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Thiosulfonates as emerging reactants : synthesis and applications

Thiosulfoantes as Emerging Reactants: Synthesis and Applications

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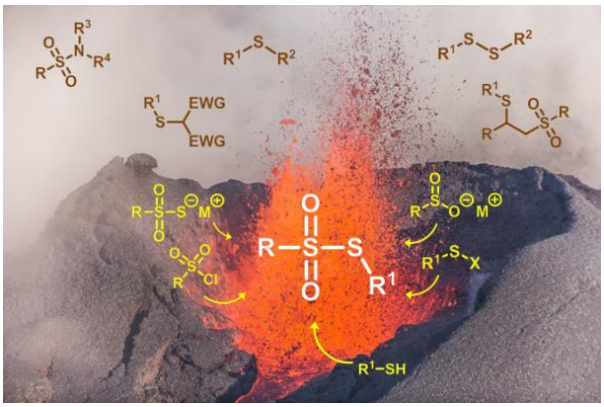
Abstract

The synthetic strategies towards thiosulfonates (RSO_2SR^1) are comprehensively reviewed from its original discovery to recent advances. Incorporation of the green credentials of the synthetic procedures towards thiosulfonates allows to judge the merits of the state of the art, beyond the typical yield of a product and availability of the reactants. As reactant for organic transformations, thiosulfonates are particularly interesting given their possibility to react with nucleophiles, electrophiles and radicals. This review aims to give researchers, not familiar with the field, a good understanding of the general applications of thiosulfonates, while not skipping the recent important advances. The related, but less explored, selenosulfonates (RSO_2SeR^1) are also covered.



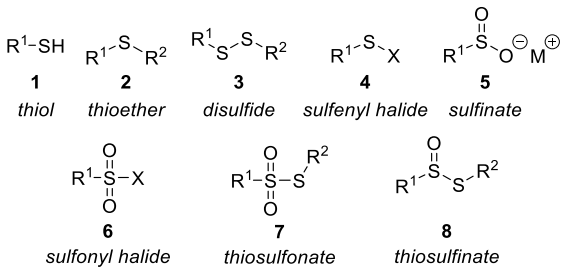
Introduction

Organosulfur compounds have received considerable attention in the past decades (Scheme 1) mainly because the thioether (**2**) functionality (or its oxidized derivatives) frequently occurs in pharmaceuticals and agrochemicals (Scheme 1**.** Overview of organosulfur compounds.

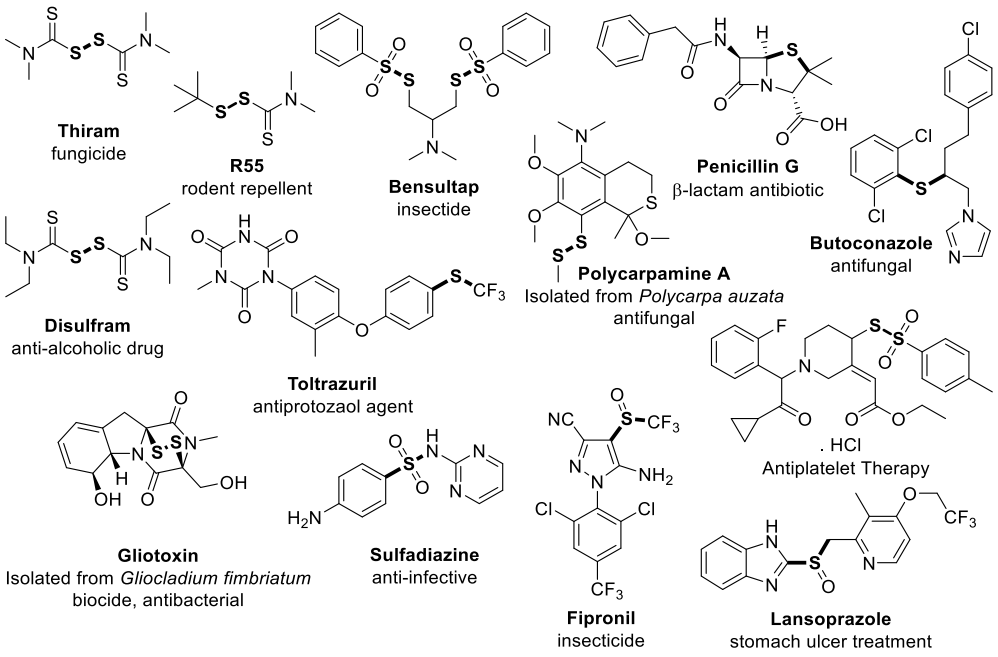
).[1] In particular compounds bearing sulfur-sulfur bonds, *i.e.* disulfides (**3**), have been widely applied in various fields. For example, the *S-S* bonds between cysteine residues stabilize the three-dimensional structure of many proteins and disulfide bridges also appear in several

natural products.[2] Industrially, disulfides (**3**) find many applications as vulcanizing agents for rubbers and elastomers. Moreover, the disulfide function also appears in several agrochemicals as illustrated in Scheme 1**.** Overview of organosulfur compounds.

.[1c, 3] Sulfur-sulfur bond-forming reactions are therefore of growing importance in modern synthetic organic chemistry.[1c, 4]

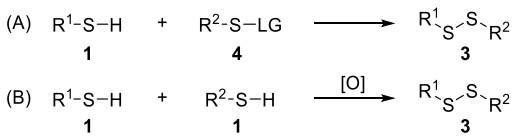


Scheme 1. Overview of organosulfur compounds.



Scheme 2. Examples of *S*-containing natural products, pharmaceuticals and agrochemicals.

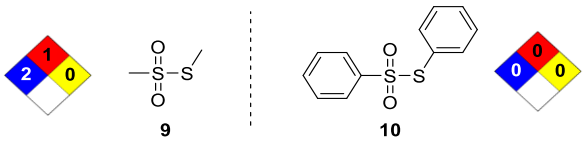
Traditionally, nucleophilic substitution of sulfenyl halides (**4**) with thiols (**1**) has been employed to achieve *S*-*S* bond formation (Scheme 3, route A). However, nowadays the oxidative coupling of two (different) thiols (**1**) is a more common method to prepare disulfides though obtaining selectivity is a challenge (Scheme 3, route B).



Scheme 3. Classical approaches to synthesize *S-S* bonds.[1c, 3] LG = leaving group.

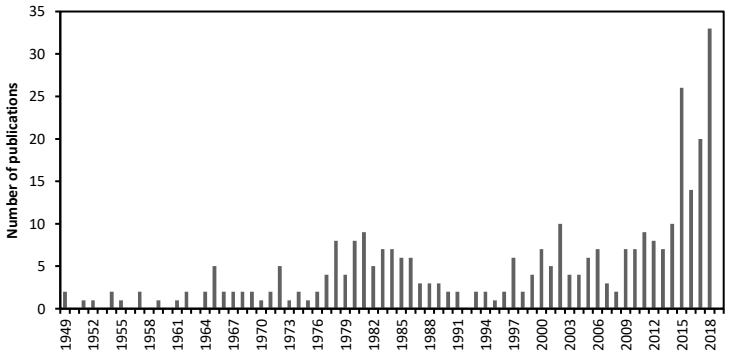
Thiosulfonates ($R^1SO_2SR^2$, **7**) - also named sulfonothioates or the *S*-esters of thiosulfonic acid - are a special class of disulfides (**3**) where one of the sulfur atoms bears two-oxygen atoms. They are easily handled liquids or solids, which generally show a low to moderate toxicity (Scheme 4). Thiosulfonates (**7**) contain one sulfur atom with oxidation state +II ($-SR^2$) and another sulfur atom with oxidation state +VI (R^1SO_2-), which enables them to react both with nucleophiles and electrophiles. They are more reactive than disulfides (**3**) - due to a polarization of the *S-S* bond - but are on the other hand bench - stable compared to the very reactive sulfenyl halides (**4**). Interestingly, depending on the reaction conditions they can either react as sulfenylating or as sulfonylating reactant. Moreover, they also have the capability to break the *S-S* bond homolytically under thermolysis or photolysis, thereby generating sulfonyl and sulfenyl radicals. Reactants that allow participation in ionic reactions, both as nucleophiles and electrophiles, in addition to radical mediated chemistries behave like chameleons and are synthetically very powerful. Weidmann and Lowig first reported thiosulfonates (**7**) in 1840, but it took more than hundred years before the organic community became interested in this compound class when Small demonstrated their antimicrobial activity in 1949.[5] A recent study revealed that thiosulfonates may operate as the first line defense system of the human body's against cyanide intoxication.[6]

Despite their use in organic synthesis, only the simplest, and unfunctionalized thiosulfonates (*S*-methyl methanethiosulfonate (**9**) and *S*-phenyl benzenethiosulfonate (**10**, Scheme 4) are readily commercial available. In most cases, access to more advanced thiosulfonate (**7**) building blocks still heavily relies on their small-scale laboratory preparation. In this review, we will discuss the current strategies for thiosulfonate (**7**) synthesis. The previous review on this topic by Zefirov *et al.* dates already more than 25 years ago.[7] Besides listing the state-of-the-art synthetic methods for thiosulfonates (**7**), some key *green* credentials will be discussed as well. With the increasing awareness and importance of *green chemistry* chemists need to design efficient synthetic sequences to access small molecules with a reduced ecological footprint involving reactants/reagents with a low toxicity and environmental impact. This review on thiosulfonates (**7**) should stimulate the scientific community to assess in a more balanced manner the literature and judge the merits of a certain reaction beyond the typical yield of a product and availability of reactants. Though not yet customary, evaluating the *green* credentials alongside classical parameters such as yield, number of reaction steps and availability of reactants is an important element to consider when selecting a suitable method. Such method comparison is not self-evident and contains important pitfalls, we therefore included a section on *green* metrics analysis (section 2) in this review.



Scheme 4. The Health, Flammability and Reactivity (HFR) rating of *S*-methyl methanethiosulfonate (left) and *S*-phenyl benzenethiosulfonate (right). Scale from 0 (low) to 4 (high).

Although thiosulfonates (**7**), as discussed above, have seen a surge of interest in the last two decades (Scheme 5) and are considered powerful electrophilic sulfenylating reactants, they are not generally known by the synthetic community. Recently the group of Pannecoucke and Besset highlighted the application of fluorinated thiosulfonates ($ArSO_2SR_f$) for the direct introduction of fluorinated alkyl groups (SR_f) into a range of different scaffolds.[8] Our review comprehensively covers the whole field of thiosulfonate chemistry beyond fluorinated thiosulfonates. Related reactants oxidized on both sulfur atoms, such as the disulfones will not be covered here.



Scheme 5. Number of publications dealing with the synthesis and applications of thiosulfonates (**7**).

2 Assessing the *green* credentials

Attributes like *straightforward*, *facile*, *efficient*, *concise*, *green* and even *sustainable* appear frequently in titles or abstracts of synthetic methodology papers to point to specific *green* aspects of the new method disclosed. However, these buzzwords become meaningless if no attempts are made to perform a broader *green* metrics analysis to check whether some basic principles of *green chemistry* are violated (e.g. proposing a catalyst to achieve a certain transformation, but still employing a toxic solvent like *N*,*N*-dimethylformamide or benzene).[9] Consequently, within this review we will go beyond a classical reactant scope and yield range and also give some key *green* credentials of the state-of-the-art synthetic methods to access thiosulfonates (**7**).[10] This will allow identifying where they are also performing well in terms of its *greenness*, whilst highlighting areas were improvements could still be made in future research. As most synthetic methods were not developed with the intention to perform well on

green metrics this specific indication will stimulate further developments taking these important contemporary aspects into account.

Over the past few decades, the *green chemistry* community has developed a considerable number of measures to better quantify the *green* credentials of a process, which the Clark group recently summarized in a comprehensive list of over 60 different metrics.[11] With the availability of so many different types of metric, the CHEM21 consortium developed a "Metrics Toolkit", which allows a more rounded comparison of a reaction's *green* credentials.[10] Notably, no reaction can be strictly qualified as *green* especially within the remit of synthetic chemistry as our efforts to better optimize our methodologies are perpetually ongoing and there is still significant scope to make better use of renewable resources. However, metrics can be used to quantify improvements in the *greenness* of new approaches by comparing them against the state-of-the-art methodologies.

For every synthetic approach towards thiosulfonates (**7**) the *atom economy* (AE), *reaction mass efficiency* (RME) and *reaction process mass intensity* (PMI) have been calculated (Scheme 6; Supporting Information) and included in the synthetic schemes. To facilitate *green* metrics assessment the stoichiometry of all reactants and reagents was included in the schemes as well. In case no stoichiometry is indicated one equivalent of that reactant/reagent is assumed. The PMI is the most complete mass-based metric as it comprises the mass of all the materials used in a synthetic route relative to the amount of isolated product. It is the key metric adopted by the pharmaceutical industry to measure the improved *greenness* of their manufacturing methods against the current technologies.[12] Another factor for selecting PMI as the metric of choice in favor of the E-factor[13] is due to its focus on process input rather than output, therefore driving innovation and efficiency from the outset.[12] The PMI value can be subdivided and is expressed as the amount of reagents, reactants and catalysts (PMI_{RRC}), solvent (PMI_{solv}) and chemicals used in the workup (PMI_{workup}) relative to the amount of isolated product (Scheme 6). As on small scale the reaction concentration is standardly not considered and the solvent is typically used in larger quantities than required, the reactions are therefore best compared in terms of their PMI_{RRC}. The dominance of solvents on the PMI has been shown by Manley *et al.*[12] They described how solvents normally account for 70% of PMI. Using PMI_{solv} and PMI_{RRC} allows the impact of solvents and reactants/reagents/catalysts to be considered separately therefore giving a clearer view of any possible issues and the variabilities in the data.

$$AE = \frac{MW_{product}}{\sum MW_{reactants}} * 100\% \quad \text{Eq. 1}$$

$$RME = \frac{mass\ of\ isolated\ product}{\sum mass\ of\ reactants} * 100\% \quad \text{Eq. 2}$$

$$PMI_{reaction} = \frac{mass_{reactants} + mass_{reagents} + mass_{catalyst}}{mass\ of\ the\ isolated\ product} \frac{mass_{solvent}}{mass\ of\ the\ isolated\ product} \quad \text{Eq. 3}$$

$$PMI_{reaction} = PMI = PMI_{RRC} + PMI_{solv} \quad \text{Eq. 4}$$

Scheme 6. Quantitative *green* metrics parameters determined for the state-of-the-art synthetic approaches. PMI = $PMI_{reaction}$ + PMI_{workup}, however workup is not considered in this review.

The $PMI_{reaction}$ can be easily calculated by adding up PMI_{RRC} and PMI_{solv}. The workup of the assessed procedures was not taken into consideration in this review as the level of information given in the experimental procedures varied from publication to publication and its inclusion can easily present misleading metric data. Moreover, typically larger volumes of solvent are taken than actually required and unfortunately halogenated solvents such as dichloromethane still commonly appear in extraction/workup methodologies, despite alternatives being available in nearly all cases. Moreover, column chromatography is standardly performed in reactions on small scale, which has a large and negative impact on the PMI_{workup}. While identifying a recrystallization procedure for each individual solid compound is certainly possible, this is not feasible and relevant in the context of a methodology paper where typically a large scope is presented. Considering PMI_{workup} would therefore provide a distorted view. Only $PMI_{reaction}$, for simplicity labeled as PMI in this review, and its constituents $PMI_{reaction}$ and PMI_{solv} are therefore used.

Based on a theoretical simulation for thiosulfonate (**7**) synthesis (Table 1 and Table 2) *via* oxidation of disulfide (**3**) with two different oxidants, the following guidelines revealed to be kept in mind when analyzing and comparing quantitative *green chemistry* parameters in sections 3 and 5 of this review:

- AE, RME and PMI of a reaction are scale-independent parameters (Table 1 and Table 2, simulations 1 and 5). A comparison of methodologies at different scale is therefore allowed.
- The yield of the reaction has a major influence on the PMI and the RME (Table 1 and Table 2, simulations 1-4), which is logical as it determines the amount of waste generated. Based on these simulations, a comparison between two routes using two different reactants/reagents was only done when the difference in yield was small.
- Methods can only be compared for scope examples with similar molecular weight of the substrate (Table 1 and Table 2, simulation 1, entries 2-4) as large variations in molecular weight also alter the PMI significantly (Table 1 and Table 2, simulation 1,

entries 1-2, 5). Relying on published data it was not always possible to select the same reaction product for every route considered. Therefore, the specific example on which the calculations have been performed has been indicated in every scheme, and our selection was based on compounds with a similar molecular weight. Consequently, the PMI will only be discussed for routes which allow a fair comparison.

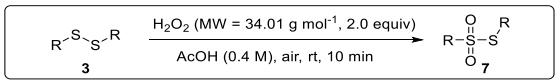
- The proportion of the PMI which can be attributed to the reactants, reagents and catalysts (PMI_{RRC}) is in absolute (versus total PMI) and relative terms rather small. However, when comparing different methods, analysis of the PMI_{RRC} allows the comparison of the *green potential* of the two synthetic approaches. Small differences in this parameter should therefore already be treated as significant (Table 1 and Table 2, simulations 1, 4, 7). Notably, with a low molecular weight oxidant, such as H_2O_2 as reactant, the PMI_{RRC} is not influenced by the molecular weight of the substrate (Table 1, simulation 1). However, with high molecular weight *m*-CPBA as oxidant, significant differences in PMI_{RRC} are observed (Table 2, simulation 1).

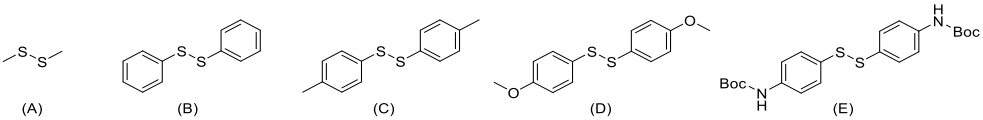
The same conclusions, revealed from simulations of other reaction types (amide synthesis, Mitsunobu reaction), support general applicability of these guidelines beyond thiosulfonate synthesis.[14]

Although the use of mass-based metrics can give an idea of the efficiency of a transformation, it only addresses 1 or 2 of the *green* chemistry principles. So besides quantitative also some qualitative parameters have therefore been considered in this review. An appraisal of the reaction solvent has been given based on a solvent selection guide ranking the solvents into four categories: *preferred* (or *recommended*), *problematic* (can be used in the lab, but special measures are required at production scale), *hazardous* (substitution is a priority) and *highly hazardous* (solvent has to be avoided, even in the laboratory).[15] Finally, the safety of the employed reagents/reactants have been included *via* the listing of their LD_{50}-values. After all, one of the twelve principles of *green chemistry* is to design and employ safer chemicals.[9, 16] Selection of a synthetic procedure towards thiosulfonates can therefore be done considering much more than the typical yield and availability of reactants/reagents.

Finally, it is important to note that when thiosulfonates (**7**) are used in a synthetic sequence the *green credentials* of all the steps, including both the downstream and upstream processes, need to be scrutinized which is beyond the scope of this review.[17]

Table 1. Influence of altering reaction conditions, substrate and excess of reagent/reactant on the quantitative *green* metrics parameters of a theoretical model reaction with H_2O_2 as oxidant through simulations.

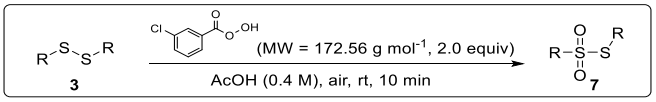


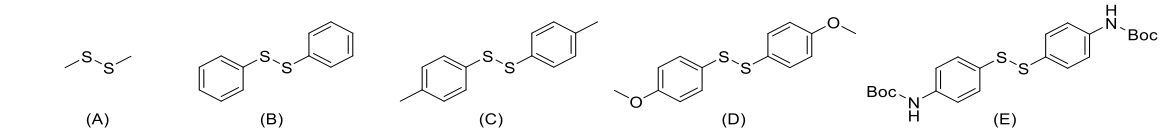


(A) MW = 94.19 g mol^{-1} (B) 218.33 g mol^{-1} (C) 246.33 g mol^{-1} (D) 278.33 g mol^{-1} (E) 449.16 g mol^{-1}

Entry	Reactant **3**	AE (%)	RME (%)	PMI (g g^{-1})	PMI$_{RRC}$ (g g^{-1})	PMI$_{solv}$ (g g^{-1})
Simulation 1: All reactions give a yield of 90%, AcOH (0.4 M)						
1	A	98	70	25.5	1.4	24.1
2	B	99	79	13.4	1.3	12.1
3	C	99	80	12.2	1.3	10.9
4	D	99	81	11.0	1.2	9.8
5	E	99	84	7.5	1.2	6.3
Simulation 2: All reactions give a yield of 80%, AcOH (0.4 M)						
6	A	98	62	28.7	1.6	27.1
7	B	99	70	15.1	1.4	13.7
8	C	99	71	13.7	1.4	12.3
9	D	99	72	12.4	1.4	11.0
10	E	99	74	8.5	1.3	7.1
Simulation 3: All reactions give a yield of 70%, AcOH (0.4 M)						
11	A	98	55	32.8	1.8	31.0
12	B	99	61	17.3	1.6	15.6
13	C	99	62	15.7	1.6	14.0
14	D	99	63	14.2	1.6	12.6
15	E	99	65	9.7	1.5	8.1
Simulation 4: All reactions give a yield of 50%, AcOH (0.4 M)						
16	A	98	39	45.9	2.6	43.4
17	B	99	44	24.2	2.3	21.9
18	C	99	44	21.9	2.3	19.7
19	D	99	45	19.9	2.2	17.6
20	E	99	46	13.5	2.2	11.4
Simulation 5: Scale reaction is multiplied by a factor 5, yield of 90%, AcOH (0.4 M)						
21	A	98	70	25.5	1.4	24.1
22	B	99	79	13.4	1.3	12.1
23	C	99	80	12.2	1.3	10.9
24	D	99	81	11.0	1.2	9.8
25	E	99	84	7.5	1.2	6.3
Simulation 6: All reactions give a yield of 90%, AcOH (0.8 M)						
26	A	98	70	13.5	1.4	12.0
27	B	99	78	7.3	1.3	6.1
28	C	99	80	6.7	1.3	5.5
29	D	99	81	6.1	1.2	4.9
30	E	99	84	4.4	1.2	3.2
Simulation 7: Excess of oxidant is multiplied by a factor 4, yield of 90%, AcOH (0.4 M)						
31	A	98	31	27.3	3.2	24.1
32	B	99	46	14.3	2.2	12.1
33	C	99	48	13.0	2.1	10.9
34	D	99	51	11.8	2.0	9.8
35	E	99	60	8.0	1.7	6.3

Table 2. Influence of altering reaction conditions, substrate and excess of reagent/reactant on the quantitative *green* metrics parameters of a theoretical model reaction with *m*-CPBA as oxidant through simulations.

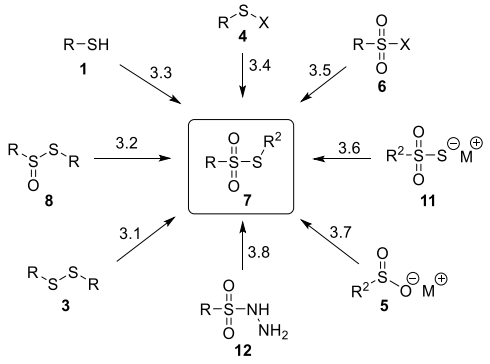




Entry	Reactant **3**	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})
Simulation 1: All reactions give a yield of 90%, AcOH (0.4 M)						
1	A	47	26	28.0	3.9	24.1
2	B	64	40	14.6	2.5	12.1
3	C	66	42	13.3	2.4	10.9
4	D	69	45	12.0	2.2	9.8
5	E	77	54	8.2	1.8	6.3
Simulation 2: All reactions give a yield of 80%, AcOH (0.4 M)						
6	A	47	23	31.5	4.4	27.1
7	B	64	36	16.5	2.8	13.7
8	C	66	38	14.9	2.7	12.3
9	D	69	40	13.5	2.5	11.0
10	E	77	48	9.2	2.1	7.1
Simulation 3: All reactions give a yield of 70%, AcOH (0.4 M)						
11	A	47	20	36.0	5.0	31.0
12	B	64	31	18.8	3.2	15.6
13	C	66	33	17.1	3.0	14.0
14	D	69	35	15.5	2.9	12.6
15	E	77	42	10.5	2.4	8.1
Simulation 4: All reactions give a yield of 50%, AcOH (0.4 M)						
16	A	47	14	50.3	7.0	43.4
17	B	64	22	26.4	4.5	21.9
18	C	66	24	23.9	4.2	19.7
19	D	69	25	21.7	4.0	17.6
20	E	77	30	14.7	3.3	11.4
Simulation 5: Scale reaction is multiplied by a factor 5, yield of 90%, AcOH (0.4 M)						
21	A	47	26	28.0	3.9	24.1
22	B	64	40	14.6	2.5	12.1
23	C	66	42	13.3	2.4	10.9
24	D	69	45	12.0	2.2	9.8
25	E	77	54	8.2	1.8	6.3
Simulation 6: All reactions give a yield of 90%, AcOH (0.8 M)						
26	A	47	26	15.9	3.9	12.0
27	B	64	40	8.6	2.5	6.1
28	C	66	42	7.8	2.4	5.5
29	D	69	45	7.1	2.2	4.9
30	E	77	54	5.0	1.8	3.2
Simulation 7: Excess of oxidant is multiplied by a factor 4, yield of 90%, AcOH (0.4 M)						
31	A	47	8	37.1	13.0	24.1
32	B	64	14	19.2	7.1	12.1
33	C	66	15	17.4	6.5	10.9
34	D	69	17	15.7	5.9	9.8
35	E	77	24	10.6	4.2	6.3

3 Thiosulfonate synthesis

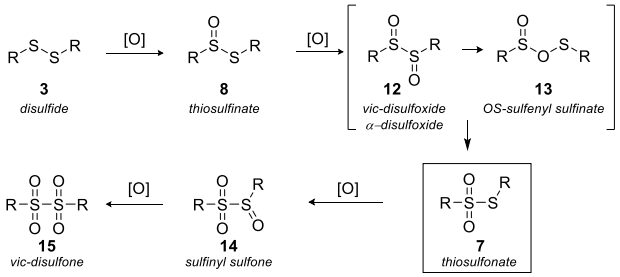
As already highlighted in the introduction, thiosulfonates (**7**) have interesting properties and a considerable number of different methods were therefore developed towards their synthesis. We have classified all known synthetic strategies based on the sulfur precursor used to generate the thiosulfonates (Scheme 7). In the following sections (3.1 - 3.8) each class of reaction is discussed in detail. To assess *green* credentials (see 2) for every approach the *atom economy* (AE), *reaction mass efficiency* (RME), and *reaction process mass intensity* (PMI) was calculated (see Supporting Information) and included in the Schemes. Furthermore, an appraisal of the reaction solvent is given based on a solvent selection guide.[15] Finally, also a discussion on the safety of the employed reagents/reactants is included in each section.



Scheme 7. Classification of synthetic approaches towards thiosulfonates (**7**) based on the reactant used. X = Cl, M = Na or K.

3.1 Thiosulfonate synthesis using disulfides

One of the most practically and widely used methods for the synthesis of symmetrical thiosulfonates (**7**) is the direct oxidation of disulfides (**3**). This approach has been well investigated by Freeman and co-workers.[18] Depending on the nature of the oxidant and the ratio between the disulfide (**3**) and the oxidant, the oxidation can result in thiosulfinates (**8**), the more stable thiosulfonates (**7**), sulfinylsulfones (**14**) or *vic*-disulfones (**15)** (Scheme 8). The *vic*-disulfoxides (**12**) and *OS*-sulfenyl sulfinates (**13**) have hitherto never been isolated, but low-temperature NMR studies suggest them as likely intermediates in the reaction



Scheme 8. Possible reaction products in the oxidation of disulfides (**3**).

pathway transforming thiosulfinates (**8**) into thiosulfonates (**7**).

Over the years various promoting agents have been reported to achieve the selective oxidation of one sulfur atom in disulfides (**3**) (Scheme 9). Peracids like *m*-chloroperoxybenzoic acid (*m*-CPBA, route 1)[18d, 19] or hydrogen peroxide (H_2O_2) in acetic acid (route 2)[20] are the most common oxidizing agents used for this purpose. Espenson and co-workers reported the use of hydrogen peroxide as stoichiometric oxidant in the presence of methyltrioxorhenium (CH_3ReO_3 = MTO) as catalyst (route 3).[21] In 2015 the Back group used a cyclic selinate ester catalyst in combination with hydrogen peroxide for oxidation of disulfides (route 4).[22] Although successful for electron-rich diaryl disulfides (**3**), in most cases thiosulfinates (**8**) instead of thiosulfonates (**7**) were obtained as the main product. Besides the toxicity of selenium compounds, the extremely high PMI-value, mainly as a result of the required volume of reaction solvent, makes this approach disadvantageous.

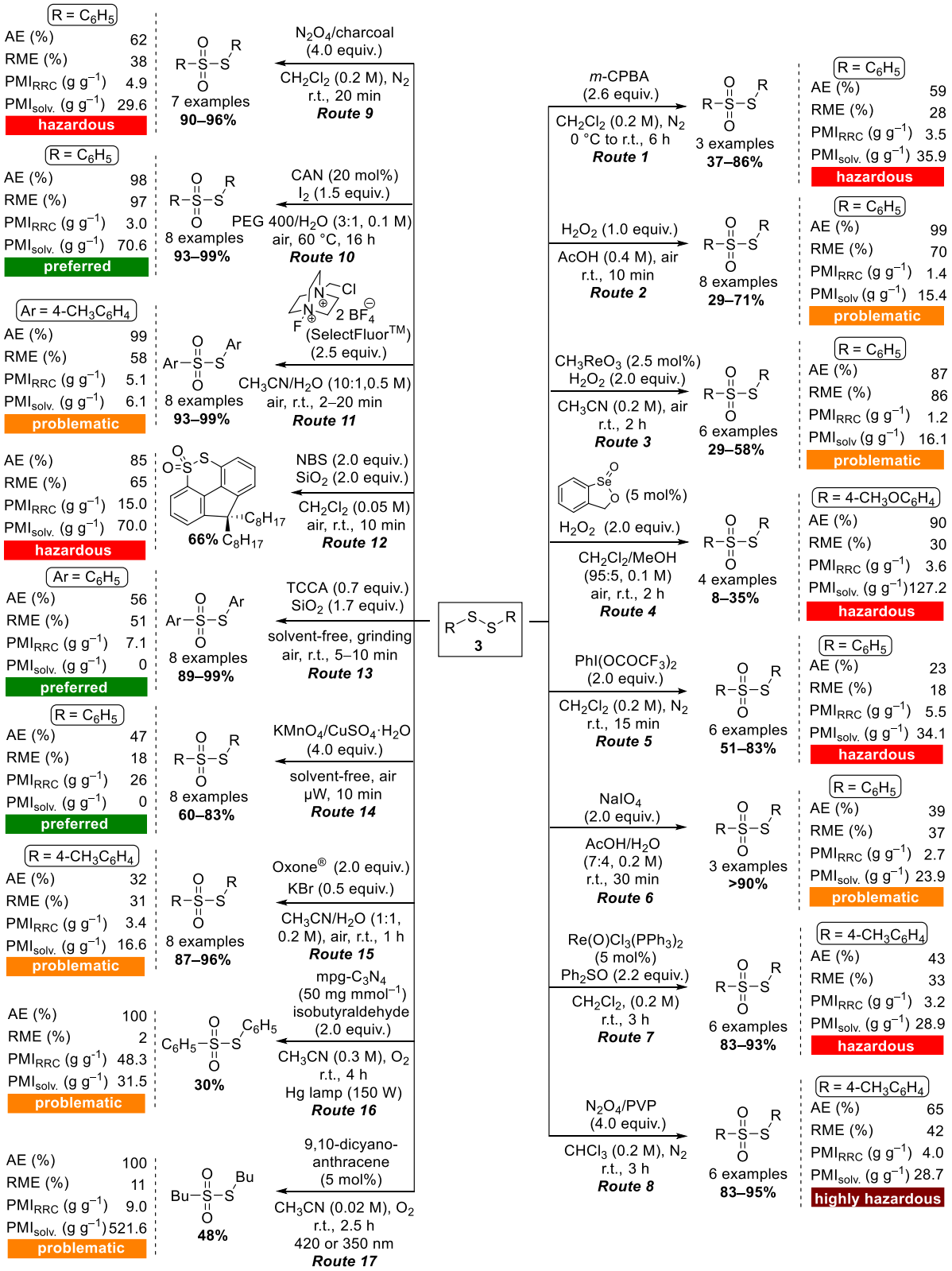
Strong oxidants like [bis(trifluoroacetoxy)iodo] benzene (BTIB, route 5)[23] or sodium metaperiodate ($NaIO_4$, route 6)[24] also deliver thiosulfonates (**7**) in moderate to good yield. The PMI-values for both routes are rather low compared to other routes in this scheme, however both oxidants have an extremely low LD_{50}-value making them less appealing (Table 3). In 1997, the group of Arterburn examined the possibility of rhenium-catalyzed oxidation of disulfides using phenyl sulfoxide (Ph_2SO) as oxidant (Scheme 9, route 7).[25] Relatively high yields were obtained, but the reaction was performed in the quite *hazardous* dichloromethane. The selective oxidation of cyclic disulfides (**3**) with this method delivered the intermediate thiosulfinates (**8**) as reaction product.

Gaseous dinitrogen tetroxide (N_2O_4) has been widely applied as well to oxidize sulfur compounds. To overcome the highly reactive, corrosive and toxic nature of N_2O_4 (Table 3), Iranpoor developed a heterogeneous reactant based on a polyvinylpyrrolidone (PVP) solid support (SP). This PVP/SP-dinitrogen tetroxide can be used for the selective oxidation of disulfides (**3**) to thiosulfonates (**7**) at room temperature (Scheme 9, route 8). Although the PMI_{RRC} is rather low for this approach, one should bear in mind the synthesis of the oxidant. It has also been employed for the coupling of thiols (**1**) to disulfides (**3**) and the selective oxidation of sulfides to sulfoxides.[26] Moreover, in 2004 activated charcoal was used as a solid support to obtain thiosulfonates (**7**) (Route 9).[27] Unfortunately, *hazardous* solvents like dichloromethane or chloroform make these approaches less interesting. The oxidants in routes 4-9 have a significant influence on the PMI_{RRC}. For these routes the solvent and the toxicity of the oxidant are more important elements to consider when selecting a method, as touched upon earlier. The group of Chen employed catalytic ceric ammonium nitrate (CAN) as oxidizing agent for disulfides (**3**) in the presence of iodine (I_2) as a co-oxidant to regenerate Ce^{IV} (route 10).[28] The purpose of this dual oxidant system is to reduce the use of CAN to catalytic amounts, but unfortunately stoichiometric iodine is then required, thereby generating

halogenated waste. The PMI of this reaction is rather high, which is mainly caused by the use of polyethylene glycol (PEG) as solvent. Although PEG is known to be a recoverable reaction medium, the authors did not attempt to reuse it in their publication.

Table 3. Acute toxicity (LD_{50}) values of several reagents/reactants employed for thiosulfonate (**7**) synthesis.[31]

Reagent	LD_{50} oral rat (mg kg^{-1})	Reagent	LD_{50} oral rat (mg kg^{-1})
$AgNO_3$	22	Cl_2	850
BTIB ($PhI[OCOCF_3]_2$)	56	Pyridine	891
$NaIO_4$	58	Isobutyraldehyde	960
$Fe(CO)_5$	62	$KMnO_4$	1090
$LiAlH_4$	85	NBS	1170
N_2O_4	85	H_2O_2	1253
$NH_2NH_2.H_2O$	108	CuI	1600
$NaHSO_3$	115	*p*-TsOH	1683
NH_2NMe_2	122	*m*-CPBA	1807
1,10-Phenanthroline	132	*N*-Methylmorpholine (NMM)	1960
S_2Cl_2	132	NBu_4I	1990
SO_2Cl_2	159	Oxone	>2000
$NaNO_2$	175	$BnNEt_3Br$ (TEBA)	2219
N-iodosuccinimide (NIS)	180	Br_2	2600
DMAP	190	HMPA	2650
TMSCl	<214	Na_2SO_3	2650
Imidazole	220	KI	2779
Na_2S	246	$BiCl_3$	3334
$CuSO_4.H_2O$	300	SiO_2	3600
^tBuONO	308	KBr	3070
TBHP	320	CAN	3900
TCT	315	$NaHCO_3$	4220
$BF_3.OEt_2$	326	Sm	4786
TCCA	406	$Na_2S_2O_3$	>8000
$TiCl_4$	460	I_2	140000
SelectFluor™	500	O_2	no data
KHS	500	TBD	no data
NBu_4Br	500	NH_4BF_4	no data
NBu_4HSO_5	550	CH_3ReO_3	no data
NEt_3	730	$Re(O)Cl_3(PPh_3)_2$	no data
Ph_2SO	750	9,10-Dicyanoanthracene	no data
$K_2S_2O_8$	825	$LiClO_4$	no data
DBU	836	CH_2FCl	no data
		CH_2FI	no data



Scheme 9. Synthesis of thiosulfonates (**7**) by direct oxidation of disulfides (**3**). *m*-CPBA = *meta*-chloroperoxy benzoic acid. CAN = ceric ammonium nitrate. NBS = *N*-bromosuccinimide. TCCA = trichloroisocyanuric acid. Oxone® = potassium peroxymonosulfate ($KHSO_5/KHSO_4/K_2SO_4$ in 2:1:1 molar ratio).

