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A Facile and Efficient Method for the Synthesis of Quinoxaline Derivatives Using [2-(Sulfooxy)Ethyl]Sulfamic Acid as a Novel Difunctional Bronsted Acid, Recyclable and Organocatalyst

Sami Sajjadifar[1]*, Hadi Noorizadeh[2], Hojat Veisi[1], Omid Louie[1], Maziar Mansouji Avval[3], Sobhan Rezayati[1]

[1]Department of Chemistry, Payame Noor University, PO BOX 19395-4697 Tehran, Iran
[2]Department of Chemistry, Faculty of Sciences, Islamic Azad University, Ilam Branch, Ilam, Iran
[3]University of Mysore, Manasagangotri, Department of Studies in Chemistry, 570 006, Mysore, India

ABSTRACT

A novel, mild, eco-friendly and efficient method has been developed for the preparation of quinoxaline derivatives in high yields *via* a one-pot condensation of aromatic diamine and 1,2-dicarbonyl compounds in the presence of [2-(sulfooxy)ethyl]sulfamic acid (SESA). Moreover, sulfamic acid has been employed as a solid acid catalyst. Recycling of the catalyst is one of the most significant advantages of the proposed method.

Keywords: [2-(Sulfooxy)Ethyl]Sulfamic Acid (SESA), Solid Acid, Quinoxaline, 1,2-Diamine, 1,2-Dicarbonyl Compound, One pot Synthesis, Catalyst.

Corresponding author

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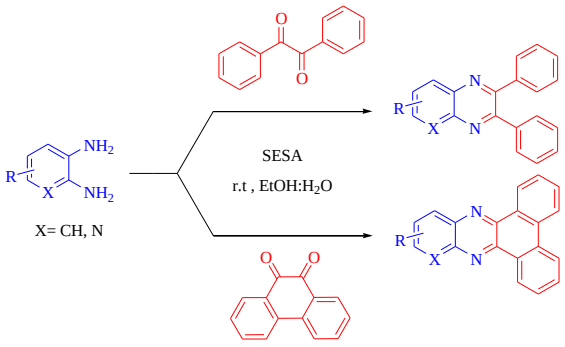
INTRODUCTION

Quinoxaline derivatives are known as the important category of nitrogen-containing heterocyclic compounds which are indispensable structural units for both the chemist and the biochemist compounds. They have been considered as important compounds from both academic and industrial perspective because they are significant intermediates for the manufacturing of pharmaceuticals and advanced materials. Derivatives from Quinoxaline are well known in the pharmaceutical industry and possess a broad spectrum of biological activities including antiviral, anticancer, antimicrobial, antifungal, antidepressant activities. Besides, they are active against various transplantable tumors [1-7]. It was found that quinoxaline ring also exists in antibiotics, such as actinomycin, levomycin, and echinomycin [8], In addition, these heterocyclic molecules have been widely used in organic semiconductors, as dyes [9,10]. In the literature, various methods for the preparation of quinoxaline derivatives using the different catalysts have been published, including Recent heating procedures using microwave [11-15], CAN [16], MnO_2 [17], Pd(OAc) [18], $Incl_3$[19], Poly aniline-sulfate salt [20], ionic liquid [21], SBA-15 [22], citric acid [23]. It is worth noting that the methods that have been established for the preparation of quinoxaline derivatives are associated with one or more of the following drawbacks, unsatisfactory yields, long reaction times, harsh reaction conditions and using poisonous and expensive catalyst. So a number of procedures are now recommended for Green involving: either new eco-friendly reagents or catalysts, selected medium such as water, supercritical fluids, ionic liquids or solvent-free reactions. Thus, it seems highly desirable to find a more efficient and milder protocol for the synthesis of quinoxalines.

In recent years, the search for environmentally benign chemical processes or methodologies has received much attention, and the development of heterogeneous catalysts for fine chemical synthesis has become a major area of research. We have found that SESA can be easily used for this purpose. we report here the synthesis of quinoxalines from aryl o-Phenylenediamine and various 1,2-diketones in the presence of solid acid like using SESA in EtOH:H_2O at room temperature (Scheme 1).



Scheme 1. Synthesis of quinoxaline derivatives using SESA

As a part of our research interest towards the development of efficient and environmentally benign synthetic methodologies using eco-friendly conditions at very short

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reaction times has been compared with other procedures. Herein, we report the synthesis of quinoxaline derivatives using various 1,2-diamines and 1,2-diketones in the presence of SESA in EtOH/H_2O at room temperature (Scheme 1).

