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Article

Synthesis of polyhydroquinoline derivatives via a four-component Hantzsch condensation catalyzed by tin dioxide nanoparticles

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ABSTRACT

Tin dioxide (SnO₂) nanoparticles efficiently catalyzed unsymmetrical four-component Hantzsch condensations of various aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate to form polyhydroquinoline derivatives in excellent yields. This novel method offers several advantages over the traditional method of synthesizing these compounds, including safety, mild conditions, short reaction times, high yields, and an easy workup.

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1. Introduction

Tin dioxide (SnO₂) exhibits desirable properties such as high transparency in the visible spectrum, strong physical and chemical interactions with adsorbed species, catalytic activity at low temperature, and high thermal stability in air (up to 500 °C) [1]. It is an *n*-type semiconducting oxide with a wide band gap ($E_g = 3.6\text{--}3.8$ eV at 300 K), and it has potential applications for dye-based solar cells [2]. It has also been used as a sensing material for gas mixtures such as CO and O₂ [3]. However, compared with other metal oxides, SnO₂ has received little attention as a catalyst [4], although it has been used to catalyze the oxidation of organic compounds [5].

SnO₂ can be synthesized by means of various techniques, including chemical vapor deposition for the preparation of thin films [6], precipitation, sol-gel reactions, carbothermal reduc-

tion, and hydrothermal and polymeric precursor methods [7]. Because one-dimensional SnO₂ structures (e.g., nanowires and nanorods) are expected to find wide applications in many fields, considerable effort has been directed at fabricating such structures by means of methods such as thermal oxidation and molten salt synthesis [8,9].

In this study, which is part of our ongoing investigations directed toward the development and improvement of new synthetic methodologies [40,41], we investigated the use of SnO₂ nanoparticles to catalyze the formation of polyhydroquinolines and 1,4-dihydropyridines (1,4-DHPs). In recent years, interest in the synthesis of 1,4-DHPs has increased, owing to their significant biological activities [10,11]. For example, various 1,4-DHPs with substituents at the 4-position have been reported to possess antiatherosclerotic, vasodilatory, antihypertensive, hepatoprotective, bronchodilatory, antitumorigenic,

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antitumor, geroprotective, and antidiabetic activities [12–16]. DHPs have found commercial utility as calcium channel blockers (e.g., Nitrendipine, Nifedipine, and Nimodipine) [17]. DHPs can be synthesized by means of the Hantzsch condensation of an aldehyde, a β -ketoester, and ammonia; and replacement of ammonia by ammonium acetate permits the reaction to be carried out in aqueous media as well as under solvent-free conditions [18,19].

Polyhydroquinolines, which are structurally related to DHPs, are another important group of nitrogen-containing heterocycles that have attracted much attention because of their diverse therapeutic and pharmacological properties, such as their ability to modulate calcium channels. Polyhydroquinolines have been synthesized under mild conditions augmented by conventional heating [20,21], microwave irradiation, and ultrasound [22,23]. In addition, various catalysts have been evaluated, including FeF_3 [24], clay-supported Ni^0 nanoparticles [25], unsupported nickel nanoparticles [26], silica-supported perchloric acid [27], titanium dioxide nanoparticles [28], Bakers' yeast [29], $\text{K}_7[\text{PW}_{11}\text{CoO}_{40}]$ [30], scandium(III) triflate [31], ethylene glycol/MW [32], *p*-toluenesulfonic acid [33], trimethylsilyl chloride [34], palladium nanoparticles [35], a hafnium(IV) bis(perfluorooctanesulfonyl)imide complex [36], cerium(IV) ammonium nitrate [37], and iron(III) trifluoroacetate [38].

Despite the availability of these methods, the development of a mild and efficient catalyst for the synthesis of polyhydroquinolines remains highly desirable. In addition, the possibility of performing the reaction in aqueous media has attracted much attention because water is safer, cheaper, and more environmentally friendly than organic solvents [39]. A water-soluble catalyst that could be recycled by separation of the insoluble products by simple filtration is an especially attractive prospect.

