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RAPID COMMUNICATION

Rapid, efficient and eco-friendly procedure for the synthesis of quinoxalines under solvent-free conditions using sulfated polyborate as a recyclable catalyst

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Abstract. An efficient and inexpensive sulfated polyborate catalyst was applied for the rapid synthesis of quinoxaline derivatives from various substituted *o*-phenylenediamines and 1,2-diketones/α-hydroxy ketones using sulfated polyborate is described. The catalyst has the advantage of Lewis as well as Bronsted acidity and recyclability without significant loss in catalytic activity. The key advantages of the present method are high yields, short reaction times, solvent-free condition, easy workup, and ability to tolerate a variety of functional groups, which give economical as well as ecological rewards.

Keywords. Sulfated polyborate; *o*-phenylenediamines; 1,2-diketone; α-hydroxy ketones; quinoxaline.

1. Introduction

The importance of quinoxaline and its derivatives has been reported in the literature.[1] Quinoxaline derivatives are valuable for their wide spectrum of biological activities *viz* antiviral,[2] anticancer,[2] antibacterial,[3] antidepressant,[4] antiamoebic,[5] anticonvulsant,[6] antimalarial,[7] anti-inflammatory-antioxidant,[8] antiprotozoal activity,[9] and activity as kinase inhibitors.[10] They are basic scaffolds for various insecticides, herbicides, and fungicides.[3] In addition, several antibiotics such as actinomycin, echinomycin, levomycin and triostins bear quinoxaline nucleus.[11] Quinoxaline moiety is also part of bioactive natural products like Izumiphenazine-C.[12] Other applications of quinoxaline as fluorescent dyes,[13] electroluminescent materials,[14] organic semiconductors,[15] cavitands,[16] DNA cleaving agents[1] have been reported. Because of such a widespread applications of quinoxaline compounds in medicinal as well as industrial fields, it remains an attractive target for an organic chemist to develop new synthetic methods for the preparation of quinoxaline derivatives.

The most common methods for the synthesis of quinoxaline is condensation of aromatic 1,2-diamines with 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid for 2–12 h with 34–85% yields.[17] Over the years, various improved methods have been developed using grinding,[18] microwave,[19] sonication,[20] ball mill heating,[21] catalytic and reagent systems. Many catalysts and reagents have also been reported such as sulfamic acid,[22] $CuSO_4.5H_2O$,[23] amidosulfonic acid,[24] polyaniline sulfate,[25] *p*-TSA,[26] ionic liquid (Hbim)BF_4,[27] Mn octahedral molecular sieves,[28] $Ga(OTf)_3$,[29] Montmorillonite K-10,[30] Keggin-type heteropolyacids ($H_4SiW_{12}O_{40}$),[31] Amberlyte-15,[32] $SnCl_2$,[33] $SnCl_2/SiO_2$,[34] $Zr(DS)_4$,[35] ZrO_2 mixed metal oxide,[36] iodine,[37] silica bonded S-sulfonic acid,[38] silica supported $SbCl_3$,[39] Zn[(*L*)proline,[40] etc. Recently, many new improved methods were also reported using silica gel,[41] alumina,[42] $Sm(OTf)_2$,[43] $KHSO_4$,[44] silica sulfuric acid in PEG,[45] glycerol,[46] $CeCl_3$-$7H_2O$ in glycerin,[47] triethylamine/O_2,[48] $FeCl_3$/morpholine,[49] $Ga(ClO_4)_3$,[50] *p*-TSA/H_2O,[51] graphite,[52] sulfated TiO_2,[53] and PEG-400.[54]

Furthermore, many of these methods have some synthetic advantages individually, but still suffer from one or more limitations, such as the use of toxic organic solvents, long reaction times, requiring anhydrous conditions, use of expensive or corrosive reagents, strong acids, strong oxidants, and toxic or expensive catalysts, harsh reaction conditions, tedious workup and most importantly unsatisfactory yields. Thus, development of a safe, environmentally benign, mild, efficient, and high yielding rapid reaction procedure using cost effective and recyclable catalyst for the preparation of quinoxalines is desirable.