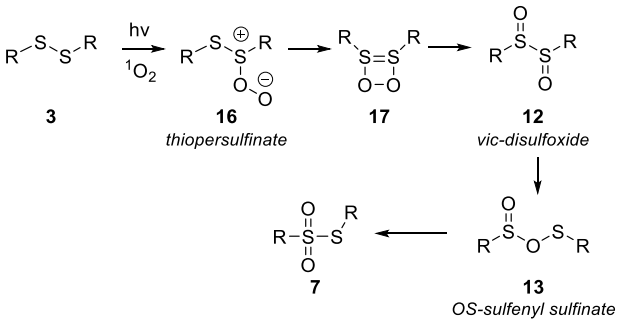
In 2011 Kirihara reported SelectFluor™ for the preparation of aromatic thiosulfonates (**7**) (Route 11).[29] When using aliphatic disulfides (**3**), the reaction rates were very slow and competitive fluorination occurred, leading to inseparable mixtures of thiosulfonates (**7**) and sulfonyl fluorides. Besides the limited scope, the PMI and solvent are acceptable for this reaction. Classical oxidants (*e.g.*, H_2O_2, NBS, *m*-CPBA) were not successful for sterically constrained biphenyl derivatives containing disulfide bridges. Bonifácio and co-workers surprisingly found that a thiosulfonate-bridged 9,9-di-*n*-octylfluorene derivative could be obtained from the corresponding disulfide *via* oxidation with *N*-bromosuccinimide (NBS) in the presence of silica gel (route 12).[30]

In recent years, in the context of *green chemistry*, solvent-free reactions became popular. The group of Chen employed trichloroisocyanuric acid (TCCA) in 2010 as promoter for the synthesis of thiosulfonates (**7**) from aromatic disulfides (**3**) by grinding them in the solid state with a mortar and pestle (route 13).[32] Unfortunately, the authors did not disclose examples of aliphatic disulfides (**3**). The reaction proceeds reasonably fast and delivers thiosulfonates (**7**) in high yield, and it represents the first example of using mechanochemistry[33] in thiosulfonate synthesis. Consequently, the lowest reaction PMI-value of all direct oxidation methodologies was obtained. Alternatively, potassium permanganate absorbed on copper(II) sulfate pentahydrate was proposed by the group of Luu as a *green* promoter for the oxidation of aliphatic disulfides (**3**) (route 14).[34] The reactions were carried out either under microwave irradiation or by conventional heating in the absence of solvent. Notably, the lower PMI-value for this reaction can be misleading at first glance, since no solvent is present. Moreover, the $KMnO_4$ promoter for this oxidation however is added in great excess and a Cu-salt is used as support generating thereby a substantial amount of waste. In accordance with this the PMI-share attributed to the reactants and reagents (PMI_{RRC}) for this route is 26 g g^{-1}, whereas in all previously discussed routes this share was limited to 7 g g^{-1}. This example illustrates the importance of examining the different parameters, like PMI_{solv} and PMI_{RRC} to assess the *green potential* for a specific reaction. Although outside the scope of this review, it should also be noted that many solvent-free routes tend to require extensive/solvent intensive workup to isolate the product.

Oxone® (potassium peroxymonosulfonate, $KHSO_5$ / $KHSO_4$ / K_2SO_4 in 2:1:1 molar ratio) is a commercially available, non-toxic and highly stable oxidant (Table 3). It was employed by Natarajan in 2015 for the oxidation of disulfides (**3**) in combination with substoichiometric MX (MX = KBr, KCl, NaBr or NaCl) in aqueous acetonitrile (Scheme 9, route 15).[35] The method has been used for the oxidation of aliphatic and aromatic disulfides (**3**) containing electron-donating and electron-withdrawing groups. The reaction probably proceeds by oxidation of MX to generate Br_2, I_2 or Cl_2 *in situ*. Subsequent hydrolysis delivers hypohalous acids (HOX),

which can react with the disulfide (**3**). Nucleophilic attack by water on the newly generated cationic intermediate finally delivers a thiosulfonate. This route generates a small amount of halogenated waste, but does have one of the lowest PMI-values given in Scheme 9.

Finally, non-toxic molecular oxygen is considered the ideal *green* oxidant[36] for the oxidation of disulfides (**3**). Afterall, such methods built in both oxygen atoms of O_2 in the product, which is reflected in a 100% AE. Therefore there is a great *green* potential. The groups of Antoinetti and Lacombe investigated photo-oxidation of disulfides (**3**) in the presence of a mesoporous graphite-like carbon nitride (mpg-C_3N_4) as a non-metal, heterogeneous photocatalyst (route 16).[37] As radical initiator isobutyraldehyde undergoes autoxidation in the presence of O_2, which promotes the oxidation of the disulfide. Alternatively, 9,10-dicyanoanthrancene or benzophenone have been used as photosensitizers to generate singlet oxygen ($^1O_2$) from triplet oxygen (route 17).[38] The mechanism of these last two routes presumably involves a photo-induced electron-transfer generating a thiopersulfinate (**16**) intermediate that rearranges *via* a *vic*-disulfoxide (**12**) into the desired thiosulfonates (**7**) (Scheme 10). Unfortunately, in both cases a sluggish photo-oxidation was observed and mixtures of the desired product, starting material and strong acids (alkane sulfonic and sulfuric acid) were obtained. The PMI-values of these routes are also extremely high, which is caused by the reagents (routes 16 and 17) or solvent (route 17).



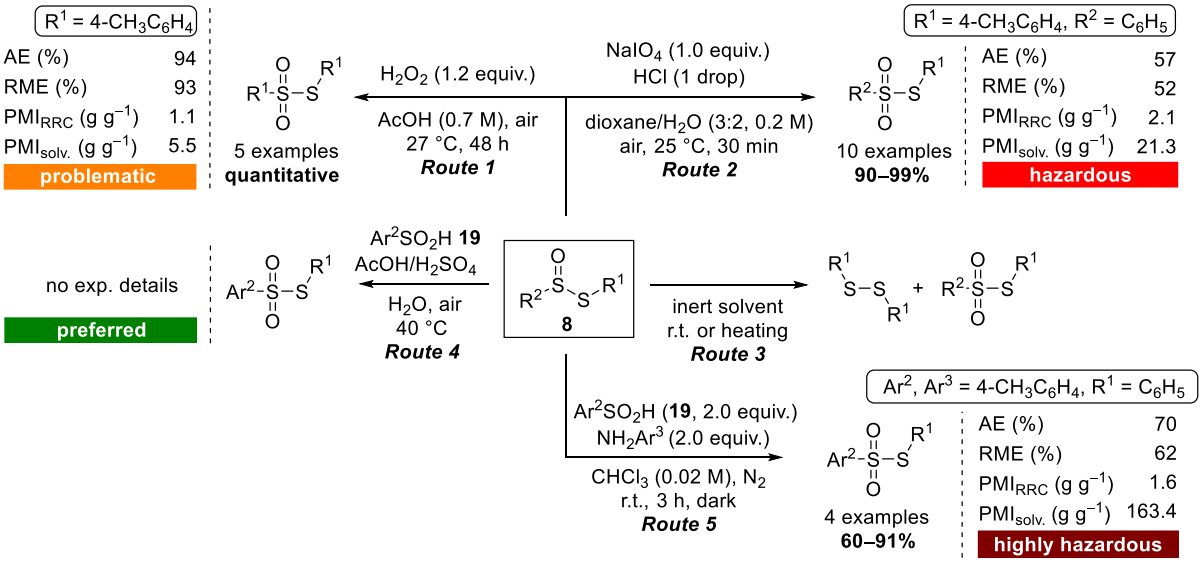
Scheme 10. Proposed mechanism for the photochemical oxidation of disulfides (**3**) into thiosulfonates (**7**).

3.2 Thiosulfonate synthesis using thiosulfinates

The above mentioned oxidation methods could also be applied to prepare thiosulfonates (**7**) using thiosulfinate (**8**) precursors, which are intermediates in the oxidation of disulfides (**3**) (Scheme 8). From a *green* perspective the route reported by Oae and co-workers is probably most efficient as they obtained thiosulfonates (**7**) quantitatively *via* the oxidation of thiosulfinates (**8**) using hydrogen peroxide in acetic acid (Scheme 11, route 1).[39] Unsymmetrical thiosulfinates (**8**) were selectively oxidized with sodium metaperiodate in aqueous media to the corresponding unsymmetrical thiosulfonates (**7**) in high yield (route

2).[40] The oxidation was accelerated by the addition of a catalytic amount of hydrochloric or trifluoroacetic acid.

Thiosulfinates (**8**) also undergo thermal decomposition in inert solvents to give symmetrical thiosulfonates (**7**) and disulfides (**3**) as the main products of disproportionation (Scheme 11, route 3).[41] A free-radical mechanism was proposed involving the homolytic scission of the *S*(O_2)-*S* bond to give a sulfinyl ($R^1SO^•$) and thiyl ($R^1S^•$) radical, which through dimerization yield the observed products. Certain *S*-alkyl alkanethiosulfinates (**8**) disproportionate spontaneously simply on standing for several days at room temperature.[42] Unsymmetrical thiosulfonates (**7**) can be obtained from arenethiosulfinates (**8**) in aqueous acetic acid containing some sulfuric acid and arenesulfinic acid. Thus arenethiosulfinates react more rapidly with arenesulfinic acids than they undergo disproportionation (route 4).[43] This so-called thiosulfinate-sulfinic acid reaction proceeds by a base-catalyzed attack of the sulfinic acid (**19**) on the protonated thiosulfinate. The nucleophilicity of the sulfinate precursor mainly determines the outcome of the reaction. In 1994, Clarke and Cole proposed therefore to use an amine salt of the sulfinic acid as this would then also provide an inherent proton carrier (route 5).[44] The high amount of *highly hazardous* chloroform used as solvent has a negative impact on the PMI of this reaction.

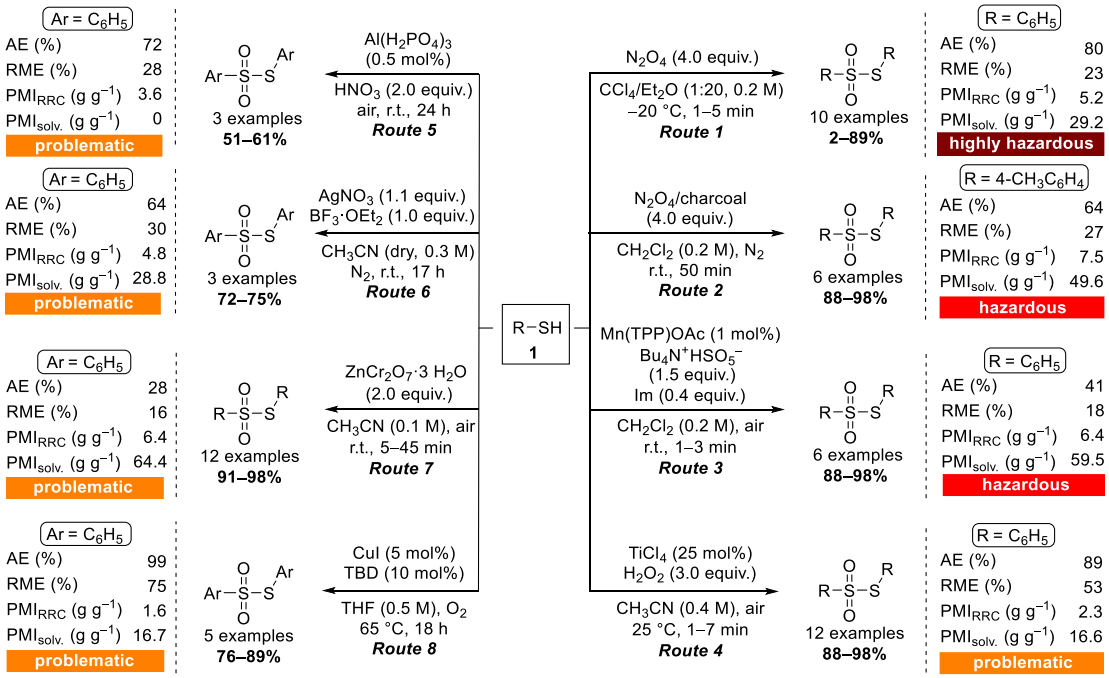


Scheme 11. Synthesis of thiosulfonates (**7**) *via* oxidation or disproportionation of thiosulfinates (**8**).

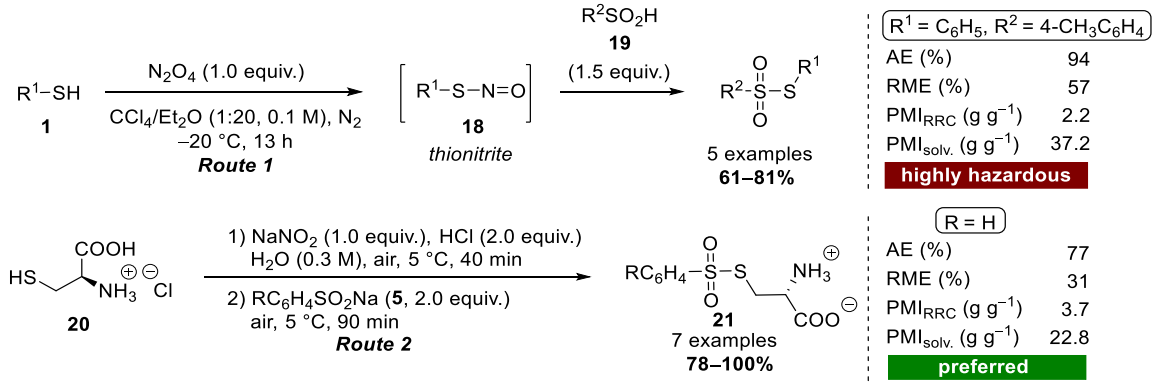
3.3 Thiosulfonate synthesis using thiols

Besides the oxidation of disulfides (**3**), several groups also investigated the direct oxidative coupling of thiols (**1**) for the preparation of symmetrical thiosulfonates (**7**). In 1978, Oae obtained thiosulfonates (**7**) from both arenethiols and alkanethiols (**1**) upon treating them with an excess of hazardous dinitrogen tetroxide (N_2O_4) at low temperature (-20 °C) (Scheme 12, route 1).[45] The dinitrogen tetroxide was also used to oxidize disulfides (**3**) (Scheme 9, routes

8 and 9). However, the method suffers from over oxidation to give sulfonic acids and the *highly hazardous* carbon tetrachloride was used as a solvent. Thionitrites (**18**) are most likely involved as highly reactive intermediates in these reactions and the corresponding thiosulfonates (**7**) are obtained upon further reaction with sulfinic acids (**19**). Unsymmetrical derivatives can be prepared by using sulfinic acids (**19**)[46] or sodium sulfinates (**5**)[47] (Scheme 13, routes 1 and 2). The reactive *S*-nitroso derivatives were also obtained with sodium nitrite and hydrochloric acid as illustrated by Hart and co-workers for the synthesis of cysteine-derived thiosulfonates (**21**) (Scheme 13, route 2).[48] Also symmetrical thiosulfonates (**7**) were successfully prepared *via* this procedure.



Scheme 12. Synthesis of thiosulfonates (**7**) *via* oxidative coupling of thiols (**1**). Im = imidazole. TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.



Scheme 13. Synthesis of thiosulfonates (**7**) from thiols (**1**) and sulfinic acids (**19**) / sulfinates (**5**) via thionitrite (**18**) intermediates.

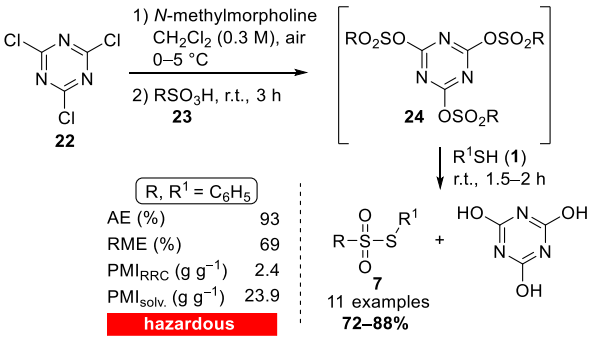
The group of Iranpoor developed a procedure to avoid the undesired overoxidation of thiosulfonates using charcoal-supported N_2O_4 (Scheme 12, route 2).[49] In an alternative

approach they reported tetrabutylammonium peroxymonosulfate as oxidant under manganese *meso*-tetraphenylporphyrin (TPP) catalysis (route 3).[50] Both methods produce high reaction PMI-values, which is due to the use of *hazardous* dichloromethane as solvent, in conjuction with an excess of oxidant (route 2) or the high molecular weight of the oxidant (route 3) resulting in a high PMI_{RRC}. As PMI_{RRC} is intrinsic to the reaction design, this cannot easily be improved. Hydrogen peroxide in combination with titanium tetrachloride as Lewis acid catalyst also proved to be a successful system for the oxidation of thiols (**1**) into the corresponding symmetrical thiosulfonates (**7**) (route 4), featuring a substantially lower PMI.[51] Two approaches with a very limited scope for the synthesis of arenethiosulfonates (**7**) from the corresponding thiols (**1**) were reported by Macedo (routes 5-6).[52] It should be noted, however, that route 5 requires concentrated corrosive nitric acid (HNO_3) while route 6 generates stoichiometric amounts of toxic silver waste. The route using nitric acid is a nice example of how one would classify the method as the best available if judging it solely on PMI. In 2011 Sobhani used zinc dichromate trihydrate ($ZnCr_2O_7 \bullet 3H_2O$) for an efficient oxidation of thiols (**1**) (route 7).[53] The method however has limited potential for application as the oxidant is prepared from $ZnCO_3$ and CrO_3 in an acidic medium. The latter has required authorization by the European Chemical Agency (ECHA) under Annex XIV of REACH for use at scale since September 2017.[54]

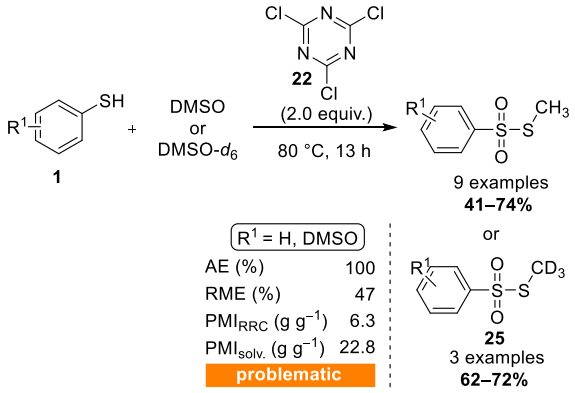
A very recent approach reported by the group of Jang delivers *S*-aryl arenethiosulfonates (**7**) in high yield in the presence of catalytic amounts of CuI and1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) under 1 atm of oxygen (route 8).[55] The proposed radical mechanism involves the dimerization of a sulfinyl radical to afford a *vic*-disulfoxide (**12**), which immediately isomerizes to the desired symmetrical thiosulfonate (**7**). The low PMI, high RME and absence of significant toxicity issues for both catalyst and oxidant make this a preferred method for symmetrical *S*-aryl arenethiosulfonates (**7**). Additionally H_2O_2 / $TiCl_4$ (route 4) possesses a good balance of PMI, RME and the innate properties of the oxidant and catalyst despite $TiCl_4$ being more toxic than CuI (Table 3).

In 2004 Bandgar applied a different strategy for the preparation of unsymmetrical thiosulfonates (**7**) using thiols (**1**) and sulfonic acids (**23**) as starting materials (Scheme 14).[56] After initial activation of the sulfonic acids (**23**) with 2,4,6-trichloro-1,3,5-triazine (**22**, cyanuric chloride) and *N*-methylmorpholine (NMM), a nucleophilic addition-elimination with a thiol (**1**) gave the desired thiosulfonates (**7**) in good yield. Based on the same reagent Li and co-workers delivered an interesting addition to the thiosulfonate field, as they were able to prepare *S*-trideuteromethyl arenethiosulfonates (**25**) from aromatic thiols (**1**) and DMSO-d_6 (Scheme 15).[57] Dimethyl sulfoxide performs a dual role in this transformation as it acts both as solvent and reactant. Cyanuric chloride (**22**) activates dimethyl sulfoxide to form an electrophilic

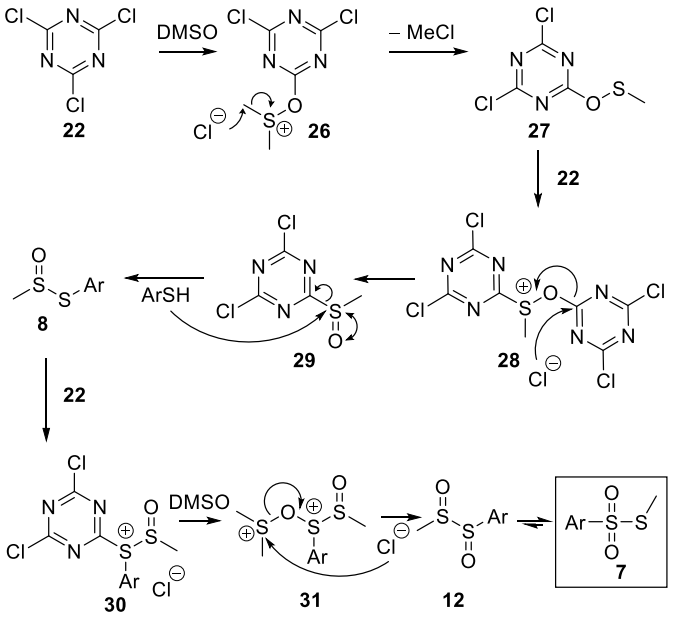
species (**29**), is then captured by a thiophenol (**1**) followed by the rearrangement of *vic*-disulfoxides (**12**) to thiosulfonates (**7**) (Scheme 16). Although the yields were moderate, if carried out using readily available and cheap deuterated DMSO, the simple incorporation of an SCD_3 group is possible.



Scheme 14. Cyanuric chloride-mediated coupling of thiols (**1**) and sulfonic acids (**23**).

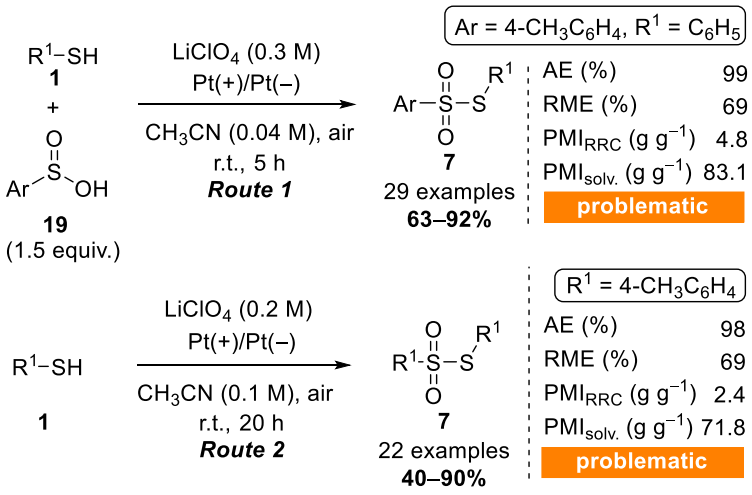


Scheme 15. Synthesis of *S*-trimethyl or *S*-trideuteromethyl arenethiosulfonates (**25**) from arenethiols (**1**), DMSO/DMSO-d_6 and cyanuric chloride (**22**).



Scheme 16. Proposed mechanism by Li *et al.* for the synthesis of *S*-trimethyl arenethiosulfonates (**7**) from arenethiols (**1**) and DMSO.

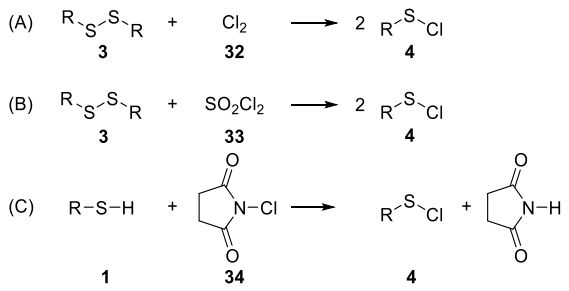
Despite the considerable advances of several methods, most of the routes so far discussed rely on stoichiometric amounts of oxidant (e.g. $NaIO_4$, I_2, N_2O_4, H_2O_2, *etc.*), which at first glance might appear detrimental towards their *green* credentials. With the increased interest in organic electrosynthesis,[58] the group of Sun examined the electrochemical oxidative cross-dehydrogenative coupling of aryl sulfinic acids (**19**) with thiophenols (**1**) (Scheme 17, route 1) or disulfides (**3**) (not shown).[59] A wide range of symmetrical and unsymmetrical thiosulfonates (**7**) could be prepared in good yield. Wu and co-workers applied a similar strategy for symmetrical thiosulfonates (**7**) from thiols (**1**) (route 2) or the intermediate disulfides (**3**) (not shown).[60] The superoxide radical anion ($^{\bullet}O_2^-$), the active species for the oxidation, is formed from H_2O (present in air) during current irradiation. At first glance maybe surprising a high PMI is associated with both approaches as the electrochemical synthesis is performed under very dilute concentration in acetonitrile using $LiClO_4$ as electrolyte. Notably, the PMI_{RRC} is still higher than the direct oxidation of thiols *via* H_2O_2 / $TiCl_4$ (Scheme 12, route 4), illustrating that an electrochemical route is not by definition the most preferred route with respect to *greenness*.



Scheme 17. Thiosulfonates (**7**) via electrochemical oxidative cross-coupling of sulfinic acids (**19**) with thiophenols or thiols (**1**).

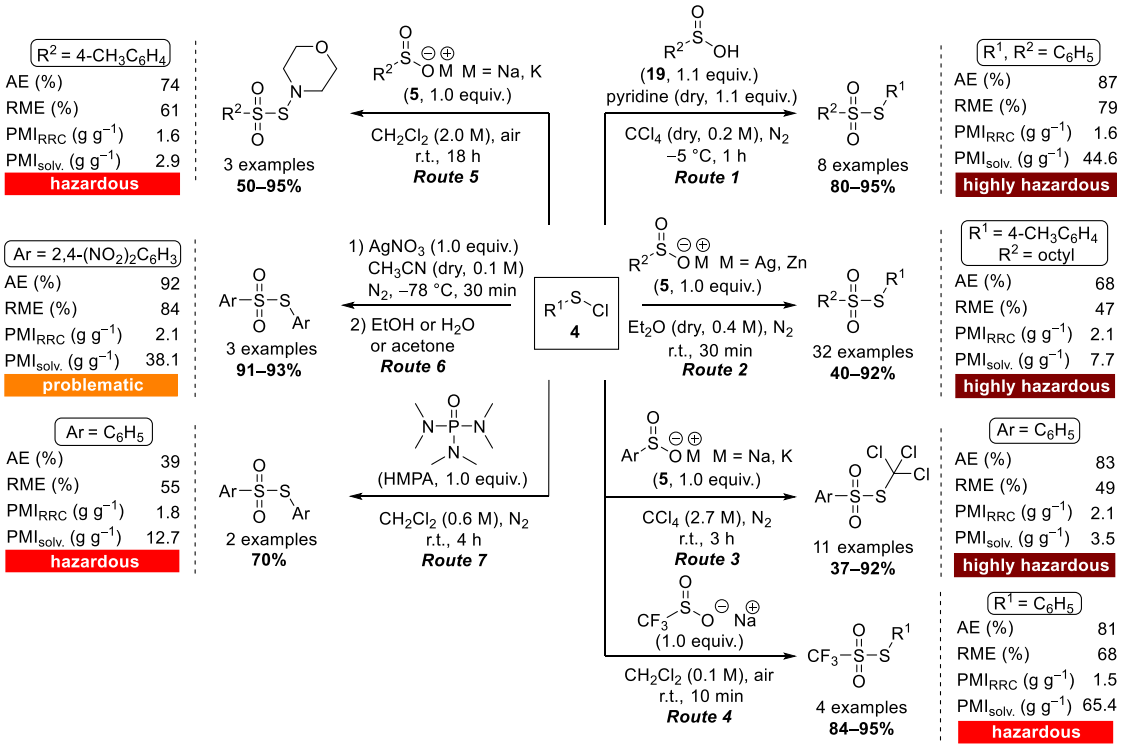
3.4. Thiosulfonate synthesis using sulfenyl halides

Sulfenyl chlorides (**4**) (RSCl) are very powerful sulfenylating agents, which have also been employed for the synthesis of thiosulfonates (**7**). They are generally prepared from the corresponding disulfides (**3**) with gaseous chlorine (**32**) at low temperatures (< 0 °C) (Scheme 18, route A) or with sulfuryl chloride (**33**) (route B).[61] An alternative approach involves the treatment of thiols (**1**) with *N*-chlorosuccinimide (NCS) (**34**) (route C).[61b] Sulfenyl chlorides (**4**) are extremely reactive and often unstable compounds, which require special handling or *in situ* preparation. This probably also explains why there are no toxicity data available for these compounds.



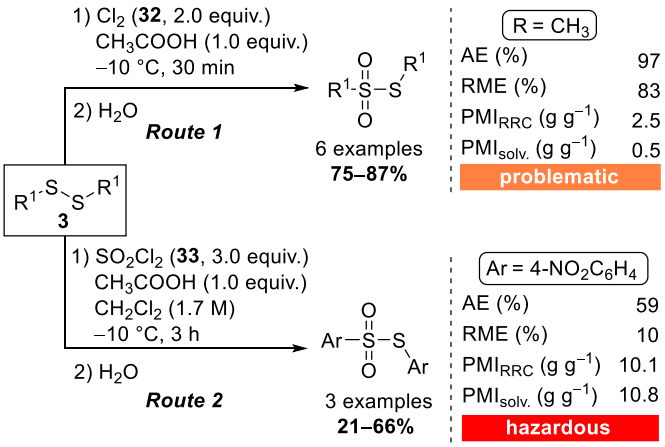
Scheme 18. General methods for the preparation of sulfenyl chlorides (**4**).

In 1957 Stirling was the first to establish the synthesis of thiosulfonates (**7**) from sulfenyl chlorides (**4**) and sulfinic acids (**19**).[62] However, a substantial improvement was reported by the group of Oae, who added pyridine as base to trap the generated acid. In this way, the yield of the reaction (Scheme 19, route 1) could be increased to over 80% for most examples. Unfortunately, the *highly hazardous* carbon tetrachloride is required as solvent and the reaction produces a high amount of (halogenated) waste, which is clearly reflected in the PMI_{solv}.[19d, 61a] Sulfinate salts (**5**), which have been frequently used with other sulfenylating agents (*vide infra*), can be used as nucleophiles in place of sulfinic acids (**19**). Unfortunately, also here only highly hazardous or hazardous solvents have been used (routes 2-5). Both *S*-tosyl, *S*-trichlorovinyl-, alkyl- and arylthiosulfonates were prepared in this manner by Weidner and Block from the corresponding sulfenyl chlorides (**4**) and silver or zinc sulfinate salts (route 2).[63] Similarly, trichloromethanesulfenyl chloride could also react with sodium or potassium arenesulfinates (**5**) to yield the corresponding *S*-trichloromethyl arenethiosulfonates (route 3).[64] Besides trichloro- also trifluorocompounds are compatible with this approach as was reported by Billard in 1996 for the synthesis of trifluoromethanethiosulfonates from sulfenyl chlorides (**4**) and sodium triflinate (CF_3SO_2Na) (route 4).[65] The reaction occurs at room temperature, but unfortunately requires *hazardous* dichloromethane as solvent to obtain high yields. The treatment of alkali metal sulfinates (**5**) with 4-morpholinosulfenyl chloride at ambient temperature delivered the 4-morpholinothiosulfonates in moderate to good yield (route 5).[66] In 1962, Kharrash *et al.* reported that sulfenyl chlorides (**4**) can be treated with an equimolar amount of silver nitrate to prepare the corresponding sulfenyl nitrates ($RSONO_2$).[67] The latter readily decompose upon addition of a polar solvent to obtain the corresponding symmetrical thiosulfonates in good yield (route 6). However, the reaction proceeds at very low temperatures. The generated silver waste results in a high PMI_{RRC}, similar to the procedures with sulfinate salts (routes 2 and 3). An alternative route towards symmetrical arenethiosulfonates (**7**) from arenesulfenyl chlorides (**4**) employs hexamethylphosphoramide (HMPA) to promote the oxidative dimerization into symmetrical thiosulfonates (route 7).[68] Although this reagent has a relatively high LD_{50}-value (Table 3), it is a known carcinogen for humans and needs to be avoided as reagent.



Scheme 19. Synthesis of thiosulfonates (**7**) from sulfenyl chlorides (**4**).

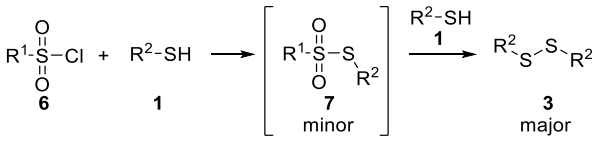
As sulfenyl chlorides (**4**) are known to be very reactive and often unstable, in 1959 Douglass and Farah introduced *in situ* formation from the corresponding disulfides (**3**) (Scheme 20, route 1), which is also beneficial for the PMI of the reaction.[69] When two molar equivalents of chlorine (**32**) are added to a cold mixture containing an equimolar amount of glacial acetic acid and dimethyl disulfide (**3**), a mixture of methanesulfenyl, acetyl and methanesulfinyl chlorides is obtained. Hydrolysis of the latter generates methanesulfinic acid, which combines with the methanesulfenyl chloride to form *S*-methyl methanethiosulfonate (**9**). Originally this approach was only reported for aliphatic disulfides, but in 1965 Field and Parsons extended this methodology to aromatic disulfides.[70] The very low PMI and use of acetic acid as solvent make this methodology preferred for symmetrical thiosulfonate (**7**) synthesis involving *S*-chlorination. Although chlorine (**32**) gas is toxic and corrosive (Table 3), it is industrially obtained *via* a *green* process, namely electrolysis of sodium chloride.[71] These authors also proposed sulfuryl chloride (**33**) as an alternative reagent for chlorination, as it has been used to convert disulfides (**3**) or thiols (**1**) into sulfenyl chlorides (**4**),[72] which are key intermediates in the original Douglass-Farah reaction (Scheme 20, route 2).[72] Unfortunately, only low yields were obtained and the PMI is significantly higher compared to the Douglass-Farah method, partly because SO_2 is formed from the reagent upon chlorination.



Scheme 20. *In situ* formation of sulfenyl chlorides (**4**) from disulfides (**3**) and chlorinating agents.

3.5 Thiosulfonate synthesis using sulfonyl halides

Sulfonyl chlorides (**6**) are inexpensive and readily available compounds. They have been used for more than a century in organic synthesis and medicinal chemistry. The synthesis of thiosulfonates (**7**) *via* reaction of sulfonyl chlorides (**6**) and thiols (**1**) is difficult to control owing to the fast nucleophilic attack of the thiol (**1**) onto the sulfenyl moiety of the thiosulfonate (**7**) product, resulting in the formation of disulfides (**3**) (Scheme 21).[73]

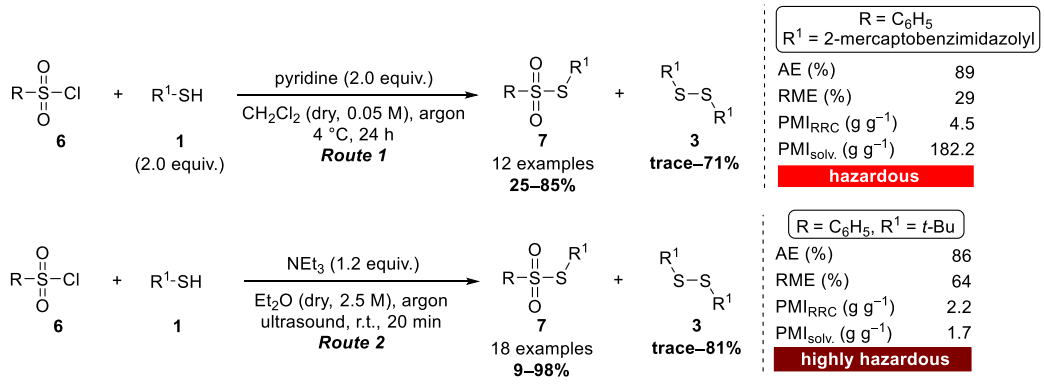


Scheme 21. Selectivity problem in the synthesis of thiosulfonates (**7**) from sulfonyl chlorides (**6**) and thiols (**1**).

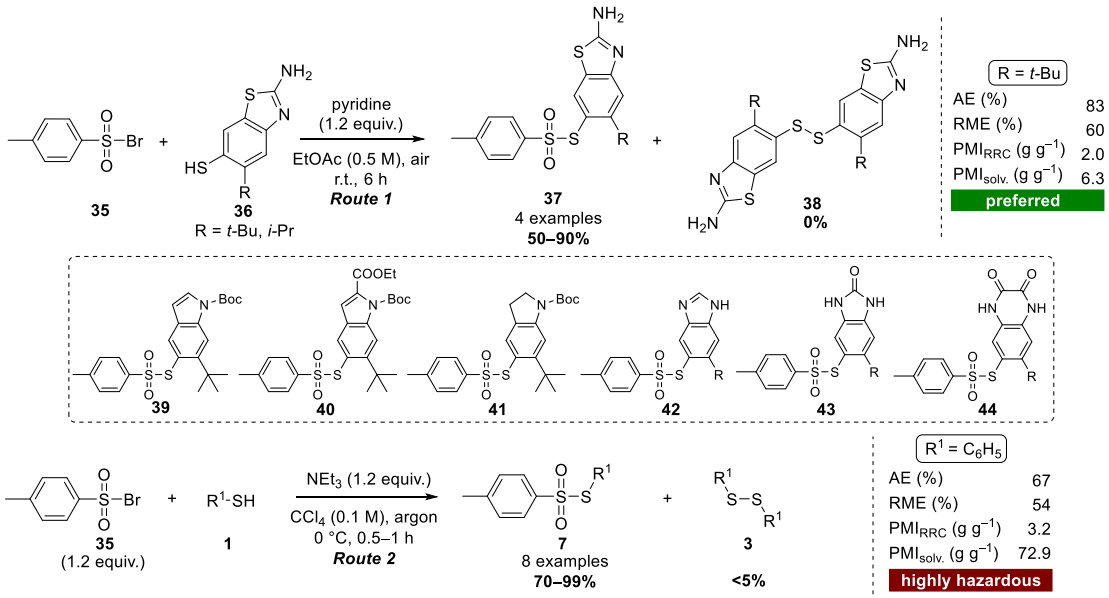
Although Mahieu and co-workers succeeded in preparing a limited number of different thiosulfonates (**7**) *via* this approach, careful monitoring of the reaction conditions (e.g. excess of thiols (**1**)) proved crucial to obtain the target compounds in only moderate yield (Scheme 22, route 1).[73a, 74] The use of *hazardous* dichloromethane as solvent is the largest contributor towards an extremely high PMI.

