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Copper-Catalyzed Divergent Synthesis of Disulfanes and Benzenesulfonothioates Bearing 2-Aminofurans From *N*-tosylhydrazone-Bearing Thiocarbamates

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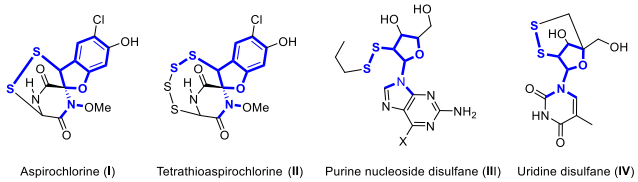
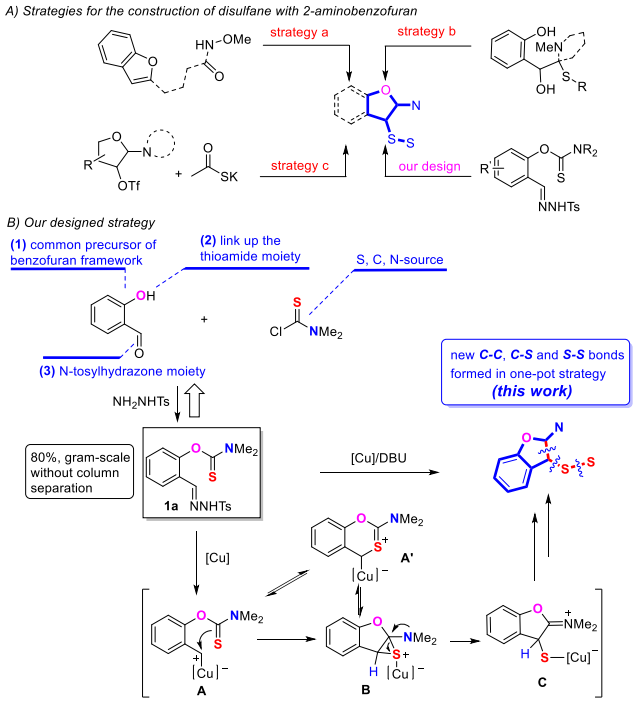
Abstract: An efficient and convenient synthesis of valuable disulfanes and benzenesulfonothioates with 2-aminofuran framework has been developed via a copper-catalyzed cascade transformation of readily available *N*-tosylhydrazone-bearing thiocarbamates. This method features inexpensive metal catalyst, mild condition, good functional group tolerance, short reaction time, and valuable and complex products. A copper carbene generated from *N*-tosylhydrazone-bearing thiocarbamate is proposed as the key intermediate for the transformation which triggered cascade processes subsequently. Remarkably, the Ts anion released from *N*-tosylhydrazone further serves as a nucleophile rendering the formation of benzenesulfonothioates under controllable conditions.

Disulfanes, an important class of molecules containing sulfur-sulfur framework that extensively exist in nature,[1] have been widely employed in biochemistry,[2] food chemistry,[3] pharmaceutical industry[4] as well as substrates for generating more complex sulfur-sulfur containing molecules.[5] Among them, disulfane-bearing 2-aminofuran frameworks are particularly attractive since they are common structural motifs in many bioactive natural products and pharmaceutical entities[6] (Scheme 1). For instance, aspirochlorine **I** (or antibiotic A30641)



Scheme 1. Selected examples of disulfanes with 2-aminofuran frameworks.

is a novel seven-membered epidithiapiperazine-2,5-dione with distinctive antifungal properties due to selective inhibition of protein biosynthesis. Its analogue tetrathioaspirochlorine **II** is slightly less potent in the antifungal assay according to the literature.[6a] In addition, the purine nucleoside disulfane **III** is an important precursor in vinylthiol chemistry,[6c] and uridine disulfane **IV** is a stable precursor to potential mechanistic probe of ribonucleotide reductases (RNRs).[6d] Given the complicated structure of disulfane-bearing 2-aminofuran, it is a big challenge to build up such scaffold with S, O, N, C sources simultaneously and careful design usually is required to achieve this goal. So far only very few synthetic strategies have been developed on how to synthesize these special molecules: e.g. the cycloaddition of a benzofuran hydroxamic ester to form spiro[benzafuran-2(3*H*),2′-piperazine] ring system followed by S-S bond formation (Scheme 2A, strategy a, 4-5 steps required from benzofuran hydroxamic ester);[7] the highly stereoselective sulfur migration manner (Scheme 2A, strategy b)[8] and the treatment of the *O*-(trifluoromethanesulfonyl)adenosine with potassium thioacetate (Scheme 2A, strategy c).[6c, 6d] Given the difficulty to access the starting materials in the above three strategies, we wondered whether a new strategy could be developed via ready accessible starting materials in one-step protocol. At this point, thiocarbamate came into our eyes: with S, O, N three different atoms on its structural motif, thiocarbamate might be an ideal



