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Authors: Julia Strehl and Gerhard Hilt

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Synthesis of Symmetrical and Unsymmetrical Thiosulfonates from Disulfides via Electrochemical Induced Disulfide Bond Metathesis and Site-Selective Oxidation

Julia Strehl and Gerhard Hilt*[a]

[a] MSc. J. Strehl, Prof. Dr. G. Hilt
Institut für Chemie, Universität Oldenburg, Carl-von-Ossietzky-Straße 9-11, 26111 Oldenburg, Germany
Fax: +49 441 798 3329
email: gerhard.hilt@uni-oldenburg.de

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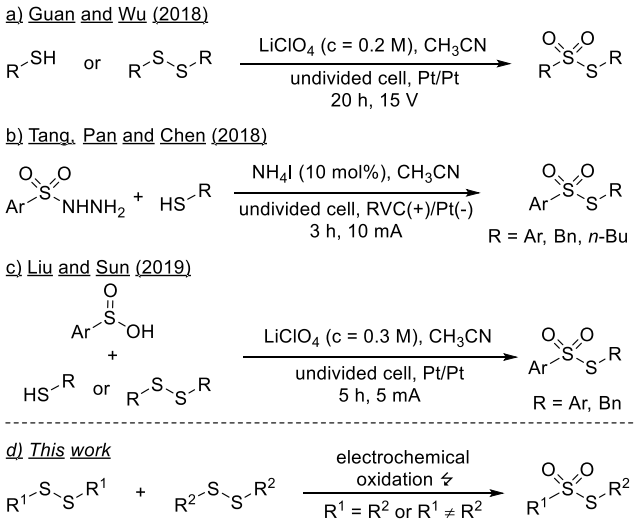
Abstract: The electrochemical, oxidative generation of symmetrical and unsymmetrical thiosulfonates is presented. First, the oxidation of disulfides yielding symmetrical thiosulfonates was realised. The direct synthesis is performed using a simple quasi-divided cell design, whereby the usage of a supporting electrolyte is unnecessary. Its principle was then expanded to the conversion of unsymmetrical disulfides that were *in situ* generated via metathesis of two symmetrical disulfides. This enables a direct access to unsymmetrical thiolsulfonates without any pre-functionalisation or elaborate synthesis of the starting materials for the first time. The scope of the reaction was investigated by converting different functionalised aliphatic and aromatic disulfides in moderate to very good yields. Furthermore, a sensitivity assessment for an improved reproducibility and a robustness screen to determine the compatibility of the reaction against functional groups were performed.

In general, organo-sulphur compounds are widespread in nature and do exhibit many biological active properties. One representative of this substance class are thiosulfonates that act antimicrobial, antifungal, and antiviral.[1-4] In addition, they might be applied in cancer treatment or as antidote in case of cyanide poisoning.[5-8] In the synthetic, organic chemistry these compounds are used as popular sulfenylating agents.[9-14] As opposed to sulfinyl halides, thiosulfonates exhibit a higher stability and compared to disulfides are accompanied by a higher reactivity at the same time.[15]

Due to the significance of this substance class, many synthetic strategies have been developed during the past decades.[15] Symmetrical thiosulfonates can be prepared by oxidative dimerisation of thiols,[16-21] oxidation of disulfides,[16,22-26] reduction of sulfonyl chlorides[27-32] or the decomposition of sulfonyl hydrazines.[22,33,34] The generation of unsymmetrical thiosulfonates is more challenging and can be accomplished for example by cross-coupling of sodium sulfinates with thiols,[35,36] disulfides[37-40] or *N*-arylthiosuccinimides.[41,42] Alternatively, they can be synthesised by reaction of thiols with sulfonyl hydrazines[43-45] or by the addition of thiols to sulfonyl halides via a nucleophilic substitution.[46-48] All of these methods require the stoichiometric use of oxidants (e.g. H_2O_2, $NaIO_4$, PIFA, I_2, oxone, CAN), reductants (e.g. Zn, Sm, $LiAlH_4$) or the application of transition metals (e.g. Zn(II), Ag(I), Cu(I), $TiCl_4$), which is highly problematic and disadvantageous from both an ecological and an economical point of view. Furthermore, the preparation of sulfonyl chlorides and hydrazines classically requires the usage of hazardous reagents as well (e.g. PCl_5, $POCl_3$ or $SOCl_2$, N_2H_4).[20,49-54]