Due to the toxicity of pyridine, several groups also screened for other bases like triethylamine (Scheme 22, route 2) in this reaction.[75] Although the use of alternative bases results in a less toxic procedure, disulfide (**3**) formation unfortunately could not be prevented. Moreover, the use of diethyl ether as the solvent does not make this a favored strategy for thiosulfonate (**7**) synthesis. This could however, be improved by selecting less hazardous ethers as the solvent. Surprisingly, no reports on such alternatives for this reactions were found in the literature. Following this approach heteroaromatic thiols (**36**) were also specifically studied in combination with tosyl bromide (**35**). Prasad and co-workers reported in 2002 on the synthesis of 2-aminobenzothiazole-containing toluenethiosulfonates (**37**) *via* treatment of

tosyl bromide (**35**) with 6-mercaptobenzothiazol-2-amines (**36**) in the presence of a weak base like pyridine (Scheme 23, route 1).[76] Remarkably, although the amine functionality on the benzothiazolamine (**36**) was not protected, no sulfonamides were obtained. This group also prepared various other toluenethiosulfonates (**39**-**44**) with a heteroaromatic moiety (e.g. indole, quinoxaline, benzimidazole derived), which are interesting sulfenylating agents to introduce heteroarenethiols to organic scaffolds (Scheme 23, rectangle).[77] A similar method was reported in 1988 by Fuchs' group (Scheme 23, route 2), but they employed the *highly hazardous* CCl_4 instead of the *preferred* EtOAc as solvent (route 1).[78]



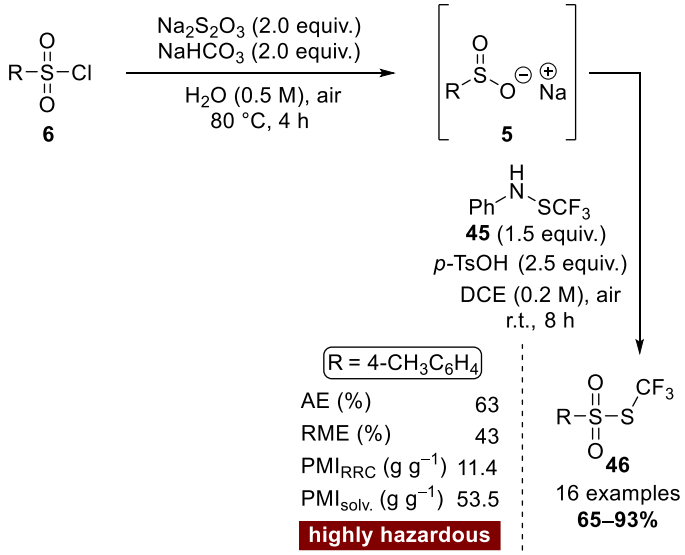
Scheme 22. Thiosulfonate (**7**) synthesis *via* reaction of sulfonyl chlorides (**6**) with thiols (**1**).



Scheme 23. *S*-Heteroaryl toluenethiosulfonate synthesis.

In 2017, Qiu reported a process for the synthesis of *S*-trifluoromethyl thiosulfonates (**46**) from sulfonyl chlorides (**6**), which avoids the disulfide (**3**) formation (Scheme 24).[79] They utilized an *in situ* reduction with sodium thiosulfate to generate sodium sulfinates (**5**). The obtained crude material, was subsequently coupled with *N*-[(trifluoromethyl)sulfanyl]aniline (**45**) to yield *S*-trifluoromethyl thiosulfonates (**46**). This new electrophilic

trifluoromethylthiolating agent has a high potential for further applications to incorporate 'CF_3S' motifs in organic molecules. A disadvantage of this methodology is the use of *highly hazardous* dichloroethane as solvent in the second step, in addition to the reagents employed in excess which in turn generates a large amount of waste and consequently a rather high PMI_{RRC}.

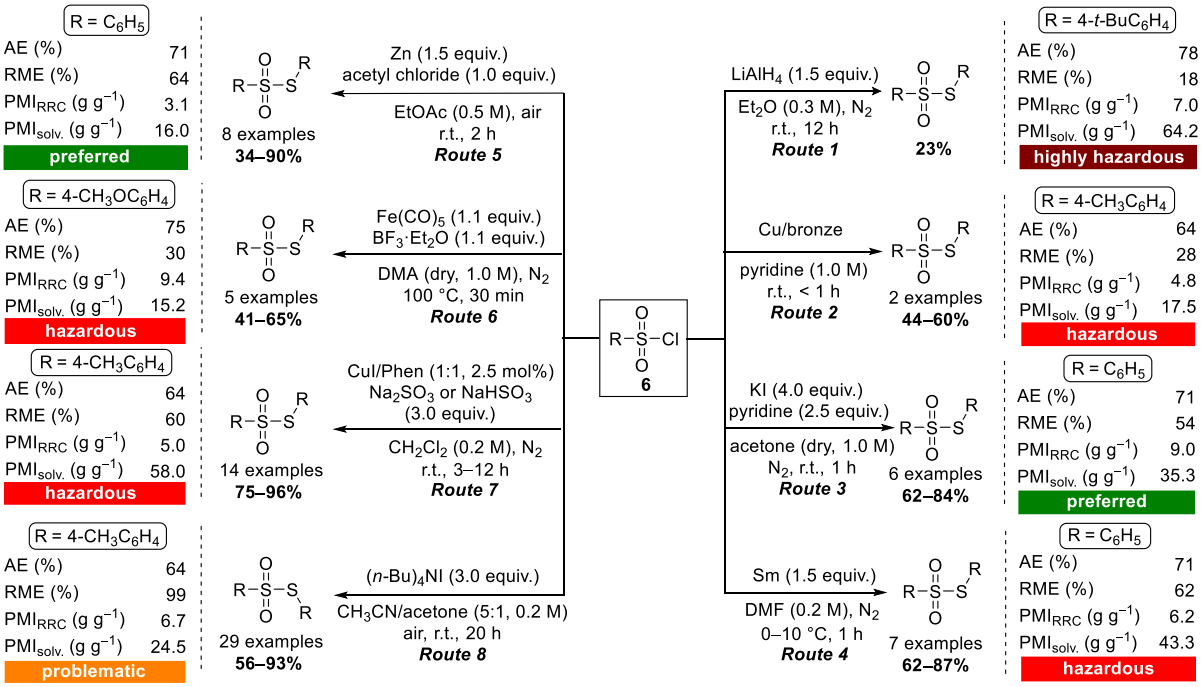


Scheme 24. Electrophilic trifluoromethylthiolation of sulfonyl chlorides (**6**).

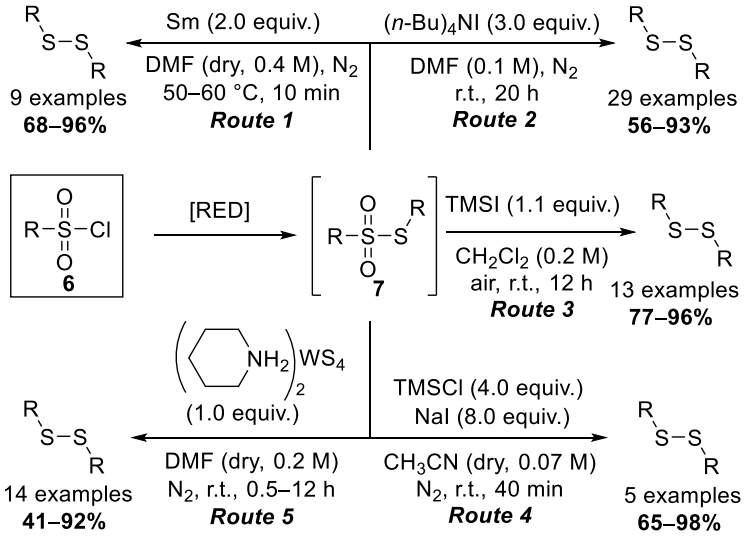
Another process towards thiosulfonates (**7**) is based on the reductive dimerization of sulfonyl chlorides (**6**). It has been frequently applied by multiple research groups as an alternative strategy for the synthesis of symmetrical thiosulfonates (**7**) (Scheme 25). Several reducing agents can be used to achieve this coupling, such as lithium aluminium hydride in diethyl ether (Scheme 26, route 1);[80] copper/bronze in anhydrous pyridine (route 2);[81] potassium iodide in anhydrous acetone / pyridine (route 3);[82] samarium powder in *N,N*-dimethylformamide (DMF) (route 4);[83] zinc dust with acetyl chloride in ethyl acetate (route 5)[84] or iron pentacarbonyl and borontrifluoride etherate in *N,N*-dimethylacetamide (DMA) (route 6).[85] The reduction of sulfonyl chlorides (**6**) by the inexpensive and readily available, non-toxic Na_2SO_3 or $NaHSO_3$ was also examined by Zhang (route 7).[86] In the presence of a copper iodide / 1,10-phenantroline (1:1) catalyst sulfonyl chlorides (**6**) were transformed into thiosulfonates (**7**) in good yield. Although the authors use an environmentally more benign reductant Table 3), a high PMI-value is unfortunately observed due to the large amount of chlorinated solvent employed. The authors also evaluated other solvents (acetonitrile, ethyl acetate or tetrahydrofuran), but selected dichloromethane as the superior solvent. In 2016 Huang disclosed an alternative reduction with tetrabutylammonium iodide in acetonitrile / acetone (5:1) at room temperature (route 8).[87] The lower PMI-value, the high LD_{50}-value for tetrabutylammonium iodide (Table 3), the use of an *acceptable* solvent and the high yield, even for heteroarenesulfonyl chlorides, make this one of the most attractive approaches for the reductive coupling of sulfonyl chlorides (**6**). Notably, the authors also applied this protocol

for the synthesis of unsymmetrical thiosulfonates (**7**), starting from two different sulfonyl compounds (**6**). The unsymmetrical thiosulfonates (**7**) were obtained as major compounds, although homo-dimerization could not be avoided in all cases.

Scheme 25. Synthesis of thiosulfonates *via* reductive coupling of sulfonyl chlorides (**6**).



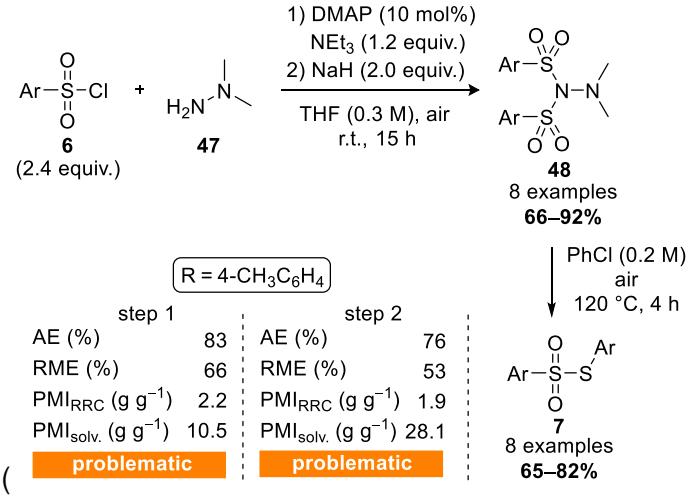
Scheme 26. Thiosulfonate (**7**) synthesis *via* reductive dimerization of sulfonyl chlorides (**6**).



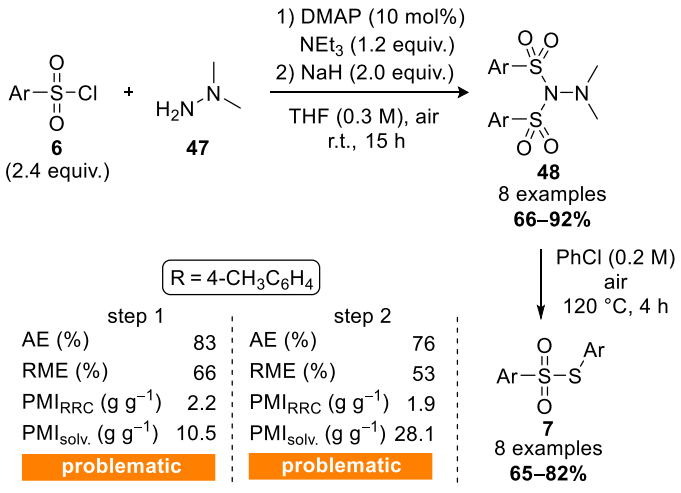
Scheme 27. Synthesis of disulfides (**3**) *via* reductive dimerization of sulfonyl chlorides (**6**).

With some of the methodologies discussed above, the reaction parameters had to be strictly monitored to prevent further reduction to the corresponding disulfides (**3**) (Scheme 27, routes 1-2 versus Scheme 26, routes 4 and 8).[83],[87] With other reductants like iodotrimethylsilane (route 3),[88] chlorotrimethylsilane with sodium iodide (route 4)[89] or piperidinium tetrathiotungstate (route 5)[90] no thiosulfonates (**7**) were observed and the corresponding disulfides (**3**) were immediately obtained.

A slightly different approach for the synthesis of *S*-aryl arenethiosulfonates (**7**) involves the reduction of sulfonyl chlorides (**6**) with *N,N*-dimethylhydrazine (**47**)

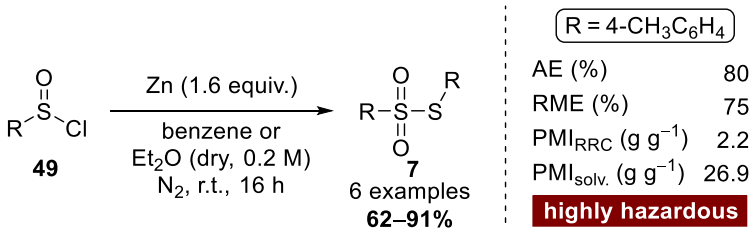


(Scheme **28**).[91] The *N,N*-di(arenesulfonyl)-*N',N'*-dimethylhydrazines (**48**) were easily transformed into thiosulfonates (**7**) upon heating in chlorobenzene. Although the assessed *green chemistry* parameters are acceptable, the toxic nature of *N,N*-dimethylhydrazine (Table 3) and the use of high-boiling non-preferred chlorobenzene as solvent make this approach less appealing for a general synthesis of *S*-aryl arenethiosulfonates (**7**).



Scheme 28. *S*-Aryl arenethiosulfonates (**7**) synthesis from arenesulfonyl chlorides (**6**) *via N,N*-di(arenesulfonyl)-*N',N'*-dimethylhydrazine (**48**).

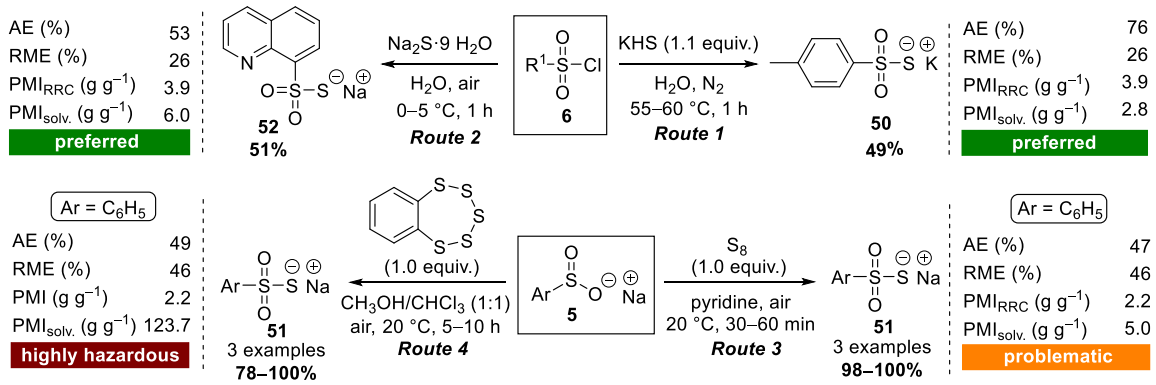
The reduction of the related sulfinyl chlorides (**49**) by zinc dust in benzene or diethyl ether has been studied by the Freeman group and can also lead to symmetrical *S*-aryl arenethiosulfonates (**7**) (Scheme 29).[18b, 92] The reaction can proceed both *via* an ionic or a radical pathway for the formation of a *vic*-disulfoxide (**12**), which subsequently rearranges into the symmetrical thiosulfonate (**7**). However, this approach is less attractive as the sulfinyl chlorides (**49**) are rather unstable compounds, which readily react with nucleophiles such as water or alcohols, and are therefore generally used immediately after their synthesis without further purification.



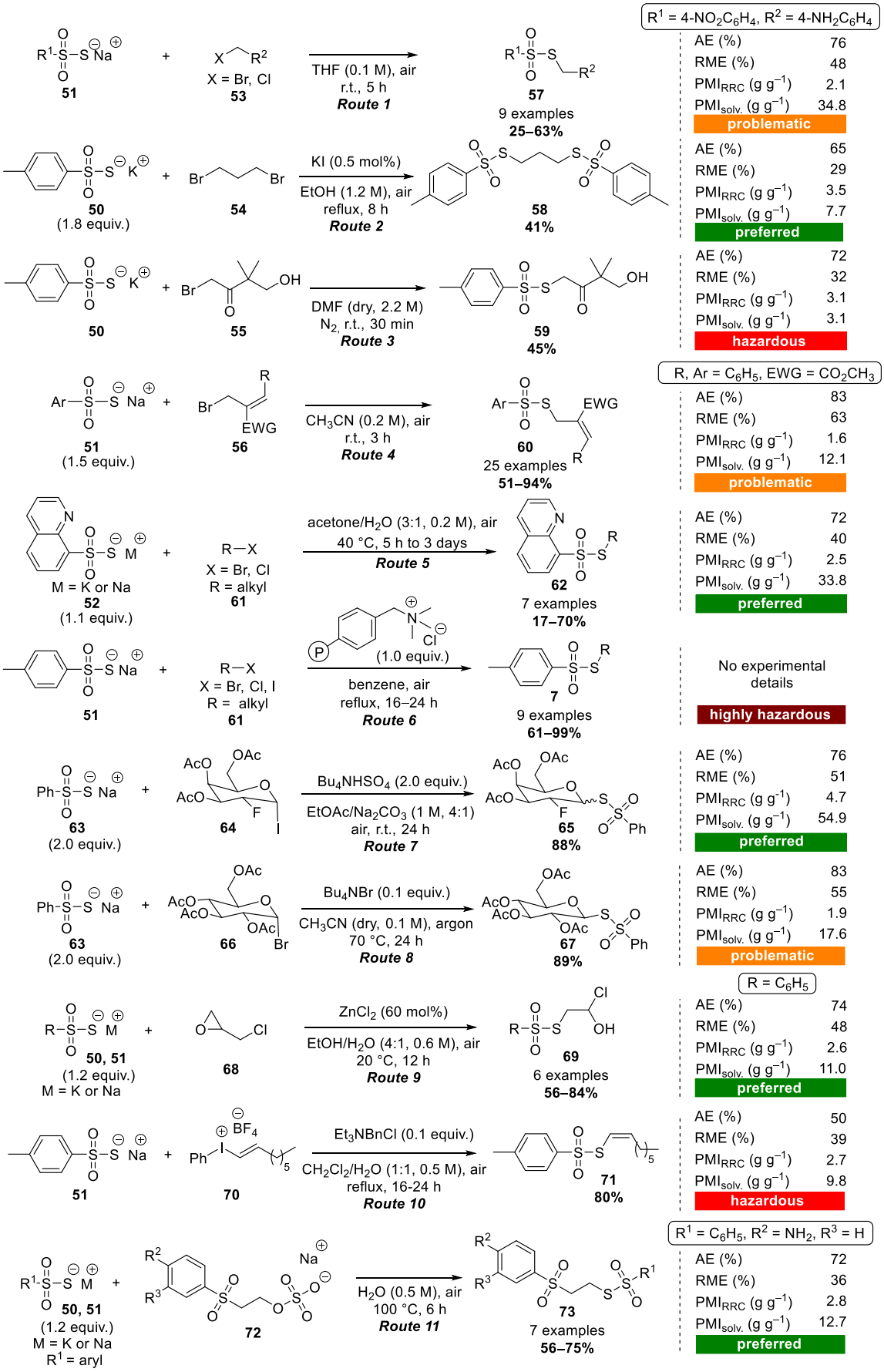
Scheme 29. Reductive coupling of sulfinyl chlorides (**49**) with Zn.

3.6 Thiosulfonate synthesis using alkali metal thiosulfonates

An alternative approach for the synthesis of unsymmetrical thiosulfonates involves a nucleophilic substitution of alkyl halides (**53**-**56**, **61**, **64**, **66**) with potassium or sodium thiosulfonate salts (**50**-**52**, **63**) (Scheme 31, routes 1-8).[93][[94] However, these methods are often substrate specific and only recently Reddy reported a more general approach for the synthesis of allyl thiosulfonates (**60**) using Morita-Baylis-Hilman type allyl bromides (**56**, route 4).[95] Several solvents have been reported for the synthesis of *S*-alkylated alkyl- or arenethiosulfonates (**57**-**59**), but based on the solvent guide of Prat[15] a reaction in an alcohol, ester or dialkyl carbonate solvent is generally preferred. Considering alkali metal thiosulfonate salts (**50**-**52**, **63**) are not readily commercially available, they need to synthesized. They are readily available *via* two general routes starting from sulfonyl chlorides (**6**, Scheme 30, routes 1[93b] and 2[96]) or sodium sulfinate salts (**5**, routes 3[157] and 4[97]). Whereas the former employs nucleophilic sulfur reactants, the latter is based on electrophilic sulfur reactants. The sodium sulfinate (**5**) precursors are preferred (route 3) since they are generally crystalline solids with low toxicity whereas sulfonyl chlorides (**6**) are corrosive solids with a pungent odor. In addition, sulfonyl chloride (**6**) routes also require sulfide salts (e.g. sodium sulfide, LD_{50} = 246 mg kg^{-1}; potassium hydrosulfide, LD_{50} = 500 mg kg^{-1}). The sulfinate (**5**) route becomes less attractive when halogenated solvents are used (compare routes 3 and 4). As mentioned above in section 3.5 reaction of sulfonyl chlorides



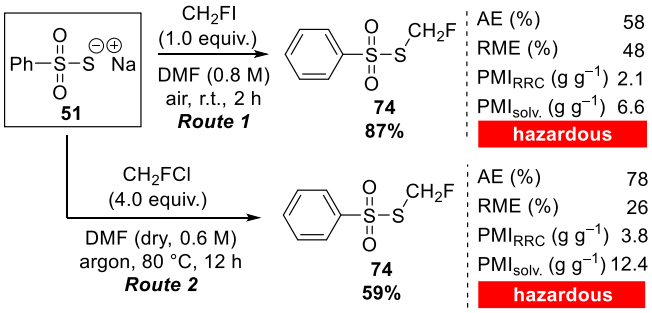
Scheme 30. Generation of sodium or potassium arenethiosulfonates (**50**-**52**) from sulfonyl chlorides (**6**, routes 1 and 2) and sodium arenesulfinates (**5**, routes 3 and 4).



Scheme 31. Examples of alkylation of alkali metal thiosulfonates (**50**-**52**, **63**) *via* nucleophilic substitution.

(**6**) with thiols (**1**) is plagued by further reaction of **1** with the target product **7** delivering undesired disulfides (**3**) which is avoided by the two step approach involving reaction with sulfide salt followed by alkylation (Scheme 30 and 31). Besides alkyl halides, other alkylating agents have been used with alkali metal thiosulfonate salts (Scheme 31). *S*-(2-hydroxy-3-chloropropyl) thiosulfonates (**69**) were for example obtained in moderate to good yield *via* reaction with oxiranes **68** in the presence of $ZnCl_2$ as Lewis acid catalyst (route 9).[98] The group of Witt prepared *Z*-1-octenyl toluenethiosulfonate (**71**) *via* a reaction of sodium *p*-toluenethiosulfonate (**51**) with the appropriate *E*-alkenyliodonium salt **70** (route 10).[94c] Also *O*-alkyl sulfate salts (**72**) can act as a leaving group in *S*-alkylation reactions (route 11).[99]

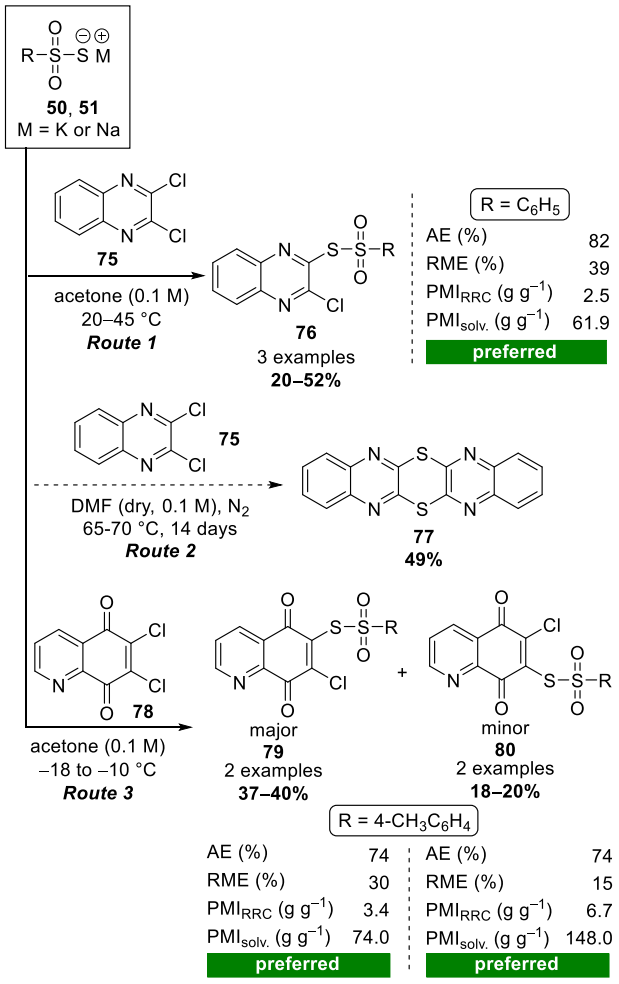
Inspired by the recent renewed interest in fluorinated thiosulfonates the group of Chen developed the first route towards *S*-(fluoromethyl) benzenethiosulfonate (**74**) *via* nucleophilic substitution of $PhSO_2SNa$ (**51**) with either CH_2FI or CH_2FCl in *hazardous* DMF as solvent (Scheme 32).[100] If route 1 could be performed in another solvent, it is attractive considering the low PMI_{RRC} and PMI. Interestingly, this thiosulfonate is bench-stable, could be prepared on 9 gram scale and is not sensitive to moisture, air or light.



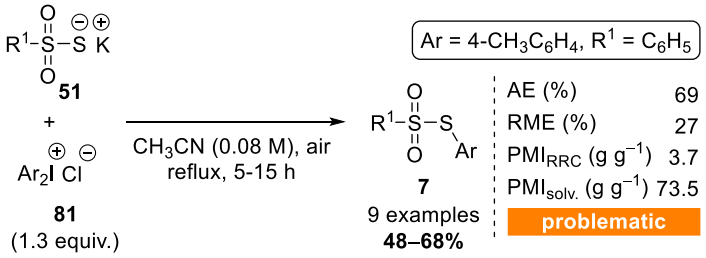
Scheme 32. Synthesis of *S*-(fluoromethyl) benzenethiosulfonate (**74**).

The group of Novikov also applied this methodology for the synthesis of *S*-heteroaryl thiosulfonates, which are valuable synthons in organic chemistry (see section 4). The scope is limited to activated heteroaryl halides (HetArX) which can undergo a nucleophilic substitution (S_NAE). When alkane and arenethiosulfonate salts (**50**-**51**) were treated with 2,3-dichloroquinoxaline (**75**) in aprotic solvents (*e.g.* acetone), the corresponding *S*-(3-chloroquinoxalin-2-yl) thiosulfonates (**76**) were obtained in moderate yield (Scheme 33, route 1).[101] However, when the reaction was performed in *N*,*N*-dimethylformamide 5a,13a-dihydro[1,4]dithiino[2,3-*b*:5,6-*b*]diquinoxaline (**77**) was isolated instead of the desired thiosulfonate (route 2).[102] A mixture of two mono-substituted regio-isomeric thiosulfonates (**79**-**80**) was obtained when the unsymmetrical 6,7-dichloroquinoline-5,8-quinone (**78**) was used as a coupling partner (route 3).[103] The group of Xia disclosed a method for arylation not based on S_NAE involving a reaction of potassium thiosulfonates (**51**) with the appropriate

diaryliodonium salts (**81**) in acetonitrile (Scheme 34).[104] The *green* metrics indicate a low RME and high reaction PMI as a result of the moderate yield, large amounts of halogenated waste and the volume of the solvent.



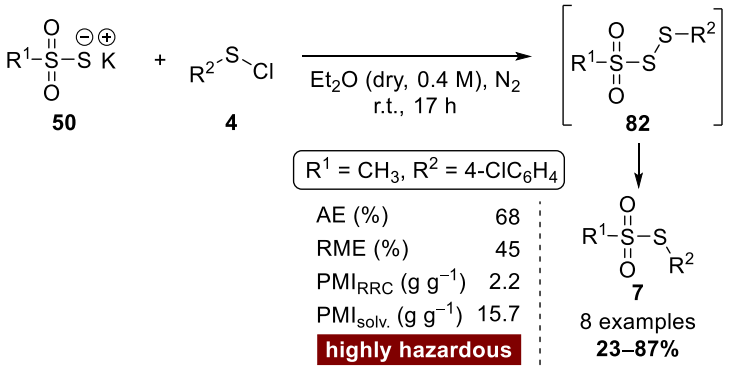
Scheme 33. Examples of *S*-heteroarylation of alkali metal thiosulfonates (**50**-**51**) with heteroaryl halides (**75**-**78**).



Scheme 34. *S*-Arylation of potassium thiosulfonates (**51**) with diaryliodonium salts (**81**).

A final rather remarkable approach towards thiosulfonates (**7**) involves alkylation of potassium thiosulfonates (**50**) with sulfenyl chlorides (**4**). The sulfenic sulfonic thioanhydride intermediates (**82**) spontaneously undergo desulfurization to emit one sulfur atom and thus yield the corresponding thiosulfonates (**7**) (Scheme 35).[105] Although the PMI is reasonable,

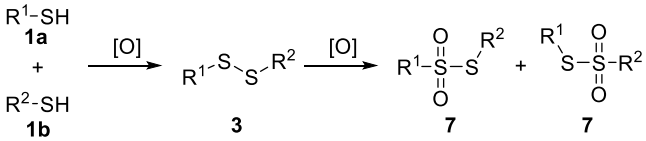
the unstable character of sulfenyl chlorides (**4**), the turning of one sulfur atom into waste and the use of a *highly hazardous* solvent make this approach less appealing. Though the latter can maybe be addressed by using other ethers.



Scheme 35. Synthesis of thiosulfonates (**7**) *via* alkylation of potassium thiosulfonates (**50**) with sulfenyl chlorides (**4**).

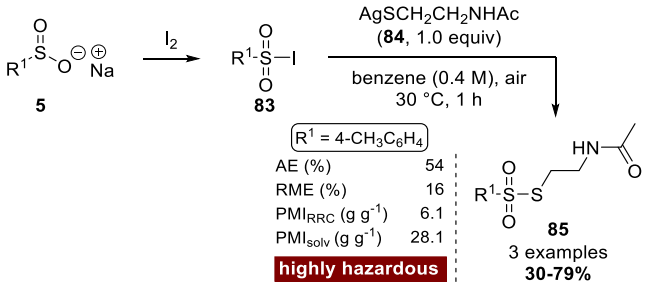
3.7 Thiosulfonate synthesis using alkali metal sulfinates

Although the majority of the reported methods for thiosulfonate synthesis are based on the direct oxidation of disulfides (**3**) or starting from thiols (**1**) giving disulfides *in situ* (*vide supra*), these methods are not well suited for the synthesis of unsymmetrical thiosulfonates (**7**), as they lead to mixtures (Scheme 36). Therefore, alternative methods based on alkali metal sulfinates (**5**), which already have the correct number of oxygen atoms in place for the sulfonyl moiety of the target compounds, have been developed.

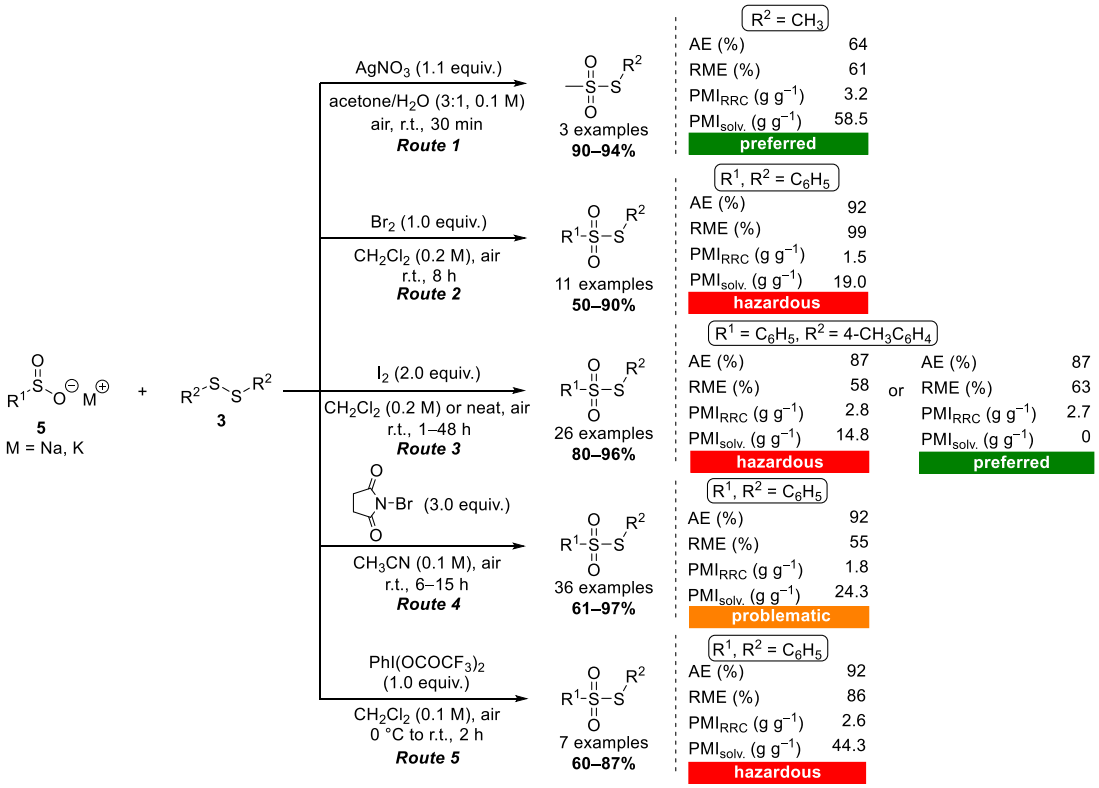


Scheme 36. Regioselectivity issue in the direct oxidation of disulfides (**3**) or thiols (**1**).

One of the early methods for the synthesis of unsymmetrical thiosulfonates (**7**) from sulfinates (**5**) was discovered by the Field group (Scheme 37).[106] Sodium sulfinates (**5**) were first transformed in the corresponding sulfonyl iodides (**83**) *via* oxidation with iodine. Subsequent nucleophilic substitution (S_NAE) with a silver thiolate (**84**) in *highly hazardous* benzene delivered the thiosulfonates (**7**) in moderate yield. This has been illustrated for *S*-(2-acetamidoethyl) thiosulfonates (**85**). Notably, in contrast to sulfonyl chlorides (**6**) (Scheme 21) no disulfide (**3**) formation, *via* nucleophilic attack of the thiol (**1**) on the thiosulfonate (**7**) reaction product, was observed when sulfonyl iodides (**83**) were employed.



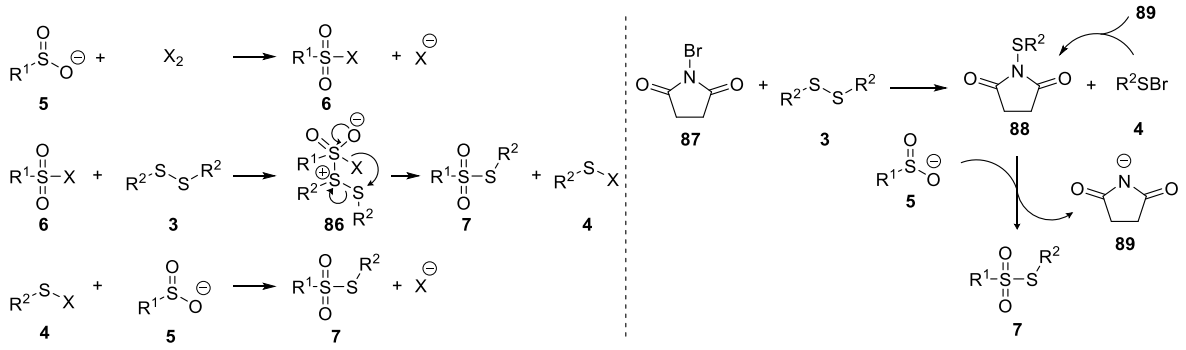
Scheme 37. Synthesis of *S*-(2-acetamidoethyl) thiosulfonates (**85**).



Scheme 38. Reactions of alkali metal sulfinate salts (**5**) with disulfides (**3**) in the presence of an activator (Lewis acid or reagent).

Another successful strategy for the synthesis of unsymmetrical thiosulfonates (**7**) comprised the coupling of alkali metal sulfinates (**5**) with disulfides (**3**) in the presence of a promoter to activate the *S-S* bond (Scheme 38). In this case sodium sulfinates (**5**) act as a nucleophile rather than being transformed into an electrophile as in the Field approach.[106] The disulfide is activated by a Lewis acid or transformed into a more electrophilic species. In 1972 Bentley reported the activation of alkyl disulfides (**3**) by silver nitrate (route 1).[107] Although unsymmetrical *S*-alkyl methanethiosulfonates (**7**) are formed in high yield in a *preferred* solvent, the stoichiometric amount of toxic silver waste is not beneficial in terms of the *green* credentials of this method. The groups of Langlois[65] and Fujiki[108] employed bromine (route 2) or iodine (route 3) for the activation of the disulfide bond resulting in a lower PMI. Unfortunately, reactions were performed in *hazardous* dichloromethane. Interestingly, the

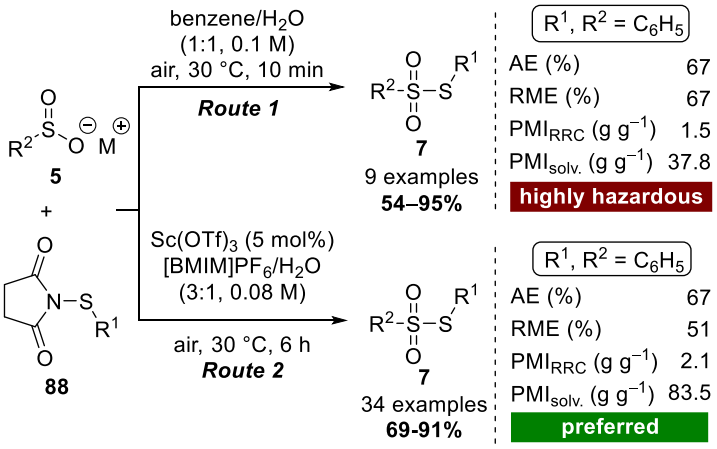
latter method can also be performed in the absence of solvent, thereby eliminating the main disadvantage associated with this route and reducing the PMI by 83%! With iodine or bromine as activator a double reaction is actually occurring in which sulfinate salt (**5**) is both transformed into an electrophile and acts directly as a nucleophile (Scheme 39, left). The mechanism starts *via* reaction of X_2 with the alkali metal sulfinate (**5**) generating a sulfonyl halide (**6**), which subsequently undergoes nucleophilic sulfenylation with the disulfide (**3**) to produce the desired thiosulfonate (**7**) and an unstable sulfenyl halide (**4**). The latter can then react with another molecule of sulfinate salt (**5**) to give an additional thiosulfonate molecule (**7**, *vide supra*). Also other leaving groups can be introduced on sulfur.



