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# Facile and efficient transformation of thiols to disulfides *via* a radical pathway with *N*-anomeric amide†

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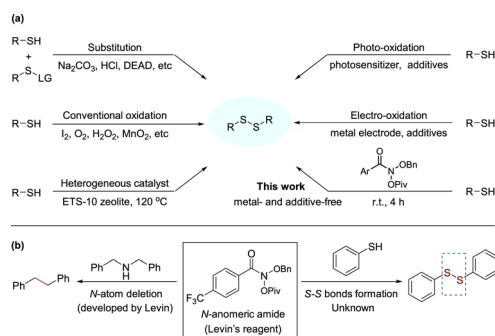
Radical coupling of thiols is an attractive route for the synthesis of disulfides, but this approach should be promoted by strong oxidants and/or metal salts in combination with additives, which limits its substrate scope and application. In this work, the *N*-anomeric amide was first found to be able to realize the conversion of thiols to sulfur radicals with high efficiency in the absence of an oxidant or any additives for the synthesis of symmetrical disulfides. The protocol features mild reaction conditions, good functional group tolerance, and moderate to excellent yields.

## Introduction

Organosulfur compounds, although usually associated with unpleasant odors, are considered non-toxic and have important functions in natural compounds,<sup>1</sup> biological agents and drugs,<sup>2</sup> as well as in advanced materials.<sup>3</sup> Among compounds containing sulfur, disulfides play a dominant role in biological systems, since they are fundamental factors in protein folding and oligomerization, as they stabilize the 3D structure and affect their biological function.<sup>4</sup> Disulfides are also important intermediates for many synthetic pathways and present various applications in agro-chemicals and pharmaceuticals.<sup>5</sup> These findings render disulfides as moieties of great importance and synthetic interest. In recent decades, various feasible strategies have been developed for the synthesis of symmetrical disulfides, such as thiolysis,<sup>6</sup> reductive dimerization of thiocyanates,<sup>7</sup> nucleophilic substitution of S–H bonds,<sup>8</sup> and reductive coupling of sulfonyl chlorides.<sup>9</sup> However, the formation of byproducts arising from leaving groups is inevitable in these strategies. In contrast, extensive studies have indicated the direct dehydrogenation of thiols to disulfides followed by sulfur radical coupling, with H<sub>2</sub> as the sole byproduct, and have attracted much attention due to their high atom and step-economy for the synthesis of disulfides (Scheme 1(a)).<sup>10</sup> Oxidative coupling of thiols as a direct method avoids the pre-activation of thiols, which was promoted by strong oxidants or oxidants assisted with various catalysts.<sup>11</sup> In order to use mild conditions, catalytic oxidation was explored by adopting various metal-based catalysts<sup>12</sup> or heterogeneous

catalysts,<sup>13</sup> on the other hand, photochemistry<sup>14</sup> and electrochemistry<sup>15</sup> recently have drawn extensive attention. However, these methods suffer from some serious drawbacks such as over-oxidation, very high or low reaction temperatures, use of strong basic or acidic media and tedious work-up procedures. Moreover, the use of metal catalysts is not preferred for late-stage functionalization of biologically active molecules, such as peptides or other pharmaceuticals.<sup>16</sup> Given the importance of organic disulfides, the development of mild and effective methods remains a major objective.

In order to skeletal editing of nitrogen-containing molecules, Levin and coworkers developed the *N*-anomeric amide (Levin's reagent) that enables straightforward nitrogen deletion of secondary amines and deamination of primary amines (Scheme 1(b)).<sup>17</sup> The transformation relies on the facile *in situ* generation of an isodiazene intermediate, which can undergo thermal homolytic N<sub>2</sub> extrusion to form a new C–C bond.<sup>17a</sup> Inspired by *N*-anomeric amide's excellent electrophilic properties<sup>17,18</sup> and our long-term interest in organosulfur chemistry,<sup>19</sup> we initially

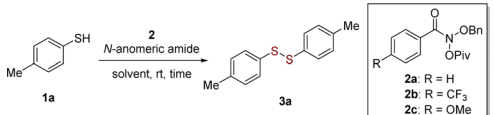


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**Scheme 1** (a) Approaches for the synthesis of disulfides from thiols. (b) Structure and applications of the *N*-anomeric amide.



