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Elemental sulfur mediated synthesis of benzoxazoles, benzothiazoles and quinoxalines via decarboxylative coupling of 2-hydroxy/mercapto/amino-anilines with cinnamic acids

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An easy and practical method has been developed for the synthesis of 2-benzylbenzoxazoles and 2-benzylbenzothiazoles using sulfur mediated decarboxylative coupling of cinnamic acids with 2-hydroxyanilines and 2-mercaptoanilines respectively under metal- and solvent-free conditions. However, the reaction of 2-aminoanilines with cinnanmic acids leads to the formation of 2-arylquinoxalines under the same set of reaction conditions. The transformation is versatile and compatible with a number of functional groups.

Introduction

Past few years have witnessed the emergence of transition metal- and photo-catalyzed decarboxylative cross-coupling reactions as a powerful tool to construct carbon-carbon and carbon-heteroatom bond, with enormous impact on organic synthesis, medicinal chemistry and material science.[1] Carboxylic acids and their derivatives are widely used coupling partners as they are non-toxic, inexpensive, stable and readily available in great structurally diversity.[2] The decarboxylative C-N coupling strategy involving the synthesis of complex molecules is a fascinating and challenging theme, yet only a few reports do exist involving this approach.[3]

Benzazoles are privileged heterocyclic scaffolds found in many natural products with various pharmaceutical applications. Particularly, 2-substituted benzazoles are widely present in drugs to combat various diseases.[4] Traditional methods for the synthesis of 2-substituted benzazoles involve the reaction of *o*-hydroxy/mercapto anilines with acylhalides[5], acids[6], aldehydes[7], β-diketones[8], alcohols[9], nitriles[10], amines[11], and methylarenes[12] under high temperature/strong oxidative conditions. Recently, 2-benzylbenzoxazoles have been synthesized by the reaction of benzoxazoles with benzyl halides[13] or benzyl carbonates,[14] whereas 2-aryl/aroyl-benzothiazoles have been prepared by the reaction of 2-aminothiophenols with acetophenones, styrenes, and phenylacetylenes.[15,16] Quinoxalines constitute another important heterocycle frequently present in biologically and pharmaceutically active compounds.[17] The commonly used methods for the synthesis of quinoxalines involve the direct cyclization reaction of *o*-phenylenediamines with 1,2-dicarbonyl derivatives,[18] α-hydroxy ketones,[19] α-haloketones,[20] vicinal diols,[21] diazoketones,[22] and phenylacetylene.[23] Recently the synthesis of quinoxalines has been achieved by the reaction of *o*-nitroanilines with phenethylamines,[24] and oxidative azidation/cyclization of *N*-arylenamines/*N*-aryl ketimines with azides under mild conditions,[25] albeit using transition metal catalysts. However, these methods are now and then cumbersome and require metal salts, harsh conditions, and longer reaction time. Therefore, development of an efficient and direct protocol for the synthesis of 2-benzylbenzazoles and quinoxalines by using simple and readily available starting materials under metal-free condition is highly exigent.

In light of the above and as a part of our recent interest in sulfur mediated reactions[26] and other protocols,[27] we disclose herein a new strategy involving elemental sulfur mediated decarboxylative coupling of 2-hydroxy/mercapto/amino-anilines with cinnamic acids/phenylpropiolic acid for the synthesis of 2-benzylbenzoxazoles, 2-benzylbenzothiazoles and 2-arylquinoxalines respectively under metal- and solvent-free conditions (Scheme 1). To the best of our knowledge, this is the first report in which aromatic amines undergo the Willgerodt-Kindler rearrangement.

Results and discussion

The study was envisioned to achieve the synthesis of 2-substituted benzoxazole by the reaction of cinnamic acid with 2-aminophenol.

