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H_2O_2-Mediated Metal-free Protocol towards Unsymmetrical Thiosulfonates from Sulfonyl Hydrazides and Disulfides in PEG-400

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A green and practical protocol between sulfonyl hydrazides and disulfides was herein unveiled for the synthesis of unsymmetrical thiosulfonates with the assistance of H_2O_2 in PEG-400, releasing N_2 and H_2O as the byproducts. The efficient and compatible method was considered to take place in the absence of metallic catalysts through radical mechanism as determined by EPR analysis.

Organosulfur compounds[1] have drawn widespread attention for the past decades and the development of novel practise to obtain the compounds with diversifications stays still severely desired, which was driven by the screening process of the drug discovery. Thiosulfonate derivatives have caught exceptional interests for expressions of broad spectrum of pharmaceutical and clinical properties, like antiviral, fungicidal, antimicrobial and bactericidal.[2] Utilizations of the organosulfur compounds have been applied in polymer production and photographic processes.[3] Furthermore, as a electrophilic sulfenylating reagent used frequently in the communities of laboratory and industrial organic synthesis, thiosulfonates enjoyed the advantages including higher reactivity and better stability than frequently used sulfenyl halides.[4] For the variety of justifications, efforts have been continuously sacrificed for the preparations of the versatile molecules and plenty of methods have been successfully established. For instance, direct oxidation of mercaptans/thiols and disulfides have been achieved for the formation of symmetric thiosulfonates with the assistance of different oxidants such as chlorine,[5] CAN (ceric ammonium nitrate),[6] CrO_2 or $K_2Cr_2O_4$,[7] selectfluor,[8] $TiCl_4$[9] and etc.[10] Besides, reduction technologies were also introduced over sulfonyl chlorides[11] or sulfonyl hydrazides[12] for the formations of thiosulfonates. Despite of successful preparations unsymmetrical thiosulfonates, toxic reagents and harsh conditions were still demanded for the transformations.

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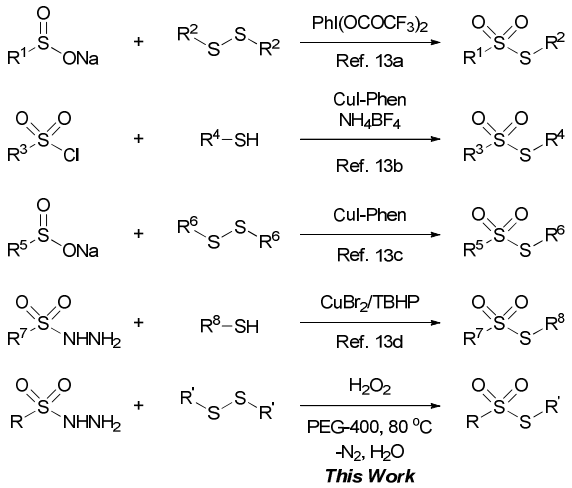
To improve the complexity of the modules, cross-coupling methodologies between sulfides/disulfides and sodium sulfinates, sulfonyl chlorides and thiols, sodium/potassium thiosulfonates with alkyl halides were turned to for the construction of unsymmetrical thiosulfonates (Scheme 1).[13] Halides wastes and participation of metallic catalysts still stayed unavoidable in the transformations, which was thought to be harmful to the environment. Within this context, we wish to disclose a green and eco-friendly technique for the preparation of unsymmetrical thiosulfonates from sulfonyl hydrazides and disulfides in the presence of H_2O_2 as oxidant and PEG-400 as solvent, emitting N_2 and H_2O as byproducts, which was in accordance with the concept of sustainability and environmental benignity.



Scheme 1. Protocols towards unsymmetrical thiosulfonates

The studies began with the reactions between *p*-tolyl sulfonyl hydrazide (**1a**) and diphenyl disulfide (**2a**) to obtain the optimal conditions, which were shown in Table 1. To our satisfactory, the combination of CuI/TBHP (*tert*-butyl hydroperoxide) rendered the occurrence of the cross-coupling reaction in DMSO (dimethyl sulfoxide), forming the desired *p*-

