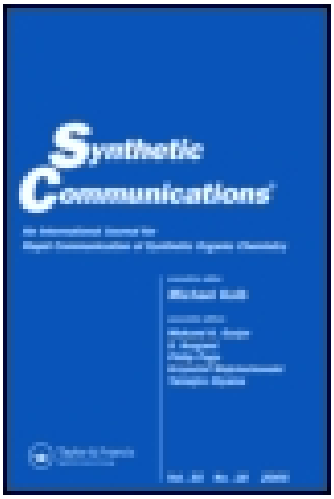

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Sulfamic Acid: A Mild, Efficient, and Cost-Effective Catalyst for Synthesis of Indoloquinoxalines at Ambient Temperature

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SULFAMIC ACID: A MILD, EFFICIENT, AND COST-EFFECTIVE CATALYST FOR SYNTHESIS OF INDOLOQUINOXALINES AT AMBIENT TEMPERATURE

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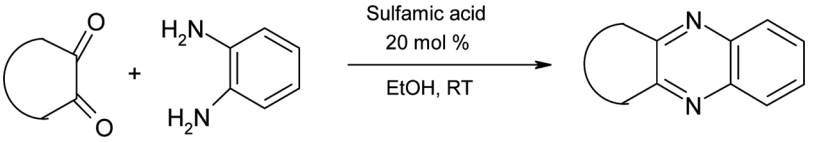
GRAPHICAL ABSTRACT



Abstract *A simple, cost-effective method for synthesis of indoloquinoxalines from isatin and* o*-phenylenediamine employing a catalytic amount of sulfamic acid at ambient temperature is reported. Moreover, the method is applicable for a variety of isatins, ninhydrin, 4-hydroxynaphthaquinone, and 1,2-diketones. The key features of the protocol include rapid reactions with good yields, simple workup procedure, and easy isolation of products.*

Keywords Cost-effective; 1,2-diaminobenzene; indoloquinoxalines; isatins; sulfamic acid

INTRODUCTION

Heterocycles play an important role in the design and discovery of new compounds for pharmaceutical applications.[1] Among the important classes of bioactive heterocycles, quinoxalines have attracted the attention of synthetic organic chemists as they are a frequently occurring framework in a number of biologically active natural products such as izumiphenazine C[2] and echinomycin[3] (Fig. 1), many pharmaceuticals, and agrochemicals.[4] They have also found applications in dyes,[5] as efficient electroluminescent materials,[6] as organic semiconductors,[7] as dehydroannulenes,[8] and in chemically controllable switches.[9] Recent reviews on the biological activities of indoles and quinoxalines highlight their medicinal importance.[10] Certainly the interest in their synthesis stems from their antibacterial, antiviral, anthelmintic, anti-inflammatory, kinase inhibitory, and anticancer activity;[11] for example, NCG555879-01 acts as BRCA1 inhibitor. Additionally, antibiotics such as echinomycin and actinomycin have quinoxaline backbones.[3a,12]

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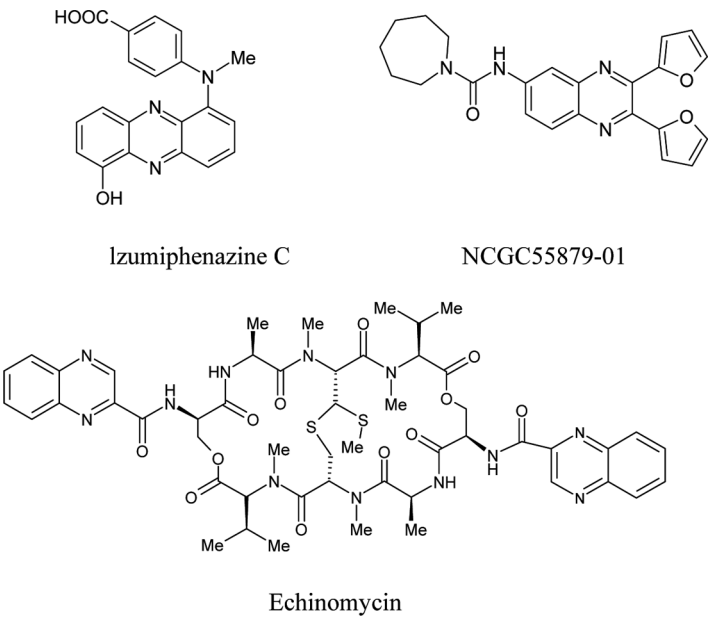
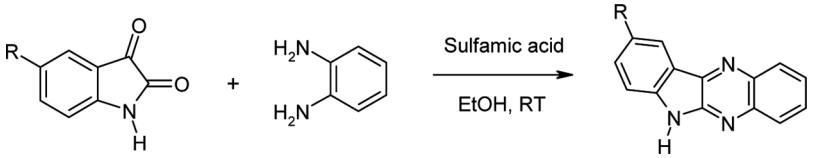


