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Metal-Free Synthesis of Thiosulfonates via Insertion of Sulfur Dioxide

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Abstract. A simple and catalyst-free strategy was developed for the synthesis of unsymmetrical thiosulfonates using readily available DABCO·$(SO_2)_2$ as a solid and bench-stable sulfur dioxide surrogate. The corresponding thiosulfonates were obtained through a radical pathway with good functional group tolerance. This strategy offers a promising synthesis method for the construction of diverse and useful thiosulfonates in the field of synthetic and pharmaceutical chemistry and extends the number of still limited sulfur dioxide fixation strategies.

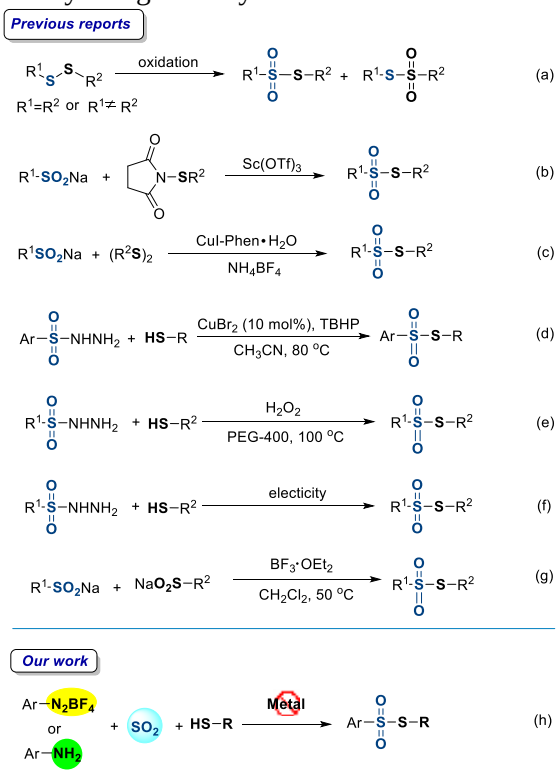
Keywords: metal-free; thiosulfonate; sulfur dioxide; organosulfur compound; thiol

Introduction

Organosulfur compounds are prevalent in natural products and subunits of diverse bioactive compounds; they are also widely used in materials chemistry.[1] Therefore, development of efficient and practical methods for the synthesis of sulfur-containing compounds is still an important topic in green organic chemistry.[2] Recently, C–S bond-forming reactions have been extensively studied, and tremendous achievements have been made.[3] Unfortunately, synthetic methods for the construction of heteroatom–S bonds have received less attention.[4] Thiosulfonate derivatives are an important class of organic compounds containing S-S bond motif. Importantly, these compounds show various biological activities such as antiviral, antimicrobial, antibacterial, and antifungicidal activities.[5] In addition, thiosulfonates are also widely used as versatile sulfenylating reagents in many organic transformations.[6] For these reasons, considerable efforts have been devoted to the development of new and efficient methods for the construction of thiosulfonates. However, a literature survey indicates that synthetic methods for the construction of thiosulfonate skeletons are rather limited. Classical methods for the synthesis of thiosulfonate compounds mainly focus on the oxidation of disulfides to the corresponding thiosulfonates, affording a mixture of isomeric products when $R^1 \neq R^2$ (Scheme 1a).[7] Several other methods including oxidation of thiosulfinates,[8] reaction of potassium thiosulfonates with diaryliodonium salts,[9] and reduction of sulfonyl chlorides[10] have also been developed for the formation of unsymmetrical thiosulfonates. Despite the success of these methods, the use of toxic and unstable sulfenylating agents, unavailability of starting materials, and low yield of these reactions have limited their wide applications. Therefore, more efficient, sustainable, and practical methods should be developed.