Scheme 2. Reported and our designed synthetic strategies for the construction of disulfanes-bearing 2-aminofuran frameworks

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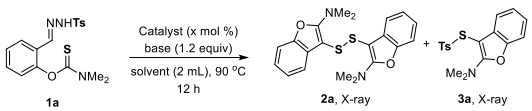
source to accomplish our target.[9] Transition-metal carbene complexes have been emerged as very active intermediates for the construction of new C-C or C-heteroatom bonds conveniently.[10, 11] In order to activate the thiocarbamate and incorporate the ideal S, O, N sources into the final products, we envision if we introduce a "carbene" or carbenoide and thiocarbamate into one molecule, thiocarbamate might attack on carbene to form a three-membered episulfide intermediate (intermediate B in Scheme 2B) which might rearrange to the disulfane-bearing 2-aminofuran framework via ring-opening[12] (Scheme 2B). In the past decades, *N*-tosylhydrazone moiety has become a readily available and widely employed precursor to access carbenes,[13] therefore, the inexpensive and commercially available salicylaldehyde catched our eyes due to its structural versatility: (1) it is the common precursor for benzofuran framework,[14] (2) phenolic hydroxyl group can link up thiocarbamate moiety through esterification, (3) aldehyde group can play as the precursor of the *N*-tosylhydrazone moiety which can generate diazo compound through a gentle Bamford-Stevens reaction.[15] Based on our strategy, we synthesized *N*-tosylhydrazone-bearing thiocarbamate **1a** as the starting material and it was easily obtained in 80% yield (gram-scale) without column separation[16] from commercially available salicylaldehyde and dimethylcarbamoyl chloride (Scheme 2B).

To explore the feasibility of our proposal, exposure of compound **1a** to a variety of conditions revealed that disulfane **2a** with 2-aminofuran framework can indeed be generated. To our surprise, we can also obtain unexpected benzenesulfonothioates **3a** under controllable conditions. The structures of products **2a** and **3a** were unambiguously ascertained by X-ray crystal structure analysis.[17] Remarkably, benzenesulfonothioates as novel potential electrophilic sulfenylating reagents (RS^+), also demonstrate valuable applications in C-S constructions.[18] Herein, we report an efficient approach toward the one-pot syntheses of disulfanes or benzenesulfonothioates bearing 2-aminofurans, which can't be easily accessed through other reported approaches in one-step strategy. We further demonstrated the synthetic potential of this strategy by converting these products into valuable compounds.