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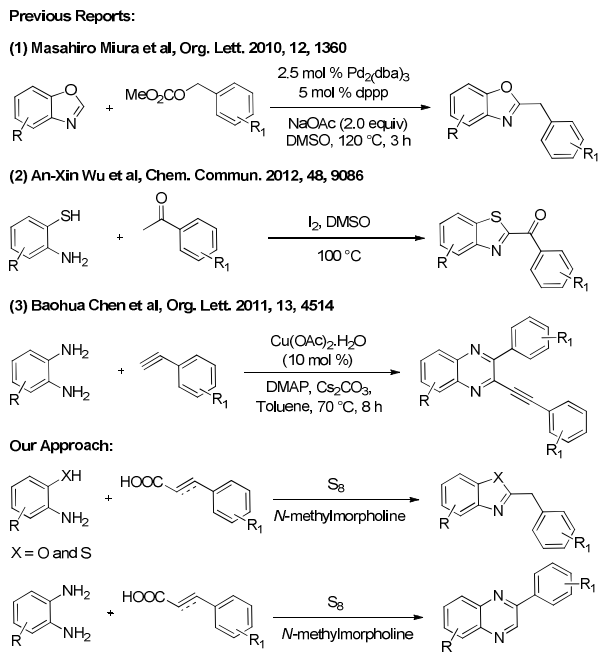
To start with, a model reaction involving 2-aminophenol (**1a**) and cinnamic acid (**3a**) was undertaken in the presence of elemental sulfur and *N*-methylmorpholine in DMSO at 120 °C for 15 h. To our utmost delight, the desired product 2-benzylbenzoxazole (**4a**) was formed in 35% (Table 1, entry 1).



Scheme 1: Previous reports and present strategy.

Table 1: Optimization of the reaction conditions[a]

1a 3a 4a

entry	base (x equiv)	solvent	temp (°C)	yield (%)[b]
1	*N*-methylmorpholine (2)	DMSO	120	35
2	*N*-methylmorpholine (2)	DMSO	130	51
3	*N*-methylmorpholine (2)	DMSO	140	48
4	*N*-methylmorpholine (2)	DMSO	130	50[c]
5	*N*-methylmorpholine (2)	DMSO	130	43[d]
6	DABCO (2)	DMSO	130	25
7	DMAP (2)	DMSO	130	27
8	Pyridine (2)	DMSO	130	15
9	-	DMSO	130	0
10	K_2CO_3 (2)	DMSO	130	0
11	Na_2CO_3 (2)	DMSO	130	0
12	K_3PO_4 (2)	DMSO	130	0
13	*t*-BuOK (2)	DMSO	130	0
14	$NaHCO_3$ (2)	DMSO	130	0
15	CH_3COONa (2)	DMSO	130	0
16	*N*-methylmorpholine (2)	-	130	67
17	*N*-methylmorpholine (3)	-	130	72
18	*N*-methylmorpholine (4)	-	130	71
19	*N*-methylmorpholine (4)	-	130	70[e]
20	*N*-methylmorpholine (3)	-	130	65[f]

[a]**Conditions**: 2-Aminophenol 1a (1 mmol), cinnamic acid 3a (1 mmol), elemental sulfur (3 mmol, 96 mg), 15 h. [b]Isolated yield. [c]20 h. [d]10 h. [e]sulfur (4 mmol). [f]sulfur (2 mmol).

Increasing the reaction temperature to 130 °C increased the product yield to 51% (entry 2). However, a further increase in the reaction temperature (140 °C) and time (20 h) did not improve the product yield again (entries 3 & 4), but a decrease in the reaction time (10 h) diminished the product yield to 43% (entry 5). To further advance the product yield, different organic bases such as DABCO, DMAP and pyridine were screened (entries 6-8), but none of them could match the efficacy of *N*-methylmorpholine. Notably, the formation of the product was not observed in the absence of the base (entry 9). Moreover, the use of inorganic bases like K_2CO_3, Na_2CO_3, K_3PO_4, *t*-BuOK, $NaHCO_3$ and CH_3COONa in the solvent DMSO remained futile (entries 10-15). Interestingly, when the reaction was conducted under solvent-free conditions, the yield of the product was improved to 67% (entry16). Increasing the molar ratio of the base (3 equiv.) brought about some improvement in the yield (entry17). Further increase in the molar equivalence of base and elemental sulfur did not make any positive change (entries 18 & 19), but decreasing the molar ratio of sulfur (2.0 equiv.) lowered down the product yield slightly (entry 20).

