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Highly efficient one-pot four-component synthesis of polyhydroquinoline derivatives catalyzed by stannous chloride under solvent-free conditions

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ABSTRACT

A rapid and efficient one-pot, four-component protocol towards the synthesis of polyhydroquinoline derivatives has been developed. The condensation of aldehyde, dimedone, ethyl acetoacetate and ammonium acetate in presence of stannous chloride was carried out under solvent free condition to synthesize a variety of polyhydroquinoline derivatives in good to excellent yields. The present method provides several advantages such as mild reaction conditions, simple work-up procedure, short reaction time and high yields.

Keywords: *Polyhydroquinoline, Stannous chloride, One-pot synthesis, Solvent-free conditions.*

1. Introduction

Multi-component reactions (MCRs) have recently gained prime interest in synthetic organic chemistry due to their ability of building up the complex molecule in a single step. They also reduce the reaction time considerably and increase the yield of products than the normal multiple step methods. These reactions are effective for the synthesis of bioactive heterocyclic compounds which gives great access to medicinal chemistry. Hence, the uses of multi-component reaction protocols for the synthesis of heterocyclic compounds have attracted considerable current interest of various medicinal chemists [1-7]. During the last decades, a central objective in synthetic organic chemistry has been to develop greener and more economically competitive processes for the efficient synthesis of biologically active compounds with potential applications in the pharmaceutical or agrochemical industries. Thus, design of solvent-free catalytic reaction has received tremendous attention in recent times in the area of green synthesis. A solvent-free or solid state reaction may be carried out using the reactants alone or supporting them in clays, zeolite, silica, alumina or other matrices to achieve high degree of stereo selectivity in the products help to reduce byproducts and to maximize reaction rate [8].

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Solvent-free reactions obviously reduce pollution and bring down handling costs due to its simplification of experimental procedure and easy work up procedure.

Polyhydroquinoline is one of scaffold which found in natural product [9]. The synthesis of polyhydroquinoline compounds has attracted considerable attention in organic synthesis due to their highly absolute biological and physiological activities [10]. Derivatives of these compounds are known to possess important pharmaceutical, antifungal, antitumor and other bio-organic properties [11,12]. In addition, these compounds have found wide usage in drugs including nifedipine, nicardipine and amlodipine [13]. Recently, several synthetic methods have been developed for the preparation of polyhydroquinoline derivatives through the four-component coupling of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate using various catalysts like Sulfamic acid [14], nickel nano-particle [15], montmorillonite, organocatalyst [16-17], acetic acid [18], Sc(OTf) [19], GuHCl [20], t-BuOK [21], cerium(IV) ammonium nitrate [22], $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ [23], ZnO [24] and CuO [25]. These methods are valuable but they suffer from different drawbacks such as long reaction times, expensive catalysts, tedious work-up and unsatisfactory yields. Hence, the development of a simple and efficient protocol is still in demand.

Stannous chloride has gained widespread use as a Lewis acid catalyst in organic chemistry due to good

catalytic performance, problems related to corrosion, handling, recovery, and reuse. Tin salts have received considerable attention in heterogeneous organic reactions in different areas of organic synthesis [26-30] which is used for the synthesis of biological active heterocyclic compounds such as Diaminopyrazoles [31], imidazole [32] and quinoxaline [33]. It is relatively non-toxic, inexpensive, possess good stability and easy to handle.

In this communication, we wish to report rapid and efficient one-pot synthesis of polyhydroquinoline derivatives by the reaction of aldehyde, dimedone, and ethyl acetoacetate and ammonium acetate in presence of stannous chloride as a catalyst under solvent free condition. In contrast to the existing methods, our method is extremely rapid, simple and high yielding (Scheme 1).

