

An Efficient and Facile Synthesis of Polyhydroquinolines through Hantzsch Reaction Catalyzed by a Novel and Reusable Cu (II) Complex

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Abstract

Usually, polyhydroquinolines have prepared effectively in a four-component Hantzsch reaction using a novel Cu (II) complex. This green and reusable Catalyst is used in one case condensation reaction of dimedone, various aldehyde, ammonium acetate and ethyl acetoacetate under solvent and free-solvent conditions. This method offers many advantages such as simple work-up procedure, mild reaction conditions, easy isolation of product, environmentally benign and high product yield.

Keywords: Polyhydroquinoline, Hantzsch Condensation, Cu (II) Complex, Dimedone, Reusable Catalyst.

Introduction

During the last decades, the application of heterogeneous reusable catalysts attracted great attention in modern chemical composition because easy work-up, easy filtration and reusability (Zeinali-Dastmalbaf *et al.*, 2011). Furthermore, an increasing interest directed to development and guidance new methods for the synthesis of heterocyclic compounds due to their significant biological and pharmaceutical activity.

Multicomponent reactions (MCRs) are the powerful tools that allow the formation of several bonds in a single action and are known as an eco-friendly method for the synthesis of organic molecules. Also, this way is very rapid and efficient without isolating any intermediary (Domling and Ugi, 2000). Multicomponent reactions have appeared as valuable tools for the synthesis of heterocyclic compounds with biological activities (Ugi *et al.*, 1994; Ugi *et al.*, 2000).

Polyhydroquinolines are a class of fused 1,4-dihydropyridine contains a variety of Biological activities like antimicrobials (Murthy *et al.*, 2012), antitubercular (Trivedi *et al.*, 2011) and

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antioxidant agents (Vijesh *et al.*, 2011).

Polyhydroquinolines are generally synthesized by one-pot Hantzsch reaction of dimedone, ethyl acetoacetate, aldehydes and ammonium acetate use various catalysts such as montmorillonite (Song *et al.*, 2005), ionic liquids (Ji *et al.*, 2004), Yb(OTf)₃ (Wang *et al.*, 2005), Ni nanoparticles (Sapkal *et al.*, 2009) and carbon nanotubes support cobalt catalyst (Trepanier *et al.*, 2011).

Many of these methodologies they suffer from certain problems including, long reaction times, harsh conditions of reaction and unsatisfactory yields. Therefore, the development of efficient, high-yielding and environmentally benign method is desired.

It is therefore of interest to the review behavior of new Cu(II) complex (CuL) as catalyst for the synthesis of some of polyhydroquinolines. In continuation of our studies toward the development of new routes to the synthesis of heterocyclic compounds (Allameh *et al.*, 2011; Khoshdast *et al.*, 2017), herein we report the catalytic effects of Cu (II) complex (CuL) for the synthesis of polyhydroquinoline derivatives (Fig. 1).

In order to optimize the reaction conditions, the reaction of dimedone, ammonium acetate, benzaldehyde, ethyl acetoacetate (1 mmol each) and various amounts of the catalyst (CuL) in various solvents and in non-solvent conditions selected as a model reaction (Table 1).

The best result is 0.03 g of catalyst under solvent-free conditions at 100°C (Table 1, Entry 7). In the absence of catalyst, the product 5a was obtained in trace amount after 150 min.

The generality of this protocol under optimized conditions was demonstrated by different aryl aldehydes to synthesize the products are good at good returns (Table 2).

Experimental

All the reagents were commercially available from Merck company. Melting point was determined on Stuart SMP3 apparatus. The IR spectra were obtained on a Tensor 27 Bruker spectrophotometer as KBr disks. The ¹H NMR spectra (300 MHz) were obtained using Bruker 300 spectrometer. The compounds were identified by the Comparison of the melting point and their spectral data with 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 new schiff base

4-amino-3-methyl-1H-1,2,4-triazole-5(4H)-thione (1mmol, 0.130 g) and 2,4-dihydroxybenzaldehyde (1 mmol, 0.138 g) was added to a solution of ethanol (2ml) and 2 drop of hydrochloric acid. The reaction mixture was It was mixed up for 80 min at reflux condition (Raouf et al., 2019). After this time, the light pink product was filtered and washed with ethanol to give the Schiff base (M.p: 280-282 °C, yield: 90%) (Fig. 2).

Synthesis of the Cu (II) complex

A solution of methanolic ligand (1mmol, in 3 mL) was added dropwise to a solution of CuCl₂·2H₂O (1mmol, in 3 mL methanol). The mixture has refluxed for 4 h to give the new complex. After completion of reaction, the copper (II) complex was filtered and washed with cold ether.

General procedure for the preparation of polyhydroquinolines (5a-5f)

A mixture of dimedone 1, aryl aldehydes 2a-f, ethyl acetoacetate 3 and ammonium acetate 4 (1 mmol of each) The existence of a catalytic amount was unpleasant (CuL) (0.05 g) was heated on the oil bath at 100°C for 29-35 min. In the end of the reaction (monitored by TLC), The reaction mixture was cooled to room temperature precipitate was filtered and washed with hot ethanol to give products 5a-f in high yields. Since the catalyst was soluble in ethanol, the filtrate was evaporated and catalyst was recycled by a simple filtration. The recycled catalyst used in model reaction without considerable reduction in the catalytic activity (92% for 1 st use, 90% for 2 nd use and 86% for 3 rd use).

