Organic LETTERS

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Convenient Synthesis of Benzothiazoles and Benzimidazoles through Brønsted Acid Catalyzed Cyclization of 2-Amino Thiophenols/Anilines with β-Diketones

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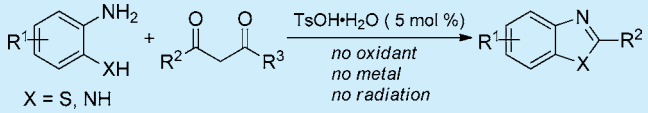
Supporting Information

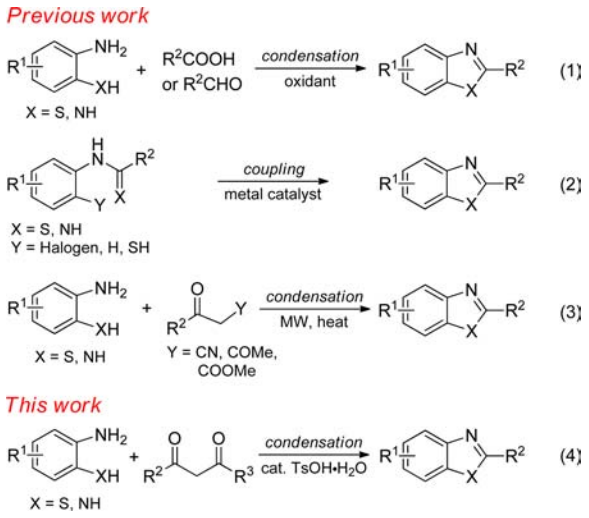
ABSTRACT: Brønsted acid catalyzed cyclization reactions of 2-amino thiophenols/anilines with β-diketones under oxidant-, metal-, and radiation-free conditions are described. Various 2-substituted benzothiazoles/benzimidazoles are obtained in satisfactory to excellent yields. Different groups such as methyl, chloro, nitro, and methoxy linked on benzene rings were tolerated under the optimized reaction conditions.



Synthesis of privileged benzothiazoles and benzimidazoles through an economical and environment friendly method is always desirable because benzothiazole moieties are of paramount interest in medicinal chemistry due to their antitumor, anticancer, and antimicrobial activities.[1] The benzimidazole structural motif is also a building block of pharmaceutics and functional materials.[2]

Over the past few decades, three main methods have been developed for the synthesis of benzothiazoles and benzimidazoles. One method involves the condensation reactions of 2-amino thiophenols/anilines with carboxylic acids[3] or aldehydes[4] under oxidative conditions (Scheme 1, eq 1). Another method involves the transition-metal-catalyzed intramolecular cyclization of 2-haloanilides/analogues (Scheme 1, eq 2).[5] The last method involves the condensation reactions of 2-amino thiophenols/anilines with β-ketonitriles,[6] β-ketoesters,[7] or β-diketones[8] under microwave radiation and high temperature conditions (Scheme 1, eq 3).

Scheme 1. Pathways for the Synthesis of Benzothiazoles and Benzimidazoles



Recently, metal-free methods for the synthesis of benzothiazoles and benzimidazoles through the cyclization reaction of 2-amino thiophenols/anilines with alkyl amines[9] or aryl ketones[10] at high temperature under oxidative conditions were also reported. However these methods have one or more shortcomings such as microwave radiation, metal catalysts, additives, and/or high temperature conditions which adversely affect the economics as well as the ecofriendly nature of the reaction.

In the course of our research on the development of efficient methods for heterocycle synthesis,[11] we found that benzothiazoles and benzimidazoles can readily be obtained from the Brønsted acid catalyzed cyclization reactions of 2-amino thiophenols/anilines with β-diketones (Scheme 1, eq 4). The results are reported in this paper.

In our initial studies, the reaction of 2-amino thiophenol (**1a**) with 2,4-pentanedione (**2a**) was chosen as a model to optimize the reaction conditions. The results are shown in Table 1. No reaction was observed when **1a** and **2a** were treated in acetonitrile (CH_3CN) at room temperature in the absence of an acid catalyst (entry 1). However, the desired product 2-methyl benzothiazole (**3a**) was obtained in more than 99% yield merely by using *p*-toluene sulfonic acid ($TsOH·H_2O$) as a catalyst (entry 2).