Figure 1. Biologically important quinoxalines.

Hence, different synthetic methods have been reported,[13] and there is a demand for development of ecofriendly methods for synthesis of quinoxalines. Among various classes of quinoxalines, synthesis of indoloquinoxalines from isatins possessing electron-withdrawing groups[14] is a challenge because of the possibility of formation of 3-(2′-amino-5′-substituted)-quinoxaline-2(1*H*)-ones via opening of the isatin ring instead of classical 6*H*-indolo[2,3-b]quinoxalines. There are sporadic reports available for synthesis of indoloquinoxalines employing catalytic amounts of tetrabutylammonium bromide (TBAB)[13a] and excess glacial acetic acid.[14] However, these methods are performed at elevated temperatures. Therefore, an environmentally benign procedure for synthesis of indoloquinoxalines from *o*-phenylenediamine and a variety of isatins at ambient temperature is highly desirable.

A commercially available sulfamic acid (NH_2SO_3H, SA) is a nonhygroscopic, white crystalline Bronsted acid available at low cost with high stability and outstanding physical properties.[15] Recently, it has been shown that SA has potential as a substitute for conventional acidic catalytic materials because of its ease of setup, mild conditions, rapid reaction, selectivity, good yields,[16] good purity of products, and low cost.[17] The most important feature of SA is its solubility in water, which could facilitate easy separation and isolation of products just by filtration when products are sparingly soluble or insoluble in organic solvents. The interesting properties of SA spurred us to investigate its catalytic potential for the synthesis of biorelevant heterocycles.

In continuation of our work in the development of efficient methodologies for synthesis of heterocycles[18] and our interest in sulfamic acid,[18h] herein we report sulfamic acid–catalyzed synthesis of indoloquinoxalines by reaction of isatin and 1,2-diaminobenzene at ambient temperature (Scheme 1).



Scheme 1. Sulfamic acid–catalyzed synthesis of indoloquinoxalines at ambient temperature.

RESULTS AND DISCUSSION

In our initial endeavor to synthesize indoloquinoxalines, a reaction of isatin and *o*-phenylene diamine was carried out in ethanol under catalyst-free conditions at room temperature. However, the reaction did not lead to the formation of the desired product (Table 1, entry 1). Even though heating conditions were employed, the reaction did not proceed to completion even after a prolonged time (12 h) (Table 1, entry 2). To explore suitable reaction conditions, the model reaction was performed in the presence of various catalysts: *p*-TSA, sulfamic acid, envirocatalysts EPZ-10 (clay-supported $ZnCl_2$) and EPZ-G (clay-supported $FeCl_3$), $AlCl_3$, $Gly \cdot NO_3^-$, $Gly \cdot Cl^-$, $Gly \cdot PF_6^-$, and $[BMIM]BF_4^-$. The results are summarized in Table 1. Among the employed catalysts, sulfamic acid was found to be best catalyst as corresponding indoloquinoxaline was obtained in comparatively good yields in short times (Table 1, entry 11). The effect of catalyst loading was optimized by carrying out reaction with 5, 10, 15, 20, and 30 mol% of the catalyst (Table 1, entries 11–15). The result revealed that 20 mol% of sulfamic acid is efficient to carry out reaction to a synthetically useful degree.