Scheme 39. Reaction of alkali metal sulfinates (**5**) with disulfides (**3**) *via* a mechanism involving halogens (X = Br or I) (left) or *N*-bromosuccinimide (**87**, right) as activator.

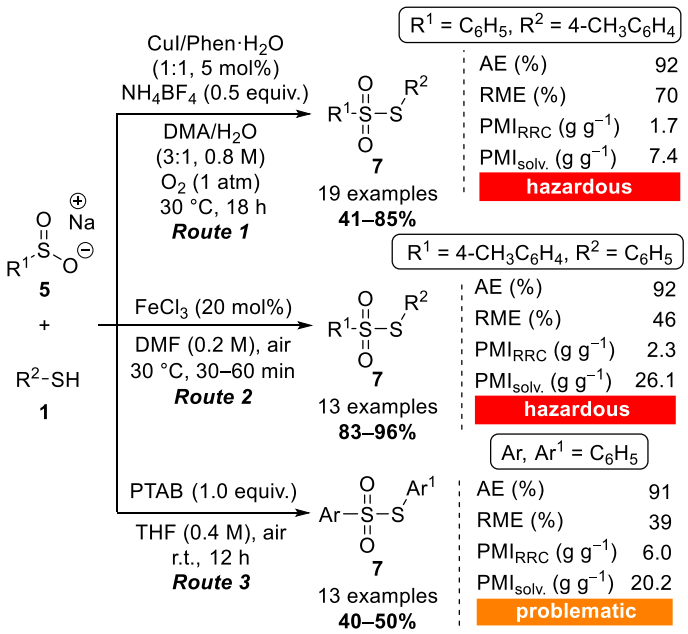
In 2012 Wu developed a strategy based on *N*-bromosuccinimide (NBS) (**87**) as oxidizing reagent (Scheme 38, route 4).[109] The NBS promotes the cleavage of the disulfide bond and thus affords reactive *N*-(organothio)succinimides (**88**) and sulfenyl bromides (**4**) as intermediates (Scheme 39, right). Next, *N*-(organothio)succinimide (**88**) can act as an electrophile and undergo sulfenylation with the alkali metal sulfinate (**5**) to produce the desired thiosulfonate (**7**) along with a succinimide salt (**89**). Sulfenyl bromide **4** can also be converted into the *N*-(organothio)succinimide reactant **88** *via* a reaction with **89**. *N*-(Organothio)succinimides (**88**) have also been used as sulfenylating reactants without *in situ* preparation. In 1972, the Abe group reported treating them with sodium sulfinates (**5**) to obtain a series of thiosulfonates (**7)** (Scheme 40, route 1).[110] *Highly hazardous* benzene as solvent is less appealing in the context of *green* chemistry, but this was later replaced by an ionic liquid (IL) / water co-solvent system in the presence of $Sc(OTf)_3$ that acts as a Lewis acid catalyst (route 2).[111] The reaction PMI for both routes is rather high, but in case of the latter the $Sc(OTf)_3$ / ILs could be reused five times without significant loss in catalytic activity, improving the overall *greenness* of the reaction. This is not taken into account in the PMI calculation shown here. Besides NBS, [bis(trifluoroacetoxy)iodo]benzene (BTIB) can also act as activator of both aliphatic and aromatic disulfides (Scheme 38, route 5).[112] This process presumably proceeds *via in situ* generated $RSOCOCF_3$. The BTIB-based method however

features a high reaction PMI mainly due to the use of *hazardous* dichloromethane and the generation of halogenated byproducts.



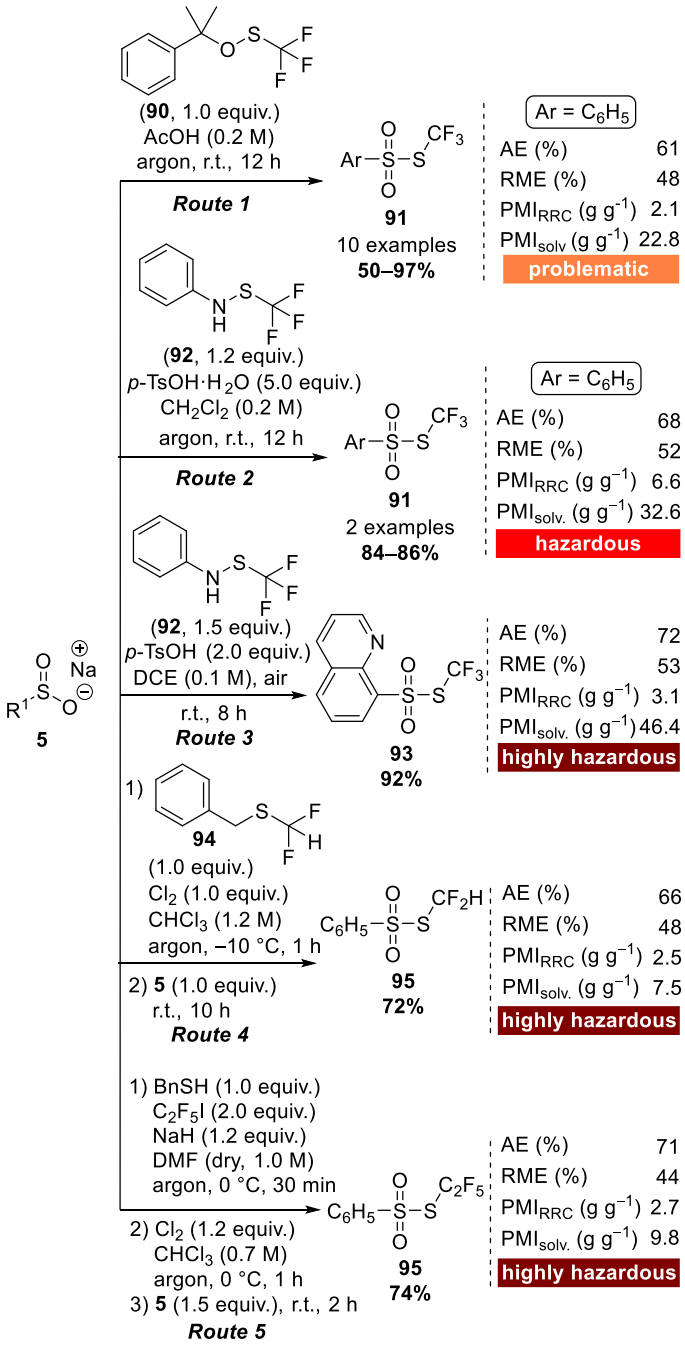
Scheme 40. Synthesis of thiosulfonates (**7**) from *N*-(organothio)succinimides (**88**) and alkali metal sulfinates (**5**). [BMIM]PF_6 = 1-butyl-3-methylimidazolium hexafluorophosphate.

Besides disulfides (**3**), thiols (**1**) have also been employed as coupling compounds with sodium sulfinates (**5**). Under oxidative conditions thiols (**1**) will also form disulfides (**3**), which should act as reactants as well. Recently, transition metal catalysts have been employed to facilitate this process, because they have the ability to cleave the *in situ* generated disulfides (**3**). For example, Taniguchi utilized a catalytic system based on CuI/1,10-phenantroline to obtain thiosulfonates (**7**) with O_2 in moderate to high yield (Scheme 41, route 1).[113] Although the role of NH_4BF_4 is not clear and *hazardous N,N*-dimethylacetamide (DMA) is employed, the PMI and PMI_{RRC} are rather low compared to the previously discussed methods (Schemes 37-38, 40). Alternatively, in 2016 a $FeCl_3$-catalyzed radical cross-coupling of thiols (**1**) with sodium sulfinates (**5**) using air as oxidant was proposed for the preparation of both symmetrical and unsymmetrical thiosulfonates (**7**) (Scheme 41, route 2).[114] Despite high yields and a short reaction time, unfortunately this route specifically requires *hazardous N,N*-dimethylformamide as solvent, although the polar aprotic solvent screening was not intensive. The PMI is also substantially higher compared to the Taniguchi conditions, mainly due to the solvent. Sarkar *et al.* identified trimethyl phenylammonium tribromide (PTAB) as an effective coupling reagent for the oxidative coupling of sodium sulfinates (**5**) and thiols (**1**) (Scheme 41 route 3).[115] The sodium sulfinate (**5**) generates the corresponding sulfonyl bromide (**6**) upon reaction with PTAB, followed by nucleophilic substitution with a thiol (**1**). The method could be extended to sulfonamide synthesis with amines instead of thiols (**1**) as nucleophiles.[115]



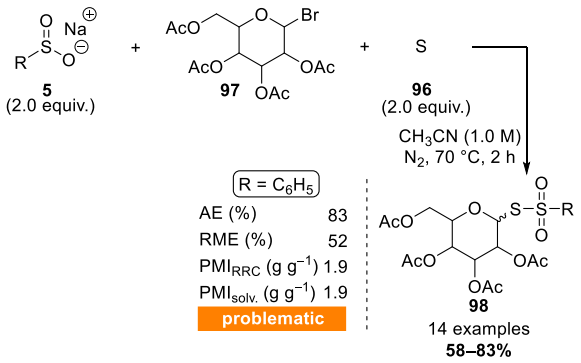
Scheme 41. Oxidative coupling of sodium sulfinates (**5**) with thiols (**1**). PTAB = trimethyl phenylammonium tribromide.

Synthetic synthons to directly introduce fluorinated groups (SR_f) onto organic molecules (see section 4) have witnessed a recent renewal of interest.[8] Therefore, a range of fluorinated thiosulfonates (**91**, **93**, **95**) have been developed as efficient reactants to incorporate SCF_3, SCF_2H, and SCH_2F groups. A common route to prepare these fluorinated thiosulfonates relies on the coupling of sodium sulfinates (**5**) with electrophilic thiolating reactants (Scheme 42). In 2015 the groups of Shen[116] and Jereb[117] applied this strategy for the synthesis of *S*-trifluoromethyl thiosulfonates (**91**) with [(2-phenylpropan-2-yl)oxy](trifluoromethyl)sulfane (**90**), (route 1) or trifluoromethanesulfenamide (**92**) (route 2) as electrophilic SCF_3 source. The transformation of Shen tolerates aromatic sodium sulfinates (**5**) bearing electron-donating and -withdrawing groups as well as heteroaromatic derivatives. On the other hand, the Jereb route was only illustrated for two examples. However, Qiu successfully applied the latter methodology for the synthesis of *S*-trifluoromethyl 8-quinolinethiosulfonate (**93**), albeit by using *highly hazardous* 1,2-dichloroethane (DCE; route 3) as a solvent.[118] In 2016 the group of Lu and Shen prepared *S*-(difluoromethyl) benzenethiosulfonate (**95**) *via* a *one-pot* two step procedure from benzyldifluoromethylsulfide (**94**) at 120 mmol (20 g) scale (route 4).[119] Nucleophilic substitution of *in situ* generated HCF_2SCl with $PhSO_2Na$ (**5**) delivers *S*-(difluoromethyl) benzenethiosulfonate (**95**) in good yield. A similar three-step approach was also followed to prepare $PhSO_2SCF_2CF_3$ (**95**) from the commercially available benzyl mercaptan (route 5).[120]



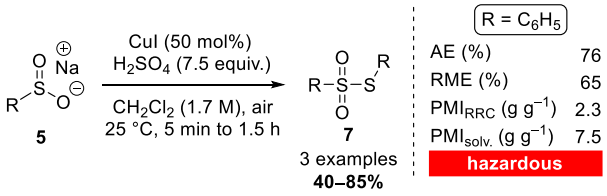
Scheme 42. Synthesis of fluorinated thiosulfonates (**91**, **93**, **95**) from sodium sulfinates (**5**).

Glycosyl benzenethiosulfonates (**98**) could also be obtained from sodium sulfinates (**5**) *via* a *one-pot* three-component coupling with sulfur powder (**96**) and glycosyl bromides (**97**).[121] The reaction probably proceeds via an sodium benzenethiosulfonate intermediate (**51**), followed by alkylation with **97** as illustrated in previous section. The authors demonstrated that those thiosulfonates are valuable reagents for *S*-glycosylation of several organic compounds and proteins.



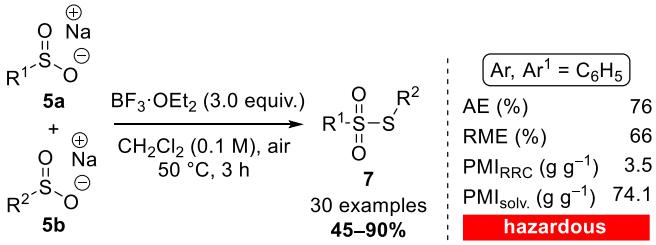
Scheme 43. Synthesis of glycosyl benzenethiosulfonates (**98**) *via* a three-component reaction.

The direct synthesis of *S*-alkyl alkanethiosulfonates and *S*-aryl arenethiosulfonates (**7**) *via* homocoupling of alkali metal sulfinates (**5**) with stoichiometric copper iodide and an excess of sulfuric acid (7.5 equiv) was also reported for a limited number of examples by the group of Oliveira (Scheme 44).[122] The authors did not propose a mechanism for this homocoupling.



Scheme 44. Synthesis of thiosulfonates (**7**) *via* homocoupling of alkali metal sulfinates (**5**).

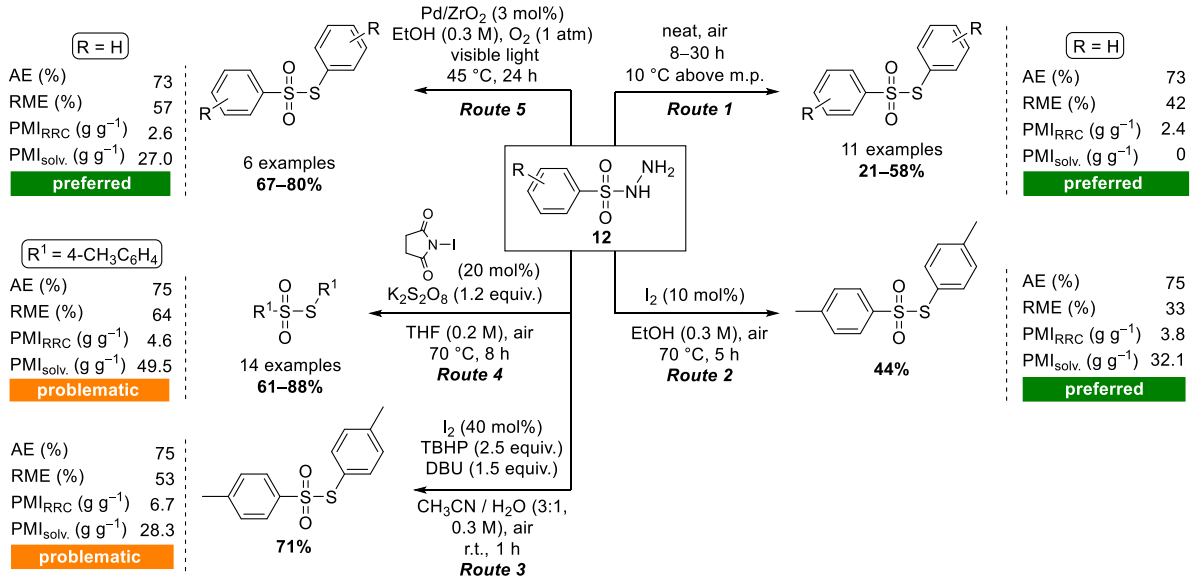
Besides being non-catalytic in nature, the use of concentrated (corrosive) sulfuric acid and *hazardous* dichloromethane makes this approach less appealing. Intrigued by this result, the group of Wang investigated the radical $BF_3{\cdot}OEt_2$-mediated disproportionate coupling reaction of sodium sulfinates (**5a** and **5b**) (Scheme 45).[123] This protocol tolerates many functional groups and is not limited to the *hazardous* dichloromethane, although significantly higher yields were obtained in this solvent. Interestingly, this methodology could even be applied for preparation of unsymmetrical thiosulfonates (**7**). A series of control experiments suggest that thiyl and sulfonyl radicals are involved in the reaction mechanism *via* initial sulfinyl radical disproportionation.



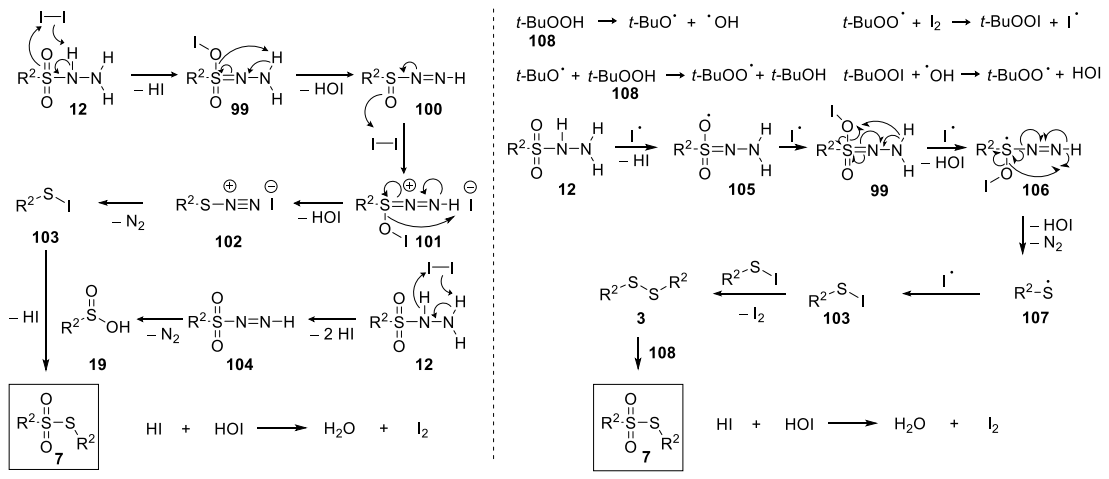
Scheme 45. Disproportionate coupling of sodium sulfinates (**5a** and **5b**) mediated by $BF_3.OEt_2$.

3.8 Thiosulfonate synthesis using sulfonyl hydrazides

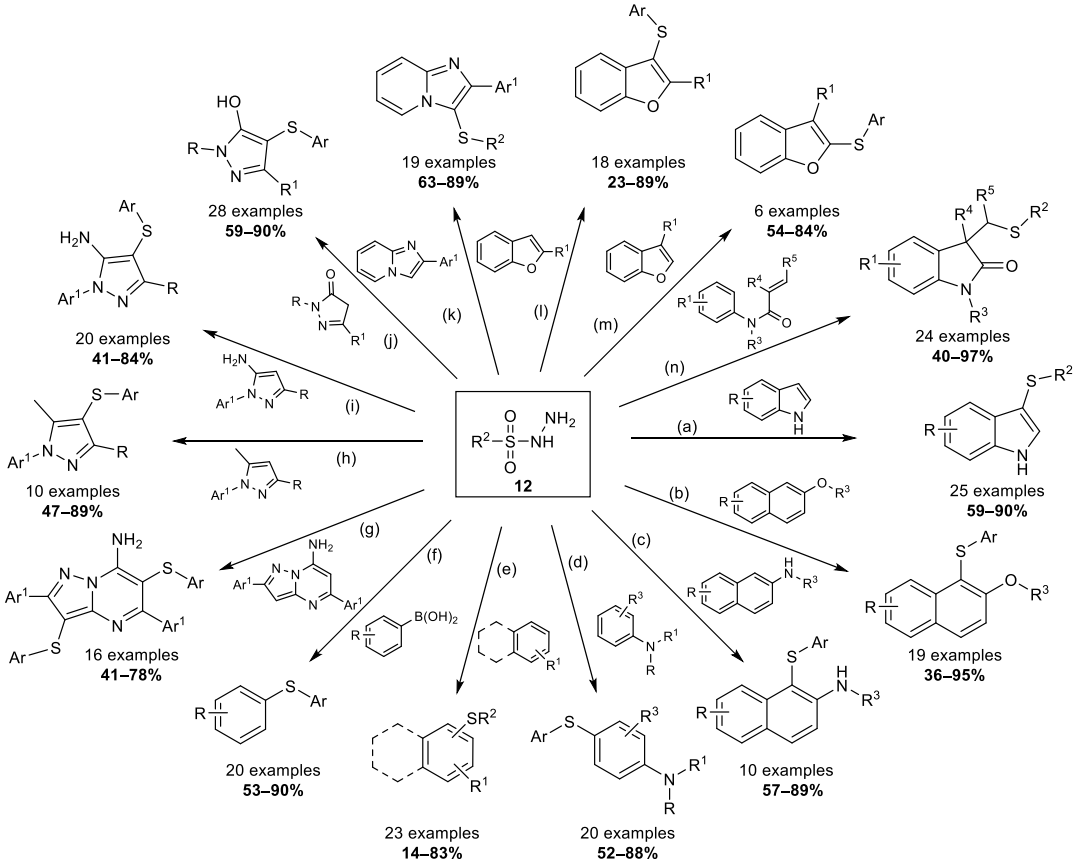
Sulfonyl hydrazides (**12**) are easily accessible and stable solids, which have also been studied for the preparation of symmetrical thiosulfonates (**7**). The first report was presented in 1972 by Meier and Menzel, who discovered the thermal decomposition of arenesulfonyl hydrazides (**12**), with N_2 evolution, upon heating above their melting point (Scheme 46, route 1).[20] The absence of solvent gives a very low PMI, although calorimetric data is required to evaluate the safety of this method for use at scale. The decomposition rate is significantly accelerated in the presence of iodine, as reported by Tian (route 2).[124] Their proposed ionic reaction pathway is depicted in Scheme 47 (left). Reaction of sulfonyl hydrazide (**12**) with iodine (HI production) (two times) and subsequent evolution of N_2 in **104** gives a sulfinic acid (**19**). This can react with a sulfenyl iodide (**103**), which is formed by the stepwise removal of a proton (HI production), proton and oxygen (HOI production) (two times) and nitrogen (N_2 production) from RSO_2NHNH_2 (**12**). The decomposition of *p*-toluenesulfonyl hydrazide (**12**) in the presence of iodine and *tert*-butyl hydroperoxide (**108**) (Scheme 46, route 3) also gave rise to the formation of *S*-*p*-tolyl 4-methylbenzenethiosulfonate as illustrated by Singh, but they proposed a radical pathway for their transformation (Scheme 47, right).[125]



Scheme 46. Decomposition of arenesulfonyl hydrazides (**12**) into thiosulfonates (**7**). TBHP = *tert*-butyl hydroperoxide. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

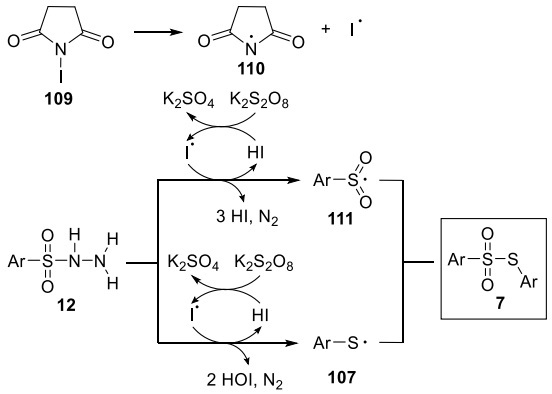


Scheme 47. Proposed reaction pathways for the iodine-catalyzed decomposition of sulfonyl hydrazides (**12**): ionic decomposition (left) and radical decomposition in the presence of TBHP (**108**, right).



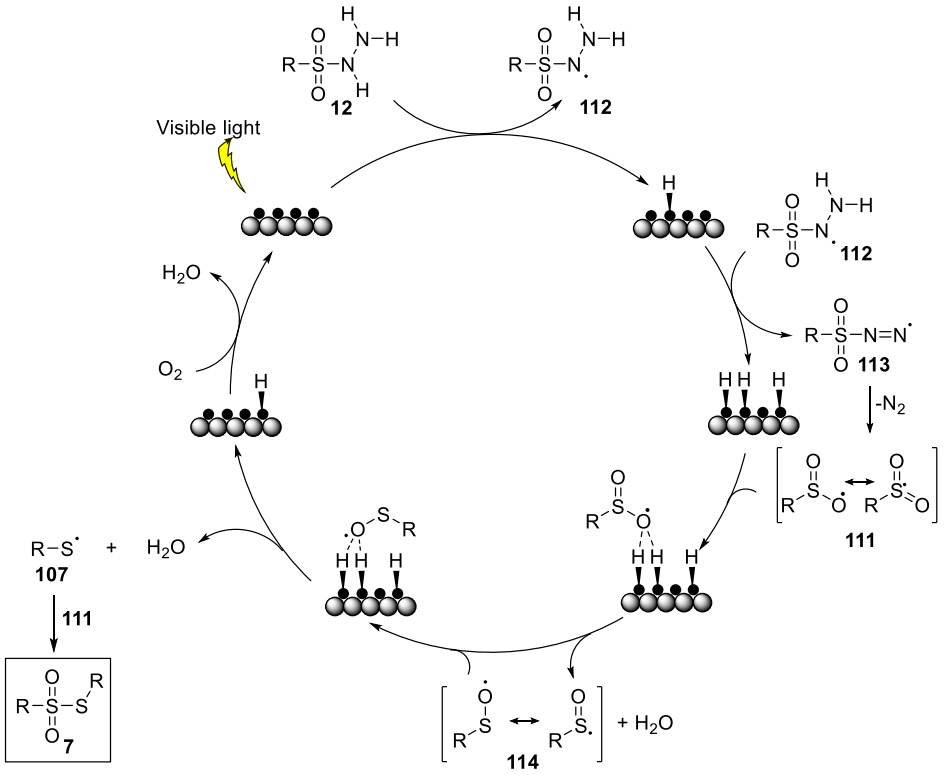
Scheme 48. Sulfonyl hydrazides (**12**) as stable sulfenylating agents for the synthesis of various alkyl/arylthiolated (hetero)cycles. *Reaction conditions:* (a) I_2 (10 mol%), ethanol, 70 °C. (b) I_2 (50 mol%), tetrahydrofuran, 100 °C. (c) I_2 (50 mol%), acetic acid (50 mol%), tetrahydrofuran, 100 °C. (d) I_2 (50 mol%), trifluoroacetic acid (1.2 equiv), tetrahydrofuran, 100 °C, 12 h. (e) I_2 (10 mol%), dichloroethane, 120 °C. (f) I_2 (40 mol%), 1,8-diazabicyclo[5.4.0]undec-7-ene (2.0 equiv), $NiCl_2.6H_2O$ (20 mol%), 2,2'-bipyridine (20 mol%), acetonitrile, rt, 48 h. (g) I_2 (5 mol%), ethanol, 110 °C, 5 h. (h) I_2 (50 mol%), acetic acid (50 mol%), ethanol, 120 °C, 5 h. (i) I_2 (50 mol%), acetonitrile, 100 °C, 5 h. (j) I_2 (5 mol%), *p*-toluenesulfonic acid (50 mol%), isopropanol, 120 °C, 1.5 h. (k) I_2 (20 mol%), ethanol, 70 °C, 10 h. (l) I_2 (10 mol%), 1,4-dioxane, 120 °C, 24 h. (m) I_2 (10 mol%), 1,4-dioxane, 120 °C, 24 h. (n) I_2 (1.0 equiv), dichloroethane, 90 °C, 24 h

The group of Guo illustrated that *N*-iodosuccinimide (NIS) (**109**) and $K_2S_2O_8$ as oxidant could also mediate the formation of a sulfonyl (**111**) and sulfenyl (**107**) radical from sulfonyl hydrazides (**12**) (Scheme 46, route 4).[126] Subsequent radical cross-coupling delivers symmetrical aromatic thiosulfonates (**7**) (Scheme 49). The employment of sulfonyl hydrazides (**12**) as sulfenylating agents has recently emerged as a powerful strategy for the sulfenylation of various heteroarenes with an iodinecatalyst (Scheme 48). The proposed mechanism of these transformations typically involves the decomposition of sulfonyl hydrazides (**12**) into thiosulfonates (**7**)[125, 127] prior to the sulfenylation reaction, although the involvement of a sulfanyldiazonium iodide **102**[124, 128] or sulfenyl iodide[129] (**103**) intermediate (Scheme 47) has been proposed as well.



Scheme 49. Proposed reaction pathway for the radical decomposition of sulfonyl hydrazides (**12**) in the presence of NIS and $K_2S_2O_8$.

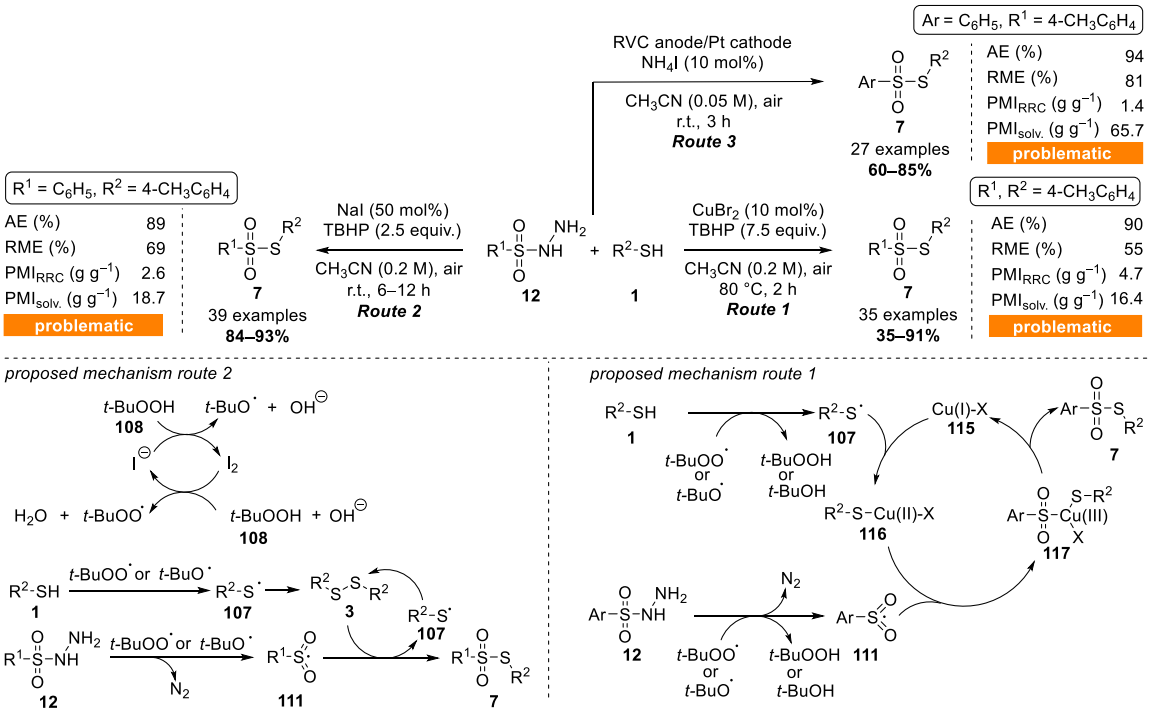
In 2017, Li reported an improved iodine-catalyzed protocol that involves the photocatalytic decomposition of sulfonyl hydrazides (**12**) (Scheme 46, route 5).[130] They employed a heterogeneous recyclable Pd/ZrO_2 photocatalyst and propose a radical decomposition mechanism (Scheme 50) in which the Pd-catalyst generates a sulfonyl radical (**111**) from the sulfonyl hydrazide (**12**) *via* hydrogen atom abstraction under visible light illumination. This is then followed by the release of N_2 from intermediate **113**. Subsequent reduction of sulfonyl radical (**111**) on the H-Pd surface generates water and a sulfinyl radical (**114**). A sulfenyl radical (**107**) is formed *via* a consecutive reduction, which finally reacts with another sulfonyl radical **111** to generate the desired thiosulfonate (**7**). Oxygen regenerates the palladium surface to close the catalytic cycle. The PMI-values in Scheme 46 are comparable to the ones observed in previous sections, the only disadvantage of this process is the lower LD_{50}-value of *tert*-butyl hydroperoxide (**108**). On the other hand, one should not forget that sulfonyl hydrazides (**12**) require hydrazine monohydrate in their preparation,[131] which is considered as a reagent/reactant of high concern (Table 3).[132] Consequently, the decomposition of sulfonyl hydrazides (**12**) is in our opinion not the preferred method for the synthesis of thiosulfonates (**7**).



Scheme 50. Proposed mechanism for the photocatalytic decomposition of sulfonyl hydrazides (**12**).

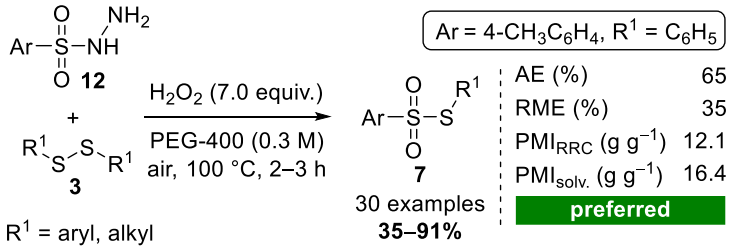
Zou and co-workers reported an alternative strategy allowing to access unsymmetrical thiosulfonates (**7**) based on a selective Cu-catalyzed radical cross-coupling between sulfonyl hydrazides (**12**) and thiols (**1**) (Scheme 51, route 1).[133] Initially a sulfonyl radical (**111**) is formed from sulfonyl hydrazide (**12**) *via* a multistep reaction with a *tert*-butoxy or *tert*-butylperoxy radical alongside the release of N_2. Simultaneously, a thiyl radical (**107**) is generated from a thiol (**1**) *via* oxidation with the same radicals, which can coordinate with a copper-catalyst. Subsequent coordination of the sulfonyl radical (**111**), followed by reductive elimination from the obtained Cu^{III}-intermediate **117** constructs the *S*-*S*(O_2) bond. The group of Chen tried to improve the *greenness* of this methodology by constructing the sulfur-sulfone bond under transition metal-free conditions and by reduction of the excess of *tert*-butyl hydroperoxide (**108**) (route 2).[134] Pleasingly, a reduction in PMI_{RRC} from 4.7 to 2.6 g g $^{-1}$ is observed. A radical mechanism was described for the latter approach (Scheme 51, route 2). After iodide-mediated decomposition of TBHP (**108**), a sulfonyl radical (**111**) ($ArSO_2^{\bullet}$) is obtained from sulfonyl hydrazides (**12**) with the release of N_2. Meanwhile, a thiyl radical (**107**) ($R^1S^{\bullet}$) is generated under the oxidative conditions, which can couple with the sulfonyl radical (**111**) to deliver a thiosulfonate (**7**). Alternatively, thiyl radicals (**107**) can undergo oxidative homocoupling to produce disulfides (**3**), which also could lead to thiosulfonates (**7**) upon reaction with a sulfonyl radical (**111**). In 2018 the Chen group also developed a process for the synthesis of thiosulfonates that did not require a stoichiometric amount of oxidant by using

an electrochemical sulfonylation of thiols (**1**) based on sulfonyl hydrazides (**12**) (route 3).[135] Consequently, the PMI_{RRC} is further reduced to 1.4 g g^{-1}. The replacement of the stoichiometric amount of chemical oxidant with electrons as mass-free reagents prevents production of waste (lowest PMI_{RRC} of routes 1-3), making electro-synthesis an interesting synthetic tool. However, one should pay attention to the very low concentrations required for these electrochemical methodologies, with solvent use actually resulting in the highest overall PMI of the three routes described in Scheme 51.



Scheme 51. Radical cross-coupling of sulfonyl hydrazides (**12**) with thiols (**1**). TBHP = *tert*-butyl hydroperoxide.

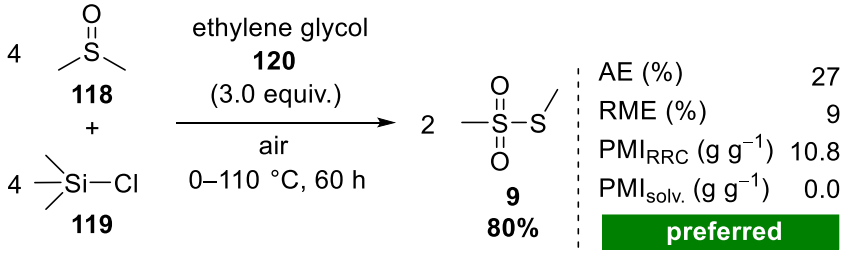
A practical methodology for unsymmetrical thiosulfonates (**7**) from sulfonyl hydrazides (**12**) and disulfides (**3**) has also been reported by Dong (Scheme 52).[136] Although the process runs in the recommended solvent PEG-400, a high PMI_{RRC} was obtained because a large excess of hydrogen peroxide was needed as oxidant. The reaction proceeds *via* a radical pathway, but without the involvement of a transition metal catalyst. The reaction is initiated *via* homolytic cleavage of H_2O_2 upon heating and proceeds *via* a sulfonyl radical (**111**) as shown in route 2 of Scheme 51, which is then transformed into a thiosulfonate (**7**) in the presence of the disulfide (**3**).



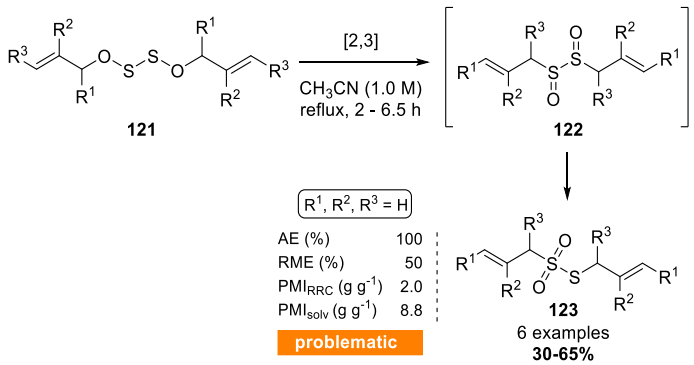
Scheme 52. Unsymmetrical thiosulfonates (**7**) from sulfonyl hydrazides (**12**) and disulfides (**3**).

3.9 Thiosulfonate synthesis using miscellaneous other strategies

S-Methyl methanethiosulfonate (**9**) is one of the most widely employed thiosulfonates (**7**) as it is the simplest representative and commercially available. In 1984, it was shown that this thiosulfonate (**9**) can be efficiently prepared from dimethylsulfoxide (**118**) with chlorotrimethylsilane (**119**) and ethylene glycol (**120**) in a good overall yield (Scheme 53), although unfortunately the authors did not provide a mechanism for this intriguing transformation as the roles of the compounds involved were not fully clear.[137] The PMI-value of this reaction is reasonably low, but on the other hand the AE values is also low due to the large number of atoms from reactants that are not found back in the final product. The RME-value is even lower, which is principally as a result of dimethylsulfoxide (**118**) being employed both as reagent and solvent (over 5 fold excess). In addition, the toxic nature of chlorotrimethylsilane (**119**) (Table 3) should not be ignored.



