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One –Pot Synthesis of Polyhydroquinoline Derivatives via Hantzsch Condensation Reaction Using Nanosized Magnesium Oxide as Heterogeneous Catalyst

Hakimeh Mirzaee[1], **Ahmad Izadyar**[1], **Abolghsem Davoodnia**[1], **Hoseyn Eshghi**[2]
1Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad
[2]Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran

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Abstract

An efficient, recyclable and environmental-friendly synthetic route to polyhdroquinoline derivatives have been developed via multi-component one-pot Hantzsch reaction of various aromatic aldehyde, 2 equivalents of 5,5-dimethyl-1,3-cyclohexanedione (dimedone), ethyl acetoacetate and ammonium acetate using nano magnesium oxide as a catalyst in ethanol under reflux condition. Reaction with 4-chlorobenzaldehyde was selected as the model reaction and different conditions for temperature, amount of catalyst and kind of solvent have been studied on it. It was found that 0.03 g catalyst in reflux condition and ethanol as solvent is the optimum condition which resulted in 94% yield. The present approach offers several advantages such as short reaction times, easy isolation and purification of product, and safe, non-toxic, recyclable and economic use of catalyst.

Keywords: *Nano magnesium oxide, Polyhydroquinolines, Hantzsch method, Solid catalyst, Dimedone.*

Introduction

4-substituted 1,4-dihydropyridine (1,4- DHP) compounds have attracted much attention due to their various important pharmacological properties such as vasodilator, antihypertensive, bronchodilator, hepato- protective and anti diabetic agents [1-5].

DHPs have found commercial utility as calcium channel blockers as exemplified by therapeutic agents such as nifedipin, nitrendipine and nimodipine [6-8]. Several methods have been reported for synthesis of polyhydroquinoline derivatives [9]. Generally, 1,4-dihydropyridines are synthesized by

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***Corresponding author:** *Hakimeh Mirzaee, Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran. Email: h.mirzaei992@yahoo.com ;Tel:+98-51-35003407; Fax: +98-51-35003408*

the Hantszch condensation method, which involves cyclocondensation of aldehyde, β-ketoester and ammonia either in acetic acid at room temperature or refluxing in alcohol for a long time [10-12]. The utilization of cyclic 1,3- diketone in Hantzsch reaction for synthesis of polyhydroquinoline demonstrated by using molecular iodine [13-14], TMS-NaI [15], and expensive metal triflates such as $Yb(OTF)_3$, $Se(OTF)_3$ [16-17], cerium(IV) ammonium nitrate[18], HY-Zeolite[19] and ionic liquid [20]. However, the use of high reaction temperature, expensive metal precursor, catalysts that are harmful to the environment and long reaction time are limiting these methods.

Thus, we investigated this method by using nano magnesium oxide as catalyst which could be easily handled and removed from the reaction mixture by simple filtration and also recovered and reused without loss of reactivity.

Experimental

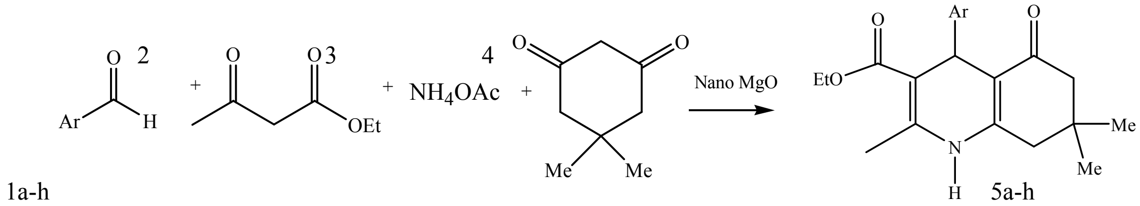
Chemicals were either prepared in our laboratories or purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products. The products were characterized by comparing their physical data with those of known samples or by their spectral data. Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using KBr disks on a Bruker Tensor 27 spectrophotometer. The 1H NMR 400 MHz spectra were recorded with a Bruker 400 spectrometer in $CDCl_3$ or DMSO as the solvent relative to TMS. The catalyst was synthesized and characterized according to the literature [21].

