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Unsymmetrical Disulfides Synthesis *via* Cs_2CO_3-Catalyzed Three-Component Reaction in Water

Dungai Wang, [a] Yuanji Gao, [a] Yunli Tong, [b] Mingteng Xiong, [a] Xiao Liang, [a] Heping Zhu, [a] and Yuanjiang Pan [a] *

[a] Department of Chemistry, Zhejiang University, Hangzhou 310027, China. Email: panyuanjiang@zju.edu.cn
[b] Zhejiang East Asia Pharmaceutical Co., Ltd, Zhejiang, China.

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Abstract: An unsymmetrical disulfides synthesis by Cs_2CO_3-catalyzed three-component coupling reaction of thioacetate, sodium thiosulfate, and benzyl halide in water is described. The safe, stable, and non-toxic $Na_2S_2O_3$ was invoked as the sulfur-source, successfully avoiding the odor generation in the process of S-S bond formation. A wide range of substrate suitability and appropriate functional group tolerance were observed for the transformation. Notably, the approach reported here was compatible with various biomolecules including glucose, coumarin, and quinolinone.

Keywords: Three-component reaction; Nucleophilic substitution; Water; Green Chemistry; Synthetic methods

The disulfide bond (S-S) formed between cysteine side chains during oxidative protein folding is a biologically important motif that plays a unique role in the stability, activity, and protease resistance of proteins.[1] In addition, the disulfide bond is also present in medicinal agents such as disulfiram, lipoic acid, and fursultiamine, and natural products such as gliotoxin, and the S-S framework is responsible for critical pharmaceutical activities (Figure 1).[2] Meanwhile, the disulfide bond is usually utilized for drug delivery and release systems because it can be cleaved during the intracellular thiol-redox process.[3] As green catalysts, disulfides can efficiently induce various reactions under mild conditions in organic synthesis,[4] including the iodination of electron-rich aromatic compounds[4a], and aerobic oxidation[4b]. Additionally, the sulfur-sulfur scaffold is a ubiquitous subunit in food chemistry.[5] Therefore, the development of efficient strategies for constructing the S-S bond has attracted intense attention in organic chemistry.[6-12]

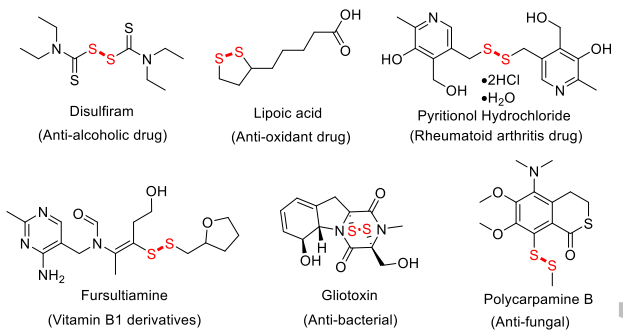

Figure 1. Disulfides in Drug and Natural Product.

Traditionally, symmetrical disulfides are readily obtained *via* the oxidative process of the same thiols,[7] and the preparation of unsymmetrical disulfides is realized by constructing the S-S bond or S-C bond with diverse substrates. The S_N2 substitution between the derivative thiols (Scheme 1a)[8] and cross-coupling between different thiophenols (Scheme 1a)[9] are typical strategies for the construction of the S-S bond, in which an unpleasant odor is unavoidable. Metal-catalyzed disulfide exchange reaction provides another approach for the synthesis of unsymmetrical disulfane by building a new disulfide bond (Scheme 1a).[10] Moreover, a two-step method for forming the S-S bond through a sulfur redox process was reported in 2015 (Scheme 1a).[11] The synthesis of unsymmetrical disulfides by constructing S-C bonds is an emerging strategy developed in recent years that adopts disulfide reagents (RSSLG) to supply the "disulfur" directly (Scheme 1b).[12] Despite significant progress, this protocol still suffers from some restrictions such as the cumbersome pre-preparation process of disulfide substrates. In addition, tetrasulfides can also be used to