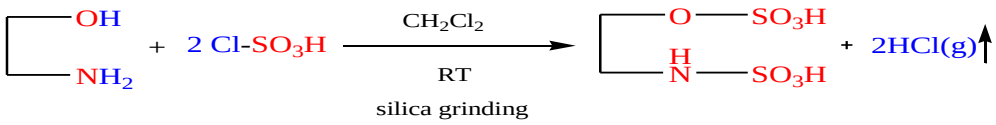
Experimental

General

Products were separated and purified by different chromatographic techniques and were identified by the comparison of their IR, NMR and Melting points with those reported for the authentic samples. All ^1H NMR and ^{13}C NMR spectra were recorded on 400 MHz Varian FT-NMR spectrometers. All chemical shifts are given as δ value with reference to Tetra methyl silane (TMS) as an internal standard. IR spectra of the compounds were obtained on a Perkin Elmer spectrometer version 10.03.06 using a KBr disk. Melting points were determined using an Electrothermal apparatus and are uncorrected. The progress of reaction was followed with thin-layer chromatography (TLC) using silica gel SILG/UV 254 and 365 plate. Commercial products (Aldrich or Fluka) were used without further purification.

Preparation of [2-(Sulfooxy)Ethyl]Sulfamic Acid (SESA)

A 50 ml suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution (water) and an alkali trap. 2-Aminoethanol (1.527 g, 25 mmol) was charged in the flask and chlorosulfonic acid (5.83 g, 50 mmol) was added drop wise over a period of 1 h at room temperature. HCl evolved immediately. After completion of the addition, the mixture was shaken for 80 min, while the residual HCl was eliminated by suction. Then the mixture was washed with diethyl ether to remove the unreacted chlorosulfonic acid (Scheme 2).



Scheme 2: Synthesis of catalyst

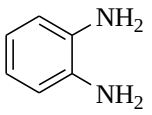
General procedure for the preparation of quinoxaline derivates

A mixture of 1,2 dicarbonyl (1 mmol) and aromatic diamine (1 mmol) in EtOH/H_2O [4/1, 10 ml] was stirred at room temperature in presence of SESA catalyst (5 mol%). The progress of the reaction was monitored by TLC (*n*-hexan:ethylacetate 20:1). After completion of the reaction, H_2O (20 ml) was added to the reaction mixture, and was allowed to stand at room temperature for 1 h. During this time, crystals of the pure product were formed and collected by filtration and then were dried. The time required for each reaction is indicated in Table 2. The obtained products were characterized by their spectral (^1H-NMR, IR and melting Point) and comparison to authentic samples.

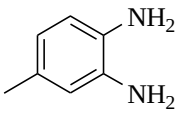
ISSN: 0975-8585

RESULT AND DISCUSSION

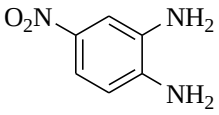
In this reaction, various 1,2-dicarbonyls including benzil, acenaphthylene-1,2-dione, phenanthrene-9,10-dione and pentane-2,3-dione and etc, and also various diamines such as benzene-1,2-diamine, 4-methylbenzene-1,2-diamine, 4-nitrobenzene-1,2-diamine, cyclohexane-1,2-diamine, cyclohexane-1,2- diamine, propane-1,2-diamine and pyridine-2,3-diamine were examined (Scheme 3).