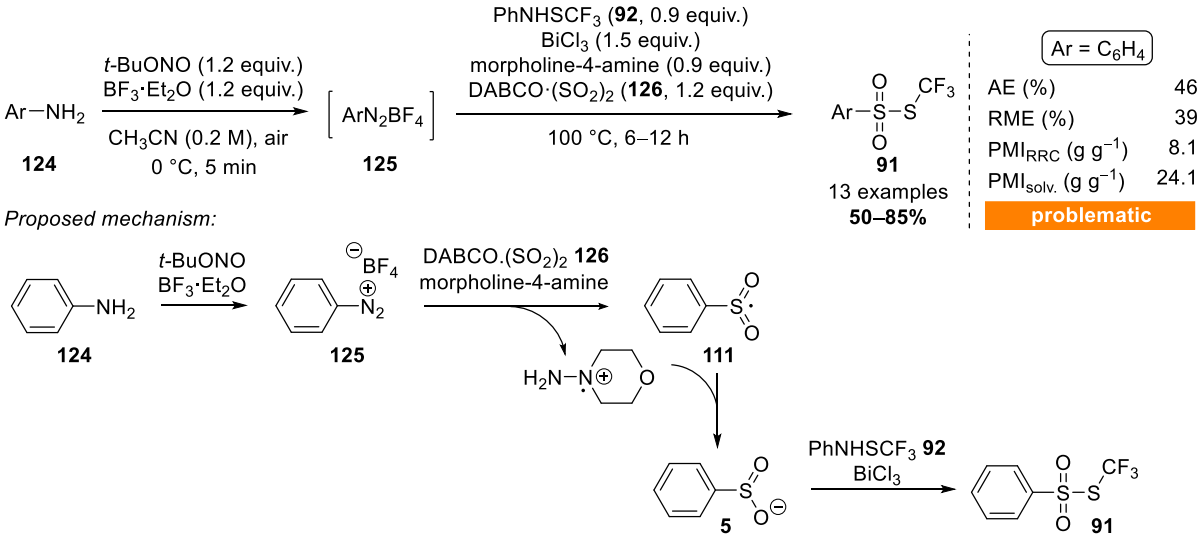
Scheme 53. Synthesis of *S*-methyl methanethiosulfonate (**9**) from DMSO (**118**).



Scheme 54. Synthesis of thiosulfonates **123** by [2,3]-sigmatropic rearrangement of diallyloxydisulfides **121** followed by rearrangement of *vic*-disulfoxides **122**.

Diallyloxydisulfides **121** also yield thiosulfonates upon refluxing in acetonitrile (Scheme 54).[138] The reaction presumably occurs *via* a double [2,3]-sigmatropic rearrangement to the unstable *vic*-disulfoxides **122**, which subsequently rearrange into thiosulfonates **123**. Although the method features low PMI-values, the diallyloxydisulfides **121** have been prepared *via* a reaction of allyl alcohol with the highly toxic disulfur dichloride (S_2Cl_2) (Table 3) in diethyl ether using triethylamine as base.

In 2017, the group of Qiu reported a sequential *one-pot* approach for the synthesis of trifluoromethyl thiosulfonates (**91**) starting from anilines (**124**) with DABCO.$(SO_2)_2$ (DABSO) (**126**) as sulfonyl source (Scheme 55).[118] Bismuth chloride was beneficial for this transformation presumably activating the Billard-Langois reactant; $PhNHSCF_3$ (**92**). Anilines (**124**) bearing both electron-donating and -withdrawing substituents were tolerated well, however the methodology could not be extended towards heteroaromatic nor aliphatic amines. To overcome this issue a complementary approach was developed starting from sulfonyl chlorides as discussed earlier (Scheme 24).[79]



Scheme 55. Synthesis of *S*-trifluoromethyl thiosulfonates (**91**) from anilines (**124**), DABSO (**126**) and $PhNHSCF_3$ (**92**).

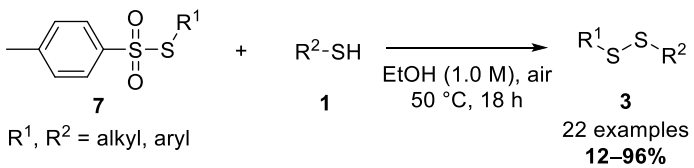
4 Applications of thiosulfonates in synthesis

As reactant for organic transformations, thiosulfonates (**7**) are particularly interesting given their possibility to react with nucleophiles, electrophiles and radicals. Use in transition metal-catalyzed cross-couplings, multicomponent reactions and in polymer chemistry will be discussed below in separate sections given their specific importance, although they obviously also involve reaction of the thiosulfonates (**7**) with nucleophiles, electrophiles or radicals. Besides being electronic chameleons, thiosulfonates exhibit themselves interesting biological activities such as antifungal, and bactericidal activity (*e.g.*, against *Aspergillus niger*, *Aspergillus flavus* or *Staphylococcus aureus*).[63, 139] Their mode of action involves the blocking of the normal metabolism of the microorganism through the sulfenylation of thiol groups in enzymes.[5, 63] Not surprisingly, thiosulfonates have proven useful as a protective group for thiols. Especially for cysteine moieties in peptides, based on the mild conditions required, the non-destructive character for the protein substrate, the high selectivity for the cysteine moieties, and finally the rapid reversibility upon addition of another thiol.[140] Recently, propyl propane thiosulfonate - responsible for the odor of freshly cut onion - has been used as residue marker to evaluate the influence of onion extract on the milk production of cows.[141] Onion extract is used as a feed supplement for dairy cows diet, acting as inhibitor for methane production.

4.1 Sulfenylation and sulfonylation of nucleophiles

4.1.1 Sulfur nucleophiles

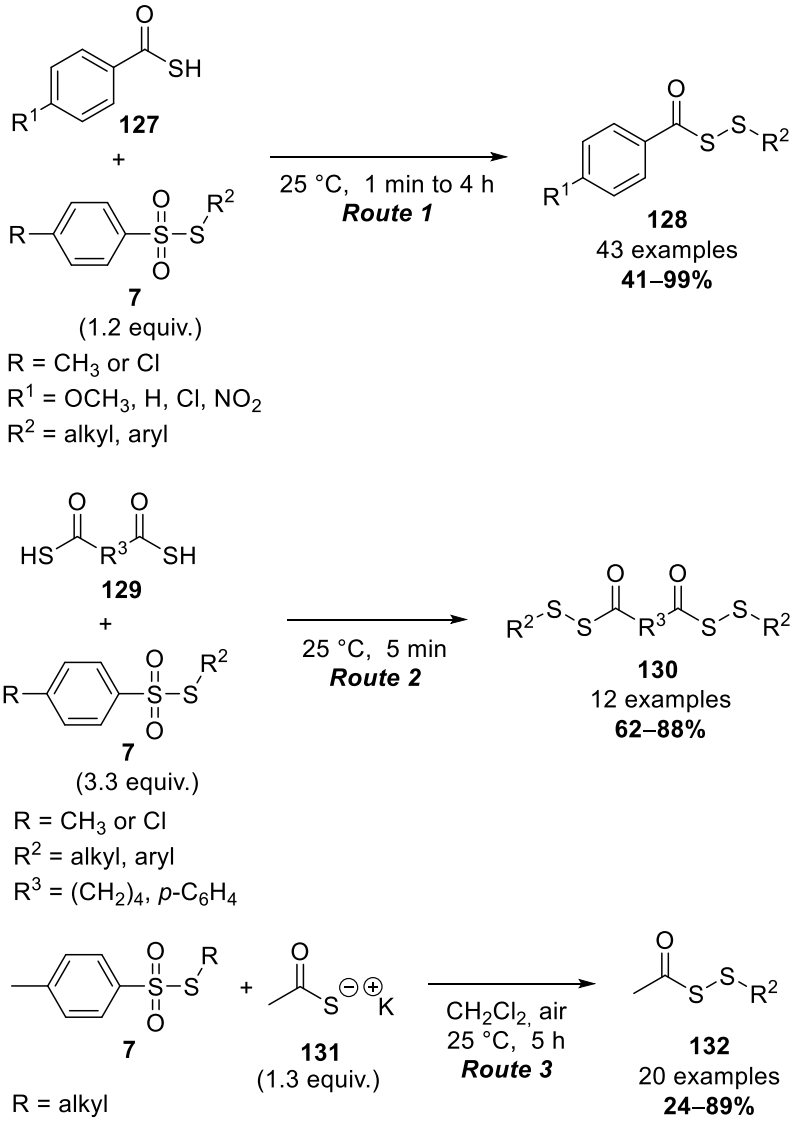
As previously indicated, the fast nucleophilic attack of a thiol (**1**) on thiosulfonates (**7**) with formation of disulfides (**3**) is an often observed side reaction during thiosulfonate (**7**) synthesis. This reactivity has also been exploited for the synthesis of unsymmetrical disulfides (**3**) by Field in 1965, although the reaction is generally difficult to control and conditions to obtain descent yields were highly substrate-dependent.[142] A generally more applicable route using ethanol as crucial polar solvent for high yields was developed recently by Taniguchi which did not require addition of base (Scheme 56).[143]



7 **1** **3**

Scheme 56. Unsymmetrical disulfide (**3**) synthesis from thiosulfonates (**7**) and thiols (**1**).

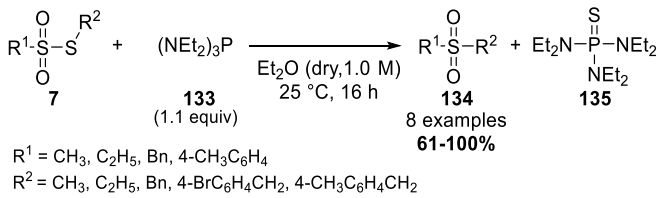
In 2001 Fujiki reported the preparation of various unsymmetrical benzoyl disulfides (**128**) (Scheme 57, route 1) and the related biscarbonyl disulfides (**130**) (route 2) *via* the sulfenylation of thiobenzoic acids **127** and **129** with thiosulfonates at room temperature under solvent-free conditions.[144] Strong electron-withdrawing groups on the thiobenzoic acids **127** (*e.g.*, nitro-groups) required longer reaction times and an amine both as activator of the thiol and as a trapping agent of the liberated sulfinic acid (**19**). Aliphatic thioacids (**129**, **131**) could also be used and in some case the salt was used (e.g. potassium thioacetate (**131**)).[145] These reactants have been used for the construction of diverse unsymmetrical disulfides by oxidative cross-coupling.[145-146]



Scheme 57. Unsymmetrical benzoyl disulfide (**128**), related biscarbonyl disulfide (**130**) and acetyl disulfide (**132**) synthesis.

4.1.2 Amine, oxygen and phosphor nucleophiles

Nucleophilic aminophosphines such as tris(diethylamino)phosphine (**133**) react with the sulfenyl sulfur moiety of thiosulfonates (**7**) releasing sulfinate anion, which can then undergo *S*-alkylation giving rise to sulfones (**134**) in good yield as illustrated by Harp in 1970 (Scheme 58).[147]

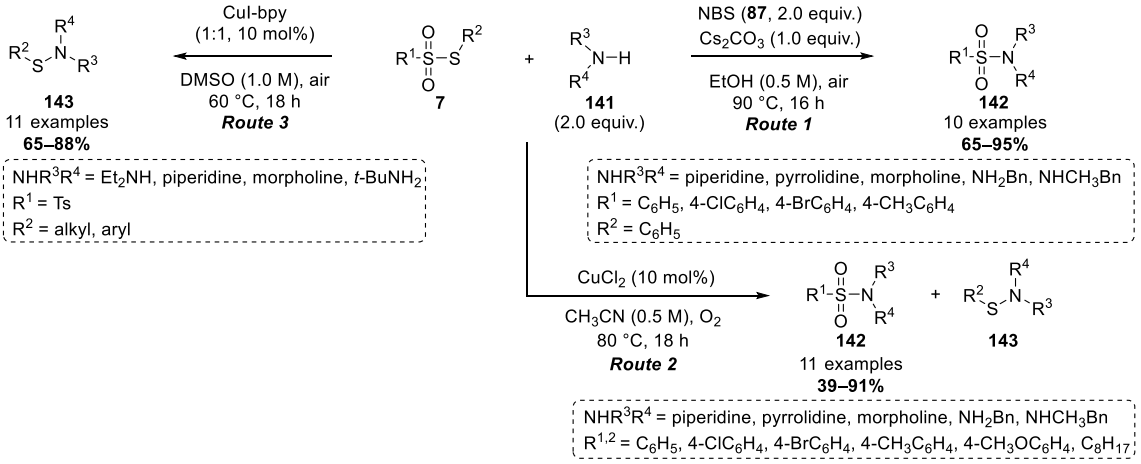


Scheme 58. Reaction of thiosulfonates (**7**) with aminophosphines (**131**).

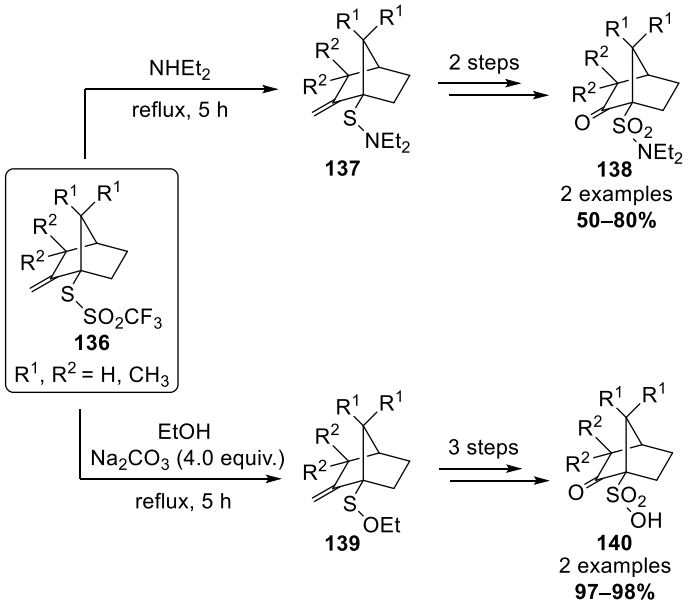
The nucleophilic attack of amines or alcohols on the *S*(II)-atom of thiosulfonates was examined by the Martinez group. Solvolysis of substituted 1-norbornyltrifluoromethanethiosulfonates (**136**) **-** thiosulfonates derived from (+)-camphor **-** in ethanol or diethylamine delivered respectively the corresponding sulfenate esters **139** and sulfenamides **137** (Scheme 60).[148] These compounds are promising precursors of a wide variety of chiral catalysts and ligands.

In 2017 the Jang group presented a strategy for the preparation of sulfonamides (**142**) from thiosulfonates (**7**) and secondary amines (**141**) in the presence of NBS (**87**) (Scheme 59, route 1).[149] Because halogenation of the amines **141** by NBS occurs prior to the reaction with sulfinate anions, sulfenamides (**143**) - formed by addition of amines to the divalent sulfur moiety of thiosulfonates (**7**) - were not observed. The sulfinate anions are presumably formed *via* initial reaction of the alcohol (solvent) with the thiosulfonate followed by reaction with the halogenated amines. The reaction does not tolerate aromatic amines as they underwent competitive aromatic bromination instead of *S*-*N* bond formation. A similar strategy was followed by Reddy and co-workers for the N^2-sulfonylation of 1,2,3-triazoles (**144**) with thiosulfonates (**7**) in the presence of NBS (**87**) or iodine (Scheme 61).[150] Jang discovered that a copper-catalyst could also facilitate the coupling of thiosulfonates and amines to give sulfonamides (**142**) though in combination with sulfenamides (**143**) (Scheme 59, route 2).[151] Initial sulfenamide (**143**) formation *via* nucleophilic attack of the amine **141** to a thiosulfonate (**7**) delivers a sulfinate anion, which then reacts with the Cu^{II}-catalyst and an amine. Subsequent reductive elimination generates a sulfonamide (**142**) and Cu^0. To continue the catalytic cycle, Cu^0 undergoes oxidative addition with a thiosulfonate (**7**), which subsequently reacts with an amine to give the desired sulfonamides (**142**). Interestingly, altering the reaction conditions gives sulfenamides (**143**) as major compound (route 3).[143, 152] When a mixture of

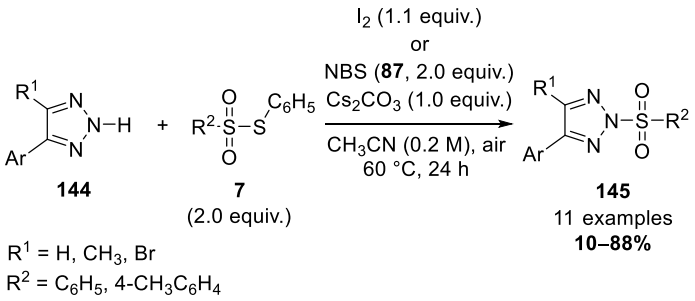
thiosulfonates (**7**) and amines (**141**) in dimethyl sulfoxide was treated with a copper-catalyst, the corresponding sulfenamides were obtained *via* a radical mechanism.[143]



Scheme 59. Synthesis of sulfonamides (**142**) and sulfenamides (**143**) from thiosulfonates (**7**) and secondary amines (**141**).



Scheme 60. Synthesis of 1-norbornanesulfenate esters **139** and sulfenamides **137**.



Scheme 61. *N*2-sulfonylation of 1,2,3-triazoles (**144**) with thiosulfonates (**7**).

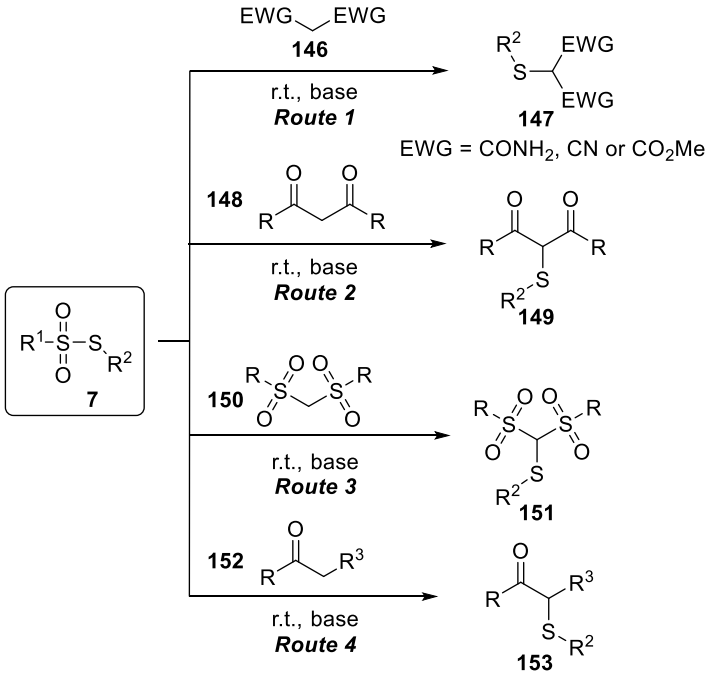
4.1.3 Carbon nucleophiles

The formation of carbon-sulfur bonds is a very important transformation in organic chemistry as this type of σ-bonds occur frequently in biologically active compounds.[1c, 3] A plethora of methods have been developed for such thioether (**2**) synthesis.[153],[154],[155] Amongst them, thiosulfonates (**7**) have proven to be very powerful sulfenylating reactants.

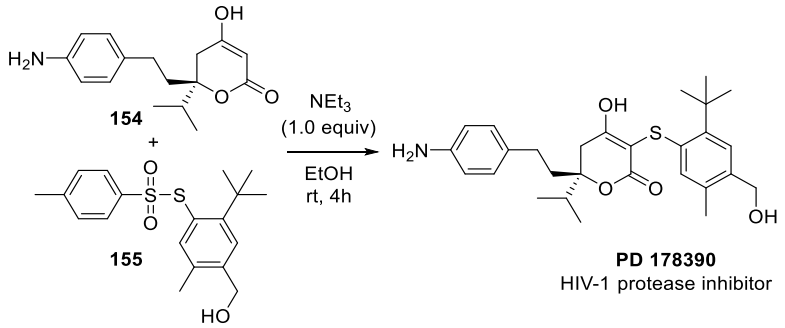
4.1.3.1 Active methylene groups

In the past decades, thiosulfonates (**7**) have been used extensively for the sulfenylation of building blocks containing active methylene groups such as: dicarboxylic esters **146** and related systems,[156] 1,3- diketones (**148**),[157] 1,1-disulfones (**150**)[158] or ketones (**152**) (Scheme 62, routes 1-4 respectively).[159] The synthetic utility is discussed below in more detail.

In 2000 Prasad described the synthesis of a lead inhibitor (PD 178390) of Human Immunodeficiency Virus-1 protease (Scheme 63).[76] The preparation of this non-peptidic inhibitor involves the introduction of a 2-*tert*-butyl-4-hydroxymethyl-5-methylphenyl-sulfenyl moiety to a 5,6-dihydropyran-2-one core *via* the corresponding thiosulfonate (**155**).[76]

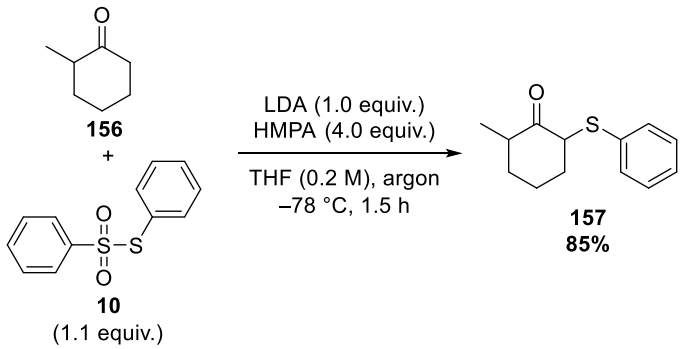


Scheme 62. Sulfenylation of building blocks containing active methylene groups with thiosulfonates (**7**).

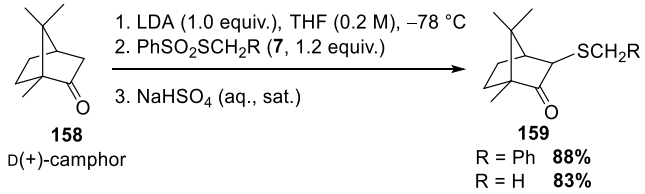


Scheme 63. Synthesis of a HIV-1 protease inhibitor PD 178390 *via* sulfenylation with thiosulfonate **155**.

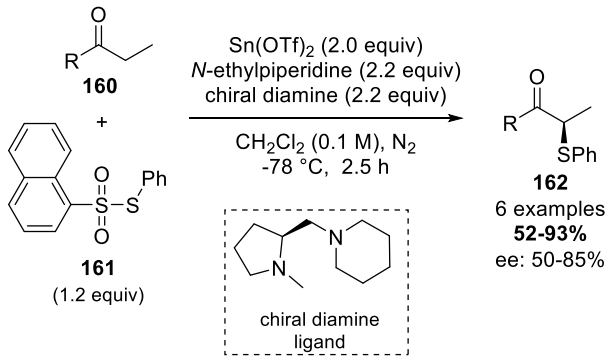
Since Trost reported the direct sulfenylation of ketone enolates (Scheme 64),[159] several bases have been examined to deprotonate the active methylene. *S*-Alkyl benzenethiosulfonates (**7**) have been employed by Dai and Tang in combination with lithium diisopropylamide (LDA) to introduce the corresponding sulfenyl moiety into D-(+)-camphor (**158**) (Scheme 65).[160] An asymmetric reaction of *in situ* generated tin enolates with thiosulfonates (**7**) delivered chiral β-keto sulfides **162** in the presence of a chiral diamine ligand (Scheme 66).[161] The total synthesis of the natural product (*R*)-(+)-thiolactomycin (**166**) was also achieved by using *S*-3,3-dimethoxypropyl (4-methylbenzene)thiosulfonate (**164**) in the key sulfenylation step. This reaction involves a deconjugative diastereoselective α–sulfenylation of (4*R*)-4-benzyl-3-[(2*E*,4*E*)-2,4-dimethylhexa-2,4-dienoyl]-1,3-oxazolidin-2-one (**163**) employing a chiral auxiliary (Scheme 67).[162]



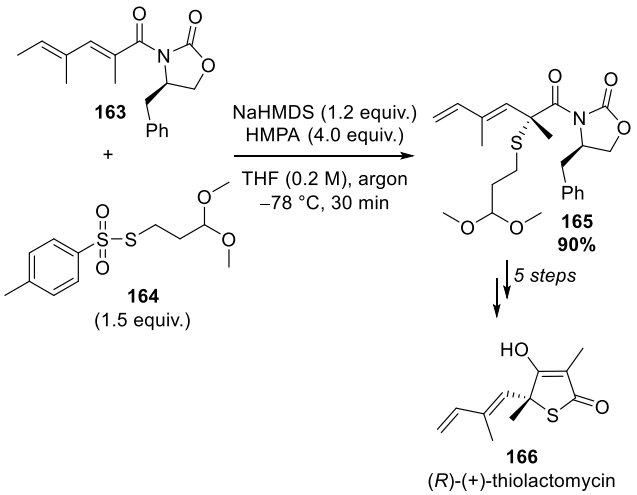
Scheme 64. Regioselective α-sulfenylation of 2-methylcyclohexanone (**156**). HMPA = hexamethylphosphoramide.



Scheme 65. α-Sulfenylation of D-(+)-camphor (**158**).

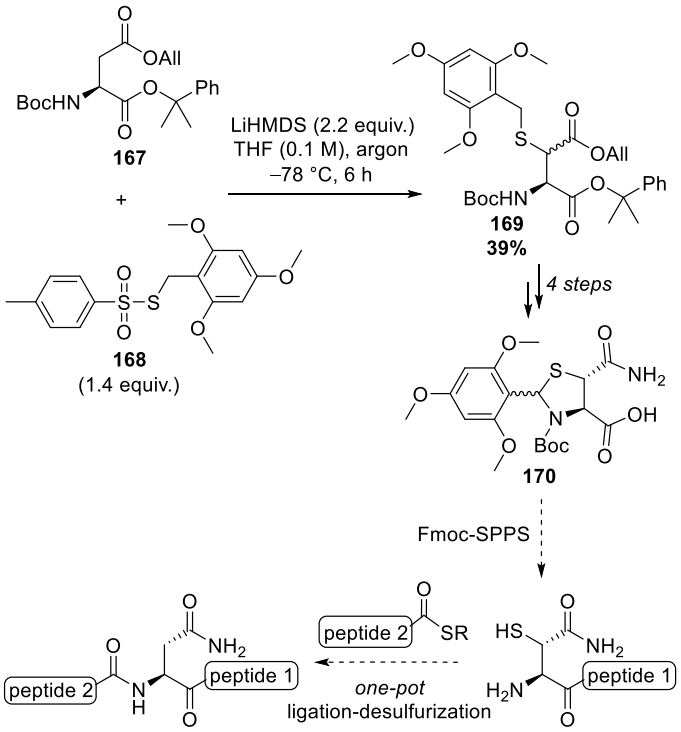


Scheme 66. Asymmetric α–sulfenylation of ketones (**160**) *via in situ* generated Sn^{II}-enolates.

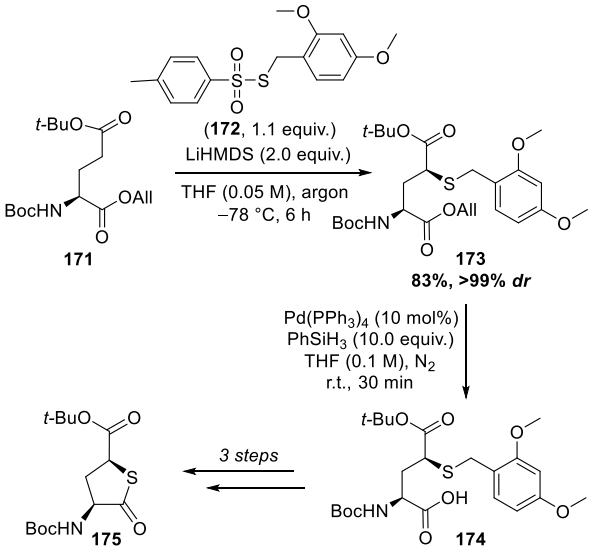


Scheme 67. Deconjugative diastereoselective α-sulfenylation for the synthesis of (*R*)-(+)-thiolactomycin (**166**). NaHMDS = sodium bis(trimethylsilyl)amide. HMPA = hexamethylphosphoramide.

As already mentioned, thiosulfonates (**7**) have shown to be useful reactants in protein chemistry for the introduction of sulfonyl moieties. As the construction of polypeptides *via* native chemical ligation (NCL) is currently limited to cysteine at the *N*-terminus of one peptide fragment, Payne tried to expand this methodology to other amino acids. His group synthesized a β–thiolated asparagine (Asn) (**169**) building block bearing a *S*-(2,4,6-trimethoxyphenyl) protection group derived from the corresponding thiosulfonate **168** (Scheme 68).[163] A similar γ-thiolated glutamic acid (Glu) (**173**) building block was prepared by the same authors from Boc-Glu(O^{t}Bu)-OAll (**171**). The procedure started with the installation of a 2,4-dimethoxybenzylsulfenyl group at the γ-position (Scheme 69).[164] This amino acid building block (**173**) could subsequently be incorporated at the *N*-terminus of peptides and once installed facilitate rapid ligation reactions with peptide thioesters in a similar manner as presented in Scheme 68. To obtain native peptides a *one-pot* radical desulfurization of the □-thiol auxiliary is, however, still required after peptide ligation.

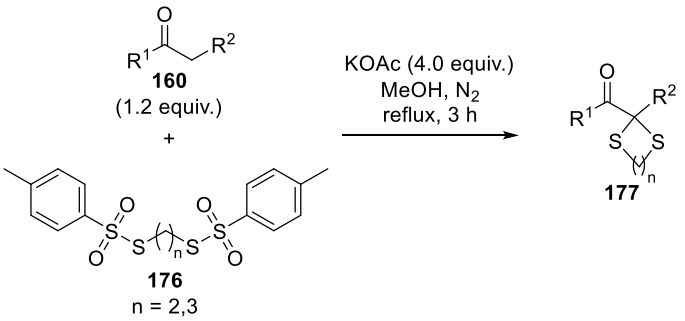


Scheme 68. Synthesis of a β-2,4,6-trimethoxyphenylsulfenyl asparagine (Asn) (**169**) building block. LiHMDS = lithium bis(trimethylsilyl)amide. SPPS = solid-phase peptide synthesis



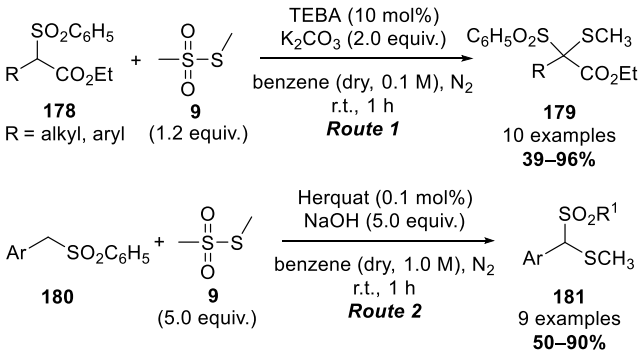
Scheme 69. Synthesis of a γ-2,4-dimethoxybenzylsulfenyl glutamic acid (Glu) (**173**) building block.

Scheinbaum introduced trimethylene and ethylene bisthiosulfonates (**176**) as alternative protecting groups for the activated methylene function in ketones **160** (Scheme 70).[165] The dithioketal group (**177**) obtained in this manner, unlike the acetal groups of analogous oxygen compounds, are remarkably stable under acidic conditions. Regeneration of the methylene compound (**160**) is achieved by using Raney nickel or, alternatively, conversion into a carbonyl can be achieved by $Hg^{(II)}$-catalyzed hydrolysis.[165]



Scheme 70. Bisthiosulfonates (**176**) as a protecting agent for active methylene groups.

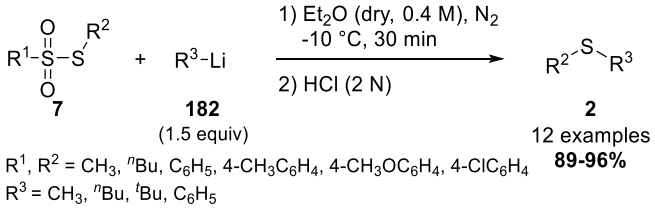
In 1997, the synthesis of α-alkylsulfanyl-α-phenylsulfonyl carboxylic esters (**179**) *via* benzyltriethylammonium chloride (TEBA)-catalyzed sulfenylation based on a solid/liquid phase transfer process (Scheme 71, route 1).[166] The CH-moiety of α-sulfonyl carboxylic esters (**178**) is quite acidic and can be easily deprotonated in basic media, followed by sulfenylation with *S*-methyl methanethiosulfonate (**9**). Earlier work of the same group showed this thiosulfonate already as more effective sulfenylating agent than disulfides for benzylic sulfones (**180**) when using Herquat (a mixture of dialkyl [75% C_{18} : 25% C_{16}] dimethylammonium chlorides)[167] as catalyst and sodium hydroxide as base (route 2).[168]



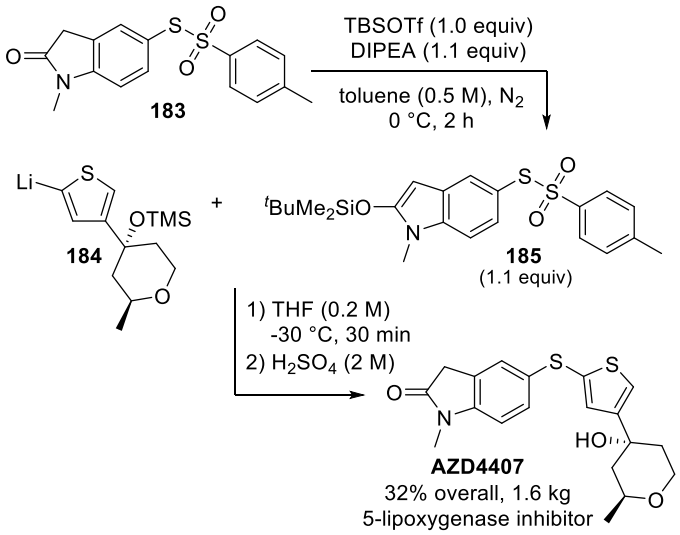
Scheme 71. Synthesis of dithioketal (**179**, **181**) derivatives.

4.1.3.2 Organometallic reactants

Thioether (**2**) formation is not limited to more stable active methylene nucleophiles, but can also be achieved by the nucleophilic attack of organometallic species on the $S^{(II)}$-atom of thiosulfonates (**7**). Palumbo transformed several alkane- and arenethiosulfonates (**7**) into sulfides (**2**) *via* a nucleophilic attack with alkyl- and aryllithium reactants (**182**) (Scheme 72).[169] In 2005 scientists of AstraZeneca applied a similar strategy for the large-scale manufacturing of AZD4407, a 5-lipoxygenase inhibitor (Scheme 73).[170]

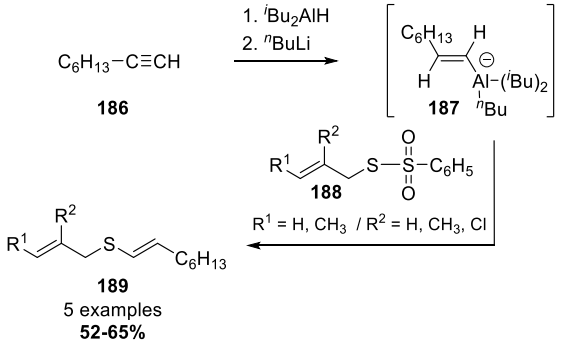


Scheme 72. Synthesis of thioethers (**2**) from thiosulfonates (**7**) and organolithium compounds (**182**).



Scheme 73. Synthesis of AZD4407.

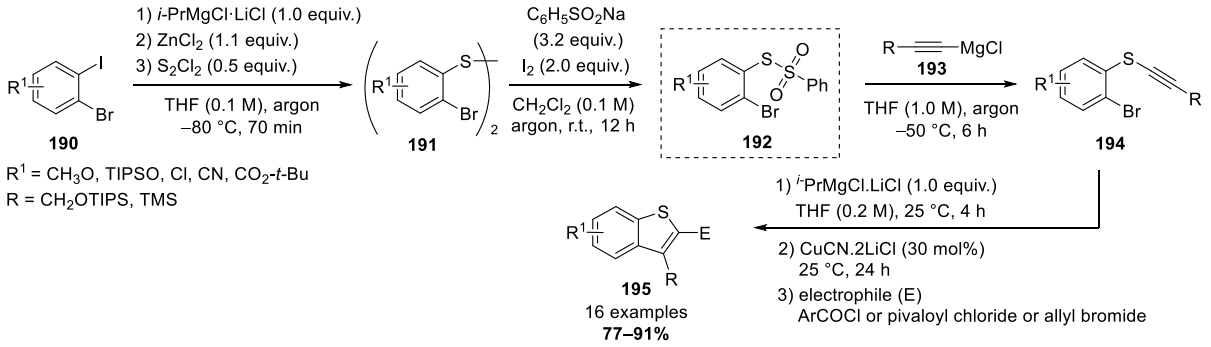
Allyl vinyl thioethers (**189**) were synthesized by a reaction of a vinylalanate **187** with an allyl thiosulfonate (**188**) (Scheme 74).[171] Vinylalanate **187** was prepared by the *cis* hydroalumination of an alkyne (**186**) followed by reaction with ^{n}BuLi. Subsequent cleavage of the carbon-aluminium bond with electrophile **188** delivers an allyl vinyl thioether (**189**) with an *E*-stereochemistry at the vinyl moiety.