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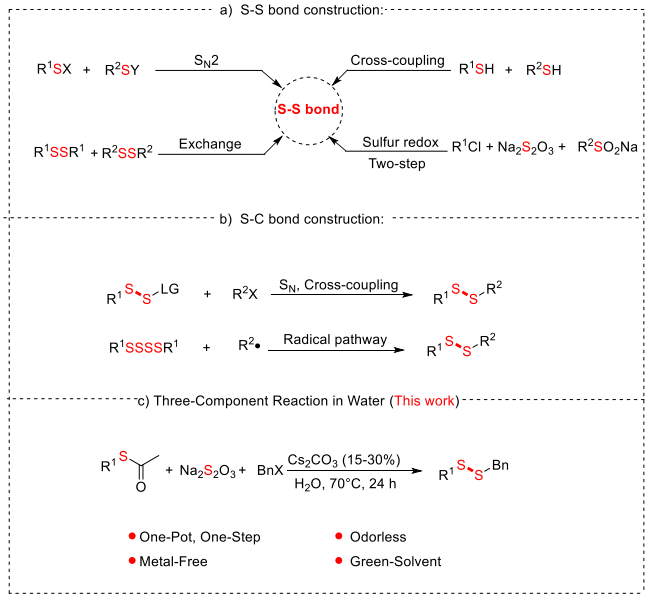
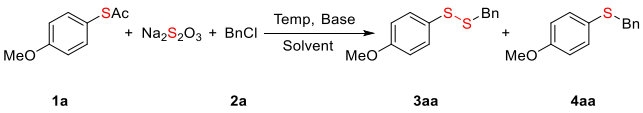


Scheme 1. Synthesis of Unsymmetrical Disulfides.

form S-C bonds through a free radical substitution (Scheme 1b).[13] Inorganic sulfur salts such as Na_2S, $Na_2S_2O_3$, and KSCN are safe, odorless and inexpensive and have been successfully used in the synthesis of organosulfide compounds.[14] As a green reaction media, water attracted much interest due to its ready availability, and lack of toxicity and flammability.[12i, 15] Herein, we report a facile method for the synthesis of unsymmetrical disulfides *via* a Cs_2CO_3-catalyzed three-component reaction of thioacetate, $Na_2S_2O_3$, and benzyl halide in water (Scheme 1c).

We carried out an optimization study for the model reaction utilizing S-(4-methoxyphenyl) ethanethioate (**1a**), $Na_2S_2O_3$, and benzyl chloride (**2a**) (Table 1). Unfortunately, the target product **3aa** was not observed under the promotion of equivalent Cs_2CO_3 when the model reaction proceeded in organic media (DMSO and DMF), but the yields of by-product **4aa** exceeded 50% (entries 1–2). Considering the solubility of inorganic salts, water was used to replace the organic solvents. To our delight, the desired compound **3aa** was acquired in 68% yield under the same condition, but 10% of **4aa** was still present (entry 3). A further investigation indicated that the amount of the base was a crucial regulating factor for the production of **3aa** and **4aa**. Significant declines were observed for the by-product with the decrease of Cs_2CO_3, while the yields of **3aa** were improved (entries 4–11). Meanwhile, **3aa** was provided with 73% isolated yield when 15% of Cs_2CO_3 was used as the additive (entry 7). Because the base was essential for the target compound formation (entries 10–11), various strong and weak bases including 1,8-

Table 1. Optimization Study[a].



1a **2a** **3aa** **4aa**

Entry	Temp (°C)	Base (%)	Solvent (mL)	**3aa** Yield [b]	**4aa** Yield [b]
1	70	Cs_2CO_3 (100)	DMSO	0	54%
2	70	Cs_2CO_3 (100)	DMF	0	56%
3	70	Cs_2CO_3 (100)	H_2O	68%	10%
4	70	Cs_2CO_3 (200)	H_2O	58%	13%
5	70	Cs_2CO_3 (50)	H_2O	58%	0
6	70	Cs_2CO_3 (20)	H_2O	74%	0
7	70	Cs_2CO_3 (15)	H_2O	76% (73) [c]	0
8	70	Cs_2CO_3 (10)	H_2O	72%	0
9	70	Cs_2CO_3 (5)	H_2O	41%	0
10[d]	70	/	H_2O	29%	0
11	90	/	H_2O	28%	0
12	70	DBU (15)	H_2O	69%	0
13	70	TEA (15)	H_2O	53%	0
14	70	DIEA (15)	H_2O	60%	0
15	70	K_2CO_3 (15)	H_2O	70%	0
16	70	Na_2CO_3 (15)	H_2O	63%	0
17	70	KH_2PO_4 (15)	H_2O	58%	0
18	70	KOH (15)	H_2O	39%	0
19	100	Cs_2CO_3 (15)	H_2O	66%	0
20	50	Cs_2CO_3 (15)	H_2O	71%	0
21[e]	70	Cs_2CO_3 (15)	H_2O	80%	0
22[e f]	**70**	**Cs_2CO_3 (15)**	**H_2O**	**85% (80)[c]**	**0**
23[e, g]	70	Cs_2CO_3 (15)	H_2O	ND	90%
24[e, h]	70	Cs_2CO_3 (15)	H_2O	ND	ND