In 1972, Bentley and co-workers attempted the direct conversion of sodium sulfinates and alkyl disulfides to thiosulfonates. Unfortunately, a stoichiometric amount of $AgNO_3$ is required, and the substrates are limited to sodium methanesulfinates. [11] In 2012, Chen's group reported an elegant $Sc(OTf)_3$-catalyzed sulfonylation of sodium sulfinates with *N*-(organothio)succinimides to afford unsymmetrical thiosulfonates in ionic liquids (ILs) and water (Scheme 1b).[12] In 2015, Taniguchi developed an elegant copper-catalyzed sulfonylation of disulfides with sodium sulfinates to access unsymmetrical thiosulfonates under mild conditions (Scheme 1c).[13] In 2017, Zou and co-workers developed an efficient method for the synthesis of thiosulfonates via copper-catalyzed TBHP-mediated radical cross-coupling of sulfonylhydrazides and thiols (Scheme 1d).[14] Very recently, Dong and An described a green and eco-friendly method for the synthesis of unsymmetrical

thiosulfonates from sulfonyl hydrazides and disulfides using PEG-400 as a solvent (Scheme 1e).[15] Notably, during the submission process of our manuscript, Chen and co-workers reported an elegant electrochemical transformation of sulfonyl hydrazides and thiols into thiosulfonates (Scheme 1f).[16a] Hao and Wang's group also developed an efficient method for the synthesis of symmetrical/unsymmetrical thiosulfonates via $BF_3{\cdot}OEt_2$-mediated disproportionate coupling reaction of sodium sulfinates (Scheme 1g).[16b] Although great achievements have been made in this field, it is still essential to develop new strategies to prepare unsymmetrical thiosulfonates with high efficiency and generality.

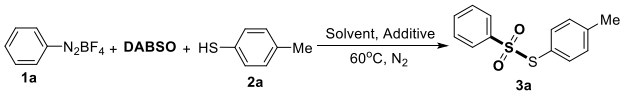


Scheme 1. Strategies for the synthesis of thiosulfonates.

Sulfur dioxide (SO_2), an abundant industrial emission product, is one of the main sources of air pollution. There is no doubt that directly fixation of sulfur dioxide into small molecules leading to sulfone-containing compounds is promising and attractive in organic chemistry. DABSO (1,4-diazabicyclo[2.2.2]octane *bis*(sulfur dioxide) adduct) as an air-stability solid sulfur dioxide surrogate has been successfully introduced by Willis and co-workers. As a pioneer work, Willis's group initially developed an elegant palladium-catalyzed aminosulfonylation method for the synthesis of aryl *N*-aminosulfonamides using DABSO as a sulfur dioxide surrogate.[17] In recent years, many sulfonylation reactions have been developed for the synthesis of sulfones, *N*-aminosulfonamides, sulfamides, and sulfonamides by using DABSO as the sulfur dioxide (SO_2) source.[18] Aryldiazonium salts are well-known arylation reagents widely used in various organic transformations [19] In 2014, Wu's group found that the combination of aryldiazonium salts and DABSO produces an arylsulfonyl radical that can be further transformed to *N*-aminosulfonamides by reacting with hydazines under metal-free conditions [20] Afterwards, sulfur dioxide insertion reactions based on aryldiazonium salts have been extensively studied, and many elegant studies have been reported.[21] Inspired by these excellent results, we envisioned that unsymmetrical thiosulfonates could be constructed starting from readily available aryldiazonium salts, DABSO, and thiols via a radical pathway with the insertion of sulfur dioxide (Scheme 1h). In continuation of our research in the synthesis of sulfur-containing compounds, herein, we report a simple and efficient method for the formation of unsymmetrical thiosulfonates using DABSO as a sulfur dioxide surrogate under metal-free conditions.

Results and Discussion

Table 1. Optimization of the reaction conditions[a]



Entry	Solvent	Additive	Yield [b] (%)
1	DMSO	None	19
2	DMF	None	11
3	DCE	None	40
4	Toluene	None	38
5	1,4-Dioxane	None	20
6	CH_3CN	None	35
7	DCE	None	Trace[c]
8	DCE	None	36[d]
9	DCE	None	40[e]
10	DCE	None	41[f]
11	DCE	None	41[g]
12	DCE/DMSO (1:1)	None	0
13	DCE/MeCN (1:1)	None	0
14	DCE/Toluene (1:1)	None	47
15	DCE/Toluene (3:1)	None	48
16	DCE/Toluene (4:1)	None	52
17	DCE/Toluene (5:1)	None	40
18	DCE/Toluene (1:2)	None	31
19	DCE/Toluene (4:1)	DABCO	16[h]
20	**DCE/Toluene (4:1)**	**TFA**	**64[i]**
21	DCE/Toluene (4:1)	$BF_3{\cdot}Et_2O$	52[j]
22	DCE/Toluene (4:1)	$FeCl_3$	21
23	DCE/Toluene (4:1)	$ZnCl_2$	30
24	DCE/Toluene (4:1)	TFA	53[k]
25	DCE/Toluene (4:1)	TFA	57[l]
26	DCE/Toluene (4:1)	TFA	59[m]
27	DCE/Toluene (4:1)	TFA	56[n]

