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Double C-S Bonds Formation *via* C-H Bonds Functionalization: Synthesis of Benzothiazoles and Naphtho[2,1-*d*]yhiazoles from N-Substituted Arylamines and Elemental Sulfur

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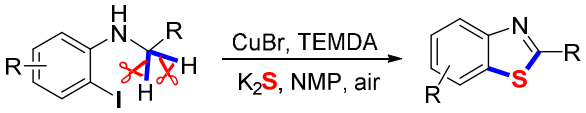
A novel, atom economic, and environmentally friendly method for the synthesis of 2-substituted benzothiazoles and 2-substituted naphtho[2,1-*d*]yhiazoles from N-substituted arylamines and elemental sulfur has been developed under metal-free conditions. The reaction underwent the process of double C-S bonds formation through C-H bonds functionalization.

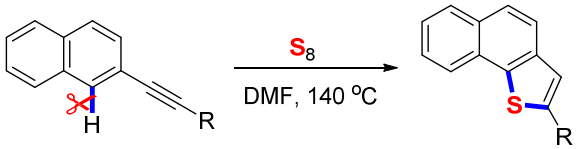
Sulfur-containing organic compounds play a particularly significant role in a variety of synthetic drugs, natural products, and functional materials, and represent a ubiquitous "privileged scaffold".[1] Therefore, the direct construction of C-S bonds for synthesis of sulfur-containing organic compounds has received considerable attention, and a lot of methods for construction of C-S bonds have been developed.[2-4] Among them, the classic strategies involved the transition-metal catalyzed traditional cross-coupling reaction of ArX (X = Cl, Br, I, OTf, and $B(OH)_2$) with sulfides[3] and oxidative coupling reaction of C-H bonds with sulfides.[4] However, the practical application of these methods are limited by the expensive metal catalysts and metal remain. Thus, considerable efforts have been made to develop metal-free approaches for the formation of C-S bonds in recent years.[5] Despite the overall efficiency and versatility of this transformation, the double thiolation reaction of inorganic sulfur source *via* C-H bonds functionalization for the straightforward synthesis of sulfur-containing compounds is less explored[6] and still highly desirable under metal-free conditions.

Benzothiazoles constitute the key moiety of many natural products and pharmaceutical drugs, and show their good biological activities.[1a,7] Accordingly, much effort has been made towards the development of diverse synthetic methods for benzothiazoles.[8-11] Classical methods involve the condensation of 2-aminothiophenols with aldehydes, ketones, nitriles, acids, and alcohols.[9] However, the unstable and readily oxidative 2-aminothiophenols limited application of these methods. In recent years, the construction of benzothiazoles framework focus on transition-metal catalyzed intramolecular cyclization of thiobenaznilides[10] and intermolecular cyclization of 2-haloanilides with thiol surrogates.[11] Although these methods are high-efficiency and diversity, most of them are limited in rigorous reaction conditions and require multistep preparation of starting materials. Accordingly, development of straightforward, atom-economic and environmentally friendly approaches for synthesis of benzothiazoles from readily available precursors is highly warranted. Our group found that benzaothiazoles could be synthesized *via* the cleavage of $C(sp^3)$-H bonds from N-benzyl-2-iodoanilines and K_2S (Scheme 1, a).[12] Recently, Itami and Segawa reported that thiophanthrenes could be synthesized *via* the cleavage of $C(sp^2)$-H bonds from napthalynes with elemental sulfur (Scheme 1, b).[13] If the $C(sp^2)$-H bonds and $C(sp^3)$-H bonds could be transformed into C-S bonds in a step reaction, this should be an ideal strategy for synthesis of sulfur-containing heterocyclic compounds. Herein, we report a method for synthesis of benzothiazoles *via* the cleavage of $C(sp^2)$-H bonds and $C(sp^3)$-H bonds from easily available N-substituted arylamines with elemental sulfur (Scheme 1, c).

a) C-S bonds formation *via* the cleavage of $C(sp^3)$-H bonds



b) C-S bonds formation *via* the cleavage of $C(sp^2)$-H bonds



c) Double C-S bonds formation *via* the cleavage of $C(sp^2)$-H bonds and $C(sp^3)$-H bonds(***This work***)

