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Efficient synthesis of polyhydroquinolines via the Hantzsch reaction Using nano-SnO_2

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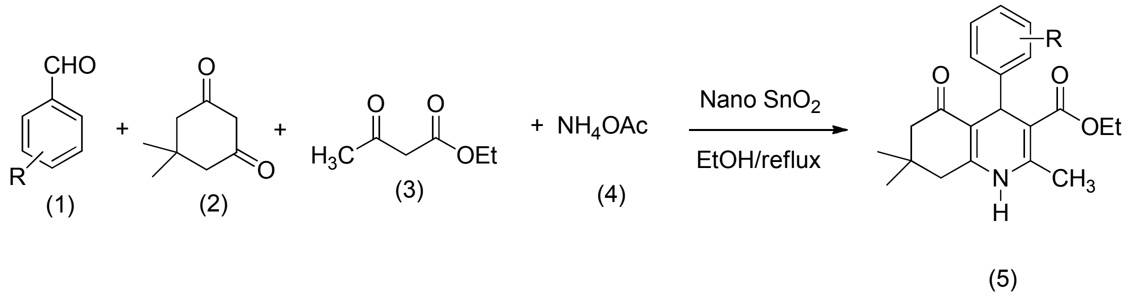
Abstract

A simple and convenient protocol is described for the preparation of polyhydroquinolines via one-pot, multi component reaction of an aromatic aldehyde, ethylacetoacetate, ammonium acetate and dimedone using nano-SnO_2 as an efficient catalyst in good yields.

Keywords Mesoporous Materials, quinolines, one-pot, multi component, nano-SnO_2

INTRODUCTION

Quinolines having a 1,4-dihydropyridine nucleus are very important compounds because of their pharmacological properties. Cardiovascular agents such as nifedipine, nicardipine, amlodipine and other related derivatives are dihydropyridyl compounds, which are effective for the treatment of hypertension [1]. 4-Aryl-1,4-dihydropyridines are analogues of NADH (Nicotinamide adenine dinucleotide) coenzymes, which have been explored for their calcium channel activity and the heterocyclic rings are found in variety of bioactive compounds such as bronchodilators, geroprotective, and heptaprotective agents [2]. Extensive studies indicate that these compounds exhibit different medical functions, acting as neuroprotectants, platelet antiaggregators, cerebral antiischemic agents, and chemosensitisers [3]. For these reasons, polyhydroquinoline compounds not only have attracted the attention of chemists to synthesize but also represent an interesting research challenge. Numerous methods have been reported for the synthesis of polyhydroquinoline derivatives, because of the biological importance associated with these compounds [4,5]. However, these methods suffer from drawbacks such as a long reaction time, an excess of organic solvent, lower yields, and harsh refluxing conditions. Consequently, there is a need to develop new methods to synthesis of these compounds. Multicomponent reactions (MCRs) offer a unique way to generate efficiently libraries of complex molecules with high degree of diversity. Among them, the Ugi four component reaction (Ugi-4CR) is without doubt one of the most powerful transformations that has been extensively investigated for the past twenty years [6]. As part of our ongoing interest in the nano catalyzed reactions for various organic transformations, we had the opportunity to further explore its catalytic activity towards the synthesis of 1,4-dihydropyridines via four component reaction of an aromatic aldehyde, ethylacetoacetate, ammonium acetate and dimedone in good yields (Scheme 1).



Scheme 1. synthesis of polyhydroquinolines

MATERIALS AND METHODS

Experimental

All products are known compounds and were characterized by mp, IR, ^{1}HNMR and GC/MS. Melting points were measured, using the capillary tube method with an electrothermal 9200 apparatus. ^{1}HNMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

Typical experimental procedure for the synthesis of Hantzsch polyhydroquinoline derivatives

A mixture of a aldehyde 1 (1 mmol), ethylacetoacetate (1.0 mmol), dimedone (1mmol), ammonium acetate (1.5 mmol) and catalyst (1 mol%) in ethanol (5mL) was refluxed. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and filtered off. The pure product was obtained by recrystallization from ethanol.

Ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenylquinoline-3-carboxylate **(5a)**: ^{1}H NMRδ(ppm): 0.91 (s,3H), 1.02 (s,3H), 1.34 (t, 3H, J=6.9), 2.2-2.35 (m,7H), 3.97 (q,2H,J=6.9), 5.02 (s, 1H), 5.87 (s,1H), 7.21-7.45 (5H,m).

Ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-p-tolylquinoline-3-carboxylate **(5b)**: ^{1}H NMRδ(ppm): 0.92 (s,3H), 1.04 (s,3H), 1.28 (t, 3H, J=7.2), 2.11-2.39 (m,7H), 2.39(s,3H), 4.07 (q,2H,J=7.2), 4.69 (s, 1H), 5.54 (S, 1H, NH), 7.03-7.45 (4H,m).

Ethyl-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-methoxyphenylquinoline-3-carboxylate (**5c**): ^{1}H NMRδ(ppm): 0.89 (s,3H), 1.06 (s,3H), 1.29 (t, 3H, J=7.2), 2.01-2.42 (m,7H), 3.31 (s,3H), 4.09 (q,2H,J=7.2), 4.67 (s, 1H), 5.44 (S, 1H, NH), 7.09-7.51 (4H,m).

Ethyl-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-chlorophenylquinoline-3-carboxylate (**5d**): ^{1}H NMRδ(ppm): 0.99 (s,3H), 1.12 (s,3H), 1.36 (t, 3H, J=6.8), 2.11-2.49 (m,7H), 4.11 (q,2H,J=6.8), 4.86 (s, 1H), 5.66 (S, 1H, NH), 7.14-7.64 (4H,m).