Herein, we report a new, convenient, mild, efficient procedure for the synthesis of polyhydroquinoline derivatives by means of a SnO_2 nanoparticle-catalyzed one-pot Hantzsch condensation of various aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate at ambient temperature in ethanol.

2. Experimental

2.1. General procedure for the Hantzsch synthesis of 1,4-DHPs

A mixture of dimedone (1.0 mmol), an aldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), ammonium acetate (1.0 mmol), and SnO_2 nanoparticles (1 mol%) in ethanol (2 ml) was stirred at room temperature until the reaction was complete, as indicated by thin-layer chromatography (*n*-hexane/ethyl acetate 5:1). The crude solid product was filtered and then purified by recrystallization from ethanol-water. The physical data (mp, NMR, IR) of known compounds were identical to the corresponding literature data.

2.2. General procedure for the synthesis of polyhydroquinolines

A mixture of dimedone (1.0 mmol), aldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), ammonium acetate (1.0 mmol) and nano SnO_2 catalyst (1 mol%) in ethanol (2 ml) were stirred at room temperature for an appropriate time. The progress of the reaction was monitored by TLC (*n*-hexane/ethyl acetate 5:1). After completion of the reaction, the resulting solid (crude product) was filtered and then recrystallized from ethanol-water to obtain pure product. The physical data (mp, NMR, IR) of these known compounds were found to be identical with those reported in the literature.

Ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 4 entry 3) Yield: 96%; mp 229–231 °C (lit. [46] 230–232 °C). ^1H NMR (400 MHz, DMSO): δ 0.84 (s, 3H, $-\text{CH}_3$), 0.99 (s, 3H, $-\text{CH}_3$), 1.14 (t, 3H, J = 7.2 Hz, $-\text{CH}_3$), 2.06 (dd, 2H, $-\text{CH}_2-$), 2.13 (dd, 2H, $-\text{CH}_2-$), 2.28 (s, 3H, $-\text{CH}_3$), 3.99 (q, 2H, J = 7.3 Hz, $-\text{OCH}_2-$), 4.95 (s, 1H, $-\text{CH}-$), 7.08 (d, 2H, J = 9.3 Hz, Ar-H), 7.18 (d, 2H, J = 9.4 Hz, Ar-H), 7.93 (brs, 1H, $-\text{NH}-$). ^{13}C NMR (100 MHz, DMSO): δ 14.8, 19.2, 27.4, 29.9, 32.8, 36.6, 40.8, 51.2, 60.1, 77.8, 105.3, 111.5, 128.2, 129.8, 131.7, 146.5, 150.1, 167.8, 195.7; IR (KBr, cm^{-1}) 3275, 3199, 3073, 2931, 2360, 1676, 1604, 1490, 1380, 1214, 1101, 857.

Ethyl 4-(4-hydroxy-3-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 4 entry 13). Yield: 96%; mp 212–214 °C (lit. [48] 210–212 °C); ^1H NMR (400 MHz, DMSO): δ 0.93 (s, 3H, $-\text{CH}_3$), 1.04 (s, 3H, $-\text{CH}_3$), 1.25 (t, 3H, J = 7.2 Hz, $-\text{CH}_3$), 1.91–2.18 (dd, 2H, $-\text{CH}_2-$), 2.27–2.39 (dd, 2H, $-\text{CH}_2-$), 2.27 (s, 3H, $-\text{CH}_3$), 3.73 (s, 3H, $-\text{OCH}_3$), 4.06 (q, 2H, J = 7.3 Hz, $-\text{OCH}_2-$), 4.71 (s, 1H, $-\text{CH}-$), 6.49–6.77 (m, 3H, Ar-H), 8.07 (brs, 1H, $-\text{OH}$), 8.58 (brs, 1H, $-\text{NH}-$). ^{13}C NMR (100 MHz, DMSO): δ 15.3, 27.1, 28.8, 33.1, 38.4, 47.6, 52.4, 58.3, 106.7, 109.1, 111.3, 115.1, 121.5, 137.2, 145.6, 147.4, 153.3, 157.1, 167.3, 197.6; IR (KBr, cm^{-1}) 3397, 3285, 3065, 2919, 1688, 1559, 1471, 1267, 1223, 829.