Having established the optimum reaction conditions (entry 17), the scope and limitations of the reaction were investigated in detail by using different cinnamic acids and 2-aminophenols. The outcome is summarized in Scheme 2. Cinnamic acids having substituent such as chloro, bromo, methyl, and methoxy at different positions were made to react with 2-aminophenol, 2-amino-4-methylphenol and 2-amino-4-chlorophenol under the established set of reaction conditions to afford the desired products **4a**-**j** in reasonably good yields. 3-(Thiophen-2-yl)acrylic acid also underwent the reaction smoothly to give the product **4e** in 59% yield. Nevertheless, 4-nitrocinnamic acid failed to provide the product **4k** under the stipulated conditions. After ascertaining the viability of sulfur mediated decarboxylative coupling of cinnamic acids with 2-aminophenols, we next turned our attention to the synthesis of 2-substituted benzothiazoles by using 2-aminothiophenols. As anticipated, when the reaction was conducted using cinnamic acid and 2-aminothiophenol under the same conditions, the product 2-benzylbenzothiazole (**5a**) was formed in 71% yield. The versatility of the reaction was further explored by using different cinnamic acids with 2-aminothiophenol and 2-amino-4-chlorobenzenethiol under the identical conditions to afford the desired products 2-benzylbenzothiazole **5** in high yields (*cf*. Scheme 2). The heteroaromatic 3-(thiophen-2-yl)acrylic acid also offered the product **5e** in 51% yield. It is worth noting that the disubstituted 3-(2,4-dichlorophenyl)acrylic acid also reacted nicely giving **5f** in 55% yield.

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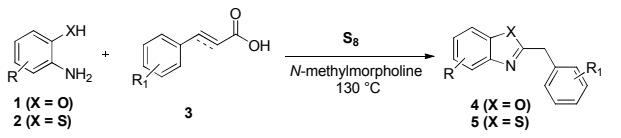
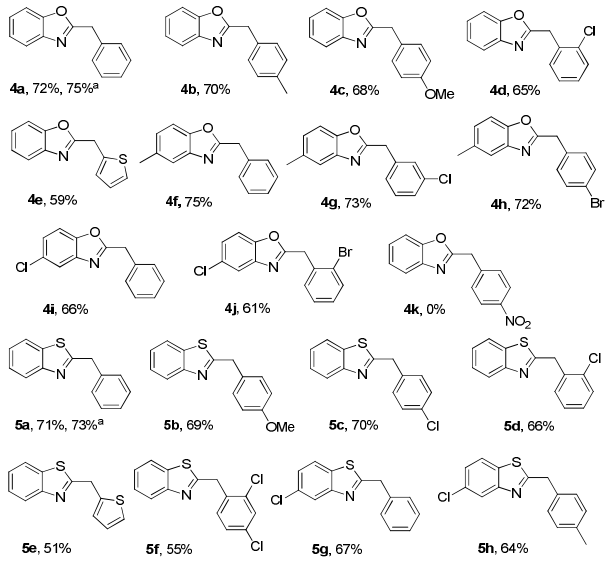
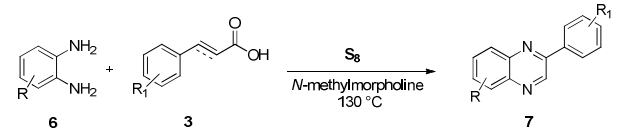
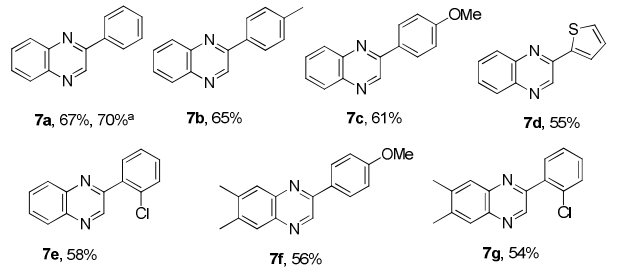




