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Selective Oxidation of Sulfides in Flow Chemistry

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Abstract: A packed bed reactor with oxone has been employed for selective oxidations of sulfur compounds. Various sulfides containing different functional groups are efficiently oxidized to the corresponding sulfoxides without formation of sulfones or other side products.

Sulfoxides are very important moieties widely used in the preparation of biologically and pharmaceutically significant compounds. They constitute a relevant motif in marketed therapeutics, such as Provigil [1] and Nexium[2] and in biologically active components of garlic extracts such as Allicin and Ajoene[3] (Figure 1). Sulfide oxidation has also been utilized in the extraction of sulfur-containing compounds from crude oil *via* catalytic oxidative desulfurization processes.[4] Sulfoxides can also serve as valuable oxo-transfer reagents in oxidation reactions[5] and as versatile ligands in asymmetric catalysis.[6]

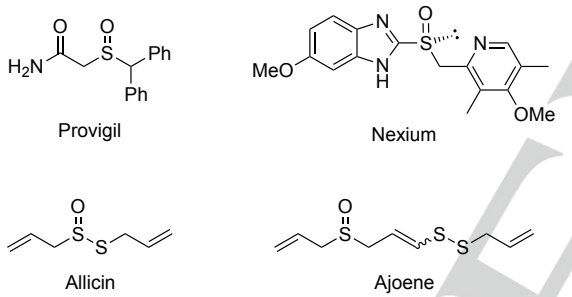


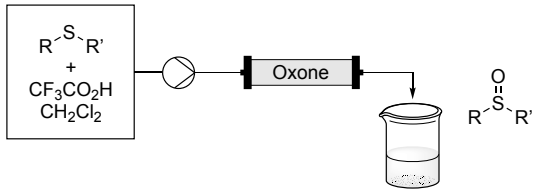
Figure 1. Biologically active compounds containing sulfoxide moieties.

Research in sulfur chemistry has addressed the selective oxidation of sulfides to sulfoxides without overoxidation to sulfones or other undesired side reactions.[7] Several oxidants have been reported for the selective oxidation of sulfur, such as hydrogen peroxide,[8] nitric acid, *m*-chloroperbenzoic acid,[9] urea-hydrogen peroxide,[10] sodium hypochlorite,[11] and sodium periodate.[12] However, most of these methods either require stoichiometric amounts of reagents or a transition metal catalyst. Therefore, efficient, selective and environmentally benign methods are still highly desired.

Oxone (2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is a free-flowing and commercially available peroxygen salt that provides powerful non-chlorine oxidation in a stable, easy-to-handle manner. Due to its high stability and efficiency, oxone has found many applications that are well documented.[13] Li *et al.* reported a selective oxidation of sulfides by employing oxone as the oxidant without utilization of any catalyst/additive under mild conditions. The degree of oxidation was achieved by solvent selection that preferentially produced the sulfoxide. Although the yields are high, the reaction had to be performed at 60 ºC for 12 h.[14]

Oxone in the presence of trifluoroacetic acid has been used for the oxidation of diarylacetylenes to 1,2-diketones,[15] ketones or alkynes to carboxylic acids[16] and perfluoroalkyl iodides to the corresponding bis(trifluoroacetoxy)iodo derivatives.[17] However, there are no reports regarding the oxidation of sulfur compounds using these reaction conditions.

Microreactors have been used in many organic synthesis transformations due to their efficiency, selectivity and high degree of safety.[18] Herein we describe the use of a simple packed-bed reactor for the selective oxidation of sulfides. The selective oxidation of sulfides in continuous-flow microreactors using electrochemical[19] and photochemical[20] methods has been reported. A simple protocol for the selective oxidation of sulfides in flow chemistry utilizing a packed-bed reactor with oxone in the presence of trifluoroacetic acid has been developed (Scheme 1).



Scheme 1. Flow setup for the oxidation of sulfur compounds using a packed-bed reactor.

