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Original Research article

Characterization of Catalyst: Comparison of BrØnsted and Lewis Acidic Power in Boron Sulfonic Acid as a Heterogeneous Catalyst in Green Synthesis of Quinoxaline Derivatives

Sami Sajjadifar[a] *, Vahid Azizkhani[a], Kaushik Pal[b], Hadi Jabbari[a], Omidali Pouralimardan[a], Faten Divsar[a], Sarvin Mohammadi-Aghdam[a], Issa Amini[a], Hoda Hamidi[a]

[a] Department of Chemistry, Payame Noor University, P.O. Box 19395-4697, Tehran, Iran

[b] Department of Nanotechnology, Bharath University, BIHER Research Park, Chennai, Tamil Nadu 600073, India

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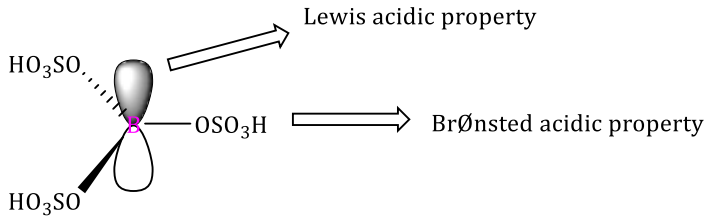
STIPB

ABSTRACT

A simple, highly efficient and green procedure for the condensation of aryl and alkyl 1,2-diamines with α-diketones in the presence of catalytic amount of boron sulfonic acid (BSA) and silica trimethyl borat (STMB) and silica triisopropyl borate (STIPB), as two novel heterogeneous Lewis acid catalysts at room temperature, is described. In this method, we proved that the BrØnsted acidic power of boron sulfonic acid (BSA) is more important than its Lewis acidity. Using this method, quinoxaline derivatives as biologically interesting compounds are produced in high to excellent yields.

*Corresponding author: E-mail: ss_sajjadifar@yahoo.com
Department of Chemistry, Payame Noor University, P.O. Box 19395-4697, Tehran, Iran, Tel: +9884 32228316

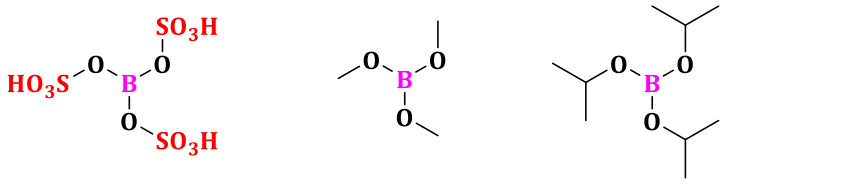
Graphical Abstract



Introduction

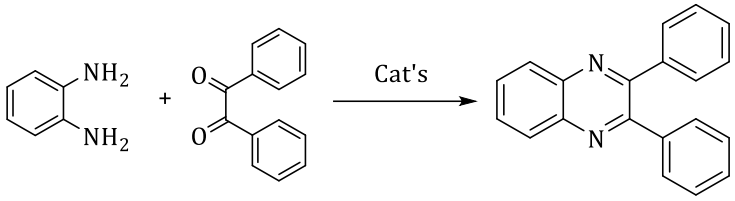
Quinoxaline derivatives are a very important class of nitrogen-containing compounds and have been widely used in dyes [1], pharmaceuticals [2, 3], and electrical/photochemical materials [4-9]. Quinoxaline ring moiety constitutes part of the chemical structures of various antibiotics such as echinomycin, levomycin and actinoleutin [10, 11] that are known to inhibit growth of gram positive bacteria and are active against various transplantable tumors. A number of synthetic strategies have been developed for the preparation of substituted quinoxalines [12-14]. By far, the most common method relies on the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid for 2–12 h giving 34–85% yields [15]. Recently, greener methods for the synthesis of quinoxaline derivatives in green solvents (EtOH/H_2O) were reported using copper sulphate pentahydrate and cerium (IV) ammonium nitrate as catalysts, respectively [16, 17]. 2,3-disubstituted quinoxalines have also been prepared by Suzuki–Miyaura coupling reaction [18], condensation of *o*-phenylenediamines and 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation [19], iodine catalyzed cyclocondensation of 1,2- dicarbonyl compounds and substituted *o*-phenylenediamines in DMSO [20], CH_3CN [21]. Different catalysts were used for quinoxaline synthesis such as IBX [22], oxalic acid [23], SBSSA [24], microwave/I_2 [25], $SnCl_2/SiO_2$ [26], I_2 [20], ultrasound irradiation [27], NH_4Cl [28], $(NH_4)_6Mo_7O_{24}.4H_2O$ [29], citric acid [30], ionic liquid [31], bentonit clay K-10 [32] and AcOH [33]. We disclose herein our results for the synthesis of quinoxalines using catalytic amounts of boron sulfonic acid/SiO_2, trimethyl borate/SiO_2, triisopropyl borate/SiO_2 (10 mol%) in mixture ethanol: water (4:1, 10 mL) as an acidic solution at room temperature (Scheme 1).

