GREEN SYNTHESIS OF QUINOXALINE DERIVATIVES AT ROOM TEMPERATURE IN ETHYLENE GLYCOL WITH H_2SO_4/SiO_2 CATALYST

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Keywords: Quinoxalines, sulfuric acid/SiO_2 catalyst, diketones, phenylene diamine, green synthesis

In this study, the preparation of quinoxaline derivatives using α-diketones, 1,2-phenylene diamines in the presence of H_2SO_4/SiO_2 catalyst in ethylene glycol and at room temperature is reported. The advantages of this method are high yields of the products, utilizing of reusable catalyst, easy separation and mild reaction conditions. Also, reusability of the catalyst was investigated and found that catalytic activity of the catalyst did not decreased after 4th times.

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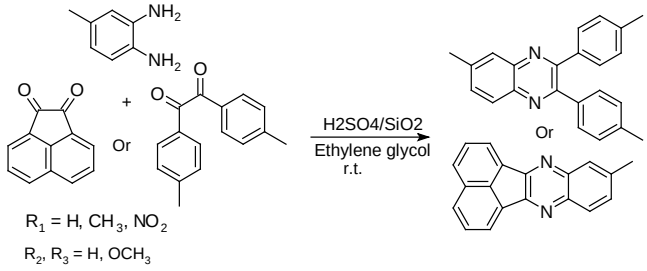
INTRODUCTION

Quinoxaline derivatives are well known in the pharmaceutical industry and have been shown to have a broad spectrum of biological activities including antibacterial, antiviral, anti- inflammatory, anticancer, and kinase inhibitory activities. [1,2] In addition, quinoxaline derivatives have been evaluated as semiconductors, dyes, and biocides.[3] In this regards, a very procedures have respectively been developed for the preparation of substituted quinoxalines.[4,5]

In these methods the condensation reaction between an aryl 1,2-diamine with a 1,2-dicarbonyl compound have been reported[4]. The others synthetic routes towards quinoxalines, including oxidative coupling of epoxides with ene-1,2-diamines using Bi-catalyst, heteroannulation of nitroketene and N,S-aryliminoacetals with $POCl_3$, cyclization of a-arylimino oximes of α-dicarbonyl compounds and from α-hydroxy ketones via a tandem oxidation process using $Pd(OAc)_2$ or $RuCl_2$-$(PPh_3)_3$-TEMPO as well as MnO_2.[5]

Most of the existing methodologies suffer from disadvantages such as the use of volatile organic solvents, unsatisfactory product yields, critical product isolation procedures, expensive and detrimental metal precursors and harsh reaction conditions, which limit their use under the aspect of environmentally benign processes. Also silica-supported reagent, H_2SO_4 / SiO_2 for its ease of preparation, low cost, high efficiency and environmental benignness,[6] has already been used in cylcoadditions,[7] Beckmann rearrangements,[8] glycosylations,[9] condensations,[10] esterification,[11] acetylation of (+)cedrol compound,[12] synthesis of 2,4,5-triaryl-1H-imidazoles,[13] and as catalyst in organic transformations: a comprehensive review.[14]

On the other hand, during our continuing efforts to develop convenient approaches to synthesize heterocycle compounds,[15] we revealed that H_2SO_4/SiO_2 was a high-efficient and recyclable catalyst for preparing the quinoxaline derivatives in a synthetically practical procedure (stoichiometric ratios of starting materials and short reaction times) with relatively widely functional group compatibility in ethylene glycol at ambient temperature (Scheme 1).



Scheme 1 Synthesis of quinoxaline derivatives in the presence of H_2SO_4/SiO_2

RESULTS AND DISCUSSION

To achieve efficient amount of catalyst, the author set up a model reaction using benzil (2.0 mmol), and 1,2-phenylene diamine (2.0 mmol) in ethylene glycol (3.0 ml) without catalyst at room temperature. In this case, the product was obtained in low yield (30%). As shown in table 1, the yield of reaction was increased in the presence of the catalyst (0.1 - 0.3 g) and raising catalyst amount toward 0.4 g did not affect to reaction yield.