[a] **1a** (0.25 mmol, 1 equiv), **2a** (0.375 mmol, 1.5 equiv), $Na_2S_2O_3$ (0.5 mmol, 2 equiv), air, solvent (1.5 mL), 24 h. [b] Yields were determined by ^1H NMR with an internal standard (toluene). [c] Isolated yield on 0.5 mmol scale based on **1a**. [d] 48 h. [e] $Na_2S_2O_3$ (0.75 mmol, 3 equiv). [f] 2.5 mL H_2O. [g] Na_2S replace $Na_2S_2O_3$. [h] Thiourea replace $Na_2S_2O_3$. ND: not detected.

diazabicyclo [5.4.0] undec-7-ene (DBU, entry 12), and triethylamine (TEA, entry 13) were screened, and Cs_2CO_3 was proved to be the most suitable catalyst (entries 7, 12–18). Temperatures above or below 70°C led to inferior yields of **3aa** (entries 19–20), possibly because the heat affects the formation of the intermediate Bunte salt. Similarly, to stimulate the generation of the intermediate salt, the dosage of $Na_2S_2O_3$ was increased. Finally, optimal conversion was achieved with three equivalents of $Na_2S_2O_3$, 15% of Cs_2CO_3 as catalyst in 2.5 mL water (entry 22). Na_2S and thiourea were further investigated (entries 23–24), but the desired transformation was not achieved.

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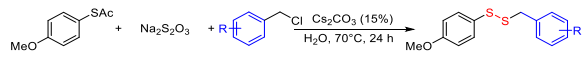
With the optimized conditions in hand, we first assessed the substrate scope of this one-pot reaction on various benzyl halides **2a**-**2q** (Table 2). We found that unsubstituted benzyl halide **2a** reacted smoothly with **1a** and $Na_2S_2O_3$ (**3aa**). Similarly, benzyl bromide also

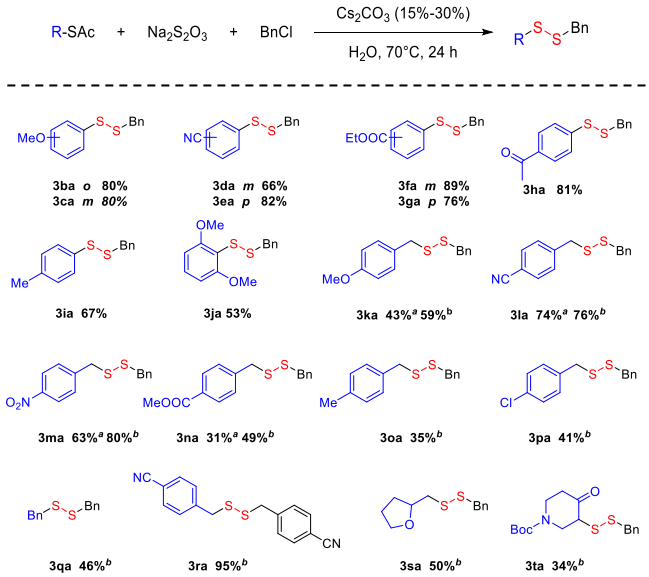
Table 2. Substrate Scope for Benzyl halides[a].



[a]**1** (0.5 mmol, 1 equiv), **2** (0.75 mmol, 1.5 equiv), $Na_2S_2O_3$ (1.5 mmol, 3 equiv), air, H_2O (5 mL), Cs_2CO_3 (0.075 mmol, 15%), 24 h. Isolated yield based on **1**. [b]benzyl bromide instead of benzyl chloride.

participated in the reaction and provided first corresponding product in 73% yield. The *ortho*, *meta*, and *para*-substituted benzyl halides bearing electron-donating groups (Me, *t*-Bu) gave the desired products (**3ab**–**3ae**) in high yields (69–84%). In addition, unsymmetrical disulfides **3af**-**3ap** were also obtained with good yields (66–90%). Functional groups,

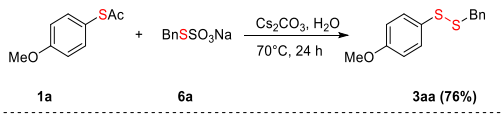
Table 3. Substrate Scope for Thioacetates [a].