To avoid the stoichiometric usage of redox reagents and/or toxic reagents Guan and Wu et al. developed an electrochemical method for the oxidation of disulfides to thiosulfonates (Scheme 1a).[55] However, it has still some severe drawbacks: Only the generation of symmetrical thiosulfonates was realised, the usage of a supporting electrolyte is unavoidable and long reaction times of 20 hours are necessary, which again diminishes the ecological and economical attraction for this procedure. In addition, the statement of the terminal voltage has only a limited informative value regarding the actual applied voltage, which complicates the reproducibility of the reaction. Shortly after, two methods for the electrochemical generation of unsymmetrical thiosulfonates were developed as well using sulfonyl hydrazines or sulfinic esters (Scheme 1 b and c).[56,57]



Scheme 1. Procedures for the electrochemical preparation of thiosulfonates.

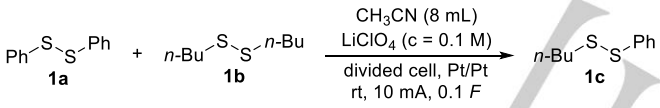
Unfortunately, these procedures are limited to the use of aromatic starting materials so that only aryl sulfinic esters and aromatic sulfonyl hydrazines can be converted with a small range of thiols.

Moreover, an elaborate preparation of the starting materials is necessary, which requires harsh reaction conditions and toxic reagents.

Although, these works represent a good beginning for the electrochemical synthesis of thiosulfonates, the procedures have severe drawbacks. For this reason, the aim of this work was the development of an oxidative, electrochemical method that enables the ecologically and economically efficient access to symmetrical and unsymmetrical thiosulfonates in a short period of time by oxidation of disulfides (Scheme 1d). For the generation of unsymmetrical thiosulfonates the required unsymmetrical disulfides should be generated *in situ* from a matrix of two symmetrical disulfides via electrochemically initiated sulfide metathesis reaction.

In our working group, the electrochemically catalysed preparation of mixed disulfides by sulphur-sulphur bond metathesis using alternating current electrolysis has already been investigated.[58] The generation of mixed disulfides can be achieved in principle also by using direct current. However, for longer lasting electrolysis the formation of a polymeric film at the electrode (electrode fouling) with concomitant diminished yields were observed, which is a common problem in electroorganic synthesis.[59-62] Herein, this expertise should be used to develop a method for the *in situ* generation of mixed disulfides via sulphur-sulphur bond metathesis with subsequent oxidation to the corresponding thiosulfonates under constant current conditions.

At first, the generation of mixed disulfides via metathesis reaction was investigated utilising catalytic amounts of electricity in a divided cell in order to determine the efficiency of the electrochemical part reactions for the metathesis (Scheme 2).[58]



Scheme 2. Test reaction for the formation of unsymmetrical disulfides via electro-catalytic metathesis reaction.

Thus, for an initial screening only 0.1 *F* were used to transform diphenyl disulfide (**1a**) and di-*n*-butyl disulfide (**1b**) to the mixed disulfide **1c**, at which different excess of di-*n*-butyl disulfide (**1b**) were used (Figure 1).

