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ONE-POT SYNTHESIS OF HANTZSCH ESTERS AND POLYHYDROQUINOLINE DERIVATIVES CATALYZED BY γ-Al_2O_3-NANOPARTICLES UNDER SOLVENT-FREE THERMAL CONDITIONS

Ali Reza KIASAT,* Hossein ALMASI and Seyyed Jafar SAGHANEZHAD

Chemistry Department, College of Science, Shahid Chamran University, Ahvaz 61357-4-3169, Iran

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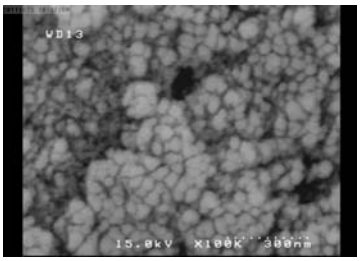
γ-Alumina nanoparticles are used as an effective and reusable catalyst for one-pot synthesis of 1,4-dihydropyridine and polyhydroquinoline derivatives via multicomponent Hantzsch reaction at 90 °C under solvent-free conditions. A broad range of structurally diverse aldehydes were applied successfully, and corresponding products were obtained in high yields without any byproduct. Compared with other methods, satisfactory results are obtained with high yields, short reaction times, and simplicity in the experimental procedure. The catalyst could easily be recycled and reused four times without noticeable decrease in catalytic activity.



INTRODUCTION

In recent decades, nanostructured materials with high specific surface area have attracted increasing research interest due to their potential catalytic applications in organic synthesis. One of the interesting studies in this area is that of metal oxide nanoparticles. In this context, alumina nanoparticles (Al_2O_3 NPs) have great potential for use as a heterogeneous catalyst for a variety of organic and inorganic reactions due to its high surface-to-volume ratio.[1] Also, since Al_2O_3 NPs are often recovered easily by simple work up, which prevents contamination of products, it may be considered as a promising safe and reusable catalyst.

1,4-dihydropyridine (DHP) and polyhydroquinoline (PHQ) derivatives are of considerable interest due to their widespread notable biological properties which expand their applications as vasodilator, antitumor, bronchodilator, antiatherosclerotic, geroprotective and hepatoprotective agent.[2] Furthermore, these compounds exhibit diverse medicinal utility such as neuroprotectant, platelet antiaggregatory activity and chemosensitizer acting in tumor therapy.[3] Experimentally, the preparation of the 1,4-DHPs was first reported by Hantzsch in 1882 through a multicomponent, one-pot cyclocondensation reaction of a β-ketoester with an aldehyde and a nitrogen donor either in acetic acid or in refluxing ethanol for long reaction times which typically leads to low yields.[3,4]

Due to the importance of DHP and PHQ derivatives in the synthesis of various drug sources, several methods have been developed for the synthesis of these compounds such as: TMSCl,[5] ionic liquids,[6,7] L-proline,[8] polymers,[9] $Yb(OTf)_3$,[10] $Sc(OTf)_3$,[11] $HClO_4$–SiO_2,[12] cerric ammonium nitrate,[13] heteropoly acid,[14] p-TSA,[15] TiO_2 nanoparticles.[16] Although most of these processes offer distinct advantages, they suffer

* Corresponding author: akiasat@scu.ac.ir; tel/fax: (+98) 611-3331746

from drawbacks such as unsatisfactory yields, acidic or basic catalysts, extended reaction times, elevated temperatures, tedious work-up, anhydrous organic solvents and the use of relatively expensive catalysts. Thus, search for finding an efficient, general and nonpolluting method for the synthesis of this nitrogen-containing heterocyclic compounds is still of practical importance.

In continuation of our interest in designing new catalysts for organic methodology, in the present study,[17-19] we report our results on the efficient and rapid synthesis of DHP and PHQ derivatives through one-pot Hantzsch condensation reaction in the presence of γ-Al_2O_3-nanoparticles under solvent-free neat conditions (Scheme 1).

EXPERIMENTAL

General

Chemicals were purchased from Merck and Fluka Chemical Companies Merck and used without further purification. All yields refer to isolated products. Products were characterized by comparison of their physical data, IR and ^{1}H NMR and ^{13}C NMR spectra with known samples. NMR spectra were recorded in $CDCl_3$ on a Bruker Advance DPX 400 MHz instrument spectrometer using TMS as internal standard. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrophotometer as KBr disks.

The melting points were recorded in open capillary tubes and were uncorrected.

