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RESEARCH ARTICLE

Electrophilic Chlorine from Chlorosulfonium Salts: A Highly Chemoselective Reduction of Sulfoxides

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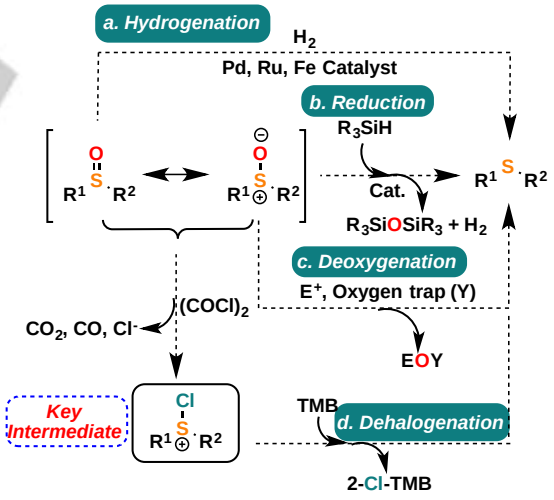
Abstract: Herein, we describe a selective late-stage deoxygenation of sulfoxides based on a novel application of chlorosulfonium salts and, a new process using them generated *in situ* from sulfoxides as the source of electrophilic chlorine. The use of highly nucleophilic 1,3,5-trimethoxybenzene (TMB) as the reducing agent is described for the first time and applied successfully in the deoxygenation of simple and functionalized sulfoxides. The method is easy to handle, economic, appropriate for gram scale and decidedly appropriate for poly-functionalized molecules, as demonstrated with more than 45 examples, including commercial medicines and analogues. We also report some competition experiments to define the more reactive sulfoxide and a mechanistic proposal based on substrate and product observations.

Introduction

Organosulfur compounds, particularly sulfides, are found in nature[1] and produced synthetically;[2] their significance is undeniable in many fields, including biochemistry,[3] agrochemistry and organic materials,[4] among others.[5] Many sulfides are also used as therapeutic agents[6] or as synthetic intermediates.[7] Despite the major advances in sulfur organic chemistry, the discovery of practical methods for making mutual transformations between oxygenated functional groups is an area of continuous growth, and amazing results continuously appear in the literature.[8]

The direct relationship among sulfides, sulfoxides and sulfones has promoted the development of valuable methods for selective sulfur oxidation in sulfides to sulfoxides[9] or sulfones[10]; unfortunately, the reduction of oxygenated functional groups to sulfides has suffered from several drawbacks,[11] principally the unsatisfactory chemoselectivity. Insufficient chemoselectivity is particularly important since several sulfides and sulfoxides are used in current medicine and their oxidation or reduction is necessary for metabolic studies of these active molecules.[12] Unfortunately, the current methods for sulfoxide reductions are based on the use of highly electrophilic reagents, making them unsuitable for late-stage transformations.[13]

During the course of our research program, we became interested in the chemoselective reduction of highly functionalized sulfoxides. Regrettably, we could not find a general and inexpensive method applicable in late-stage transformations. Actually, the existing methods to reduce sulfoxides can be divided in three categories: hydrogenations (Scheme 1a),[13a-c] when the reducing agent is molecular hydrogen (produced *in situ* or inserted), are usually catalyzed by expensive transition metal catalysts and are impractical with unsaturated or reducible functions; reductions, (Scheme 1b)[13e-h] when the reducing agent is a hydride, usually a silane, and catalysts include boron compounds or transition metals; the functional group tolerance for reductions is fairly poor since other electrophilic groups react with the reductive mixture. Finally, deoxygenations,[13i-p] (Scheme 1c) which are promoted by the activation of a sulfoxide with strong electrophiles, need low temperatures and, in most cases, stoichiometric amounts of base. An alternative photocatalytic deoxygenation was described very recently.[13q] It is noteworthy that deoxygenations methods produce strong acids, making them traditionally incompatible with labile acid and nucleophilic functional groups. In addition, an oxygen trap or a reducing agent is also in the reaction mixture.



Scheme 1. Traditional reduction of sulfoxides and association with our approach.