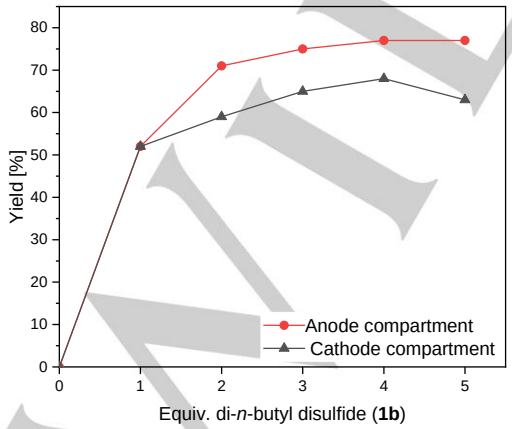
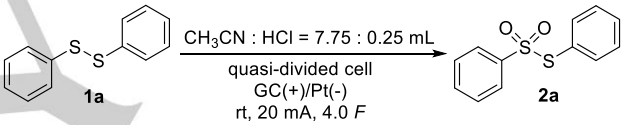


Figure 1. Screening of the required disulfide ratio for an efficient disulfide metathesis reaction in a divided cell. The yields were determined by GC-FID analysis of the crude reaction mixture using mesitylene as internal standard.

It was noted that good yields of the mixed disulfide **1c** of 71% in the anodic and 59% in the cathodic compartment are already generated at a ratio of **1a**:**1b** of 1:2. A further increase of one disulfide only slightly increased the yield of **1c**, although this should be possible from a statistical point of view. This indicates that the formation of the mixed disulfides reaches a kinetic limit. Fortunately, around 10% higher yields were generated in the anode compartment than in the cathode compartment, which can be explained by an increased appearance of electrode fouling at the cathode. This observation is adjuvant for the aimed thiosulfonate generation.

Before the development of a method for the generation of unsymmetrical thiosulfonates was started, the oxidation of a symmetrical disulfide to a thiosulfonate was optimised using diphenyl disulfide (**1a**) as test system (Table 1). The quasi-divided cell design combines a relatively large surface area with a low current density for the desired transformation (metathesis and oxidation of one sulphur atom) while on the counter electrode, which is typically just a Pt wire, the solvent is electrolysed, based on the relatively high current density when applying constant current electrolysis conditions, which might be advantageous for the aimed reaction.

Table 1. Selected examples of the optimisation of the reaction conditions.



Entry	Variations from above	Yield[a]
1	None	76%
2	Undivided cell	52%
3	Divided cell	75%
4	15 mA	73%
5	25 mA	69%
6	**CH_3CN : HCl : H_2O = 7.5 : 0.25 : 0.25 mL[b]**	**>99% (93% isol.)**
7	Graphite anode	88%
8	Stainless steel anode	0%
9	0 °C	88%
10	40 °C	84%
11	Stirring at 250 rpm	93%
12	Stirring at 650 rpm	93%

The reactions were performed in a quasi-divided cell on a 0.5 mmol scale using a glassy carbon anode (surface area: 1.0 · 3.0 cm^2) and a platinum wire cathode (electrode distance: 11 mm; diameter: 1.0 mm; depth of immersion: 14 mm) at room temperature. Concentrated $HCl_{aq.}$ (37%) was used. [a] The yield was determined by GC-FID analysis of the crude reaction mixture using mesitylene as internal standard. [b] This change was kept for entries 7-12.

We started our investigation using a mixture of acetonitrile and aqueous concentrated (37%) hydrochloric acid (7:1) as solvent and a quasi-divided cell design with a platinum wire cathode and a glassy carbon anode applying a constant current of 20 mA and

10.1002/ejoc.202101007

observed the formation of the desired product **2a** in a good yield of 76% (Table 1, entry 1). Afterwards, different cell designs were tested as well (entries 2,3) but to no significant prevail. While the yield could be reproduced in a divided cell, the yield decreased to 52% using an undivided cell. Neither the increase nor the decrease of the current ameliorated the yield of **2a** (entries 4-5). By the addition of 0.25 mL water and adjusting the amount of CH_3CN and hydrochloric acid to 7.5 mL and 0.25 mL respectively, thiosulfonate **2a** was isolated in an excellent yield of 93% (entry 6). The variation of the anode material (graphite, stainless steel), the temperature (0 °C, 40 °C) or the stirring rate (250 rpm, 650 rpm) did not result in a further improvement of the yield (entries 7-12).