Considering the unique properties of boron sulfonic acid with Brønsted acidic property, and their successful applications in organic transformations [9], more recently, we have synthesized BSA as a trifunctional sulfonic acid and successfully applied it as highly efficient catalyst in organic synthesis [13].



Boron sulfonic acid (BSA) **Trimethyl borate (TMB)** **Triisopropyl borate (TIPB)**

Structure of catalysts (BSA, TMB and TIPB)



Scheme 1. Quinoxaline synthesis by using BSA, TMB and TIPB

Experimental

General

All chemical materials were purchased from Merck company. IR spectra of the compounds were obtained on a Shimadzu IR-435 spectrometer using a KBr disk. The ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AQS 300 Avance instrument at 300 MHz in dimethyl sulfoxide (DMSO-d_6) using tetramethylsilane as an internal standard. The progress of reaction was followed with thin-layer chromatography (TLC) using silica gel SILG/UV 254 and 365 plates. All the products are known compounds and were characterized by comparing the IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data and their melting points with the literature values.

General procedure of preparation of catalysts

Silica gel is added to trimethyl borate and triisopropyl borate, (W/W, 1:1). Silica-supported of this catalyst was used as novel catalysts.

General procedure of preparation of quinoxalines

A solution of aromatic *o*-diamine (1 mmol) and a 1,2-dicarbonyl compound (1 mmol) in ethanol: water (4:1, 10 mL) was stirred at room temperature in the presence of catalytic amount of acid (10 mol%). The progress of the reaction was monitored by TLC (*n*-hexan:ethylacetate 10:1). After completion of the reaction, water (20 mL) was added to the mixture and was allowed to stand at room temperature for 30 min. During this time, crystals of the pure product were formed which were collected by filtration and dried. For further purification, if needed, the products recrystallized from hot ethanol (Results summarized in Table 3).

Result and Discussion

To optimize and select the best solvent for the reaction, the synthesis of quinoxaline **1a** was examined as a model in different solvents (Table **1**). Higher yields and shorter reaction times were obtained when the reaction was carried out in EtOH:H_2O (1:1). Thus, EtOH:H_2O (1:1) was used as a reaction media for all reactions. Water is a desirable solvent for chemical reactions for a host of reasons such as cost, safety and environmental concerns.

Table 1. The condensation of 1,2-diamine **1a** (1 mmol) with benzyl **2b** (1 mmol) in the presence of different ratios of BSA (0.03 mmol, 3 mol%) at room temperature

