

Scolecite Catalyzed Facile and Efficient Synthesis of Polyhydroquinoline Derivatives through Hantzsch Multi-component Condensation

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A facile and efficient synthetic route has been developed for the polyhydroquinoline via four component reactions of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of catalytic amount of scolecite in ethanol at 70 °C through Hantzsch reaction. This method gives remarkable advantages such as simple work-up procedure, environmentally friendly, inexpensive, non-toxic and recyclable catalyst, shorter reaction time along with excellent yields.

Key Words: Heterogeneous catalyst, Reusable catalyst, Multicomponent reaction, Polyhydroquinoline

Introduction

1,4-dihydropyridine (1,4-DHP) and its derivatives represent the most promising group of compounds having broad spectrum of biological activities such as vasodilator, bronchodilator, anti-atherosclerotic, anti-tumor, geroprotective, hepatoprotective and antidiabetic agents.¹ Recent studies have revealed that 1,4-DHPs exhibits several medicinal applications which include neuroprotectant² and platelet anti-aggregatory activity.³ Also they have been reported for their applications in treatment of Alzheimer's diseases⁴ due to their cerebral antischematic activity and chemo-sensitizer in tumor-therapy.⁵ These examples clearly demonstrate the remarkable potential of 1,4-DHPs as a source of valuable drug candidate.

Owing to the wide range of biological and medicinal activities, the synthesis of such compounds has become an important target in recent years. In 1882, Arthur Hantzsch reported first synthesis of substituted 1,4-dihydropyridines by one-pot condensation of ethylacetoacetate, aromatic aldehydes and ammonia. The reaction was conducted in acetic acid or at reflux in ethanol⁶ for long periods resulting low to moderate yields. It is reported that such condensations can be accelerated by molecular iodine,⁷ HClO₄-SiO₂,⁸ TMSCl,⁹ ceric (IV) ammonium nitrate,¹⁰ L-proline,¹¹ ionic liquids,¹² silica sulphuric acid,¹³ Ni-nanoparticle,¹⁴ expensive metal triflate Yb(OTf)₃,¹⁵ Sc(OTf)₃,¹⁶ Bakers yeast,¹⁷ solid phase organic synthesis technique¹⁸ and without catalyst.¹⁹ Each of the above methods has its own merits, while some of the methods are plagued by limitations of poor yields, longer reaction time, difficult work-up procedure, effluent pollution and use of expensive metal precursors as a catalyst that are harmful to the environment.

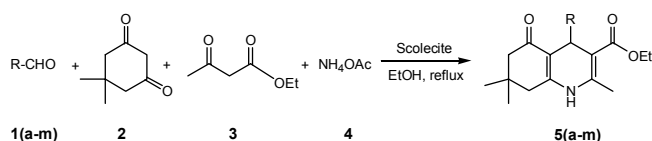
The problems associated with the reported methods avoided by using green, efficient and safe catalyst i.e. zeolite.²⁰ Green chemistry approaches are significant due to the reduction in byproducts, a reduction in waste produced and lowering of energy costs. The possibility of performing multi-component reactions with a natural heterogeneous catalyst could enhance their efficiency from an economic as well as ecological point of view.

In continuation to our work on the applications of heterogeneous catalysts in organic transformations,^{20,21} We report here a convenient and efficient method for the synthesis of polyhydroquinoline derivatives using scolecite as a catalyst (Scheme 1).

Experimental Part

All chemicals are purchased from Aldrich and Rankem chemical suppliers and used as received. The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. IR spectra were recorded on a Jasco FTIR-4100 spectrophotometer. ¹H NMR spectra were recorded on an 80 MHz FT-NMR spectrometer in CDCl₃ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me₄Si) as an internal standard.

The naturally occurring scolecite zeolite is a calcium zeolite with NAT topology and an ordered (Si : Al) distribution. The chemical composition of natural scolecite (atom%) were Si, Al, Fe, Na, Ca and O in the ratio 16.03, 10.34, 0.03, 0.20, 7.05, 66.34 respectively. It was collected from the Ellora valley, Aurangabad (MS), Deccan traps of India. It was subsequently washed with distilled water and acetone for several times, dried and crushed into fine powder which was further washed with distilled water 3 - 4 times and dried at 110 °C in an oven. The resulting sample was heated at 500 °C in high temperature muffle furnace (SONAR) for 1h at rate 3 °C per minute. The sample was naturally cooled and used in organic synthesis. We have shown its application earlier in the synthesis of 3,4-dihydropyrimidin-2(1H)-ones²⁰ and 2,4,5-triarylimidazoles.^{21c}



Scheme 1

The surface area, pore volume, pore diameter of the catalyst was determined by the nitrogen adsorption on Quantachrome Autosorb Instrument and Acidity of the sample measured by Temperature Programmed Desorption (TPD) of ammonia on Quantachrome TPR.