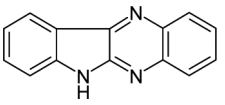
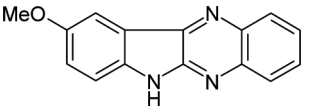
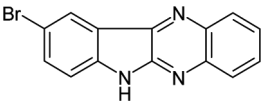
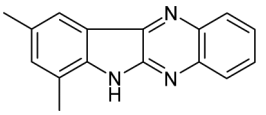
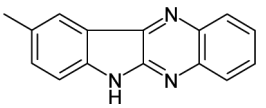
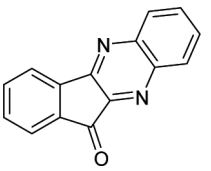
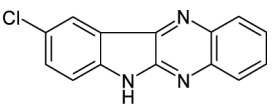
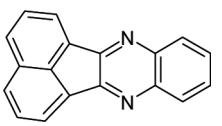
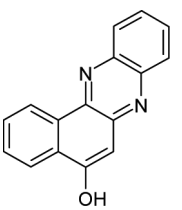
With the optimal reaction conditions in hands, we extended the scope of reaction by screening a variety of substrates (Table 2). The catalytic system is

Table 1. Optimization of reaction conditions

Entry	Catalyst	Catalyst load (mol%)	Temp. (°C)	Time (h)	Yield (%)[a]
1	Catalyst-free	00	RT	12	00
2	Catalyst-free	00	Reflux	12	20
3	*p*-TSA	20	RT	3	45
4	Glycine nitrate	20	RT	3	54
5	EPZ-10	20	RT	3	43[b]
6	EPZ-G	20	RT	3	38[b]
7	$AlCl_3$	20	RT	3	62
8	Glycine chloride	20	RT	3	50
9	Glycine PF_6^-	20	RT	3	53
10	$[BMIM]BF_4^-$	20	RT	3	40
11	Sulfamic acid	20	RT	1	83
12	Sulfamic acid	05	RT	3	67
13	Sulfamic acid	10	RT	3	71
14	Sulfamic acid	15	RT	2	73
15	Sulfamic acid	30	RT	1	83

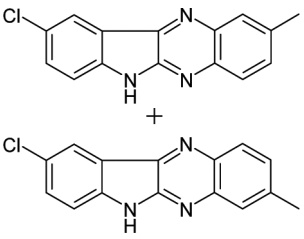
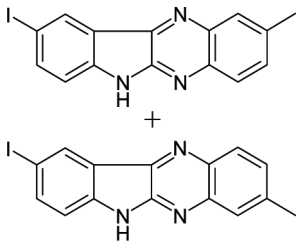
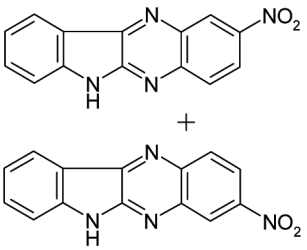
Note. Reaction conditions: Isatin (1 mmol), *o*-phenylene diamine (1 mmol), solvent = 10 mL 95% ethanol.
[a]Isolated yields.
[b]As catalyst is insoluble in water, extraction of reaction mixture with ethyl acetate is carried out for isolation of product.

Table 2. Sulfamic acid–catalyzed synthesis of substituted quinoxalines at ambient temperature

Entry	Product	Time (h)	Yield[a] (%)
1		1	83
2		1.5	95
3		2	85
4		1.5	91
5		1.5	94
6		1	90
7		1.5	84
8		1	86
9		1.5	87

(*Continued*)