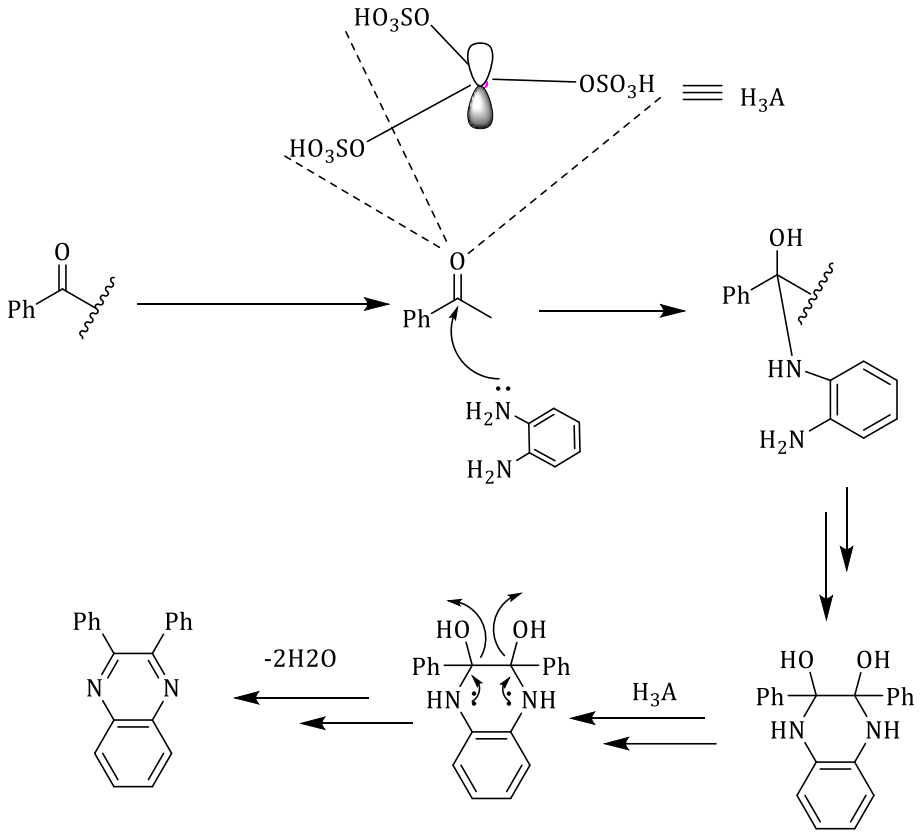
Entry	solvent	% BSA	Time (min)	Yield (%)
1	EtOH	5	30	78
2	EtOH	10	30	78
3	CH_3CN	5	60	72
4	CH_3COOEt	5	45	80
5	EtOH:H_2O (1:1)	15	10	81
6	EtOH:H_2O (1:1)	10	10	85
7	EtOH:H_2O (1:1)	5	10	85
8	EtOH:H_2O (1:1)	3	5	98
9	EtOH:H_2O (1:1)	2	25	87
10	EtOH:H_2O (1:2)	10	20	85
11	EtOH:H_2O (1:2)	5	20	85
12	EtOH:H_2O (1:2)	3	30	87
13	EtOH:H_2O (2:1)	3	25	84
14	H_2O	10	30	78
15	H_2O	5	30	78
16	CH_2Cl_2	5	80	45
17	$CHCl_3$	5	80	50

Quinoxalines were synthesized by using boron sulfonic acid in comparison with trimethyl borate and triisopropyl borate as two novel catalysts in order to identify BrØnsted acidic power and Levis acidic power of boron sulfonic acid (BSA). For easy handling of all catalyst, silica gel should be added to these catalysts (1:1). These catalysts in comparison with SBSA are weaker and either their reaction times are longer or yield of their reaction are lower (Table 1 and 2), so the BrØnsted acidic power of BSA is more important and stronger than Lewis acidic power. The reaction was carried out in green condition at room temperature.

Table 1. Comparison of catalysts for 2,3-diphenylquinoxaline synthesis

Number	Catalyst	Condition Cat's %	Time(h:min)	Yield%
1	SBSA	R.T.	00:05	98
2	STMB	R.T.	20:00	74
		Reflux	10:00	72
3	STIPB	R.T.	28:00	80
		Reflux	10:30	75

In summary, we have developed an efficient green method for the synthesis of quinoxaline derivatives *via* the condensation of 1,2-diamines with *α*-diketones. Suggested mechanism of quinoxaline synthesis is drawn in Scheme 2.



