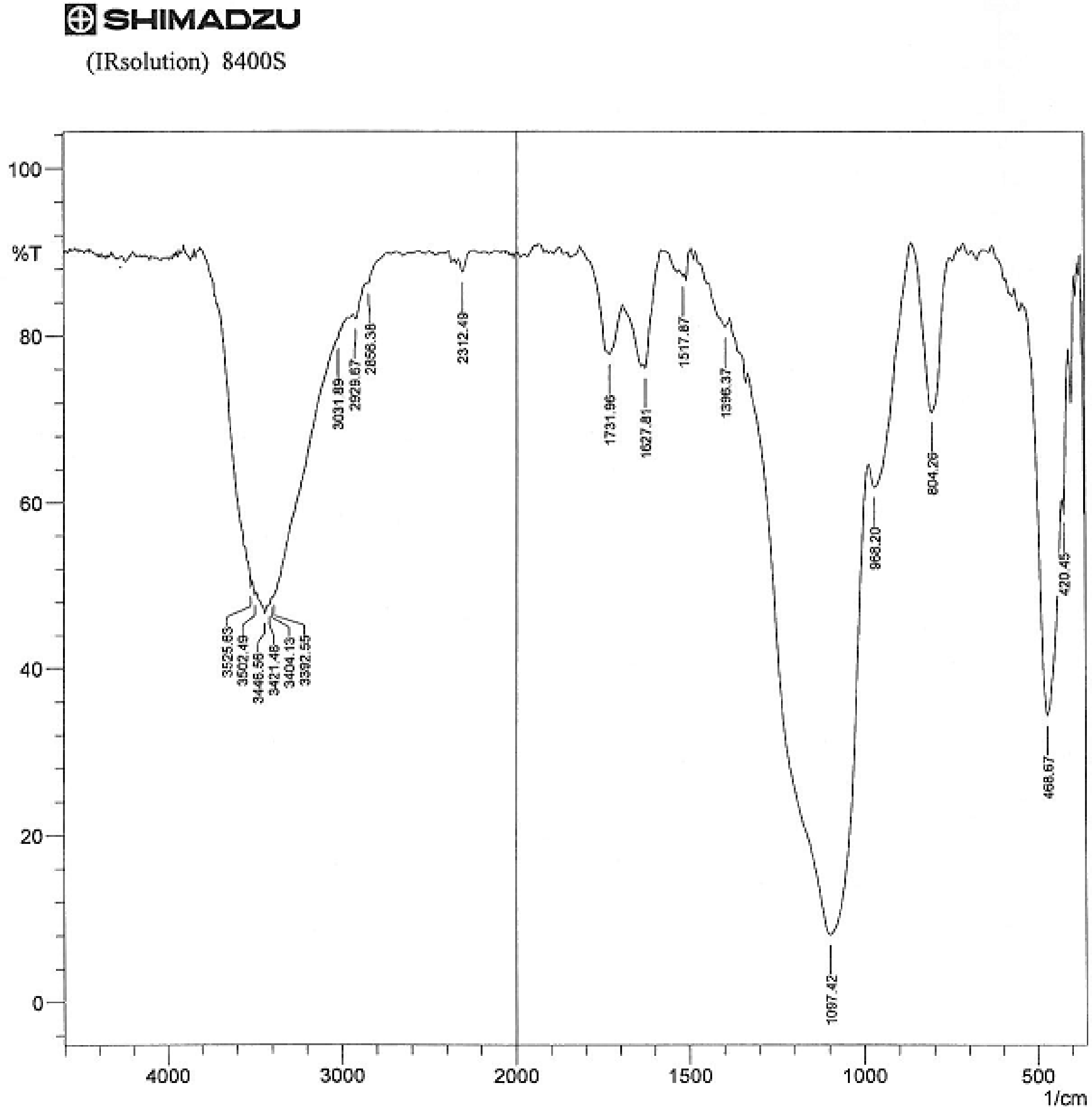
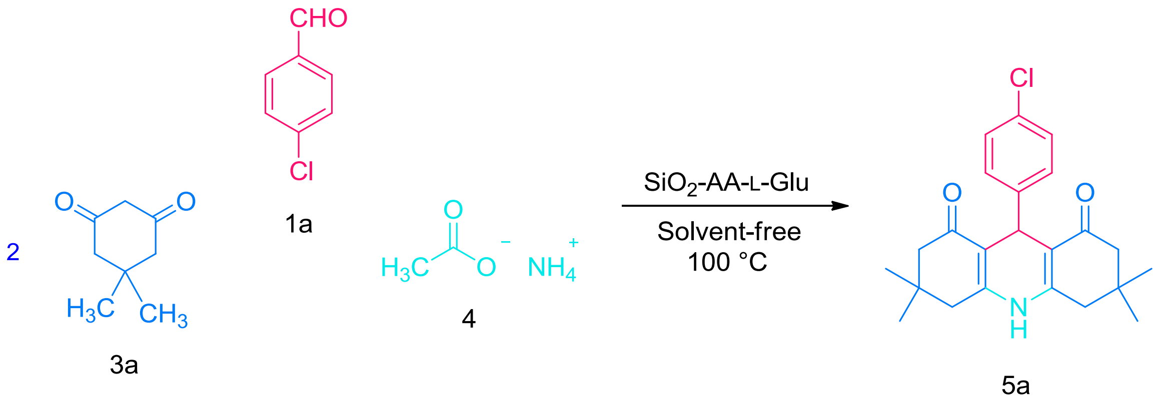


