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Synthesis of quinoxalines in the presence of $Mg(HSO_4)_2$ as an efficient catalyst

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Abstract: Quinoxalines as building blocks in many drugs were synthesized *via* condensation of *α*-diketones and *o*-phenylenediamines in the presence of $Mg(HSO_4)_2$ as a catalyst. The reaction was carried out at room temperature and sonication conditions with high to excellent yields.

Keywords: $Mg(HSO_4)_2$; Heterogeneous conditions; Quinoxalines; Sonication; Synthesis; Diketones and 1,2-diamines.

Introduction

The quinoxaline core is present in many drugs with antitumor [1-3], anticancer [4], antiamoebic [5], anticonvulsant [6], antimalarial [7], antiinflamatory-antioxidant [8], and antiprotozoal activity [9]. Some fluorescent dyes [10], electroluminescent materials [11], chemically controllable switches [12], and organic semiconductors also contain the quinoxaline moiety [13]. Because of The important application of quinoxaline compounds in both medicinal and industrial fields, a number of protocols have been developed for the synthesis of quinoxaline derivatives. The best reported method for their synthesis is the reaction of aryl 1,2-diamine with a 1, 2-dicarbonyl compound in the presence of an acid as catalyst. Acetic acid [14], iodine [15], $CuSO_4.5H_2O$ [16], Zn[(L) proline] [17], Ni-Nanoparticles [18], galliun(III)triflate [19], Montmorillonite K10 [20], task-specific ionic liquids [21], $MnCl_2$ [22], and ZrO_2/Ga_2O_3/MCM-41 [23] have been applied in the above mentioned method.

The use of ultrasound in organic transformation is now well known to enhance rates, yields and selectivity of reactions. Ultrasound in several cases facilitates organic transformation at ambient conditions which otherwise require drastic conditions of temperature and pressure.

$Mg(HSO_4)_2$ as an inorganic solid acid, was used as catalyst for various organic transformation [24]. This solid acid has many advantages such as low cost, simple preparation, easy handling and it is eco-friendly.

Results and discussion

In continuation of our investigations on the applications of solid acids in organic synthesis (25-29), we investigated the synthesis of quinoxalines in the presence of $Mg(HSO_4)_2$ at room temperature or under sonication conditions. Herein, we report that $Mg(HSO_4)_2$ is an efficient catalyst for the synthesis of quinoxaline derivatives comparable with some other applied catalysts. The reaction of 1, 2-phenylenediamine with benzil was investigated for optimization of the reaction conditions. Reaction at different temperatures and various molar ratios of substrates in the presence of $Mg(HSO_4)_2$ revealed that the best results were obtained under solvent-free conditions at room temperature and a molar ratio of 1, 2-phenylenediamine/ benzil/$Mg(HSO_4)_2$ equal to 1:1:0.1. The feasibility of the ultrasonic-assisted synthesis of quinoxaline in the presence of $Mg(HSO_4)_2$ was also demonstrated. The results obtained show that

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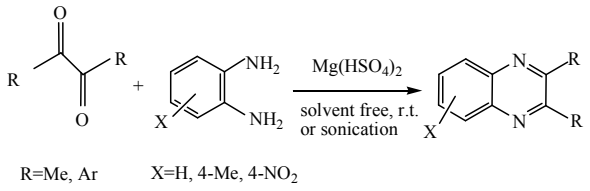
sonications in $CHCl_3$ at room temperature reduced the reaction time to 5 min (Table **1**).

Table 1. The synthesis of quinoxaline from 1, 2-phenylenediamine (1mmol) with benzil (1mmol) under various conditions.

