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Elemental Sulfur as Sulfuration Agent in Copper-Catalyzed C-H Bond Thiolation of Electron-Deficient Arenes

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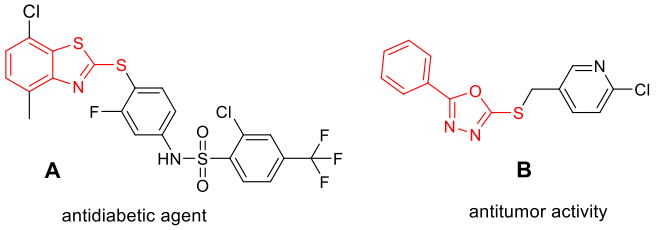
By utilizing elemental sulfur as the thiolation agent and oxidant, a copper-catalyzed direct C-H bond thiolation of electron-deficient arenes was demonstrated. Various electron-deficient arenes were proved to be suitable for this transformation. Preliminary mechanistic studies indicated that this reaction underwent a radical pathway, in which trisulfur radical anion ($S_3^{\bullet-}$) might play a vital role. Meanwhile, KIE experiments suggested that C-H bond cleavage was not involved in the rate-determining step.

Elemental sulfur is non-toxic and abundant substrate, which occurs naturally in the environment. Since it is regarded as a promising oxidant and sulfuration agent in synthetic chemistry,[1-7] in the past decades, a lot of methods towards the construction of C-S bond were developed by utilizing elemental sulfur. For example, organometallic reagents[8-15] and organic halides[16-21] could successfully react with elemental sulfur to afford the desired organosulfur compounds. However, directly employing C-H bond to react with elemental sulfur for building up C-S bond still remains a challenge.[22,23] Undoubtedly, direct C-H bond thiolation would be an ideal synthetic process for thiophenol, which does not require prefunctionalized starting materials that have to be prepared through additional steps.[24,25] In the past few years, our group make a continuous contribution in C-H bond functionalization by oxidative coupling strategy.[26-30] Based on the previous results, here we would like to share our latest discoveries in a copper-catalyzed direct Csp^2-H bond thiolation of electron-deficient arenes by employing elemental sulfur as oxidant and sulfuration agent.

Organosulfur compounds are useful building blocks in the synthesis of complex compounds, which exhibit extraordinary biological and pharmaceutical properties.[30-35] For example, the molecule **A** containing benzothiazole is a potential antidiabetic agent,[36] the molecule **B** involving 2-phenyl-1,3,4-oxadiazole shows excellent antitumor activity[37] (Scheme 1). Consequently, developing synthetic methods for organosulfur compounds by direct C-S bond construction has received considerable attention in recent years.[38-45] Up to now, although tremendous progress has been made in C-S bond formation through S_N2 substitution or cross-coupling reactions with thiols as sulfuration agents,[46-50] highly selective and effective methods for C-S bond construction are still in demand. Here, we demonstrate a straightforward strategy towards the synthesis of thiophenols by directly introducing the odorless elemental sulfur as the sulfuration agent.

Scheme 1. Representative organosulfur compounds.



Inspired by our previous work,[51] in which a breakthrough was made in the Csp^2-H bond aerobic hydroxylation, we commenced the direct oxidative thiolation of benzothiazole by employing copper chloride as the catalyst, *t*BuONa as the base and elemental sulfur as the oxidant (Table 1). Interestingly, benzothiazole could react smoothly with elemental sulfur to produce the thiolation product in 76% yield at 25 °C (Entry 1). Various copper salts were tested for this transformation, but they all gave lower yields except for CuCl (Entries 2, 3 and 4). Several commonly used ligands for copper-catalyzed reactions were also tested (Entries 6, 7 and 8). The results indicated that a better yield was obtained when 1,10-phenanthroline was employed. The addition of TMEDA resulted in 71% isolated yield, while a much lower yield was obtained with the addition of dppp. No better results were found after screening several solvents (Entries 9, 10 and 11). *t*BuONa and copper salt turned out to be essential for

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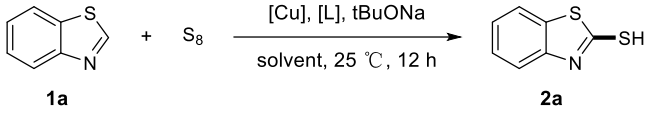
this transformation, since no product was observed in the absence of *t*BuONa or $CuCl_2$ (Entries 5 and 12). Therefore, the combination of $CuCl_2$ (5 mol%), 1,10-phenanthroline (10 mol%), *t*BuONa (1.2 eq) in DMF at 25 °C was found to be the best reaction conditions for the thiolation reaction between arene and elemental sulfur, currently.

