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Nano CeO_2/ZnO: A powerful catalyst for the very fast synthesis of quinoxaline

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Quinoxaline derivatives were efficiently synthesized from the condensation of the *o*-phenylenediamines and 1, 2-dicarbonyl compounds in the presence catalytic amounts of Nano CeO_2/ZnO in good yields.

Nano CeO_2/ZnO was found to be an effective catalyst for the synthesis of quinoxaline derivatives from the condensation of the 1, 2-diamines and 1, 2-dicarbonyl compounds in good yields. The catalyst is recyclable and reusable.

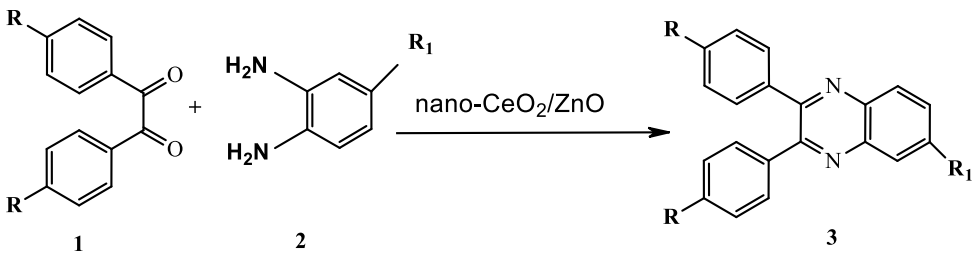
Keywords: Quinoxaline; 1,2-Diketones; *o*-phenylenediamines; Nano CeO_2/ZnO

INTRODUCTION

Quinoxalines are important heterocycles in medicinal chemistry [1]. Quinoxalines display a broad spectrum of biological activity [2] which has made them privileged structures in combinatorial drug discovery libraries [3]. They have also found applications as dyes, efficient electroluminescent materials, organic semiconductors, dehydroannulenes, cavitands and chemically controllable switches [4]. They have been reported for their applications in dyes [5], pharmaceuticals [6], and have also been used as building blocks for the synthesis of organic semiconductors [7].

Quinoxaline ring is a part of various antibiotics such as Echinomycin, Levomycin and Actinoleutin [8] that are known to inhibit growth of gram positive bacteria and are active against various transplantable tumors [9]. Despite remarkable efforts made in the last decade, the development of an effective method for the synthesis of quinoxaline ring is still an important challenge. A number of synthetic strategies have been developed for the preparation of substituted quinoxalines [10-12]. Most common method is the condensation of aromatic 1, 2-diamine with 1, 2-dicarbonyl compound in refluxing ethanol or acetic acid [13]. However, many improved methods have been reported for the synthesis of quinoxalines using catalytic amounts of various metal precursors such as $Pd(OAc)_2$, $RuCl_2$-$(PPh_3)_3$-TEMPO, MnO_2, acids and zeolites[14]. In addition, microwave [15], solid phase synthesis [16], bicatalyzed (bismuth and copper) oxidative coupling of peroxides and ene-1, 2-diamines [17] were also reported. Very recently molecular iodinewas used as catalyst for the synthesis of quinoxaline derivatives by Shivaji et al. [18a] in acetonitrile medium and by Rajesh et al. [18b] in dimethyl sulfoxide medium.

Many of these methods suffer from one or more limitations such as harsh conditions, low yields, long reaction times, critical product isolation procedures and co-occurrence of several side products. The main disadvantage of the existing methods is that the catalyst cannot be recovered and reused. Hence, there is still a need to develop improved methods for the synthesis of quinoxaline derivatives paying attention avoid toxic reagents, economic viability and operational simplicity. In connection with our recent interested aimed at the development of efficient protocols for the preparation of biological active heterocycles [19], we herein report an efficient method for the synthesis of quinoxaline derivatives from the condensation of the 1, 2-diamines and 1, 2-dicarbonyl compoundsin good yields. (Scheme 1)



1 2 3

Scheme 1

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In our attempts to develop new catalyst systems, we are selected nano CeO_2/ZnO as a new catalyst for the synthesis of quinoxaline derivatives.

RESULT AND DISCUSSION

In a typical procedure, *o*-phenylenediamine (1 mmol) and benzil (1 mmol) in the presence of a catalytic amount of nano CeO_2/ZnO in methanol at reflux temperature for 10 min afforded the desired quinoxaline (3a) in 96% yield (Entry 1, Table 1).