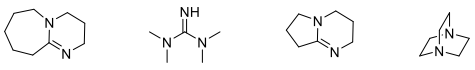
We commenced our investigations with *N*-tosylhydrazone-bearing thiocarbamate (**1a**) as the model substrate in the presence of LiO^tBu (1.2 equiv) and 1,4-dioxane (2 mL) (Table 1). As a potential catalyst in carbene chemistry, [$Rh_2(OAc)_4$] was examined firstly yet only decomposition was observed (entry 1).[12a-e] Copper salt were subsequently examined and CuI only led to a trace amount of the desired product **2a** in the presence of LiO^tBu (entry 2). A series of inorganic bases, such as KO^tBu, NaO^tBu, and Cs_2CO_3 were further investigated and the former two afforded 10-38% of compound **2a** (entries 2-5). Noteworthily, Cs_2CO_3 delivered the unexpected transformation: in addition to the disulfane **2a** (in 20% yield), unexpected benzenesulfonothioate **3a** was obtained in 54% yield, which might come from the reaction between the released *p*-$MePhSO_2^-$ moiety (from *N*-tosylhydrazone through Bamford-Stevens reaction in the presence of inorganic base) and disulfane **2a** (entry 5). We speculated that the poor reactivity of the transformation might be due to the low effective collision between disulfane **2a** and the *p*-$MePhSO_2^-$ moiety in organic phase. And we envision that the problem could be overcome by employing organic base. To our delight, when organic bases such as DBU and TMG were employed, much cleaner conversion to compound **3a** was indeed observed (entries 6-7). Interestingly, other organic bases such as DBN, Et_3N and DABCO just led to trace amounts of **2a** and **3a** (entry 8) due to unknown reasons. By reducing the reaction temperature to 60 ^oC and shortening the reaction time to 30 min, **3a** was obtained in 76% yield as the major product (entry 9). Further copper salts screening indicated that $CuBr_2$ was the optimal one among CuI and $Cu(CH_3CN)_4PF_6$ etc. with compound **3a** isolated in 90% yield (entries 9-11). Gratifyingly, when $CuCl_2$ was employed as catalyst under dilute THF (0.05 M), disulfane **2a** became the major product in 72% yield at 70 ^oC (entry 12), this result indicated that Cu species plays an essential role on the selectivity of this transformation though the reasons are still uncertain. Remarkably, compound **3a** was obtained in 78% yield by simply extending the reaction to 2 h (entry 13). These results suggested that **2a** should be the key intermediate in the formation of **3a**. Further two more control experiments which were performed under N_2 atmosphere and in the absence of Cu salt respectively clearly showed that both oxygen (from air) and metal salt are crucial for the success of these transformations (entry 14-15).

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	mol %	Base	Solvent	yield [%] [b]	
					2a	3a[c]
1	$Rh_2(OAc)_4$	5	LiO^tBu	1,4-dioxane	-	-
2	CuI	20	LiO^tBu	1,4-dioxane	Trace	-
3	CuI	20	KO^tBu	1,4-dioxane	10	-
4	CuI	20	NaO^tBu	1,4-dioxane	38	-
5	CuI	20	Cs_2CO_3	1,4-dioxane	20	54
6	CuI	20	DBU	1,4-dioxane	Trace	75
7	CuI	20	TMG	1,4-dioxane	Trace	70
8	CuI	20	Organic base[d]	1,4-dioxane	Trace	-
9[e]	CuI	20	DBU	1,4-dioxane	Trace	76
10[e]	$Cu(CH_3CN)_4PF_6$	20	DBU	1,4-dioxane	Trace	86
11[e]	$CuBr_2$	20	DBU	1,4-dioxane	Trace	**90**
12[f]	$CuCl_2$	20	DBU	THF	**72**	-
13[f, g]	$CuCl_2$	20	DBU	THF	Trace	78
14[e, h]	$CuBr_2$	20	DBU	1,4-dioxane	Trace	-
15[e]	none	0	DBU	1,4-dioxane	-	-

[a] General conditions: **1a** (0.2 mmol), solvent (2 mL), 90 ^oC, 12 h, under air. [b] Isolated yield. [c] The yields of **3a** was based on the full conversion of **2a**. [d] Other organic bases tested: DBN, Et_3N, and DABCO. [e] The reaction was carried out at 60 ^oC for 0.5 h. [f] 2 equiv DBU and 4 mL THF were used at 70 ^oC for 35 min. [g] For 2 h. [h] Under N_2.