[a] Reaction conditions: phenyldiazoniumtetrafluoroborate **1a** (0.6 mmol), DABSO (0.4 mmol), 4-methylbenzenethiol **2a** (0.4 mmol), solvent (3 mL), at 60 °C, reaction time (30 min). [b]Isolated yield. [c]At room temperature. [d]At 50 °C. [e]At 70 °C. [f]At 80 °C. [g]At 90 °C. [h]DABCO (0.4mmol). [i]TFA (0.4mmol). [j]$BF_3{\cdot}Et_2O$ (0.4 mmol). [k]TFA (0.08mmol). [l]TFA (0.2mmol). [m]TFA (0.6mmol). [n]TFA (0. 8mmol).

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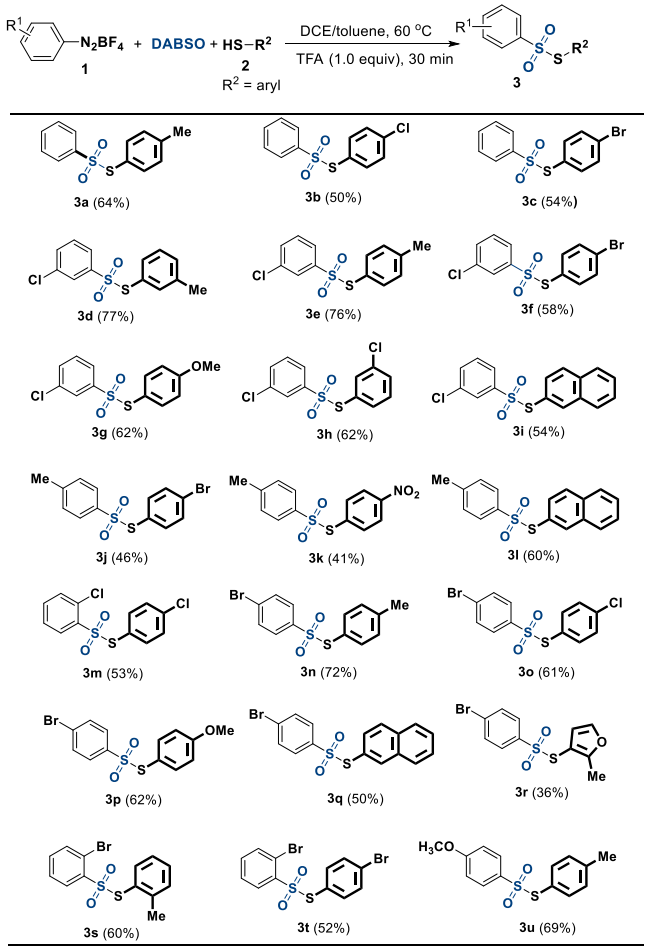
As shown in Table 1, phenyldiazoniumtetrafluoroborate (**1a**), DABSO, and 4-methylbenzenethiol (**2a**) were selected as model substrates to explore the optimal reaction conditions, including solvents, additives, and reaction temperature under nitrogen atmosphere. Six solvents such as DMSO, DMF, DCE, toluene, 1,4-dioxane, and CH_3CN were evaluated at at 60 °C, DCE provided *S*-(*p*-tolyl) benzenesulfonothioate (**3a**) in 40% yield. Furthermore, various temperatures were evaluated (Table 1, entries 3, 7–11) using DCE as the solvent, 60 °C was found to be the best choice. Notably, a higher reaction temperature did not increase the conversion efficiency. In addition, mixed solvents were evaluated; to our delight, the yield of product reached 52% when the volume ratio of DCE/Toluene was 4:1 (Table 1, entry 16). Finally, DABCO (1,4-Diazabicyclo[2.2.2]octane), TFA (Trifluoroacetic acid), $BF_3{\cdot}Et_2O$, $FeCl_3$ and $ZnCl_2$ were used as the additives to further optimize the efficiency of this transformation. Gratifyingly, DABCO (1,4-diazabicyclo[2.2.2]octane; triethylenediamine) was not suitable for this transformation, but 1 equiv of TFA (trifluoroacetic acid) produced the desired thiosulfonate in 64% yield (Table 1, entry 20). Changing the content of trifluoroacetic acid in the reaction system could not significantly increase the yield of the reaction (Table 1, entries 24-27).