Synthesis of MgO nano particles

The MgO nanoparticles were synthesized by the precipitation of magnesium hydroxide gels in aqueous solution using $Mg(NO_3)_2{\bullet}6H_2O$ as a salt and ammonia solution as the precipitating agent. Initially, 0.1 mol/L magnesium nitrate solution was prepared by dissolving $Mg(NO_3)_2{\bullet}6H_2O$ (Merck) in deionized water. The pH of 200 ml deionized water was adjusted to 10.5 by the addition of ammonia solution (25%), and then, 0.1 mol/L prepared magnesium nitrate solution was added dropwise with vigorous stirring. During the addition, the pH of the mixture decreased due to the hydrolysis of the salt. The pH was maintained at 10.5 by the controlled addition of ammonia solution. After completion of the precipitation procedure, the $Mg(OH)_2$ gel was transferred into the Milestone microwave oven (Micro SYNTH) operated at 350 W for 15 min. During the microwave irradiation, the temperature of the solution reached 80°C. The resulting precipitate was then cooled to room temperature, filtered, and washed with deionized water more than five times. The solid obtained was dried at 120 °C for 1 h and calcinated at 500 °C for 2 h to give the final product. Structure and morphology of MgOnano particles investigated by SEM and TEM images, TGA and BET curves and XRD spectra [21].

General procedure for the synthesis of polyhydroquinolines

A mixture of an aromatic aldehyde 1a-h (1mmol), ethyl acetoacetate 2 (1mmol), ammonium acetate 3 (1mmol), dimedone 4 (1mmol) and MgO nano particles (0.03 g) as catalyst in ethanol (5ml) was heated under reflux for the appropriate time. The progress of the reaction was monitored by TLC. After completion the reaction, catalyst removed from reaction mixture by filtration and washed with hot ethanol. Then, the reaction mixture was cooling to room temperature and scratched. The solid product was appeared and then filtered and recrystallized from ethanol to give polyhydroquinolines 5a-h in good to high yields (Scheme1).



Scheme1. General procedure for the synthesis of polyhydroquinolines

All of the polyhydroquinoline derivatives are known, so these products were identified by comparison of their physical data with those of authentic samples [22-24]. In spite of physical comparison, spectroscopic data (IR, ^{1}H-NMR) was also studied and showed excellent accordance. Representative IR and1H- NMR spectral data for the selected products:

Product 5a

IR (KBr): 3274, 2958, 1706, 1648, 1604, 1488, 1381, 1214, 1031, 770 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): ∂ 7.29–7.42 (m, 2H), 7.20–7.24 (m, 2H), 7.10–7.14 (m, 1H), 6.0 (1H, NH), 5.08 (s, 1H), 4.08 (q, 2H, J = 7.2 Hz), 2.38 (s, 3H), 2.16–2.34 (m, 4H), 1.22 (t, 3H, J = 7.2 Hz), 1.10 (s, 3H), 0.93 (s, 3H).

Product 5c

IR (KBr): 3274, 2958, 1706, 1648, 1604, 1488, 1381, 1214, 1031, 770 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): ∂ 0.95 (s, 3H), 1.09 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H), 2.14–2.36 (m, 4H), 2.39 (s, 3H), 4.08 (q, J = 7.2 Hz, 2H), 5.03 (s, 1H), 6.21 (s, 1H, NH), 7.19–7.22 (d, J = 8.4 Hz, 2H), 7.29–7.35 (d, J = 8.4 Hz, 2H).

Product 5d

IR (KBr): 3416, 3280, 2959, 1676, 1611, 1485, 1379, 1220, 1033, 766 cm^{-1}.^{1}H NMR

(400 MHz,DMSO+D_2O): ∂ 0.84 (s, 3H), 1.12 (s, 3H), 1.14 (t, J = 7 Hz, 3H), 2.03–2.51 (4S, 4H), 2.38 (s, 3H), 3.97 (q, J = 7 Hz, 2H), 4.71 (s, 1H), 7.55 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H).

