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EXPEDITIOUS ENTRY TO 1,5-BENZODIAZEPINES CATALYZED BY SULFAMIC ACID AT ROOM TEMPERATURE IN TAP WATER SUSPENSION

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Abstract – 2,3-Dihydro-1*H*-1,5-benzodiazepines have been synthesized in tap water suspension as well as in neat condition in good to excellent yield from direct condensations of *o*-phenylenediamines with ketones promoted by sulfamic acid at room temperature.

INTRODUCTION

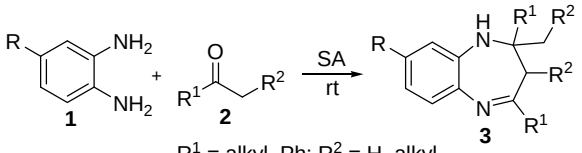
Benzodiazepines have received much attention due to their pharmacological properties.[1] Several types of 1,5-benzodiazepines have been investigated for their potential activities against cancer, HIV, and central nerve system disorders.[2] The widely application of 1,5-benzodiazepines in clinical practice in anti-anxiety, anticonculsant, and anti-depressive is well known. Although a few synthetic routes to 1,5-benzodiazepines have been established,[3] there still existed rooms for further development of the methodology in pursuing more efficient, mild, green, and simple preparations.

Direct condensations of *o*-phenylenediamines and ketones catalyzed by acid are straightforward and facile approach among the devised methods. Recently, some Lewis acids were employed in the direct transformations, several of them,[4] such as $Yb(OTf)_3$, polyacid $Ag_3PW_{12}O_{40}$, molecular iodine, and $Ce(NH_4)_2(NO_3)_6$, have shown good catalytic performances. However, some of these methods suffered in one or more drawbacks such as drastic reaction conditions, using of special apparatus, unusual self-prepared catalyst, moisture sensitivity, expensive reagents, and last but the most impressive issues in the employing of hazardous organic solvents. Thus, mild, efficient and simple method using economy, safely disposable catalyst in alternative solvents or in neat condition would worthy to explore.

In continuation of our interest in the three-component condensations afford α-amidosulfones by using sulfamic acid (SA) in water media,[5] we envisioned a broader applications of this SA plus water strategy in some condensations formerly carried out in moisture-free conditions or by dehydrating measures. SA as a powerful solid catalyst has been used in many organic preparations.[6] It has unique structure[7] and

prominent properties, such as, it has outstanding physical stability, is insoluble in common organic solvent, is inexpensive, and readily available.[8]

Using aqueous media for green, sustainable organic process is of significant importance.[9] To carry out organic synthesis in neat conditions[10] is another useful alternative to conventional organic solvents in organic synthesis. In water suspension, unique reactivity has been observed with intriguing phenomena.[11]



Methods. **I**: neat mixture of **1** and **2**; **II**: **1** and **2**, suspension on water

Scheme 1 Condensations of *o*-phenylenediamines with ketones catalyzed by sulfamic acid (SA) in neat and on water at room temperature

RESULTS AND DISCUSSION

Table 1 Condensations of *o*-phenylenediamine with ketones catalyzed by sulfamic acid (SA) in neat condition at room temperature

Entry	**1**	**2**		**3**[a]	SA[b]	**1 : 2**[c]	Time / h	Yield[d] (%)
	R	R^1	R^2					
1	H	Me	H	**3a**	10	1 : 4	3	83
2						1 : 3		75
3						1 : 2.2		72
4					5			66
5					20			71
6	H	Me	Me	**3b**	10			64
7	H	Et	Me	**3c**				59
8	H	Me	*i*-Pr	**3d**			4.5	51
9	H	$(CH_2)_3$		**3e**			6	48
10		$(CH_2)_4$		**3f**				45
11	H	Ph	H	**3g**			4.5	29

[a] All benzodiazepines gave satisfactory mps and spectroscopic data agreed with those of the literature.[4] [b] In mol %, based on **1**. [c] Molar ratio. [d] Isolated yield.