Inspired by the abovementioned difficulties, we report herein the development of a new (Scheme 1d), practical, economic and highly chemoselective method for the reduction of sulfoxides that can be easily applied to polyfunctionalized substrates. The reported method is compatible with oxygen- and nitrogen-protecting groups, unsaturated functional groups, chiral centers near the sulfoxide, and most importantly, can be applied in late-stage functionalization, as demonstrated with commercial drugs, drug precursors and some drug derivatives. This method is based

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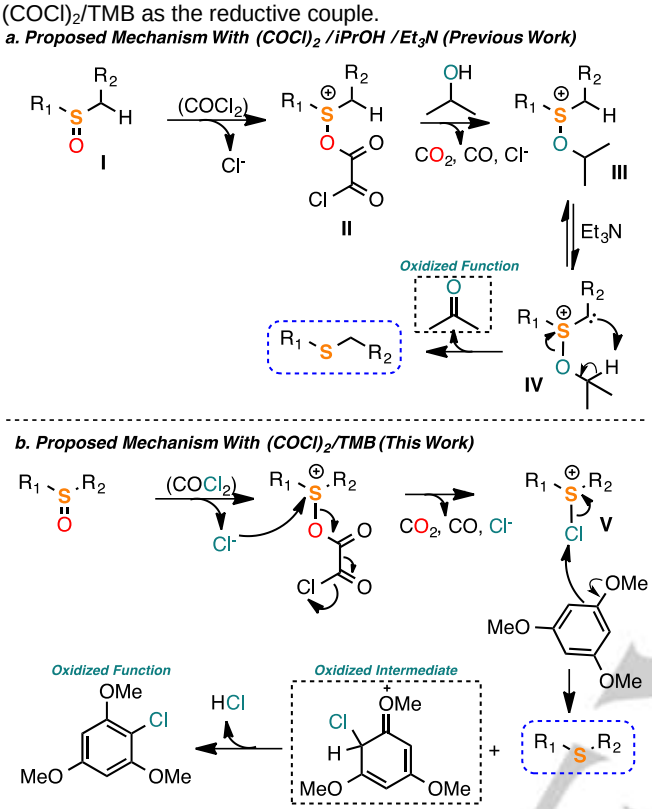
on the use of oxalyl chloride $(COCl)_2$, which reacts as an electrophile and as a chloride source to produce an intermediate chlorosulfonium salt (the key intermediate in Scheme 1d). Then, 1,3,5-trimethoxybenzene (TMB) is used as a chlorine trap, producing a chlorinated aromatic and equimolar amounts of hydrogen chloride. In other words, we propose the use of $(COCl)_2$/TMB as the reductive couple.



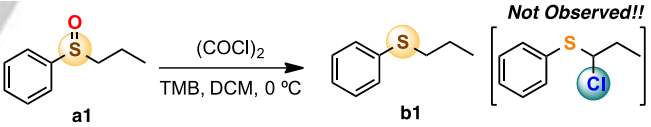
Scheme 2. Mechanistic hypothesis and comparison between previous studies and the current work.

Graczyk and coworkers[13k] vaguely explored the use of oxalyl chloride in combination with low-molecular weight alcohols in the deoxygenation of sulfoxides. The method was based on the mechanism of Swern oxidation;[14] basically, in this classic reaction, DMSO is reduced by an alcohol, so the use of other sulfoxides can be complemented with low molecular weight alcohols. Unfortunately, this method has several drawbacks. First, it uses excess organic bases and very low temperatures (-78ºC). Also, the reaction is incompatible with aryl-aryl sulfoxides since, according to the proposed mechanism, α-hydrogens on sulfur atoms are imperative for the reaction; thus, α-chiral centers will result in racemization. Our primary hypothesis is compared with the previous work shown in Scheme 2.