For this study, thioanisole **1a** was used as the model substrate to find suitable reaction conditions. Initial reactions were carried out by pumping a dichloromethane solution containing thioanisole **1a** (0.05 M) and trifluoroacetic acid (TFA) (15 vol%) through an Omnifit column packed with oxone (Table 1, entry 1). The flow rate of 0.5 mL/min corresponds to a residence time of 4 minutes within the reactor. Upon collection, ^{1}H NMR spectroscopic analysis showed that 100% conversion was achieved. Increasing the concentration of the sulfide solution to

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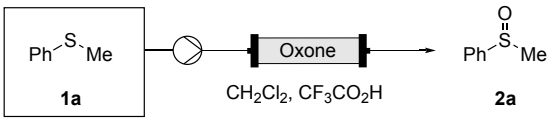
either 0.1, 0.15 or 0.2 M (Table 1, entries 2-4) did not affect the conversion of the reaction. Only when the concentration of the sulfide solution was further increased to 0.4 M, the conversion dropped to 55% (Table 1, entry 5). The volume percentage of trifluoroacetic acid in dichloromethane was a crucial for obtaining high conversion. Decreasing from 15 vol% to 10 vol% reduced the conversion by a factor of 4 (Table 1, entries 4 and 6) when performed at 0.5 mL/min. To improve the conversion when using low concentration of TFA, longer reaction times were needed. However, full conversion was not even obtained after 60 minutes residence time while pumped at 0.03 mL/min (Table 1, entry 9). Other researchers have also reported that TFA activates oxone in other oxidation reactions.[21]

Table 1. Optimization of the reaction conditions in a solution of TFA in dichloromethane.

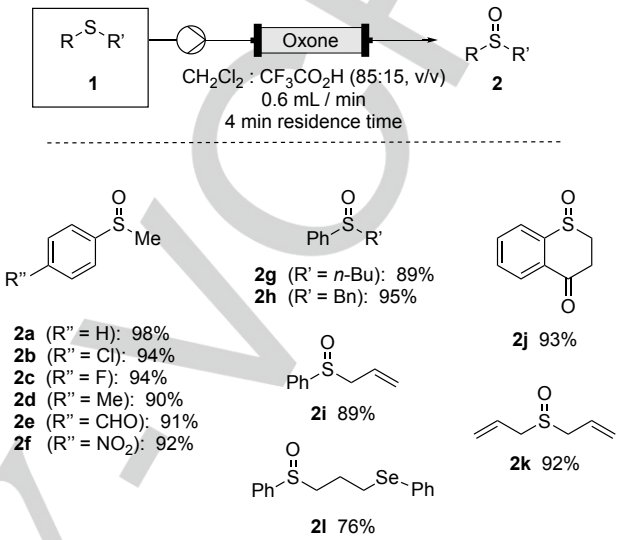


Entry	Concentration **1a** [M]	TFA [vol%]	Residence time [min]	Conversion [%][a]
1	0.05	15	4	100
2	0.10	15	4	100
3	0.15	15	4	100
4	0.20	15	4	100
5	0.40	15	4	55
6	0.20	10	4	20
7	0.20	10	17	33
8	0.20	10	30	50
9	0.20	10	60	68

[a] Determined by ^{1}H NMR spectroscopic analysis.

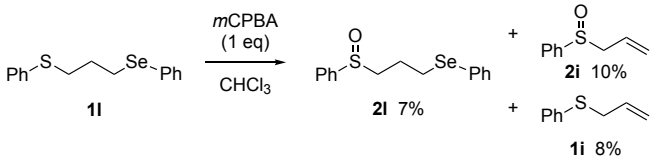
The packed bed reactor with oxone contains approximately 9.1 mmol oxone (5.6 g) and can be used to oxidize up to 10 mmol of sulfide without affecting the conversion and with no change in residence time. The oxone in the packed bed reactor can also be washed with dichloromethane allowing a reuse of the reactor with a different substrate until the oxone is fully consumed. In order to find an alternative solvent for dichloromethane and TFA, other solvents such as acetone and ethanol were investigated. However, the conversions were not exceeding 45%. The temperature effect was also briefly investigated. Generally, it was observed that an increase in temperature leads to a lower selectivity (sulfoxide vs. sulfone).

