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Synthesis of Pharmaceutical Polyhydroquinolines Catalyzed by Cobalt (II) Complex as Reusable Catalyst

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ABSTRACT

Polyhydroquinolines have been synthesized efficiently using a novel Co(II) complex based on5-nitro-N^1-((pyridin-2-yl)methylene)benzene-1,2-diamine(CoL_2). This green catalyst has been utilized in a one-pot four-component Hantzsch condensation of dimedone, aldehydes, ethyl acetoacetate and ammonium acetate under solvent and free-solvent conditions. This method offers several advantages such as easy isolation of product, environmentally benign and excellent yields.

Keywords: Polyhydroquinoline, Hantzsch Condensation, Co(II) Complex, Dimedone, Ethyl Acetoacetate

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INTRODUCTION

During the last decades, an increasing interest has been paid to the application of heterogeneous reusable catalysts in organic synthesis owing their easy work-up, easy filtration, high their surface-to-volume ratio and minimization of cost and waste generation [1-3].

Multi Component Reactions (MCRs) allow the creation of several bonds in a single operation and are known as an efficient and powerful tool for the synthesis of complex organic molecules. Also, this manner is very fast and impressive without the isolation of any intermediate [4-8]. Multicomponent reactions have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [9, 10].

In recent years, great attention has been focused to the synthesis of polyhydroquinolines because of its high biological and pharmacological applications such as antimicrobial [11], antitubercular [12] and neuroprotectant agents [13].

The general procedures for the preparation of polyhydroquinolines include a multicomponent condensation of dimedone, aldehydes, ethyl acetoacetate and ammonium acetate (Hantzsch reaction) in the presence of various catalysts such as montmorillonite [14], $HClO_4$-SiO_2[15], ionic liquids [16], $Yb(OTf)_3$ [17], Ni nanoparticles [18] and microwave [19].

However, most of these methodologies suffer from certain drawbacks such as long reaction times, tedious workup, harsh reaction conditions, high costs and unsatisfactory yields. Therefore, the development of efficient, high-yielding, environmentally benign and versatile method for the preparation of polyhydroquinolines is required. In continuation of our efforts in the development of new routes for the synthesis of heterocyclic compounds using green catalysts [20-22], herein we would like to report an efficient Hantzsch synthesis in the presence of catalytic amount of Co(II) complex (CoL_2) under solvent-free conditions, using dimedone (1), aromatic aldehydes (2), ethyl acetoacetate (3) and ammonium acetate (4) to produce the polyhydroquinoline derivatives(5) in excellent yields (Fig. 1).

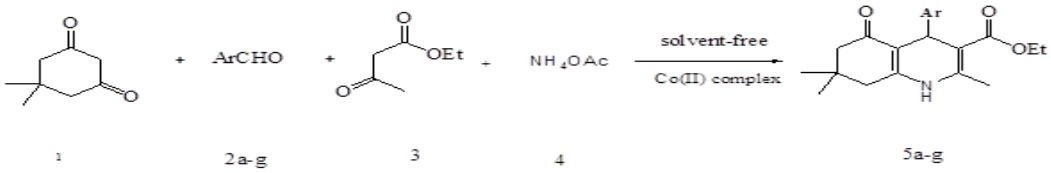

Figure 1: Co(II) complex catalyzed synthesis of polyhydroqunolines

Table 1: Effect of amount of catalyst, solvent and temperature in the model reaction

Entry	Catalyst (g)	Solvent	Temp (°C)	Time (min)	Yield (%)
1	----	----	25	18	trace
2	0.03	----	25	60	30
3	0.05	----	25	60	42
4	0.07	----	25	60	60
5	0.10	----	25	25	86
6	0.15	----	25	25	87
7	0.10	----	45	25	86
8	0.10	----	60	25	88
9	0.10	EtOH	Reflux	60	55
10	0.10	DMF	Reflux	60	50
11	0.10	MeCN	Reflux	60	45

Table 2: Synthesis of polyhydroquinolines under optimized conditions

Entry	Ar	Product	Time (min)	Yield (%)	Melting point (°C)	
					Found	Reported
1	C_6H_5	5a	28	86	186-189	180-185[3]
2	4-ClC_6H_4	5b	33	84	244-247	246-248[3]
3	3-$NO_2C_6H_4$	5c	38	91	180-181	181-183[3]
4	4-OHC_6H_4	5d	25	89	232-236	239-241[3]
5	4-$MeOC_6H_4$	5e	30	90	253-255	257-259[3]
6	3-BrC_6H_4	5f	35	85	232-234	234-36[23]
7	4-BrC_6H_4	5g	25	86	250-253	259-260[3]
8	4-$NO_2C_6H_4$	5h	38	93	240-243	245-247[3]
9	2,4-$(MeO)_2C_6H_3$	5i	30	88	207-210	--------
10	2,4-$Cl_2C_6H_3$	5j	30	84	242-245	242-44[23]

Initially, in order to find the optimal conditions, the reaction of dimedone, benzaldehyde, ethyl acetoacetate and ammonium acetate (1 mmol each**)** in the presence of various amounts of the catalyst (CoL_2) in different solvents and under solvent-free conditions used as a model reaction (Table 1).