Scheme 2. Suggested mechanism for quinoxaline synthesis

One advantage of this catalyst is being metal free. On the other hand, the dual nature of BSA (Lewis and BrØnsted acidic properties) causes a better effect (Figure 1).

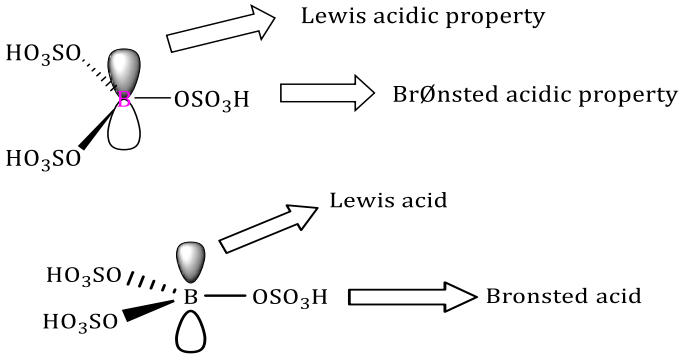


Figure 1. Dual nature of BSA

Table 2. Comparison of BSA, TMB and TIPB (3 mol%) in quinoxaline synthesis at room temperature

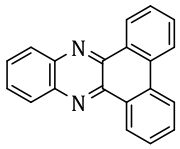
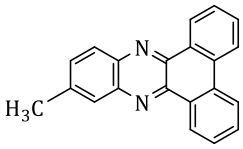
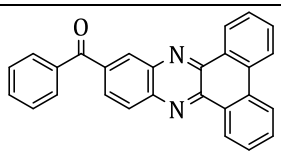
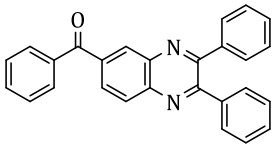
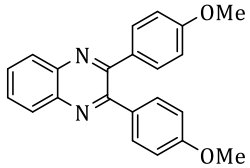
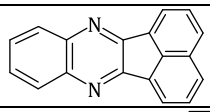
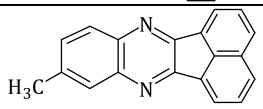
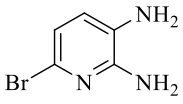
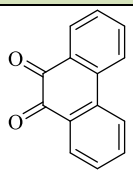
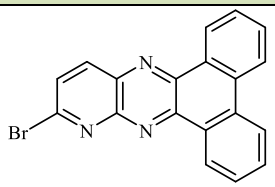
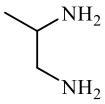
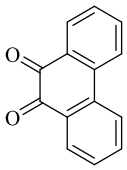
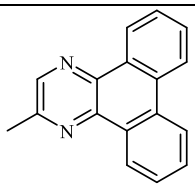
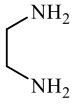
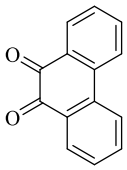
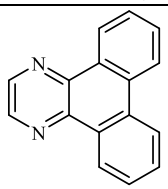
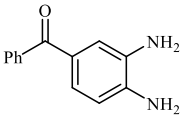
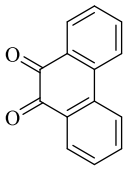
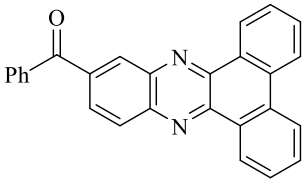
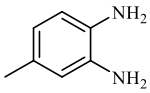
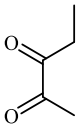
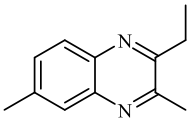
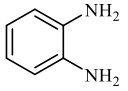
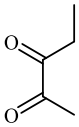
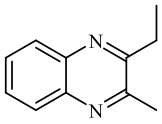
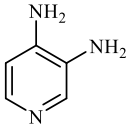
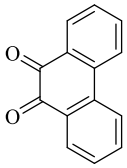
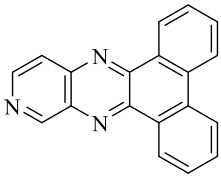
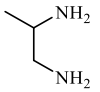
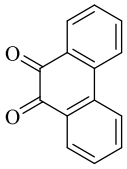
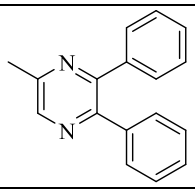
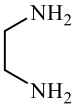
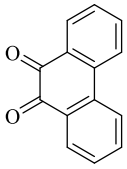
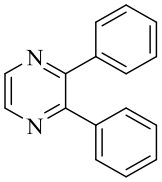
