Chinese Chemical Letters 33 (2022) 4269–4272

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

NFSI-catalyzed S–S bond exchange reaction for the synthesis of unsymmetrical disulfides

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ARTICLE INFO

Article history:
Received 17 October 2021
Revised 26 December 2021
Accepted 28 December 2021
Available online 2 January 2022

Keywords:
Metal-free
S–S bond exchange
NFSI
Unsymmetrical disulfides
Organic synthesis

ABSTRACT

The metal-free S–S bond exchange reaction of symmetrical disulfides catalyzed by NFSI is described. This novel protocol provides a facile and efficient approach to accessing important unsymmetrical disulfides. Furthermore, this strategy could also be utilized in the late-stage functionalization of amino acids, drugs, and natural products. The broad substrate scope, good functional group tolerance and easy accessibility of catalyst indicate that this strategy affords a green and practical complementary method to various unsymmetrical disulfides.

Unsymmetrical disulfides, as important organic sulfur-containing motifs, are widely present in drugs and natural products (Fig. 1a) [1–4]. Furthermore, unsymmetrical disulfides also play a vital role in life science [5]. Due to their importance in different fields, the synthesis of unsymmetrical disulfides has received extensive attention. Previous reports on the construction of such skeletons are divided into two categories: one is S–S bond formation [6–25] and the other is C–S bond formation [26–33]. The S–S bond-forming methods (Fig. 1b) usually include the direct oxidative dehydrogenation coupling [6–14], S_N2 replacement [15–20], and exchange reaction [21–25]. While the C–S bond formation strategy (Fig. 1c) generally involves the cross-coupling or nucleophilic substitution of masked disulfuration reagents [26–32], and the radical substitution of tetrasulfides [33]. Among these, disulfide exchange reaction has been regarded as one of the most direct and effective approaches to construct unsymmetrical disulfides [21–25]. Furthermore, disulfide exchange process, one of the most popular dynamic covalent chemistries, has also been widely applied in biological and material systems [34,35]. Some early pioneering works by utilizing Rh catalysts have proven to be successfully. Yamaguchi group developed a Rh-catalyzed disulfide exchange strategy to access unsymmetrical disulfides [21,22]. Since then, only a few methodologies on disulfide exchange process have been reported [23–25]. Therefore, the development of a facile, efficient and green method to access a variety of unsymmetrical disulfides is still challenging [36].

In the past decade, *N*-fluorobenzene sulfonimide (NFSI) has attracted much attention due to its widely applications in fluorination and amination reactions [37,38]. However, the use of NFSI as the organic catalyst to achieve the disulfide metathesis has not been reported. In our continuing efforts for developing novel strategies for sulfur-containing compounds [39–46], herein, we disclosed a NFSI-catalyzed S–S bond exchange reaction to access various important unsymmetrical disulfide derivatives (Fig. 1d).

The investigation began with the disulfide exchange reaction between 1,2-bis(4-methoxyphenyl)disulfane **1a** and dimethyl disulfide **2a** in the presence of NFSI (10 mol%) at 50 °C (Table 1). To our delight, the initial reaction solvent screening indicated that DCE (1,2-dichloroethane) was the optimal solvent, providing the desired product **3a** in 83% isolated yield (Table 1, entries 1–7). The subsequent examination of different F^+ reagents, including Selectfluor and NFPT, showed that none of other F^+ reagents provided better results than NFSI (Table 1, entries 8 and 9). It should be noticed that the yield of desired product **3a** could not be improved any more by increasing or decreasing the amounts of NFSI (Table 1, entries 10–12). Furthermore, this disulfide exchange process at room temperature (25 °C) also provided the desired product **3a** in 61% isolated yield (Table 1, entry 13). Finally, only trace of product **3a** could be detected when NFSI was absent (Table 1, entry 14).

With the optimized reaction conditions in hand, we explored the exchange reaction between diaryl and dialkyl disulfide. As

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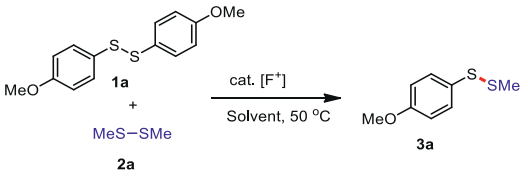
https://doi.org/10.1016/j.cclet.2021.12.073
1001-8417/

Table 1
Optimization of reaction conditions.[a]



Entry	F⁺ reagent (mol%)	Solvent	Yield (%)[b]
1	NFSI (10)	MeCN	77
2	NFSI (10)	DCM	73
3	NFSI (10)	DCE	83
4	NFSI (10)	THF	trace
5	NFSI (10)	PhMe	50
6	NFSI (10)	DMF	13
7	NFSI (10)	DMSO	trace
8	Selectfluor (10)	DCE	70
9	NFPT (10)	DCE	65
10	NFSI (20)	DCE	78
11	NFSI (5)	DCE	80
12	NFSI (2.5)	DCE	68
13[c]	NFSI (10)	DCE	61
14	–	DCE	trace

Selectfluor: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate). NFPT: 1-fluoropyridinium triflate. NFSI: *N*-fluorobenzenesulfonimide.