After optimization of the reaction conditions, the substrate scope was explored (Scheme 2). Different sulfides were reacted affording the desired sulfoxides in good to excellent yields. Specifically, phenyl sulfides bearing aliphatic (**1g**), benzyl (**1h**) and allyl (**1i**) substituents afforded the sulfoxides in high yields. The yields were not affected by the electronic structure of the phenyl sulfides. As it can be seen in Scheme 2, *para*-substituted phenyl sulfides (**1b-1f**) with electron-donating or electron-withdrawing groups gave the sulfoxides **2** in good yields. Similarly, sulfide **1j** bearing a ketone also underwent efficient oxidation to afford the corresponding sulfoxide **2j**, where a possible Baeyer-Villiger reaction product was not observed. Moreover, the present protocol was also applied to the oxidation of diallyl sulfide **1k**. In the case of allyl sulfides **1i** and **1k** no epoxide formation was observed.[22]



Scheme 2. Substrate scope for the oxidation of sulfides using flow conditions.

Interestingly, compound **1l** contains both a phenyl sulfide and a phenyl selenide moiety (Scheme 2), but the only product obtained was the sulfoxide **2l** in 76% yield. To demonstrate the chemoselectivity of this procedure, the same substrate **1l** was treated with one equivalent of *m*CPBA (*meta*-chloroperbenzoic acid) under batch conditions. The reaction now afforded sulfoxide **2l** in very low yield (7%), together with compound **1i** (8%) and **2i** (10%). The starting material **1l** was recovered in 43% yield. Under the oxidizing conditions, also the selenide is partially oxidized to the selenoxide, which then undergoes elimination[23] generating the corresponding alkenes **1i** and **2i** (Scheme 3). However, when the oxidation with *m*CPBA was carried out in the presence of 10 vol% TFA, only compound **2l** was obtained in 70% yield. The cyclic voltammetry of compound **1l** showed two different oxidation potentials (1.17 V and 1.70 V). In the presence of 10 vol% TFA a slight decrease in the oxidation potentials (1.00 V and 1.50V) was observed. Maybe protonation of the selenide prevents its oxidation in the presence of TFA.



Scheme 3. Oxidation of compound **1l** with *m*CPBA.

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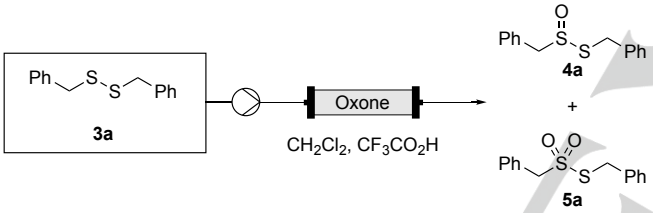
Using the optimal reaction conditions found for oxidizing sulfides, different disulfides such as dibenzyl disulfide **3a** (Table 2, entry 1) were investigated. The ^{1}H NMR spectra of the crude reaction mixture revealed the presence of disulfide **3a** (35%), thiosulfinate **4a** (35%) and thiosulfonate **5a**. Further optimization studies were carried out using dibenzyl disulfide **3a** as a test substrate, in order to obtain the thiosulfinate **4a** selectively (Table 2). Decreasing the concentration of disulfide to 0.1 M and 0.05 M, a slightly increased conversion was observed but thiosulfonate **5a** was still detected (Table 2, entry 2). Only when the concentration of **3a** was reduced to 0.025 M, the conversion increased to 82% (Table 2, entry 4). Reducing the percentage of TFA in the mixture from 15% to 10%, resulted in almost full conversion to thiosulfinate **4a** and thiosulfonate **5a** was no longer detected by ^{1}H NMR (Table 2, entry 5). Increasing the concentration of disulfide **3a** to 0.05 M and 0.1 M, while using 10 vol% TFA lead to a diminished conversion (Table 2, entries 6 and 7). Increasing the residence time barely affected the conversion (Table 2, entry 8).

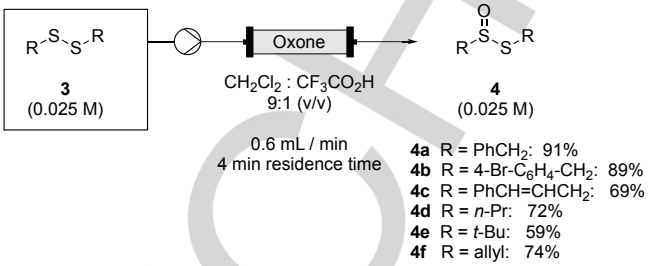
Table 2. Optimization of the reaction conditions of disulfide **3a** in dichloromethane / TFA.