Table 1 Optimization of the reaction conditions<sup>a</sup>


Entry	<i>N</i> -Anomeric amide (equiv.)	Solvent	Time (h)	Yield <sup>b</sup> (%)
1	—	MeCN	4	0
2	2a (1.0)	MeCN	4	58
3	2a (1.2)	MeCN	4	73
4	2a (2.0)	MeCN	4	70
5	2a (1.2)	MeCN	6	65
6	2a (1.2)	MeCN	2	51
7	2b (1.2)	MeCN	4	94
8	2c (1.2)	MeCN	4	62
9	2b (1.2)	DMF	4	43
10	2b (1.2)	DMSO	4	65
11	2b (1.2)	THF	4	76

<sup>a</sup> Unless otherwise noted, reactions were performed with **1a** (0.2 mmol), *N*-anomeric amide **2**, solvent (1.0 mL), room temperature, under argon atmosphere. <sup>b</sup> Yields of isolated product are shown after silica gel chromatography.

programmed a project aiming at the formation of S–S bonds starting from thiols. Subsequently, we have successfully detected of disulfide product when the reaction was conducted in thiol with Levin's reagent at room temperature (Scheme 1(b)). To the best of our knowledge, this is the first construction of S–S bond using *N*-anomeric amide beyond deaminative functionalization.<sup>20</sup> Herein, we report our realization of a mild and efficient method for the synthesis of organic disulfides *via* a sulfur radical mechanism with *N*-anomeric amide.

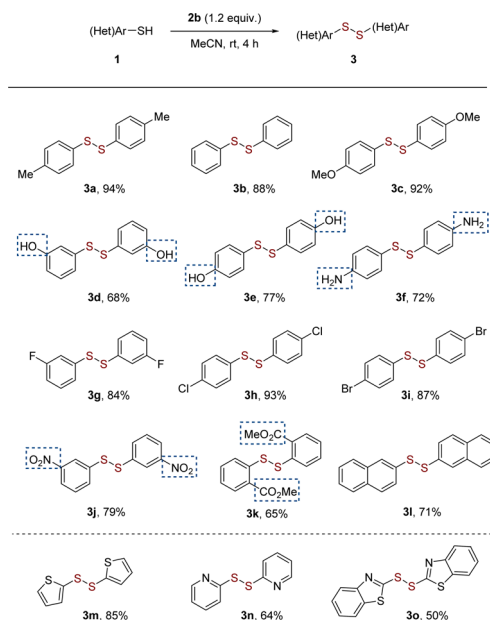
## Results and discussion

We mainly investigated several *N*-anomeric amide reagents to achieve S–S bond formation of 4-methylbenzenethiol **1a** to yield disulfide **3a** (Table 1). The reaction did not occur in the absence of the *N*-anomeric amide **2a** (Table 1, entry 1). Using MeCN as a solvent at room temperature, the addition of *N*-anomeric amide **2a** resulted in a successful formation of disulfide to give a desired product **3a** in 58% yield (entry 2). The increase of **2a** loading (1.2 equiv.) resulted in significantly increased yields (73%, entry 3), but the doubling of it did not give better reaction outcome (70%, entry 4). While the extension or reduction of reaction time led to a decreasing product yields in this reaction (entries 5 and 6). Another *N*-anomeric amide bearing electron-deficient substituent (**2b**) showed outstanding reactivity and smoothly afforded the corresponding disulfide **3a** in superior yield (94%) (entry 7). However, the anomeric amide bearing electron-rich substituent (**2c**) was used to give inferior efficiency (entry 8). Screening of different solvents revealed the initially used MeCN was the best (entries 9–11).

Having established the optimum reaction conditions, we then investigated the scope of substrate, such as aryl and

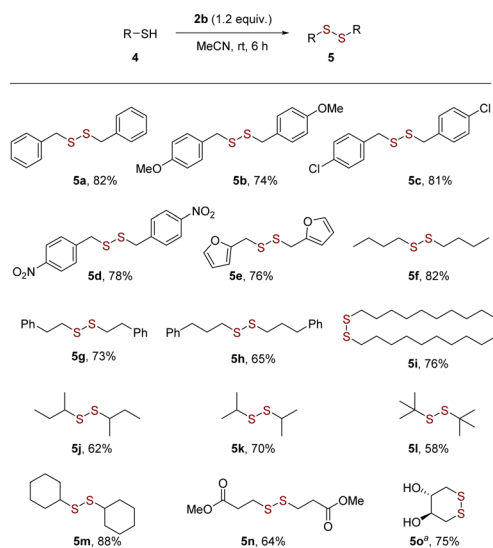
heteroaryl thiols **3a–3o** (Scheme 2). Substituted thiophenols bearing weak-electron-donating group (EDG) of *para*-Me and strong EDG of *para*-OMe reacted to yield the corresponding disulfides in excellent yields of 92–94% without obvious substituted effect (Scheme 2, **3a–3c**). For *meta*- and *para*-substitutions of unprotected hydroxyl group on aromatic moiety were well tolerated, leading to products in 68–77% yields (Scheme 2, **3d** and **3e**). It is noteworthy that the homocoupling of functionalized aromatic thiols with amino group worked well to produce desired disulfide **3f** in moderate yield. It follows that thiols have more reactivity than amines even in the presence of nitrogen-atom deletion reagent in this reaction.<sup>17b</sup> The substrates bearing electron-withdrawing groups (EWGs), such as F, Cl, Br and NO<sub>2</sub> groups, also provided mediocre to satisfactory yields (up to 93%) (Scheme 2, **3g–3j**). The bulky group *ortho*-CO<sub>2</sub>Me group induced a slight drop in the yield of 65% (Scheme 2, **3k**). 2-Naphthyl disulfide (**3l**) with an extended  $\pi$ -framework was synthesized in 71% yield. Extending the scope beyond the aforementioned substrates, the protocol effectively facilitated the conversion of heteroaromatic (**3m** to **3o**) thiols into their respective disulfides.