Scheme 2: The scope of the reaction between cinnamic acids and 2-hydroxy/mercapto anilines. Conditions: **1**/**2** (1 mmol), cinnamic acid **3** (1 mmol), *N*-methylmorpholine (3 mmol), sulfur (3 mmol, 96 mg) for 15 h. [a]With phenylpropiolic acid

Finally, the process was extended to the reaction of cinnamic acids and *o*-phenylenediamines with an aim to achieve the synthesis of 2-benzylbenzimidazoles. Surprisingly, the formation of 2-phenylquinoxalines **7a-g** instead of expected 2-benzylbenzimidazoles was observed in good yields by the reaction of different cinnamic acids with 2-aminoanilines under the established conditions (Scheme 3).

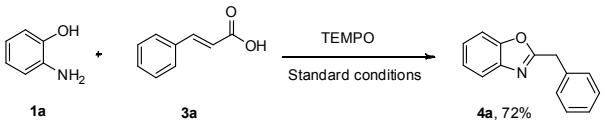




Scheme 3: The scope of the reaction between cinnamic acids and 1,2-phenylenediamines. Conditions: 2-Aminoaniline **6** (1 mmol), cinnamic acid **3** (1 mmol), *N*-methylmorpholine (3 mmol), sulfur (3 mmol, 96 mg) for 15 h. [a]With phenylpropiolic acid

After concluding the above results, the reaction was also carried out under the same set of reaction conditions by replacing cinnamic acid with phenylpropiolic acid. Notably, the representative reaction between 2-hydroxy/mercapto/amino-anilines and phenylpropiolic acid under the established conditions led to the formation of 2-benzylbenzoxazole (**4a**), 2-benzylbenzothiazole (**5a**) and 2-arylquinoxaline (**7a**) in 75%, 73% and 70% yields respectively.

In order to gain an insight into the mechanistic pathway, a typical reaction was undertaken in the presence of a radical scavenger TEMPO (Scheme 4). As a result, the reaction proceeded well without any effect, thereby excluding the possibility of involvement of any radical intermediate.



Scheme 4: Radical trapping experiment

Based on the radical trapping experiment and existing literature,[28] a plausible mechanism is outlined in figure 1.

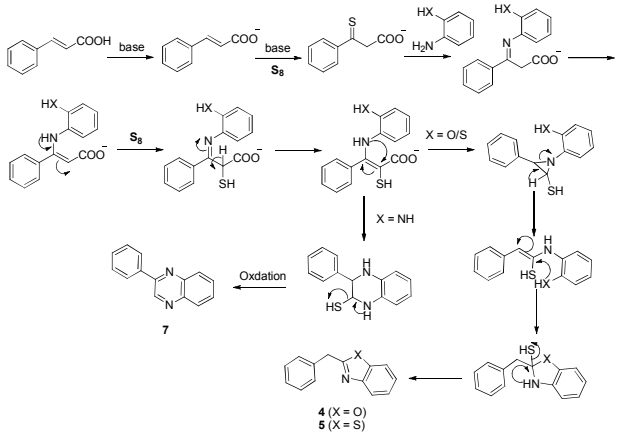


Figure 1: Plausible mechanism

Conclusion

In summary, a practical approach has been developed to accomplish 2-benzylbenzoxazoles, 2-benzylbenzothiazoles and 2-arylquinoxalines by the reaction of cinnamic acids and 2-hydroxy/mercapto/amino-anilines via decarboxylative C-N coupling followed by cyclization. Aromatic amines have been successfully employed for the first time in Willgerodt-Kindler type rearrangement. The methodology is operationally simple, uses readily available starting materials, and is free from the use of metals, solvents and external oxidants.

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