Ethyl 2,7,7-trimethyl-5-oxo-4-*p*-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 4 entry 15). Yield: 96%; mp 263–265 °C (lit. [45] 260–261 °C). ^1H NMR (400 MHz, DMSO): δ 0.81 (s, 3H, $-\text{CH}_3$), 1.07 (s, 3H, $-\text{CH}_3$), 1.18 (t, 3H, J = 7.2 Hz, $-\text{CH}_3$), 1.98 (s, 3H, $-\text{CH}_3$), 2.03 (dd, 2H, $-\text{CH}_2-$), 2.21 (dd, 2H, $-\text{CH}_2-$), 2.41 (s, 3H, $-\text{CH}_3$), 4.06 (q, 2H, J = 7.1 Hz, $-\text{OCH}_2-$), 5.11 (s, 1H, $-\text{CH}-$), 7.44 (d, 2H, J = 9.2 Hz, Ar-H), 8.15 (d, 2H, J = 9.2 Hz, Ar-H), 8.21 (brs, 1H, $-\text{NH}-$). ^{13}C NMR (100 MHz, DMSO): δ 14.3, 18.9, 23.1, 27.1, 28.5, 31.9, 37.6, 40.7, 51.3, 61.9, 77.7, 104.3, 110.9, 122.8, 129.1, 146.5, 150.3, 155.1, 168.1, 197.1; IR (KBr, cm^{-1}) 3270, 3185, 3075, 2967, 2366, 1669, 1614, 1567, 1490, 1372, 1276, 1151, 875.

Ethyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 4 entry 20). Yield: 98%; mp 244–246 °C (lit. [25] 242–244 °C). ^1H NMR (400 MHz, DMSO): δ 0.84 (s, 3H, $-\text{CH}_3$), 1.01 (s, 3H, $-\text{CH}_3$), 1.13 (t, 3H, J = 7.2 Hz, $-\text{CH}_3$), 2.01 (dd, 2H, $-\text{CH}_2-$), 2.15 (dd, 2H, $-\text{CH}_2-$), 2.32 (s, 3H, $-\text{CH}_3$), 4.01 (q, 2H, J = 7.3 Hz, $-\text{OCH}_2-$), 5.10 (s, 1H, $-\text{CH}-$), 7.44 (d, 2H, J = 9.3 Hz, Ar-H), 8.01 (d, 2H, J = 9.4 Hz, Ar-H), 8.12 (brs, 1H, $-\text{NH}-$). ^{13}C NMR (100 MHz, DMSO): δ 14.6, 19.3, 27.4, 29.8, 32.9, 37.6, 40.9, 51.1, 60.2, 77.9, 104.5, 110.8, 123.6, 129.3, 146.4, 150.3, 155.3, 167.5, 195.8; IR (KBr, cm^{-1}) 3276, 3189, 3072, 2967, 2360, 1679, 1604, 1557, 1490, 1342, 1276, 1105, 879.

Table 1

Effect of catalyst amount on the yield of the Hantzsch condensation reaction.

Amount of catalyst (mol%)	Isolated yield (%)
0.5	89
1	94
2	93
5	89
10	87

Reaction conditions: benzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1 mmol), ethanol volume (2 ml), room temperature.