Scheme 1. Methods for the formation of C-S bonds

Inspired by our previous work on synthesis of sulfur-containing cyclic compounds using K_2S as sulfur source,[12,14] we started our investigation by taking N-benzyl 2-naphthylamine

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1a and K_2S as model substrate in DMSO at 140 °C under nitrogen atmosphere (Table 1). Intriguingly, the desired product 2-phenylnaphtho[2,1-*d*]thiazole **2a** was obtained in 43% yield (entry 1). Encourage by this result, sulfur sources such as elemental sulfur and $Na_2S_2O_3$ were used to react with **1a**, and the results demonstrated that elemental sulfur was the best sulfur source and gave 95% yield (entries 2 and 3). Then, the solvents including DMF, MeCN, and NMP were screened (entries 4-6), and exhibited less efficiency in promoting the reaction than DMSO. When the cyclization reaction performed under air or oxygen atmosphere (entries 7 and 8), the yield of the desired product was decreased. To our delight, no improvement of the yield was obtained with the reduction of elemental sulfur dosage (entry 9). The yield was decreased significantly with lowering the reaction temperature (entry 10). Therefore, the optimized yield of the reaction was obtained using elemental sulfur as sulfur source in DMSO at 140 °C under nitrogen atmosphere for 22 h (entry 9).

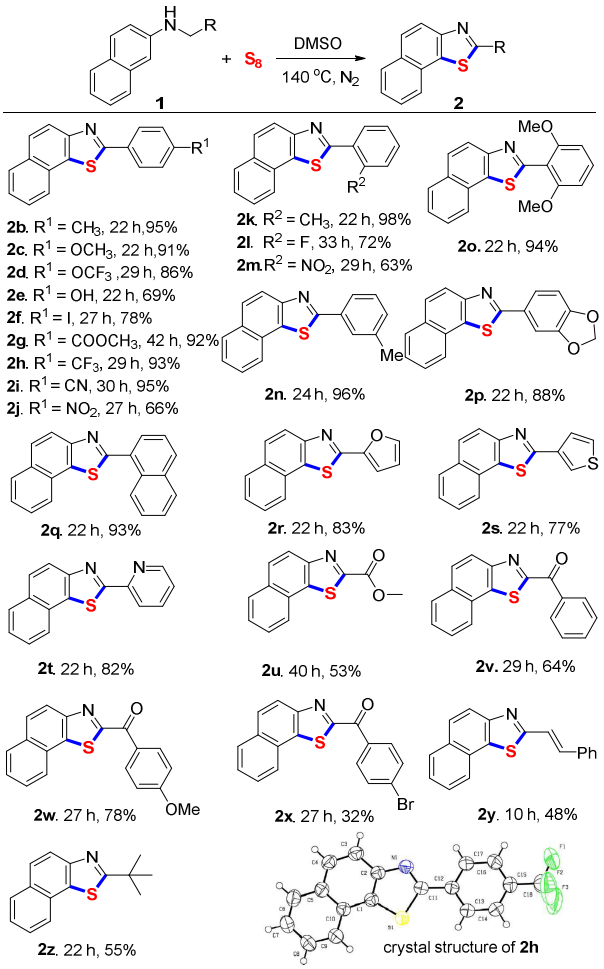
Table 1. Optimization of reaction conditions [a]

Entry	Sulfur source	Solvent	Isolated yield
1	K_2S	DMSO	43
2	S_8	DMSO	95
3	$Na_2S_2O_3$	DMSO	59
4	S_8	DMF	13
5	S_8	MeCN	37
6	S_8	NMP	40
7[b]	S_8	DMSO	73
8[c]	S_8	DMSO	39
9[d]	S_8	DMSO	95
10[e]	S_8	DMSO	52

[a] Reaction conditions: **1a** (0.3 mmol), S_8 (0.1125 mmol), DMSO (2 mL), under N_2 atmosphere in sealed Schlenk tube, at 140 °C for 22 h. [b] Air. [c] O_2. [d] S_8 (0.075 mmol). [e] 120 °C, S_8 (0.075 mmol).