General procedure for synthesis of 1,4-dihydropyridines derivatives catalyzed by γ-Al_2O_3 nanoparticles under solvent free conditions

A mixture of ethyl acetoacetate (2 mmol), aromatic aldehyde (1 mmol), ammonium acetate (2 mmol) and γ-Al_2O_3 nanoparticles (0.2 g) was heated on the oil bath at 90 ^{o}C. The reaction mixture was monitored by TLC. After completion, the resultant material was washed with brine and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure to yield the crude product, which was then purified by recrystallization from hot ethanol and water to afford 1,4-dihydropyridines derivatives in high yield.

General procedure for synthesis of polyhydroquinoline derivatives catalyzed by γ-Al_2O_3 nanoparticles under solvent free conditions

A mixture of ethyl acetoacetate (1 mmol), dimedone (1 mmol), aromatic aldehyde (1 mmol), ammonium acetate (2 mmol) and γ-Al_2O_3 nanoparticles (0.2 g) was heated on the oil bath at 90 ^{o}C. The reaction mixture was monitored by TLC. After completion, the resultant material was washed with brine and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure to yield the crude product, which was then purified by recrystallization from hot ethanol and water to afford 1,4-dihydroquinoline derivatives in high yield.

Spectral data for respective compounds

4-(4-chlorophenyl)- 2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (**1b**)

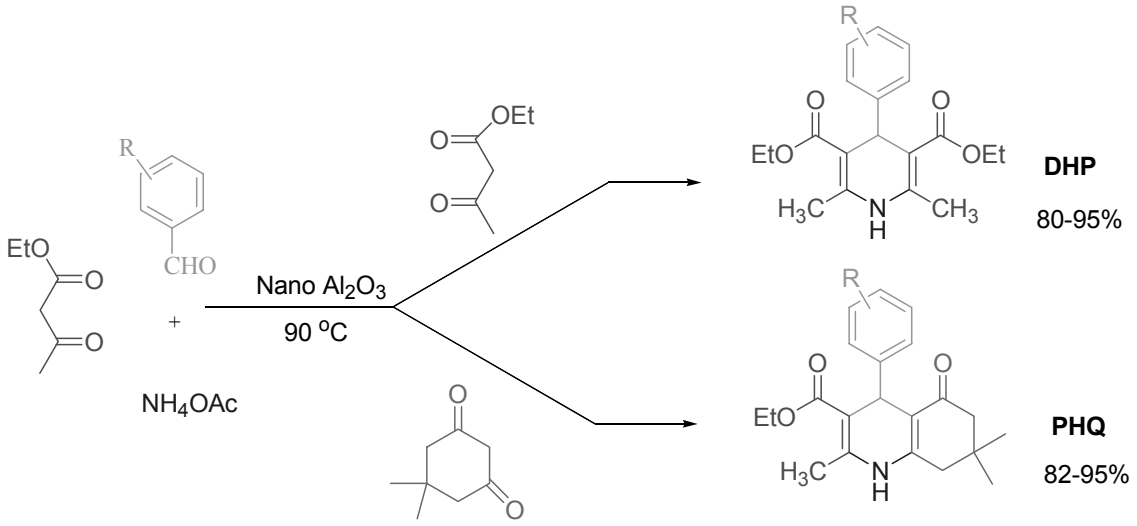
IR (KBr) ν_{max}: 3350, 1691, 1648, 1212, 1126, 777. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, 6H, *J* 6 Hz), 2.36 (s, 6H), 4.19 (q, 4H, *J* 4 Hz), 4.89 (s, 1H), 5.72 (s, 1H), 7.17–7.25 (Aromatic).^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 19.5, 39.4, 59.8, 103.4, 126, 129, 131.8, 143, 146.9, 167.4.

4-(4-cyano-phenyl) -2,6-dimethyl- 1,4-dihydro- -pyridine-3,5-dicarboxylic acid diethyl ester (**1e**)

IR (KBr) ν_{max}: 3355, 2233, 1705, 1680, 1207, 1109, 774. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, 6H, *J* 6 Hz), 2.38 (s, 6H), 4.16 (m, 4H, *J* 4 Hz), 5.15 (s, 1H), 5.69 (s, 1H), 7.26–7.59 (Aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 19.4, 40.8, 59.9, 105.2, 109.7, 117.6, 128.8, 131.8, 146.6, 153.2, 167.1.