2. Experimental

All chemicals were purchased from Sigma-Aldrich, SD fine chemicals companies and used without further purification. The progress of reaction was monitored by thin layer chromatography (TLC). The melting points of compounds were taken in an open capillary in a paraffin bath and uncorrected. FT-IR spectra were obtained with a Bruker, Germany (Model 3000 Hyperion microscope with vertex 80 FTIR system) spectrometer. ^{1}HNMR spectra were recorded on a Bruker Advance 400 and ^{13}CNMR was recorded on a Bruker DRX-300 instrument using TMS as an internal reference. Mass spectra were recorded on Waters UPLC-TQD Mass spectrometer using electrospray ionization technique.

2.1. General procedure for the synthesis of polyhydroquinoline derivatives

A mixture of aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1.5 mmol) and stannous chloride (0.12g) was heated in oil bath at 80°C, for the appropriate time. The progress of reaction was monitored by thin layer chromatography.

After completion of reaction, the reaction mixture was poured on crushed ice and stirred well. The solid product was filtered, washed with ice-water and recrystallized by using hot ethanol to get corresponding polyhydroquinoline derivatives in pure form. All the products (5a-m) were fully characterized by ^{1}HNMR, ^{13}C NMR and Mass spectroscopy techniques.

Selected spectral data

Ethyl-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenyl-quinoline-3-caboxylate (***5a***):

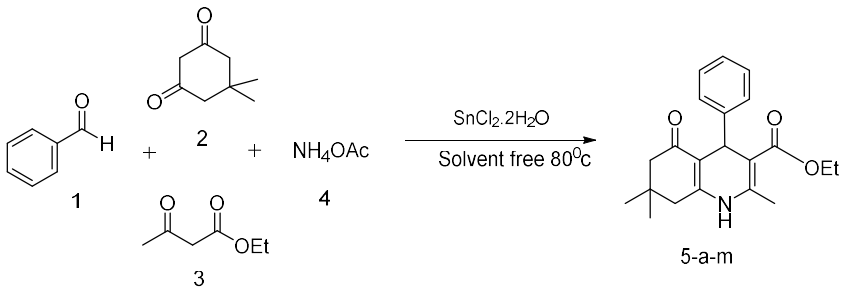
Yellow solid. m.p.= 203-205°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 0.92 (s, 3H, CH_3), 1.05 (s, 1H, CH_3), 1.80 (s, 3H, CH_3), 1.19-1.25 (t, 3H, CH_3), 2.10 (s, 2H, CH_2), 2.32 (s, 2H, CH_2) ,4.02-4.09 (q, 2H, CH_2), 5.05 (s, 1H), 6.78 (s, 1H, NH), 7.11-7.31 (m, 5H, Ar) ppm. ^{13}CNMR ($CDCl_3$, 75 MHz): δ= 14.40, 19.39, 27.30, 29.63, 32.83, 36.82, 41.05, 50.99, 59.97, 106.16, 112.09, 126.21, 128.05, 128.18, 143.97, 147.33, 149.14, 167.72, 195.94 ppm. EI-MS (%): m/z= 340.10 (M+1).

Ethyl-1,54,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-(4-bromophenyl)-quinoline-3-caboxylate (***5e***):

White solid. m.p.= 251-253°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 0.88-0.92 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.09-1.25 (t, 3H, CH_3), 1.69 (s, 3H, CH_3), 2.11 (s, 2H, CH_2), 2.32 (s, 2H, CH_2), 4.02-4.09 (q, 2H, CH_2), 5.01 (s, 1H), 6.25 (s, 1H, NH), 7.26-7.33 (m, 4H, Ar) ppm. ^{13}CNMR ($CDCl_3$, 75 MHz): δ= 14.41, 19.58, 27.33, 29.62, 29.89, 32.89, 36.53, 41.25, 50.90, 60.12, 105.87, 111.96, 120.00, 130.06, 131.14, 143.90, 146.30, 148.53, 167.41,1 95.71 ppm. EI-MS (%): m/z= 419.9(M+1).