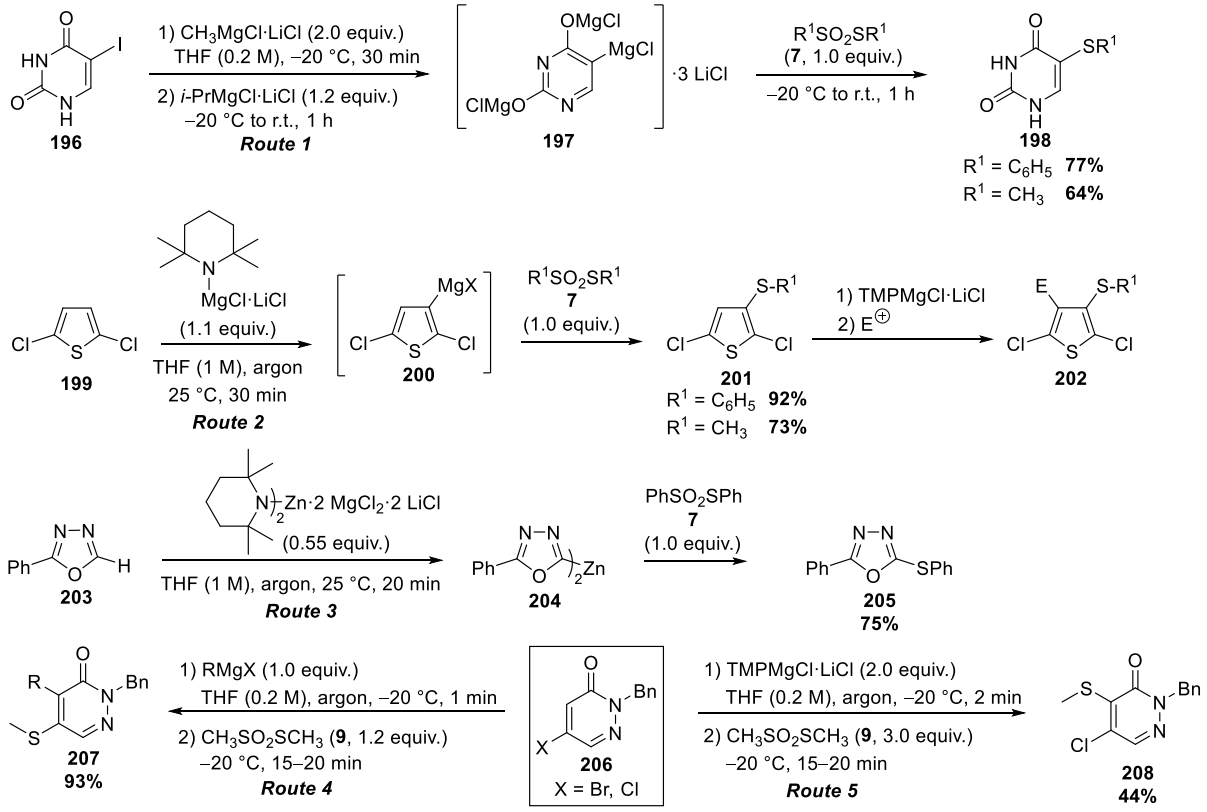
Scheme 74. Synthesis of allyl vinyl thioethers (**189**) *via* sulfenylation of alkynes (**186**) with thiosulfonates (**188**). No experimental details given in the publication.

Knochel combined *S*-(2-bromophenyl) benzenethiosulfonates (**192**) with alkynyl magnesium chlorides (**193**) for the preparation of alkynyl(2-bromophenyl)thioethers (**194**) (Scheme 75).[172] Subsequent bromo-magnesium exchange followed by intramolecular carbocupration and quenching with electrophiles nicely delivered substituted benzo[*b*]thiophenes **195**, which are

biologically active heterocyclic scaffolds.[172] These authors also employed this efficient strategy for the sulfenylation of haloheteroarenes or heteroarenes involving halogen-metal exchange or direct(ed) metalation respectively (Scheme 76). This has been illustrated on 5-iodouracil (**196**) (Scheme 76, route 1),[173] 2,5-dichlorothiophene (**199**) (route 2)[174] and 2-phenyl-1,3,4-oxadiazole (**203**) (route 3).[175] The Maes group used *S*-methyl methanethiosulfonate (**9**) as an electrophile to quench magnesiated pyridazin-3(2*H*)-ones (**206**) (routes 4 and 5).[176] 4,5-Disubstituted pyridazin-3(2*H*)-ones (**207**) were unexpectedly obtained *via cine*-substitution on 2-benzyl-5-halopyridazin-3(2*H*)-ones (**206**) when these substrates were treated with a Grignard reactant followed by thiosulfonate quenching (route 4). However, less nucleophilic and basic magnesium amides (*e.g.*, TMPMgCl.LiCl) allowed the regioselective C-4 magnesiation of 2-benzyl-5-chloropyridazin-3(2*H*)-one (**206**). Quenching of this magnesiated pyridazin-3(2*H*)-one gave access to 2-benzyl-5-chloro-4-(methylthio)pyridazin-3-(2*H*)-one (**208**) (route 5).



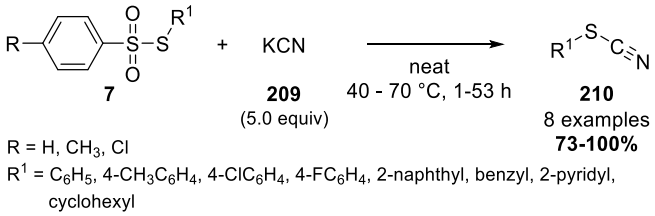
Scheme 75. Synthesis of alkynyl(2-bromophenyl)thioethers (**194**) and subsequent transformation into benzo[*b*]thiophenes (**195**). TIPS = triisopropylsilyl. TMS = trimethylsilyl.



Scheme 76. Thioether synthesis *via* halogen-metal exchange of haloheteroarenes and direct(ed) metalation of heteroarenes followed by quenching with thiosulfonates. TMP = 2,2,6,6-tetramethylpiperidine.

4.1.3.3 Cyanide as nucleophile

Nucleophilic SO_2-*S* bond scission *via* attack of cyanide on the $S^{(II)}$-atom of thiosulfonates (**7**) gives a range of thiocyanates (**210**) by only mixing the solid thiosulfonates (**7**) with potassium cyanide (**209**). This reaction does not require solvent and occurs at 40 to 70 °C (Scheme 77).[177]

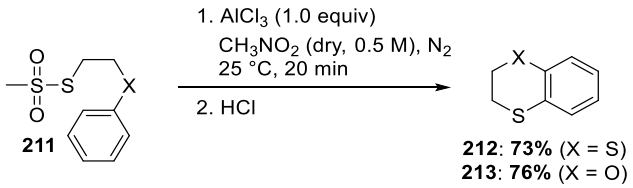


Scheme 77. Reaction of thiosulfonates (**7**) with potassium cyanide (**207**).

4.1.3.4 Electrophilic aromatic substitution

Thiosulfonates (**209**) can react with aromatic compounds in the presence of aluminium trichloride as Lewis acid (Scheme 78).[178] Benzo-1,4-dithiin (**212**) and benzo-1,4-oxathiin

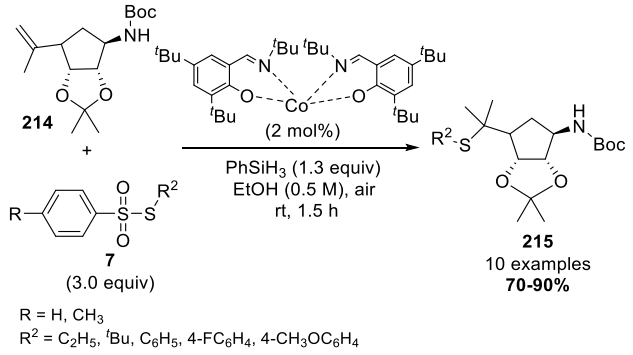
(**213**) have been prepared in this manner *via* an intramolecular electrophilic aromatic substitution.



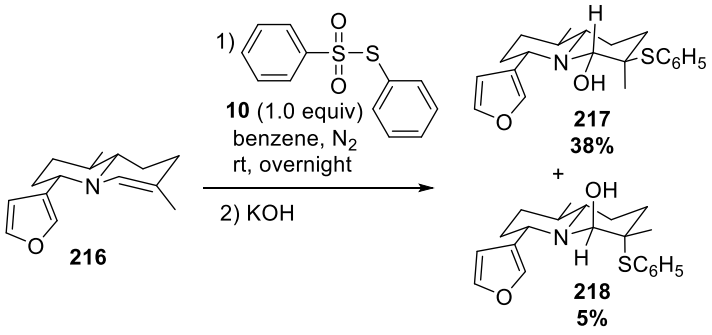
Scheme 78. Electrophilic aromatic substitution.

4.1.4 Sulfenylation of alkenes and arenes

Girijavallabhan employed thiosulfonates (**7**) for the hydrosulfenylation of unactivated alkenes **214** *via* cobalt catalysis (Scheme 79).[179] Silanes were used as proton source. *S*-Phenyl benzenethiosulfonate (**10**) has also been used to convert the enamine functionality in 6-dehydrodeoxynupharidine (**216**) to the corresponding diastereomeric mixture of α-phenylthiohemiaminals (**217**-**218**), which are active against human pathogenic fungi (Scheme 80).[180] α-Phenylthiohemiaminal is obtained from the reaction of *S*-phenyl benzenethiosulfonate (**10**) with the enamine followed by quenching with KOH.

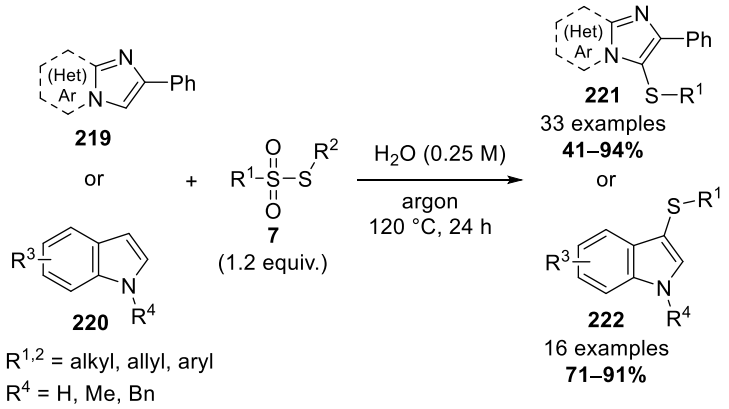


Scheme 79. Cobalt-catalyzed hydrosulfenylation of alkenes.



Scheme 80. Synthesis of α–phenylthiohemiaminal (**217**-**218**) from 6-dehydrodeoxynupharidine (**216**).

Adimurthy *et al.* developed a catalyst-free route for the C-H sulfenylation of a variety of imidazo[1,2-*a*]pyridines (**219**) and imidazothiazoles (Scheme 81).[181] This protocol has a broad functional group tolerance and could easily be extended to C-3 sulfenylation of indoles (**220**). Interestingly, the reaction does not proceed *via* a radical pathway, but rather *via* an electrophilic sulfenylation of the C3 position of the *N*-heteroarene. The authors argue that water as solvent facilitates an initial dissociation of thiosulfonates (**7**) into a sulfinate anion and a sulfenyl cation, the latter is trapped by the electron-rich heteroarenes. However, the observed dissociation could also be induced by the high reaction temperature applied.

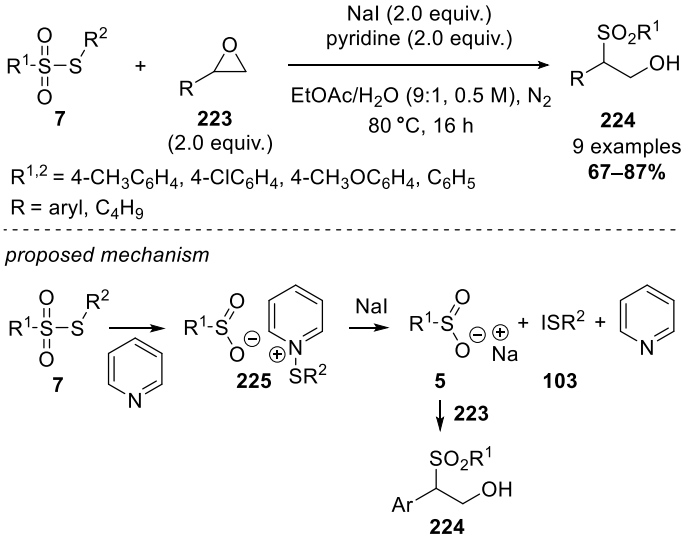


Scheme 81. Sulfenylation of *N*-heteroarenes in water.

4.2. Reaction with electrophiles

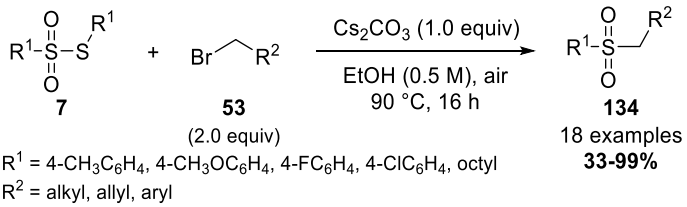
Thiosulfonates (**7**) are not only a very powerful class of electrophilic sulfenylating reactants, but are also capable of reacting with electrophiles such as alkyl bromides (**53**) or epoxides (**223**). However, if one carefully examines the reaction mechanisms of those procedures, it is always an *in situ* transformation of the thiosulfonate (**7**) into a good nucleophile, which facilitates the reaction with the electrophile. Therefore those reactions could formally also be considered as a sulfonylation or sulfenylation of an electrophile.

An example is the regioselective synthesis of variously substituted β-hydroxysulfones (**224**) from thiosulfonates (**7**) and epoxides (**223**), which has been reported by the group of Jang (Scheme 82).[182] A nucleophilic ring opening mechanism involving sulfinate anions (**5**) has been proposed by the authors. The coordination of the sodium cation may build up cationic character proximal to the phenyl group of the epoxides (**223**), which could explain the observed regiochemistry. Sulfinate is formed *in situ via* reaction of thiosulfonate (**7**) with pyridine.



Scheme 82. Synthesis of β-hydroxysulfones (**224**) from thiosulfonates (**7**) and epoxides (**223**).

Similarly, a range of sulfones (**134**) can be prepared when thiosulfonates (**7**) are treated with alkyl bromides (**53**) in the presence of a non-nucleophilic base forming *in situ* alcoholate (Scheme 83).[149] The thiosulfonates (**7**) are first converted into the corresponding sulfinate with alcoholate, which can be further *S*-alkylated with alkyl bromides (**53**) to afford the corresponding sulfones (**134**) in good yields.



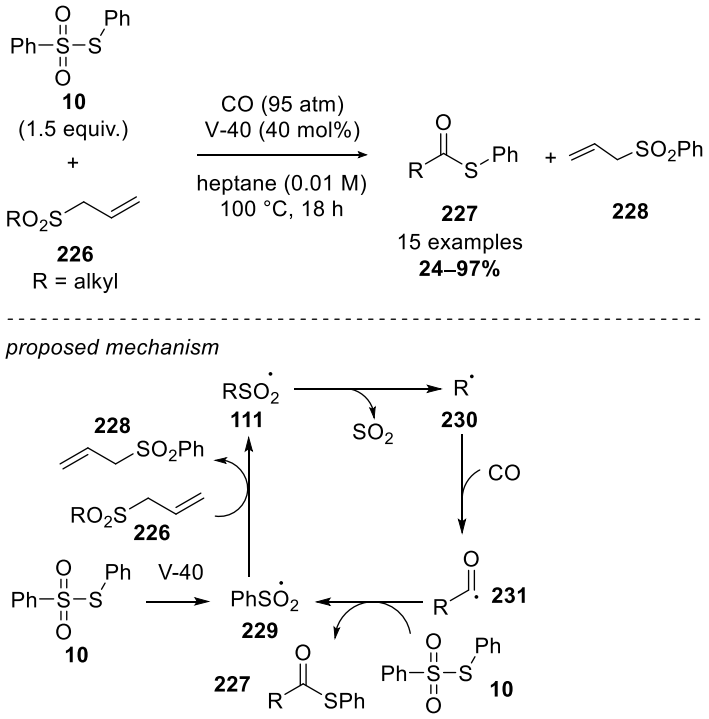
Scheme 83. Synthesis of sulfones (**134**) from thiosulfonates (**7**).

4.3. Radical sulfenylations and sulfonylation

The thermolysis and photolysis of thiosulfonates (**7**) has been extensively studied to generate sulfonyl (**111**, $RSO_2^{\bullet}$) and sulfenyl (**107**, $RS^{\bullet}$) radicals.[183] Whereas *S*-aryl arenethiosulfonates (**7**) are relatively stable to thermolysis below 100 °C, *S*-alkyl alkane-thiosulfonates and *S*-alkyl arenethiosulfonates decompose readily to generate these radical species upon heating. The homolytic cleavage of the *SO2-S* bond however could also occur under much milder conditions utilizing photo-irradiation (*vide infra*).[183a]

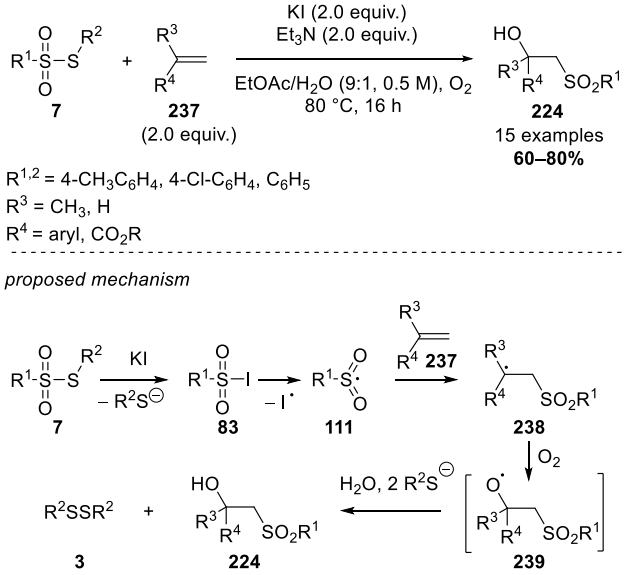
Thiosulfonates (**7**) have only in the last decade been exploited as radical-trapping agents for cascade reactions. In 2005 a radical carbonylation was achieved from alkyl allylsulfones (**226**), delivering an alkyl radical (**230**), under a carbon monoxide atmosphere using *S*-phenyl benzenethiosulfonate (**10**) as the trapping agent (Scheme 84).[184] In the presence of a radical

initiator (V-40; 1,1'-azobis(cyclohexane-1-carbonitrile)), the *SO_2-S* bond of the thiosulfonate undergoes homolytic cleavage to generate a benzenesulfonyl radical (**229**, $PhSO_2^{\bullet}$), which subsequently produces an alkyl radical (**230**, $R^{\bullet}$) through the thermal desulfonylation of the initially generated alkanesulfonyl radical (**111**, $RSO_2^{\bullet}$). The alkyl radical then reacts with CO and finally with **10**, delivering benzenesulfenyl radical (**107**, $PhS^{\bullet}$) trapping agent, to generate a thioester reaction product **227** and a benzenesulfonyl radical **229** for a subsequent reaction cycle (Scheme 84).[184]



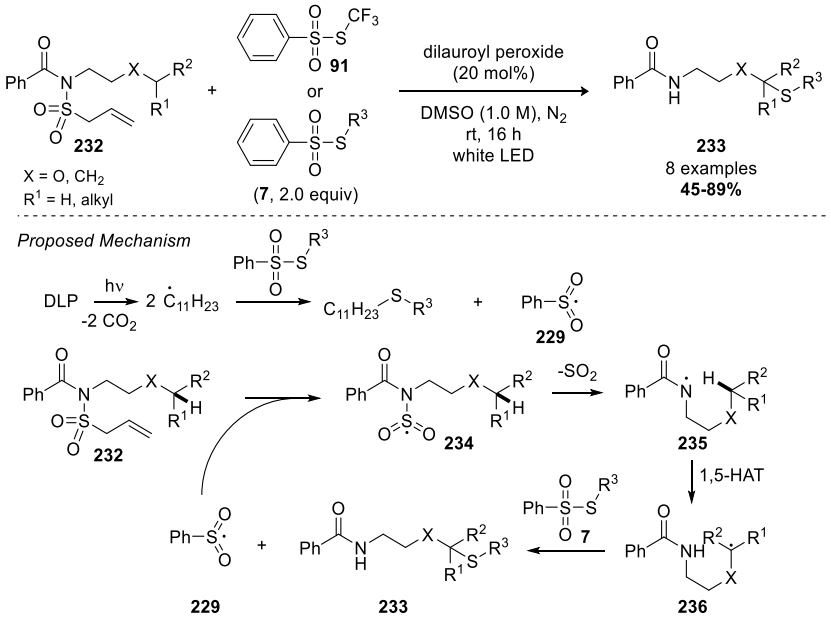
Scheme 84. Synthesis of *S*-phenyl thioesters (**227**) from carbon monoxide, alkyl allylsulfone (**226**) and *S*-phenyl benzenethiosulfonate (**10**). V-40 = 1,1'-azobis(cyclohexane-1-carbonitrile).

Studer and co-workers employed thiosulfonates (**7**) for the remote site-selective functionalization of unactivated aliphatic C-H bonds in various amides **232** *via* radical chemistry (Scheme 865).[185] The reaction is initiated by light induced dilauroylperoxide decarboxylation, which produces benzenesulfonyl radical (**229**, $PhSO_2^{\bullet}$) in reaction with *S*-alkyl benzenethiosulfonate (**7**). The thiolation of the C-H bond is achieved by using a *N*-allylsulfonyl moiety as *N*-radical precursor, *via* reaction with **229**, which engages in an intramolecular 1,5-hydrogen atom transfer (HAT) process to generate a carbon centered radical **236**. Subsequent radical trapping with a thiosulfonate (**7**), provides a thiolated amide **233** along with a benzenesulfonyl radical (**229**), which starts another cycle.



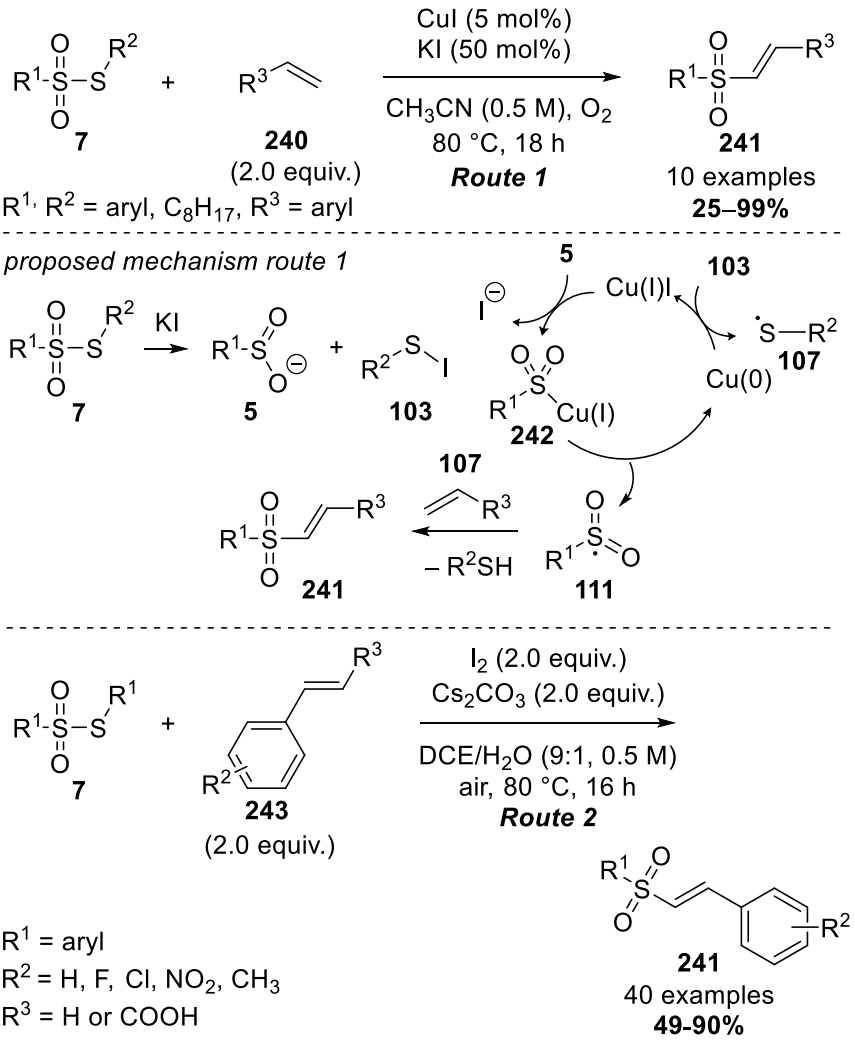
Scheme 855. Synthesis of β-hydroxysulfones (**224**) from thiosulfonates (**7**) and alkenes (**237**).

The regioselective synthesis of variously substituted β-hydroxysulfones (**224**) from thiosulfonates (**7**) and substituted styrenes or electron-deficient alkenes (**237**) - such as methyl methacrylate or benzyl methacrylate - has been discovered by the group of Jang (Scheme 856).[182] In their radical-based mechanism, thiosulfonates (**7**) react with iodide to afford R^1SO_2I (**83**), and a thiolate, the former dissociates into a sulfonyl radical (**111**) and an iodine radical. However, other mechanisms involving iodide propose the formation of sulfenyliodide (**103**) and sulfinate (**5**) (*e.g.* Scheme 87). Upon introduction of styrene (**237**) and molecular oxygen a radical intermediate **239** is formed, which is then converted into a β-hydroxysulfone (**224**) with the aid of thiolate and water.



Scheme 866. Remote radical C-H functionalization of amides **232** *via* thiosulfonates (**7** and **91**).

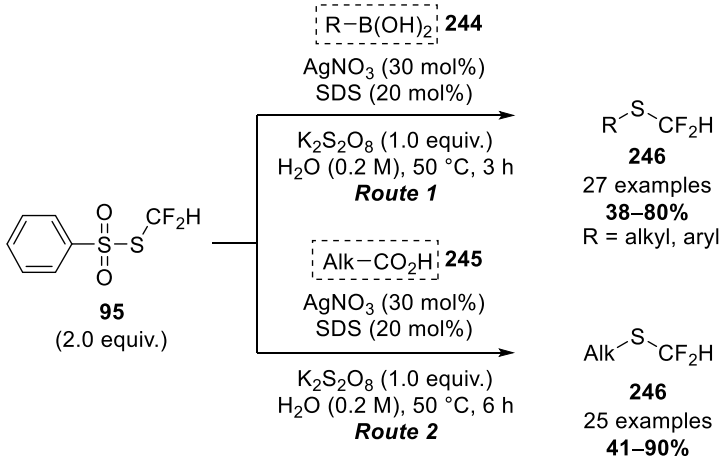
This group further examined the direct coupling of alkenes (**240**) and thiosulfonates (**7**) and synthesized a range of vinylsulfones (**241**) in the absence of water employing a combination of iodide and a copper catalyst (Scheme 87, route 1).[151] A sulfonyl radical (**111**) plays also a crucial role in the mechanism of this transformation. The role of oxygen is assumed to involve the removal of the thiol R^2SH by-product by forming disulfide (**3**). Iodine can also promote the formation of sulfonyl radicals (**111**) from thiosulfonates, which subsequently react either with styrenes or cinnamic acids (**243**) to afford a range of synthetically interesting vinylsulfones (**241**) in moderate to good yield (route 2).[186]



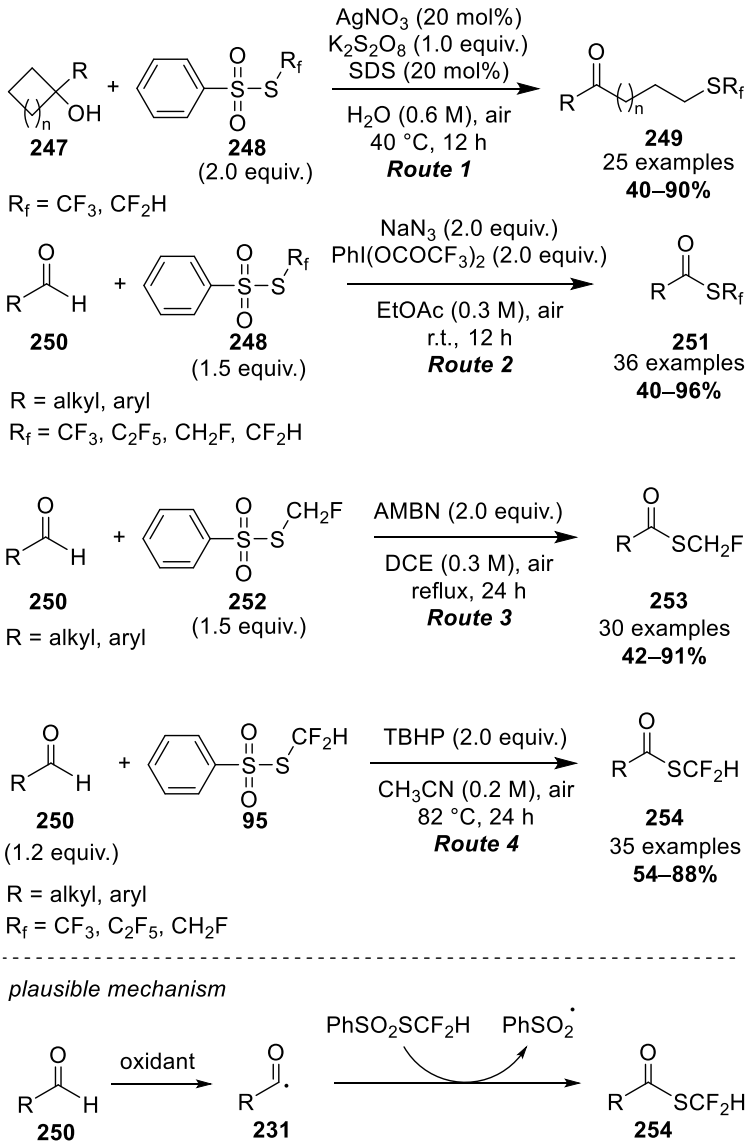
Scheme 87. Synthesis of vinylsulfones (**241**) from thiosulfonates (**7**) and alkenes (**240**, **243**).

Shen designed *S*-(difluoromethyl) benzenethiosulfonate (**95**) as a powerful reactant for radical difluoromethylsulfenylation of aryl- and alkylboronic acids (**244**) in the presence of silver nitrate as catalyst (Scheme 88, route 1).[119] Unfortunately, the authors did not propose a mechanism for this transformation. However, the Baran group[187] has shown that an aryl radical could be generated upon treatment of arylboronic acid (**244**) with Ag^I/persulfate. In the presence of a silver(I) salt the persulfate anion ($S_2O_8^{2-}$) disproportionates into a sulfate dianion (SO_4^{2-}) and

a sulfate radical anion ($SO_4^{\bullet-}$). This radical could then react with the aryl boronic acid (**244**), providing boric acid and an aryl radical of which the latter could react with the sulfenyl moiety of a thiosulfonate (**7**). To close the catalytic cycle the Ag^{II}-salt needs to be reduced again to Ag^{I} probably by the sulfonyl radical (**111**) derived from **7**. Secondary and tertiary alkylboronic acids were less effective in this coupling. The authors therefore extended the methodology towards alkanoic acids (**245**, route 2). The alkyl radicals are presumably generated from the carboxylic acid (**245**) by an oxidative decarboxylation process. Interestingly, *S*-(difluoromethyl) benzenethiosulfonate (**95**), proved to be a very effective radical acceptor for the ring-opening difluoromethylthiolation of 3 to 7-membered cycloalkanols (**247**) (Scheme 89, route 1)[188] and for the preparation of fluoroalkylthioesters (**251**, **253**, **254**) with acyl radical generated from aldehydes (**250**) (routes 2-4).[120, 189]

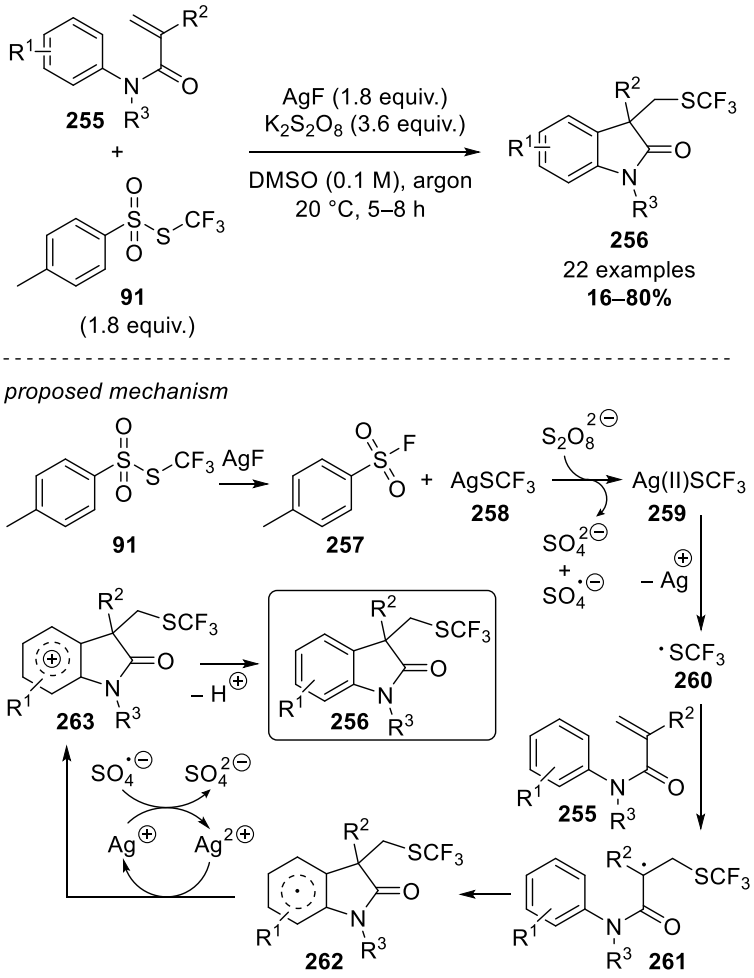


Scheme 88. Radical difluoromethylthiolation of arene/alkane boronic acids (**244**) and alkanoic acids (**245**). SDS = sodium dodecyl sulfate. NMP = *N*-methylpyrrolidone.



Scheme 89. Thiosulfonates as radical acceptors. AMBN = 2,2'-azodi(2-methylbutyronitrile). SDS = Sodium dodecylsulfate. TBHP = *tert*-butyl hydroperoxide.

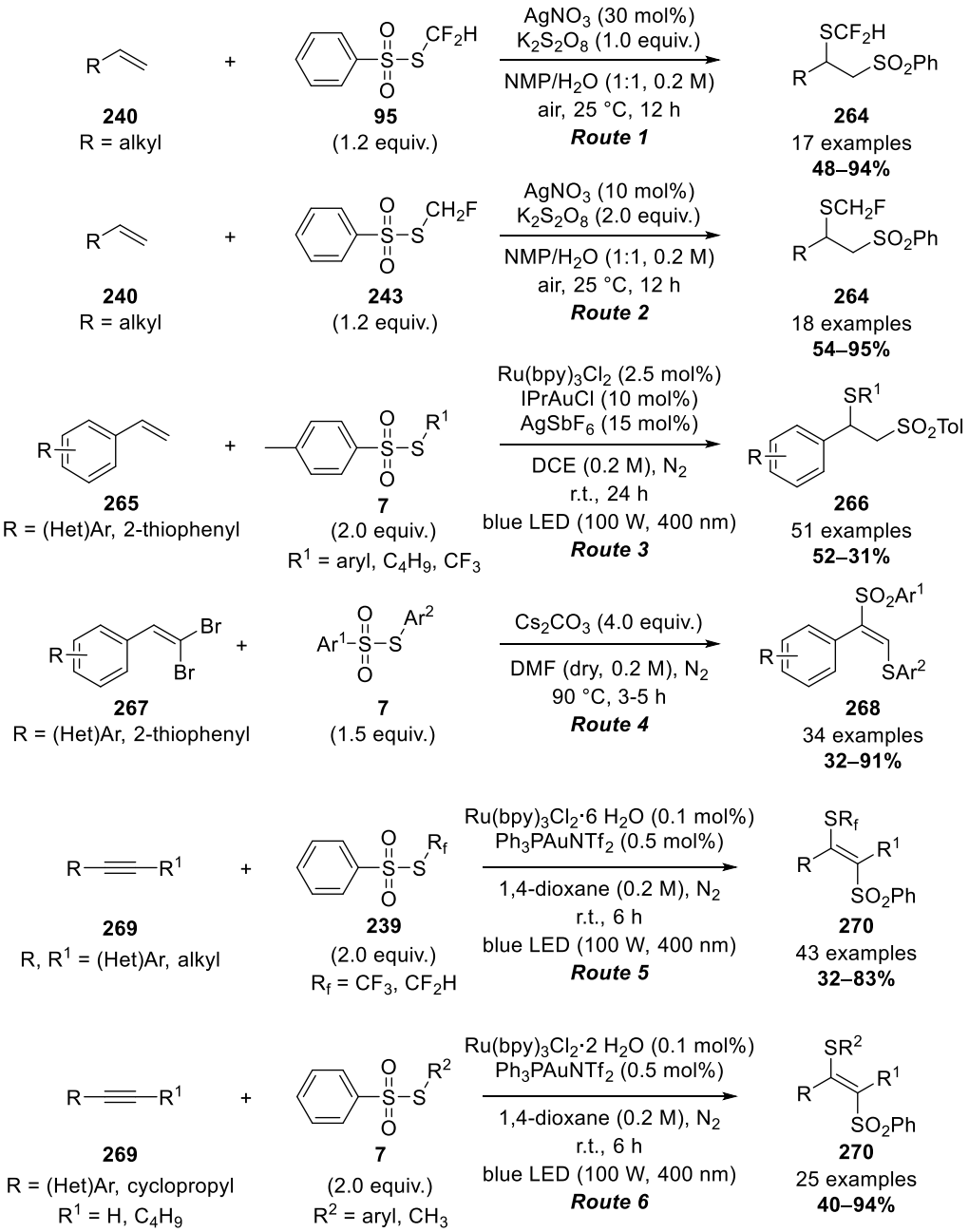
Inspired by the results of Shen, the Zhu group reported a silver-mediated radical trifluoromethylthiolation of activated alkenes **255** with *S*-trifluoromethyl 4-methylbenzenethiosulfonate (**91**) as CF_3S radical source (**260**) (Scheme 90).[190] Initially, the thiosulfonate (**91**) reacts with AgF to form sulfonylfluoride **257** and $AgSCF_3$ (**258**), which delivers a $CF_3S^{\bullet}$ (**260**) after oxidation by potassium persulfate. Subsequent addition of **260** to *N*-methyl-*N*-phenylmethacrylamide (**255**) affords an alkyl radical (**261**) that cyclizes to generate an aryl radical (**262**). Finally, oxidation of the latter by Ag^{II}, generated from Ag^{I} by potassium persulfate, followed by deprotonation of the kation **263** affords trifluoromethylthiolated oxindoles (**256**).