Our purpose was to explore the condensations (Scheme 1) in neat condition or in water suspension at ambient temperature. Initially, direct condensations of *o*-phenylenediamine with ketones mediated by catalytic amount of SA (10 mol %) were carried out in neat condition (Scheme 1, Method **I**). As we have focused on the solvent-free protocol, near stoichiometric amount of acetone (1.1 equiv) (Table 1, entry 3) was used and (**3a**) was obtained in good yield. The loading of catalyst was adjusted by half (entry 4) and

by double (entry 5) of the initial amount (10 mol %) and 10 mol% of SA was shown enough for the condensation. Encouraged by these promising results, we expanded the preparation to array of aliphatic ketones and benzophenone. Although the low boiling point ketones (entries 6 to 10) gave acceptable yields, benzophenone (entry 11) was poor in yield. In retrospective runs (entries 1 and 2), excessive acetone (50 and 100 equiv % excess, respectively) facilitated the condensations. We attributed these increases to the effect of acetone as solvent. The low yield of benzophenone (mp 19–20 °C) was mainly incurred by the partial solidification of the mixture in reaction progress, which hampered further mass transfer. Thus the performance of the namely solvent-free protocol (entries 3–11) by using marginally 10 equiv % excess of ketones reached the ceiling.

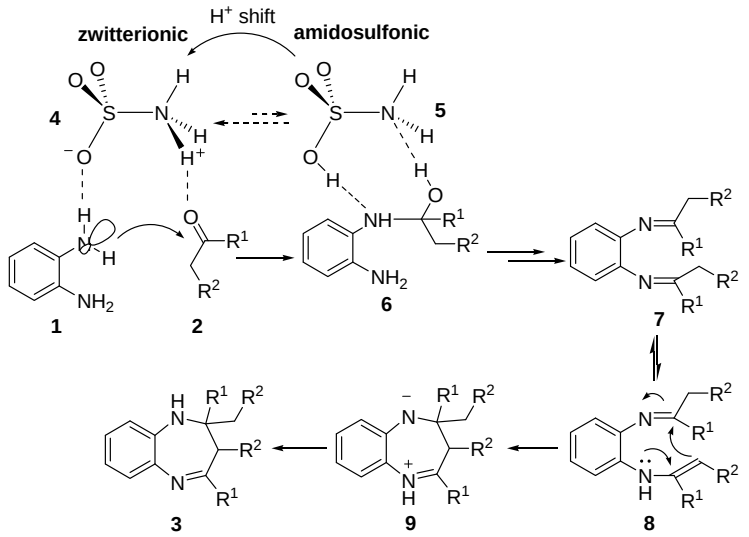
Table 2 Condensations of *o*-phenylenediamines with ketones catalyzed by sulfamic acid in water suspension at room temperature

Entry	**1**	**2**		**3**[a]	Time / h	Yield[b] (%)
	R	R^1	R^2			
1	H	Me	H	**3a**	3	92
2	H	Me	Me	**3b**		89
3	H	Et	Me	**3c**		86
4	H	Me	*i*-Pr	**3d**	6	80
5	H	$(CH_2)_3$		**3e**		77
6		$(CH_2)_4$		**3f**		83
7	H	Ph	H	**3g**		92
8	Me	Me	H	**3h**		91[c]
9	Me	Me	Me	**3i**		85[c]
10	Me	Ph	H	**3j**		83[c]
11	Cl	Me	H	**3k**[d]		88[c]

[a] All benzodiazepines gave satisfactory mps and spectroscopic data agreed with those of the literature.[4] [b] Isolated yield. [c] Single isomer confirmed by HPLC. [d] 7-Chloro isomer was obtained as major product.[12]

In light of the recent resurgence of interest in organic synthesis in water,[9, 11] we decided to try the preparations in water suspension (Scheme 1, Method **II)**. Much better than we had expected, the typical condensations (Table 2, entries 1 and 7) proceeded remarkably efficient. Then we enlarged this protocol to other five ketones (entries 2 to 6) and substituted *o*-phenylenediamines (entries 8 to 11), excellent yields were obtained. In comparison between the two methods, condensations in water suspension excelled in mild reaction conditions, simple work-up, and excellent yields. Preparation in neat condition (10 mol % SA, 1.1 equiv of ketone) had merits on its own as a solvent-free and facile green protocol, although it was overshadowed by the subsequent modified “on water” method in every aspects. At the early stage trails in neat mixture condensations (Table 1, entries 8 and 11), when the reaction mixtures

were treated by water and stand for some time, the amount of **3** as precipitate increased obviously, and well-shaped crystals formed. Clued by these findings, reactions in water suspension, or "on water", turned out to be a reasonable expansion.