Ethyl-1,54,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-(4-Hydroxy,3-methoxyphenyl)-quinoline-3-caboxylate (***5f***):

White solid. m.p.= 218-219°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 0.95-0.97 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.19-1.25 (t, 3H, CH_3), 1.61 (s, 3H, CH_3), 2.13 (s, 2H, CH_2), 2.37 (s, 2H, CH_2), 3.84-3.86 (s, 3H, CH_3), 4.04-4.11 (q, 2H, CH_2), 4.97 (s, 1H, OH, Ar), 5.44 (s, 1H, CH), 5.86 (s, 1H, NH), 6.67-7.26 (m, 3H, Ar) ppm. ^{13}CNMR ($CDCl_3$, 75 MHz): δ= 14.51, 19.71, 27.31, 29.67, 32.92, 36.25, 41.39, 50.94, 56.03, 60.01, 106.52, 111.55, 112.65, 114.08, 120.41, 139.65, 143.19, 143.95, 145.96, 147.86, 167.71, 195.82 ppm. EI-MS (%): m/z= 387.87(M+1).



Scheme 1. Synthesis of polyhydroquinoline.

Ethyl-1,54,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-(4-Thionyl phenyl)-quinoline-3-caboxylate (***5g***):

Brown solid. m.p.= 238-240°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 1.02-1.06 (s, 3H, CH_3), 1.09-1.11 (s, 3H, CH_3), 1.23-1.29 (t, 3H, CH_3), 1.68 (s, 3H, CH_3), 2.09 (s, 2H, CH_2), 2.40 (s, 2H, CH_2), 4.10-4.18 (q, 2H, CH_2), 5.41 (s, 1H), 6.79 (s, 1H, NH), 6.80-7.26 (m, 3H, Ar) ppm. ^{13}CNMR ($CDCl_3$, 75 MHz): δ= 14.51, 19.64, 27.49, 29.73, 31.47, 32.93, 41.32, 50.92, 60.19, 111.96, 123.28, 123.66, 126.64, 144.06, 148.47, 151.22, 167.39, 195.55 ppm. EI-MS (%): m/z= 346.88 (M+1).

3. Results and Discussion

In search of the best experimental reaction conditions for the preparation of polyhydroquinoline, reaction of benzaldehyde **1**, dimedone **2**, ethyl acetoacetate **3** and ammonium acetate **4** was selected as a model reaction (Scheme 1). During our initial study, various acid catalysts bearing chloride functionalities were screened, owing to their widespread catalytic applications in organic synthesis. For this purpose, $ZnCl_4$, $TiCl_4$, $SbCl_4$, $AlCl_3$ and $SnCl_2$. H_2O were screened. (Table No. 1) no reaction occurs in the absence of catalyst. (Table 1, entry 1)

During optimization studies, all the above mentioned catalysts were examined under solvent-free condition. When $ZnCl_4$ and $TiCl_4$ were used as catalyst, reaction rate was very slow and product was obtained in lower yield (Table 1, entries 2 and 3). While $SbCl_4$ and $AlCl_3$ afforded the desired compound in acceptable yield, (Table 1, entries 4 and 5). In comparison, $SnCl_2.2H_2O$ proved as an excellent catalyst and providing the product in excellent yield (Table 1, entry 6) and therefore, it was selected as a catalyst of choice for further studies.

For comparison of solvents, the same reaction was performed in the presence of solvents like ethanol, water, chloroform, DMF, DMSO and under solvent-free conditions (Table-2, entries 1-6). Among the solvents examined, ethanol proved to be the most effective. The yield of product was lower in water, chloroform, DMF and DMSO. It was found that in a solvent less system, the yield of product was increased and reaction time decreased. However, solvent-free reactions are preferable not only for their efficiency and simplicity but also as green and sustainable procedures.

To establish the appropriate amount of the catalyst, we investigated the model reaction using varied concentrations of $SnCl_2$. H_2O such as 0.02, 0.04, 0.06, 0.08, 0.10, 0.12 and 0.14 g. In this study, formation of the product was observed in 61%, 69%, 75%, 84%, 92% and 92% yield, respectively. It was found that maximum yield (92%) obtained, when the reaction was loaded with 0.12 g of $SnCl_2.2H_2O$ Further increase in the concentration of catalyst up to 0.14 g. was not increase the yield of product. This indicated that 0.12 g of $SnCl_2.2H_2O$ is sufficient to carry out the reaction smoothly.