Table 1. Copper-catalyzed thiolation reaction between 1a and elemental sulfur: effects of reaction parameters.[a]



1a **2a**

Entry	[Cu]	solvent	ligand	yield%[b]
1	$CuCl_2$	DMF	-	76
2	CuI	DMF	-	68
3	CuOAc	DMF	-	37
4	CuCl	DMF	-	75
5[c]	$CuCl_2$	DMF	-	n.d.
6	$CuCl_2$	DMF	TMEDA	(71)
7	$CuCl_2$	DMF	dppp	39
8	$CuCl_2$	DMF	1,10-phen	81 (82)
9	$CuCl_2$	DMSO	1,10-phen	5
10	$CuCl_2$	toluene	1,10-phen	5
11	$CuCl_2$	THF	1,10-phen	50
12	-	DMF	1,10-phen	n.d.

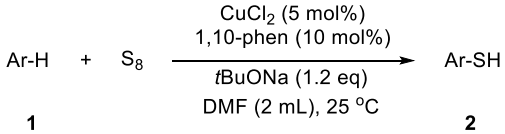
[a]Reaction conditions: all of the reactions were performed with **1a** (0.5 mmol), S_8 (16 mg), copper salts (5 mol%), ligand (10 mol%) and *t*BuONa (0.6 mmol) in DMF (2 mL) at 25 °C for 12 h under N_2. [b]Yield determined by HPLC analysis with naphthalene as the internal standard. Isolated yields for entries 6 and 8 in the parentheses. [c]Without *t*BuONa.

With the optimized conditions in hand, we further explored the substrate scope of this $CuCl_2$-catalyzed thiolation reaction. As shown in Table 2, various arenes were tested. Benzoaxzoles containing Cl, *t*Bu or Me group on the aryl ring are suitable for this transformation, affording the corresponding thiolation products in 30% to 95% yields (entries 2-5). 2-Aryl-1,3,4-oxadiazoles could also be converted to the desired product smoothly, and Cl, Br, Me and MeO groups were well tolerated (entries 6-10). Electron-deficient arenes instead of electron-deficient heteroarenes could also react with elemental sulfur successfully to afford the desired thiophenols in moderate yields (entries 11-12).

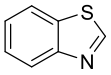
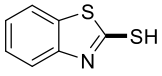
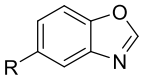
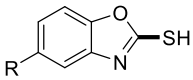
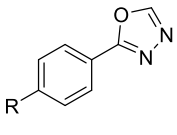
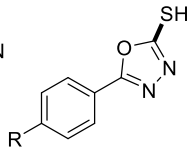
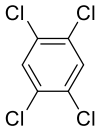
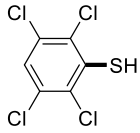
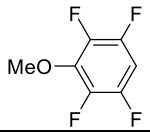
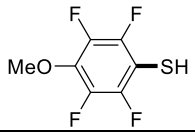
In order to gain some mechanistic insights about this transformation, several experiments were performed. Firstly, this thiolation reaction between **1a** and elemental sulfur was monitored by electron paramagnetic resonance (EPR). As shown in Figure 1, a strong signal, for which g-factor is 2.029, was detected when elemental sulfur was mixed with *t*BuONa in DMF at 25 °C. According to our current research,[52] this radical signal was assigned to trisulfur radical anion ($S_3^{\bullet-}$). The $S_3^{\bullet-}$ signal was still observed clearly even if CuCl was added into the mixture. However, once benzothiazole **1a** was introduced, this signal disappeared immediately, accompanying with the formation of the desired thiophenol in 80% yield. These phenomena disclosed that $S_3^{\bullet-}$ was involved in this transformation and might be a reactive intermediate.

Kinetic isotope effect (KIE) was also measured to understand this transformation. As shown in Eq. 1, KIE of 1.24 was observed from two parallel reactions, suggesting that C-H bond cleavage may not be involved in the rate-determining step.

