Room Temperature Facile Synthesis of Quinoxalines Catalyzed by Amidosulfonic Acid

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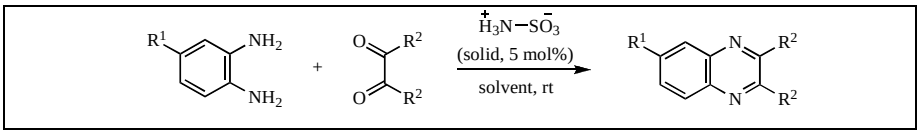

Amidosulfonic acid NH_2–SO_3H catalyzed direct condensations of *o*-phenylenediamines with α-diketones at room temperature in organic solvents to afford quinoxalines in excellent yields. The amidosulfonic acid as a solid acid catalyst in this preparation was efficient and recoverable.

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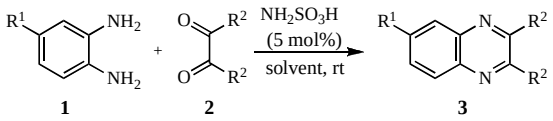
INTRODUCTION

In aromatic multi-nuclear *N*-containing heterocyclic compounds, quinoxaline derivatives exhibit special and wide range of functions in biological active compounds [1], electroluminescent materials [2], dyes [3], and anion sensors [4]. Their extraordinary potentials in pharmacological research and practice have attracted much attention. Although rarely recorded in nature, synthetic quinoxaline derivatives showed variety of pharmaceutical activities encompassed major types of drug target families and effective in many clinical applications such as anti-tumor agents [5], kinase inhibitors [6], HIV drugs [7], antibiotics [8], ion channel regulators [9], and anti-protozoal agents [10]. Several synthetic routes to quinoxaline have been developed [11] and the well established preparation method is the direct condensation [12] of *o*-phenylenediamines with α-diketones in refluxing ethanol [13] or in boiling acetic acid [14]. Most recently, several preparative methods through direct condensations to quinoxalines have been reported which using $Yb(OTf)_3$ [15], molecular iodine [16], or $Ce(NH_4)_2(NO_3)_6$ [17] as catalysts. Indirect alternative routes through tandem oxidation-condensation [18] are useful diversity oriented approaches. In comparison with the variety use of quinoxalines in many fields, their preparation methods are limited in number. Some of the established methods suffered in one or more drawbacks, such as drastic reaction conditions, special apparatus, expensive reagents or catalyst, or complicated work-up.

In continuation of our preliminary investigation on the condensations afford α-amidosulfones by using NH_2SO_3H as efficient catalyst [19–23], we envisioned broader applications of this solid acid in some condensations formerly carried out in moisture-free conditions or by dehydrating measures. NH_2SO_3H as a powerful solid catalyst has been used in many organic preparations [24]. It has unique structure [25] and prominent properties, such as, it has outstanding physical stability, is insoluble in common organic solvent, is inexpensive, and readily available [26]. As part of our on going interest in using of economical reagents for organic transformations, we had the opportunity to look into the synthesis of quinoxalines by using NH_2SO_3H as solid catalyst in proper solvent.

Scheme I



1 **2** **3**

RESULTS AND DISCUSSION

In the beginning, NH_2SO_3H was tested for the catalytic activity in the condensation of *o*-phenylenediamine **1a** with benzil **2a** in dichloromethane at room temperature and showed good performance (entry 3, Table 1). On the contrary, without catalyst, similar condensations in alcohols and other protic or polar solvents are not observed at room temperature [12–14], which was reconfirmed by blank contrasts (entries 1 and 2, Table 1). Encouraged by these promising results, we decided to expand the reactions in array of diketones in various solvents at room temperature by using NH_2SO_3H as catalyst (Scheme I).

Initially, condensations of *o*-phenylenediamine **1a** (2 mmol) with benzil **2a** (2 mmol) mediated by NH_2SO_3H in different solvents (5 mL) at room temperature were conducted (Table 1). The optimization on the loading of the catalyst and reaction time was carried out (entries 3–5, Table 1), 5 mol % of NH_2SO_3H and 2 h showed to be an optimal condition for preparation of quinoxaline **3aa**. Next, the reactions of **1a** (2 mmol) with **2a** (2 mmol) catalyzed by NH_2SO_3H (5 mol %) were tested in common organic solvents (entries 6–13) at room temperature and showed polar solvents were preferred. Since NH_2SO_3H is slightly soluble in alcohols, DMF, and CH_3CN, but

Table 1

Condensation of *o*-phenylenediamine with benzil as model reaction at room temperature.