Then we tried different acids such as benzoic acid (PhCOOH), trifluoroacetic acid (CF_3COOH), and acetic acid (CH_3COOH). The results show that CF_3COOH and $TsOH·H_2O$ are equally effective for this reaction (entries 2−5). However $TsOH·H_2O$ was chosen as a catalyst for solvent

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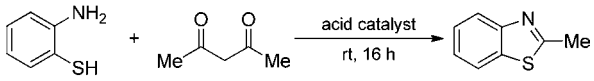
Table 1. Reaction Condition Screening[a]



1a 2a 3a

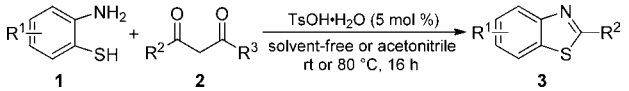
entry	acid catalyst/mol %	solvent	yield (%)[b]
1	none	CH_3CN	NR[c]
2	$TsOH{\cdot}H_2O$/10	CH_3CN	>99
3	PhCOOH/10	CH_3CN	67
4	CF_3COOH/10	CH_3CN	>99
5	CH_3COOH/10	CH_3CN	65
6	$TsOH{\cdot}H_2O$/10	THF	93
7	$TsOH{\cdot}H_2O$/10	DCE	>99
8	$TsOH{\cdot}H_2O$/10	EtOH	91
9	$TsOH{\cdot}H_2O$/10	none	>99[d]
10	$TsOH{\cdot}H_2O$/5	none	>99[d]
11	$TsOH{\cdot}H_2O$/2	none	88[d]
12	$TsOH{\cdot}H_2O$/1	none	71[d]

[a]Reaction conditions: 2-amino thiophenol (**1a**, 0.5 mmol), 2,4-pentanedione (**2a**, 0.75 mmol), acid catalyst, and solvent (4 mL) at room temperature for 16 h. [b]GC yield; 5-methoxy indole was used as an internal standard. [c]No reaction. [d]1.0 mmol of **1a** and 1.5 mmol of **2a** were used.

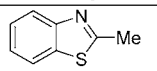
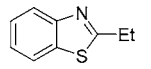
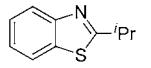
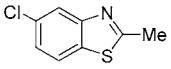
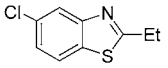
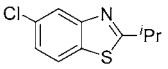
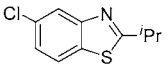
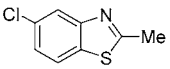
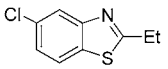
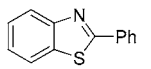
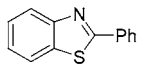
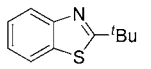
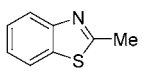
screening due to its low cost and ease in handling. The product **3a** was obtained in almost the same excellent yield when the solvents CH_3CN, tetrahydrofuran (THF), 1,2-dichloroethane (DCE), and ethanol (EtOH) were examined (entries 2 and 6–8). These results indicate that the solvent has negligible influence on the reaction. Therefore, the reaction of **1a** with **2a** under solvent-free conditions was performed. As expected, the product **3a** was obtained in the same yield, as was obtained by using the solvent (entry 9). The product **3a** was also obtained in more than 99% yield when the acid catalyst loading was decreased from 10 to 5 mol % (entry 10). However, a further decrease in acid catalyst loading resulted in relatively low yields of **3a** (entries 11 and 12). Therefore, we decided to perform the subsequent reactions of the 2-amino thiophenols with various β-diketones in the presence of $TsOH{\cdot}H_2O$ as a catalyst at room temperature under solvent-free conditions for 16 h.

Table 2 shows the results of Brønsted acid ($TsOH{\cdot}H_2O$) catalyzed cyclization reactions of 2-amino thiophenols with various β-diketones. An excellent yield similar to that of **3a** was observed when the reaction of **2a** with 3,5-heptanedione (**2b**) was carried out under optimized reaction conditions (entry 1 vs 2; **3a**, 92%; **3b**, 90%). The reaction of **1a** with a sterically hindered β-diketone 2,6-dimethylheptane-3,5-dione (**2c**) provided the desired product **3c** in moderate yield (entry 3, 65%). Reactions of 4-chloro-2-amino thiophenol (**1b**), a solid substrate, with **2a** or **2b** also proceeded smoothly under the solvent-free conditions to provide the desired products **3d** and **3e** in satisfactory yields (entries 4 and 5; 75% and 71%, respectively). No reaction was observed when a mixture of the solid **1b** and the sterically hindered **2c** was treated under the solvent-free conditions (entry 6). Delightfully, the benzothiazole product **3f** was finally obtained in 63% yield when the reaction of **1b** with **2c** was performed in CH_3CN at 80 °C (entry 7). As expected, the yields of **3d** and **3e** were improved by using CH_3CN as a solvent at 80 °C (entries 8 and 9; 86% and 89%, respectively). The 2-aryl-substituted product, 2-phenyl benzothiazole (**3g**), could also be obtained from the reaction of **1a** with 1,3-diphenylpropane-1,3-dione (**2d**) in

Table 2. Synthesis of Benzothiazoles[a]