Table 2. Substrate scope.[a]



1 **2**

Entry	substrate	product	yield%
1			82 %
2			R=H, 67 %
3			R=Cl, 30 %
4			R=tBu, 95 %
5			R=Me, 64 %
6			R=H, 73 %
7			R=Cl, 62 %
8			R=Br, 66 %
9			R=Me, 54 %
10			R=OMe, 79 %
11			64 %
12			64 %

[a]Reaction conditions: all of the reactions were performed with **1a** (0.5 mmol), S_8 (16 mg), $CuCl_2$ (5 mol%), 1,10-phenanthroline (10 mol%) and ^{t}BuONa (0.6 mmol) in DMF (2 mL) at 25 °C for 12 h under N_2. Isolated yield.

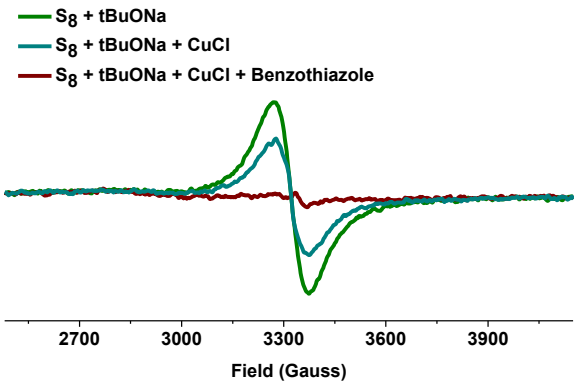
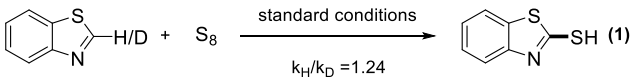
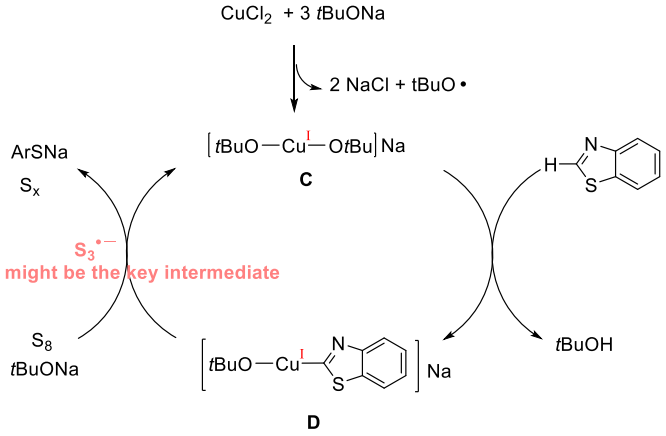


Figure 1. EPR experiments.



According to the above mechanistic investigations and our previous work,[53,54] a plausible mechanism is proposed for this thiolation reaction. As shown in Scheme 2, the transformation commences by the formation of the active Cu(I) species **C** by the reaction of *t*BuONa and $CuCl_2$. Then, a C-H activation process occurs between species **C** and benzothiazole to afford the intermediate **D**, which will further react with sulfur to give the desired product. Since the EPR results suggested that the $S_3^{\bullet-}$ is an active species in this transformation, we guess it might plays a key role in the thiolation process of **D**.

Scheme 2. Plausible mechanism.



Conclusions

In conclusion, a copper-catalyzed direct C-H bond thiolation of electron-deficient arenes was demonstrated by utilizing elemental sulfur as the thiolation agent. Various electron-deficient arenes were proved to be suitable for this transformation. Preliminary mechanistic studies indicated that this reaction underwent a radical pathway, in which trisulfur radical anion ($S_3^{\bullet-}$) might play a vital role. Meanwhile, KIE experiments suggested that C-H bond cleavage was not involved in the rate-determining step. According to the current investigations, a plausible mechanism is proposed. More detailed mechanism is currently under investigation in our laboratory and will be reported in the near future.

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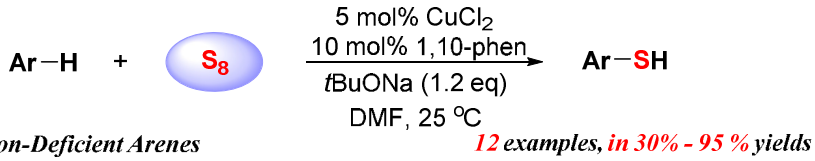

Electron-Deficient Arenes *12 examples, in 30% - 95 % yields*