Entry	Solvent	NH_2SO_3H / mol%	Time / h	Yield / %
1	EtOH	0	48	—
2	CH_2Cl_2	0	48	6
3	CH_2Cl_2	10	4	91
4	CH_2Cl_2	15	6	96
5	CH_2Cl_2	5	2	92
6	MeOH	5	2	84
7	EtOH	5	2	78
8	DMF	5	2	81
9	CH_3CN	5	2	85
10	EtOAc	5	4	77
11	Et_2O	5	4	71
12	Toluene	5	6	72
13	Hexane	5	8	58

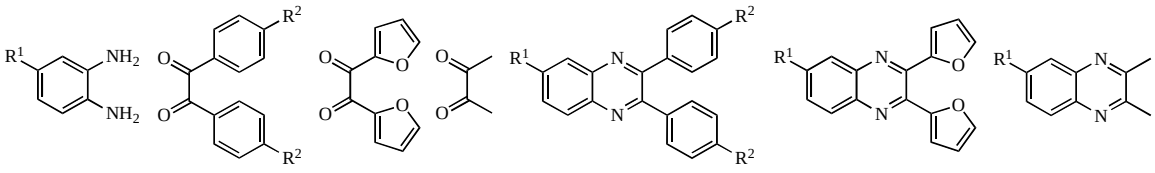
insoluble in dichloromethane, we decided to use CH_2Cl_2 in the expanded experiments for its good performance and the simple separation and recovery of the solid acid catalyst. Further, the procedure was extended to substituted aromatic (entries 2 and 3, Table 2), heterocyclic (entry 4), and aliphatic (entry 5) α-diketones with excellent yields. *o*-Phenylenediamines with electron-donating (R^1 = Me, entries 6–10) and electron-withdrawing (R^1 = Cl, entries 11–15) substitutions were employed to expand the scope of this protocol. As indicated in Table 2, substitutions (R^1 = Me, Cl) on the phenyl group of *o*-phenylenediamine exerted minor influence on the reactions (take entries 2, 7 and 12 as examples), and similar yields resulted. On the other hand, electron-donating groups on the aryl of the diketones made the reactions slower and it took longer time to obtain comparable yields (see entries 11–13 as examples). The reactions proceeded smoothly at ambient temperature, after completion of the condensation, the solid catalyst and the product **3** was separated by simple work-up.

Although the structures of NH_2SO_3H were investigated in gas phase [25] and in molecular clusters (condensed phase) [27] as zwitterionic units in the form of $^+NH_3SO_3^-$ (see Scheme 2, compound **4**), the structures of the catalyst in crystalline and in solution were not explored further to our knowledge. Since NH_2SO_3H is not soluble in common organic solvents, the catalysis should take place heterogeneously at the interface of the solid catalyst and the solution. A tentative mechanism was proposed in Scheme 2. Due to the zwitterionic nature of the catalyst, it may work as *bi*-functional catalyst by the simultaneous coordination of the negatively charged O atom on the sulfonic

Table 2

Synthesis of quinoxalines using *o*-phenylenediamines and symmetrical α-diketones

Entry	*o*-Phenylenediamine **1**	1,2-Diketone **2**	Quinoxaline **3**	Time / h	Yield / %	Ref
1	**1a**	**2a**	**3aa**	2	92	[15]
2	**1a**	**2b**	**3ab**	2	85	[16]
3	**1a**	**2c**	**3ac**	2	82	[15]
4	**1a**	**2d**	**3ad**	2	89	[18]
5	**1a**	**2e**	**3ae**	2	88	[17]
6	**1b**	**2a**	**3ba**	2	91	[15]
7	**1b**	**2b**	**3bb**	4	89	[15]
8	**1b**	**2c**	**3bc**	6	84	[15]
9	**1b**	**2d**	**3bd**	3	87	[16]
10	**1b**	**2e**	**3be**	2	86	[16]
11	**1c**	**2a**	**3ca**	3	92	[15]
12	**1c**	**2b**	**3cb**	5	87	[16]
13	**1c**	**2c**	**3cc**	6	79	[16]
14	**1c**	**2d**	**3cd**	3	90	[18]
15	**1c**	**2e**	**3ce**	2	89	[18]