Table 1. Screening of different catalysts[a].

Entry	Catalyst	Time (min.)	Yield[b] (%)
1	No Catalyst	6h	Nr
2	$ZnCl_4$	20	58
3	$TiCl_4$	20	62
4	$SbCl_3$	20	65
5	$AlCl_3$	20	68
6	$SnCl_2.2H_2O$	10	92

[a]Reaction conditions: aldehyde (1mmol), dimedone (1 mmol), ethyl acetoacetate (1mmol), ammonium acetate (1.5 mmol) and respective catalyst (0.12g) at 80°C under solvent free conditions.
[b]Isolated yield.

Table 2. Screening of various solvents[a].

Entry	Solvent	Amount of $SnCl_2$ (g)	Temp. (°C)	Time (min.)	Yield[b](%)
1	Ethanol	0.12	78	3h	55
2	Water	0.12	100	4h	26
3	Chloroform	0.12	65	4h	25
4	DMF	0.12	45	6h	0
5	DMSO	0.12	56	3h	15
6	Solvent-free	0.12	80	10	92

[a]Reaction conditions: Aldehyde (1mmol), dimedone (1 mmol), ethyl acetoacetate (1mmol), ammonium acetate (1.5 mmol), $SnCl_2$ (0.12 g).
[b]Isolated yield.

Table 3. Screening of catalyst concentration[a].

Entry	Amount of $SnCl_2$ (g.)	Time (min.)	Yield[b](%)
1	No Catalyst	6h	Nr
2	0.02	30	61
3	0.04	26	69
4	0.08	21	75
5	0.10	14	84
6	0.12	10	92
7	0.14	10	92

[a]Reaction conditions: aldehyde (1mmol), dimedone (1mmol), ethyl acetoacetate (1mmol), ammonium acetate (1.5 mmol), $SnCl_2$ (in g) at 80°C under solvent free conditions.
[b]Isolated yield.

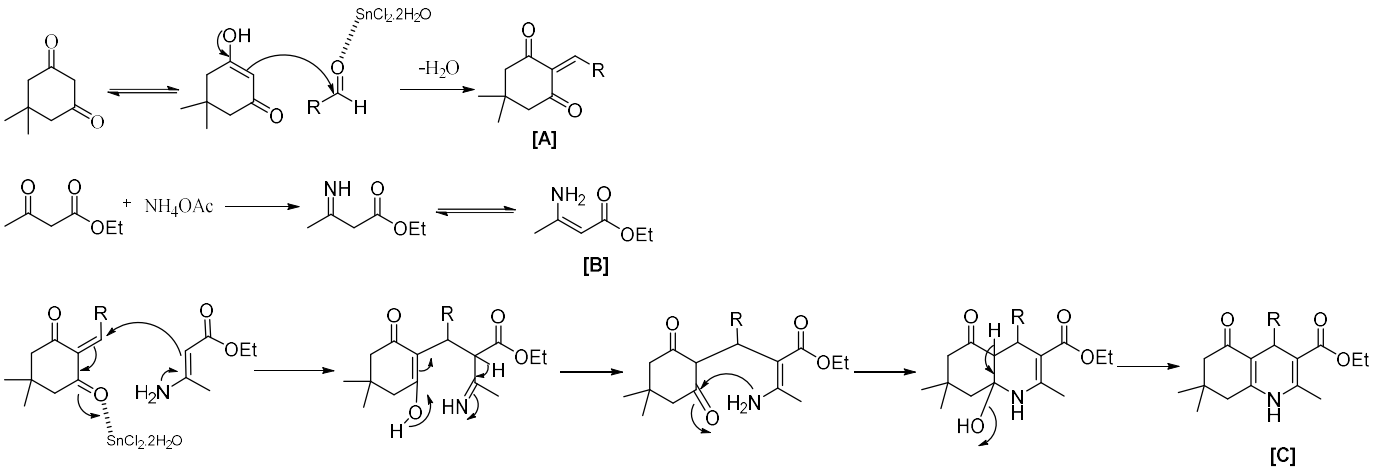
In further attempts, to reduce the reaction time and increase the product yield, the model reaction was tested at different temperatures. The product yield increases as we increase the temperature. Further enhancement in temperature does not affect the product yield. We found that stannous chloride dehydrates showed high catalytic activity with very short reaction times. Moreover, can be recovered and reused without significant loss of activity.