In order to show the generality and scope of this new protocol, we used various 1, 2-diamine and 1, 2-dicarbonyl compounds in the presence of nano CeO_2/ZnO, and the results are summarized in Table 1. Most of the reactions proceeded very cleanly at reflux temperature and no undesirable side-reactions were observed. The variations in the yields were very little and both substituted aromatic diamines such as 4-nitro and 4-methyl gave the condensed products in excellent yields with substituted 1, 2-diketones.

Yields refer to isolated products.

We performed the effect of various solvents on the synthesis of **3a**. This reaction was carried out in various solvents such as CH_3CN, Ethanol, methanol, CH_2Cl_2, chloroform, and DMSO. As shown in Table 2, the best result in terms of yield and time was obtained in methanol.

Table 1. Synthesis of quinoxalines using nano CeO_2/ZnO under refluxing condition.

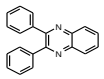
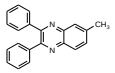
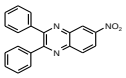
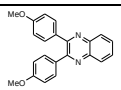
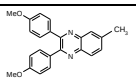
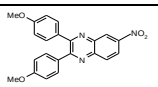
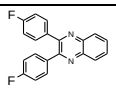
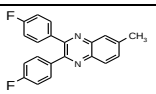
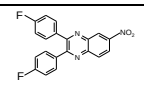
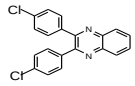
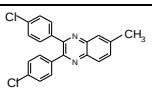
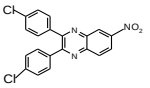
Entry	R	R1	product	Time (hr)	m.p.(°C)	Yield(٪)a
3a	H	H		1	128-129	96
3b	H	CH_3		1	117-118	96
3c	H	NO_2		1	193-194	94
3d	OCH_3	H		1	151-152.5	92
3e	OCH_3	CH_3		1	125-127	96
3f	OCH_3	NO_2		1	192-194	95
3g	F	H		1	135-137	94
3h	F	CH_3		1	165-167	93
3i	F	NO_2		1	174-176	95
3j	Cl	H		1	195-196	96
3k	Cl	CH_3		1	180	94
3l	Cl	NO_2		1	176	93

Table 2. Solvent effect on the synthesis of 6-Methyl-2, 3-diphenylquinoxaline catalyzed by Nano CeO_2/ZnO

Entry	Solvent	Conditions	Time	Yield (%)
1	$CHCl_3$	reflux	24h	40
2	CH_3CN	reflux	1h	40
3	H_2O	reflux	1h	87
4	EtOH	reflux	1h	91
5	CH_3OH	reflux	1h	96

Reusability of NANO CeO_2/ZnO

Next, we investigated the reusability and recycling of nano CeO_2/ZnO. At the end of the reaction, the catalyst could be recovered by a simple filtration. The recycled catalyst could be washed with ethylacetate and subjected to a second run of the reaction process. In Table 3, efficiency of nano CeO_2/ZnO in synthesis of **3a** for the five runs is reported. As it is shown in Table 3, the first reaction using recovered nano CeO_2/ZnO afforded similar yield to those obtained in the first run. In the second, third, fourth and fifth runs, the yield were gradually decreased.

Table 3. Reuse of the nano CeO_2/ZnO for synthesis of 3a

Entry	Time(min)	Yield (%)[a]
First run	10	96
Second run	10	94
Third run	10	92
Fourth run	10	85
Fifth run	10	83

(a) Isolated yields

In order to show the merit of the present work in comparison with some reported protocols, we compared the results of the synthesis of **3a** (entry1 in Table 1) in the presence of several catalysts with respect to the reaction times (Table 4). The best condition was obtained in the presence of nano CeO_2/ZnO.

Table 4. Comparison the results of the synthesis of (3a) using different catalysts

Entry	Catalyst	Time (min)	Yield (%)	References
1	polyaniline-sulfate salt	20	95	[20]
2	I_2	35	95	[21]
3	[TMPSA] HSO_4	15	90	[22]
4	Zn[(L)proline]	10	95	[23]
5	$CuSO_4.5H_2O$	15	96	[24]
6	Mont K-10	150	100	[25]
7	nano CeO_2/ZnO	10	96	This work

a) Isolated yields.