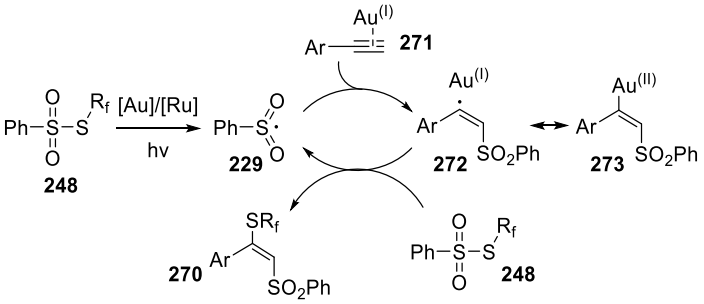
Scheme 90. Radical trifluoromethylthiolation of (activated) alkenes (**255**).

The difunctionalization of olefins employing thiosulfonates (**7**) has recently received significant attention (Scheme 91). In this manner, two different sulfur moieties can be installed to the vicinal carbons of an alkene/alkyne in a single operation. The group of Shen found that reactions of unactivated alkenes (**240**) with *S*-(difluoromethyl) benzenethiosulfonate (**95**) reactant occurred smoothly in the presence of silver nitrate as catalyst and potassium persulfate as stoichiometric oxidant (Scheme 91, route 1).[119] In addition, this methodology was also applied to introduce a monofluoromethylthio group onto sp^3-hybridized carbon atoms via a reaction involving **240** under slightly modified conditions (route 2).[100] Xu and co-workers developed an efficient intermolecular atom transfer thiosulfonylation of styrenes **265** *via* the combination of visible-light photoredox and gold catalysis (route 3).[191] Later on, they extended this methodology towards trifluoromethylthio- and difluoromethylthio-functionalized vinylsulfones (**270**) synthesis with high regio- and stereoselectivity by employing alkynes (**269**) (route 5).[192] The gold(I)-catalyst is crucial for these transformations, to initiate the reaction and to deliver a good stereoselectivity *via* an interaction between the gold catalyst and the *in situ* formed vinylsulfone radical intermediate (**272**) (Scheme 92). Furthermore, this

concept could be extended to non-fluorinated thiosulfonates (**7**), which are more challenging because of a lower oxidation potential (-1.64 V vs. SCE for $PhSO_2SC_4H_9$ versus -1.11 V vs SCE for $PhSO_2SCF_3$ (**91**)) (Scheme 91, route 6).[193] The group of Reddy envisioned that 1,1-dibromo-1-alkenes (**267**) could also be good reactants for a similar Cs_2CO_3-mediated installation of two different C-S bonds while retaining the C-C double bond (route 4).[194] In contrast to the visible light-mediated approaches (*E*)-1,2-thiosulfonylethene (**268**) products are obtained, however the authors do not propose an explanation for the different regioselectivity.

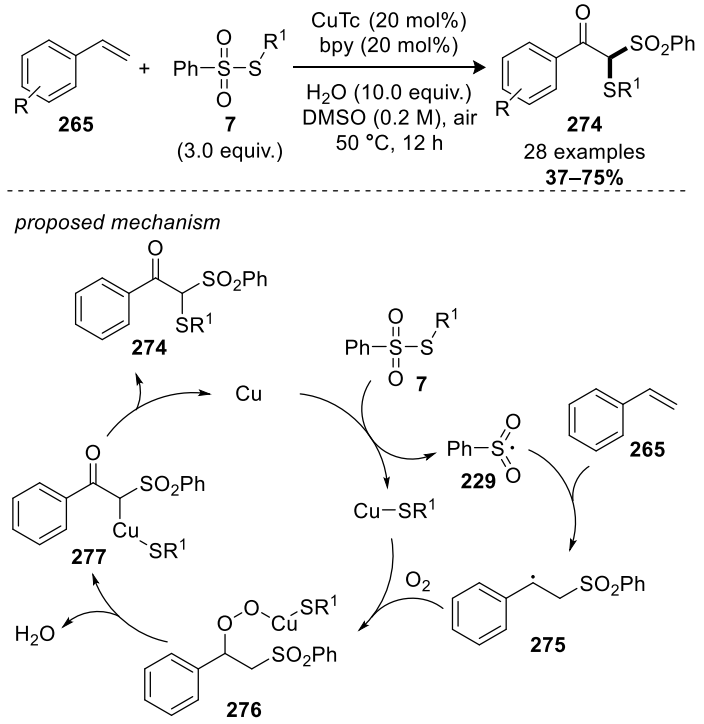


Scheme 91. Thiosulfonylation of alkenes and alkynes.



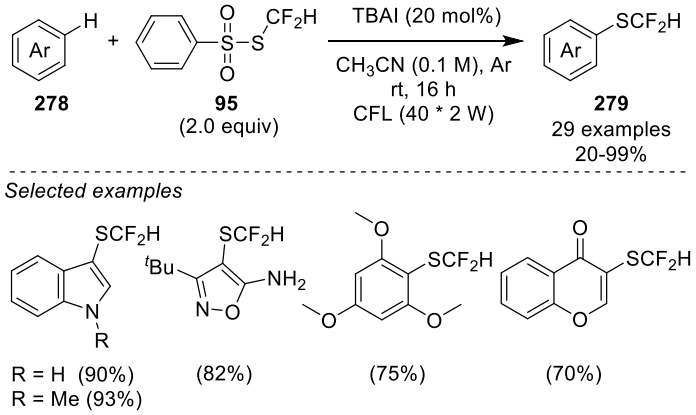
Scheme 92. Proposed mechanism for the gold/photoredox-catalyzed thiosulfonylation of alkynes (**269**).

In the past decades, the oxidative difunctionalization of styrenes (**265**) has attracted great attention as it introduces diverse functional groups *via* the formation of a carbonyl group and another C-C or C-heteroatom bond. Especially, α-sulfenyl β-ketosulfones (**274**) have been well studied. Interestingly, the group of Xu described in 2018 the first aerobic copper-catalyzed oxidative trifunctionalization of styrenes (**265**) via benzenethiosulfonates (**7**) for the synthesis of α-sulfenyl β-keto sulfones (**274**).[195] The copper catalyst facilitates the production of a benzenesulfonyl radical (**229**), which than reacts with an olefin. Subsequent trapping with molecular oxygen and fragmentation of the generated peroxy Cu^{II} complex **276** produces a β-ketosulfone (**277**), which is α-sulfenylated in the final step via reductive elimination. In this manner, two new C-S bonds are formed in a single operation.



Scheme 93. Synthesis of α-sulfenyl β-ketosulfones (**274**) from styrenes (**265**). bpy= 2,2'-bipyridine. CuTc= copper thiophene-2-carboxylate.

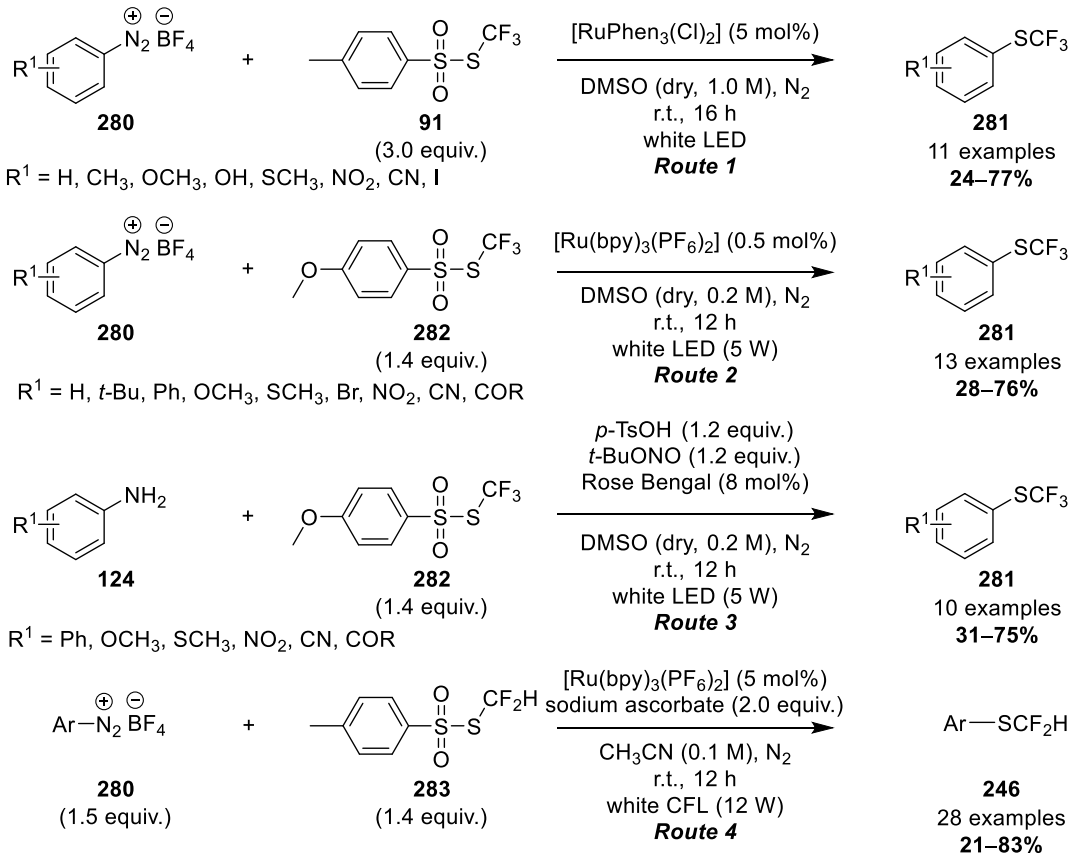
With the recent increased interest in visible light photo-redox catalysis, already touched upon in Scheme 91, the homolytic splitting of the SO_2-S σ–bond of thiosulfonates (**7**) - which studied before under UV irradiation[183a] - has been reinvestigated. Li and co-workers reported in 2018 that under irradiation with visible light *S*-(difluoromethyl) benzenethiosulfonate (**95**) underwent homolytic cleavage of the SO_2-S bond, to generate difluoromethyl radicals, which could then be trapped by a broad range of electron-rich arenes (**278**) and heteroarenes to give difluoromethylthioethers (**279**) (Scheme 94).[196] Interestingly, this method proceeds in the absence of noble metal photoredox catalyts and only uses tetrabutylammonium iodide as additive. Presumably sulfenyliodide or sulfonyliodide are the active intermediates here splitted by light, although the authors did not comment on this.



Scheme 94. Radical difluoromethylthiolation of aromatics enabled by visible light.

The direct trifluoromethylthiolation of arenes could also occur under visible light catalysis starting from arenediazonium salts (**280**) (Scheme 95). These diazonium salts (**280**) are first reduced through a single electron transfer (SET) by the triplet state of a (ruthenium) photocatalyst (Scheme 95, routes 1 and 2).[197] The resulting aryl radical (**230**) then interacts with the transient dimer CF_3SSCF_3, obtained from the reagent **2** under light irradiation. The obtained trivalent sulfur radical $ArS(CF_3)_2^{\bullet}$ is then oxidized by the diazonium salt (**280**) furnishing a cationic species ($ArS(CF_3)_2^{+}$) and a new aryl radical (**230**). Finally, the cationic intermediate could then react with a nucleophile from the reaction media (*e.g.* DMSO can play this role), yielding the desired product **281**. In 2018 the same group illustrated that aryl trifluoromethyl thioethers (**281**) can also be directly obtained from arylamines (**124**) and *S*-(trifluoromethyl) 4-methoxybenzenethiosulfononate (**282**) *via* visible light photo-redox catalysis (route 3).[197b] In that case, the diazonium salts were generated *in situ* upon treatment with *tert*-butyl nitrite and *p*-toluenesulfonic acid. Inspired by the work of Li (Scheme 94),[196] the group of Wang wondered whether the aryl radical generated from aryldiazonium salts (**280**) could also be trapped by *S*-(difluoromethyl) benzenethiosulfonate (**283**) (Scheme 95, route

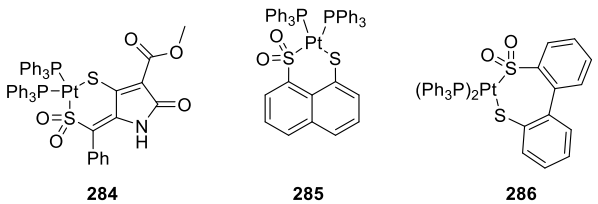
4).[198] A variety of difluoromethylthioethers (**246**) were successfully obtained utilizing aryldiazonium salts (**280**) containing different functional groups.



Scheme 95. Direct fluoroalkylthiolation of arenes.

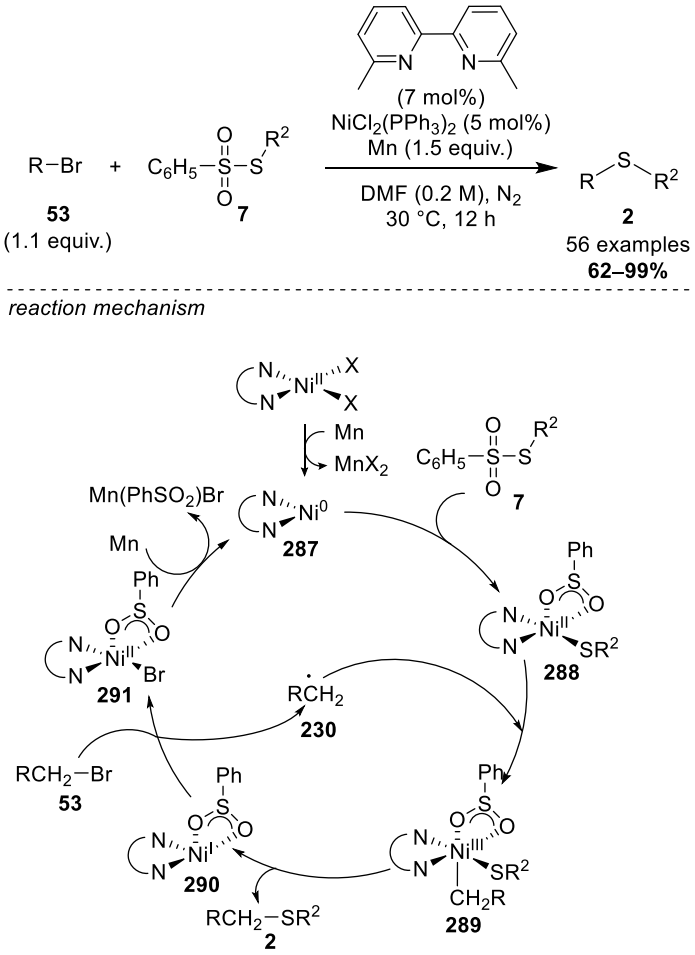
4.4 Transition metal-catalyzed cross-couplings with thiosulfonates

While many classical methods have been developed for preparing organic sulfides, most of them exploited transition metal-catalyzed cross-coupling of aryl/alkyl halides or pseudo halides with thiols. Interestingly, the groups of Woollins[199] and Stachel[200] reported that oxidative insertion of metal atoms could also occur into the *S*O_2-*S* bond (to S-M-SO_2) from thiosulfonates. They reported and characterized several Pt^0-, Pt^{II}- (**284**-**286**) (Scheme 96) and Ti^{II}-complexes of the RS-M-SO_2R^1 type *via* their crystal structure. However, no applications in cross-coupling reactions were explored by these authors.



Scheme 96. Examples of isolated RS-Pt-SO_2R^1 complexes.

Inspired by these results, the groups of Ji and Ackermann reported the nickel-catalyzed reductive thiolation of unactivated primary and secondary alkyl bromides (**53**) with thiosulfonates (**7**) to afford a wide range of unsymmetrical alkyl-aryl or alkyl-alkyl sulfides (**2**).[201] While transition metal-catalyzed cross-coupling reactions of C(sp^2)-X containing species have been well developed, the construction of C(sp^3)–S σ-bonds with unactivated alkyl halides (**53**) are much more challenging as undesired β-hydride elimination and homodimerization pathways could be prevalent. Based on detailed mechanistic studies, the authors propose a catalytic cycle starting with the *in situ* reduction of Ni^{II}-catalyst by manganese to afford a Ni^0 species (**287**). Subsequent oxidative addition of a thiosulfonate (**7**), followed by coupling with an alkyl radical (**230**) furnishes a Ni^{III} intermediate **289**. Reductive elimination of the thioether (**2**) generates a Ni^{I} species **290**, which reacts with an alkyl bromide (**53**) to generate an alkyl radical (**230**) with concomitant Ni^{II} species **291** formation. Further reduction regenerates Ni^0-catalyst **287**.

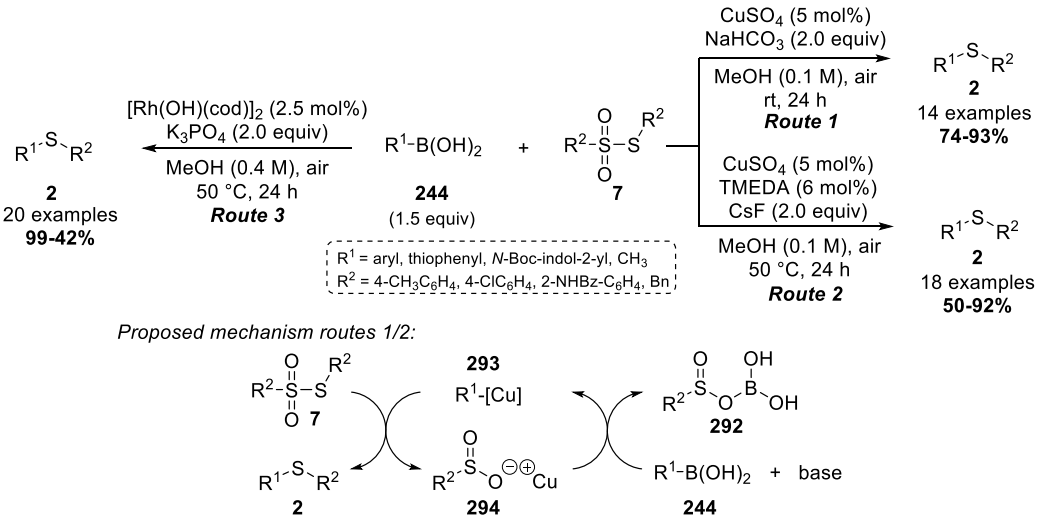


Scheme 97. Nickel-catalyzed reductive thiolation of unactivated alkyl bromides (**53**).

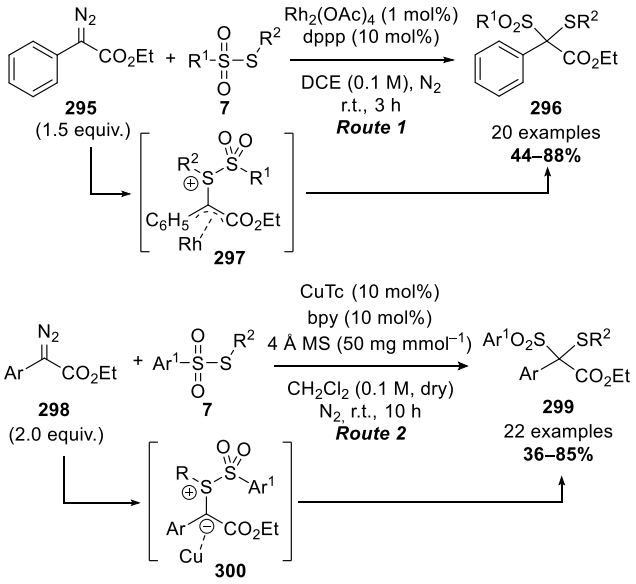
Aryl and alkyl sulfides (**2**) could also be prepared *via* a copper-catalyzed sulfenylation of stable aryl- and alkenylorganoboronic acids (**244**) with thiosulfonates (**7**) in the presence of a

weak base (Scheme 98, route 1).[202] The proposed catalytic cycle includes a reaction between the thiosulfonate (**7**) and a copper-species **293**, generated from boronic acid (**244**) *via* a metal-exchange reaction with a base, affording the desired sulfide (**2**) and regenerating the catalyst. The oxidation state of the Cu species involved is not indicated. Unfortunately, the substrate scope of the reactions was rather limited, which is related to the deactivation of the copper catalyst. To address this issue, a rhodium-catalyzed deborylthiolation of borylated arenes (**244**) and *S*-aryl thiosulfonates (**7**) was developed for the synthesis of various diaryl sulfides (**2**) (route 3).[203] The group of Yoshida also reported in 2018 an improved version of their copper-catalyzed deborylthiolation as they discovered that TMEDA and cesium fluoride as respectively ligand and base, dramatically facilitated the desired *ipso*-thiolation of a wide range of arylboronic acid esters (**244**) (route 2).[204]

Simultaneous construction of two C–S bonds has rarely been explored, especially if the two newly-built C–S bonds are on the same carbon atom. Another example included in this review is the synthesis of α-sulfenyl β-ketosulfones (**274**) (Scheme 93). Given the unique potential of dithioketal (**296**, **299**) derivatives, the group of Song employed thiosulfonates (**7**) as sulfenylating agent for the bis-sulfuration of ethyl 2-diazo-2-phenylacetate (**295**) (Scheme 99, route 1).[205] The transformation proceeds through a Rh-associated sulfur ylide intermediate (**297**), generated *via* a $Rh^{(II)}$-catalyzed decomposition of the diazocompound with concomitant loss of N_2, followed by R^1SO_2-SR^2 bond cleavage and rearrangement. Diverse α-disulfur functionalized esters (**299**) could also be synthesized via a copper-catalyzed *SO_2-S* bond insertion between ethyl 2-aryl-2-diazoacetates (**298**) and benzenethiosulfonates (**7**) (route 2).[206] The initially formed copper carbene generates a copper associated sulfur ylide **293**, which undergoes a [1,2]-Stevens rearrangement to generate two C–S bonds on the same carbon atom.



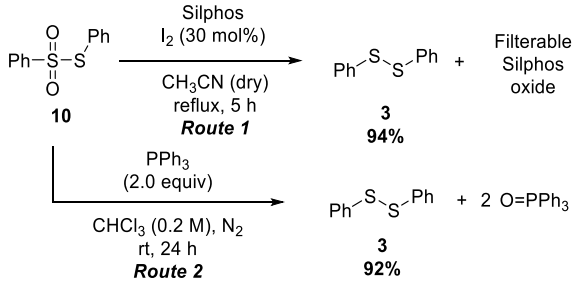
Scheme 98. Synthesis of sulfides (**2**) *via* copper- (routes 1 and 2) or rhodium-catalyzed (route 3) deborylthiolation. Bz = Benzoyl. Bn = Benzyl. TMEDA = Tetramethylethylenediamine.



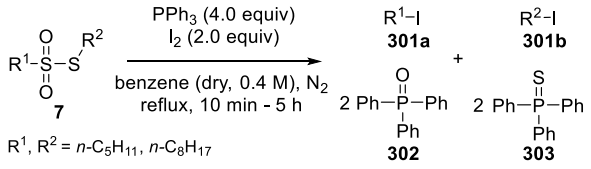
Scheme 99. Synthesis of dithioketal (**296**, **299**) derivatives.

4.5 Reduction/oxidation

Thiosulfonates (**7**) are generally prepared from disulfides (**3**) *via* oxidation as illustrated in section 3. Interestingly, the reverse reaction has also been reported by Iranpoor (Scheme 100, route 1). The deoxygenation of *S*-phenyl benzenethiosulfonate (**10**) could be achieved by Silphos [$PCl_{3-n}(SiO_2)_n$], a heterogeneous phosphine reagent, in the presence of a catalytic amount of iodine.[207] Phosphor-based deoxygenation was already discovered by Horner and Nickel in 1955 (route 2).[208] On the other hand, Oae and Togo reduced *S*-alkyl alkanethiosulfonates (**7**) by treatment with triphenylphosphine and iodine to afford the corresponding alkyl iodides (**301**) quantitatively (Scheme 101).[209]



Scheme 100. Reduction of thiosulfonates (**7**) to disulfides (**3**).

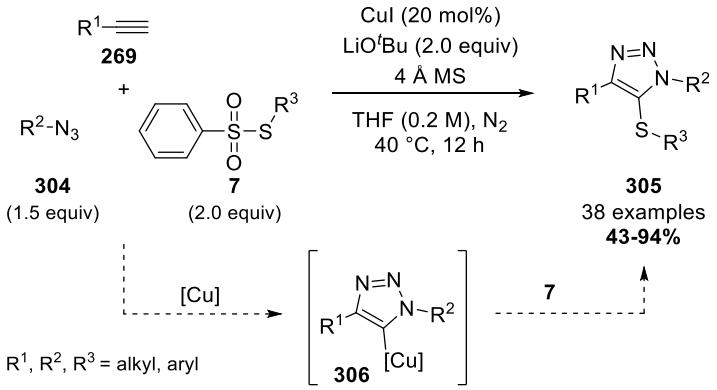


Scheme 101. Conversion of *S*-alkyl alkanethiosulfonates (**7**) to alkyl iodides (**301**) by reaction with triphenylphosphine/iodine.

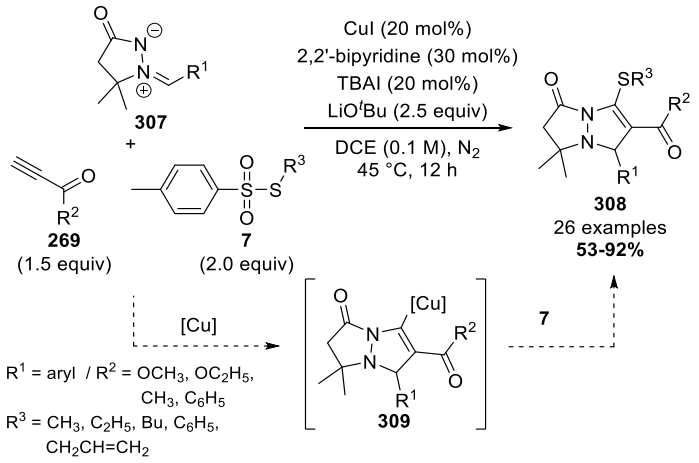
4.6 Thiosulfonates in multicomponent reactions

Multicomponent reactions (MCRs) have attracted much attention by the organic community, particularly in the areas of biotechnology, drug discovery and materials science, to face the new challenges of *greener* transformations.[210] MCRs are convergent reactions, in which three or more starting materials engage simultaneously, resulting in products that incorporate elements of all starting materials in their frameworks.[211] An intrinsic advantage of multicomponent reactions is the step economy, since several bond-forming steps are combined in a single operation. In the recent MCR literature, thiosulfonates (**7**) have proven to be interesting synthetic building blocks. They obviously also involve reactions with nucleophiles, electrophiles and radicals, as discussed in previous sections, but because of the importance of MCRs, these examples are treated separately in this section.

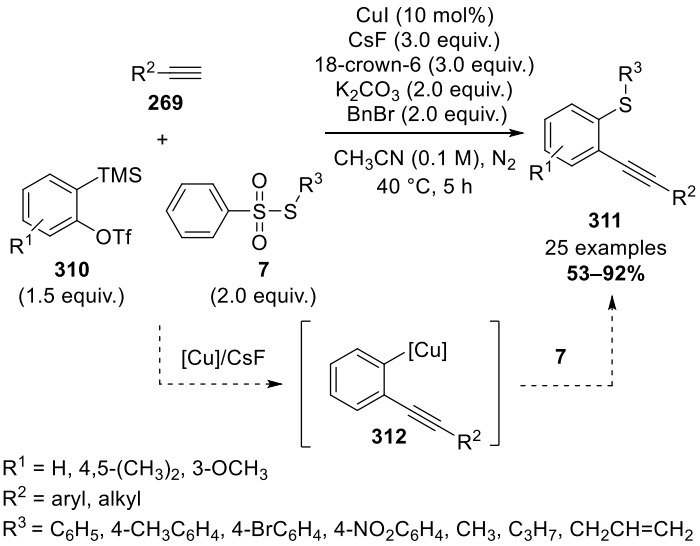
Xu reported a copper-catalyzed click reaction of alkynes (**269**) and azides (**304**) in which the triazolyl-copper complex intermediate **306** was intercepted by *S*-aryl/alkyl benzenethiosulfonate (**7**) electrophiles (Scheme 102).[212] A similar 1,3-dipolar cycloaddition between azomethine imines (**307**) and alkynes (**269**) generates a pyrazolidinonate-copper intermediate **309**, which was trapped by *S*-alkyl/aryl benzenethiosulfonates (**7**) to generate *N*,*N*-bicyclic pyrazolidiones (**308**) (Scheme 103).[213] (*o*-Alkynylaryl)sulfides (**311**) were prepared by Xu *via* a copper-catalyzed three-component coupling of terminal alkynes (**269**), thiosulfonates (**7**) and *in situ* formed arynes (Scheme 104).[214] Two equivalents of benzyl bromide were added into the reaction system as a scavenger to trap the benzenesulfinate (**5**) leaving group as a benzyl phenylsulfone by-product.



Scheme 102. Synthesis of 5-alkyl-/arylthiotriazoles (**305**) *via* Cu-catalyzed click reaction.



Scheme 103. Synthesis of *N,N*-bicyclic pyrazolidiones (**308**) *via* a Cu-catalyzed 1,3-dipolar cycloaddition reaction. TBAI = tetrabutylammonium iodide.

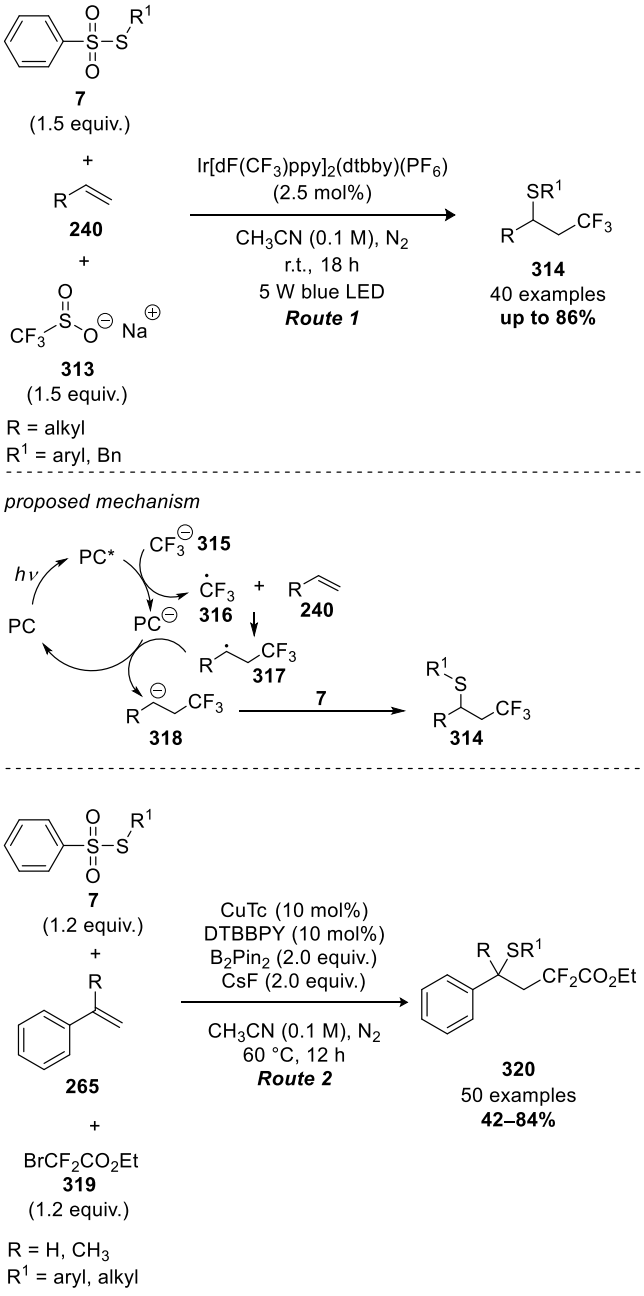


Scheme 104. Cu-catalyzed three-component synthesis of (*o*-alkynylaryl)sulfides (**311**). TMS = trimethylsilyl.

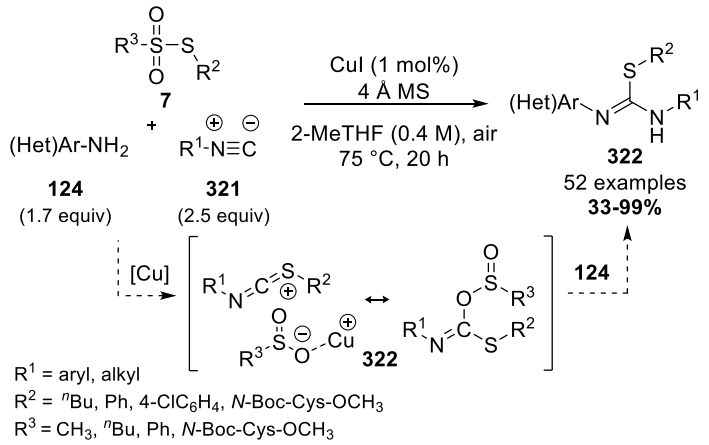
Thiosulfonates (**7**) have been used as electrophilic reactants to install two different groups across the C=C double bound of alkenes (**240**) in a single operation (*vide supra*). Song *et al.* employed benzenethiosulfonates (**7**) as sulfenyl source and sodium triflinate (**313**) (Langlois reactant) as easy-handled CF_3 (**316**) radical source (Scheme 105, route 1), obtained via involvement of a photoredox catalyst, in a three-component reaction with unactivated alkene (**240**).[215] The reaction is believed to go *via* a reductive quenching cycle, generating an anion intermediate **318**, formed from **317** by accepting an electron from the photoredox catalyst. **317** is obtained via $CF_3^{\bullet}$ (**316**) addition to **240**. Nucleophilic substitution with a thiosulfonate (**7**) on **318** delivers a trifluoromethyl-thiolated alkane (**314**) reaction product. As styrenes (**265**) were not compatible with these conditions, a Cu catalyst with superstoichiometric B_2pin_2 was envisioned to achieve a radical (ethoxycarbonyl) (difluoro)alkylation-thiolation (route 2).[216] A SET process between $BrCF_2CO_2Et$ (**319**) and a $Cu^{(I)}$−Bpin intermediate, formed *in situ* from

CuTc/B_2pin_2 with the aid of base, generates a $^{\bullet}CF_2CO_2Et$ and the Br-Cu^{II}-Bpin, of which the former adds to **265**. Subsequent trapping by Br-Cu^{II}-Bpin, delivers a Bpin-Cu^{III}-C(β-CF_2CO_2Et) intermediate, which then undergoes reductive elimination to deliver a Cu^{I}-C(β-CF_2CO_2Et) nucleophile intermediate. Finally nucleophilic attack to thiosulfonate (**7**) delivers an (ethoxycarbonyl)(difluoro)alkyl-thiolated product **320**.

In 2014 the Maes group applied thiosulfonates (**7**) as electrophilic sulfenylating reactants in a three-component copper-catalyzed synthesis with (hetero)aromatic amines (**124**) and isocyanides (**321**) to yield isothioureas (**322**) in a single synthetic step (Scheme 106).[17, 217] The reaction proceeds via an S-subsituted isothiocyanate **323**.

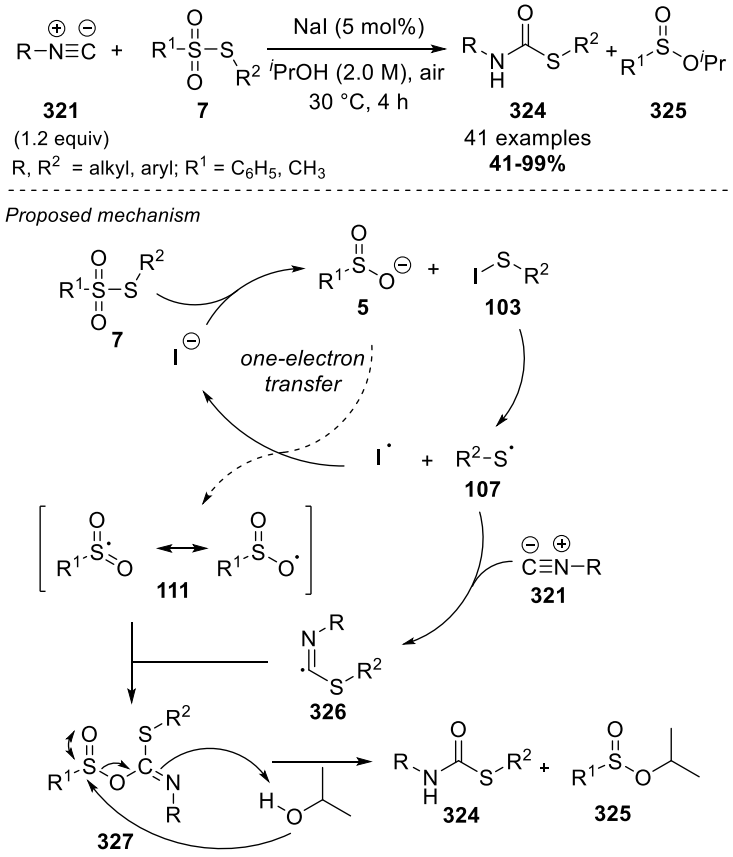


Scheme 105. Di/trifluoroalkylation-thiolation of alkenes (**240**, **265**).



Scheme 106. Three-component approach for the synthesis of isothioureas (**322**) involving thiosulfonates (**7**).

Two years later the same group also developed a direct approach towards secondary *S*-alkyl and *S*-aryl thiocarbamates (**324**) based on readily available isocyanides (**321**) and thiosulfonates (**7**) (Scheme 107).[218] The reaction mechanism involves in this case a radical pathway and is accelerated in the presence of a sodium iodide catalyst. EPR studies with radical traps support the involvement of sulfonyl (**111**) and sulfenyl (**107**) radicals. An alcohol solvent is crucial as it plays an active role in the reaction mechanism.

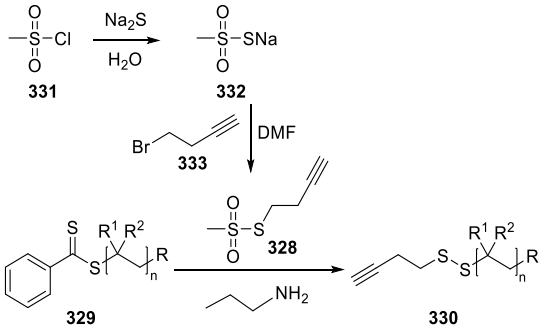


Scheme 107. Thiocarbamate (**324**) synthesis from isocyanides (**321**), thiosulfonates (**7**) and isopropanol.