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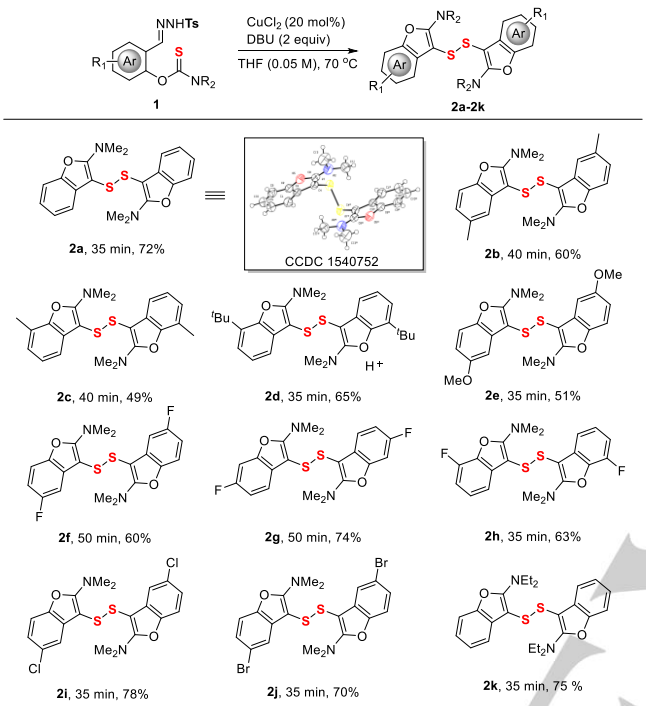
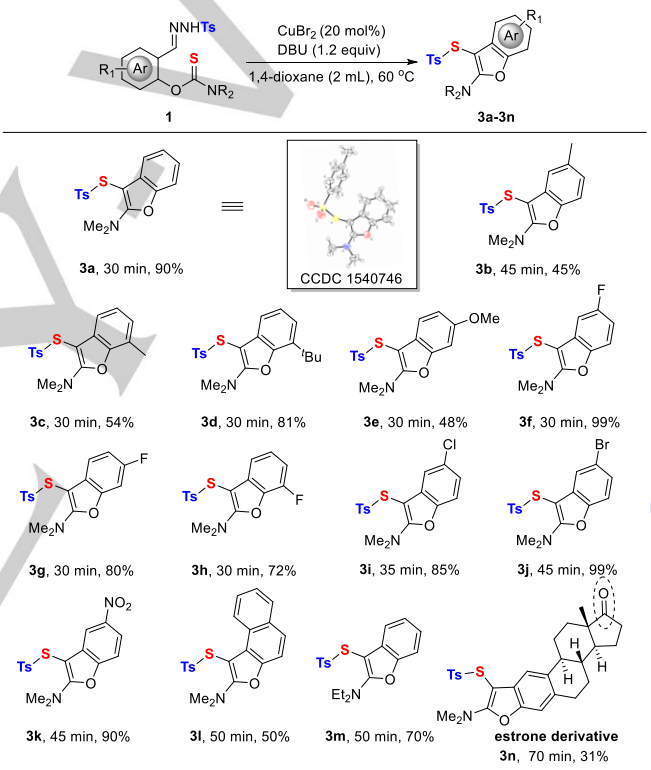
With the optimal conditions in hands, we firstly investigated the scope of disulfane formation under the reaction conditions shown in Table 1, entry 12 (Scheme 3). Gratifyingly, substrates with both EDGs and EWGs on the benzene ring of compound **1** all furnished the disulfane derivatives in good yields (**2b**−**2j**). Of note, *N, N*-diethyl disulfane **2k** was also obtained in 75% yield under the standard conditions.



Scheme 3. Copper-catalyzed synthesis of disulfane drivatives. Reaction conditions: **1** (0.2 mmol) was carried out at 60 °C in the presence of $CuCl_2$ (20 mol%) and DBU (2 equiv) in THF (0.05 M) under air.

We subsequently investigated the substrate scope for the synthesis of benzenesulfonothioate derivatives under the reaction conditions shown in Table 1, entry 11, and the results are summarized in Scheme 4. Substrates with electron-withdrawing groups usually gave the corresponding products in higher yields (**3f**−**3k**) than those with electron-donating groups (**3b**−**3e**). Notably, halo groups (**3f**−**3j**) were also well tolerated under the optimal conditions, which may offer a potential synthetic handle for further functionalization. Naphthyl *N*-tosylhydrazone **1l** was also good candidate for this transformation and the corresponding desired product **3l** was obtained in 50% yields. In addition to *N*, *N*-dimethyl substrates, the substrate **1m** bearing *N*, *N*-diethyl was also capable under the standard conditions (**3m**). It is noteworthy that estrone derivative **3n** containing ketone carbonyl group was obtained in 31% yield, which demonstrated our strategy has good functional group tolerance and might be used for late-stage modification in drug discovery.