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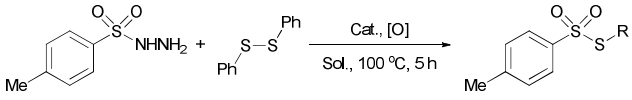
tolyl sulfonothioic phenyl ester (**3aa**) in 30% yield (entry 1). Addition of the ligand 1,10-phenanthroline increased the yield of **3aa** to 35% (entry 2). Other organic oxidants, for instance, DTBP (di-*tert*-butyl peroxide for entry 3), DCP (dicumyl peroxide for entry 4), AIBN (azodiisobutyronitrile for entry 5), DDQ (2,3-dicyano-5,6-dichlorobenzoquinone for entry 6), $PhI(OAc)_2$ (entry 7) failed to afford better performance to the reaction, for lower yields of **3aa** were observed, even only trace **3aa** was isolated in the presence of DDQ. However, beyond our expectations, inorganic oxidants increased the efficiency of the transformation and the employment of $K_2S_2O_8$ produced **3aa** in 33% yield, inferior to that H_2O_2 (2.0 equiv.) and O_2 (1.0 atm) did, which gave the desired **3aa** in 42% and 40% yields, respectively (entries 8 – 10). Generally, decomposition of sulfonyl hydrazide **1a**, which led to the formation of the symmetric thiosulfonate **3ab**, was observed in trace amount (footnote c), thus the combination of CuI/1,10-phenanthroline was ruled out to depress the decomposition of the hydrazide substrates. Despite reduced yield of **3aa** (38% for entry 11) was observed along with the absence of the CuI-catalysis, higher efficiency (72%) was detected when the loading of H_2O_2 increased to 7.0 equiv. (entry 12) and gratifyingly, no **3ab** was observed under the oxidative environment. Other solvents, like DMF (*N,N*-dimethyl formamide for entry 13), acetonitrile (entry 14), DCE (1,2-dichloroethane for entry 15), toluene (entry 16) and chlorobenzene (entry 17) were incapable to surpass the performance of DMSO, for a range of 45% - 65% yields of **3aa** were gained within 2 hours. Worthy of note, the coupling reaction took place in the alcoholic solvents, like methyl alcohol (entry 18) and ethyl alcohol (entry 19), generating the unsymmetrical thiosulfonate **3aa** in medium yields. PEG-400, which is famous for low toxicity, prevailed from all the solvents tested, for the highest 78% yield of **3aa** was successfully isolated (entry 20). However, the cross-coupling reaction was completely depressed when the reaction was carried out in H_2O (entry 21).

Table 1. Optimization of Reaction Conditions[a]



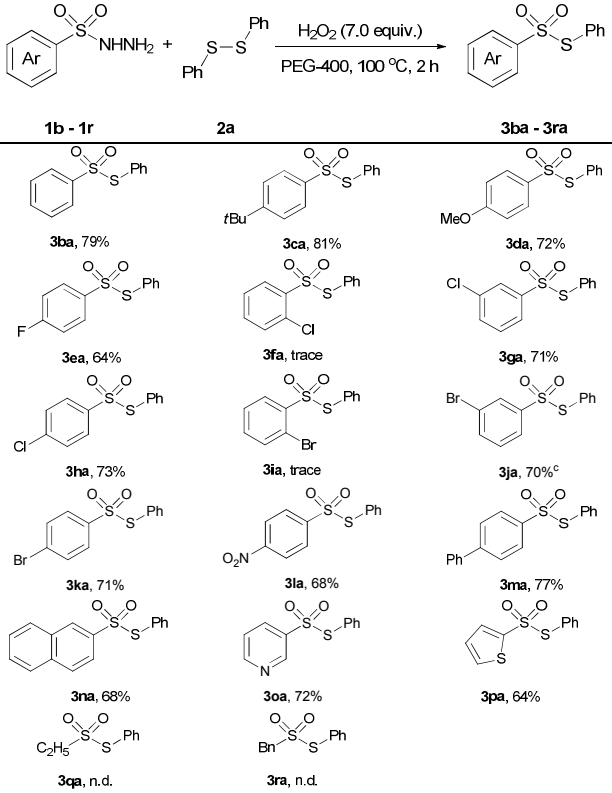
1a **2a** **3aa**, R = Ph; **3ab**: R = 4-tolyl