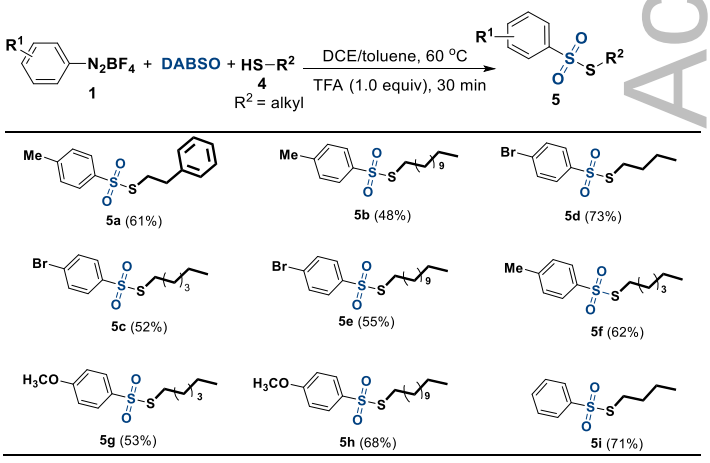
Table 2. Substrate scope of phenyldiazonium tetrafluoroborates with aryl thiols[a], [b]



[a] Reaction conditions: phenyldiazonium tetrafluoroborates **1** (0.6 mmol), DABSO (0.4 mmol), thiophenol **2** (0.4 mmol), TFA (0.4 mmol), DCE (2.4 mL), toluene (0.6 mL), reaction time (30 min). [b] Isolated yield.

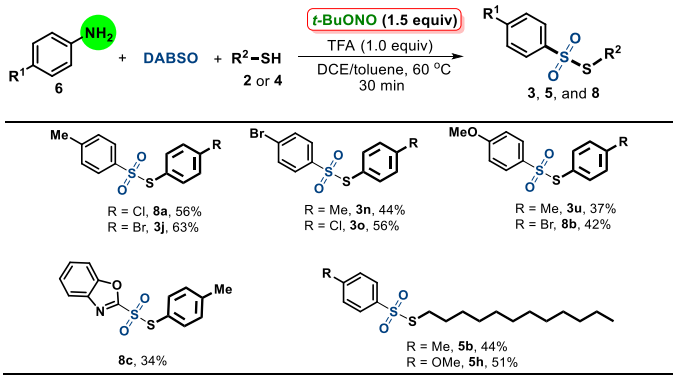
With the optimized conditions in hand, we next began to explore the scope and generality of the sulfur dioxide insertion process, and the results are summarized in Table 2. To our delight, diverse phenyldiazonium tetrafluoroborates bearing either electron-donating groups (-Me, -OMe), or electron-withdrawing groups (-Cl, -Br, and $-NO_2$), smoothly reacted with thiols, affording the corresponding thiosulfonates in moderate yields. Additionally, the steric effect was evaluated and found that this transformation is not sensitive to steric hindrance, Phenyldiazonium tetrafluoroborates bearing -Me, -Cl, or -Br at different positions efficiently reacted with thiols (**3m**, **3n**, **3k**, and **3s**). Furthermore, the effects of substituent on thiols were also investigated. Interestingly, the thiols bearing an electron-donating group showed a slightly higher reactivity than those bearing an electron-withdrawing group (**3a**, **3d**, **3f**, and **3k**). Naphthyl group was compatible in this reaction with a moderate reactivity (**3i**, **3l**, and **3q**). Notably, a strong electron-withdrawing group such as nitro was also tolerated under the reaction standard conditions (**3k**). Gratifyingly, a heterocycle thiol such as 2-methylfuran-3-thiol afforded the desired product in 36% yield (**3r**). Subsequently, the coupling reactions of phenyldiazonium tetrafluoroborates with alkyl thiols were evaluated (Table 3). Luckily, the more challenging and simple linear alkyl thiols showed good reactivity,[10–14] affording the corresponding thiosulfonates in moderate-to-good yields, irrespective of the chain length (**5a**–**5i**). Although thiols exhibited high reactivity, unfortunately, phenols and aliphatic alcohols were poor substrates, and no desired products were obtained under the standard conditions. The domino multicomponent reactions tolerated some functional groups such as C–Cl bonds, C–Br bonds, methyl group, nitro group, and methoxy group, leaving ample room for further modification.