The proposed mechanism shows the preparation of the polyhydroquinoline (Scheme 2). In initial stage $SnCl_2.2H_2O$ enhances the elecrophilicity of carbonyl carbon of aldehyde, then dimedone react with the aldehyde to form intermediate (**A).** Intermediate (**B**) was formed by the reaction of ethyl acetoacetate and ammonium acetate. Then intermediate 1 and 2 undergoes cyclocondensation to yield final desired product (**C**).

Table 4. Screening of temperature.

Entry	Amount of $SnCl_2$ (g.)	Temp. (°C)	Time (min.)	Yield[b](%)
1	0.12	r.t.	6h	0
2	0.12	50	4h	15
3	0.12	60	3h	25
4	0.12	70	25	75
5	0.12	80	10	92
6	0.12	90	10	92

[a]Reaction conditions: aldehyde (1mmol), dimedone (1 mmol), ethyl acetoacetate (1mmol), ammonium acetate (1.5 mmol), $SnCl_2$ (0.12 g).
[b]Isolated yield



Scheme 2. A plausible mechanism for the synthesis of polyhydroquinoline.

The scope of the reaction was verified by taking various aldehydes and subjected to the reaction along with dimedone, ethyl acetoacetate and ammonium acetate as their counterparts in the reaction. The results of synthesis of polyhydroquinoline derivatives are summarized in Table 5. The aromatic aldehydes bearing electron donating and electron withdrawing groups as well as heterocyclic aldehydes gave good yields.

4. Conclusions

In conclusion, we have developed a very simple and efficient method for the high yielding synthesis of polyhydroquinoline derivatives by one-pot four-component condensation of dimedone, ethyl acetoacetate, aldehydes and ammonium acetate using stannous chloride as a catalyst**.** The catalyst is inexpensive and easily available. Moreover, mild reaction conditions, simple procedure, cleaner reactions, short reaction times, easy workup and excellent yields of products are salient features of the presented work.

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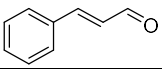
Table 5. Synthesis of polyhydroquinoline derivatives.

Entry	R	Product	Time (min)	Yield[a] (%)	m.p. (°C) Found	m.p. (°C) Reported	Ref.
1	C_6H_5	5a	5	92	203-204	202-204	[21]
2	4-OH-C_6H_4	5b	7	90	231-232	232-233	[23]
3	4-NO_2-C_6H_4	5c	9	87	241-243	245-247	[12]
4	4-OMe-C_6H_4	5d	5	88	260-261	254-256	[23]
5	4-Br-C_6H_4	5e	7	91	251-253	251-252	[21]
6	3-OMe-4-OH-C_6H_3	5f	6	91	205-209	202-204	[21]
7	2-Thienyl	5g	5	90	238-240	-	-
8	4-$(CH_3)_2$-N-C_6H_4	5h	7	88	262-264	261-263	-
9	4-Cl-C_6H_4	5i	10	92	243-244	244-246	[12]
10	4-F-C_6H_4	5j	9	87	183-185	184-185	[21]
11	3,4-$(OME)_2$-C_6H_3	5k	7	89	195-197	197-199	[23]
12	4-Me-C_6H_4	5l	5	86	261-262	265-268	[28]
13		5M	6	86	203-205	204-206	[29]

[a]Isolated yield.

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