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RESEARCH LETTER

Green synthesis of quinoxaline derivatives using *p*-dodecylbenzenesulfonic acid as a surfactant-type Bronsted acid catalyst in water

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Quinoxaline derivatives have been synthesized in high yields in the presence of *p*-dodecylbenzenesulfonic acid as an inexpensive, nontoxic, and efficient Bronsted acid-surfactant-combined catalyst in water at room temperature.

Keywords: quinoxaline; Bronsted acid; surfactant; *p*-dodecylbenzenesulfonic acid (DBSA); green synthesis

Introduction

Performing organic reactions in water has attracted much attention over the past decades due to its numerous advantages such as being considerably safe, nontoxic, environmentally friendly, and cheap (1–5). In addition, reactions in water can facilitate access to different reactivity and selectivity patterns compared with those observed in common organic solvents due to its unique physical and chemical properties.

Quinoxalines and its derivatives are an important class of nitrogen-containing heterocyclic compounds and have shown a broad spectrum of biological activities such as antiviral (4), antibacterial (6), anti-inflammatory (7), and anticancer (8), which have made them privileged structures in pharmacologically active compounds.

Various methods have been reported for synthesis of quinoxaline derivatives via a condensation process catalyzed by zeolites (9), CuSO₄·5H₂O (10), cerium ammonium nitrate (11), Zn [(L)praline] in HOAc (12), molecular iodine in DMSO (9) or CH₃CN (13), ionic liquids (14), montmorillonite K-10 (15), H₆P₂W₁₈O₆₂·2H₂O (16), Yb(OTf)₃ (17), or using Bi (18), Pd(OAc)₂ (19), and MnO₂ (20), via a oxidative coupling reaction. Some of these processes suffer from some limitations such as use of volatile organic solvents, low product yields, expensive reagents, tedious work-up procedures, or harsh reaction conditions.

Results and discussion

DBSA (21) as a Bronsted acid-surfactant-combined catalyst (BASC) has been known to play an important role not only for the activation of the substrate but

also for the solubilization of organic substrates by the formation of colloidal dispersions. DBSA works well for dehydration reactions such as the esterification and etherification in water (22), synthesis of bis(indol-3-yl)alkanes (23), xanthenes (24,25), 3-arylmethyl-4-hydroxycoumarins (26), selective α -aminoallylation (27), as well as in polymerization reactions (28–30). Herein, we wish to report a green and efficient method for the synthesis of quinoxaline derivatives in good to excellent yields by the condensation of 1,2-diamines with 1,2-dicarbonyl compounds catalyzed by DBSA.

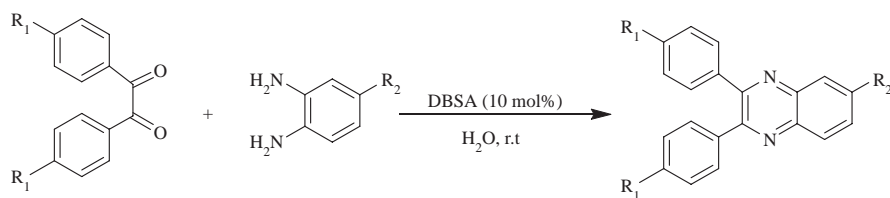
Our studies were initiated with a model condensation reaction, between benzil (PhCOCOPh) and 1,2-diaminobenzene in H₂O at room temperature, using a catalytic amount of DBSA (Scheme 1).

To optimize the reaction conditions, we carried out the model reaction in various solvents. As shown in Table 1, condensation reaction catalyzed by DBSA (10 mol%) in various solvents including water, ethanol, ethanol/water, methanol, *n*-hexane, acetone, acetonitril was investigated resulting in the product being 96%, 80%, 84%, 84%, 74%, 75%, 40% isolated in yields, respectively. Thus, water is obviously the best choice for this reaction.

In addition to DBSA, we screened the effect of other surfactants such as cetyl trimethylammonium bromide (CTAB), tetradecyl trimethyl ammonium bromide (TTAB), dodecyl trimethyl ammonium bromide (DTAB), and Esterquat, on the time and yield of the model reaction. The results in Table 2 show that reducing surface tension has a great effect on the rate of the reaction so that it progresses to great extent in the absence of any Bronsted acid (Entries 2–5).

The effect of the amounts of DBSA on the yields of condensation reaction in water has been shown in

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Scheme 1. DBSA catalyzed synthesis of quinoxalines.