Table 1. Optimizing of the catalyst amount for the synthesis of quinoxaline derivatives

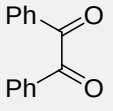
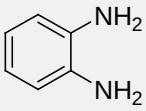
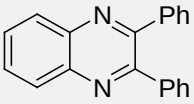
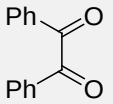
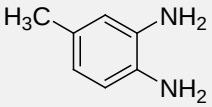
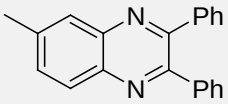
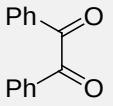
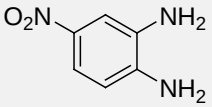
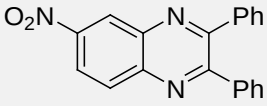
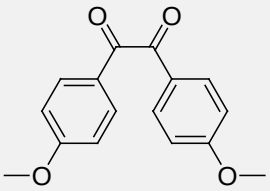
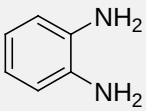
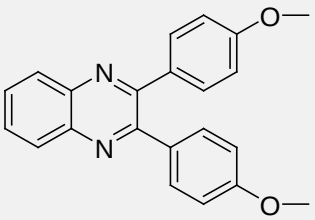
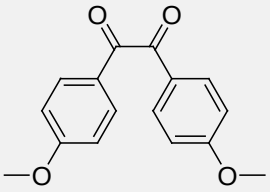
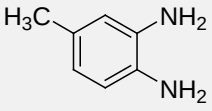
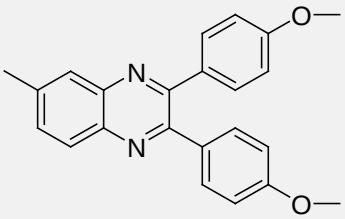
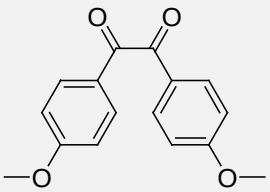
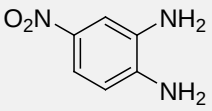
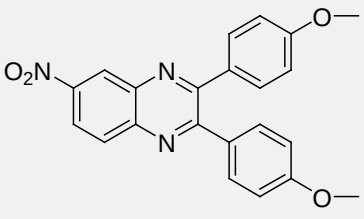
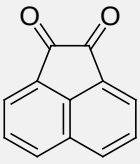
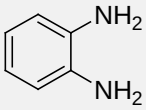
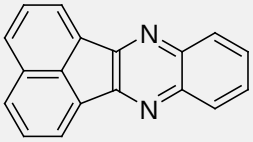
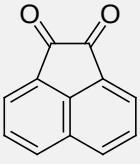
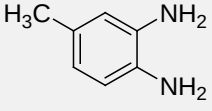
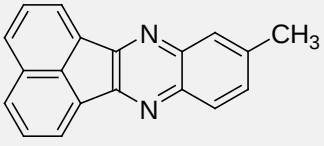
Catalyst g	Yield%[a]
Free	30
0.1	50
0.2	55
0.3	92
0.4	92

[a]Reaction condition: Benzyl (2.0 mmol), 1,2-phenylenediamine (2.0 mmol) and catalyst in ethylene glycol (3.0 ml) at room temperature

When we examined model reaction (entry1, table 2) in the presence of SiO_2, the desired product was obtained in very low yield (< 10 %), but the product was resulted in 90% using H_2SO_4 in similar condition as well as sulfuric acid/SiO_2 combination. Therefore, we decided to use sulfuric acid/SiO_2 combination due to its safe, to be solid and its reusability than H_2SO_4 alone that is dangers and corrosive.