Table 3. Substrate scope of phenyldiazonium tetrafluoroborates with alkyl thiols [a], [b]



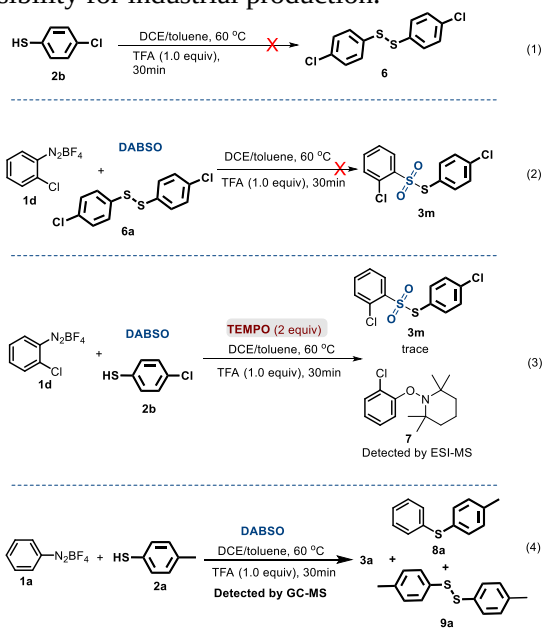
[a] Reaction conditions: phenyldiazonium tetrafluoroborates **1** (0.6 mmol), DABSO (0.4 mmol), thiols **4** (0.4 mmol), TFA (0.4 mmol), DCE (2.4 mL), toluene (0.6 mL), reaction time (30 min). [b] Isolated yield.

Table 4. One pot synthesis of thiosulfonates from arylamines [a], [b]



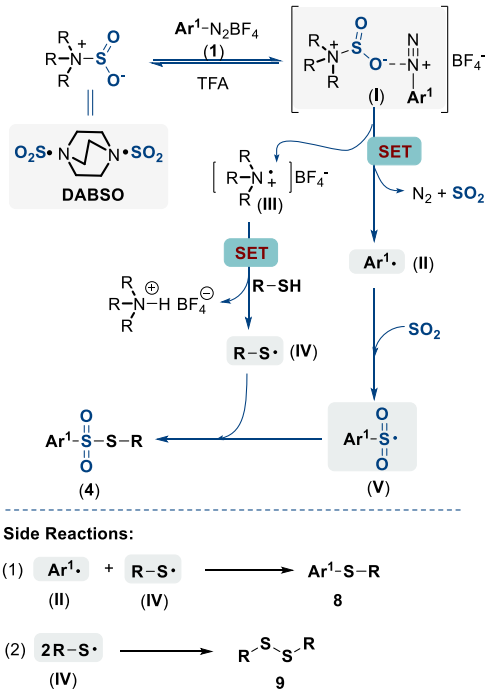
[a] Reaction conditions: aniline **6** (0.6 mmol), DABSO (0.4 mmol), thiols **2** or **4** (0.4 mmol), *t*-BuONO (0.9 mmol), TFA (0.4mmol), DCE (2.4 mL), toluene (0.6 mL), reaction time (30 min). [b]Isolated yield.