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Table 6 entry 2). Yield: 95%; mp 145–147 °C [lit. [53] 144–146 °C]. ^1H NMR (400 MHz, DMSO): δ 1.23 (t, 6H, J = 7.1 Hz, $-\text{CH}_3$), 2.27 (s, 6H, $-\text{CH}_3$), 4.17 (m, 4H, J = 5.7 Hz, $-\text{OCH}_2$), 4.87 (brs, 1H, $-\text{NH}-$), 5.68 (s, 1H, $-\text{CH}-$), 7.41 (d, 2H, J = 7.9 Hz, Ar-H), 7.57 (d, 2H, J = 7.8 Hz, Ar-H). ^{13}C NMR (100 MHz, DMSO): δ 14.3, 14.9, 45.9, 61.3, 97.6, 127.1, 128.3, 134.8, 143.2, 147.1, 167.8; IR (KBr, cm^{-1}) 3273, 3180, 2967, 1687, 1557, 1495, 1341, 1267, 879.

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Table 6 entry 7): Yield: 98%; mp 131–133 °C [lit. [53] 130–132 °C]. ^1H NMR (400 MHz, DMSO): δ 1.27 (t, 6H, J = 7.3 Hz, $-\text{CH}_3$), 2.13 (s, 6H, $-\text{CH}_3$), 4.35 (m, 4H, J = 5.9 Hz, $-\text{OCH}_2$), 4.85 (brs, 1H, $-\text{NH}-$), 5.79 (s, 1H, $-\text{CH}-$), 7.51 (d, 2H, J = 7.8 Hz, Ar-H), 7.59 (d, 2H, J = 7.8 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO): δ 15.1, 17.8, 45.7, 63.3, 96.6, 128.1, 128.7, 132.5, 145.2, 148.3, 167.5; IR (KBr, cm^{-1}) 3275, 3191, 2975, 1657, 15357, 1491, 1356, 1265, 875.

3. Results and discussion

First, we optimized the reaction conditions for the four-component Hantzsch condensation with respect to yield and reaction rate by varying the catalyst amount (Table 1), the solvent (Table 2), and the reaction temperature. We obtained the maximum yield of the desired polyhydroquinolines (94%) with 1 mol% of catalyst at room temperature in ethanol, and

Table 2

Effect of solvent on the reaction time and yield of the Hantzsch condensation reaction.

Solvent	Time (min)	Isolated yield (%)
H_2O	23	71
$\text{C}_2\text{H}_5\text{OH}$	9	94
CH_3CN	12	93
THF	15	91
Toluene	19	89

Reaction conditions: benzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1 mmol), SnO_2 nanoparticles (1 mol%), solvent volume (2 ml), room temperature.

under these conditions, the reaction was complete within 9 min (Scheme 1).

We compared the results we obtained with SnO_2 nanoparticles as a catalyst with the results reported in the literature for various other catalysts in similar reactions (Table 3). Two of the literature methods required a catalyst ratio of >1 mol% (entries 4 and 7), and some of the methods required much longer reaction times (entries 2, 7, and 8).

We next evaluated the substrate scope of the reaction with a series of aromatic, aliphatic, and heterocyclic aldehydes and found that all the tested substrates underwent the electrophilic substitution reaction to produce a wide range of polyhydroquinoline derivatives in good to excellent yields (Table 4). Aromatic aldehydes with electron-withdrawing groups on the aromatic ring (entries 18–21) reacted faster than aldehydes bearing electron-donating groups (entries 10, 12, and 15). Aliphatic aldehydes also required relatively long reaction times (entries 25–28), most likely because of the electron-donating and steric effects of the aliphatic moieties.

We evaluated the reusability of the catalysts by carrying out multiple reactions of dimedone, 4-nitrobenzaldehyde, ethyl acetoacetate, and ammonium acetate to form **4at** (Table 5). After completion of each reaction, the product was extracted with ethanol, and the catalyst was recovered from the aqueous layer. The SnO_2 nanoparticles were more soluble in ethanol than in water. In this medium, the recovered catalyst could be reused five times without appreciable loss of catalytic activity.