The synthetic value of these novel transformations was emphasized by the transformations of the disulfane **2a** into a myriad of valuable compounds (Scheme 5): disulfane **2a** was readily converted into benzenesulfonothioate **3a** in 90% yield under mild conditions; [19] *N, N*-dimethyl-3-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)thio)benzofuran-2-amine **4**, which contains two heterocyclic rings, was obtained in 36% yield by mixing **2a** and imidazo[1,2-*a*]pyridine at 90 °C employing I_2/DMSO as catalytic oxidation system;[20] Furthermore, 5-functionalized triazole **5** was obtained in 55% yield via the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC).[18b] Silvestri and co-workers have found that arylthioindoles with nitrogen substituents at C2 are highly potent anticancer agents.[21a] To our delight, 2-aminoarylthiobenzofurans and benzothiophenes are also bioactive, which are the potential inhibitors of the kynurenine pathway.[21b] Therefore, compound **6** containing this valueable skeleton could be synthesized by the deborylthiolation of phenylboronic acid with **3a** in 60% yield[18a] that was previously difficult to access, which could further demonstrate the synthetic value of our methodologies.



Scheme 4. Copper-catalyzed synthesis of benzenesulfonothioate drivatives. Reaction conditions: **1** (0.2 mmol) was carried out at 60 °C in the presence of $CuBr_2$ (20 mol%) and DBU (1.2 equiv) in 1,4-dioxane (2 mL) under air.

To gain more insights into the reaction mechanism, we carried out a set of control experiments (scheme 6). Firstly, addition of a radical inhibitor (TEMPO) just slightly hampered the reaction, and the desired product **2a** was still obtained in 50% yield along with 35% of aldehyde **7** (Scheme 6a), which inferred that this transformation did not take a SET pathway. Secondly, treatment of **8** or **10** (Scheme 6b) under the standard conditions did not lead to any desired products, which demonstrates that both aldehyde *N*-tosylhydrazone and thiocarbamate are indispensable in this transformation. Thirdly, in order to understand the formation of **2a**, 4-methylbenzenethiol **12** was

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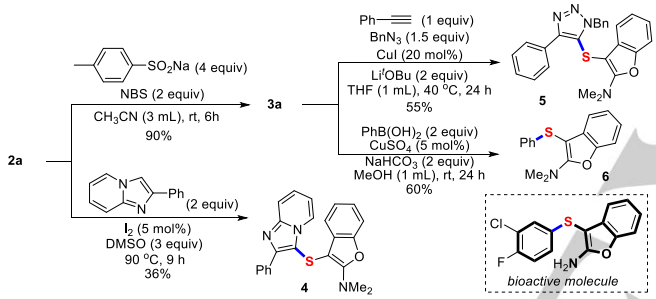
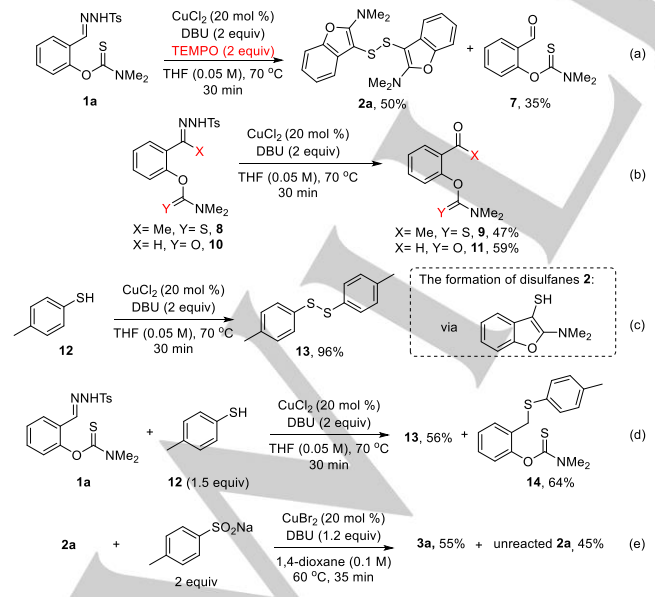
subjected to the standard conditions and corresponding disulfane **13** was obtained in 96% yield, which suggested that our standard conditions provide an oxidative environment for the dimerization of aryl thiophenol, in another word, disulfanes **2** might come from the dimerization of aryl thiophenols (Scheme 6c). Remarkably, when 4-methylbenzenethiol **12** was introduced to the reaction with **1a**, compound **14** was obtained in 64% yield along with 56% of **13**, and no corresponding desired product was obtained (Scheme 6d), which demonstrated that intramolecular carbene insertion into thiocarbamate might be the rate-determing step in this transformation. In addition, exposure of **2a** to 2 equiv of sodium 4-methyl-benzenesulfinate provided benzenesulfonothioate **3a** in 55% yield along with 45% of unreacted disulfane **2a**. This experiment suggested that *in situ* formed disulfanes **2a** might be the key intermediate for the formation of **3a** in our transformation, which further confirmed our observation in entry 13 in Table 1. The salt form of *p*-$MePhSO_2^-$ obviously affected its nucleophilicity since under the same conditions starting material **1a** could lead to 90% yield of **3a**, yet this one only had ca. 50% conversion with significant amount of starting material **2a** remained (Scheme 6e).