2,7,7-Trimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (**2b**)

IR (KBr) ν_{max}: 3281, 3221, 3074, 1710, 1649, 1279, 1215.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.07 (s, 3H), 1.19 (t, *J* 7.2 Hz, 3H), 2.12–2.35 (m, 4H), 2.37 (m, 3H), 4.06 (q, *J* 7.2 Hz, 2H), 5.12 (s, 1H), 6.13 (s, 1H), 7.15 (d, *J* 8 Hz, 2H), 7.33 (d, *J* 8 Hz, 2H).



Scheme 1 – Synthesis of DHP & PHQ derivatives.

RESULTS AND DISCUSSION

Although, α-Al_2O_3 is commonly considered as the thermodynamically stable phase of Aloxide, γ-Al_2O_3 becomes more stable than α-Al_2O_3 at the nanoscale.[12] In addition to stability, due to the large pore volume, high activeness and strong adsorption, γ-Al_2O_3 nanoparticles has found a wide range of industrial applications as catalysts or catalyst carriers. In the present work, we decided to test the catalytic ability of γ -Al_2O_3 nanoparticles, possessing an average diameter of 50 nm (Fig 1), in Hantzsch condensation reaction (Scheme 1).

In order to carry out the synthesis of 1,4-dihydropyridine under environmentally benign conditions, Initially, the synthesis of 2,6-dimethyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by heating a mixture of benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1.5-2 mmol) in the presence of various amount of γ-Al_2O_3 nanoparticles at different temperatures under solvent free conditions. As can be seen from Table 1, the shortest time and best yield were achieved in the presence of 0.2 gr of catalyst at 90 °C (Entry 8).

In order to elucidate the role of the γ -Al_2O_3 nanoparticles as catalyst, a control reaction was set up using benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (2 mmol) in the absence of catalyst. The control reaction ended up with the formation of 10% of corresponding Hantzsch ester. However the test reaction set up with the same substrate, using 0.2 g of γ -Al_2O_3 nanoparticles at 90 °C under solvent free conditions afforded the product in 95% yield in 5 min.

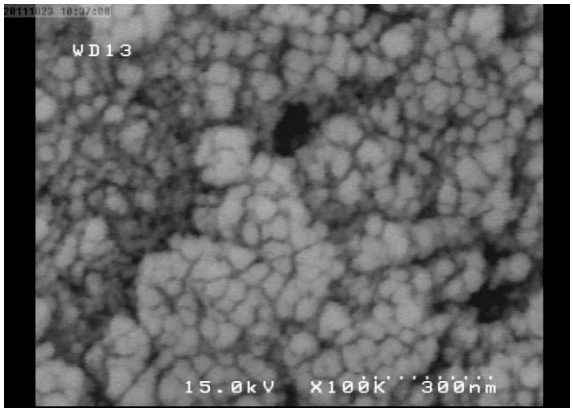


Fig. 1 – The SEM image of γ -Al_2O_3 nanoparticles.

Table 1

Optimization of conditions for the condensation reaction of benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate under solvent-free conditions

Entry	NH_4OAc (mmol)	Catalyst (gr)	Temp. (°C)	Time (min)	Yield (%)
1	2	0.2	40	90	15
2	1.5	0.25	90	15	80
3	1.5	0.2	90	20	90
4	1.5	0.15	90	30	82
5	1.5	0.2	80	25	85
6	1.5	0.15	100	15	93
7	1	0.2	90	40	62
8	2	0.2	90	5	95

In order to establish the true effectiveness of the nanostructure of catalyst, the condensation reaction was also tested using γ -Al_2O_3 under the same reaction condition. It clearly shows that although the reaction proceeded in the presence of γ-Al_2O_3 (45%, 75 min), the best result was obtained in the presence of γ -Al_2O_3 nanoparticles. This may be due to considerable ratio of surface to volume in nanoparticles.

To investigate the feasibility of this synthetic methodology for the synthesis of 1,4-dihydropyridine derivatives, we extended the one pot cyclocondensation reaction of ethyl acetoacetate (2 mmol) and ammonium acetate with a range of aromatic aldehydes possessing either electron-donating or electron-withdrawing substituents under similar conditions, furnishing the respective DHP derivatives in high yields (Table 2). The products synthesized thus were obtained in high isolated yields and characterized by ^{1}H NMR, ^{13}C NMR and physical constant. Physical and spectral data of known compounds are in agreement with those reported in the literature.