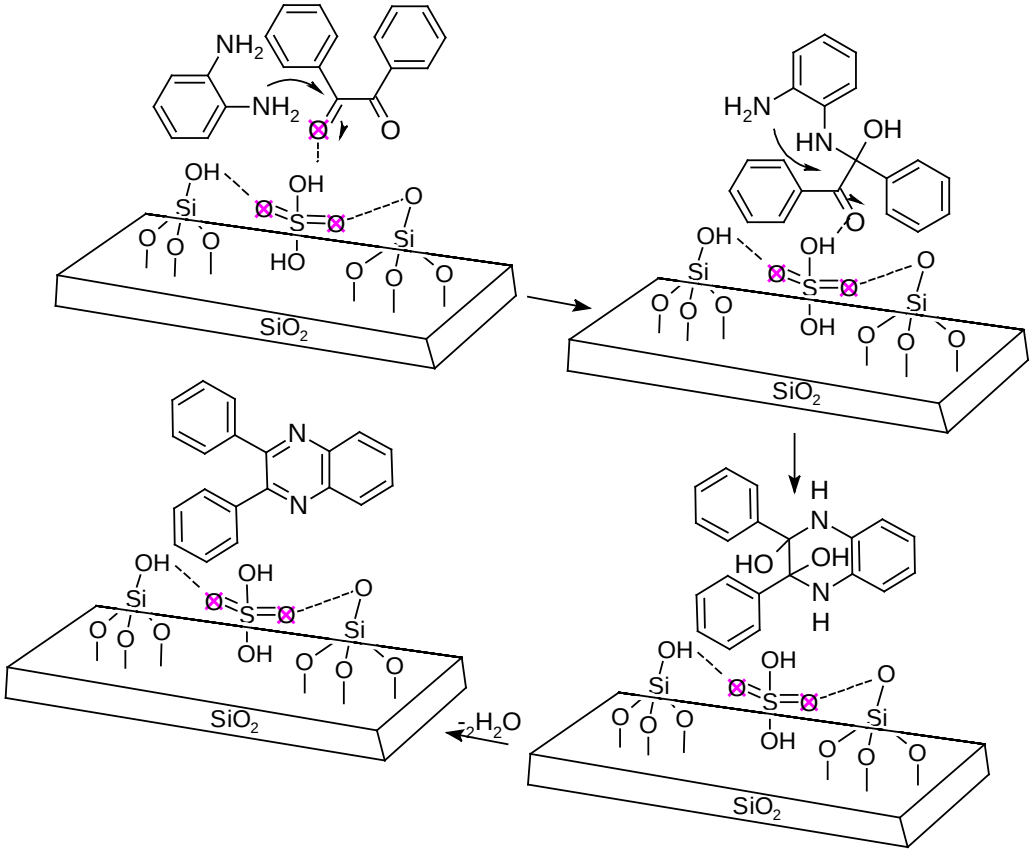
To evaluate the efficiency of this methodology, a number of 1,2-dicarbonyl compounds and 1,2-diamines were further subjected to condensation using very low amount of H_2SO_4/ SiO_2 (Table 2). When the electron-donating substituents present in diamine part, decreased reaction time, whereas the effect is reverse with the electron withdrawing substituents.

Table 2. Synthesis of quinoxaline derivatives in the presence of H_2SO_4/SiO_2 in ethylene glycol

1,2-Diketone	Amine	Product	Time, h	Yield, %	m.p., °C
			3.0	92	124-126[16]
			2.5	88	110-114[16]
			4.0	85	168-172[16]
			3.5	88	145-148[17]
			3.0	90	132-134[17]
			4.0	85	193-195[18]
			2.5	92	240-243[19]
			2.0	90	239-241[19]

On the other hand, electron-donating substituents with aromatic 1,2-diketone increased reaction time and the effect is reverse with electron withdrawing groups.

Proposed mechanism for the preparation of quinoxaline derivatives in the presence of H_2SO_4/SiO_2 has been shown in Scheme 2.



Scheme 2. Suggested mechanism for the synthesis of quinoxaline derivatives using H_2SO_4/SiO_2

EXPERIMENTAL

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on Perkin Elmer FT-IR spectrometer did scanning between 4000–400 cm^{-1}. ^1H NMR spectra were obtained on Bruker DRX-300MHz NMR instrument in $CDC1_3$. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60F-254 on aluminum). All compounds are known and spectra and physical data were compared with those of authentic samples.[16-19] The catalyst was prepared according to the reported procedure in the literature.[20]

Preparation of quinoxaline derivatives using H_2SO_4/SiO_2: general procedure:

To a mixture of an appropriate *o*-phenylenediamine (1 mmol, 0.108 g) and a 1,2-dicarbonyl compound (1 mmol) in ethylene glycol (3 ml), a catalytic amount of H_2SO_4/SiO_2 (0.3 g) was added and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC (ethyl acetate:n-hexane, 1:3). After completion of the reaction, chloroform (10 ml) 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 H_2O (15 mL) and the product was extracted with chloroform (2 × 10 mL). The combined organic layers was dried over Na_2SO_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.