It is noteworthy to mention that in the absence of Nano CeO_2/ZnO, the reaction gave only a 20% yield at the same temperature after 24 h. Nano CeO_2/ZnO, therefore, was crucial to this type of reaction.

We also evaluated the amount of Nano CeO_2/ZnO required for this transformation and the best result is 0.05 g of the catalyst

Table 5. Synthesis of 3a using various maount of CeO_2/ZnO

Entry	Nano- CeO_2/ZnO (g)	Time (min)	Yield(%)a
1	No catalyst	24h	20
2	0.03	50	91
3	0.05	50	96
4	0.07	50	96
5	0.1	50	96

EXPERIMENTAL

All products are known compounds and were characterized by mp, IR, ^{1}H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H NMR 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.

PREPARATION OF QUINOXALINE DERIVATIVES: GENERAL PROCEDURE

To a mixture of an appropriate o-phenylenediamine (1mmol) and a 1, 2-dicarbonyl

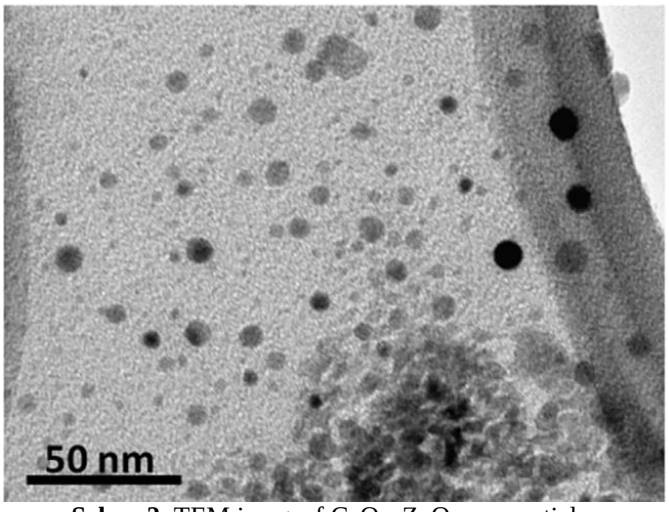
compound (1mmol) in methanol (5 mL), a catalytic amount of nano CeO_2/ZnO (0.05g) was added and the mixture was refluxed. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated, then diethylether was added to the solidified mixture in order to separation of catalyst from the mixture since the catalyst is not soluble in organic solvent. The residue was then diluted with 5% $NaHCO_3$ (5mL) and the product was extracted with diethyl ether (2×5mL). The combined organic layers was washed with brine (2×5mL) successively, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the pure product was obtained without any further purification. A variety of substituted o-phenylenediamines were condensed with different 1, 2-dicarbonyl compounds. The results are shown in Table 2.

Physical and spectral data of the selected products:

2,3-diphenylquinoxaline (3a): mp=128-129°C;1HNMR (CDC13, 300MHz) δ(ppm): 8.2(dd, J=3.43,6.30Hz, 2H), 7.79 (dd, J=3.43,6.30Hz, 2H), 7.55 (m, 4H), 7.39 (m, 6H); IR (KBr) νmax (cm-1): 3055, 1541, 1345, 768, 729.

CATALYST PREPARATION

ZnO-CeO_2 nanostructures were synthesized by magnetic stirrer method in which $CeCl_2$ (1.04 g)and $ZnCl_2$ (4.09 g) were dissolved in distilled water (300 ml) with a constant stirring for about 30 min at room temperature and then the pH value was adjusted to 10.15 by drop wise addition of NH_4OH solution. The resultant solution was then stirred at80ºC for 6 h. After terminating the reaction, white precipitates were obtained which were washed with water and ethanol several times and dried at room-temperature. The resulting white powders were calcined at 400ºC for 5 h. [26].



Schem2. TEM imageof CeO_2–ZnO nanoparticles.

CONCLUSION

In summary, we describe a simple, efficient, and eco-friendly method for the synthesis of quinoxalines from various 1, 2-diketones and 1, 2-diamines using inexpensive and readily available nano CeO_2/ZnO as a catalyst. The ambient conditions, good product yields, easy workup procedure and minimal environmental impact make it a useful and attractive process for the synthesis of these compounds.

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