Ethyl-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-hydroxyphenylquinoline-3-carboxylate (**5f**): ^{1}H NMRδ(ppm): 0.94 (s,3H), 1.08 (s,3H), 1.22 (t, 3H, J=7.1), 2.08-2.34 (m,7H), 4.03 (q,2H,J=7.1), 4.97 (s, 1H), 5.56 (S, 1H, NH), 5.98 (s,1H, OH), 7.11-7.42 (4H,m).

Catalyst reusability

The catalyst was separated from the reaction using simple filtration technique, washed with acetone, air dried and used for subsequent runs of the reaction process. In Table 1, the comparison of efficiency of nano-SnO_2 in synthesis of 5a after five times recovery is reported. As it is shown in Table 1, this catalyst can be used efficiently after reusing.

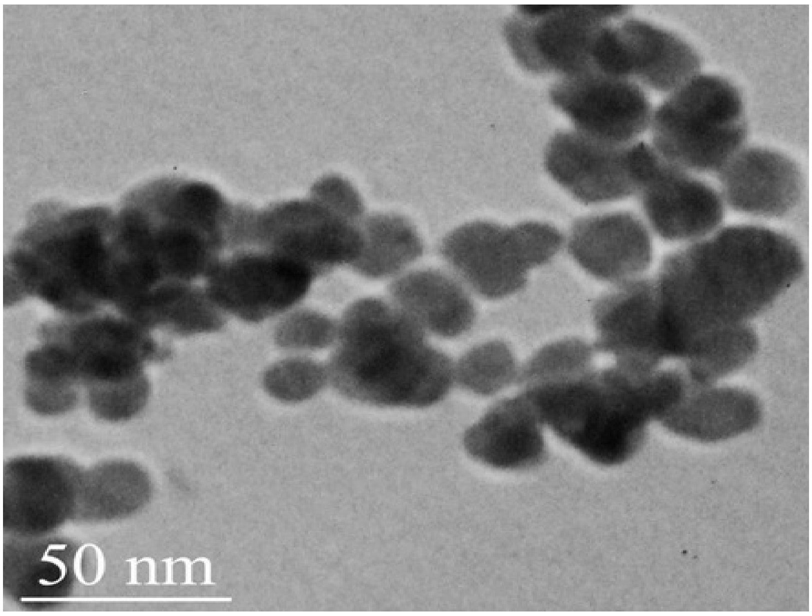
Table 1. Reuse of nano-SnO_2 for the synthesis of 5a

Entry	Time(min)	Yield (%)[a]
1	30	95
2	30	93
3	30	92
4	30	90
5	30	90

(a) Isolated yields.

RESULTS AND DISCUSSION

It is known that, the specific surface area and surface-to-volume ratio increase dramatically as the size of a material decreases. The high surface area brought about by nanoparticle size is beneficial to many SnO_2-based devices, as it facilitates reaction/interaction between the devices and the interacting media. The previous research works on SnO_2 were reported by Seiyama [7] in 1962 as semiconductor materials for gas sensor materials and alternative energy. Its outstanding electrical, optical an delectro-chemical properties of SnO_2 enable applications in solar cells, catalytic support materials, transparent electrodes, and solid state chemical sensors [8]. They were successfully synthesized by different methods. Various methods, including molten-salt synthesis [9] sol–gel [10], microwave technique [11,12], carbothermal reduction [13], chemical precipitation [14], laser-ablation synthesis [15], hydrothermal method [16,17], and sonochemical [18] have been developed to synthesize SnO_2 nanostructures. The investigation on nano-SnO_2 catalytic activity for the synthesis of many organic molecules is current work in our laboratory. The dimensions of applied SnO_2 nanoparticles were determined with TEM (Fig. 1).



TEM image of nano-SnO_2

In an initial endeavor, 1 equiv each of benzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate afforded the desired quinolines (5a) in 95% yield (Entry 1, Table 2). We performed the effect of various solvents on the synthesis of 5a. This reaction was carried out in various solvents such as water, chloroform, ethanol, CH_2Cl_2. The best results in terms of yield and time obtained in ethanol. In each reaction, the yield is a function of the reaction time and the best time for all reactions was completed after 30 min. A variety of aldehydes were submitted to this reaction condition and the desired products were obtained in good to excellent yields (Table 2). It is evident that both electron rich and electron deficient aldehydes reacted smoothly with ethylacetoacetate to produce high yields of products. The reaction proceeds very cleanly at room temprature and free of side products. In the absence of the catalyst, the reaction did not complete even after 24h.

Table 2. nano-SnO_2 catalyzed the synthesis of polyhydroquinolines

Entry	Ar	Product	Time (h)	Mp (^0C) Observed	Reported	Yield (%)[a]
1	Ph	**5a**	2	207	204-206[19]	95
2	4-Me-Ph	**5b**	2.5	263	261-262[20]	91
3	4-MeO-Ph	**5c**	2.5	245	243-245[19]	92
4	4-Cl-Ph	**5d**	2	231	230-232[19]	96
5	3-NO_2-Ph	**5e**	2	179	177-178[20]	96
6	4-OH-Ph	**5f**	2.5	239	237-238[19]	90
7	4-NO_2-Ph	**5g**	2	242	240-242[22]	97

[a] *Isolated yields.*

CONCLUSION

In conclusion, we have developed a simple and efficient method for the synthesis of polyhydroquinoline derivatives via Hantzsch condensation using nano-SnO_2 as a catalyst. The mildness of the conversion, experimental simplicity, compatibility with various functional groups, efficient yields, short reaction times, and the easy workup procedure, makes this procedure attractive to synthesize a variety of these derivatives.

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