Table 3. It showed that when a mixture of 1 mmol benzil, and 1 mmol *o*-phenylenediamine was stirred for 24 h in the absence of DBSA, no product was detected (Entry 1), which showed that the catalyst should be necessary for this condensation reaction.

Afterward, we selected 5 mol% of DBSA to catalyze the model reaction and found that the desired quinoxaline was obtained in 92% yield. The reaction worked well when the amount of DBSA was increased to 10 mol%. (Table 1, Entry 3). When the amount of catalyst increased to 20%, the yields did not increase noticeably (Table 3, Entry 4). Thus, 10 mol% DBSA was chosen as the optimum amount of catalyst.

Besides DBSA, we also used catalytic amounts of other inorganic and organic acids such as HCl and *p*-toluenesulfonic acid (PTSA) for synthesis of quinoxaline from *o*-phenylenediamine and benzil in water as solvent. The results are depicted in Table 4. From these results, it is clear that DBSA is more efficient catalyst in water than common Bronsted acids.

After optimization, in model condensation reaction, the scope and the generality of the present method was demonstrated by the condensation of various substituted 1,2-diaminobenzen with 1,2-dicarbonyl compounds using catalytic amount of DBSA in water and the results are presented in Table 5.

Experimental

General method for preparation of quinoxaline in water

A mixture of 1,2-diketone (1 mmol), 1,2-diamino derivatives (1 mmol), and *p*-dodecylbenzenesulfonic acid (DBSA) (10 mol%) in water (3 mL) was stirred

Table 1. Effect of solvents on the synthesis of 2,3-diphenylquinoxaline.^a

Entry	Solvent	Time (h:min)	Yield (%)
1	H ₂ O	2:00	96
2	EtOH	2:00	87
3	EtOH/H ₂ O	2:00	93
4	MeOH	2:00	86
5	<i>n</i> -Hexane	2:00	75
6	Acetonitril	2:00	87

^aBenzil (1.0 mmol), *o*-phenylenediamine (1.0 mmol) in the presence of DBSA (10 mol%) at room temperature in various solvents.

Table 2. Effect of different surfactants on the reaction time and yield of 2,3-diphenylquinoxaline.^a

Entry	Surfactant	Time (h:min)	Yield (%)
1	DBSA	2:00	96
2	CTAB	3:30	85
3	TTAB	5:00	85
4	DTAB	4:00	86
5	Esterquat	3:00	76

^aBenzil (1.0 mmol), *o*-phenylenediamine (1.0 mmol) in the presence of 10 (mol%) of various surfactants.

Table 3. Effect of amount of DBSA on the reaction times and yields.^a

Entry	DBSA (mol%)	Time (h:min)	Yield (%)
1	0	24	–
2	5	2:10	92
3	10	2	96
4	20	2	96

^aReaction conditions: benzil (1.0 mmol), *o*-phenylenediamine (1.0 mmol) in the presence of various amount of DBSA at room temperature in water.

at room temperature. Progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the precipitated solid which is almost a pure product was filtered. Further purification could be done by recrystallization from a suitable solvent like ethanol or tetrahydrofuran (THF). All of the obtained quinoxalines are known compounds and identified by ¹HNMR and melting points compared with the literature values.

Table 4. Effect of different Bronsted acids on the synthesis of 2,3-diphenylquinoxaline.^a

Entry	Catalyst	Time (h:min)	Yield (%)
1	DBSA	2:00	96
2	HCl	2:00	85
3	PTSA	4:00	90
4	H ₂ SO ₄	4:00	80
5	H ₃ PO ₄	2:30	84

^aBenzil (1.0 mmol), *o*-phenylenediamine (1.0 mmol), catalyst (10 mol%) at room temperature in water as solvent.

Table 5. Synthesis of quinoxaline derivatives using DBSA as a BASC.