Scheme 1. SnO_2 nanoparticle-catalyzed synthesis of polyhydroquinolines **4**.

Table 3

Comparison of various catalysts in the four-component Hantzsch condensation.

Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Yield (%)	Ref.
1	$\text{SnO}_2/1$	$\text{C}_2\text{H}_5\text{OH}$	r.t.	9	94	this work
2	Bakers' yeast-D-glucose/200–300 mg	phosphate buffer (pH=7.0)	r.t.	1440	79	[29]
3	MCM-41/1	solvent free	90	15	89	[38]
4	$\text{ZnO}/10$	$\text{C}_2\text{H}_5\text{OH}$	80	60	92	[42]
5	SBA-Pr- $\text{SO}_3\text{H}/0.05$ g	solvent free	80	10	85	[43]
6	$\text{K}_7[\text{PW}_{12}\text{CoO}_{40}]/1$	$\text{CH}_3\text{CN}/\text{reflux}$	—	35	80	[30]
7	L-proline/10	$\text{C}_2\text{H}_5\text{OH}/\text{reflux}$	—	360	92	[44]
8	$\text{Hf}(\text{NPf}_2)_4/1$	perfluorodecalin ($\text{C}_{10}\text{F}_{18}$)	60	180	95	[36]

Table 4SnO₂ nanoparticle-catalyzed Hantzsch synthesis of polyhydroquinoline derivatives from various aldehydes (RCHO).

Entry	R	Product	mp (°C)	Reaction time (min)	Yield (%)	Ref.
1	C ₆ H ₅	4aa	203–205	9	94	[45]
2	2-Cl-C ₆ H ₄	4ab	209–211	7	95	[34]
3	4-Cl-C ₆ H ₄	4ac	229–231	6	96	[46]
4	2,4-Cl ₂ -C ₆ H ₃	4ad	240–242	6	96	[29]
5	3,4-Cl ₂ -C ₆ H ₃	4ae	200–202	7	95	[47]
6	2,6-Cl ₂ -C ₆ H ₃	4af	243–245	6	95	[29]
7	4-F-C ₆ H ₄	4ag	185–187	6	96	[37]
8	4-Br-C ₆ H ₄	4ah	253–255	6	95	[45]
9	3-OH-C ₆ H ₄	4ai	216–218	9	94	[26]
10	4-OH-C ₆ H ₄	4aj	228–230	8	95	[45]
11	3-OMe-C ₆ H ₄	4ak	201–203	8	94	[34]
12	4-OMe-C ₆ H ₄	4al	258–260	7	95	[45]
13	4-OH-3-OMe-C ₆ H ₃	4am	212–214	8	96	[48]
14	3,4,5-(OMe) ₃ -C ₆ H ₂	4an	197–199	8	95	[20]
15	4-Me-C ₆ H ₄	4ao	263–265	6	96	[45]
16	4-(Me) ₂ CH-C ₆ H ₄	4ap	181–183	7	96	[49]
17	4-(Me) ₂ N-C ₆ H ₄	4aq	231–233	5	97	[27]
18	4-CF ₃ -C ₆ H ₄	4ar	190–192	2	98	[24]
19	3-NO ₂ -C ₆ H ₄	4as	175–177	3	97	[20]
20	4-NO ₂ -C ₆ H ₄	4at	244–246	1	98	[25]
21	4-CN-C ₆ H ₄	4au	143–145	2	97	[24]
22	cinnamaldehyde	4av	203–205	10	94	[31]
23	furane-2-carbaldehyde	4aw	246–248	9	95	[50]
24	thiophene-2-carbaldehyde	4ax	225–227	10	95	[34]
25	CH ₃ CH ₂	4ba	143–145	15	91	[45]
26	CH ₃ (CH ₂) ₂	4bb	148–150	14	92	[45]
27	(CH ₃) ₂ CH	4bc	161–163	15	92	[44]
28	CH ₃ (CH ₂) ₄	4bd	165–167	15	91	[51]

Table 5Evaluation of catalyst reusability for the synthesis of **4at**.

