Versatile Method for the Preparation of Unsymmetrical Disulfides from Thioacetates and Thiosulfonates

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Abstract: A method for the transformation of organic thioacetates, a widely used functionality for the preparation of self-assembled monolayers on gold surfaces, into unsymmetrical disulfides is reported. Disulfides are readily immobilized on gold in contrast to thioacetates, which usually require a deprotection step prior to bonding to the metal surface. The potential of the method for the controlled preparation of unsymmetrical disulfides has been demonstrated with model compounds comprising several thioacetates, which were readily converted into the corresponding unsymmetrical disulfides.

Introduction

The thiol (sulfhydryl) group is one of the most prominent anchor groups for the immobilization of organic molecules on noble metal surfaces, mainly due to the balanced features of the resulting metal sulfur bond. For example, the sulfur-gold bond is strong enough to retain a molecule on the surface even under ultra-high vacuum conditions, but weak enough to provide the mobility required to enable self-assembly behaviors. The anchor group is thus not only frequently used for the preparation of self-assembled monolayers (SAMs),[1-4] but also for the immobilization of functional structures in single molecule junctions.[5-7] In the latter case, the molecule of interest bridges the gap between two metal electrodes and thus exposes a thiolate anchor group at both ends. The tendency of free thiols to form disulfides in the presence of an oxidizing agent like oxygen makes their handling challenging. While this is a minor issue in the case of molecules with a single anchor group forming SAMs, it becomes a serious handicap for structures exposing several thiol groups due to the formation of insoluble polymers upon disulfide formation. The strategies addressing this issue are either to make disulfides on purpose, or to mask the thiol group e.g., by an acetyl group, which is hydrolyzed prior to bond formation with the noble metal surface.[8]

The disulfide approach is particular advantageous for SAM precursors, as the disulfide bond is cleaved electrochemically by the reduction potential of the noble metal surface. Consequently, a SAM formed from the corresponding homo-disulfide contains exclusively the molecule of interest.[9]

For molecules exposing several thiol anchor groups, like e.g., functional rods bridging the electrodes of a single molecule junction[9-12] or tripod platforms controlling the spatial arrangement of molecular architectures on surfaces,[13,14] the disulfide strategy is still appealing, as the cleavage of the disulfide bond on the noble metal sample renders the presence of additional deprotection chemicals unnecessary. The approach however requires the ability of forming unsymmetrical disulfides. Ideally, the thiol anchor groups of the molecule of interest should be engaged in the disulfide formation with a small alkylthiol, guaranteeing the differentiation of both immobilized thiolates in the experiment.

Guided by this thought, we became interested in a general method for the synthesis of unsymmetrical disulfides, which would allow the preparation of discrete molecular species bearing disulfides as sulfur anchor groups. Numerous functional model compounds for single molecule junctions are available as acetyl protected derivatives, but the required additional deprotection reagents might interfere with the transport experiments. Thus making those derivatives available as unsymmetrical disulfides releasing the experiment form the presence of additional reagents would increase its trustworthiness. Consequently, we focused our efforts towards methods enabling the transformation of an acetyl-protected thiophenol into an unsymmetrical 1-alkyl-2-aryl-disulfane.

The synthesis of unsymmetrical disulfides has been extensively investigated[15] whereby two general concepts have been employed. (i) Generation of an electrophilic sulfenyl derivative followed by reaction with a thiol or one of its derivatives[16-24] or (ii) oxidative heterocoupling.[25-27] The concept of an electrophilic reagent is appealing since it allows for a more controlled reactivity without the inherent distribution of products usually observed in oxidative heterocoupling, which relies on the electronic difference between the thiols.

In order to convert thioacetates into unsymmetrical disulfides, we investigated the suitability of thiosulfonates as a sulfenylation agent, with the aim of applying this method to compounds bearing multiple disulfide functionalities. Formation of unsymmetrical disulfides from thioacetate and thiosulfonates was already reported for the synthesis of 1,6-disulfide-bridged D-hexopyranoses[28] and ajene analogues[29-31] containing unsymmetrical alkyl vinyl disulfides. However, these reported synthetic methods require methanol as a solvent which limits its application for larger polyaromatic structures of interest.

In comparison to other electrophilic agents used to prepare unsymmetrical disulfides such as N-sulfenamides,[21] sulfenyl chlorides[22] or dialkoxynitroxidophosphorane disulfides,[23,24] thiosulfonates[32] are both, easily prepared in one step and highly reactive towards thiolates. This is necessary in order to prevent thiolysis of the formed product and therefore giving rise to symmetrical disulfides as a side reaction.

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Results and Discussion

From literature precedence\textsuperscript{[28,29]} we expected that the electrophile S-pentyl benzenethiosulfonate 1 (prepared from pentylihol and sodium benzene sulfinate using a modified literature procedure\textsuperscript{[30]} and thioacetate 2 should form the unsymmetrical disulfide 3 upon in situ formation of the thiolate of 2 (Scheme 1). To our delight, addition of sodium methoxide (NaOMe, 5.4 m in methanol) to a solution of thiosulfonate 1 and thioacetate 2 in either THF or DMF at room temperature led to fast and clean conversion to the desired unsymmetrical disulfide 3 whereby no symmetric disulfide was monitored by GC-MS.