Ent.	Catal. (mmol)	Solv.	Cond.	Time(min)/ yield(%)[ref.]
1	$Mg(HSO_4)_2$ / 0.12	$CHCl_3$	r.t.	10/85
2	$Mg(HSO_4)_2$ / 0.10	$CHCl_3$	ref.	10/92
3	$Mg(HSO_4)_2$ / 0.12	EtOH	r.t.	8/89
4	$Mg(HSO_4)_2$ / 0.10	EtOH	ref.	6/89
5	$Mg(HSO_4)_2$ / 0.10	-	r.t.	9/98
6	$Mg(HSO_4)_2$ / 0.10	EtOH	ult./ r.t.	5/48
7	$Mg(HSO_4)_2$ / 0.10	EtOH	ult./ r.t.	5/68
8	$Mg(HSO_4)_2$ / 0.10	EtOH	ult./ ref.	5/52
9	$Mg(HSO_4)_2$ / 0.10	$CHCl_3$	ult./ r.t.	4/78
10	$Mg(HSO_4)_2$ / 0.10	$CHCl_3$	ult./ r.t.	5/97
11	$Mg(HSO_4)_2$ / 0.10	$CHCl_3$	ult./ ref.	3/95
12	I_2 / 0.10	CH_3CN	r.t	3/98[15a]
13	I_2 / 0.10	DMSO	r.t	35/95[15b]
14	CuSO4 .5H_2O / 0.10	H_2O	r.t	15/96[16]
15	CuSO4 .5H_2O / 0.10	EtOH	r.t.	8/97[16]
16	Zn[(L)proline] / 0.10	HOAc	r.t.	5/99[17]
17	$Ga(OTf)_3$ / 0.05	EtOH	r.t.	5/96[19]
18	HOAc / 0.15 mL	MeOH	MW	5/99[14]
19	HOAc / 0.15 mL	ETOH	ref.	12(h)/85[14]
20	K10 / 0.10	H_2O	r.t.	2.5(h)/100[20]
21	ZrO_2/Ga_2O_3/MCM-41/0.2 g	CH_3CN	r.t.	2h/97[23]

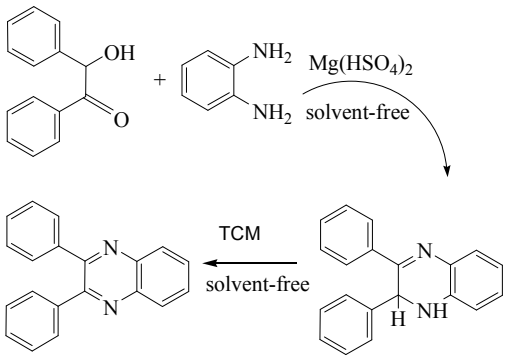
The applicability of the present method to a large scale process was examined with condensation of 10 mmol of 1,2-phenylenediamine and 10 mmol of benzil under solvent free condition at room temperature which gave 2, 3-diphenylquinoxaline in 90% yield. Various 1, 2-phenylenediamines and 1, 2-diketones were used as substrates for the synthesis of quinoxalines under solvent free at room temperature or sonication conditions (Scheme **1** and Table **2**).



R=Me, Ar X=H, 4-Me, 4-NO_2

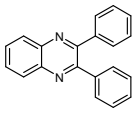
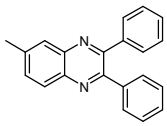
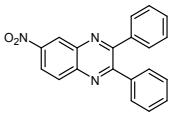
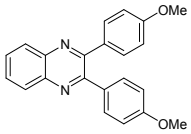
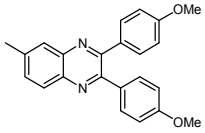
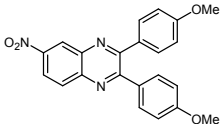
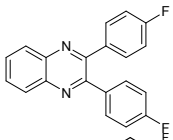
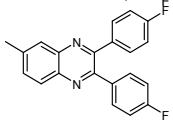
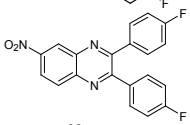
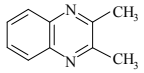
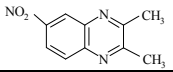
Scheme 1: Synthesis of quinoxalines in the presence of $Mg(HSO_4)_2$