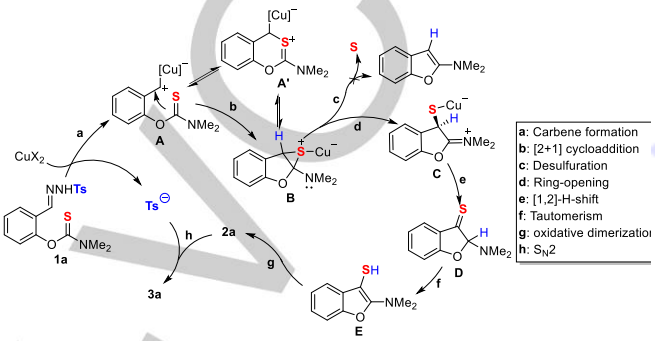


Scheme 5. Synthetic transformations from **2a** and **3a**.



Scheme 6. Investigation of the reaction mechanism.

On the basis of the preliminary mechanistic studies and precedent reports[12, 22], a plausible cyclization pathway is proposed in Scheme 7. First, **1a** undergoes carbene formation in the presence of Cu salt and base rendering intermediate **A**. Thiocarbamate attacking on carbene forms a S-containing three-membered ring intermediate **B**, which produces aryl thiophenol **E** via ring-opening, [1, 2]-H shift, and tautomerism. The dimerization of aryl thiophenol **E** gives the disulfane **2a**, and the Ts anion released from *N*-tosylhydrazone can further serve as a nucleophile rendering the formation of benzenesulfonothioate **3a**.



Scheme 7. Proposed mechanism.

In conclusion, a copper-catalyzed controlled divergent syntheses of disulfanes and benzenesulfonothioates bearing 2-aminofurans from *N*-tosylhydrazone-bearing thiocarbamates has been disclosed. This is the first example of a copper-catalyzed, intramolecular cyclization leading to 2-aminofuran-bearing disulfanes and benzenesulfonothioates in one-step strategy. Given that the ready availability of the starting materials, the high efficiency, and simple operation of the process, the high functional-group compatibility as well as the valuable products, it can be expected that this methodology will be a useful tool for the construction of sulfur-containing heterocyclic systems. Further exploration on the synthetic applications of the transformations and mechanistic studies are under way in our laboratory.

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Keywords: copper • disulfane • benzenesulfonothioate • *N*-tosylhydrazone • thiocarbamate

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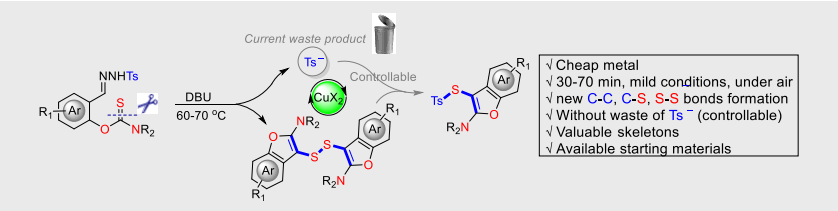

Waste? No! Valuable! *N*-tosylhydrazones-bearing thiocarbamate proves itself to be a valuable substrate since complex disulfane and benzenesulfonothioate with 2-aminofuran framework was readily accessible via a copper-catalyzed cascade transformation. Remarkably, the Ts moiety, which usually is considered as a waste released from *N*-tosylhydrazone, can serve as a nucleophile rendering the formation of benzenesulfonothioates under controllable conditions, and at certain stage, disulfane was delivered as the major product.

*Shaoyu Mai, and Qiuling Song**

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Copper-Catalyzed Divergent Synthesis of Disulfanes and Benzenesulfonothioates Bearing 2-Aminofurans From *N*-tosylhydrazone-Bearing Thiocarbamates