A literature search revealed that boric acid catalyzes many important organic transformations at a temperature above 100°C.[55–57] Boric acid dehydrates

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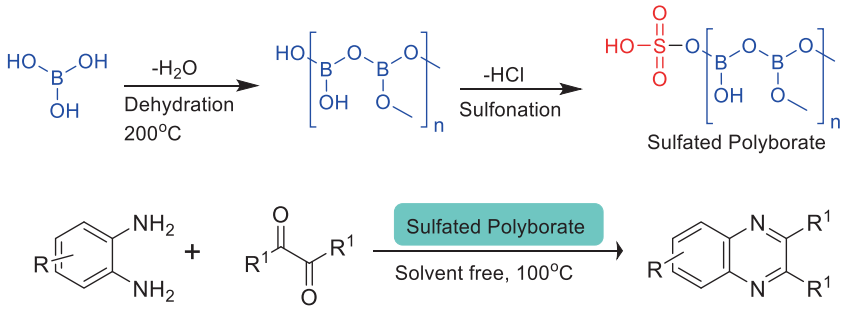


Scheme 1. Schematic representation of sulfated polyborate catalyzed quinoxaline synthesis.

above 100°C and converts to its polymeric forms, which presumably are the active species catalyzing the reaction.[58,59] Dehydrative polymerization liberates water molecules which may hamper the progress of the reactions. This inspired us to develop a polymeric boric acid catalyst with mild Bronsted acidity. To accomplish this, boric acid was dehydrated at 200°C to convert it into its polymeric Lewis acid form and then sulfonated using chlorosulphonic acid to introduce the mild Bronsted acid character. Boron is an electron deficient element and electron withdrawing effect of adjacent sulfate enhances its Lewis acidity, hence, it has both Lewis as well as Bronsted acid characters (Scheme 1).

The development of a novel methodology which serves green chemistry purpose by maximizing efficiency and minimizing waste is currently in demand. To achieve these objectives, herein we report sulfated polyborate as a mild, efficient and eco-friendly catalyst for synthesis of quinoxalines under solvent-free condition with high yields and short duration of times. The catalyst was prepared from readily available boric acid, as economic and non-toxic starting material. This is the first report on the use of sulfated polyborate for the synthesis of quinoxalines (Scheme 1). The catalyst is environmentally benign due to its mild acidity and non-toxic nature.

2. Experimental

2.1 *Materials and methods*

Melting points of all the compounds were recorded by Analab ThermoCal melting point apparatus in the open capillary tube and are uncorrected. The FTIR spectra (KBr) were recorded on Shimadzu FTIR Affinity-1 Fourier Transform Infrared spectrophotometer. ^{1}H NMR spectra were recorded on MR400 Agilent Technology NMR spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 or $CDCl_3$ as a solvent. Chemicals and solvents used were of LR grade and purchased from SD fine, Avra Synthesis and Spectrochem and used without purification. The purity determination of the starting materials and reaction monitoring were accomplished by thin layer chromatography (TLC) on Merck silica gel G F_{254} plates.

2.2 *Preparation of sulfated polyborate*

Sulfated polyborate catalyst was prepared from boric acid as reported in the literature.[60]

2.3 *General procedure for the synthesis of quinoxaline derivatives*

To a mixture of substituted *o*-phenylenediamines derivative (2.0 mmol) and 1,2-diketone / α-hydroxy ketone (2.0 mmol), was added sulfated polyborate (10 wt%). The reaction mixture was stirred at 100°C in an oil bath. The reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the mixture was cooled to room temperature and quenched by water. The resultant product was filtered/extracted with EtOAc to get the product. Crude products were either recrystallized from ethanol or purified by column chromatography using silica as the stationary phase and EtOAc: pet. ether as mobile phase. The products obtained were known compounds and were identified by melting point and ^{1}H and ^{13}C NMR spectroscopy. The spectral data were compared with the literature values.