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), F^+ reagent, solvent (2.0 mL), 50 °C, 4 h.

[b] Isolated yields (based on 0.4 mmol of **3a**).

[c] Room temperature (25 °C).

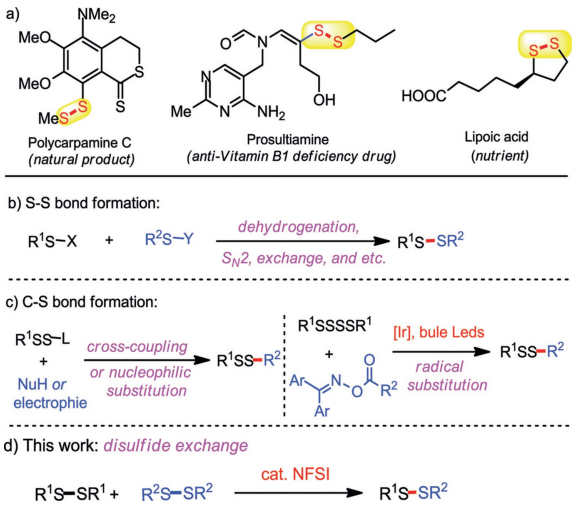
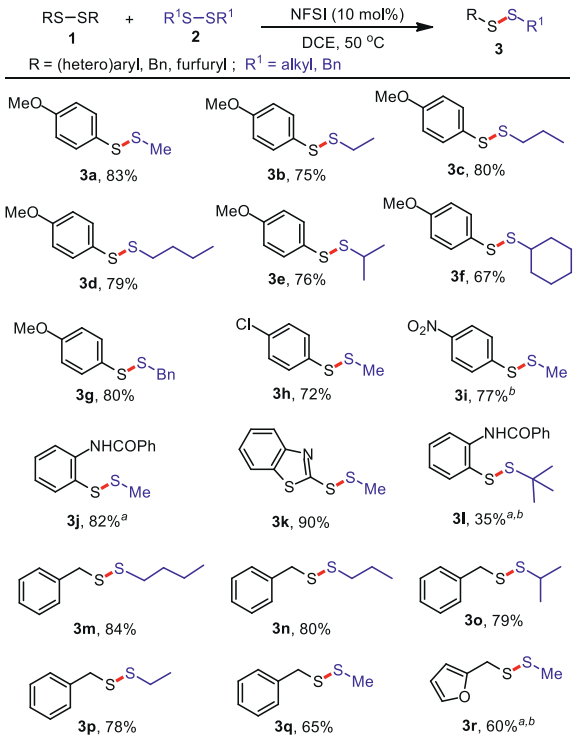


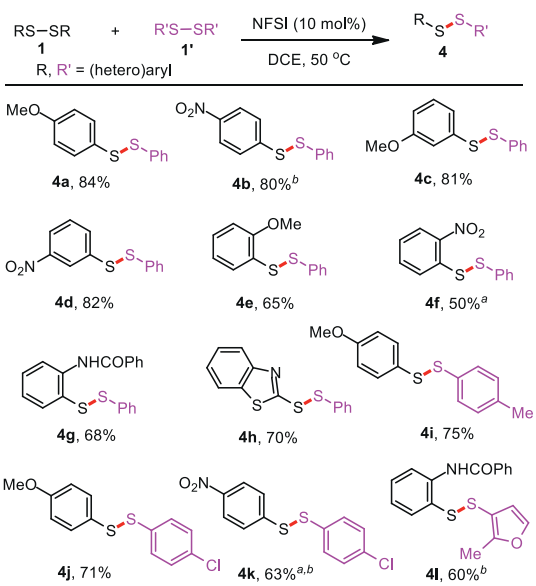
Fig. 1. Selected important unsymmetrical disulfide derivatives and strategies for unsymmetrical disulfide derivatives.

shown in Scheme 1, the dialkyl disulfides bearing different substituent groups, including methyl, ethyl, *n*-Pr, *n*-Bu, *i*-Pr, cyclopentyl and benzyl, were smoothly converted to the corresponding products **3a–3g** in good yields. Reactions of dimethyl disulfide with different di(hetero)aryl disulfides also generated the desired products **3h–3k** in good yields. Furthermore, two different hindered disulfides afforded the desired product **3l** in 35% yield. In addition, two different kinds of symmetrical dialkyl disulfides were used to exchange with each other, providing unsymmetrical dialkyl disulfides **3m–3r** in moderate to good yields.