Entry	Cat.	[O] (equiv.)	Sol.	Yield (%)[b]
1[c]	CuI	TBHP (2.0)	DMSO	30
2[c,d]	CuI+1,10-phen	TBHP (2.0)	DMSO	35
3	CuI+1,10-phen	DTBP (2.0)	DMSO	28
4	CuI+1,10-phen	DCP (2.0)	DMSO	32
5	CuI+1,10-phen	AIBN (2.0)	DMSO	26
6	CuI+1,10-phen	DDQ (2.0)	DMSO	trace
7	CuI+1,10-phen	$PhI(OAc)_2$ (2.0)	DMSO	30
8	CuI+1,10-phen	$K_2S_2O_8$ (2.0)	DMSO	33
9	CuI+1,10-phen	H_2O_2 (2.0)	DMSO	42
10	CuI+1,10-phen	O_2 (1 atm)	DMSO	40
11	--	H_2O_2 (2.0)	DMSO	38
12	--	H_2O_2 (7.0)	DMSO	72
13	--	H_2O_2 (7.0)	DMF	65
14	--	H_2O_2 (7.0)	MeCN	60
15	--	H_2O_2 (7.0)	DCE	57
16	--	H_2O_2 (7.0)	$PhCH_3$	48
17	--	H_2O_2 (7.0)	PhCl	45
18	--	H_2O_2 (7.0)	MeOH	62
19	--	H_2O_2 (7.0)	*t*BuOH	68
20	--	H_2O_2 (7.0)	PEG-400	78
21	--	H_2O_2 (7.0)	H_2O	n.d.

[a]Conditions: **1a** (0.6 mmol), **2a** (0.3 mmol), Cat. (10 mol%), [O] (noted equivalent), sol. (1.0 mL) at 100 °C for 2 h. [b]Isolated yields. [c]trace **3ab** was observed in the Cu-catalysis. [d]1,10-phen stands for 1,10-phenanthroline.

With the optimal conditions established, the scope and limits of the arylsulfonyl hydrazides were evaluated in the metal-free system, as shown in table 2. Phenylsulfonyl hydrazide (**1b**) coupled with diphenyl disulfide (**2a**) readily under the oxidative conditions, furnishing the symmetric thiosulfonate **3ba** in almost the same yield (79%).

Table 2. Substrate Scope of Arylsulfonyl Hydrazides



[a]Conditions: **1** (1.0 mmol), **2a** (0.5 mmol), H_2O_2 (7.0 equiv.), PEG-400 (1.5 mL) at 100 °C for 2 h. [b]Isolated yields. [c]3 hours required for the completion of the reaction.

In the same pattern, electron-sufficient phenyl decorated sulfonyl hydrazide enjoyed the high efficiency in the transformation. For instance, 4-*tert*-butylphenyl sulfonyl