The catalyst was prepared and characterized by various analytical techniques such as potentiometric analysis, Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and scanning electron microscopy (SEM) energy dispersive X-ray spectroscopy (EDAX).[60]

3. Results and Discussion

The acidity of the catalyst was determined by potentiometric titration in a mixture of water and glycerine (2:1) against standard 0.1 N NaOH solution and the total concentration of H^+ was found to be 19.5 mmol/g which is due to both SO_3H as well as associated B–O–H.

FTIR spectrum of the catalyst showed the presence of a band at 3221 cm^{-1} corresponding to O–H stretching of B–O–H and at 1469 cm^{-1} for B–O stretching, and bands at 1294 cm^{-1} for O = S = O asym. stretching, 1068 cm^{-1} for sym. stretching, 1004 cm^{-1} for S = O

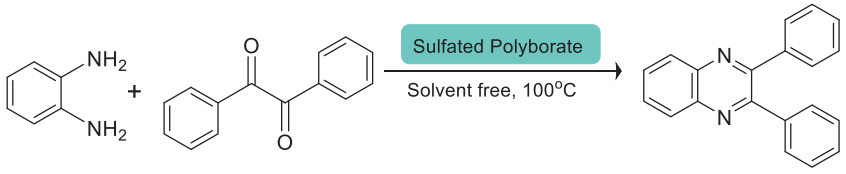
stretching of the SO_3H group. Powder XRD pattern showed significant peaks positioned at $2\theta = 28.1°$ which confirms the presence of B–O bonds in the crystal structure of the catalyst. EDAX shows boron: oxygen: sulfur signal ratio of 30.32: 68.73: 0.96 wt% over different areas.

Recently, we have reported the efficiency of sulfated polyborate as a catalyst for one-pot multicomponent synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones *via* Biginelli[60] reaction and synthesis of α-aminophosphinates via Kabachnik-Fields reaction[61] both under solvent-free conditions. Its ease of preparation, high stability, mild acidity, and reusability prompted us for exploration of its potential to catalyze other useful reaction transformations.

In continuation of the development of greener, eco-friendly catalysts for the synthesis of various heterocycles, herein, we report sulfated polyborate used as a catalyst for synthesis of quinoxalines from aromatic 1,2-diamines and 1,2-diketone/α-hydroxy ketone with good to excellent yields (Scheme 2).

Initially, we designed our study to investigate the suitability of sulfated polyborate as a catalyst at different reaction conditions for synthesis of the quinoxaline derivatives. An equimolar mixture of *o*-phenylenediamines, a representative substrate and benzil were used (Scheme 2). The effect of the catalyst loading on time and yields of the reaction was assessed (Table 1, entries 2–6). In the absence of the catalyst, the reaction proceeded at 100°C but it required longer time with poor yield (Table 1, entry 1), while increased catalyst loading resulted in an increased product yield with significant reduction in reaction time. (Table 1, entries 2–5). The catalyst loading beyond 10 wt% was not advantageous (Table 1, entries 6). Hence, a 10 wt% catalyst loading was optimum for further study.

Temperature played a significant role in the synthesis of quinoxaline (Table 1, entries 5, 7 and 8). The temperature effect was observed at ambient, 70°C and 100°C in presence of sulfated polyborate as a catalyst. The reaction proceeded at 70°C but took longer reaction time with a lower yield (Table 1, entry 7). The reaction did not proceed at room temperature (Table 1, entry 8), while it proceeded at 100°C with increased product yield in a shorter reaction time (Table 1, entry 5). Therefore, 100°C was chosen as optimum temperature for the reaction. The effect of different solvents on yield and time of the reaction was assessed (Table 1, entries 9–14). None of the solvents presented an advantage over solvent-free condition. Therefore, the solvent-free condition was regarded as the best for the cost and ecological benefits.



Scheme 2. Synthesis of quinoxaline from *o*-phenylenediamines and benzil.

Table 1. Catalyst loading, temperature and solvent optimization study.