Figure 1. IR spectrum of Silica-supported Alginic Acid-L-Glutamic Acid (cm^{-1}).

To find the best reaction conditions, the one pot four-component condensation reaction of 4-chlorobenzaldehyde (**1a**, 1mmol), dimedone (**3a**, 2mmol) and ammonium acetate (1.5mmol) was examined under various reaction conditions. Initially, the effect of the solvent, catalyst and temperature was tested. According to the obtained results (Table 1), 5mg SiO2-AA-L-Glu under solvent-free condition at 100 °C, as optimized conditions (entry 11, Table 1), was developed to other aromatic aldehydes.

Table 1. Optimization conditions for the synthesis of (**5a**)[a].

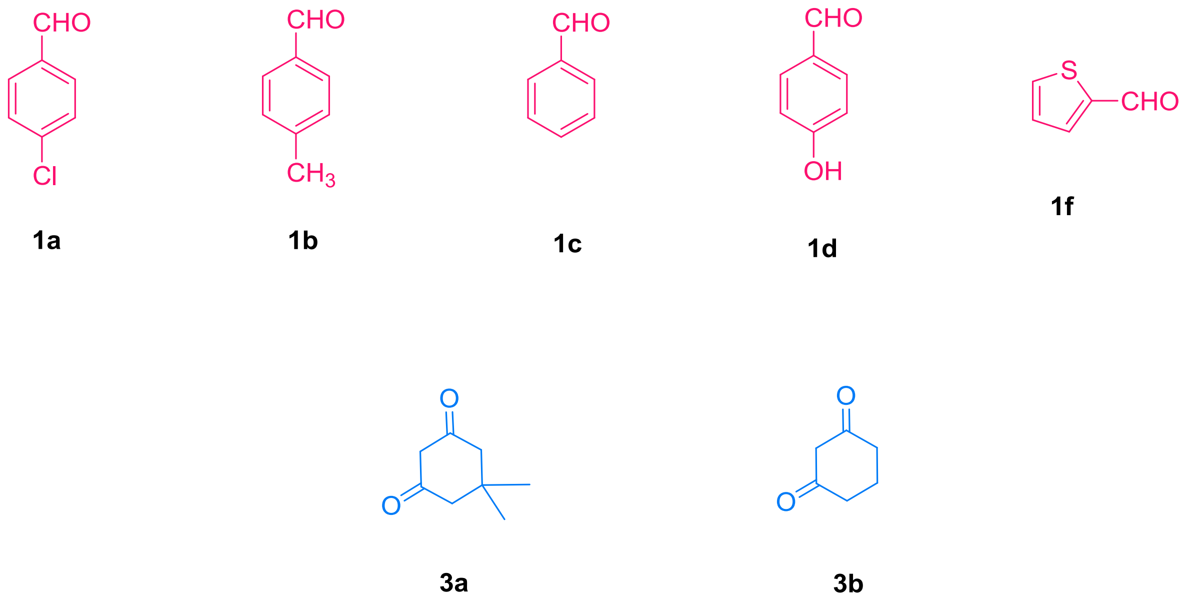


Entry	catalyst	Amount of Catalyst (mg)	Solvent	Temp (°C)	Time (min)	Yield[b] (%)
1	-	-	H_2O	Reflux	60	Trace
2	-	-	EtOH	Reflux	60	Trace
3	L-proline	5	EtOH	Reflux	30	63
4	ZnO	5	EtOH	Reflux	30	75
5	CuO	5	EtOH	Reflux	30	77
6	SiO_2-AA-L-Glu	5	EtOH	Reflux	30	85
7	SiO_2-AA-L-Glu	5	H_2O	Reflux	30	78
8	SiO_2-AA-L-Glu	5	EtOH	r.t	45	65
9	SiO_2-AA-L-Glu	5	-	r.t	30	60
10	SiO_2-AA-L-Glu	5	-	70	20	75
11	SiO_2-AA-L-Glu	5	-	100	10	92
12	SiO_2-AA-L-Glu	3	-	100	10	87
13	SiO_2-AA-L-Glu	1	-	100	10	85

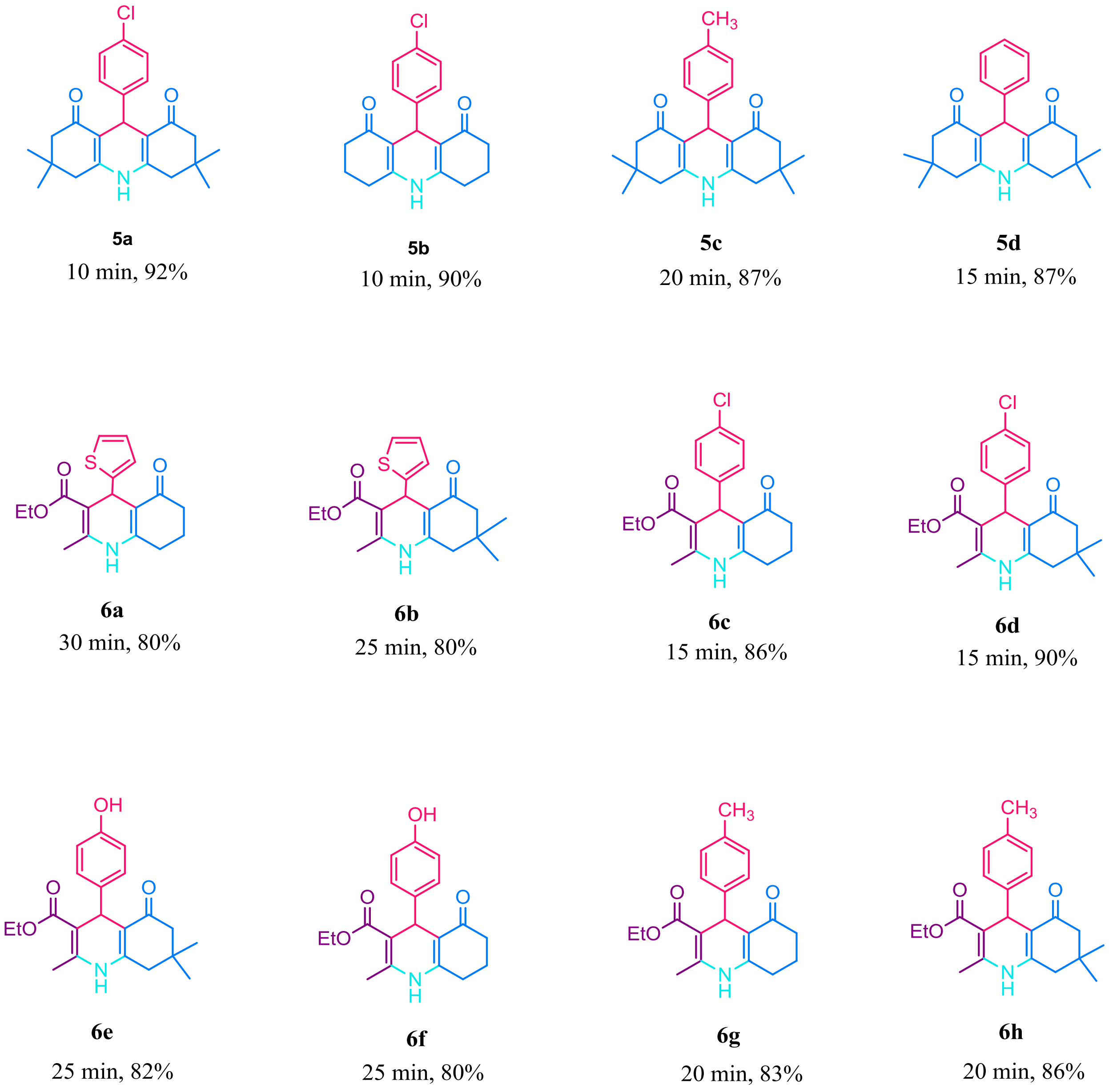
[a] Reaction conditions: 4-chlorobenzaldehyde (1mmol), dimedone (2mmol) and ammonium acetate (1.5mmol) for 5a