The substrate scope of previous reports mainly focused on preparing unsymmetrical dialkyl or aryl-alkyl disulfides [21,22]. In this protocol, the generality of the exchange reaction for preparing different unsymmetrical diaryl disulfides was carefully examined in Scheme 2. Diaryl disulfides **1** bearing electron-withdrawing

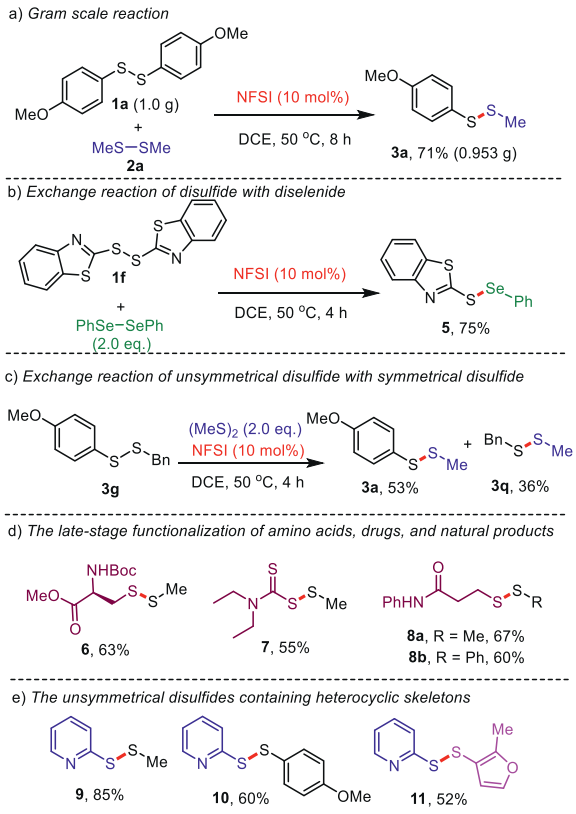


Scheme 1. Substrate scope for unsymmetrical aryl-alkyl and dialkyl disulfides. Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), NFSI (0.02 mmol), DCE (2.0 mL), 50 °C, 4 h. Isolated yields (based on 0.4 mmol of **3**), [a]NFSI (0.04 mmol). [b]80 °C.

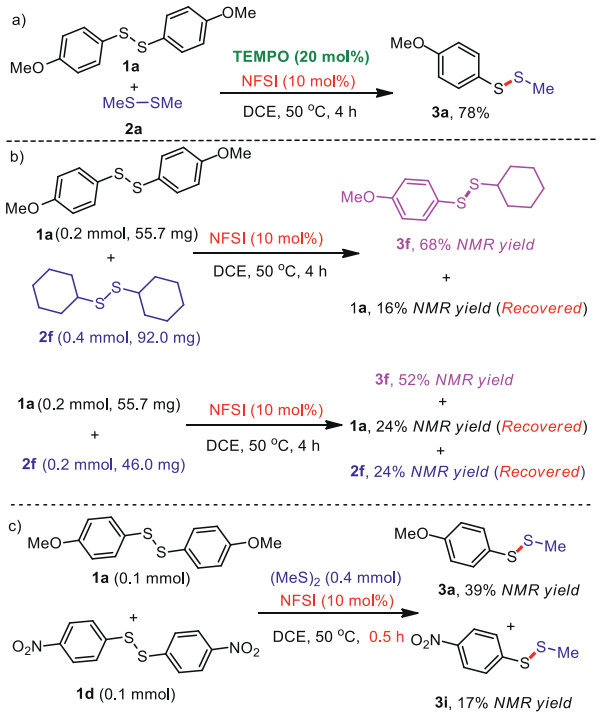


Scheme 2. Substrate scope for unsymmetrical diaryl disulfides. Reaction conditions: **1** (0.2 mmol), **1′** (0.4 mmol), NFSI (0.02 mmol), DCE (2.0 mL), 50 °C, 4 h. Isolated yields (based on 0.4 mmol of **4**). [a]NFSI (0.04 mmol). [b]80 °C.