Entry	Catalyst (wt%)	Solvent	Temperature (°C)	Time (min)	Yield[a] (%)
1.	0	solvent-free	100	320	52
2.	2.5	solvent-free	100	60	84
3.	5.0	solvent-free	100	30	90
4.	7.5	solvent-free	100	10	96
5.	10.0	solvent-free	100	5	99
6.	15.0	solvent-free	100	5	99
7.	10	solvent-free	70	60	50
8.	10	solvent-free	RT	60	NR[b]
9.	10	water	Reflux	60	95
10.	10	ACN	Reflux	60	91
11.	10	THF	Reflux	60	85
12.	10	Ethanol	Reflux	60	89
13.	10	Toluene	Reflux	60	93
14.	10	DMSO	100	60	94

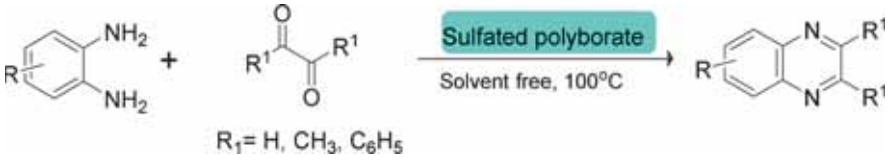
[a]Isolated yield, [b]No reaction.

Table 2. Efficiency of sulfated polyborate in comparison with polyborate and boric acid.

Entry	Catalyst	Conditions	Time (min)	Yield[a] (%)
1.	Sulfated polyborate	solvent-free/100°C	5	99
2.	Polyborate	solvent-free/100°C	30	97
3.	Boric acid	solvent-free/100°C	40	96

[a]Isolated yield.

Table 3. Substrate scope for quinoxaline synthesis.



R_1= H, CH_3, C_6H_5

					Melting point (°C)	
Entry	1,2-Diamine (R)	Diketone (R^1)	Time (min)	Yield[a] (%)	Obtained	Literature
1.	H	C_6H_5	5	99	126–128	128–129[52]
2.	6-CH_3	C_6H_5	5	98	113–115	112–114[52]
3.	5-CH_3	C_6H_5	5	97	118–120	120–121[62]
4.	6-C_4H_9	C_6H_5	7	97	80–82	83[63]
5.	6-Cl	C_6H_5	5	96	122–124	124–126[62]
6.	6-NO_2	C_6H_5	10	95	187–189	188–190[52]
7.	H	CH_3	3	99	111–113	109–110[62]
8.	6-CH_3	CH_3	3	98	93–95	94–95[62]
9.	5-CH_3	CH_3	3	98	74–76	76–77[62]
10.	6-C_4H_9	CH_3	3	97	liquid	NA[b]
11.	6-Cl	CH_3	3	96	94–96	92–93[62]
12.	6-NO_2	CH_3	7	96	132–134	130–132[64]
13.	H	H	3	99	31–33	29–30[67]
14.	6-CH_3	H	3	98	liquid	liquid[67]
15.	5-CH_3	H	3	98	liquid	18–20[68]
16.	6-C_4H_9	H	3	97	liquid	NA[b]
17.	6-Cl	H	3	97	64–66	63–64[65]
18.	6-NO_2	H	5	96	172–173	174[66]

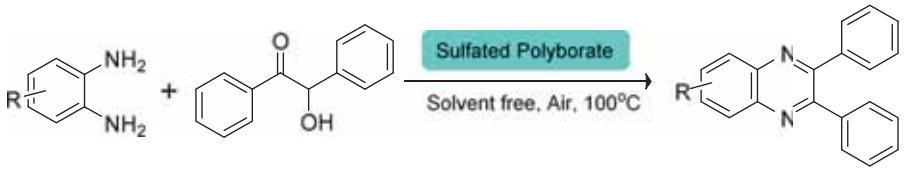
[a]Isolated yields, [b]Not Available in literature.

Herein, the comparison of sulfated polyborate with polyborate and boric acid is shown in Table 2, which revealed that sulfated polyborate showed advantages over its precursors with respect to time and yields (Table 2).