Product 5e

IR (KBr): 3276, 2956, 1701, 1649, 1605, 1496, 1379, 1214, 1032, 763 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): ∂ 0.98 (s, 3H), 1.08 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H), 2.16–2.35 (m, 4H), 2.38 (s, 3H),3.75(s,3H), 4.08 (q, J = 7.2 Hz, 2H), 5.01 (s, 1H), 6.2 (1H, NH), 6.74–6.76 (d, J = 6.8 Hz, 2H), 7.22–7.29 (d, J = 6.8 Hz, 2H).

Product 5h

IR (KBr): 3274, 2925, 1703, 1649, 1607, 1497, 1378, 1215, 1071, 830 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): ∂ 0.9 (s, 3H), 1.10 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H), 2.16–2.35 (m, 3H), 2.24-2.38 (m, 1H), 2.42 (s, 3H), 4.08 (q, J = 7.2 Hz, 2H), 5.18 (s, 1H), 6.3 (1H, NH), 7.49-7.52 (m, J = 8.8 Hz, 2H), 8.09-8.11 (m, J = 8.8 Hz, 2H).

Recycling and reusing of the catalyst

Due to the fact that the catalyst is insoluble in hot ethanol, it can be recycled by simple filtration. The separated catalyst was washed with hot ethanol, dried at 80 °C under vacuum for 2 h, and reused in the reaction.

Results and Discussion

In order to evaluate the catalytic efficiency of the MgO nanoparticles in the synthesis of polyhydroquinolines and to determine the most appropriate reaction conditions, initially a model study was carried out on the synthesis of compound 5c (Scheme 2) by thecyclocondensation of 4-chlorobenzaldehyde (1mmol), ethyl acetoacetate (1mmol), dimedone (1mmol) and ammonium acetate(1 mmol) under different sets of reaction conditions (Table1) such as the various solvents of EtOH, $CHCl_3$, H_2O, CH_3CN, and also under solvent-free conditions, and with various amounts of the catalyst and various temperature .There action was faster and gave the highest yield with 0.03 g ofMgO nanoparticles in EtOH at reflux temperature (Entry 4). Careful monitoring of the model reaction by TLC showed 0.04 and 0.10 g of the catalyst would cause production of small amounts of undesirable side-products and therefore the yield of compound 5c decreased (Entries 7 and 8).

Encouraged by this success and in order to evaluate the generality of this model reaction, we extended the reaction to the use of other aromatic aldehydes with ethyl acetoacetate, dimedone and ammonium acetate under the optimized reaction conditions. As shown in Table 2, different aromaticaldehydes were reacted successfully and gave the expected products 5a–h in good to high yields.

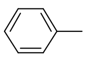
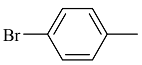
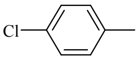
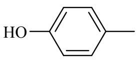
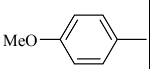
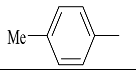
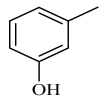
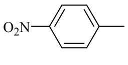
Table 1. Synthesis of compound 5c in the presence of MgOnano particles as catalyst under different reaction conditions.

Entry	Catalyst (g)	Solvent	T(C^0)	Time (h)	Yield (%)*
1	………..	EtOH	Reflux	2:00	Trace
2	0.01	EtOH	Reflux	2:00	67
3	0.02	EtOH	Reflux	1:45	88
4	**0.03**	**EtOH**	**Reflux**	**1:20**	**94**
5	0.03	EtOH	r.t	1:38	88
6	0.03	EtOH	50	1:25	90
7	0.04	EtOH	Reflux	1:20	90
8	0.1	EtOH	Reflux	1:20	85
9	0.03	$CHCl_3$	Reflux	2:25	79
10	0.03	H_2O	Reflux	1:28	88
11	0.03	CH_3CN	Reflux	2:10	80