After successfully synthesizing a series of Hantzsch esters in high isolated yields, we turned our attention towards the synthesis of polyhydroquinoline derivatives via unsymmetrical Hantzsch reaction under similar conditions. We carried out the four-component coupling reaction of dimedone, aldehyde, acetoacetate ester, and ammonium acetate under solvent-free conditions (Scheme 1 & Table 3). It is noteworthy to mention that the structural variation of the aldehyde and substituents on the aromatic ring did not show any obvious effect on this conversion.

With the increasing interest in human health and environmental protection, more attention is being paid to green chemistry. With this view we studied the recyclability and reusability of the catalyst. After completion of the cyclocondensation reaction of dimedone, benzaldehyde, acetoacetate ester and ammonium acetate, the reaction mixture was cooled to room temperature and washed with brine. The catalyst was separated by filtration, washed with ethyl acetate, dried and reused for the similar reaction. As it is shown in Fig. 2, the catalyst could be used at least four times with only slight reduction in catalytic activity.

Table 2

Synthesis of 1,4-dihydropyridine derivatives catalyzed by γ-Al_2O_3 nanoparticles under solvent-free thermal conditions

Entry	R	Product	Time (min)	Yield (%)	Mp (^{o}C)	
					Found	Reported [16]
1	H	1a	5	95	158-160	157-158
2	4-Cl	1b	8	92	144-146	145-147
3	4-OH	1c	25	80	225-227	225-226
4	4-CH_3	1d	20	87	136-137	135-138
5	4-CN	1e	35	88	140-142	141-142
6	4-NO_2	1f	15	95	130-131	128-130
7	2-Cl	1g	20	93	83-85	82-84
8	2-OCH_3	1h	30	82	160-161	160-162

Table 3

Synthesis of polyhydroquinoline derivatives catalyzed by γ-Al_2O_3 nanoparticles under solvent free thermal conditions

Entry	R	Product	Time (min)	Yield (%)	Mp (°C)	
					Found	Reported [16]
1	H	2a	10	92	198-201	201-203
2	4-Cl	2b	10	87	244-246	244-245
3	4-OH	2c	20	89	228-231	232-233
4	4-CH_3	2d	15	93	259-262	261-262
5	4-$N(CH_3)_2$	2e	25	94	224-227	230-231
6	2-NO_2	2f	12	82	208-210	210-215
7	2-Cl	2g	10	95	208-211	208-210
8	4-NO_2	2h	8	86	240-243	241-243

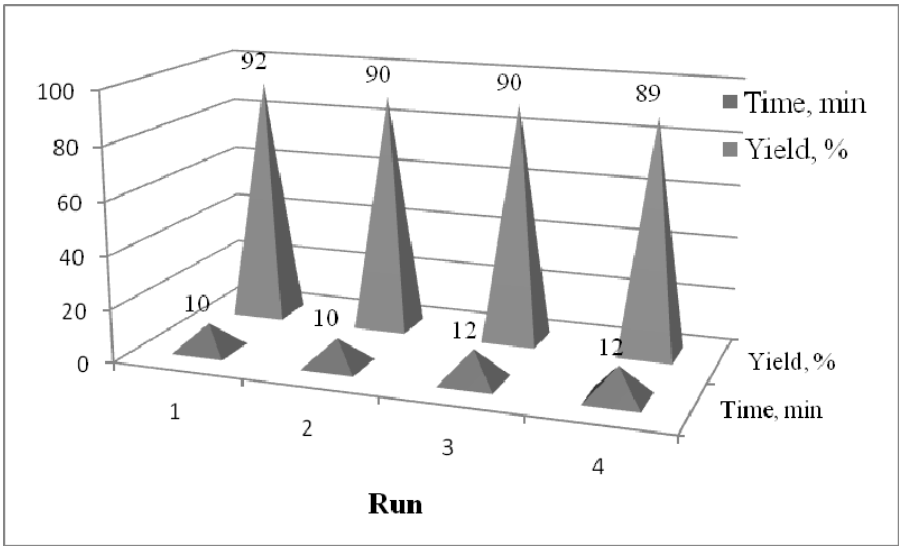


Fig. 2 – Reusability of γ -Al_2O_3-nanoparticles for model reaction.

CONCLUSIONS

In summary, we have developed a convenient and cost effective green synthetic procedure for the preparation of various 1,4-dihydropyridine and polyhydroquinoline derivatives via one pot multicomponent Hantzsch reaction in the presence of γ -Al_2O_3 nanoparticles as the catalyst with high isolated yields. This method offers several advantages including high yield, short reaction time, a simple work-up procedure with solvent-free conditions, ease of separation and recyclability of the catalyst, as well as the ability to tolerate a wide variety of substitutions in the components.

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