As mentioned before, the methods based on electrophilic activation need an oxygen trap, in other words, a reducing agent. Scheme 2a shows the proposed mechanism for the deoxygenation of sulfoxides promoted by $(COCl)_2$/Et_3N/*iso*-propanol. The low temperature promotes the stability of sulfonium salt **II**. The reaction of **II** with the nucleophilic secondary alcohol helps in the formation of the sulfonium salt **III,** which has at least one acidic proton. Therefore, the base is essential for carrying out the deprotonation to **IV**, and the intramolecular protonation/deoxygenation leads to the sulfide as the product and the ketone as the oxidized functional group. Previously, we have described an intramolecular reductive chlorination of some special sulfoxides,[15] but we did not identify the utility of chlorosulfonium salts in intermolecular reductions. Herein, we hypothesize that using strong nucleophilic aromatics could eliminate the use of the base (Scheme 2b). Put differently, we propose the use of aromatics as reducing agents, and the re-aromatization step of an electrophilic aromatic substitution as the driving force for the reduction of sulfoxides. Sulfonium salt **II** is somehow stable at temperatures below -60ºC, so carrying out the reaction at higher temperatures should promote the spontaneous generation of chlorosulfonium salt **V** by the nucleophilic reaction of chlorine with **II**. Then, the reaction of **V** with the aromatic should be fast enough to prevent the spontaneous degradation of the sulfonium. Consequently, the temperature may be higher than in previous methods, thus making our proposal inexpensive for large scale operations. The use of chlorosulfonium salts as the source of electrophilic chlorine is fairly rare.[16] Usually, the reaction of halosulfonium salts with nucleophiles leads to the substitution on the more electrophilic sulfur atom, generating another sulfonium salt;[7d] it has been described as the spontaneous degradation of halosulfonium salts by the action of nucleophilic halides to generate molecular halogens and the corresponding sulfide.[16b] However, the yields of sulfides are very low, and the reaction needs alkenes as halogen scavengers. Halogenations of aromatics with halosulfonium salts have only recently appeared in the literature[17] and apparently evolve by the *in situ* formation of molecular halogens. However, their potential application as halogenating agents needs a good balance between the electrophilic character of the halogen linked to the sulfur and the nucleophilic character of the aromatic counterpart.

Results and Discussion

Table 1. Optimization Experiments[a]



entry	$(COCl)_2$:TMB:a1	Solvent	Yield (%) b1[b]
1	1.2:1:1	CH_2Cl_2	92
2	**1.2:0.8:1**	**CH_2Cl_2**	**92[c]**
3	1.2:0.5:1	CH_2Cl_2	90[d]
4	1:0.5:1	CH_2Cl_2	87
5	0.8:0.5:1	CH_2Cl_2	33[e]
6	1.2:0.8:1	THF	49
7	1.2:0.8.1	Et_2O	25
8	1.2:0.8:1	$CHCl_3$	90

[a] All the reactions were performed at the 0.15M concentration of sulfoxide. [b] Isolated yields. [c] Reaction time, 10 min. [d] Reaction time, 1 hour. [e] The starting material was recovered after a reaction time of 8 hours.

Based on our previous observations, we reasoned that any chlorosulfonium salt might be able to be used as a source of

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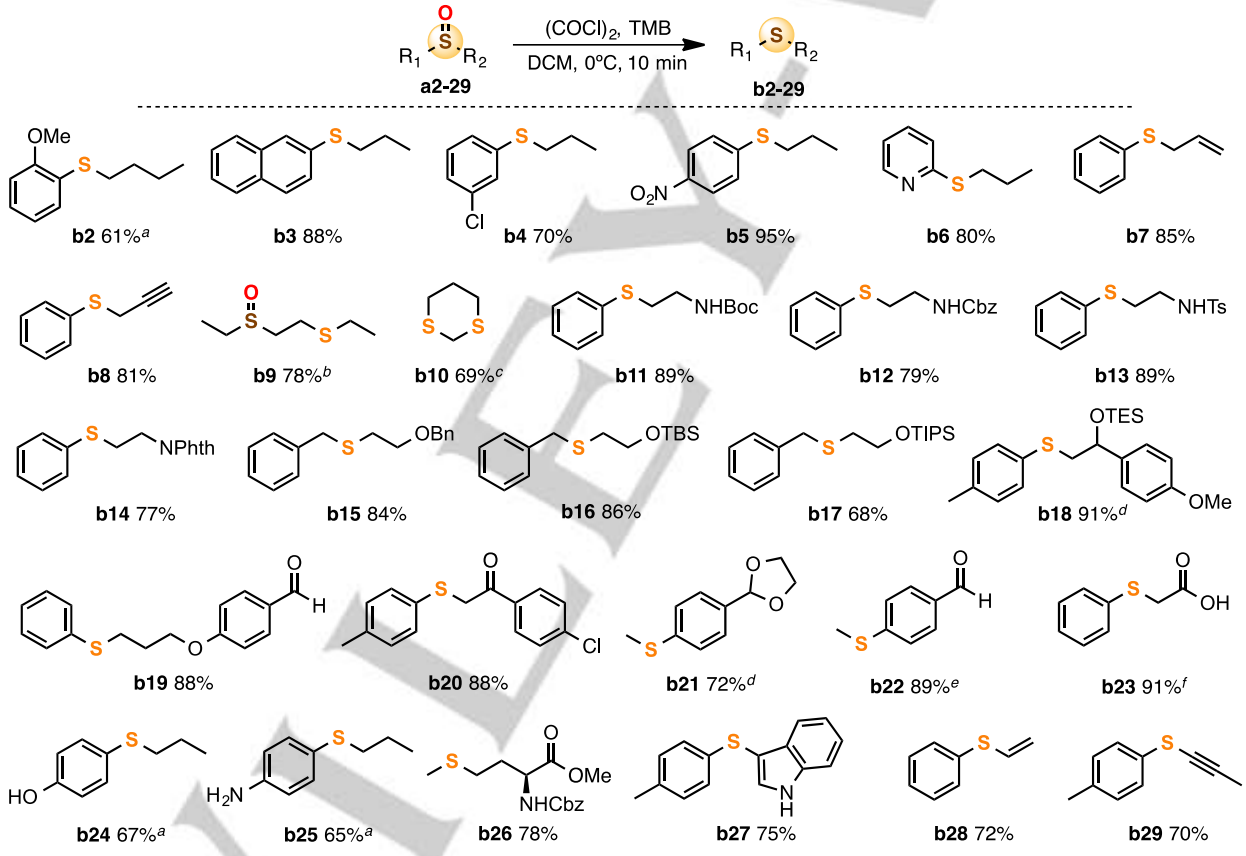
electrophilic chlorine if it can react with a very strong aromatic nucleophile; different options appear plausible. However, 1,3,5-trimethoxybenzene TMB is solid, inexpensive, stable to oxidation in air, does not form stable radicals, is easy to handle, has low toxicity, can be stored dry without special conditions and has three reactive nucleophile positions. Therefore, TMB seems to be a very good alternative to act as the chlorine scavenger. To our delight, the reaction proceeded smoothly, and only few experiments for optimization were required.