We also have reported the synthesis of quinoxalines *via* the reaction of *α*-hydroxyketones with *o*-phenylenediamines followed by oxidation with trichloromelamine (TCM). The best conditions for reaction of 1, 2-phenylenediamine with benzoine in the presence of $Mg(HSO_4)_2$ was solvent-free at room temperature and a molar ratio of 1, 2-phenylenediamine: benzoin: $Mg(HSO_4)_2$, equal to 1:1:0.10. After completion of the reaction, the mixture washed with EtOH (10 mL) and filtered to obtain 2,3-diphenyl-1, 2-dihydroquinoxaline as intermediate (yield 93%, mp 136°C). The intermediate was oxidized in the presence of TCM (0.5 mol %) under solvent-free and room temperature condition. After completion of the reaction, the mixture was washed with EtOH (10 mL) and filtered to obtain 2, 3-diphenylquinoxaline (96% yield, Scheme **2**).



Scheme 2: Conversion of benzoine to quinoxaline in the presence of $Mg(HSO_4)_2$

Table 2. The synthesis of 2, 3-quinoxaline in the presence of $Mg(HSO_4)_2$, at room temperature or under ultrasonic irradiation.[a]

Ent.	Prod.	Method A Time(min)/ Yield (%)[b]	Method B Time(min)/ Yield (%)[b]	m.p (°C)[ref]
1		9/98	5.00/97	127-128[15a]
2		7/97	4.00/94	115-116[20]
3		8/93	4/92	191-192[20]
4		6/94	4 /95	151-152[16]
5		5/95	3 /96	126-127[16]
6		7/91	4 /92	192-193[16]
7		4/97	3/97	134-135[17]
8		5/98	3/98	164-165[17]
9		7/96	4/93	175-176[17]
10		5/82	3/80	98-99[23,20]
11		5/73	3/71	135-136[23]

[a] All the products are known and were characterized by IR and ^{1}H-NMR and by comparison of their physical properties with those reported in the literature.
[b] Isolated yield.

Conclusion

In conclusion, we have demonstrated a simple method for the synthesis of quinoxaline using $Mg(HSO_4)_2$ as an eco-friendly, inexpensive, less time-consuming and efficient reagent. Short reaction times, high yield, simplicity of operation and easy work-up are some advantages of this method.

Experimental

The materials were purchased from Sigma–Aldrich and Merck and were used without any additional

purification. The compounds gave all satisfactory spectroscopic data. A Bruker (DRX-500 Avanes) NMR was used to record the ^{1}H-NMR and ^{13}C-NMR spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature. Melting points were measured on an Electrothermal. BANDELIN Sonopuls HD 3200 ultrasonic apparatus (20 kHz, 150 W) was used for sonication. All of the products are known and were characterized by IR and ^{1}H-NMR and comparison of their physical properties with those reported in the literature.

General procedure for the synthesis of quinoxalines:

Method A: A mixture of 1, 2-phenylenediamine (1 mmol), benzil (1 mmol) and $Mg(HSO_4)_2$ (0.1 mmol) was stirred at r.t. The reaction was monitored by TLC. After completion, the mixture was washed with $CHCl_3$ (5 ml) and filtered to recover the catalyst. The solvent was evaporated and the crude product recrystallized from EtOH (5 ml) to afford pure quinoxaline derivatives.

Method B: The mixture of 1, 2-phenylenediamine (1 mmol), benzil (1 mmol), $Mg(HSO_4)_2$ (0.1 mol) and $CHCl_3$ (10 ml) was placed in a flat bottom flask and irradiated in the ultrasonic apparatus. After completion, the mixture was filtered to recover the catalyst. The solvent was evaporated and the residue was crystallized from EtOH (5 ml). All products were known and were identified by comparison of their physical and spectroscopic data with those of authentic samples.

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