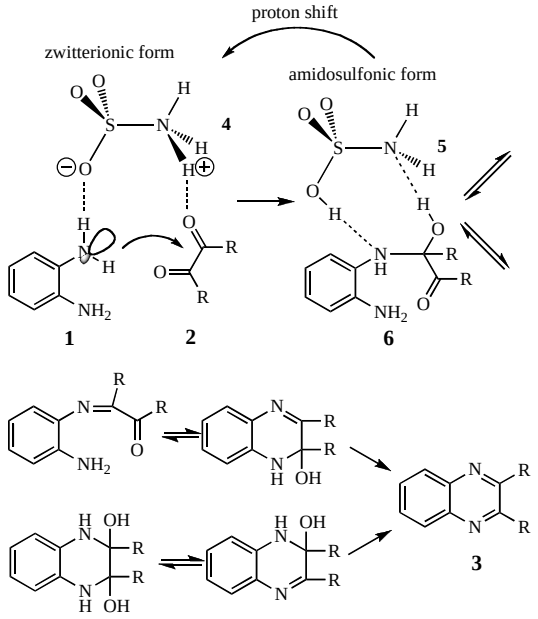


1a-c **2a-c** **2d** **2e** **3aa-ac; 3ba-bc; 3ca-cc** **3ad-cd** **3ae-ce**

1a R^1 = H **2a** R^2 = H **3aa-ac** R^1 = H; R^2 = H, Me, OMe **3ad-cd** R^1 = H, Me, Cl **3ae-ce** R^1 = H, Me, Cl
1b R^1 = Me **2b** R^2 = Me **3ba-bc** R^1 = Me; R^2 = H, Me, OMe
1c R^1 = Cl **2c** R^2 = OMe **3ca-cc** R^1 = Cl; R^2 = H, Me, OMe

moiety with the amine proton NH on **1** and the coordination of the positively charged H atom on the amido- moiety with ketone O on **2**. Thus the reaction in the first step was facilitated in two ways; one was the double activation of the nucleophile **1** and the electrophile **2**, another was the proximity of **1** and **2**. The latter part of the schematic approach from freed **6** to **3** was proposed and confirmed [28].

Scheme II



In summary, we have developed an efficient approach to quinoxalines by direct condensations of *o*-phenylenediamines with α-diketones catalyzed by NH_2SO_3H in dichloromethane at room temperature. The protocols featured with mild reaction conditions, easy work-up, and excellent yields.

EXPERIMENTAL

All reactants and solvents are commercially available and were used as received without purification. Melting points were determined using a microscope hot stage type apparatus without correction. ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$ on a Bruker DRX-500 instrument. Chemical shifts were expressed in ppm using TMS as internal standard for ^{1}H NMR. High-resolution electrospray mass spectra were obtained on a Mariner ESI-TOF spectrometer.

General Procedure for the Preparation of Quinoxalines 3. A mixture of *o*-phenylenediamine **1a** (0.54 g, 5.0 mmol), 1,2-diketone **2a** (1.41 g, 5.0 mmol), and sulfamic acid (24 mg, 5 mol %) in CH_2Cl_2 (25 mL) was stirred for appropriate time (Table 2) at ambient temperature. After completion of the reaction, the solid catalyst NH_2SO_3H was filtered off, the solution was subject to silica column directly and eluted with CH_2Cl_2–MeOH (95:5, v/v), the fractions of product was combined and solvents were evaporated *in vacuo* to afford the product **3aa**. All the products gave mp in good accordance with the reported data [15–17]. Each ^{1}H NMR spectrum of **3** agreed with the assigned structure. Representative compounds were given below.

2,3-Diphenylquinoxaline (3aa). White crystal (EtOH), 1.3 g (92 %), mp 124–125 (lit. [15] 123–125) °C; ^{1}H nmr ($CDCl_3$): δ 7.35 (m, 6H), 7.56 (m, 4H), 7.76 (m, 2H), 8.20 (m, 2H); HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{20}H_{14}N_2Na^+$ 305.1055, found 305.1058.

2,3-Di(furan-2-yl)-6-methylquinoxaline (3bd). Light brown crystal (EtOH), 1.2 g (87 %), 119–120 (lit. [16] 118–119) °C; ^{1}H nmr ($CDCl_3$): δ 2.56 (s, 3H), 6.47 (m, 2H), 6.62 (d, 2H, J = 3.6 Hz), 7.56 (dd, 1H, J = 8.6, 1.3 Hz), 7.93 (s, 1H), 8.06 (d, 1H, J = 8.6 Hz,); HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{17}H_{13}N_2O_2^+$ 277.0977, found 277.0972.

6-Chloro-2,3-dimethylquinoxaline (3ce). Light orange crystal (EtOH), 0.86 g (89%), 85–86 (lit. [18] 83–84) °C; ^{1}H nmr ($CDCl_3$): δ 2.77 (s, 6H), 7.64 (dd, 1H, J = 9.0, 2.2 Hz), 8.01 (d, 1H, J = 9.0 Hz), 8.09 (d, 1H, J = 2.2 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{10}H_{10}ClN_2^+$ 193.0533, found 193.0529.

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