Encouraged by the results, the substrate scope was further expanded to benzylic and aliphatic thiols **5a–5o** (Scheme 3). The reported aerobic approaches to symmetrical disulfides always suffered from limited substrate scopes or unavailable catalysts. To our delight, the present strategy showed a broad substrate scope in the synthesis of both dibenzyl and dialkyl disulfides (Scheme 3). Compared to aryl thiols, the dimerization of aliphatic thiols to disulfides was more difficult and require longer reaction time. The benzylic thiols bearing electron-donating groups or electron-withdrawing groups, such as OMe, Cl and NO<sub>2</sub> groups, also smoothly to afford disulfides **5a–**

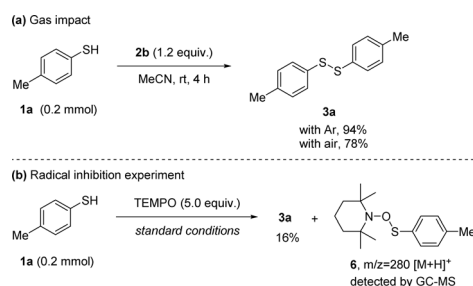


Scheme 2 Substrate scope of aryl and heteroaryl thiols **1**. Reaction conditions: **1** (0.2 mmol) and **2b** (0.24 mmol), MeCN (1 mL), room temperature, 4 h, under argon atmosphere. Isolated yields.

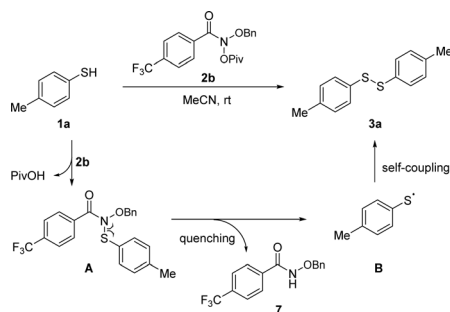




**Scheme 3** Substrate scope of benzylic and aliphatic thiols **4**. Reaction conditions: **4** (0.2 mmol) and **2b** (0.24 mmol), MeCN (1 mL), room temperature, 6 h, under argon atmosphere. Isolated yields. <sup>a</sup>**2b** (0.48 mmol), MeCN (4 mL).



**Scheme 4** Mechanistic studies.



**Scheme 5** Plausible mechanism.

**5d** in high yields. The heterocycle thiols bearing furan (**5e**) exhibited good coupling ability with acceptable product yields (76%). The straight-chain and branched aliphatic thiols (**5f–5m**) were also suitable reaction partners. The reaction has good compatibility with ester group (Scheme 3, **5n**). Notably, the successful intramolecular coupling of unprotected 1,4-dithiothreitol afforded *trans*-4,5-dihydroxy-1,2-dithiane **5o** with 75% yield, which revealed the potential in chemoselective construction of disulfide bridge in nature product synthesis.

To gain further understanding about the reaction mechanism, control experiments were conducted. First, performing the reaction under air atmosphere instead of Ar resulted in product **3a** with reduced yield, implying that the processes were partly restrained by the introduced air (Scheme 4(a)). Next, a radical capture experiment was performed and 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) was used as a radical scavenger in the reaction.<sup>21</sup> When using 5.0 equiv. of TEMPO, the yield of **3a** was decreased from 94% to 16%, the product yields were sufficiently suppressed, indicating radical intermediates were involved in the reaction. Then, we analyzed both reaction mixtures *via* GC-MS (Scheme 4(b)). The corresponding adduct 2,2,6,6-tetramethyl-1-((*p*-tolylthio)oxy)piperidine **6** of the thiyl radical with TEMPO was identified,<sup>22</sup> illustrating that thiyl radical was produced during the reaction process. These results demonstrate our hypothesis that the *N*-anomeric amide under room temperature is able to generate a thiyl radical.

