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An Efficient and Facile Synthesis of Quinoxaline Derivatives Catalyzed by $KHSO_4$ at Room Temperature

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Summary. A facile synthesis of quinoxaline derivatives catalyzed by $KHSO_4$ in very high yields at room temperature is reported.

Keywords. 1,2-Diketones; *o*-Phenylenediamines; $KHSO_4$; Quinoxaline derivatives.

Introduction

The synthesis of quinoxaline derivatives has been of considerable interest to chemists because of their wide range of biological and pharmaceutical properties. Quinoxaline is an important component of pharmacologically active compounds. Although rarely occurring in Nature, the synthetic quinoxaline ring is a part of various antibiotics such as Echinomycin, Levomycin, and Actinoleutin [1] that are known to inhibit growth of *Gram*-positive bacteria and are active against various transplantable tumors [2]. In addition, quinoxaline derivatives have been reported to possess significant biological activities, such as antihelmintic, anticancer [3], antimicrobial, antifungal, and antidepressant [4, 5], and have applications in dyes [6]. They are efficient electroluminescent materials [7], organic semiconductors [8], building blocks for the synthesis of anion receptors [9], cavitands [10], dehydroannulenes [11], and *DNA* cleaving agents [12].

Thus, the synthesis of quinoxalines currently is of great interest. Various methods have been developed for the preparation of substituted quinoxalines [13]. To the best of our knowledge the following methods have been applied: Bi-catalysed oxidative coupling of epoxides and *ene*-1,2-diamines [14], from α-hydroxy ketones *via* a tandem oxidation process using $Pd(OAc)_2$ or $RuCl_2$-$(PPh_3)_3$-*TEMPO* [15] and MnO_2 [16], heteroannulation of nitroketene *N*,*S*-aryliminoacetals with $POCl_3$ [17], solid-phase synthesis on SynPhase™ Lanterns [18], cyclization of α-arylimino oximes of α-dicarbonyl compounds under reflux in acetic anhydride [19], condensation of 1,2-dicarbonyl compounds and *o*-phenylenediamines in *Me*OH/*Ac*OH under microwave irradiation [20], iodine catalyzed cyclocondensation of 1,2-dicarbonyl compounds and substituted *o*-phenylenediamines in *DMSO* [21] and CH_3CN [22]. However, these methods have many disadvantages, such as low yields, long reaction times, the use of toxic solvents, and harsh reaction conditions. Thus, the development of a new catalyst for the synthesis of quinoxaline derivatives would be highly desirable.

$KHSO_4$ is one of the components of a triple salt with the formula $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, the so-called Oxone, which is used as highly efficient, mild, and sole oxidizing agent in many organic reagents [23]. Synthesis of 2-arylsubstituted benzimidazoles by oxidative condensation of aldehydes with *o*-phenylenediamine in the presence of $KHSO_4$ has also been reported [24].

Recently, we have reported the use of $KHSO_4$ as an efficient catalyst for the synthesis of 1,1-diace-

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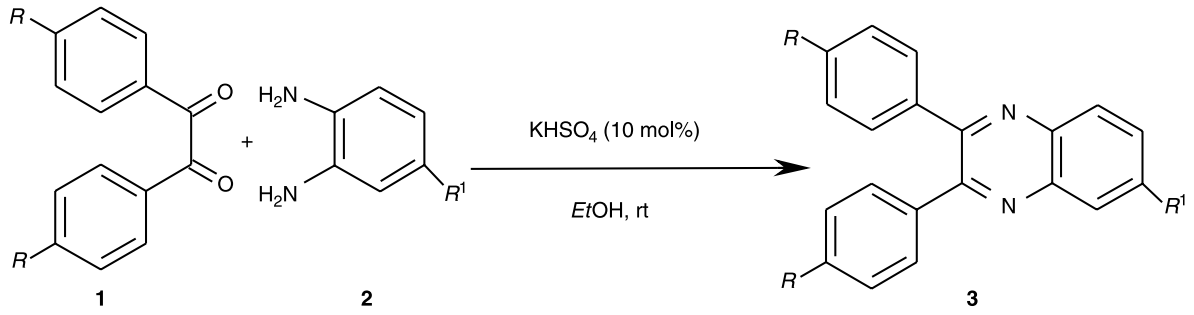

Scheme 1

tates under solvent-free conditions [25]. Because we are interested in the synthesis of heterocyclic compounds [26], very recently, we have reported the synthesis of quinoxaline derivatives catalyzed by $CuSO_4 \cdot 5H_2O$ [27a], *IBX* [27b], Zn[L-proline] [28], and heteropolyacid [29]. Herein, we wish to report an efficient and facile methodology for the synthesis of quinoxalines of high purity using $KHSO_4$ as catalyst at room temperature.