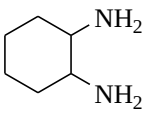
Benzene-1,2-diamine



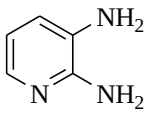
4-methylbenzene-1,2-diamine



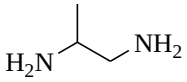
4-nitrobenzene-1,2-diamine



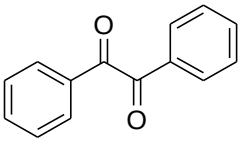
cyclohexane-1,2-diamine



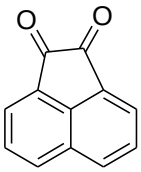
pyridine-2,3-diamine



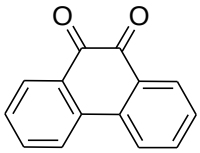
propane-1,2-diamine



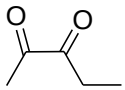
benzil



acenaphthylene-1,2-dione



phenanthrene-9,10-dione



pentane-2,3-dione

Scheme 3: Structure of diamines and diketones

SESA was identified by its spectral data. IR spectrum showed the characteristic peak of S-O group at 450-600 cm^{-1}, S=O at 1000-1200 cm^{-1} and broad peak at 2900-3600 cm^{-1} related to the OH of SO_3H groups. Moreover, the two peaks were observed at 1085 cm^{-1} and 1285 cm^{-1} correspond to vibrational modes of N-SO_2 bond. The IR spectrum of the catalyst showed a broad peak at 3100-3400 cm^{-1}. ^1H NMR spectrum of SESA, showed the unmistaken acidic hydrogens (SO_3H) peaks at 12.86 and 11.96, and peak of NH group at 9.806, peak of O-CH_2 group between 3.417-3.442, N-CH_2 group between 3.809-3.840 and peak of NH group at 9.806. These spectrums confirmed that this catalyst was exactly synthesized. In the present article, as a continuation of our previous investigations on quinoxaline derivatives a simple, efficient, and high-yielding method for the synthesis of its derivatives using [2-(sulfooxy)ethyl]sulfamic acid as a reusable eco-friendly catalyst in solvent EtOH:H_2O (Scheme 1) is described.

In another study, the effect of different solvents upon the reaction was investigated. The results showed that the examined solvents were not separately suitable. The satisfactory results were obtained when a mixture of EtOH and H_2O was used as solvent. The best ratio of EtOH/H_2O was found to be 4/1. Therefore we used only mixture of EtOH/H_2O as a solvent because it is recyclable, non-toxic and thermally stable (Table 1).

ISSN: 0975-8585

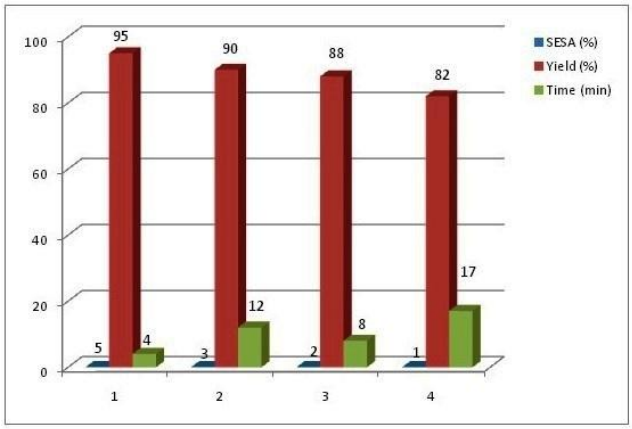


Figure 1: Catalytic activity evaluation for quinoxaline synthesis. Reaction conditions: o- phenylenediamine (1 mmol), 1,2-diketone (1 mmol) in EtOH:H_2O (10 mL).

In this reaction, the effect of catalyst loading on the condensation was studied (Figure 1). We found that 5 mol% of SESA could effectively catalyze the reaction for the synthesis of the desired product. It is notable that when 1 mol% of catalyst was used, the yield of the desired product decreased dramatically. Thus, under the optimized reaction conditions, this reaction was effected using various 1,2-diketones and *o*-phenylenediamines and the results were summarized in Table 2.

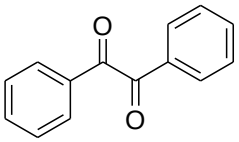
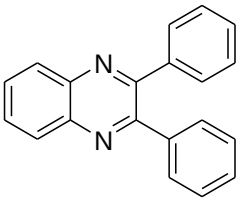
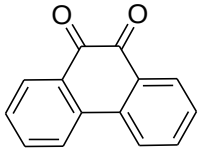
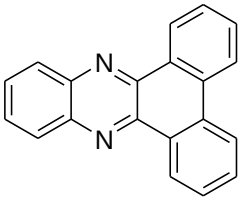
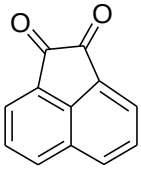
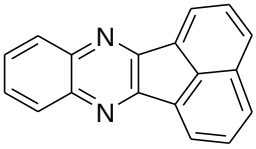
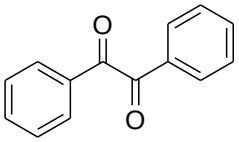
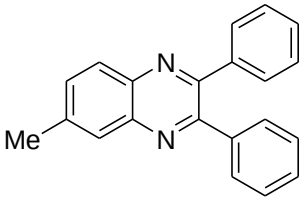
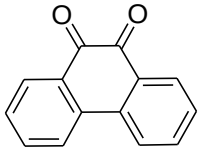
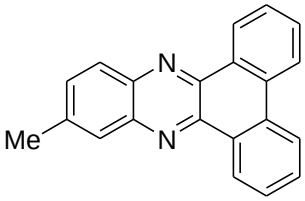
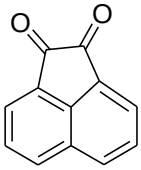
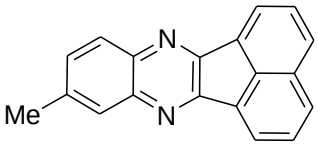
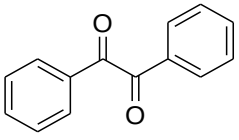
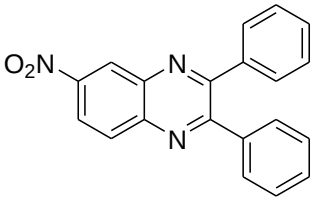
Table 1: The solvent effect for synthesis of quinoxalines[a]