[a]**1** (0.5 mmol, 1 equiv), **2** (0.75 mmol, 1.5 equiv), $Na_2S_2O_3$ (1.5 mmol, 3 equiv), air, H_2O (5 mL), Cs_2CO_3 (0.075 mmol, 15%), 24 h. [b]Cs_2CO_3 (0.15 mmol, 30%). Isolated yield based on **1**.

including halogen (**3af**-**3ak**), trifluoromethyl (**3al**), cyano (**3am**, **3an**), nitro (**3ao**), and ester group (**3ap**), were well compatible under optimal conditions. Notably, **2i** with steric hindrance could be well carried out to offer the target **3ai** with 74% isolated yield. Furthermore, 1-chloromethyl naphthalene (**2q**) reacted with **1a** and $Na_2S_2O_3$ in water, and provided **3aq** with 78% yield. Next, we evaluated the scope of thioacetates (Table 3). Substantial amounts of the aryl-benzyl unsymmetrical disulfides were accessed with

excellent yields (**3ba**-**3ja**). The three-component reaction efficiency was not affected by the electronic properties of the substituents. Electron-withdrawing group (cyano, ester, *etc.*) or electron-donating group (methyl) substituted aryl thioacetates successfully reacted with **2a** and $Na_2S_2O_3$. However, the di-substituted thioacetate **1j** led to only 53% yield (**3ja**), suggesting that steric hindrance affected the transformation. A further investigation of benzyl-benzyl type disulfides indicated that 15% of the catalyst did not promote the substrate to fully participate in the reaction, and therefore, it is necessary to increase the Cs_2CO_3 amount to 30% (**3ka**-**3ra**). Notably, symmetrical products were also obtained from moderate to high yields with this one-pot reaction in an aqueous medium (**3qa**-**3ra**). Additionally, heterocyclic and alkyl substrates were also suitable for this conversion with moderate yields (**3sa**-**3ta**).



Scheme 2. Control Experiment.

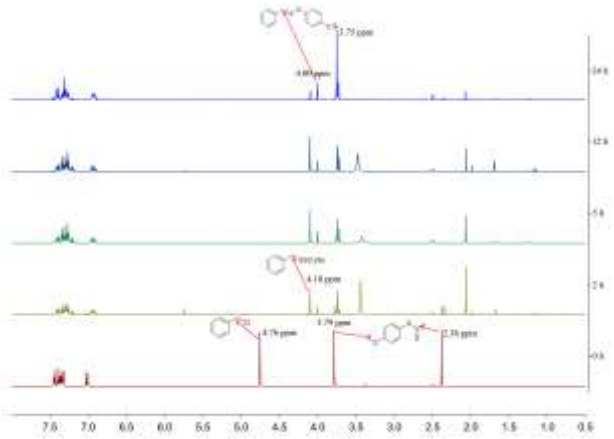
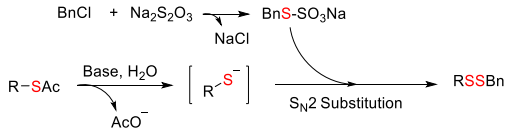


Figure 2. ^{1}H NMR Tracking Experiments.

Control and track experiments were performed to investigate the possible reaction mechanism (Scheme 2). 76% yield of **3aa** was obtained under standard conditions when Bunte salt **6a** replaced BnCl and $Na_2S_2O_3$ (Scheme 2), implying that Bunte salt was present during the transformation as an intermediate.