Table 1 shows the optimization of the reaction conditions. We started with a molar ratio of 1.2:1:1 (oxalyl chloride:TMB:substrate). The reaction worked very well (entry 1), so we decided to reduce the quantity of TMB (entries 2 and 3) since each molecule has the ability to accept three chlorine atoms. Reducing the quantity of TMB resulted in longer reaction times but comparable yields. When decreasing the quantity of oxalyl chloride, the yield dropped, and some starting material was recovered (entries 4 and 5), showing that each molecule of oxalyl chloride reacts only with one molecule of sulfoxide. Consequently, the production of CO_2, CO and Cl^- is well supported. It is noteworthy that the Cl^- remains in solution and eventually acts as a base in the rearomatization producing HCl. Careful analysis of the crude ^{1}H NMR spectra showed variable amounts of 2-chloroTMB and 2,4-dichloroTMB. However, the α-chlorinated sulfide was not observed. This product has been described in the absence of nucleophiles or in some reductions performed with chlorinated reagents, such as $SOCl_2$,[13m] since the Pummerer reaction is often in competition when basic species are present. The optimal conditions required a molar ratio of 1.2:0.8:1 (entry 2), and the reaction was completed within 10 minutes in excellent yield. Changing the solvent to THF or ethyl ether resulted in lower yields (entries 6 and 7), but $CHCl_3$ can be used without a significant loss of effectiveness. It is noteworthy that even if TMB can accept three chlorine atoms, 2-chloroTMB is less nucleophilic than TMB. Consequently, with highly nucleophilic substrates, the use of low amounts of TMB should result in competitive reactions, which is why we decided to use the conditions described in entry 2 in all subsequent experiments, even though we found comparable results in entries 3 and 4. However, as we will mention (*vide infra)*, with highly nucleophilic substrates, we were forced to increase the quantity of TMB to avoid the aforementioned competition.