Scheme 2 Plausible mechanism of the catalysis of $NH_3^+SO_3^-$ and the formation of 1,5-benzodiazepines

The key step in this condensation was most probable an imine formation between amino group of **1** and carbonyl of **2** (see Scheme 2). Due to the zwitterionic nature of the catalyst sulfamic acid,[7] it may work as *bi*-functional catalyst by the simultaneous coordination of the negatively charged oxygen atom on the sulfonic moiety with amine hydrogen on **1** and the coordination of the positively charged hydrogen atom on the amido- moiety with ketone oxygen 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**. Two molecules of H_2O were eliminated to afford **7**, which was rearranged into enamine (**8**). Irreversible ring-closure was the driving force in the next step to **9**, which was transformed into the final product 1,5-benzodiazepines (**3**) by proton shift. In case of unsymmetrical *o*-phenylenediamines,[12] electron-donating-group such as methyl (**3h**, **3i**, and **3j**) made the enamine moiety *para*- to it more stable and more electrophilic, thus 8-substituted **3** was obtained. On the contrary, electron-withdrawing-group such as Cl (**3k**) gave 7-substituted **3** as major product. Attention should be paid to the fact that in water suspension, 1,5-benzodiazepines precipitated as soon as it was formed and added another favorable factor to facilitate the reaction to the right side. Thus water exerted positive influence on the dehydration or condensation reactions.[13]

In conclusion, we have developed a highly efficient approach to 1,5-benzodiazepines by direct condensations between *o*-phenylenediamines and ketones catalyzed by sulfamic acid in water suspension as well as in neat condition 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. IR spectra were recorded for KBr pellets on a Thermo Nicolet Nexus 870 spectrometer. ^{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 procedures for the synthesis of 1,5-benzodiazepines: Method **I —** A mixture of *o*-phenylenediamine (1.08 g, 10 mmol), sulfamic acid (0.1 g, 10 mol%) and ketones (22 mmol) was stirred at rt for the appropriate time (Table 1) as indicated by TLC (EtOAc–*n*-Hexane, 1:2), the reaction mixture was treated with water (30 mL), extracted with EtOAc (2 × 40 mL). The combined organic phase was dried ($MgSO_4$), evaporated in vacuo, and purified by silica gel column (EtOAc–*n*-Hexane, 1:3) to afford **3** (Table 1). Method **II —** *o*-Phenylenediamine (5 mmol), sulfamic acid (0.05 g, 10 mol%) and ketone (11 mmol) was well mixed and water (15 mL) was added, the reaction mixture was stirred at rt for the specified time (Table 2) as indicated by TLC (EtOAc–*n*-Hexane, 1:2), the precipitated crystals was filtrated, washed with water (2 × 10 mL), and air dried to afford **3**. Recrystallization of **3** in EtOH gave pure samples for characterization. All the products are reported before.[4] Representative products are given below.

2,2,4-Trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (**3a**). mp 136–138 °C. IR (KBr): ν = 3343, 1650, 1597 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 1.34 (s, 6 H), 2.26 (s, 2 H), 2.34 (s, 3 H), 3.46 (br s, 1 H, NH), 6.61–7.28 (m, 4 H). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{17}N_2^+$: 189.1392; found 189.1390.

2-Methyl-2,4-diphenyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (**3g**). mp 150–152 °C. IR (KBr): ν = 3328, 1644, 1598 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 1.79 (s, 3 H), 2.98 (d, J = 12.5 Hz, 1 H), 3.16 (d, J = 12.5 Hz, 1 H), 3.43 (br s, 1 H, NH), 6.56–7.02 (m, 3 H), 7.14–7.35 (m, 7 H), 7.58–7.62 (m, 4 H). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}N_2^+$: 313.1705; found 313.1768.

7-Chloro-2,2,4-trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (**3k**).[12] mp 90–92 °C. IR (KBr): ν = 3288, 1647, 1590 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 1.32 (s, 6 H), 2.27 (s, 2 H), 2.33 (s, 3 H), 4.07 (br s, 1 H, NH), 6.57–6.60 (m, 1 H), 6.85–6.91 (m, 1 H), 7.00–7.07 (m, 1 H). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{16}ClN_2^+$ 223.1002; found 223.1005.

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