Entry	Solvent	Loading Catalyst (%)	Time (min)	Yield (%)[b]
1	H_2O	5	30	0
2	H_2O:EtOH(7:3)	5	42	2
3	H_2O:EtOH(9:1)	5	88	33
4	H_2O:EtOH(4:6)	5	5	80
5	H_2O:EtOH(1:1)	5	3	85
6	H_2O:EtOH(6:4)	5	12	85
7	H_2O:EtOH(1:9)	5	5	87
8	H_2O:EtOH(8:2)	5	20	90
9	H_2O:EtOH(3:7)	5	5	94
10	H_2O:EtOH(1:4)	5	4	95
11	EtOH	5	2	100

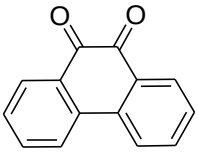
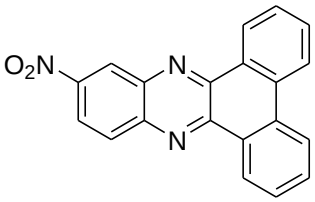
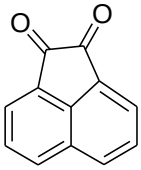
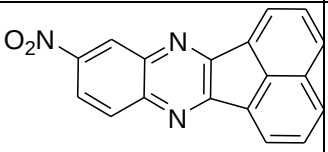
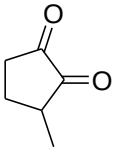
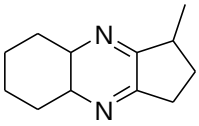
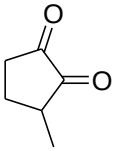
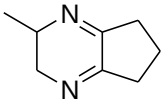
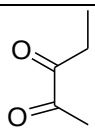
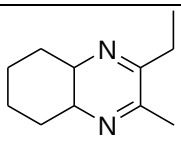
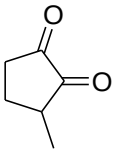
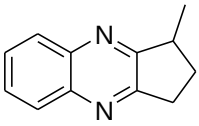
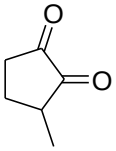
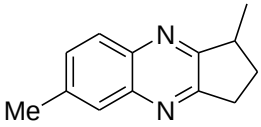
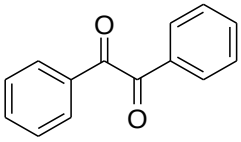
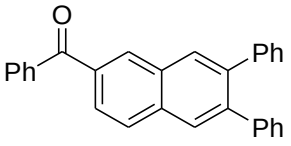
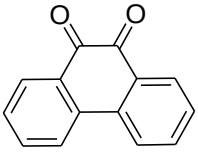
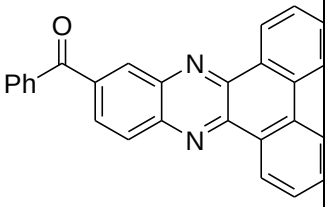
[a]reaction of 1,2-dibenzylketone (1 mmol) and *o*-phenylenediamine (1 mmol), SESA (5 mol%).
[b]Yield of isolated products.

ISSN: 0975-8585

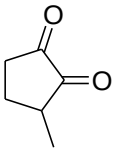
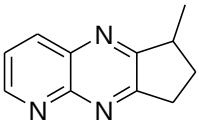
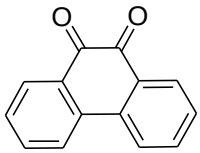
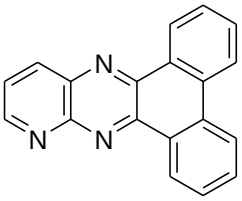
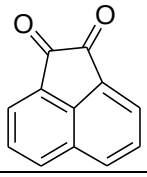
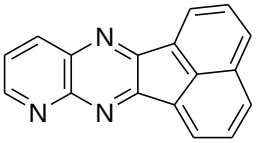
Table 2: Synthesis of quinoxaline derivatives are catalyzed by SESA at room temperature