Due to its many advantages (e.g. less waste, mild reaction conditions and only electrons as reagents)[63-68] electro-organic synthesis has experienced a renaissance during the past decade and is focused in different research areas. As recently reported by Waldvogel,[69] this might lead to reproducibility issues, since researches with various scientific backgrounds report the applied parameters differently. To ensure the reproducibility of this reaction, a sensitivity assessment was performed in addition to the reaction optimisation (Figure 2).[70]

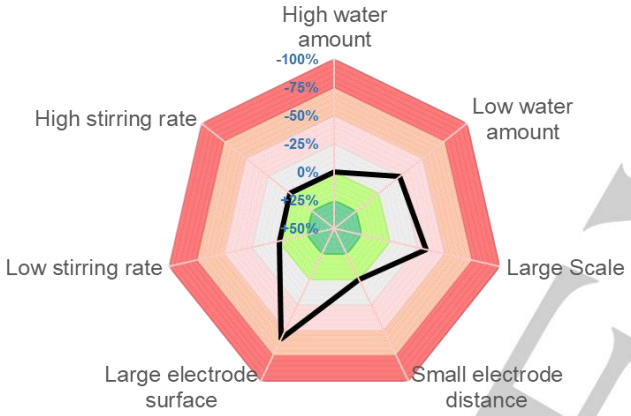
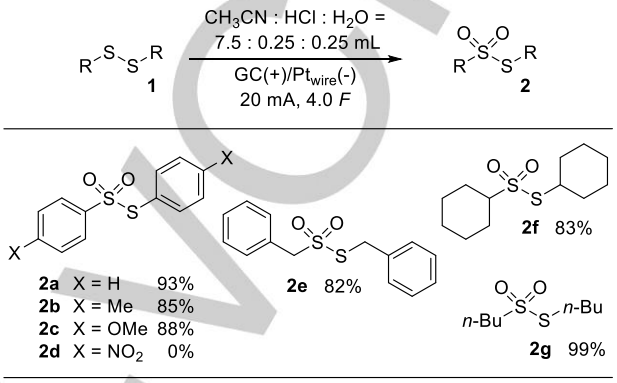


Figure 2. Sensitivity assessment for the electrochemical generation of thiosulfonates.

This test is based on the adoption, that small variations of the reaction conditions, that can be made accidently by other researches, might have an impact on the reproducibility of the reaction.[70] Here, parameters have been investigated, that are often neglected in common electrochemical optimisations. Special attention has been paid to the electrochemical set-up, because most working groups use their individually manufactured equipment.[69] The electrochemical generation of thiosulfonates is insensitive against many parameters, but the enlargement of the anode leads to a bisection of the yield. On a larger scale the yield was decreased by 23%, which can be rationalised by physical adsorption at the electrode surface due to the increased concentration, resulting in a reduced reaction rate. This is confirmed by the recovery of the starting material **1a** based on which the yield of **2a** is the same as for the optimal reaction conditions.