Results and Discussion

When a mixture of benzil (**1a**, 1 mmol) and *o*-phenylenediamine (**2a**, 1 mmol) and a catalytic amount of $KHSO_4$ (10 mol%) in *Et*OH was stirred at room temperature, the mixture solidified after 15 min. At this stage, TLC analysis showed that the reactands were completely consumed and the corresponding quinoxaline **3a** was formed (Scheme 1). Upon heating the reaction mixture, the product dissolved in ethanol and the catalyst could be separated by simple filtration. The pure product **3a** (Scheme 1) was obtained (99% yield) without any further recrystallization.

The scope and the generality of the present method was then further demonstrated by condensation of various substituted *o*-phenylenediamines with 1,2-dicarbonyl compounds. The results are presented in Table 1. In general, with electron donating substituents in the amine part, high yields of products were obtained, whereas the effect is contrary with electron withdrawing substituents. On the other hand, electron donating substituents associated with aromatic 1,2-diketone decreased the product yields and the effect is contrary with electron withdrawing groups. However, the variations in the yields were very small and both substituted *o*-phenylenediamines, 4-nitro and 4-methyl, gave the condensed products in excellent yields with differently substituted 1,2-diketones.

Table 1. Synthesis of 2,3-disubstituted quinoxalines **3** catalyzed by $KHSO_4$

Product	R	R^1	Time/min	Yield/%[a,b]	mp/°C
3a	H	H	15	99	128–129
3b	OCH_3	H	12	97	151–152.5
3c	H	NO_2	30	92	193–194
3d	OCH_3	NO_2	10	93	192–194
3e	H	CH_3	14	99	117–118
3f	OCH_3	CH_3	12	98	125–127

[a] Yields refer to isolated pure products
[b] All products were well characterized using melting point, ^{1}H NMR, and IR spectra [21, 22, 27–29]

Though the role of $KHSO_4$ is not clear, we think that it can act as a mild *Brønsted* acid. In the absence of $KHSO_4$ the reaction was slow and also requires refluxing conditions providing unsatisfactory yields. We also evaluated the amount of $KHSO_4$ required for this transformation. As less as 5 mol% of the $KHSO_4$ can catalyze the reaction to the same extent, but needs a little longer reaction times (>1 h).

In conclusion, we developed a simple, clean, convenient, and efficient method for the synthesis of quinoxalines from various 1,2-diketones and *o*-phenylenediamines using $KHSO_4$ as catalyst under mild reaction conditions at room temperature and without any side products. Some of the major advantages of this procedure are the ambient conditions, very good yields, very short reaction times, and use of an inexpensive, green, readily available, and easily to handle catalyst, simple work-up procedure, and absence of volatile and hazardous solvents.

Experimental

All chemicals were purchased from commercial suppliers and were used as received. Melting points were measured by using the capillary tube method with an electrothermal 9200 appa-

ratus. ^{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. All products were well characterized by comparison with authentic samples by TLC, spectral, and physical data [21, 22, 27–29].

Preparation of Quinoxalines Catalyzed by $KHSO_4$: General Procedure

A mixture of 1 mmol 1,2-diketone **1**, 1 mmol 1,2-diaminoarene **2**, and 10 mg $KHSO_4$ (10 mol%) in 3 cm^3 *Et*OH was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was heated, the product dissolved in ethanol, and the catalyst was separated from the reaction mixture by simple filtration. After cooling the solvent to room temperature the pure product **3** was obtained. The structures of the synthesized products were confirmed by FT-IR and ^{1}H NMR spectra.

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