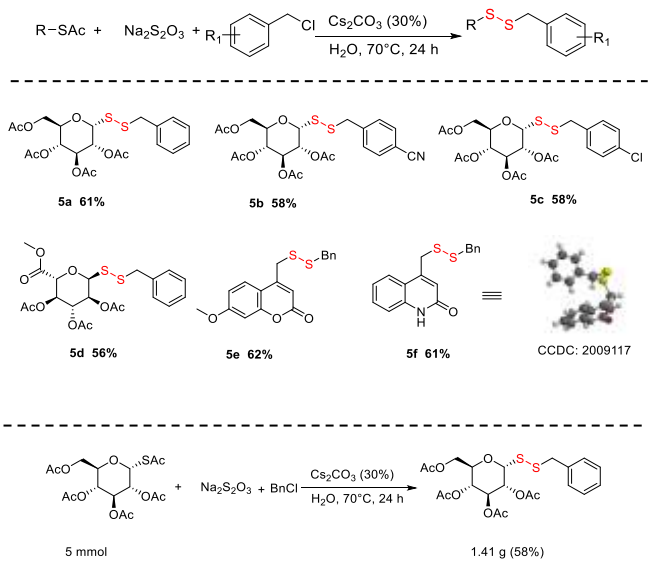
^{1}H NMR spectra (Figure 2, DMSO-d_6, δ 0.5–8.0 ppm) clearly indicated the capability of this method for the production of the intermediate product Bunte salt (4.10 ppm) and the conversion process to the target product (4.00 ppm, 3.75 ppm).



Scheme 3. Proposed Reaction Mechanism.

A proposed reaction mechanism is outlined in Scheme 3 based on the results of control and track experiments. Initially, thioacetate is hydrolyzed to generate a thiolate ion RS^- in the presence of base and water.[16] On the other hand, Bunte salt $BnSSO_3Na$ is rapidly generated from BnCl and $Na_2S_2O_3$ (Figure 2),[14d, 17] is attacked by the thiolate ion RS^- and releases the target product RSSBn.

Table 4. Late-Stage Modification of Natural Product [a].



[a] **1** (0.5 mmol, 1 equiv), **2** (0.75 mmol, 1.5 equiv), $Na_2S_2O_3$ (1.5 mmol, 3 equiv), air, H_2O (5 mL), Cs_2CO_3 (0.15 mmol, 30%), 24 h. Isolated yield based on **1**.

Subsequently, the robustness of this strategy was demonstrated by the late-stage biological scaffolds modification (Table 4). Glycosylated thioacetates easily participated in the Cs_2CO_3-catalyzed one-pot reaction and provided unique glycosyl disulfides in water with good yields (**5a**-**5d**). Fortunately, in this simple method, gram-scale preparation of glycosylated disulfide was also achieved (1.41 g, 58%). Meaningfully, the modification of coumarin and quinolinone that form the cores of many drugs were also achieved to deliver **5e** and **5f** in moderate yields (62% and 61%), and the structure of **5f** was characterized using single-crystal X-ray diffraction[18].

In summary, we have developed a simple and green carbonate salt catalyzed three-component strategy to synthesize unsymmetrical disulfanes in water. Cheap and stable $Na_2S_2O_3$ and thioacetate used as sulfur sources successfully avoid the odor and homo-coupling in the traditional S-S bonds construction. Broad substrate scope and excellent functional group tolerance are achieved in this aqueous one-pot reaction. Moreover, the realization of the late-stage modification of biomolecules, and particularly the preparation of glycosyl disulfide on gram-scale, means that this facile protocol will be attractive for industry.

Experimental Section

Procedure for the synthesis of unsymmetrical disulfides: A mixture of S-(4-methoxyphenyl) ethanethioate (**1a,** 0.5 mmol), $Na_2S_2O_3$ (1.5 mmol), benzyl chloride (**2a,** 0.75 mmol), Cs_2CO_3 (15 mol%), and H_2O (5 mL) was placed into a test tube equipped with a magnetic stirring bar. The resulting mixture was stirred at 70°C in the air for 24 h. Extract 3 times with ethyl acetate (5 mL × 3), organic solvent was removed, and the residue was separated by column chromatography to give a pure sample by using mixed petroleum ether/ethyl acetate 50:1 (v/v) as an eluent to afford the desired product **3aa**. The remaining substituted disulfides were prepared in a similar manner.

Procedure for the ^{1}H NMR tracking experiments: 4 groups of 0.1 mmol scale reactions were performed in parallel, and the reactions were stopped at 2 h, 5 h, 12 h, and 24 h respectively. Water was removed under reduced pressure, DMSO-d_6 was used as a solvent to dissolve the residue, and detection was carried out with ^{1}H NMR.

Acknowledgements

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[18] CCDC 2009117 (**5f**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.