1 2 3

entry	substrate 1	substrate 2	product 3		yield (%)[b]
1	**1a** R^1 = H	**2a** $R^2 = R^3$ = Me		**3a**	92
2	**1a**	**2b** $R^2 = R^3$ = Et		**3b**	90
3	**1a**	**2c** $R^2 = R^3$ = ^{i}Pr		**3c**	65
4	**1b** R^1 = 4-Cl	**2a**		**3d**	75
5	**1b**	**2b**		**3e**	71
6	**1b**	**2c**		**3f**	NR[c]
7	**1b**	**2c**		**3f**	63[d]
8	**1b**	**2a**		**3d**	86[d]
9	**1b**	**2b**		**3e**	89[d]
10	**1a**	**2d** $R^2 = R^3$ = Ph		**3g**	51[d]
11	**1a**	**2d**		**3g**	85[e]
12	**1a**	**2e** $R^2 = R^3$ = ^{t}Bu		**3h**	NR[c]
13	**1a**	**2f** R^2 = Me, R^3 = Ph		**3a**	75[d]

[a]Reaction conditions: 2-amino thiophenol (**1**, 1.0 mmol), β-diketone (**2**, 1.5 mmol), and $TsOH{\cdot}H_2O$ (5 mol %, 9.51 mg) at room temperature under solvent-free conditions for 16 h. [b]Isolated yield. [c]No reaction. [d]The reaction of 0.5 mmol of 2-amino thiophenol with 0.75 mmol of β-diketone was carried out in acetonitrile (4 mL) at 80 °C for 16 h. [e]Toluene was used as the solvent instead of acetonitrile; the reaction was carried out in a sealed reactor at 130 °C.

CH_3CN at 80 °C though the yield was relatively low (entry 10, 51%). The yield of **3g** was increased to 85% when the reaction was performed at high temperature (entry 11, 130 °C). No reaction was observed when a mixture of **1a** and a more sterically hindered β-diketone, 1,3-di(*tert*-butyl)propane-1,3-dione (**2e**), was treated even at high temperature (entry 12). Finally, the reaction of **1a** with an unsymmetric β-diketone, 1-methyl-3-phenyl-1,3-dione (**2f**), was examined, and product **3a** was obtained in 75% yield (entry 13). This result indicates that the reactivity of the acetyl group is higher than that of the benzoyl group.

Then, we examined the reactions of 2-amino anilines with various β-diketones in the presence of $TsOH{\cdot}H_2O$ as a catalyst at room temperature with or without solvent. No reaction was observed under those conditions as mentioned above. However, we found that the desired reaction could occur in the presence of $TsOH{\cdot}H_2O$ as a catalyst in CH_3CN at 80 °C to furnish benzimidazoles in satisfactory to excellent yields. The results are shown in Table 3. Benzimidazole products **5a–5c**

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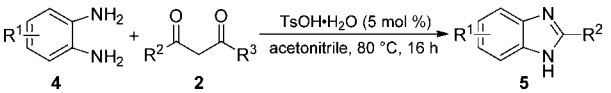
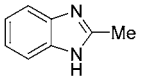
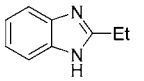
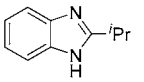
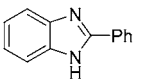
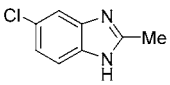
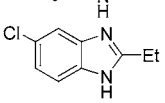
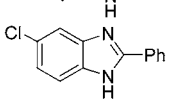
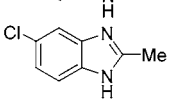
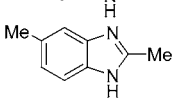
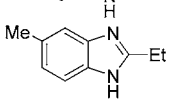
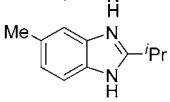
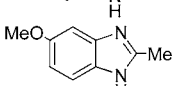
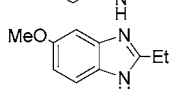
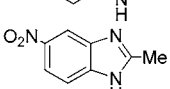
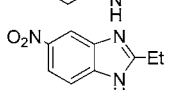
Table 3. Synthesis of Benzimidazoles[a]