To simplify the process of this SO_2 fixation method, we tried to replace phenyldiazonium tetrafluoroborates by directly using arylamines as the substrates (Table 4). Luckily, we found that in the presence of 1.5 equiv of *t*-BuONO, the reaction efficiently occurred at 60°C, and the desired products were obtained in moderate yields. Not only aryl thiols but also alkyl thiols were well tolerated in this reaction. To our delight, benzo[*d*]oxazol-2-amine also furnished the corresponding thiosulfonate **8c** in 34% yield, indicating that the developed metal-free sulfur dioxide insertion protocol can be applied to heterocyclic phenyldiazonium tetrafluoroborates and anilines. This simplified approach provides a possibility for industrial production.



Scheme 2. Control experiments

In order to explore the possible mechanism of this sulfur dioxide insertion pathway, several control experiments were conducted (Scheme 2). When 4-chlorobenzenethiol (**2b**) was added independently under the standard conditions, no 1,2-bis(4-chlorophenyl)disulfane (**6**) was observed [eq (1), Scheme 2]. Furthermore, treatment of 2-chlorophenyldiazoniumtetrafluoroborate (**1d**), DABSO with 1,2-bis(4-chlorophenyl)disulfane (**6**) under the standard conditions, no desired product was obtained [eq (2), Scheme 2]. These results indicated that disulfides might not be intermediates for this reaction. Additionally, When 2.0 equiv of TEMPO was added into the reaction solution, the formation of **3m** was completely suppressed, and the TEMPO-phenyl adduct **7** was detected by ESI-MS (see Fig. 1 in the ESI†), showing that aryl radical might be generated in this transformation.



Scheme 3. A proposed mechanism for the direct transformation

On the basis of the preliminary results above and together with the previous related reports,[19, 20] a plausible mechanism would be herein presented (Scheme 3). Initially, arydiazonium cation might react with DABCO·$(SO_2)_2$ to give the complex (**I**) which could be further transformed into the intermediate (**III**) and aryl radical (**II**) with releasing of N_2 and SO_2 through a single electron transfer (SET) pathway. Subsequently, the aryl radical would react with SO_2 to afford the sulfonyl radical (**V**). Meanwhile, the radical cation (**III**) abstracted hydrogen from thiols (**2**), leading to the thiyl radical (**IV**). Finally, sulfonyl radical (**V**) coupled with thiyl radical (**IV**), forming the coupling product (**4**). On the other hand, direct cross-coupling of aryl radical (**II**) with thiyl radical (**IV**) leads to thioether **8**, and homo-

coupling of thiyl radical (**IV**) gives sulfide **9** as by-products in the present transformation.

Conclusion

In conclusion, a novel and efficient protocol was developed for the synthesis of unsymmetrical thiosulfonates via three-component coupling reactions of phenyldiazonium tetrafluoroborates/arylamines, DABSO, and thiols. A series of unsymmetrical thiosulfonates were conveniently obtained through a radical pathway with excellent functional group tolerance. Notably, more challenging linear alkyl thiols showed good reactivity, affording the corresponding thiosulfonates in moderate-to-good yields. This easy and simple method provides a highly attractive approach for the synthesis of various unsymmetrical thiosulfonates, and it will broaden the strategies of sulfur dioxide fixation in the field of organic chemistry.

Experimental Section

General procedure for synthesis of compounds 3a-u: Under nitrogen atmosphere, phenyldiazonium tetrafluoroborates (0.6 mmol), DABSO (0.4 mmol), thiols (0.4 mmol), were introduced to a 20 mL oven-dried Schlenk tube. Then a solution of TFA (0.4 mmol), DCE (2.4 mL) and toluene (0.6 mL) were introduced by a injection syringe. The solution was stirred at 60°C for 30 min under N_2. After completion of the reaction, the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the corresponding products.

General procedure for synthesis of compounds 5a-i: Under nitrogen atmosphere, Arylamines (0.6 mmol), *t*-BuONO (0.6 mmol), DABSO (0.4 mmol), thiols (0.4 mmol), were introduced to a 20 mL oven-dried Schlenk tube. Then a solution of TFA (0.4 mmol), DCE (2.4 mL) and toluene (0.6 mL) were introduced by a injection syringe. The solution was stirred at 60 °C for 30 min under N_2. After completion of the reaction, the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the corresponding products.

Acknowledgements

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Metal-Free Synthesis of Unsymmetrical Thiosulfonates via Insertion of Sulfur Dioxide

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