General procedure for the synthesis of polyhydroquinoline.

A mixture of aldehydes (2 mmol), dimedone (2 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (3 mmol) and scolecite catalyst (200 mg) was refluxed in ethanol (15 mL) for the time mentioned in Table 2. The reaction was monitored by TLC. After completion of reaction, the reaction mixture filtered in hot condition to separate the catalyst, poured into crushed ice and the solid product, which separated was filtered and recrystallized from ethanol to get pure yellow colored crystalline polyhydroquinoline derivatives.

Spectroscopic data of some compounds. Ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenylquinoline-3-carboxylate (**5a**): ^1H NMR (80 MHz, CDCl_3): δ 0.94 (s, 3H), 1.09 (s, 3H), 1.14 (t, $J = 7.3$ Hz, 3H), 2.13-2.34 (m, 4H), 2.37 (s, 3H), 4.05 (q, $J = 7.3$ Hz, 2H), 5.02 (s, 1H), 5.74 (s, 1H), 7.03-7.34 (m, 5H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 14.2, 19.1, 21.3, 27.6, 36.5, 37.3, 59.8, 106.0, 113.7, 126.3, 127.8, 128.0, 143.3, 147.1, 149.2, 167.3, 194.8; IR (KBr in cm^{-1}): 3233, 3210, 3080, 1696, 1602, 1059, 692; $m/z = 340$ (M+H) $^+$.

Ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-4-(3-nitrophenyl)-5-oxoquinoline-3-carboxylate (**5b**): ^1H NMR (80 MHz, CDCl_3): δ 0.96 (s, 3H), 1.04 (s, 3H), 1.22 (t, $J = 7.3$ Hz, 3H), 2.10-2.34 (m, 4H), 2.38 (s, 3H), 4.01 (q, $J = 7.3$ Hz, 2H), 4.96 (s, 1H), 6.32 (s, 1H), 6.74-7.38 (m, 4H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 14.18, 19.32, 21.1, 27.3, 33.1, 33.90, 59.5, 105.4, 112.3, 121.2, 122.8, 128.6, 134.8, 144.6, 148.3, 149.5, 151.0, 166.9, 196.0; IR (KBr in cm^{-1}): 3303, 2954, 1683, 1610, 1167, 759; $m/z = 385$ (M+H) $^+$.

Ethyl 1,4,5,6,7,8-hexahydro-4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**5g**): ^1H NMR (80 MHz, CDCl_3): δ 0.96 (s, 3H), 1.06 (s, 3H), 1.22 (t, $J = 7.2$ Hz, 3H), 2.10-2.26 (m, 3H), 2.34-2.40 (m, 4H), 3.77 (s, 3H), 4.02 (q, $J = 7.2$ Hz, 2H), 5.08 (s, 1H), 5.85 (s, 1H), 6.71-7.24 (m, 4H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 14.3, 17.9, 26.3, 28.8, 32.4, 35.0, 50.1, 50.4, 55.1, 59.2, 102.7, 109.5, 113.4, 128.3, 128.5, 140.0, 144.9, 149.1, 156.8, 168.2, 193.8; IR (KBr in cm^{-1}): 3281, 3199, 3080, 1708, 1607, 1224, 837; $m/z = 370$ (M+H) $^+$.

Results and Discussion

The cumulative Desorption surface area of catalyst from adsorption-desorption isotherm of nitrogen, pore volume at $p/p_0 = 0.993$ and pore diameter was determined by BJH method and it was found to be $S_{\text{BJH}} = 26.39 \text{ m}^2/\text{gm}$, $P_v = 0.0344 \text{ cm}^3/\text{gm}$ and $P_d = 11.08 \text{ \AA}$ respectively. Temperature Programmed Desorption method (TPD) was used to determine the acidic properties of solid catalyst. This provides information about the total concentration and strength of acidic sites (Bronsted and Lewis). It was found that the total ammonia desorbed is 0.376 mmol/gm of the catalyst.



