EFFICIENT ROUTE TO QUINOXALINES CATALYZED BY SULFAMIC ACID IN TAP WATER SUSPENSION

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Abstract: Quinoxalines were synthesized *via* direct condensations of *o*-phenylenediamines with α-diketones promoted by sulfamic acid at room temperature in tap water suspension in high yields and by simple work-up.

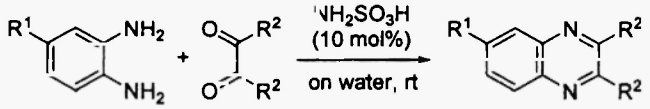
Introduction

Quinoxaline derivatives exhibit wide range of functions in biological active compounds, electroluminescent materials, dyes, and anion sensors (1). Special attention has been paid to their extraordinary potentials in pharmacological research and practice. A few synthetic routes to quinoxaline have been developed and the well known common preparation method is the direct condensation of *o*-phenylenediamines with α-diketones in refluxing ethanol or boiling acetic acid (2). Most recently, several preparative methods *via* direct condensations to quinoxalines have been reported which using $Yb(OTf)_3$, acetic acid (under microwave radiation), or molecular iodine as catalysts (3). In contrast to the various uses of quinoxalines in many fields, their preparation methods are limited in number, and some of them suffered in one or more drawbacks such as drastic reaction conditions, special apparatus, unusual reagents, and hazardous solvents.

Green principles and practice in process chemistry are widespread in the last couple of years and gained ever increasing importance (4). The development of green, sustainable organic synthesis in alternative media, especially in water (5), is a promising solution with prominent advantages (6). In water suspension (7), or "on water" (8), unique reactivity has been observed with intriguing phenomena.

In continuation of our preliminary investigation on the condensations afford α-amidosulfones by using sulfamic acid (SA) in water media (9), we envisioned broader applications of this SA plus water strategy in some condensations formerly carried out in strict moisture-free conditions or by dehydrating measures. SA as a powerful solid catalyst has been used in many organic preparations (10). It has unique structure (11) and prominent properties, such as, it has outstanding physical stability, is insoluble in common organic solvent, is inexpensive, and readily available (12). As part of our on going interest in the using of economy reagents in aqueous media for organic transformations, we had the opportunity to look into the

synthesis of quinoxalines by using sulfamic acid as catalyst in tap water suspension (Scheme-1).



1 2 3

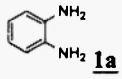
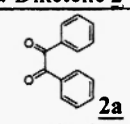
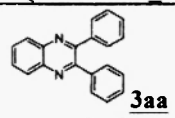
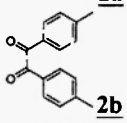
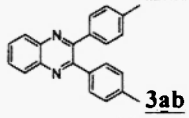
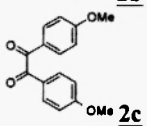
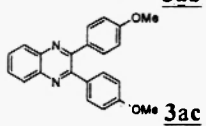
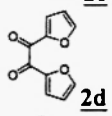
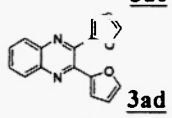
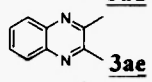
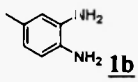
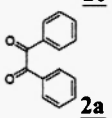
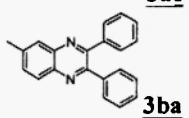
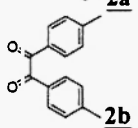
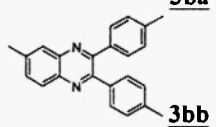
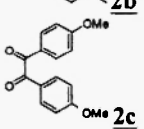
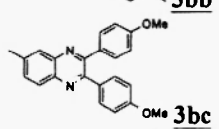
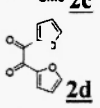
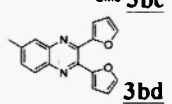
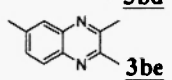
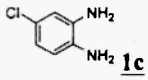
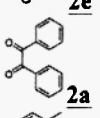
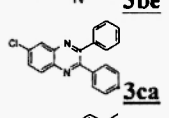
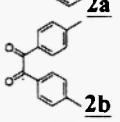
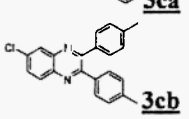
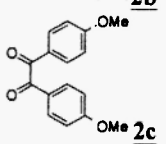
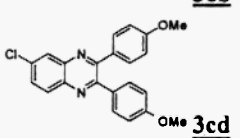
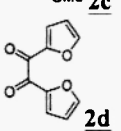
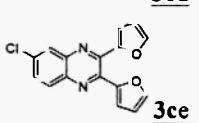
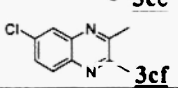
Scheme-1 Direct condensations of *o*-phenylenediamines with α-diketones mediated by sulfamic acid in water suspension.