4.7 Applications in polymer chemistry

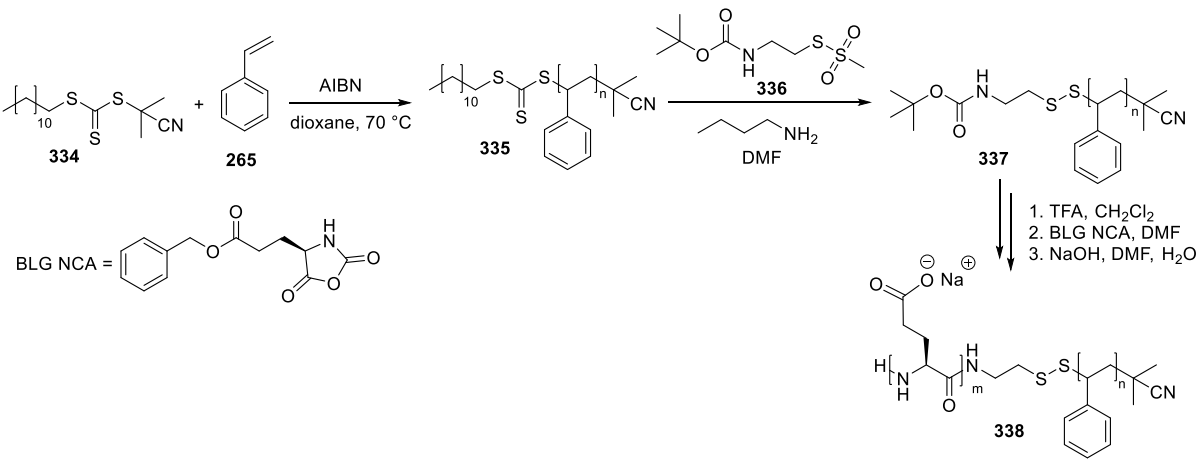
Thiosulfonates (**7**) have proven to be valuable building blocks for polymer chemistry to introduce functional end groups into polymers prepared *via* the RAFT (reversed addition fragmentation chain transfer) process. Post-modification through *one-pot* aminolysis of dithioester (**329**) and subsequent thiol capping has proven to be an efficient way to convert chain ends to the desired disulfide (**330**) functional groups. For poly(methyl methacrylate) (PMMA) the formation of side products (thiolactone) during aminolysis of the terminal dithioester can be suppressed by the addition of *S*-methyl methanethiosulfonate (**9**).[219] The released thiol at the polymer end group preferably reacts with *S*-methyl methanethiosulfonate, thus tolerating an excess of amine. This technique can also be used to attach functional groups (e.g. acetylene) to various polymers *via* the use of functionalized thiosulfonates (**328**) (Scheme 108).[219] Subsequent click-type chemistry then allows further on-demand post-functionalization of the obtained polymers.

A similar strategy has also been employed by Wang and Ling who used 2-cyano-2-propyl dodecyl trithiocarbonate as a RAFT chain transfer reagent.[220]



Scheme 108. Synthesis of *S*-butynyl methanethiosulfonate (**328**) and its reaction with thiol terminated polymers, obtained *via* aminolysis of the corresponding dithioester (**329**) terminated polymers.

The post-functionalization is also performed by combining aminolysis of the trithiocarbonate with *in situ* thiol capping with a thiosulfonate. This approach is illustrated for *S*-(2-(*tert*-butoxycarbonylamino)ethyl) methanethiosulfonate (Scheme 109). Deprotection of the Boc-group released an amino group, which can be used in ring-opening polymerization to generate block copolymers as exemplified for γ-benzyl-λ-glutamate *N*-carboxyanhydride (BLG NCA).



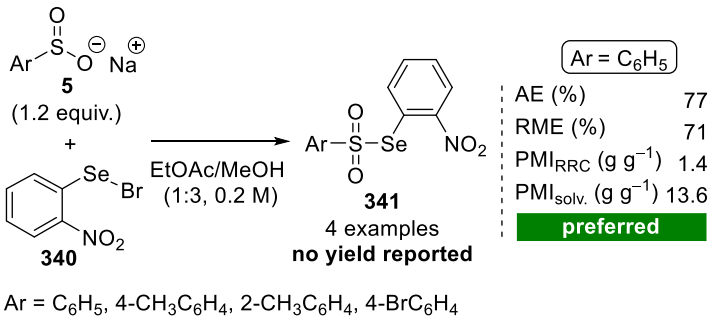
Scheme 109. Synthesis of PS-SS-PGlu block copolymers with a cleavable disulfide linkage.

5 Selenosulfonates

Selenosulfonates ($R^1SO_2SeR^2$) (**339**) are the seleno-variants of thiosulfonates (**7**). They have proven to be attractive synthons in organic chemistry as they readily undergo electrophilic or free-radical addition to unsaturated molecules. To the best of our knowledge reactions with nucleophiles have not been studied. The so-called 'selenosulfonylations' will be discussed in section 5.2, but first an overview will be given of the synthetic procedures towards selenosulfonates (**339**) similarly to the thiosulfonates (**7**).

5.1 Synthesis

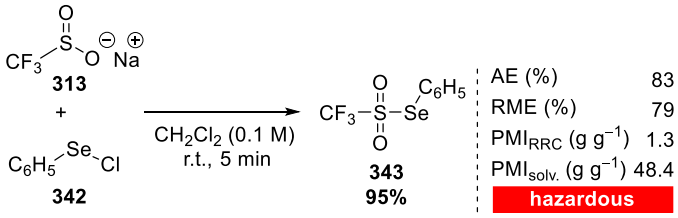
Several convenient methods for the preparation of unsymmetrical thiosulfonates (**7**) are based on sodium sulfinates (**5**) (*vide supra*). Likewise these have been used for selenosulfonate (**339**) synthesis. In 1947, Foss discovered the synthesis of *Se*-(2-nitrophenyl) areneselenosulfonates (**341**) from *o*-nitrobenzeneselenyl bromide (**340**) and sodium arenesulfinates (**5**) (Scheme 110).[221] With this method, unfortunately, only four kinds of selenosulfonates were successfully obtained.



Ar = C_6H_5, 4-$CH_3C_6H_4$, 2-$CH_3C_6H_4$, 4-BrC_6H_4

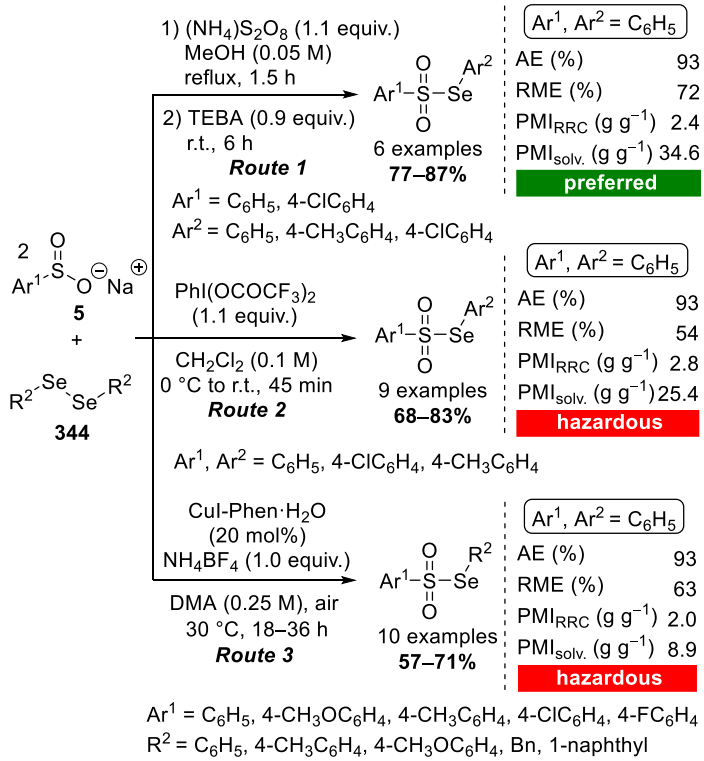
Scheme 110. First report on the synthesis of selenosulfonates (**341**).

Similarly, Billard reported in 1996 the synthesis of *Se*-phenyl trifluoromethaneselenosulfonate (**343**) from sodium trifluoromethanesulfinate (**313**) and benzeneselenyl chloride (**342**) (Scheme 111).[65] The reaction occurs at room temperature, but requires *hazardous* dichloromethane to obtain a decent yield.



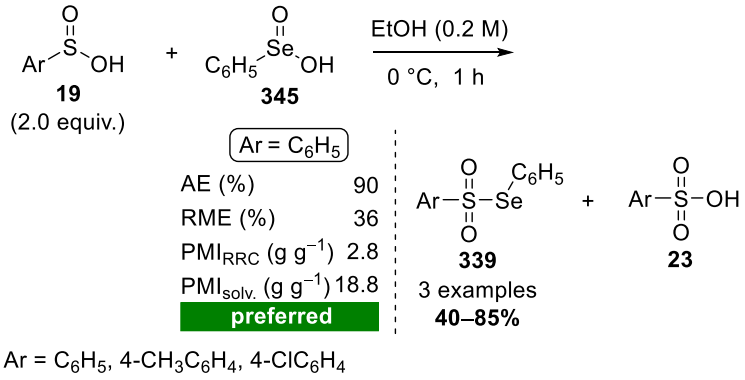
Scheme 111. Synthesis of *Se*-phenyl trifluoromethaneselenosulfonate (**343**).

Areneselenium cations, generated from diaryl diselenides (**344**) with ammonium persulfate, could also react with these nucleophilic reactants to obtain *Se*-aryl areneselenosulfonates (**339**) (Scheme 112, route 1).[222] Benzyltriethylammonium chloride was used as a phase transfer catalyst. Although a higher PMI was obtained, the reaction proceeds in a *preferred* solvent. Alternatively, the *Se*-*Se* bond in diaryl diselenides (**344**) could be oxidatively cleaved by using [bis(trifluoroacetoxy)iodo]benzene (BTIB) in dichloromethane (route 2).[223] Taniguchi also coupled diselenides (**344**) with sodium sulfinates (**5**), but in this case the reaction was performed in the presence of a copper catalyst under air (route 3).[113b] Slightly improved conditions compared to the previously reported coupling of sodium sulfinates (**5**) with thiols (**1**) or disulfides (**3**) were used (Scheme 41),[113a] although *hazardous N*,*N*-dimethylacetamide (DMA) could still not be avoided.



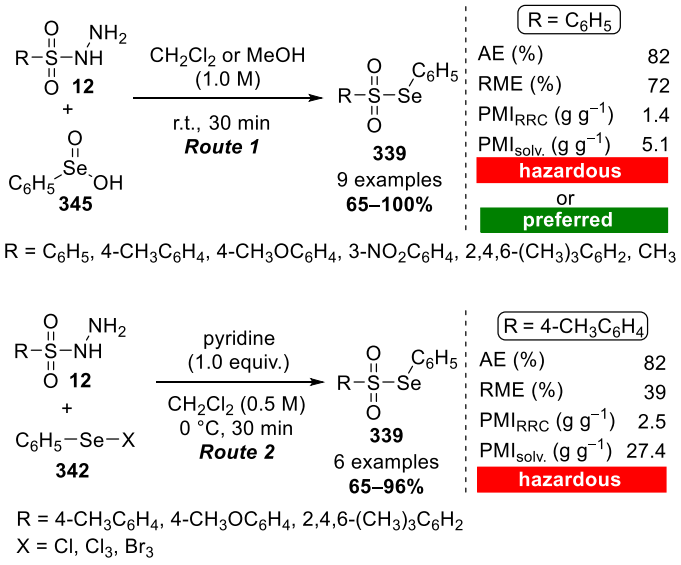
Scheme 112. Oxidative coupling of sodium arenesulfinates (**5**) with diselenides (**344**). TEBA = benzyltriethylammonium chloride.

Arenesulfinic acid (**19**) react rapidly with benzeneseleninic acid (**345**) at low temperatures to form *Se*-phenyl areneselenosulfonates (**339**) (Scheme 113).[224] First the arenesulfinic acid (**19**) is oxidized to the arenesulfonic acid (**23**) by the benzeneseleninic acid (**345**), the latter being reduced to the benzeneselenenic acid (C_6H_5SeOH). Most of the benzeneselenenic acid is then trapped by arenesulfinic acid (**19**) in which the hydroxyl acts as a leaving group to obtain the *Se*-phenyl areneselenosulfonates (**339**). Protonation of benzeneseleninic acid (**345**) by the arenesulfonic acid (**23**) is observed as a side reaction, thereby generating the corresponding salt as a byproduct. However, this step is reversible and by working in a polar solvent like ethanol the selenosulfonate (**339**) still could be obtained in acceptable yields.

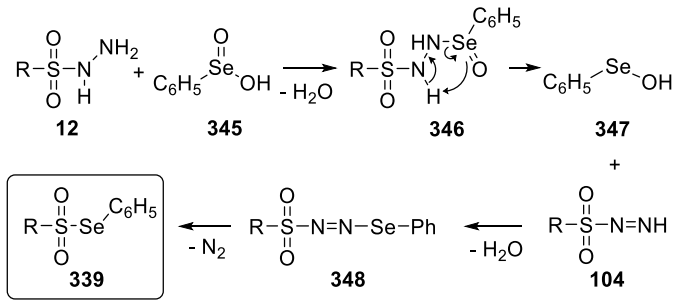


Scheme 113. Coupling of arenesulfinic acids (**19**) with benzeneseleninic acid (**345**).

Back and Collins also used benzeneseleninic acid (**345**), but combined it with sulfonyl hydrazides (**12**) to furnish a series of selenosulfonates (**339**) in good yield (Scheme 114, route 1).[225] A plausible mechanism for the reaction is presented in Scheme 115. Seleninohydrazide formation of the sulfonyl hydrazide (**12**) is followed by elimination of benzeneselenenic acid (**347**) to produce the corresponding sulfonyldiazene **104**. Further reaction of these intermediates generates 1-sulfonyl-2-phenylselanyldiazene **348** from which the desired *Se*-phenyl selenosulfonates (**339**) are obtained upon nitrogen extrusion. Although the reaction was originally performed in dichloromethane (*hazardous*), the authors improved their method by employing methanol (*preferred*) as solvent, because the *Se*-phenyl selenosulfonates (**339**) then crystallized directly from the reaction medium in high purity. Moreover, the authors successfully coupled benzeneselenenyl chloride, phenylseleniumtribromide and phenylselenium-trichloride (**342**) with sulfonyl hydrazides (**12**) in the presence of pyridine as acid scavenger (route 2), but the *green* metrics parameters are definitely in favor of the first method.[225]

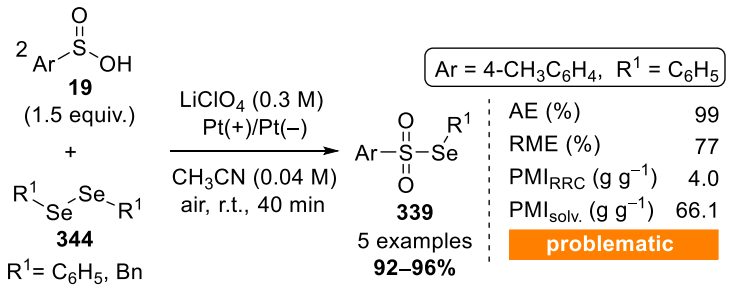


Scheme 114. Preparation of *Se*-phenyl selenosulfonates (**339**) from sulfonyl hydrazides (**12**).



Scheme 115. Proposed mechanism for the synthesis of *Se*-phenyl selenosulfonates (**339**) from sulfonyl hydrazides (**12**) and benzeneseleninic acid (**345**).

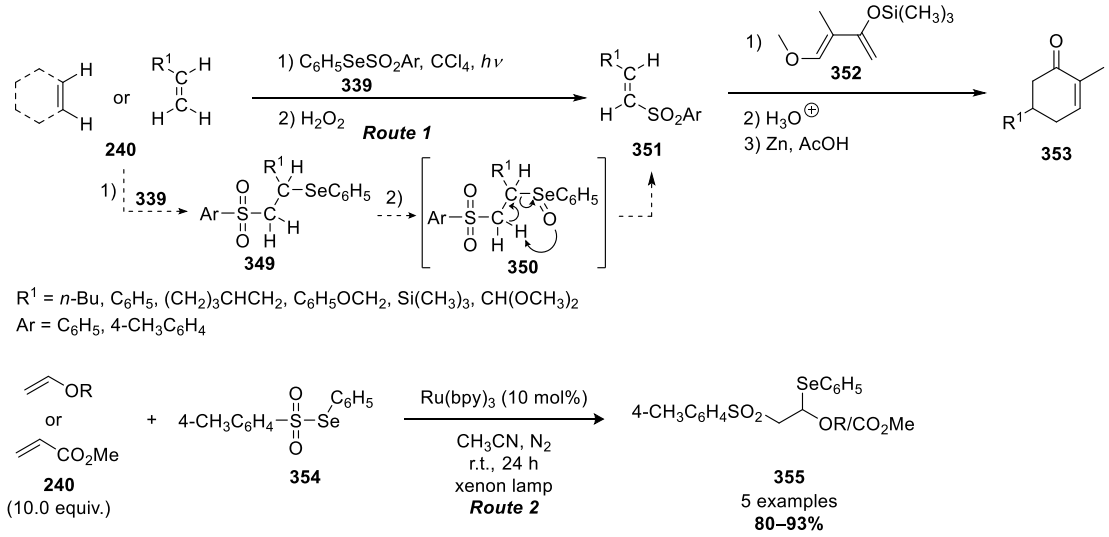
The increased interest in organic electrosynthesis,[58] led the group of Sun to prepare a wide range of symmetrical and unsymmetrical thiosulfonates (**7**) *via* electrochemical oxidative cross-coupling of arenesulfinic acids (**19**) with either thiols (**1**) or disulfides (**3**) (Scheme 17).[59] They also illustrated that the methodology could be extended to the synthesis of selenosulfonates (**339**) using diselenides (**344**) as reactants (Scheme 116). Due to the high reactivity of diselenides (**344**), full conversion was achieved in 40 minutes, compared with 5 h of reaction time with disulfides (**3**). A drawback is the high PMI_{solv} due to the dilution.



Scheme 116. Electrochemical oxidative cross-coupling reaction of arenesulfinic acids (**19**) and diselenides (**344**) into selenosulfonates (**339**).

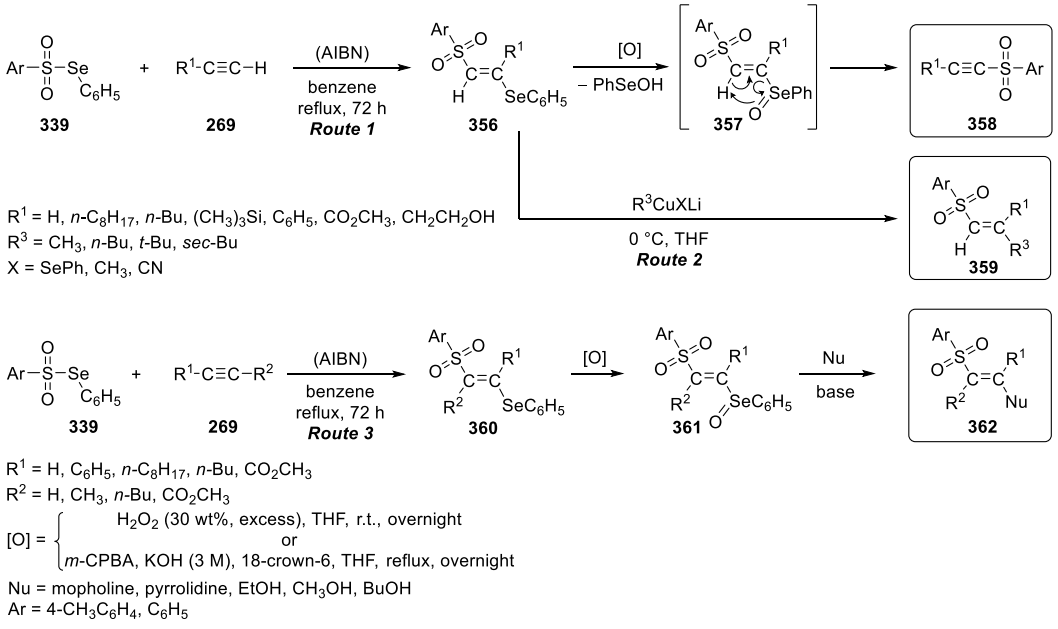
5.2. Applications

In comparison to *S*-phenyl arenethiosulfonates (**7**), *Se*-phenyl areneselenosulfonates (**339**) are extremely photosensitive and undergo quite rapidly photodecomposition. Therefore, they have been often employed in organic synthesis since the eighties. In the presence of alkenes (**240**), selenosulfonates (**339**) can undergo facile free-radical addition to give β-phenylselanylsulfones (**349**) under UV-irradiation. These reactants can then be converted in good yield to the corresponding α,β-unsaturated sulfones (**351**) by oxidative elimination of the phenylselanyl group (Scheme 117).[226] These sulfones have been extensively used in subsequent cycloaddition reactions,[227] for instance in Diels-Alder reactions with activated electron-rich dienes (**352**) like those developed by Danishefsky.[228] The group of Barton envisioned, that catalytic amounts of tris(2,2'-bipyridine)ruthenium could also initiate the addition reaction upon photolysis with visible light. They tried to add *Se*-phenyl tolueneselenosulfonate (**354**) with electron-deficient olefins (**240**) such as methyl acrylate or electron-rich olefins of the vinyl ether type (route 2).[229]



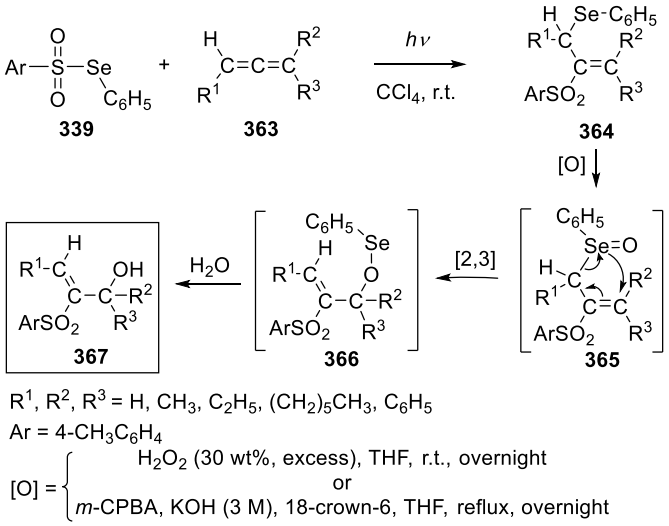
Scheme 117. β-Phenylselanylsulfones (**349**) of alkenes (**240**) *via* photodecomposition of selenosulfonates (**339**, **354**).

Besides photochemical activation, *Se*-phenyl areneselenosulfonates (**339**) can also add to olefins under thermal free-radical conditions making use of an initiator, such as 2,2'-azobis(2-methylpropionitrile) (AIBN). Treatment of β-(phenylselanyl)vinylsulfones (**356**) derived from terminal acetylenes (**269**) with an excess of *m*-CPBA delivered the acetylenic arene sulfones (**358**) in good yield (Scheme 118, route 1).[228a, 230] Alternatively, they can also be treated with organocuprate reactants, which effect the stereoselective substitution of the phenylselanyl moiety by the cuprate alkyl group (route 2).[231] β-(Phenylselanyl)vinylsulfones (**360**) prepared by selenosulfonylation of internal alkynes (**269**) could not eliminate the phenylselanyl group upon oxidation. These selenoxides (**361**) could then be treated *in situ* with alcohols or secondary amines to afford enol ethers or enamines (**362**) (route 3).[232]



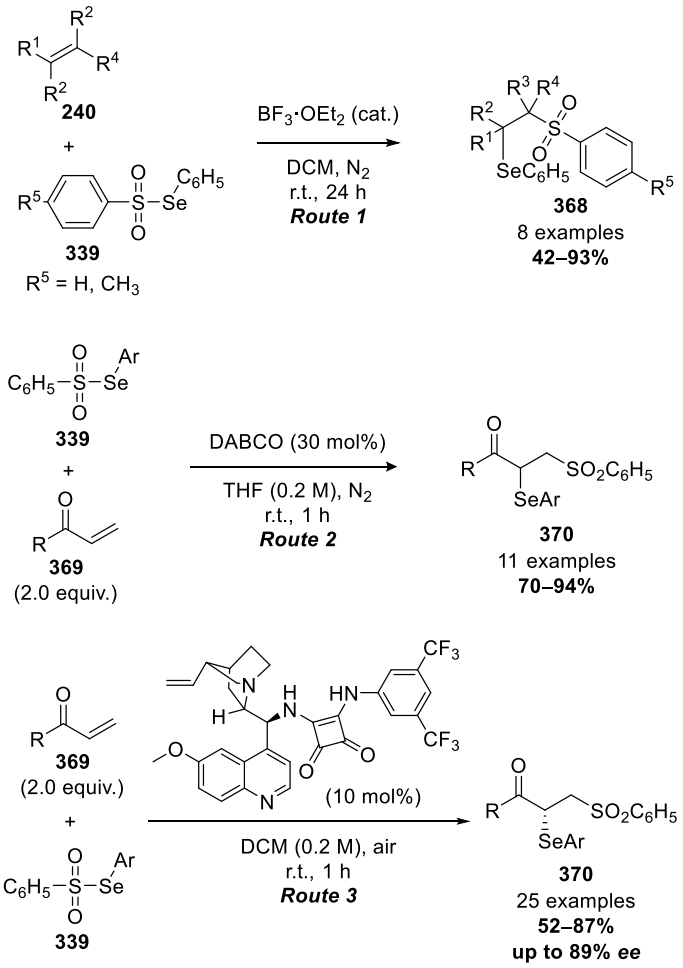
Scheme 118. Selenosulfonylation of acetylenes (**269**) and post-modification reactions. AIBN = 2,2'-azobis(2-methylpropionitrile).

Areneselenosulfonates (**339**) can also readily undergo free-radical addition to allenes (**363**) (Scheme 119).[233] The addition is regioselective because the arenesulfonyl group is adding to the central carbon and the phenylselenyl group is attached to the less substituted of the two terminal carbon atoms of the allenic system.[234] In contrast to alkenes (**240**), upon oxidization of the PhSe-group no elimination occurs, but rather a [2,3]-sigmatropic rearrangement and subsequent hydrolysis forms β–arylsulfonyl-substituted allylic alcohols (**367**).



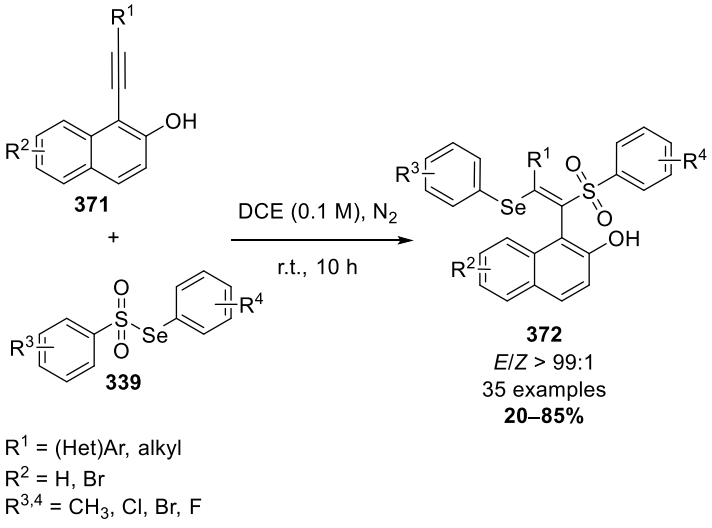
Scheme 119. Selenosulfonylation of allenes (**363**) and subsequent [2,3]-sigmatropic rearrangement and hydrolysis.

The addition of selenosulfonates (**339**) to olefins and other carbon– carbon unsaturated bonds discussed above, proceed through a radical reaction pattern with either photochemical initiation, or upon heating with a radical initiator such as AIBN. Besides, ionic pathways are also possible. Lewis acids such as boron trifluoride diethyl etherate ($BF_3.OEt_2$) could also promote the selenosulfonation of unhindered olefins (**240**) at room temperature (Scheme 120, route 1).[235] However, for α,β-unsaturated ketones (**369**), such as methyl vinyl ketone (MVK), no reaction occurred under these reaction conditions. Shi and co-workers demonstrated that Lewis bases such as 1,4-diazobicylco[2.2.2]octane (DABCO) were more effective in that case and catalyze the addition of various selenosulfonates (**339**) to α,β-unsaturated ketones (**369**) to afford racemic α-selanyl β-sulfonylketones (**370**) in good yield (route 2).[236] The enantioselective addition of such a reaction was demonstrated by the group of Yang and employed a chiral squaramide as efficient organo-catalyst (route 3).[237] The desired **370** were obtained with high enantioselectivities up to 89% ee.



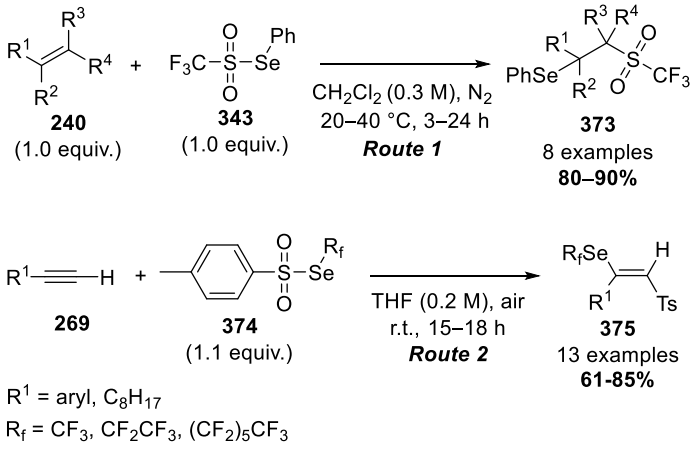
Scheme 120. Selenosulfonation of alkenes (**240**, **369**) under Lewis acid or Lewis base catalysis.

Sometimes no catalyst is required. Qin described the spontaneous diastereoselective selenosulfonylation of alkynes (**371**) under mild conditions (Scheme 121).[238] The generated selenosulfonylation adducts **372** can be transformed into useful naphtho[2,1-*b*]furan and benzofuran scaffolds.



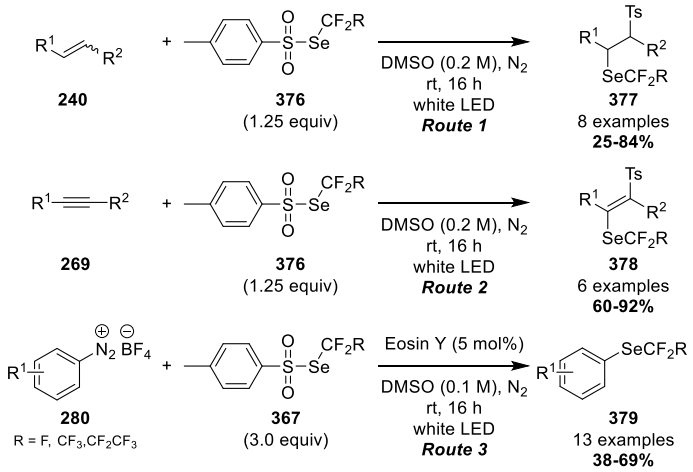
Scheme 121. Selenosulfonylation of 1-alkynylnaphth-2-ols (**371**).

Over the last decades, fluorinated compounds have been the subject of growing interest. Interestingly, the group of Langlois and Billard observed that trifluoromethaneselenosulfonates (**343**) are very reactive in comparison to the non-fluorinated selenosulfonates (**339**). These compounds readily add to olefins (**240**) and full conversion was achieved for most examples in 2 hours even at room temperature (Scheme 122, route 1).[239] The β-phenylselanyl triflones (**373**), could then be converted to vinyl triflones *via* the oxidation of the chalcogen atom, followed by spontaneous elimination of benzeneselenenic acid (**345**). Whereas thiosulfonates (**7**) with a CF_3S-substituent have been studied, the CF_3Se-group has gained only little attention. These authors therefore also developed an electrophilic diastereoselective perfluoroalkylselanylation approach, which couples terminal alkynes (**269**) with *Se*-(perfluoroalkyl) 4-methylbenzeneselenosulfonates (**374**) (Scheme 122, route 2).[240]



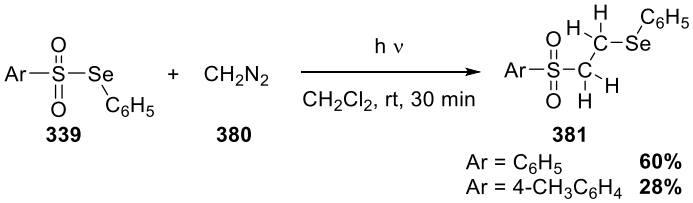
Scheme 122. Addition of *Se*-phenyl trifluoromethaneselenosulfonate (**343**) to olefins (**240**) and *Se*-perfluoroalkyl 4-methylbenzeneselenosulfonates to terminal alkynes (**269**).

Billard *et al.* recently investigated the cleavage of the *SO_2–Se* bond of *Se*-perfluoroalkyl 4-methylbenzeneselenosulfonate (**376**) upon visible-light irradiation. Subsequent radical coupling with alkenes (**240**) (route 1)[241] or alkynes (**269**, route 2)[241] furnished respectively α-[(perfluoroalkyl)selanyl]alkyl (**377**) or -vinylsulfones (**378**) in medium to good yield. Perfluoroalkylselanylation of aromatic diazonium salts (**280**) with an organic photocatalyst yields perfluoroalkylselanyl arenes (Scheme 123, route 3).[241-242]



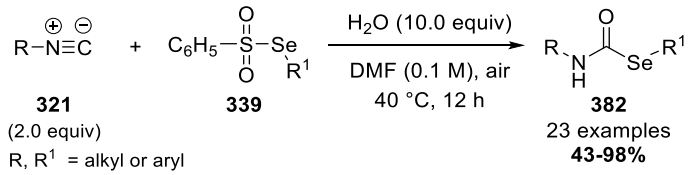
Scheme 123. Radical perfluoroalkylselanylation of alkenes (**240**), alkynes (**269**) and diazonium salts (**280**) upon visible-light irradiation.

When *Se*-phenyl areneselenosulfonate (**339**) was treated at room temperature with a fluorescent lamp in the presence of diazomethane an aryl □-(phenylselanyl)ethyl sulfone was obtained in 60% yield (Scheme 124).[243]



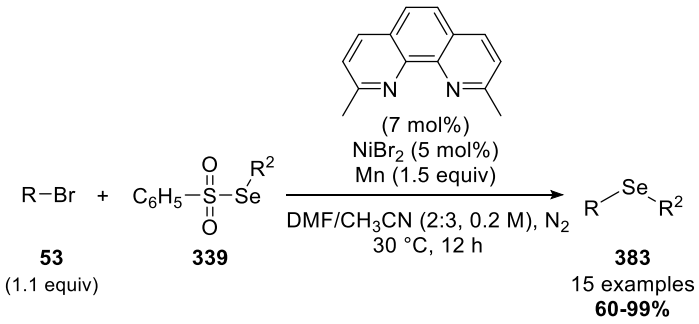
Scheme 124. Reaction of *Se*-phenyl areneselenosulfonate (**339**) with diazomethane (**380**).

In continuation of the work of Maes for thiocarbamate synthesis (**322**) from isocyanides (**321**) and thiosulfonates (**7**),[218] the group of Ji recently prepared selenocarbamates (**382**) through a metal-free multicomponent reaction between isocyanides (**321**), selenosulfonates (**339**) and water (Scheme 125).[244] The reaction proceeds *via* a similar radical mechanism as proposed earlier (Scheme 107).

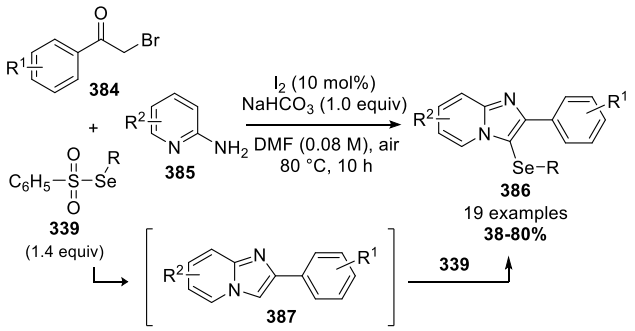


Scheme 125. Three-component reaction for selenocarbamate (**382**) synthesis.

The groups of Ji and Ackermann prepared a series of selenides (**383**) in a similar fashion as their nickel-catalyzed reductive thiolation of unactivated primary and secondary alkyl bromides (**53**) by using selenosulfonates (**339**) instead of thiosulfonates (**7**) (Scheme 126).[201]



Scheme 126. Nickel-catalyzed reductive selenolation of unactivated alkyl bromides (**53**).



Scheme 127. Three-component reaction for the synthesis of 3-(alkylselanyl)-2-arylimidazo[1,2-*a*]pyridines (**386**).

Finally, the group of Ji applied aliphatic selenosulfonates (**339**) in a three-component reaction for the synthesis of 3-(alkylselanyl)-2-arylimidazo[1,2-*a*]pyridines (**386**) (Scheme 127).[245] The reaction proceeds *via* the *in situ* functionalization of imidazoheterocycles **387** generated from 2-bromoacetophenone (**384**) and 2-aminopyridine (**385**). Iodine enhances the electrophilic character of selenosulfonates **339**.

Conclusion

This review entailed an overview of the current synthetic strategies towards thiosulfonates ($R^1SO_2SR^2$). They were classified based on the precursors used (disulfides, thiosulfinates, thiols, sulfenyl halides, sulfonyl halides, thiosulfonate salts, sulfinate salts and sulfonyl hydrazides). The direct oxidation of disulfides (and thiols) proved the most efficient approach towards symmetrical thiosulfonates from a *green* chemistry point of view, provided a low molecular weight oxidant with low toxicity is selected, whereas the oxidative coupling of alkali metal sulfinates with disulfides is currently the best route to prepare the unsymmetrical ones. Considerable efforts have been made in the past decades to improve the *green* credentials of each of these routes by evaluating several oxidants, promoters, catalysts and solvents. Notably, it was illustrated that routes which are naturally associated with *green* chemistry such as solvent-free synthesis or electrochemical procedures do not necessarily score particularly

well! A critical evaluation of the different subcategories of the PMI (PMI_{solv}, PMI_{RRC}) is important when comparing several routes on a discovery scale, as the total PMI-value can sometimes be deceitful when PMI_{workup} is also considered. As has been emphasized in this review, thiosulfonates are a very powerful class of sulfenylating reactants based on their chameleon behavior, able to react with nucleophiles, electrophiles and radicals. However, despite the achievements made so far, the focus is still largely on their use as electrophiles. An increasing awareness of the features of these reactants will hopefully lead to further exploration of their synthetic power in multicomponent and radical reactions. Finally, the last part of this review focused on the seleno-variants of thiosulfonates (i.e. selenosulfonates, $R^1SO_2SeR^2$), which are less explored. They can readily undergo electrophilic or free-radical addition to unsaturated molecules.

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