4 2 5

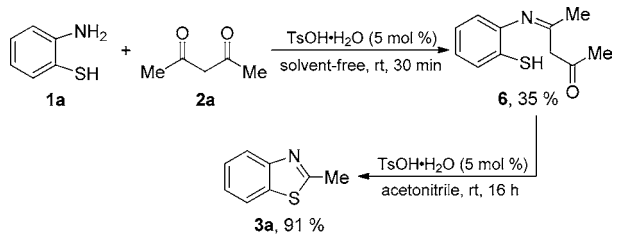
entry	substrate 4	substrate 2	product 5		yield (%)[b]
1	**4a** R^1 = H	**2a** R^2 = R^3 = Me		**5a**	88
2	**4a**	**2b** R^2 = R^3 = Et		**5b**	95
3	**4a**	**2c** R^2 = R^3 = ^{i}Pr		**5c**	55
4	**4a**	**2d** R^2 = R^3 = Ph		**5d**	49
5	**4b** R^1 = 4-Cl	**2a**		**5e**	91
6	**4b**	**2b**		**5f**	95
7	**4b**	**2d**		**5g**	54
8	**4b**	**2f** R^2 = Me R^3 = Ph		**5e**	72[c]
9	**4c** R^1 = 4-Me	**2a**		**5h**	84
10	**4c**	**2b**		**5i**	95
11	**4c**	**2c**		**5j**	60
12	**4d** R^1 = 4-OMe	**2a**		**5k**	65
13	**4d**	**2b**		**5l**	60
14	**4e** R^1 = 4-NO_2	**2a**		**5m**	75[d]
15	**4e**	**2b**		**5n**	84[d]

[a]Reaction conditions: 2-amino aniline (**4**, 0.5 mmol), β-diketone (**2**, 0.75 mmol), and TsOH·H_2O (5 mol %, 4.755 mg) in CH_3CN (4 mL) at 80 °C for 16 h. [b]Isolated yield. [c]Benzimidazole **5g** was also isolated as a minor product in 23% yield. [d]The reaction was carried out in the presence of 10 mol % TsOH·H_2O for 24 h.

were isolated in 55%−95% yields from the reactions of 2-amino aniline (**4a**) with β-diketones **2a**, **2b**, and **2c** bearing aliphatic groups (Me, Et, and ^{i}Pr) on their 1,3-positions, respectively (entries 1−3). The product 2-phenyl benzimidazole (**5d**) was also obtained in relatively low yield (49%) due to the low reactivity of β-diketone **2d** bearing aromatic groups on its 1,3-position (entry 4). The reactions of 2-amino-4-chloro aniline (**4b**), 2-amino-4-methyl aniline (**4c**), 2-amino-4-methoxy aniline (**4d**), and 2-amino-4-nitro aniline (**4e**) with β-diketones **2a** and **2b**, respectively, proceeded smoothly to give benzimidazole products **5e**, **5f**, and **5h**−**5n** in 60%−95% yields (entries 5, 6, and 9−15). These results indicate that substituent property (electron-donating or -withdrawing) has almost no influence on the reactivity of 2-amino aniline substrates. The low reactivity of **2d** was demonstrated again in its reaction with **4b**. 2-Phenyl-substituted benzimidazole **5g** was isolated in 54% yield (entry 7). Benzimidazole **5e** was obtained in 72% yield as a major product along with 23% of benzimidazole **5g** when the unsymmetric β-diketone **2f** was treated with **4b** (entry 8).

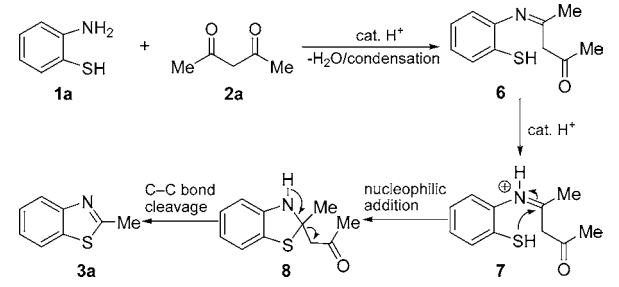
To explore the mechanism of this type of cyclization reaction, a mixture of **1a** and **2a** was treated under solvent-free conditions at room temperature for a short time (30 min). The result is shown in Scheme 2. As expected, an intermediate 4-[(2-mercaptophenyl)imino]pentan-2-one (**6**) was isolated in 35% yield along with the final product **3a** (61% yield). It was found that the intermediate **6** could easily be transformed to the final product **3a** in the presence of TsOH·H_2O as the catalyst in CH_3CN at room temperature.

Scheme 2. Controlled Experiment



A plausible mechanism for the Brønsted acid catalyzed cyclization reactions of 2-amino thiophenols/anilines with β-diketones is shown in Scheme 3. The Brønsted acid catalyzed condensation reaction of **1a** with **2a** would take place to generate a ketimine intermediate **6**. Ketiminium intermediate **7** would generate in the presence of TsOH·H_2O. The intramolecular nucleophilic addition of **7** would produce adduct **8**. The C−C bond cleavage reaction would finally occur to generate product **3a**.

Scheme 3. A Proposed Mechanism



In summary, we have developed a convenient and efficient method for the synthesis of benzothiazoles and benzimidazoles. The mild reaction conditions (no oxidant, no metal catalyst, no radiation, and low temperature), experimental simplicity, simple and readily available starting materials, and broad substrate scope are the features of the novel and general method proposed in this paper. Further study focusing on the extension of the reaction scope using 2-hydroxy anilines is underway.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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