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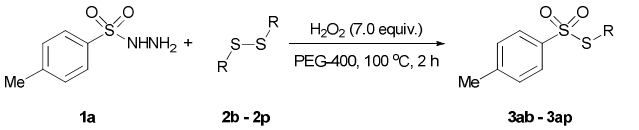
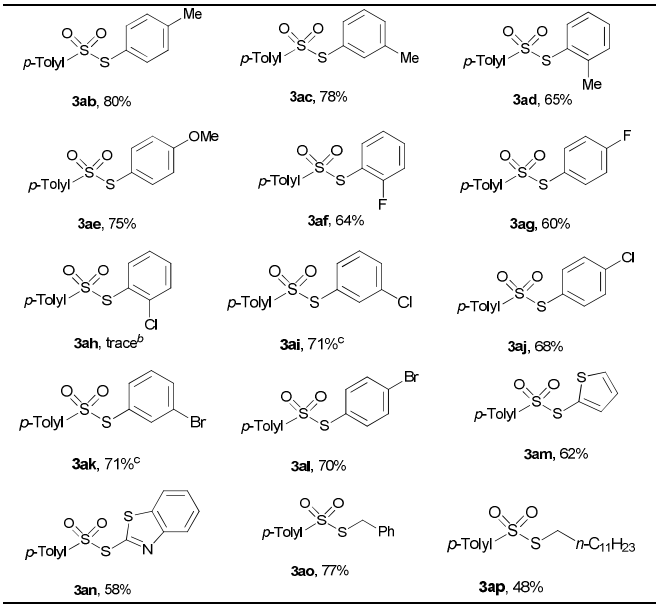
hydrazide (**1c**) and 4-methoxyphenyl sulfonyl hydrazide (**1d**) underwent the cross-coupling reaction, furnishing the desired unsymmetrical thiosulfonates **3ca** and **3da** in 81% and 72% yields, respectively. Halo groups were also found compatible in the system, but declined yields were also observed on the substrates. For example, 4-fluorophenyl sulfonyl hydrazide (**1e**) reacted with **2a** smoothly, offering the desired fluorinated thiosulfonate **3ea** in 64% yield. Positions of the halo groups affected the efficiency of the transformation significantly, which was exemplified by Cl and Br groups. 2-Chlorophenyl- (**1f**) and 2-bromophenyl sulfonyl hydrazides (**1i**) were incapable to couple with **2a** in high yields, probably due to the steric hindrance factors and only trace **3fa** and **3ia** were detected by GC-MS. However, 3-halophenyl- (Cl for **1g**, Br for **1j**) and 4-halophenyl sulfonyl hydrazides (Cl for **1h**, Br for **1k**) made the generation of the corresponding thiosulfonates **3ga**, **3ha**, **3ja** and **3ka** in yields from 70% to 73%. Traditional electron-withdrawing NO_2 group decorated sulfonyl hydrazide (**1l**) was also well-tolerated under the oxidative conditions, forming **3la** as the exclusive product in 68% yield. Polyaryl sulfonyl hydrazides, for example, 4-biphenyl- and 2-naphthyl-sulfonyl hydrazides (**1m** and **1n**) allowed the supply of unsymmetrical products **3ma** and **3na** in 77% and 68% yields, separately. It was noteworthy that heteroaryl groups-installed substrates were also successfully thioesterificated in the system, and the generations of 3-pyridinyl- and 2-thiophenyl sulfonothioic phenyl esters (**3oa** and **3pa**) were gratifyingly observed in 72% and 64% yields, respectively. Disappointingly, no reaction was detected upon the employments of the aliphatic sulfonyl hydrazides, such as ethyl- and benzyl sulfonyl hydrazides (**1q**, **1r**) in the system probably due to the decomposition of the substrates in the presence of H_2O_2.

The evaluation of the scope the substrate was successively extended on disulfides in the oxidative system, as shown in Table 3. Gratifyingly, di-*p*-tolyl disulfide (**2b**) coupled with *p*-tolyl sulfonyl hydrazide (**1a**) successfully, furnishing the desired *p*-tolyl sulfonothioic *p*-tolyl ester (**3ab**) in 80% yield. Variation of the methyl group on the disulfide substrate did not affect the efficiency of the transformation severely, for *p*-tolyl sulfonothioic *m*-tolyl ester (**3ac**) was generated in 78% yield. And *p*-tolyl sulfonothioic *o*-tolyl ester (**3ad**) was obtained in 65% yield probably due to the steric hindrance. Disulfide bearing electron-rich phenyl groups was also compatible in the system, which was exemplified by the generation of *p*-tolyl sulfonothioic *p*-methoxyphenyl ester (**3ae**) in 75% yield. Successively, haloed disulfides were also found tolerated under the oxidative conditions and the positions of the halo groups have did not perform significant influence on the efficiency of the protocol, either. As illustrated, *p*-tolyl sulfonothioic halophenyl esters **3af** – **3al** were favourably provided in 60 - 71% yields, except that **3ah**, which was isolated in trace amount likely because of the inductive effect of the Cl on the *ortho*-position. Furthermore, the compatibility of the diheteroaryl disulfides were also examined in the system and dithiophenyl disulfide (**2m**) and bis(2-benzothiazolyl) disulfide (**2n**) underwent the thioesterification reaction successfully with **1a**, forming the corresponding esters **3am** and **3an** in 62% and 58% yields, respectively. Beyond our expectations, di-arylmethyl disulfide such as dibenzyl disulfide (**2o**) and didodecyl disulfide (**2p**) allowed the formation of *p*-tolyl sulfonothioic benzyl ester (**3am**) and *p*-tolyl sulfonothioic dodecyl ester (**3ap**) in 77% and 48% yields, respectively.

Table 3. Substrate Scope of Disulfides[a]

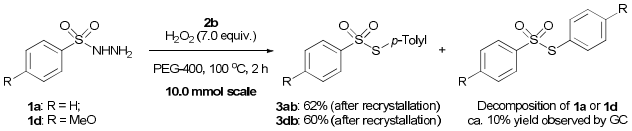


1a | 2b - 2p | 3ab - 3ap



[a]Conditions: **1** (1.0 mmol), **2a** (0.5 mmol), H_2O_2 (7.0 equiv.), PEG-400 (1.5 mL) at 100 °C for 2 h. [b]homo-coupling of **1a** was detected. [c]3 hours for the completion of the reaction.