Table 2. Continued

Entry	Product	Time (h)	Yield[a] (%)
10		1.5	82
11		1.5	93
12		2	85

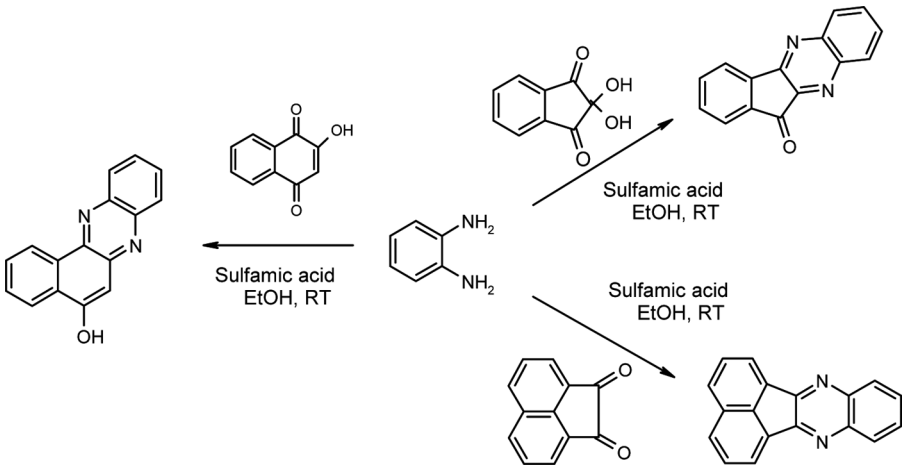
Notes. Reaction conditions: Isatin/acenaphthoquinone/2-hydroxynaphthoquinone/ninhydrin (1 mmol), *o*-phenylene diamine (1 mmol), sulfamic acid (20 mol%), ethanol 10 mL; temp. = RT.

[a]Isolated yields.

suitable to structurally diverse isatins bearing both electron-deficient and electron-donating substituents.

The electron-donating substituents on isatin enhanced the rate of reaction and furnished corresponding products in good yields (Table 2, entries 2, 4, and 5) better than the electron-withdrawing substituents (Table 2, entries 3 and 7). The noteworthy feature of the procedure is that the presence of electron-withdrawing substituent on isatin leads to indoloquinoxalines instead of classical quinoxalines.[14] It was interesting to note that the presence of methyl group at the fourth position of 1,2-phenylenediamine (Table 2, entries 10, 11, and 12) resulted into two isomeric products (approx. 60:40) depending on the course of cyclization. This observation may be attributed to the electron-donating nature of methyl group, which may favor the nucleophilic character of the 1,2-diamino moiety.

Encouraged by these results to explore the generality of the procedure, we decided to carry out reactions with ninhydrine/2-hydroxynaphthoquinone/acenaphthoquinone and *o*-phenylene diamine (Scheme 2). Interestingly, ninhydrine



Scheme 2. Sulfamic acid–catalyzed synthesis of quinoxaline of ninhydrine/2-hydroxynaphthoquinone/acenaphthoquinone at ambient temperature.

and acenaphthoquinone react smoothly with *o*-phenylene diamine to yield the desired product in 90% and 86% yield respectively (Table 2, entries 6 and 8). Fascinatingly, quinoxaline obtained from 2-hydroxynaphthaquinone also resulted in good yield (Table 2, entry 9). Results summarized in Table 2 showcase the broad scope of the method.

CONCLUSION

In summary, sulfamic acid was shown to be an efficient catalyst for the preparation of structurally diverse quinoxalines. The reported protocol offers several advantages over traditional methods, making it an important contribution under the umbrella of efficient methodologies for quinoxaline synthesis.

EXPERIMENTAL

IR spectra were recorded on an Agilent Cary (IR-630) spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC (300 MHz and 75 MHz) spectrometer in dimethylsulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Shimadzu QP2010 GCMS.

Typical Procedure

A solution of isatin (1 mmol) and *o*-phenylene diamine (1 mmol) in ethanol (95%, 10 mL) and sulfamic acid (20 mol%) was stirred at ambient temperature for the time mentioned in Table 2, monitored by TLC. After completion of reaction, product was isolated by filtration and washed it with ethanol, dried to furnish the desired products in good yields.

FUNDING

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SUPPORTING INFORMATION

Full experimental details with IR spectra, ^{1}H and ^{13}C NMR, and MS spectra for this article can be accessed on the publisher's website.

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