Results and Discussion

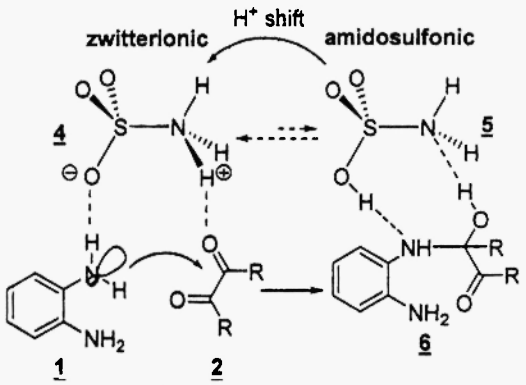
In the beginning, SA was tested for the catalytic activity in the condensation of *o*-phenylenediamine with benzil in ethanol at room temperature as a model reaction and showed good performance. On the contrary, without catalyst, the similar condensations in alcohols and other protic or polar solvents are not observed at rt (2). We decided to try the reactions in tap water suspension instead of the traditional methods in organic solvents (Scheme 1 and Table 1).

Initially, condensation of *o*-phenylenediamine (**1a**) (2 mmol) with benzil (**2a**) (2 mmol) mediated by SA (10 mol %) in water (5 mL) at room temperature was conducted as a model reaction (entry 1, Table 1) and excellent result was obtained. Next, the procedure was extended to substituted aromatic (entries 2 and 3), heterocyclic (entry 4), and aliphatic (entry 5) α-diketones with good to 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 1, substitutions (R^1 = Me, Cl) on the phenyl group of *o*-phenylenediamine exerted slight 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 comparable yields were obtained in longer reaction time (see entries 6–8 as examples). The reactions proceeded smoothly and cleanly at ambient temperature. After completion of the condensation, product (**3**) was separated by simple filtration. The key step of this type of condensation proceeded most probably *via* a nucleophilic attack of amine *N* of (**1**) toward carbonyl of (**2**), the carbonyl is activated by Lewis acid or acetic acid in boiling solution or in acetic acid under microwave irradiation (2,3). A plausible mechanism mediated by SA was suggested in Scheme 2, in the first step, sulfamic acid in its predominant zwitterionic form (11) (**4**) coordinated with both (**1**) and (**2**), which facilitated the addition reaction to afford (**6**), the coordinated or liberated (**6**) may proceeded to quinoxaline (**3**) by subsequent intramolecular addition and eliminations, probably mediated by SA, too.

Table-1 : Synthesis of quinoxalines using *o*-phenylenediamines and symmetrical α-diketones

Entry	*o*-Phenylenediamine **1**	α-Diketone **2**	Quinoxaline **3**[a]	Time / h	Yield[b] / %
1	 **1a**	 **2a**	 **3aa**	1	92
2		 **2b**	 **3ab**	1	85
3		 **2c**	 **3ac**	1	82
4		 **2d**	 **3ad**	1	89
5		 **2e**	 **3ae**	1	88
6	 **1b**	 **2a**	 **3ba**	1	91
7		 **2b**	 **3bb**	2	89
8		 **2c**	 **3bc**	3	84
9		 **2d**	 **3bd**	1.5	87
10		 **2e**	 **3be**	1	86
11	 **1c**	 **2a**	 **3ca**	1.5	92
12		 **2b**	 **3cb**	2.5	81
13		 **2c**	 **3cd**	3	75
14		 **2d**	 **3ce**	1.5	90
15		 **2e**	 **3cf**	1	80

[a] All quinoxalines gave satisfactory spectroscopic data agreed with those of the literature (2,3).
[b] Isolated yield



Scheme-2 : Plausible mechanism of the catalysis by sulfamic acid in its zwitterionic and amidosulfonic forms

Conclusion

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

General Experimental Procedure: *o*-phenylenediamine (**1**) (2 mmol), *α*-diketone (**2**) (2 mmol), and sulfamic acid (10 mol%) were well mixed and suspended in tap water (5 mL), the suspension was stirred for the appropriate time (Table 1) at ambient temperature in open vessel. After completion of the reaction (indicated by TLC), the crude product was filtered off, washed with water (3 × 2 mL), and air dried to afford the product (**3**), which can be recrystalled from EtOH to afford pure (**3**) for characterization. All the products gave mps in good accordance with the reported data (2,3). ^{1}H NMR spetrum of each (**3**) agreed with the assigned structure. *Representative compounds*. (**3aa**): White crystal (EtOH), mp. 124–125 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, TMS): δ 8.20 (m, 2 H), 7.76 (m, 2 H), 7.56 (m, 4 H), 7.35 (m, 6 H); HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{14}N_2Na^+$ 305.1055, found 305.1058. (**3bd**): Pale brown crystal (EtOH), mp. 119–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.06 (d, J = 8.6 Hz, 1 H), 7.93 (s, 1 H), 7.56 (dd, J = 8.6, 1.3 Hz, 1 H), 6.62 (d, J = 3.6 Hz, 2 H), 6.47 (m, 2 H), 2.56 (s, 3 H); HRMS (ESI): *m/z* $[M + H]^+$ calcd $C_{17}H_{13}N_2O_2^+$ 277.0977, found 277.0972. (**3ce**): Pale orange crystal (EtOH), mp. 85–86 °C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.09 (d, J = 2.2 Hz, 1 H), 8.01 (d, J = 9.0 Hz, 1 H), 7.64 (dd, J = 9.0, 2.2 Hz, 1 H), 2.77 (s, 6 H); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{10}ClN_2^+$ 193.0533, found 193.0529.

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12. Sulfamic acid is 31.5 $/kg, see at: *http://www.sigmaaldrich.com/catalog/search/*.

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