Successively, scaled-up reactions were carried out to claim the potential industrious interests of the protocol. Sulfonyl hydrazides **1a** and **1d** reacted with disulfide **2b** respectively at 10.0 mmol scale, and the desired sulfonothioic esters **3ab** and **3db** were provided in 62% and 60% yields separately after recrystallization. However, symmetric sulfonothioic esters were also observed by GC-MS detections, which were likely generated by the decomposition of sulfonyl hydrazides **1a** or **1d** under the H_2O_2-mediated conditions.



Scheme 2. Scale-up Reactions

To determine the pathway of the facile reaction, TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl, 4.0 equiv.) was added to the mixture of **1a** and **2a** in H_2O_2/PEG-400, and the formation

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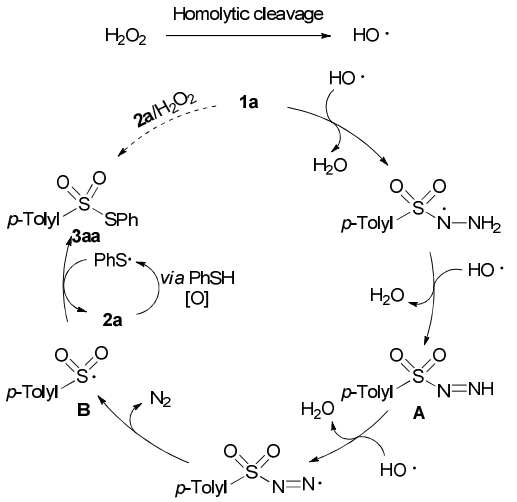
of **3aa** was completely depressed for no reaction was detected after 2 hours. To take a deeper insight into the mechanism, mixtures were subjected to the EPR (electron paramagnetic resonance) measurement to determine the species of the free radical particles. The value of g_e obtained from the mixtures of **1a**/H_2O_2/PEG-400, **2a**/H_2O_2/PEG-400 and **1a**/**2a**/H_2O_2/PEG-400 turned out to be 2.0086, 2.0072, 2.0075. Despite the boundary of the g_e values between the species *p*-tolyl$(O)_2S$· and PhS· stayed inexplicit, the result still ensured the fact that the formation of the radical particle was involved in the metal-free transformation. Thus, based on the results of EPR spectra and extensive documental investigation,[12,16] generally accepted mechanism involving the sulfonyl free radical particle was proposed with the reaction between **1a** and **2a** as shown in scheme 3. Initially, homolytic cleavage of H_2O_2 took place with heating, generating HO· particle easily for the next step. Successively, a sulfonyl diazene intermediate **A** was presumed to be formed from the interaction between *p*-tolyl sulfonyl hydrazide **1a** and HO· particle, releasing H_2O as byproduct. Thereafter, treatment of HO· and subsequent emission of N_2 rendered the formation of sulfonyl radical intermediate **B**, which was transformed into the desired thiosulfonate **3aa** in the presence of **2a**, and another radical PhS· for the generation of **2a** *via* PhSH for the next circle.



Scheme 3. Plausible Mechanism

Conclusions

It was summarized that a green and practical methodology towards unsymmetrical thiosulfonates was herein disclosed in the presence of H_2O_2 in PEG-400. The efficient and compatible transformation was proved to take place through the radical pathway without the participation of any transition metal-catalysts, providing a bright avenue towards the compounds of great significance. Additionally, further explorations of the molecules in the communities of synthetic and clinical chemistry are still on-going in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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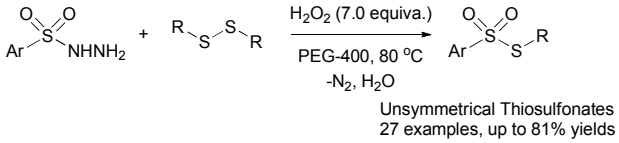

A serial of unsymmetrical thiosulfonates was successfully prepared from sulfonyl hydrazides and disulfides with the assistance of H_2O_2 (7.0 equiva.) in PEG-400 at 80 ^{o}C, releasing N_2 and H_2O as byproducts. EPR analysis proved the protocol proceeded through the free radical pathway and plausible mechanism was proposed.