Entry	Isolated yield (%)	Catalyst recovery (%)
1	98	98
2	97	96
3	97	95
4	96	93
5	95	90

The morphologies of fresh SnO₂ nanoparticles, a composite sample containing SnO₂ nanoparticles and product, and SnO₂ nanoparticles recovered after three reactions were studied by field emission scanning electron microscopy (Fig. 1). The images of the fresh nanoparticles showed spherical grains with diameters of 30–60 nm with condensed structure and no aggregation (Fig. 1(a)). The image of the composite sample

Fig. 1. Field emission scanning electron microscopy images of fresh SnO₂ nanoparticles (a–c), a composite sample containing SnO₂ nanoparticles and reaction product (d–f), and SnO₂ nanoparticles recovered after three uses (g–i).

Scheme 2. SnO₂ nanoparticle-catalyzed synthesis of 1,4-DHPs.**Table 6**SnO₂ nanoparticle-catalyzed three-component Hantzsch synthesis of 1,4-DHPs from various aldehydes (RCHO).

Entry	R	Product	mp (°C)	Time (min)	Yield (%)	Ref.
1	Ph	5a	158–160	11	93	[52]
2	4-Cl-C ₆ H ₅	5b	145–147	7	95	[53]
3	4-OH-C ₆ H ₅	5c	231–233	9	94	[53]
4	4-OMe-C ₆ H ₅	5d	151–153	7	94	[52]
5	4-Me-C ₆ H ₅	5e	137–139	8	95	[54]
6	3-NO ₂ -C ₆ H ₅	5f	166–168	5	97	[54]
7	4-NO ₂ -C ₆ H ₅	5g	131–133	2	98	[53]
8	cinnamaldehyde	5h	120–122	14	93	[53]
9	furan-2-carbaldehyde	5i	161–163	11	93	[52]

showed the presence of cubic rectangular structures with lengths of >200 nm for reaction products and the presence of nanoparticles in the solution. The images of the nanoparticles recovered from the reaction medium revealed that some aggregates were present.

We also evaluated the use of SnO₂ nanoparticle-catalyzed three-component Hantzsch reactions for the efficient synthesis of 1,4-DHPs at room temperature (Scheme 2). The condensation of 2 mmol of ethyl acetoacetate with 1 mmol of each of various arylaldehydes and NH₄OAc in ethanol in the presence of SnO₂ nanoparticles rapidly furnished the desired 1,4-DHPs in high yields (Scheme 2).

Evaluation of the substrate scope of the reaction revealed that aromatic aldehydes with electron-withdrawing groups on the aromatic ring (Table 6, entries 6 and 7) reacted faster than aldehydes bearing electron-donating groups (entries 3–5).

4. Conclusions

SnO₂ nanoparticles efficiently catalyzed the Hantzsch condensation of various aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate in ethanol to produce polyhydroquinolines in excellent yields. The catalyst offered several advantages over previously reported catalysts, including fewer byproducts, mild reaction conditions, high yields, shorter reaction times, and lower catalyst loads; in addition, the reactions were simple to carry out, and the products were easy to isolate. The nanoparticle catalyst could be reused at least five times with only minimal reduction in catalytic activity of the recovered catalyst. These advantages of this catalyst make this method a benign, economical, and waste-free process for the synthesis of polyhydroquinolines.

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Graphical Abstract

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Synthesis of polyhydroquinoline derivatives via a four-component Hantzsch condensation catalyzed by tin dioxide nanoparticles

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A simple procedure for the SnO₂ nanoparticle-catalyzed preparation of polyhydroquinoline derivatives in aqueous ethanol at ambient temperature is described.

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