With the optimized reaction conditions in hand, we explored the substituted group scope of 2-naphthylamines (Table 2). Various N-substituted 2-naphthylamines were successfully applied to react with elemental sulfur and the corresponding 2-substituted naphtho[2,1-*d*]thiazoles were obtained in good to perfect yields. Substituents at different positions of the benzene ring were tested firstly, which did not affect the efficiency obviously. For example, para-, meta-, and ortho-methylbenzyl substituted 2-naphthylamines can give the corresponding products in 95%, 96%, 98% yields respectively. The efficiency of the cyclization reaction is not much affected by the electronic property of the substituted benzyl, which are affected by their inherent tolerance. The electron-rich groups such as methyl, methoxyl, and trifluoromethoxyl and electron-deficient groups such as trifluoromethyl, ester and cyano substituted benzyl naphtho[2,1-*d*]thiazoles were obtained in perfect yields. However, the electron-donating group such as hydroxyl and electron-withdrawing groups such as nitryl and fluorine atom substituted-phenyl naphtho[2,1-*d*]thiazoles were given only in moderate yields. To our delight, the iodine atom was compatible under optimized reaction conditions, affording the corresponding cyclic product in 78% yield, which could be readily used for further transformations. Fortunately, the polyclic naphthyl and heterocyclic groups such as 2-furyl, 3-thienyl, and 2-pyridyl substituted naphtho[2,1-*d*]thiazoles were afforded in 93%, 83%, 77%, 82% yield respectively. Further, the α-keto group substituted 2-naphthylamines could react with elemental sulfur in DMSO at 140 °C, and the desired products were isolated in moderate to good yields. Notably, the N-cinnamylnaphthalen-2-amine could give the product **2y** in 48% yield. Finally, we found that the inter $C(sp^3)$-H bond could occur sulfur functionalization, and the product of 2-(*tert*-butyl)naphtho[2,1-*d*]thiazole was obtained in 55% yield.

Table 2. Synthesis of naphtho[2,1-*d*]thiazoles [a,b]



[a] Reaction conditions: **1** (0.3 mmol), S_8 (0.075 mmol), DMSO (2 mL), N_2, at 140 °C. [b] Isolated yields.

To further expand the substrate scope, the arylamines such as anilines, 1-naphthylamines, and 2-anthranylamine instead of 2-naphthylamines were examined in this cyclization reaction (Table 3). Under optimized reaction conditions, only electron-

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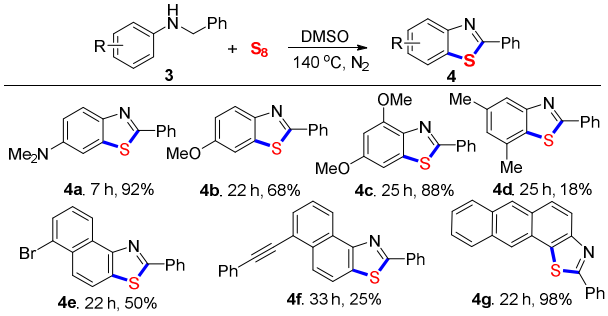
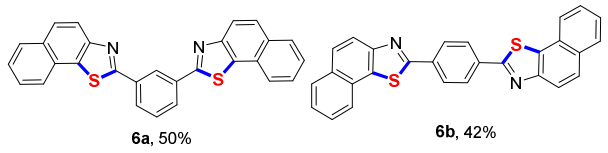
donating groups such as methyl, methoxyl, and N,N-dimethylamino substituted anilines could smoothly transformed into the target products, and a close examination of the results shows that the product yield decreases in the order: *(Me)$_2$N-> MeO- > Me-*. These results indicate the reaction underwent a process of electrophilic attack. It is worth noting that bromo- and alkynyl-substituted N-benzyl-1-naphthylamines were also smoothly converted into the corresponding products in 50%, 25% yield. Furthermore, when N-benzylanthracen-2-amine was employed as substrate, polycyclic 2-phenylanthra[2,1-*d*]thiazole **4g** was obtained in 98% yield.