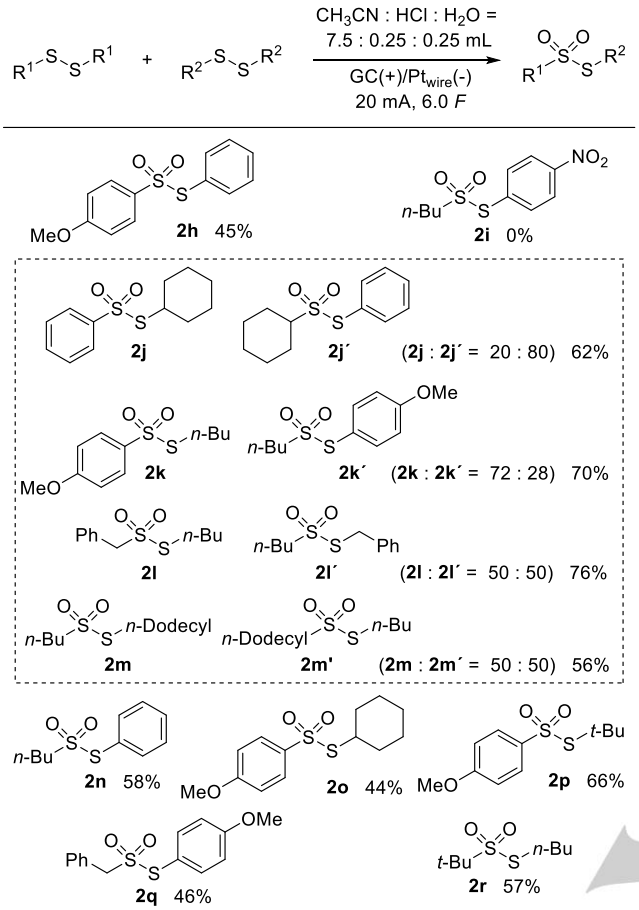
With the optimised reaction conditions in hand, the substrate scope for the generation of symmetrical thiosulfonates was investigated (Scheme 3). First, different functionalised diphenyl disulfides were converted according to the optimised reaction conditions. While the methyl-substituted product **2b** and the methoxyphenyl-substituted compound **2c** were isolated in very good yields (85% and 88% respectively), 4-nitrophenyl disulfide could not be converted to product **2d** and stayed unaffected. Alkyl substituted disulfides were converted to thiosulfonates as well. Dibenzyl disulfide yielded the desired product **2e** in a good yield of 82%. While dicyclohexyl disulfide yielded product **2f** in 83%, di-*n*-butyl thiosulfonate (**2g**) was isolated in an almost quantitative yield (99%).



Scheme 3. Substrate scope of the electrochemical generation of symmetrical thiosulfonates.

After these encouraging results the aimed synthesis for the generation of unsymmetrical thiosulfonates should be realised. For this, the reaction conditions for the synthesis of symmetrical thiosulfonates were adopted, but the amount of charge of the electrolysis was increased (Scheme 4).

Following the results of the required disulfide ratio (see Figure 1), the disulfides were applied in a ratio of 1:2 (for further information see SI). As a first example, the conversion of diphenyl disulfide and bis(4-methoxyphenyl) disulfide gave the unsymmetrical aromatic compound **2h** in 45%. The identity of the oxidised sulphur atom of the products was determined by ^{13}C NMR spectra and the fragmentation patterns of the GCMS spectra. The synthesis of compound **2i** by using bis(4-nitrophenyl) disulfide as starting material failed, probably due to the strong electron-withdrawing character of the nitro group. It is interesting to note, that mixtures of thiosulfonates are obtained when aryl disulfides are reacted with dialkyl disulfides as in the case of the products **2j**/**2j´**-**2l**/**2l´**. For the products **2j**/**2j´** and **2k**/**2k´** the preference for one regioisomer is inverted from 1:4 in favour of **2j´** to almost 4:1 (**2k**). The cross-combination gave the thiosulfonate **2n** (as well as **2o**) as a pure regioisomer, although in moderate (to acceptable) yield. While a benzyl group and a *n*-butyl group have the same effect on the regioselectivity of the thiosulfonate formation resulting in a 1:1 mixture (**2l**/**2l´**), it is surprising that the product **2q** was isolated as single regioisomer. As expected, the same can be observed for *n*-dodecyl and *n*-butyl (**2m**:**2m'** = 1:1), which create the same electronic environment at the sulphur atom. The 4-methoxyphenyl has a strong directing effect on the regioselectivity of the oxidation of one sulphur atom as in **2o** and **2p**. However, the benzyl group inverted this regioselectivity completely, resulting in the formation of **2q** in 46% yield. The regioselective formation of **2r** can be attributed to the stronger electron-donating effect of the *t*-butyl group over the *n*-butyl group.



Scheme 4. Substrate scope of the electrochemical generation of unsymmetrical thiosulfonates.