Other conditions: 1mmol 4-chlorobenzaldehyde, 1mmol ethyl acetoacetate, 1mmol ammonium acetate, 1mmol

*The yields were calculated based on 4-chlorobenzaldehyde and refer to the pure isolated product

Table 2. Synthesis of Hantzschpolyhydroquinolines 5a-h[a] using MgOnano particles as catalyst under optimized conditions

Entry	Ar	Products [b]	Time (h)	Yield (%)[c]	Melting point(°c)	
					Found	Reported
1		5a	1:30	88	204-206	203-204 [22]
2		5b	1:35	90	254-256	252-253 [22]
3		5c	1:20	94	245-247	245-246 [22]
4		5d	00:50	95	230-232	231-233 [23]
5		5e	00:55	96	254-257	256-257 [22]
6		5f	00:50	98	261-264	260-261 [22]
7		5g	00:55	80	216-218	218-220 [24]
8		5h	1:40	75	243-245	242-244 [22]

[a] Reaction conditions: 1mmol aryl aldehyde , 1mmol ethyl acetoacetate , 1mmol ammonium acetate ,1mmol dimedone, 0.03 g MgOnano particles in ethanol at reflux condition.

[b] All the products were characterized by IR spectral data and comparison of their melting points with those of authentic samples. Also, the structures of some products were confirmed by ^{1}H NMR spectral data.

[c] Isolated yield of the pure product based on aryl aldehyde.

In order to study catalyst useful life reusability of the catalyst was also investigated. For this purpose, the same model reaction was again studied under the optimized conditions. The catalyst was recovered according to the procedure mentioned in experimental section and reused for a similar reaction. As shown in Figure 1, the catalyst could be used at least three times without significant loss of activity. However, the slight reduction of catalytic activity of the catalyst after recycling is probably due to the blockage a few part of active sites in the catalyst.

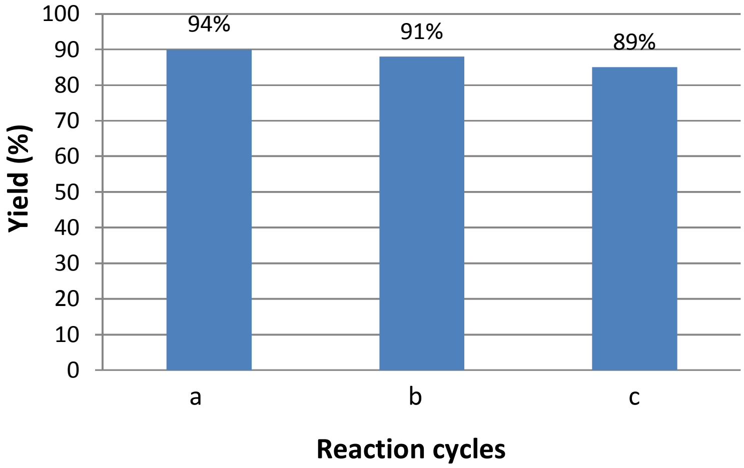


Figure 1. Reusability of the catalyst for model reaction: **a:** 94% yield for 1st use **b:** 91% yield for 2nd use **c:** 89% yield for 3rd use

Conclusion

In conclusion, we have developed a simple new catalytic method for the synthesis of polyhydroquinoline derivatives via one-pot four-component Hantzsch condensation of dimedone, aryl aldehydes, ethyl acetoacetate and ammonium acetate in the presence of MgO nanoparticles as an efficient, reusable, and heterogeneous catalyst. Some attractive features of this protocol are high yields, simple procedure, relatively short reaction times, easy work-up, high catalytic activity and recyclability and reusability of the catalyst. The catalyst can be used at least three times without substantial reduction in its catalytic activity. We believe this applicability of MgO nano particles with mentioned advantages makes our method superior over other reported methods to synthesis of polyhydroquinoline derivatives.

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