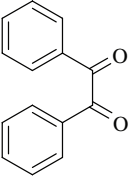
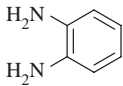
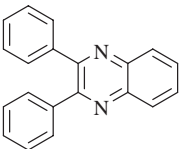
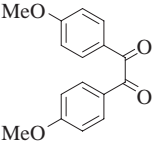
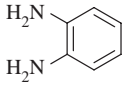
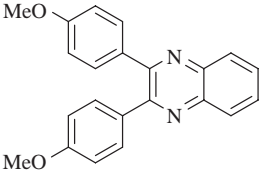
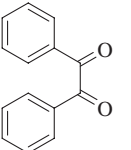
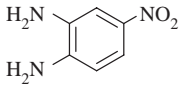
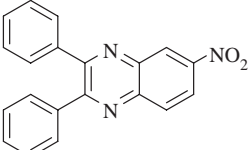
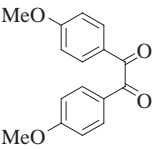
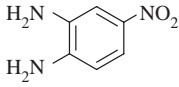
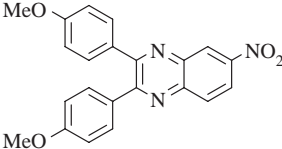
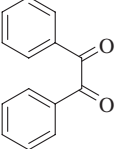
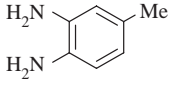
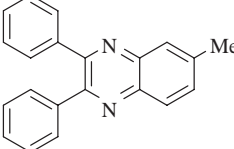
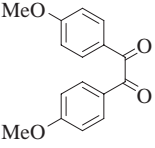
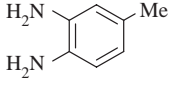
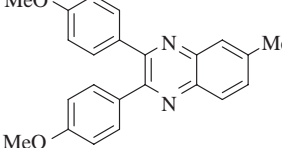
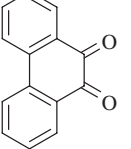
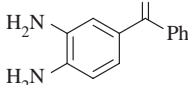
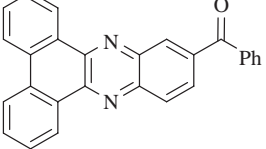
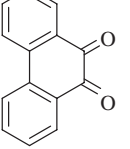
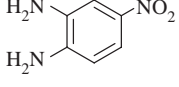
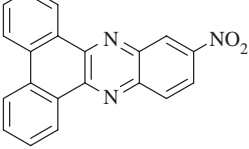
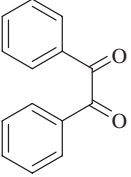
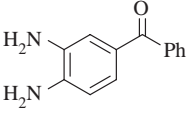
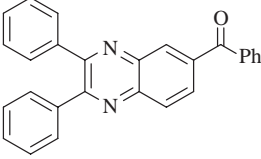
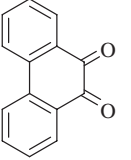
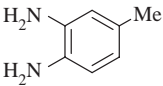
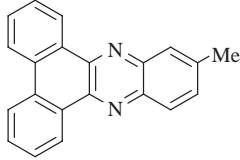
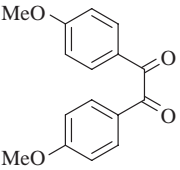
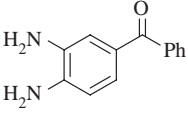
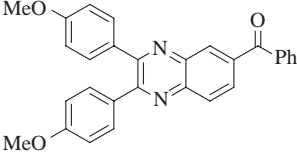
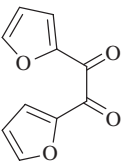
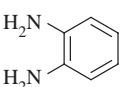
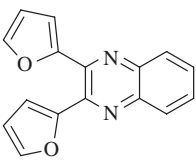
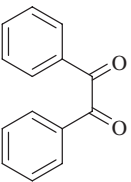
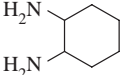
Entry	1,2-Dicarbonyl	1,2-Diamine	Product	Time (h)	Yield (%) ^{a,b}	Mp (°C)
1				2	96	126–127
2				2	92	151–152
3				6	90	191–192
4				6	86	192–194
5				2	93	117–118
6				2	94	125–127
7				2	95	242–244
8				2	93	240–242

Table 5 (Continued)

Entry	1,2-Dicarbonyl	1,2-Diamine	Product	Time (h)	Yield (%) ^{a,b}	Mp (°C)
9				10	98	133–135
10				2	98	218–219
11				10	94	129–132
12				1	95	129–131
13			–	24	0	–

^aRefers to isolated yields.^bAll products were characterized by spectra and physical data.

Conclusions

In conclusion, we developed a simple, eco-friendly, convenient, and efficient procedure for synthesis of quinoxaline from the various 1,2-dicarbonyl and 1,2-diamin compounds using catalytic amount of DBSA under mild reaction conditions at room temperature.

Moreover, the procedure offers several advantages including high yields, operational simplicity, cleaner reactions and minimal environmental impact, which make it a useful process for the synthesis of quinoxaline derivatives.

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