Entry	Diketone	Product	Time (h:min)	M.p. ºC (Found) M.p. ºC (Lit)	Yield[b] (%)
1			00:04	125-127 (128-129) [1,2]	95
2			00:05	225-227 223-225[3]	80
3			00:30	241-244 238-240 [3]	78
4			00:25	114-118 116-117 [3]	60
5			00:15	209-212 208 -210[3]	85
6			00:25	297-298 300 [3,21]	95[d]
7			04:15	190-191 193-194 [1]	85[d]

ISSN: 0975-8585

8			05:00	262-264 New	88[d]
9			00:50	319.3[c]	99
10			05:50	237-239[c]	98[d]
11			12:00	180-182[c]	95[d]
12			12:00	98-101	94[d]
13			01:00	142-146[c]	58[d]
14			00:50	185-189[c]	99[d]
15			00:20	139.3-141	99
16			00:05	243-245	100

ISSN: 0975-8585

17			72:00	-	N.R[d]
18			72:00	-	N.R[d]
19			72:00	-	N.R[d]

[a]Condition reaction: 1,2 dicarbonyl compound (1 mmol), aniline derivatives (1 mmol), SESA (5 mol %) in EtOH-H_2O (4/1, 10 mL), room temperature. [b]Yield of Isolated Products. [c]Decomposed. [d]In Reflux Condition

As Table 2 showed, a variety of substituted 1,2-diketone compounds with various 1,2-phenylenediamines , bearing either electron-donating or electron-withdrawing substituents, afforded the products in excellent yields and high purities. Condensation of [(3,4-diaminophenyl)(phenyl)methanone] with phenanthrene-9,10-dione gave 11-Benzoil-dibenzo[a,c]phenazine in 100% yield within 5 min (Table 2, Entry 16). The presence of electron donating substituents leads to increased yields (Table 2, Entry 6, 14 and 15) within 20-50 minute compared to electron withdrawing substituents (Table 2, Entry 7, 8 and 9) in spite of more reaction period of 50-420 minute. On the other hand, aromatic ring attached to 1,2-diketone and aliphatic ring attached to 1,2-diketone gave the low yield among all the studied 1,2-diketone substrates (Table 2, Entry 3, 4 and 13). In order to further validate our work, the current protocol was compared with the data in the literature based on the catalysts content, reaction time, and percentage yields (See Table 3).

Table 3: Comparison of the catalytic efficiency of SESA with some reported catalysts in the reaction

Entry	Catalyst	Condition	Time	Reference
1	polyaniline-sulfate salt	CH_2Cl_2	15 min	20
2	Keggin type heteropolyacids	water	1 h	21
3	Citric Acid	EtOH:H_2O	8 min	23
4	Montmorillonite K-10	water	2.5 h	27
5	molecular iodine	DMSO	50 min	28
6	PEG-400	Solvent Free	10-60 min	29
7	SBA-Pr-SO3H	CH_2Cl_2	5 min	30
8	NH_4Cl	CH_3OH	7 min	31
9	silica bonded *S*-sulfonic acid	EtOH/H_2O	5 min	32
10	[2-(Sulfooxy)ethyl]sulfamic acid	EtOH/H_2O	5 min	This Work

The reaction in ionic liquid is much better, because it can be recycled and reused in subsequent reactions. We believe that the method is simple, clean, efficient, convenient and, thereby avoids the generation of waste, and may contribute to the of green chemistry. When the reaction was complete, the mixture was filtered, the residue was washed with warm ethanol and recycled catalyst was reused in the next reaction, No significant loss of the product yield was observed when SESA was reused even after three times recycling (Table 4).

Table 4: The synthesis of quinoxaline in the presence of recycled catalyst

Entry	Cycle	Time (min)	Yield (%)
1	1st use	5	95
2	2st use	7	93
3	3st use	10	92

The catalyst system is a free flowing powder that can be stored at room temperature for several months without losing its catalytic potentiality and it may be considered a very cheap source of solid supported acidic catalyst compared to other commercially available expensive solid supported acids.

CONCLUSION

In sum, a novel and highly efficient method for the synthesis of quinoxaline derivatives by using the reusable and environmentally benign [2-(sulfooxy)ethyl]sulfamic acid functionalized silica as a solid acid catalyst in EtOH/H_2O at room temperature described. This simple method is important from both environmental and economic viewpoints as it produces little waste and also the catalyst can be recovered from the reaction mixtures and be reused. The simple experimental procedure, utilization of an inexpensive and readily available catalyst, non-toxicity of reagent, Time minimizing and excellent yields are the advantages of the present method.

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