The best result has been obtained at (0.1g) of catalyst under solvent- free conditions at 25°C(Table1, Entry 5). In the absence of catalyst, the product5a was obtained in trace amount after 150 min.

The generality of this process was demonstrated by the wide range of aromatic aldehydes to synthesize the corresponding products in high yields (Table 2).

MATERIALS AND METHODS

All the reagents and solvents were purchased from Merck Company and used without further purification. Melting points were recorded on a Stuart SMP3 melting point apparatus. IR spectra were recorded on a Tensor 27 Bruker spectrophotometer using KBr disks. The ^{1}HNMR and ^{13}CNMR spectra were obtained on Bruker 300 and 75 MHz spectrometer using TMS as an internal standard. The compounds were identified by the comparison of their physical and spectroscopic data with those of known compounds. All products were known by spectral

data and comparison of their melting points with those of authentic sample (Table 2).

Synthesis of the Co(II) complex

The Schiff base ligand and cobalt (II) complex was synthesized according to earlier work. A metanolic solution of the ligand (1 mmol in 3 mL) was added dropwise to a solution of $Co(OAc)_2.4H_2O$ (1 mmol) in 3 mL methanol. The mixture was refluxed for 4 h. The products formed were filtered and washed with diethyl ether. Finally, the complex was left to dry at room temperature[21].

General procedure for the synthesis of polyhydroquinolines(5a-5j)

A mixture of dimedone 1 (1 mmol), an aromatic aldehydes 2a-j (1 mmol), ethyl acetoacetate 3 (1 mmol), ammonium acetate 4(1 mmol) and catalyst (CoL_2)(0.10 g) was stiredat 25°C for 25-38 min. The reaction was monitored using thin- layer chromatography (TLC). After completion of the reaction, cold ethanol was added. The precipitate was filtrated and recrystallized from ethanol to give products 5a-j in high yields.

Because of solubility of the catalyst in ethanol, the filtrate was evaporated under reduced pressure and catalyst was recycled by a simple filtration. The separated catalyst reused in model reaction without appreciable reduction in the catalytic activity. The results of the first experiment and subsequent experiments were almost consistent in yields (84, 82 and 79%).

Selected Spectral data

Ethyl4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5e)

IR (KBr disk) ν: 3280 (N-H), 1609 (C=O), 1499 (C=C), 1220 (C-N) cm^{-1}.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.87 (S, 3H, CH_3), 1.02 (S, 3H,CH_3), 1.13 (t, 3H, CH_3), 2.15-2.32 (m, 4H, $2CH_2$), 3.68 (S, 3H, OCH_3), 4.00 (q, 2H, OCH_2), 4.80 (S, 1H, CH), 9.03 (S, 1H, NH), 6.74-6.77 (d, 2H, arom-H), 7.05-7.08 (d, 2H, arom-H).

^{13}C-NMR (75 MHz, DMSO-d_6) δ: 14.64, 18.73, 26.98, 29.61, 32.60, 35.39, 50.75, 55.32, 59.46, 104.40, 110.67, 113.56, 128.86, 140.49, 145.09, 149.72, 157.75, 167.41, 194.66.

Ethyl4-(3-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5f)

IR (KBr disk) ν: 3273 (N-H), 1603 (C=O), 1486 (C=C), 1211 (C-N) cm^{-1}.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.15 (S, 3H, CH_3), 1.17 (S, 3H,CH_3), 1.98 (t, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.21-2.31 (m, 4H, $2CH_2$), 3.95 (q, 2H, OCH_2), 4.84 (S, 1H, CH), 9.16 (S, 1H, NH), 7.14-7.31 (m, 4H, arom-H).

^{13}C-NMR (75 MHz, DMSO-d_6) δ:14.57, 18.79, 26.84, 29.56, 31.70, 32.66, 36.54, 50.60, 59.64, 103.45, 109.89, 121.47, 126.98, 129.05, 130.62, 130.83, 146.06, 150.33, 150.71, 167.05, 194.78.

RESULTS AND DISCUSSION

Treatment of dimedone, aromatic aldehydes, ethyl acetoacetate and ammonium acetate in the presence of a catalytic amount of Co(II) complex gave products which were identified as polyhydroquinolines. All products gave satisfactory spectral data in accord with the assigned structures.

CONCLUSION

In conclusion, a simple and convenient method for the synthesis of polyhydroquinolinesthrough a Hantzsch condensation using a new solid acidic catalyst, Co(II) complex was reported. The catalyst showed high catalytic activity in the synthesis of polyhydroquinolines. Some attractive features of this method are high yields, short reaction times and recyclability and reusability of the catalyst.

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