![Scheme 1. Proof-of-concept reaction using 1 (1.10 eq.), 2 (1.00 eq.) and sodium methoxide (1.20 eq.) in THF at room temperature.](image)

To investigate the scope of the method a series of thiosulfonates were prepared from their corresponding thiols, following the modified literature protocol.\textsuperscript{[32]} Using pyridine as a base allows thiosulfonates to be prepared in one-pot fashion together with sodium benzene sulfinate and iodine in dichloromethane (DCM) (Table 1). Different alkyl- and aryl- benzene thiosulfonates were prepared in good yields, but the limitations of the protocol became obvious as soon as bulky thiols were considered.

1-Adamant ethiol (entry 1) showed low reactivity as after 3 hours, the desired S-adamantyl benzene thiosulfonate could be isolated in only 6% yield after column chromatography. Conducting the reaction in DCM at reflux for 3 hours yielded only 1-adamantyl iodide as a side product together with unreacted intermediary symmetric disulfide. Further, S-pentyl-, S-4-methoxyphenyl-, and S-1H,1H,2H,2H-perfluorodecyl benzene thiosulfonate (entries 2, 4 and 5) could be prepared in excellent yield. Electronic effects appear to have a minor role in the formation of thiosulfonates as both electron withdrawing (entries 7 and 8) and donating substituents (entry 2) could be isolated in excellent yield. However, S-triphenylmethyl benzenethiosulfonate (entry 6) could not be obtained using this method, as the only isolatable product from this reaction was triphenylethanol-1-ol. The transformation of 2-(2-ethoxyethoxy) ethane-1-thiol\textsuperscript{[33]} to the benzenethiosulfonate derivative (entry 3) provided only a moderate isolated yield of 36% after purification by column chromatography. Similarly, methyl thiosalicylate and 4-amino thiophenol (entries 8 and 10) could be transformed to the corresponding thiosulfonates in moderate yield. In the case of methyl thiosalicylate (entry 8) the moderate reactivity appears to arise due to steric reasons, since after 3 h the corresponding disulfide was still present in the reaction mixture. This stands in contrast to the reaction of 4-aminothiophenol where complete conversion of the disulfide was observed after 1 h, yet accompanied by oxidative side reactions resulting in a lower yield of the thiosulfonate of 40%.

![Table 1. One-pot sulfonylation of thiols.](image)

| Entry | R-SH | t [h] | Yield [%] |
|-------|------|-------|-----------|
| 1     | 1-AdamantylSH | 3     | 6         |
| 2     | 4-MeOC6H4SH   | 0.5   | 97        |
| 3     | CH3CH2(CH2CH3)2SH | 2    | 36        |
| 4     | CF3(CF3)2CH2CH3SH | 3\textsuperscript{[a]} | 87        |
| 5     | PentylSH      | 0.5   | 95        |
| 6     | (C6H5)2CSH    | 3     | -         |
| 7     | 4-NO2C6H4SH   | 1     | 81        |
| 8     | 2-COOMeC6H4SH | 3     | 40        |
| 9     | 3,5-F3C6H4SH  | 0.5   | 88        |
| 10    | 4-NH2C6H4SH   | 1     | 52        |

\textsuperscript{[a]} Reaction conditions: mixture of thiol (1.00 eq.), pyridine (1.05 eq.), iodine (2.90 eq.) in dichloromethane with added sodium benzene sulfinate (1.7 eq.) under ambient conditions. \textsuperscript{[b]} Yield of isolated product after column chromatography. \textsuperscript{[c]} Reaction at 40°C.

With these thiosulfonates derivatives in hands, the previously evaluated reaction conditions were used to synthesize unsymmetrical disulfides using S-4-methylphenyl thioacetate as model substrate (Table 2, entries 1-5). With the exception of S-(2-(2-ethoxyethoxy)ethyl thiosulfonate (entry 3), all thiosulfonates of this first series behaved as anticipated and the corresponding unsymmetrical disulfides could be isolated in excellent yield (84-89%) after purification by column chromatography. In the case of S-(2-(2-ethoxyethoxy)ethyl thiosulfonate only the symmetrical tolyldisulfide was obtained. To explore the scope of the reaction sequence, hexyl thioacetate as an unactivated thioacetate (Table 2, entries 6-9) was exposed. And indeed, the reaction with electron deficient 4-nitrophenyl benzenethiosulfonate (entry 6) at room temperature provided the unsymmetrical disulfide in low yield (33% isolated) and favored the formation of symmetrical disulfides upon work up. Upon inverting the reacting groups however (entry 10), the unsymmetrical product was isolated in 75% yield. It appears that 4-nitrophenyl benzenethiosulfonate undergoes methanolysis competing with the unactivated hexyl thioacetate leading to low formation of the unsymmetrical product. Therefore the reaction (entry 6) was repeated at 0 °C and the selectivity towards the unsymmetrical product increased considerably with 67% isolated yield.
To further investigate the functional group tolerance of the method 4-aminophenyl benzenethiosulfonate and hexyl thiocarbonate (entry 7) were reacted yielding the unsymmetrical product in moderate yield of 57%. Another challenging issue of the method was spotted upon reacting the methyl ester substituted phenyl benzenethiosulfonate and hexyl thiocarbonate (entry 9). In this case the symmetrical disulfides were formed as major product and the unsymmetrical target compound could be isolated in only 15% yield.