Selected Spectral data

Ethyl 4-phenyl-2, 7, 7-trimethyl-5-oxo-1, 4, 5, 6, 7, 8-hexahydroquinoline-3-carboxylate (5a)

¹H NMR (300 MHz, DMSO-d₆): δ 0.8 (s, 3H, CH₃), 1.0 (s, 3H, CH₃), 1.2 (t, 3H, CH₃, OEt), 2.3 (s, 3H, CH₃), 2.0 (m, 4H, 2CH₂), 4.0 (q, 2H, OCH₂), 4.9 (s, 1H, CH), 7.1-7.4 (m, 5H, arom-H), 9.1 (s, 1H, NH). IR (KBr disc): 1617 (C=O, keton), 1699 (C=O, ester), 3290 (NH) cm⁻¹.

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

¹H NMR (300 MHz, DMSO-d₆): δ 0.9 (s, 3H, CH₃), 1.0 (s, 3H, CH₃), 1.2 (t, 3H, CH₃, OEt), 2.1 (s, 3H, CH₃), 2.3 (m, 4H, 2CH₂), 2.5 (s, 3H, OCH₃), 4.0 (q, 2H, OCH₂), 4.8 (s, 1H, CH), 6.8-7.3 (m, 4H, arom-H), 9.1 (s, 1H, NH). IR (KBr disc): 1607 (C=O, keton), 1700 (C=O, ester), 3277 (NH) cm⁻¹.

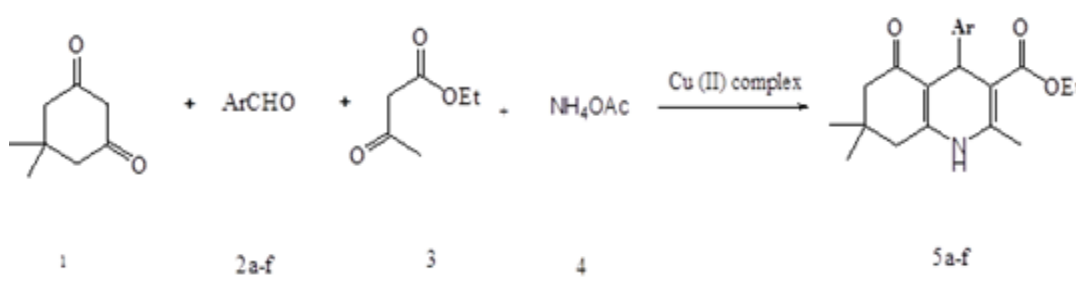


Figure 1: synthesis of polyhydroquinolines catalyzed by Cu(II) complex

Table 1- Optimization of model reaction conditions catalyzed Cu (II) complex

Entry	Catalyst (g)	Solvent	Temp (°C)	Time (min)	Yield (%)
1	----	----	110	150	----
2	0.01	----	80	45	52
3	0.02	----	80	45	58
4	0.03	----	80	45	61
5	0.01	----	90	30	72
6	0.02	----	90	30	80
7	0.03	----	100	30	92
8	0.03	----	110	30	94
9	0.03	----	120	30	94
10	0.10	H ₂ O	Reflux	90	47

11	0.05	EtOH	Reflux	80	72
12	0.05	MeOH	Reflux	120	55
13	0.05	CHCl ₃	Reflux	100	52

Table 2- Synthesis of polyhydroquinolines under optimized conditions

Entry	Ar	Product	Time (min)	Yield (%)	Melting pint (°C) (Davoodnia <i>et al.</i> , 2013)	
					Found	Reported
1	C ₆ H ₅	5a	30	92	220-222	214-216
2	4-BrC ₆ H ₄	5b	35	88	252-255	259-260
3	4-MeOC ₆ H ₄	5c	32	87	260-262	257-259
4	4-NO ₂ C ₆ H ₄	5d	31	95	241-242	245-247
5	4-MeC ₆ H ₄	5e	29	87	263-266	257-260
6	4-HOC ₆ H ₄	5f	34	85	234-236	239-241

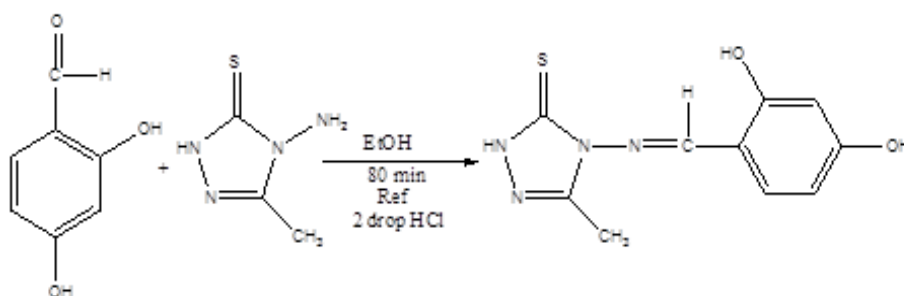


Figure 2: Synthesis of new schiff base

Results and Discussion

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

Conclusion

It should be noted that, we reported an efficient and green method for synthesis a some of polyhydroquinolines using a new Cu (II) complex as a catalyst from the Hantzsch condensation. The catalyst showed high activity for the synthesis polyhydroquinolines. Some advantaes of this method are high yields, short reaction times and recyclability of the catalyst.

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