Thereafter, the tolerance of the electrochemical reaction for the thiosulfonate formation towards functional groups was tested by applying a functional group compatibility test.[71,72] Selected results of this investigation are summarised in Table 2 (for further information see SI).

Overall, several functional groups are compatible to the reaction conditions of the electrochemical generation of thiosulfonates. Nitriles, alkyl/ aryl halides, alkyl ketones, alcohols and esters were not converted and detected in good yields after the electrochemical reaction, whereas the formation of the desired product was not significantly inhibited. In general, functional groups that lack redox or acid stability, only showed a moderate or bad compatibility: Amines are protonated by the hydrochloric acid and precipitated of the solution, which slightly diminished the product formation (Table 2, entries 6-7). However, *n*-octanal was converted to several side-products due to its redox lability, the epoxide was protonated by the hydrochloric acid and some side reactions occurred. 1,3-Dimethoxybenzene representing an electron-rich arene was chlorinated. Benzothiazole was not stable under the reaction conditions, so that no additive was found after the reaction took place, but the formation of product **2a** stayed unaffected.

Table 2. Functional group tolerance test using diphenyl disulfide as substrate.

Entry	Additive	Yield (2a)	Yield (additive)
1	None	>99%	---
2	octanenitrile	64%	87%
3	bromobenzene	79%	96%
4	1-chlorooctane	82%	91%
5	heptanone	74%	71%
6	dodecylamine	50%	0%
7	2,6-lutidine	70%	0%
8	*n*-octanal	43%	14%
9	1,2-epoxy-*n*-octane	59%	40%
10	1,3-dimethoxy-benzene	51%	14%
11	1-octanol	86%	70%
12	methyl benzoate	100%	73%
13	benzothiazole	71%	0%

Colour code: green: yields >66%, yellow: yields between 34-66%, red: yields <34%. [a] The yield was determined by GC-FID analysis of the crude reaction mixture using mesitylene as internal standard.

In conclusion, an electrochemical method for the oxidative synthesis of symmetrical thiosulfonates is described. Its principle was then successfully expanded for the synthesis of unsymmetrical thiosulfonates starting from two different symmetrical disulfides. Compared to the known electrochemical methods for the synthesis of thiosulfonates, the reaction time was reduced significantly, the reaction set-up was simplified and unsymmetrical thiosulfonates can be generated directly without the need of an elaborate starting material synthesis. Thereby, the use of alkyl and aryl substituted disulfides is possible. On top of this, the generation of unsymmetrical thiosulfonates can be accomplished in high regioselectivity: Due to the mild oxidative conditions of the electrochemical procedure, the selective oxidation of one sulphur atom can be controlled in some cases by the electronic character of the residue. The scope and limitations of both reactions were investigated. Thereby, the conversion of alkyl and aryl substituted disulfides works well. Lastly, a sensitivity assessment and a robustness screen according to Glorius were performed to ensure a good reproducibility and to determine the group tolerance of the reaction.

Acknowledgements

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Keywords: Disulfides• Electrochemistry • Metathesis • Oxidation • Thiosulfonates

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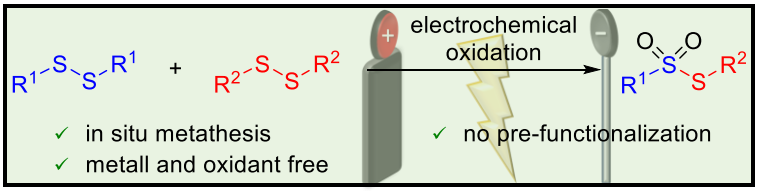

The electrochemical, oxidative generation of symmetrical and unsymmetrical thiosulfonates is presented. The principle of the oxidation of symmetrical disulfides was expanded to the conversion of *in situ* generated unsymmetrical disulfides yielding the respective thiosulfonates. A strong dependency of the regioselectivity for the formation of the unsymmetrical thiosulfonates was encountered and allows their regioselective formation in the future.