The methanolysis of thiosulfonates seems to be the major competing side reaction decomposing the starting material. To investigate this hypothesis, 3,5 difluoro phenyl benzene thiosulfonate was treated with 1 equivalent of sodium methoxide in THF at room temperature without any thiocarbonate present (Scheme 2). And indeed, the quantitative formation of methyl 3,5-difluoro sulfinyl (entry 6) was observed. Sulfinates are known to hydrolyze under basic or neutral conditions giving rise to symmetric disulfides. This competing reaction path is more pronounced with thiosulfonates bearing electron withdrawing groups and thus rationalizes the observed lower yields in the formation of unsymmetrical disulfides in entries 6 and 9.

### Table 2. Sulfenylation reactions

| Entry | R<sup>1</sup> | R<sup>2</sup> | Yield [%]<sup>[a]</sup> |
|-------|----------------|----------------|----------------------|
| 1     | 1-Adamantyl    | 4-MeC<sub>6</sub>H<sub>4</sub> | 88                   |
| 2     | 4-MeOC<sub>6</sub>H<sub>4</sub> | 4-MeC<sub>6</sub>H<sub>4</sub> | 89                   |
| 3     | CH<sub>3</sub>CH<sub>2</sub>(OCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub> | 4-MeC<sub>6</sub>H<sub>4</sub> | -                    |
| 4     | CF<sub>3</sub>(CF<sub>2</sub>)<sub>2</sub>CH<sub>2</sub> | 4-MeC<sub>6</sub>H<sub>4</sub> | 88                   |
| 5     | Pentyl         | 4-MeC<sub>6</sub>H<sub>4</sub> | 84                   |
| 6     | 4-NO<sub>2</sub>Ph | Hexyl         | 33 (67)<sup>[b]</sup> |
| 7     | 4-NH<sub>2</sub>Ph | Hexyl         | 57                   |
| 8     | 3,5-F<sub>2</sub>C<sub>6</sub>H<sub>3</sub> | Hexyl         | 81                   |
| 9     | 2-COOCH<sub>3</sub>H<sub>2</sub> | Hexyl         | 15                   |
| 10    | Pentyl         | 4-NO<sub>2</sub>Ph | 75                   |
| 11    | Pentyl         | 4-MeOC<sub>6</sub>H<sub>4</sub> | 85                   |

*a* Reaction conditions: Mixture of thiocarbonate (1.00 eq.), thiosulfonate (1.10 eq.), sodium methoxide (1.20 eq.) in tetrahydrofuran under argon at room temperature. *b* Yield of isolated product after column chromatography. *c* Isolated yield after reaction at 0°C.
Indeed, the unsymmetrical disulfides of all the three compounds could be isolated with yields varying from 25% in case of the four-fold disulfide formation (compound 9 in Scheme 3), 62% and 78% for the two-fold reaction (compounds 7 and 8, respectively).

Conclusions

In conclusion, we report a versatile and robust method to synthesize unsymmetrical disulfides. The in situ deprotection of thioacetates in presence of a variety of thiosulfonates gave after 15 to 30 minutes at room temperature unsymmetrical disulfides in good yields, thus enabling the synthesis of compounds bearing multiple unsymmetrical disulfide moieties. The preferential formation of unsymmetrical disulfides and the polarity difference of the starting material and the product facilitates the purification by column chromatography, as the desired product is the first eluting substance.

With this versatile and convenient synthetic access to unsymmetrical disulfides we are currently investigating their potential as anchor groups on noble metal substrates.

Experimental Section

General procedure for the preparation of thiosulfonates:

To a solution of thiol (1.00 eq.) and pyridine (1.05 eq.) in DCM (1 M in respect to the thiol) iodine (2.00 eq.) was added slowly. After all the disulfide intermediate was consumed (as monitored by TLC SiO\textsubscript{2}, cyclohexane/EtOAc 10:1, UV\textsubscript{254nm}) the reaction was quenched by addition of water and diluted with EtOAc. The organic phase was separated, washed with water (2x), sat. Na\textsubscript{2}SO\textsubscript{4} (2x), dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered and the solvent was removed under reduced pressure affording the crude product. The mixture was further purified by column chromatography (SiO\textsubscript{2}, pentane/DCM 10:1 or pure pentane) affording the asymmetric disulfide.

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Keywords: unsymmetrical disulfides • gold anchor group • thiosulfonate • SAM • MCBJ

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Unsymmetrical disulfides, gold anchor group
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