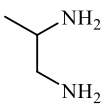
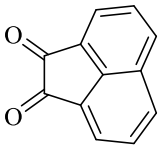
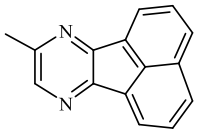
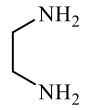
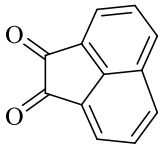
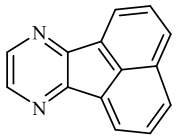
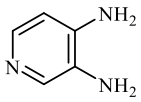
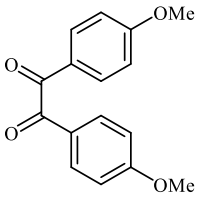
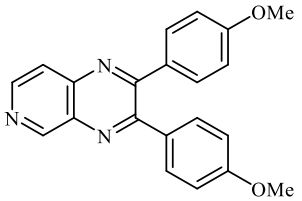
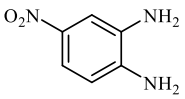
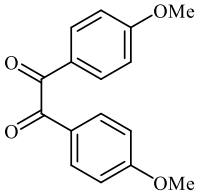
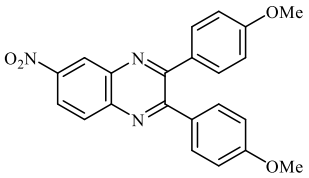
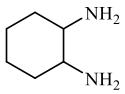
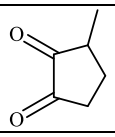
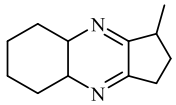
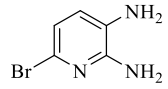
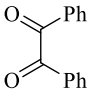
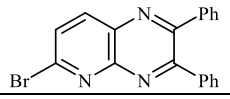
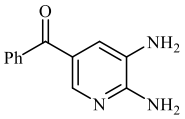
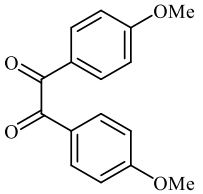
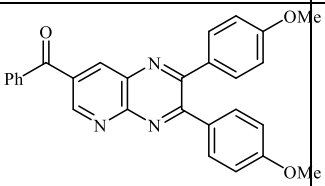
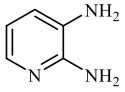
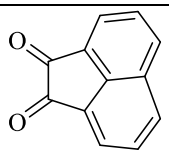
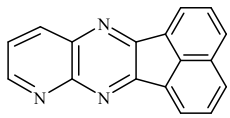
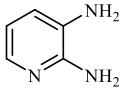
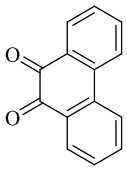
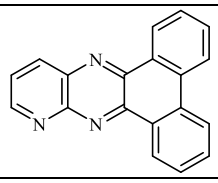
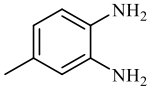
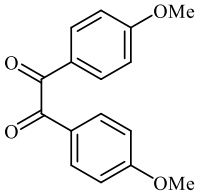
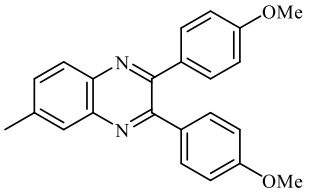
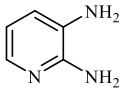
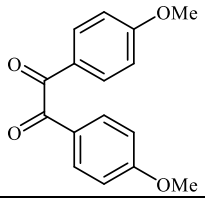
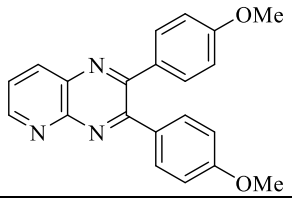
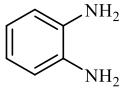
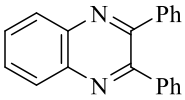
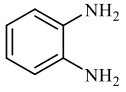
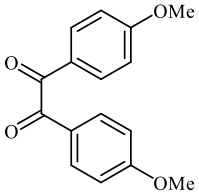
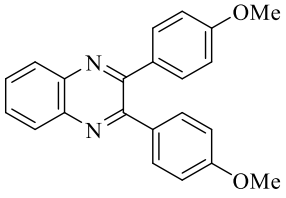
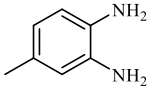
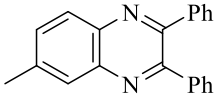
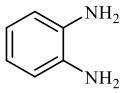
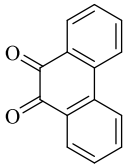
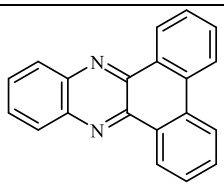
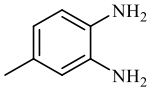