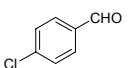
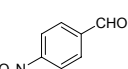
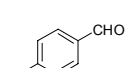
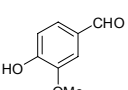
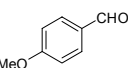

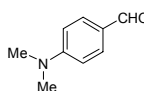

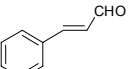
In the Hantzsch condensation solvents are especially important, because they are generally used in large quantities. In the present work, attempt is made to optimize the reaction condi-

Table 1. Optimization of reaction condition.

Solvent	Wt of catalyst (mg)	Reaction time	Yield (%) ^a
Water	200	2 hr	27
Ethanol	200	45 min	93
Ethanol: water	200	1 hr	53
Acetonitrile	200	45 min	79
Acetonitrile: water	200	1 hr	67
Dichloromethane	200	1 hr	61
Dichloromethane: water	200	1 hr	44
Ethanol	150	45 min	86
Ethanol	250	45 min	93

^aYield refers to isolated product.

Table 2. Synthesis of polyhydroquinoline derivatives.

Compound	Aldehyde	Time (min)	Yield (%) ^a	M. P. (°C)	
				Found	Lit.
5a		45	93	203-204	202-205 ¹¹
5b		60	87	176-177	176-179 ¹¹
5c		50	95	230-232	232-234 ¹¹
5d		55	89	240-242	241-243 ¹¹
5e		60	87	232-233	234-237 ¹¹
5f		50	91	209-210	208-210 ¹¹
5g		35	90	254-255	252-254 ¹¹
5h		45	92	209-210	208-209 ²²
5i		45	94	228-230	228-230 ¹¹
5j		50	89	210-212	208-211 ¹¹
5k		55	85	205-206	204-206 ¹⁵
5l	$\text{C}_2\text{H}_5\text{CHO}$	55	82	145-146	145-146 ¹⁵
5m	$n\text{-C}_3\text{H}_7\text{CHO}$	60	81	146-147	147-148 ¹⁵

^aYield refers to isolated product.

Table 3. Recovery and reusability of catalyst.

Entry	Cycle	Yield (%) ^a
1	Fresh	93
2	First	92
3	Second	91
4	Third	91

^aYield refers to isolated product.

tion by using bezaldehyde, dimedone, ethyl acetoacetate and ammonium acetate as a model reaction at different solvents and catalyst amount in the Hantzsch condensation (Table 1) and we hereby report a very simple, green and highly efficient method for the condensation of various aromatic aldehydes, ethyl acetoacetate, dimedone and ammonium acetate (Scheme 1).

The reactions were carried out in ethanol and 200 mg scolecite catalyst by avoiding the use of hazardous and expensive solvents or catalysts. The scolecite is natural zeolites are hydrophilic, thermally stable, non-toxic, possesses Bronsted and Lewis acidity. Upon heating Bronsted acid sites are converted to Lewis acidic and basic sites so the catalyst acts as a bi-functional catalyst, which help to expedite the overall rate of condensation reactions. Different aromatic aldehydes, ethyl acetoacetate, dimedone and ammonium acetate are refluxed in ethanol using 200 mg scolecite as a catalyst.

All the reactions run rapidly and were found to furnish good to excellent yields of polyhydroquinoline derivatives (Table 2) and no other byproducts were formed during the course of the reaction. This method has the ability to tolerate a variety of other functional groups such as methoxy, hydroxyl, nitro, halides, etc. Both the electron-rich and electron-deficient aldehydes worked well leading to high yields of product. We have extended our methodology towards aliphatic aldehydes but we got comparatively low yields (Table 2, Entry 5 k-5 m). After completion of the reaction (monitored by TLC), the reaction mass was filtered in hot condition to separate the catalyst and poured on ice-water. The obtained solid condensation product was further purified by recrystallization in ethanol. The recovered catalyst was washed with ethyl acetate, then dried at 70 °C and activated at 120 °C prior to use for next run in model reaction. And it was found that the recovered catalyst shows good yield with three successive reactions (Table 3).

Conclusion

In conclusion, we have developed a convenient and efficient protocol for one-pot synthesis of polyhydroquinolines by four-component coupling reactions of aldehydes, ethylacetoacetate, dimedone and ammonium acetate in the presence of scolecite catalyst. The method is associated with several advantages such as simple experimental procedure, utilization of heterogeneous catalyst, milder conditions, short reaction times, excellent yields and reusability of the catalyst. We feel the

method will find important applications for the synthesis of polyhydroquinolines.

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