2,3-Diphenylquinoxaline

White solid, IR (KBr, cm^{-1}): 3055, 1541, 1495, 1477, 1441, 1346, 1315. ^1H NMR ($CDCl_3$, 300 MHz): 8.16-8.20 (m, 2H), 7.76 -7.79 (m, 2H), 7.56-7.50 (m, 4H), 7.25-7.29 (m, 6H).

6-Methyl-2,3-diphenylquinoxaline

Light yellow solid, IR (KBr, cm^{-1}): 3055, 2941, 1619, 1554, 1485, 1444, 1393, 1344. ^1H NMR ($CDCl_3$, 300 MHz): 2.63 (s, 3H), 7.25-7.35 (m, 5H), 7.45-7.55 (m, 5H), 7.89-8.08 (m, 3H).

6-Nitro-2,3-diphenylquinoxaline

Light brown solid, IR (KBr, cm^{-1}): 3433, 3328, 3055, 1658, 1521, 1434, 1398, 1337. ^1H NMR ($CDCl_3$, 300 MHz): 7.30-7.45 (m, 6H), 7.95 (d, 4H), 8.25 (d, 1H), 8.54 (d, 1H), 9.08 (s, 1H).

2,3-Bis(4-methoxyphenyl)quinoxaline

White solid, IR (KBr, cm^{-1}): 3054, 2926, 2871, 2349, 1743, 1441. ^1H NMR ($CDCl_3$, 300 MHz): 3.85 (s, 6H), 6.89 (d, 4H), 7.5 (d, 4H), 7.74 (q, 2H), 8.14 (q, 2H).

2,3-Bis(4-methoxyphenyl)-6-methylquinoxaline

Light yellow solid, IR (KBr, cm^{-1}): 3054, 2922, 1955, 1810, 1735, 1614. ^1H NMR ($CDCl_3$, 300 MHz): 2.61 (s, 3H), 3.84 (s, 6H), 6.88 (d, 4H), 7.48 (d, 4H), 7.56 (d, 1H), 7.91 (s, 1H), 8.03-8.0 (d, 1H).

2,3-Bis(4-methoxyphenyl)-6-nitroquinoxaline

Yellowish brown solid, IR (KBr¸ cm^{-1}): 3055, 3027, 1950, 1659, 1540, 1477. ^1H NMR ($CDCl_3$, 300 MHz): 3.73 (s, 6H), 6.98 (m, 4H), 7.56 (m, 4H), 8.24 (d, 1H), 8.49 (d, 1H), 9.1 (d, 1H).

Acenaphtho[1,2-*b*]quinoxaline

Yellow solid, IR (KBr, cm^{-1}): 3051, 2926, 1613, 1588, 1528, 1497, 1418, 1343. ^1H NMR ($CDCl_3$, 300 MHz): 8.37-8.40 (m, 2H), 8.18-8.21 (m, 2H), 8.05-8.08 (m, 2H), 7.78-7.83 (m, 2H), 7.73-7.76 (m, 2H).

9-Methylacenaphtho[1,2-*b*]quinoxaline

Light Brown solid, IR (KBr, cm^{-1}): 3051, 2909, 2861, 1719, 1613, 1585, 1483, 1419. ^1H NMR ($CDCl_3$, 300 MHz): 2.56 (s, 3H), 7.49 (d, 1H, Ar-H), 7.70 (t, 2H, Ar-H), 7.88 (s, 1H, Ar-H), 7.94 (d, 2H, Ar-H), 7.99 (d, 1H, Ar-H), 8.27 (t, 2H, Ar-H).

Reusability of the catalyst

At the end of the reaction, the catalyst could be successfully recovered by a simple filtration. The removed catalyst was washed with chloroform, dried at 80 ºC for 1 h and reused up to four times in the others reactions without appreciable reduction in the catalytic activity.

CONCLUSIONS

In conclusion, an efficient catalytic method for the synthesis of quinoxaline derivatives using sulfuric acid adsorbed on silica gel as catalyst in ethylene glycol at room temperature is reported. The catalyst can be reused after a simple work-up, with a gradual decline of its activity being observed.

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Received: 26.07.2019
Accepted: 11.11.2019.