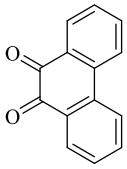
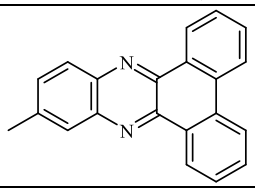
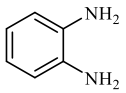
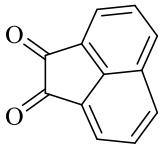
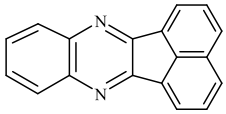
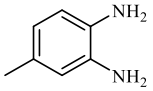
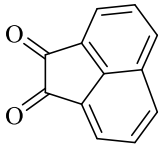
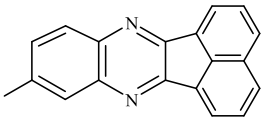
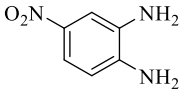
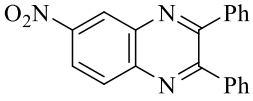
Entry	Product (Q)	BSA/SiO_2 (SBSA)		TMB/SiO_2 (STMB)		$TIPB/SiO_2$ (STIPB)	
		Time (h:min)	Yield%	Time (h:min)	Yield%	Time (h:min)	Yield%
1		00:05	98	23:00	74	28:00	80
2		00:02	94	19:00	77	24:00	79
3		02:00	93	23:00	71	28:00	77
4		02:30	94	23:00	81	27:00	85
5		03:20	91	22:00	59	28:00	67
6		00:25	97	24:00	75	26:00	90
7		00:10	99	21:00	75	24:00	88

Table 3. Synthesis of others quinoxalines by using BSA at room temperature in water

Entry	Diamine (DA)	Diketone (DK)	Product (Q)	Time (min)	Yield (%)	m.p. [Found] m.p. [Lit.]
1				12 h	96	216-218

2				5	94	124-126
3				10	95	184-186
4				40	96	245-247
5				10	90	Liquid
6				5	98	58-61
7				24h	89	212-215
8				5	98	121-123
9				10	97	161-164
10				5	98	68-70

11				5	98	114-116
12				7h	93	120-122
13				3h	80	188-189
14				45	87	Oil
15				4.45h	90	143-145
16				41	86	145-147
17				5.5h	90	225-227
18				20	93	259-260
19				5	90	109-111

20				2.45h	90	109-111
21				3	98	125-127
22				30	89	134-136
23				15	97	113-115
24				3	96	224-226
25				5	97	219-221
26				25	97	241-242
27				10	99	231-233
28				12h	93	185-187

Conclusion

Trimethyl borate and triisopropyl borate are Lewis acids. When we use these catalysts, the time of quinoxaline synthesis is increased and reaction yield is decreased, so the BrØnsted acidic power of boron sulfonic acid is more important than its Lewis acidic power.

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