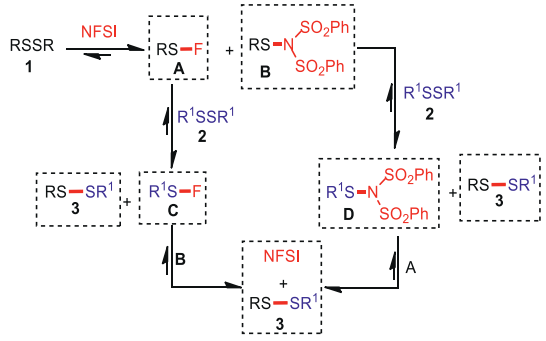
or electron-donating groups at the *para*-, *meta*- and *ortho*-position on the phenyl ring were well compatible with PhSSPh under the current catalytic conditions, affording the desired products **4a–3g** in moderate to good yields. Next, the exchange reaction of 1,2-bis(benzo[*d*]thiazol-2-yl)disulfane and diphenyl disulfide also led to the corresponding product **4h** in 70% yield. In addition, diaryl disulfides **1′** with different substituent groups (Me and Cl) smoothly coupled with 1,2-bis(4-methoxyphenyl)disulfane to produce the desired products **4i** and **4j** in good yields. Furthermore, two substrates with different electron-withdrawing groups (NO_2



Scheme 3. Further exploration of the reaction scope.



Scheme 4. The control experiments.



Scheme 5. The plausible reaction mechanism.

and Cl) also generated the desired product **4k** in 63% yield. Notably, the desired product **4l** was isolated in 60% yield, indicating that the steric hindrance of aryl disulfides has a slight effect on this catalytic system.

To study the synthetic utility of this catalytic system, further exploration of the reaction scope was carried out in Scheme 3. A gram-scale reaction was performed to afford the product **3a** with 71% isolated yield (Scheme 3a). Furthermore, the exchange reaction between **1f** and $(PhSe)_2$ provided the desired product **5** in 75% yield (Scheme 3b). Next, unsymmetrical disulfide **3g** could react with $(MeS)_2$ to produce two different unsymmetrical disulfides **3a** and **3q** in 53% and 36% yields, indicating that the aryl-alkyl disulfide formation may be preferred than alkyl-alkyl disulfide formation (Scheme 3c). To our delight, this protocol could also be utilized in the late-stage functionalization of amino acids, drugs, and natural products (Scheme 3d). Amino acid derivatives $(Boc\text{-}L\text{-}Cys\text{-}OMe)_2$ produced the desired product **6** in 63% yield. The disulfiram drug could be functionalized to synthesize the product **7** in moderate yield. In addition, dithiodipropionamides, as important intermediates for the synthesis of biological activity isothiazolone derivatives, were transformed to the corresponding products **8a** and **8b** in 67% and 60% yields, respectively. Finally, both unsymmetrical disulfides containing pyridine moieties **9**,**10** and bishetroaryl disulfide **11** were prepared in moderate to good yields under the optimized reaction conditions.

To obtain some insights into this reaction, some control experiments have been carried out (Scheme 4). The radical trapping experiment was performed and this result suggests that a single electron transfer (SET) may not be involved in this catalytic process (Scheme 4a). In addition, substrate proportion control experiments between **1a** and **2f** indicate that an excess of one partner can enhance the efficiency of reaction (Scheme 4b). Intermolecular competition results between **1a** and **1d** reveal that the reaction rate of electron-rich substrate is superior to electron-deficient substrate (Scheme 4c).

Based on the control experiments and previous reports [23,24,47–53], a plausible catalytic cycle is depicted in Scheme 5. It is believed that this catalytic cycle is a reversible process in the presence of NFSI. First, treatment of RSSR **1** with a catalytic amount of NFSI catalyst generates the intermediate **A** and **B**. Then, the subsequent exchange reaction between intermediate **A** and R^1SSR^1 **2** affords the intermediate **C** and desired unsymmetrical disulfide **3**. Meanwhile, the intermediate **B** can also react with R^1SSR^1 **2** to provide intermediate **D** and product **3**. Finally, the reaction of intermediate **B** and **C** (or intermediate **D** and **A**) produces the desired product **3** and regenerates the NFSI catalyst again. It is worth mentioning that this process can also be initiated from the reaction of NFSI with R^1SSR^1 **2**.

In summary, we have demonstrated a novel disulfide exchange reaction for the efficient construction of unsymmetrical disulfides by employing NFSI as the catalyst. To the best of our knowledge, this is the first NFSI-catalyzed disulfide exchange process. Moreover, this green strategy also provides a complementary approach to diverse unsymmetrical disulfides, which of them are important skeletons of amino acids, drugs and natural products. Further study

on the reaction mechanism and application is ongoing in our laboratories.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (Nos. 21572026, 21702019), Postgraduate Research & Practice Innovation Program of Jiangsu Province (No. SJCX20_0952), Advanced Catalysis and Green Manufacturing Collaborative Innovation Center, Changzhou University. We also acknowledge the analytical testing support from Analysis and Testing Center, NERC Biomass of Changzhou University.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.12.073.

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