Table 3. Synthesis of 2-phenylbenzothiazoles[a,b]



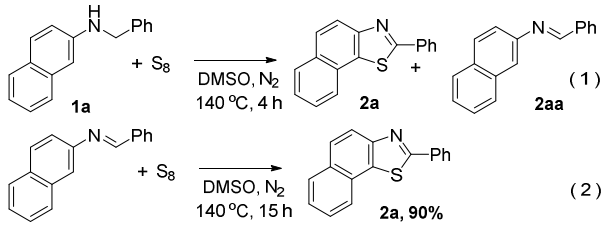
[a] Reaction conditions: **3** (0.3 mmol), S_8 (0.075 mmol), DMSO (2 mL), N_2, at 140 °C. [b] Isolated yields.

As a further demonstration of the application of the protocol, the benzene-bridged 1,3-bisnaphtho[2,1-*d*]thiazole **6a** and 1-4-bisnaphtho[2,1-*d*]thiazole **6b** with its extended π-conjulated system were obtained in moderate yield when the 1,3-bisbenzyl- and 1,4-bisbenzyl-bridged naphthylamines was treated with four equivalent of elemental sulfur under the standard reaction conditions in one-step synthesis (Scheme 2).



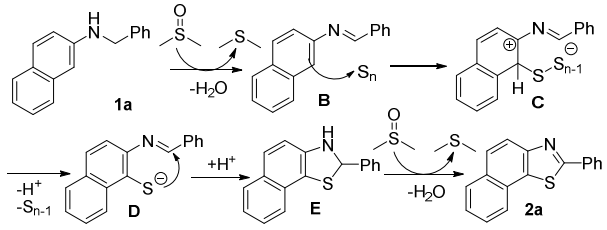
Scheme 2. Synthesis benzene-bridged bisnaphtho[2,1-*d*]thiazoles

To interpret the reaction pathway, several control experiments were performed (Scheme 3). Firstly, under the standard reaction conditions, when the reaction of N-benzyl 2-naphthylamine with elemental sulfur performed in 4 hours, the imine **2aa** could be detected from the reaction mixture by GC-MS analysis (see the SI for details). Subsequently, the imine **2aa** was also detected in the absence of elemental sulfur (see the SI for details). These results show that DMSO could be performed as an oxidant in this reaction. Crucially, **2aa** can be transformed into the final product 2-phenylnaphtho[2,1-*d*]thiazole **2a** in 90% yield. These results indicate this reaction probably involved the imine as the intermediate. Finally, dimethyl sulfide was obviously observed *via* GC analysis of the model reaction (see the SI for details). This result proved that DMSO act as an oxidant to promote this cyclization reaction again.



Scheme 3. Controlled experiments

Based on the experimental results and previous reports.[13,15] a proposed reaction mechanism for the formation of **2a** is demonstrated in Scheme 4. Under the action of DMSO, the **1a** can transform into imine **B**. Subsequently, electrophilic attack of elemental sulfur (S_n) to the α-position of β-naphthylamine gives **C**, which eliminates elemental sulfur (S_{n-1}) and hydrogen proton along with the generation of sulfurated imine **D**. Intermolecular nucleophilic cyclization of intermediate **D** would generate thiazoline **E**, which proceeds through oxidative aromatization to give the desired product 2-phenylnaphtho[2,1-*d*]thiazole **2a**.



Scheme 4. Proposed reaction mechanism for the formation of **2a**

In conclusion, we have demonstrated an efficient and metal-free method for the synthesis of 2-substituted benzothiazoles and 2-substituted naphthothiazoles from N-substituted arylamines and elemental sulfur. In this reaction, the double C-S bonds are formed through the cleavage of C(sp^2)-H bond and C(sp^3)-H bonds. Furthermore, the experimental results indicate that the DMSO acts as an oxidant and solvent for the cyclization reaction. Notably, readily available starting material and tolerance of a wide range of functional groups are the advantages of this protocol.

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Conflicts of interest

There are no conflicts to declare.

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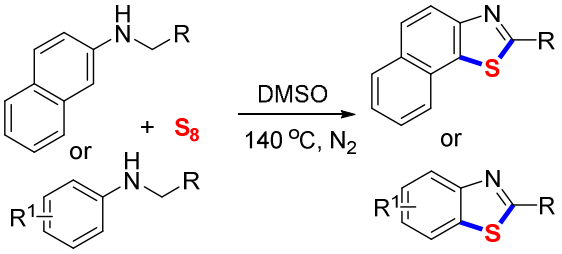

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