To study the scope and generality of the present protocol, the optimized reaction conditions were applied for the synthesis of a variety of quinoxaline derivatives from substituted *o*-phenylenediamines and 1,2-diketones in the presence of a sulfated polyborate catalyst (Table 3, entries 1–18, Table 4, entries 1–6). All the substrates gave excellent yields in short reaction times. All reactions proceeded very cleanly and no undesirable side reactions were observed, while the reaction time for a 100% conversion of the substrates and reaction yields of products were highly dependent on the substituent. It was observed that *o*-phenylenediamines with either electron donating groups or electron withdrawing groups gave the corresponding products in good to excellent yields. The differences in the yields were very small but substrates having electron-withdrawing groups gave lower yields in increased reaction times compared to substrates having electron-donating groups (Table 3, entries 1–18). On the other hand, structurally diverse 1,2-diketone had no significant effect on the yields and the reaction times.

The optimized protocol was also applied to the reaction of α-hydroxy ketone, benzoin with substituted *o*-phenylenediamines for the synthesis of quinoxalines derivatives. The reaction gave lower yield with longer

Table 4. Quinoxaline synthesis using benzoin under solvent-free condition.



Entry	1,2-Diamine (R)	Time (min)	Yield[a] (%)	Melting point (°C) Obtained	Literature
1.	H	20	96	126–128	128–129[52]
2.	6-CH_3	20	95	113–115	112–114[52]
3.	5-CH_3	20	93	118–120	120–121[62]
4.	6-C_4H_9	20	94	80–82	83[63]
5.	6-Cl	20	92	122–124	124–126[52]
6.	6-NO_2	30	89	187–189	188–190[52]

[a]Isolated yields.

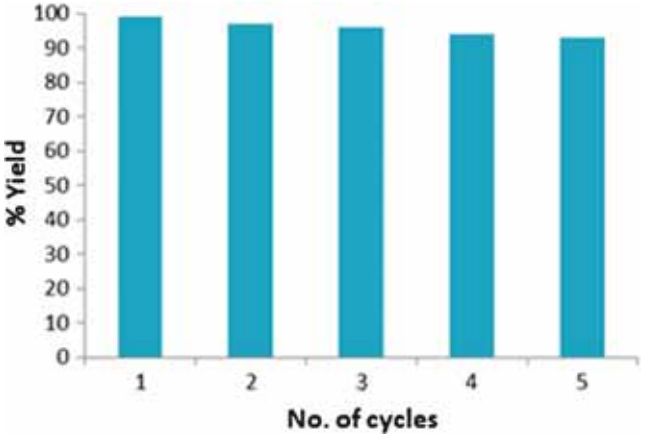


Figure 1. Reusability of the catalyst.

reaction time presumably due to subsequent air oxidation of 2,3-diphenyl-1,2-dihydroquinoxaline, an intermediate, to give 2,3-diphenylquinoxaline (Table 4, entries 1–6).

The reusability of the catalyst in the model reaction under solvent-free conditions at 100°C was evaluated. After completion of each cycle of the reaction, the catalyst was recovered by adding water and the product was filtered off. The filtrate was evaporated under reduced pressure to recover the catalyst quantitatively. The recovered catalyst was reused four times with no significant loss in a catalytic activity (Figure 1).

4. Conclusions

In conclusion, sulfated polyborate is a mild, efficient, eco-friendly and inexpensive catalyst for the synthesis of quinoxalines of various substituted *o*-phenylenediamines and 1,2-diketones/α-hydroxy ketones under optimal conditions. Mild reaction conditions, shorter reaction times, higher yields, ease of workup, recyclability of the catalyst and environment-friendliness are the key features of the present protocol. Moreover, this method has the ability to tolerate a wide variety of substituents.

Supplementary Information (SI)

Full experimental details, ^{1}H and ^{13}C NMR spectra of compounds are available in Supplementary Information at www.ias.ac.in/chemsci.

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