[b] The yields refer to the isolated product.

To explore the scope and generality of the present method, different aromatic aldehydes and 1,3-dicarbonyle compounds (Scheme 3) were tested under the optimized reaction conditions to furnish the corresponding products (**5a-d**) and (**6a-h**) in good yields. The results are summarized in Scheme 4.



Scheme 3. Different aldehydes (**1a-f**) and cyclic 1,3-dicarbonyl compounds (**3a,3b**) examined in the Hantzsch MCR



5a
10 min, 92%

5b
10 min, 90%

5c
20 min, 87%

5d
15 min, 87%

6a
30 min, 80%

6b
25 min, 80%

6c
15 min, 86%

6d
15 min, 90%

6e
25 min, 82%

6f
25 min, 80%

6g
20 min, 83%

6h
20 min, 86%

Scheme 4. Four-component synthesis of different 1,8-dioxohexahydroacridine(**5a-d**) and polyhydroquinoline(**6a-h**) derivatives catalysed by SiO_2-AA-L-Glu under solvent-free conditions.

Experimental

Instruments and characterization:

All chemicals were purchased from Merck, Fluka and Sigma-Aldrich companies and were used without further purification, except for benzaldehyde, which was used as a fresh distilled sample. Analytical thin layer chromatography (TLC) for monitoring reactions was performed using Merck 0.2 mm silica gel 60 F-254 Al-plates using ethyl acetate and n-hexane as eluents. Melting points were determined in open capillaries using an Electrothermal 9100 instrument. Infrared (IR) spectra were acquired on a Shimadzu FT-IR-8400S spectrometer. All yields refer to the isolated products.

Preparation of SiO_2-AA-L-Glu:

In a beaker, 1 g of sodium alginate was dissolved in 20 ml of water, and 1 g of L-glutamic acid was dissolved in 10 ml of water in another beaker. Then the L-glutamic acid aqueous solution and sodium alginate aqueous solution were mixed together. After that, 3 g of silica was added to the mixture, and mixed to form a paste. Then drop by drop 3 ml of 1 M HCl aqueous solution was added to the paste to form a sediment. The sediment was heated slowly to evaporate water and milled. Then washed with water until the water became neutral. After drying and powdering, about 4.8 g of a white fine powder, SiO_2-AA-L-Glu was obtained.

General procedure for the synthesis of 1,8-dioxohexahydroacridine and polyhydroquinoline derivatives:

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol for polyhydroquinoline), dimedone/1.3-cyclohexanedione (2 mmol for 1,8-dioxohexahydroacridine or 1 mmol for polyhydroquinoline) and ammonium acetate (1.5 mmol) and SiO2-AA-L-Glu (5 mg) was heated on a oil bath at 100°C . The reaction progress was monitored by TLC. After completion of the reaction appropriate amount of hot EtOH (96%) was added and the mixture stirred for 10 min. After that, the catalyst was separated by filtration. Eventually, the solvent was evaporated under vacuum to furnish a solid which was recrystallized from ethyl acetate-hexane.

conclusion

In summary, we have reported that four-component Hantzsch condensation reaction can effectively be performed using silica-supported alginic acid-L-glutamic acid as a highly efficient and green catalyst for the synthesis of polyhydroquinoline and 1,8-dioxohexahydroacridine derivatives under solvent-free conditions and produced the corresponding products in good yields. The procedure offers several advantages including shorter reaction times, mild and solvent-free conditions, cleaner reactions, use of noncorrosive and non-toxic catalyst, high yields of the products, and simple isolation procedures.

Acknowledgements

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