Entry	Concentration **3a** [M]	TFA [vol%]	Residence time [min]	Conversion [%][a]		
				3a	**4a**	**5a**
1	0.200	15	4	35	35	30
2	0.100	15	4	23	50	27
3	0.050	15	4	20	53	27
4	0.025	15	4	8	82	8
5	0.025	10	4	3	97	0
6	0.050	10	4	7	87	6
7	0.100	10	4	28	66	6
8	0.100	10	8	14	70	16

[a] Determined by ^{1}H NMR spectroscopic analysis.

With optimized reaction conditions in hand, the oxidation of various symmetric disulfides was examined to explore the scope of the protocol (Scheme 4). The oxidation reaction with disulfides proved to be more sensitive to overoxidation and thiosulfinates are less stable when compared with the corresponding sulfoxides. Benzyl disulfide with an electron-withdrawing group **3b** was oxidized to thiosulfinate **4b** in good yield (89%). Moreover, cinnamyl and allyl disulfides were also oxidized in moderate yields. This system is also applicable to the oxidation of dialkyl disulfides into the corresponding thiosulfinates **4e** (72%) and **4f** (59%), even in the case of the hindered *t*-butyl disulfide **3e**.



Scheme 4. Substrate scope for the oxidation of disulfides **3** using flow conditions.

In conclusion, a rapid, versatile and selective oxidation system is described for a variety of sulfides and disulfides. The use of oxone as oxidant has the advantages of being readily available, inexpensive and non-toxic. The packed-bed reactor with oxone could be washed with dichloromethane and reused. The method shows high functional group tolerance. Compounds bearing both sulfur and selenium atoms were selectively oxidized to the sulfoxides with no formation of other products.

Experimental Section

General Procedure for oxidation of sulfides:

Sulfide (2 mmol) dissolved in a solution of 15 vol% CF_3COOH in CH_2Cl_2 (10 mL, 0.2 M). After flushing the column with CH_2Cl_2, the reagent solution was pumped through the column with a flow rate of 0.6 mL/min by using Vapourtec E-series equipment (with a peristaltic pump). Alternatively, a syringe pump can be used. The first column volume was discarded, and the remaining solution collected. The solution was washed with saturated solution of $NaHCO_3$ (3 x 5 mL), dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude mixture was purified by column chromatography.

General Procedure for oxidation of disulfides:

Disulfide (0.25 mmol) dissolved in a solution of 10 vol% CF_3COOH in CH_2Cl_2 (10 mL, 0.025 M). After flushing the column with CH_2Cl_2, the reagent solution was pumped through the column with a flow rate of 0.6 mL/min by using a syringe pump. The first column volume was discarded, and the remaining solution collected. The solution was washed with saturated solution of $NaHCO_3$ (3 x 5 mL), dried over $MgSO_4$, filtered, and

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the solvent was removed in vacuo. The crude mixture was purified by column chromatography.

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Keywords: sulfoxide • oxone • flow chemistry • packed-bed reactor • oxidation

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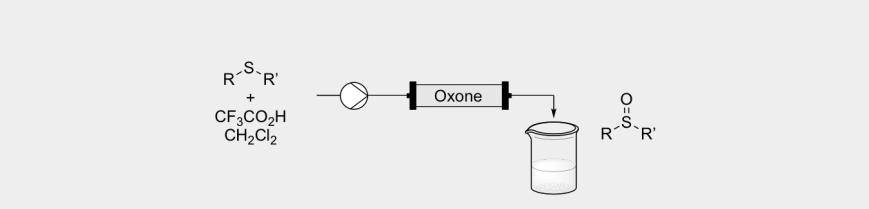

Fixed-bed oxone reactors achieve a selective sulfide oxidation in flow chemistry.

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Page No. – Page No.

Selective Oxidation of Sulfides in Flow Chemistry

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