Based on the aforementioned experimental results and preceding reports,<sup>17</sup> a mechanistic scenario has been proposed to rationalize the observed reaction outcomes, as illustrated in Scheme 5. The reaction commences with the nucleophilic substitution of thiol **1b** with Levin's reagent **2b**, producing intermediate **A**. Subsequently, **A** undergoes homolysis of C–N bond to generate the *p*-toluenethiyl radical **B** and *N*-benzyloxy 4-(trifluoromethyl)benzoyl amide **7**. Finally, the self-coupling of *p*-toluenethiyl radical **B** forms target product *p*-tolyl disulfide (**3a**).

## Conclusions

In summary, we have developed a mild and convenient method for the S–S bonds homocoupling reaction of aromatic, hetero-aromatic, benzylic and aliphatic thiols, offering a valuable complement to established methods for aerobic oxidation. This reaction is promoted by the readily accessible Levin's reagent in absence of metal and additive under room temperature. Significantly, this is the first application of *N*-anomeric amide in the synthesis of disulfides. Experimental mechanistic investigations have unveiled a radical mechanism in this reaction. Given the potential applications of the products and the synthetic practicality of the protocol, we anticipate that this method will find valuable utility in the realms of organic synthesis and medicinal chemistry.

## Experimental section

### General procedure for the synthesis of disulfides

To a solution of thiol **1a** (0.2 mmol) and *N*-anomeric amide **2b** (0.24 mmol) in dry MeCN (1.0 mL) under argon atmosphere at room temperature. After 4 h the reaction was completed, the reaction was quenched with H<sub>2</sub>O (5 mL), and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, washed with saturated brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and then concentrated under vacuum. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 50/1–10/1) on silica gel to afford the desired product **3a**. The products obtained were known compounds and were identified by NMR spectroscopy.



## Spectroscopy data of disulfides

**1,2-Di-*p*-tolylidysulfane (3a).** Followed the general procedure of disulfide synthesis, product obtained as a white solid (46 mg, yield 94%),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 7.38 (d,  $J = 7.6$  Hz, 4H), 7.09 (d,  $J = 7.6$  Hz, 4H), 2.31 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 137.41, 133.86, 129.77, 128.50, 21.04. MS (ESI+): calculated  $\text{C}_{14}\text{H}_{14}\text{S}_2$  as 246.05,  $[\text{M}^+]$  found 246.04  $m/z$ .

**1,2-Diphenyldisulfane (3b).** Followed the general procedure of disulfide synthesis, product obtained as a white solid (38 mg, yield 88%),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 7.49 (d,  $J = 7.6$  Hz, 4H), 7.28 (t,  $J = 7.2$  Hz, 4H), 7.20 (t,  $J = 7.2$  Hz, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 136.99, 129.03, 127.47, 127.12. MS (ESI+): calculated  $\text{C}_{12}\text{H}_{10}\text{S}_2$  as 218.02,  $[\text{M}^+]$  found 218.10  $m/z$ .

**1,2-Bis(4-methoxyphenyl)disulfane (3c).** Followed the general procedure of disulfide synthesis, product obtained as a yellow oil (51 mg, yield 92%),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 7.39 (d,  $J = 7.6$  Hz, 4H), 6.83 (d,  $J = 7.6$  Hz, 4H), 3.79 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 159.85, 132.60, 128.35, 114.56, 55.30. MS (ESI+): calculated  $\text{C}_{14}\text{H}_{14}\text{O}_2\text{S}_2$  as 278.04,  $[\text{M}^+]$  found 278.00  $m/z$ .

**3,3'-Disulfaneyldiphenol (3d).** Followed the general procedure of disulfide synthesis, product obtained as a yellow solid (34 mg, yield 68%),  $^1\text{H}$  NMR (400 MHz, DMSO):  $\delta$  (ppm) 9.77 (s, 2H), 7.18 (t,  $J = 8.0$  Hz, 2H), 6.92 (d,  $J = 12.0$  Hz, 4H), 6.68 (d,  $J = 8$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO):  $\delta$  (ppm) 158.16, 136.76, 130.30, 117.25, 114.62, 113.04. MS (ESI+): calculated  $\text{C}_{12}\text{H}_{10}\text{O}_2\text{S}_2$  as 250.01,  $[\text{M}^+]$  found 249.96  $m/z$ .

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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