Scheme 3. Selective reduction of sulfoxides to sulfides. [a] One equiv. of TMB was used. [b] Approximately 10% of the doubly reduced product was observed. [c] This product was obtained from the monosulfoxide. [d] Two point four equiv. of Et_3N was added to the reaction mixture to neutralize the liberated HCl. [e] This product was obtained from **a21** without using Et_3N. [f] The corresponding ester was obtained under the presence of low-molecular weight alcohols

According to these results, we started our study of the reaction scope using simple sulfoxides. The results are summarized in Scheme 3. The reaction with **a2** was performed with two different quantities of TMB; as we anticipated, using a molar ratio of 1.2:0.8:1 was problematic for deoxygenation since the substrate is in competition with TMB. Consequently, a low yield was observed. However, increasing the amount of TMB (molar ratio 1.2:1:1) allowed us to isolate compound **b2** in good yield; this particular issue was not observed in the reaction with less activated (compound **b3**) or deactivated substrates (see products **b4**-**b6**), and products were obtained in good to excellent yields. Products **b7** and **b8** were isolated in very good yields and

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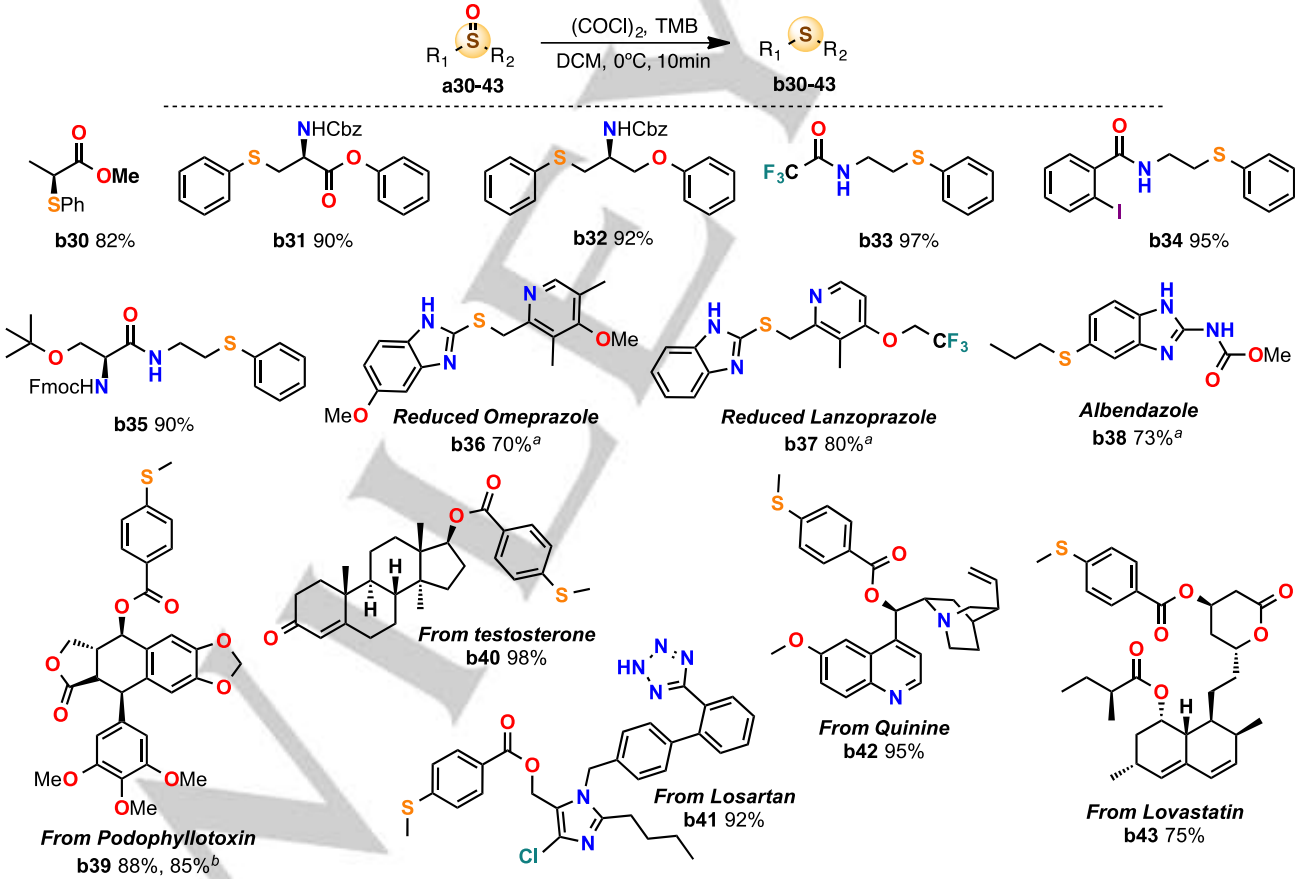
therefore proved the compatibility of our method with unsaturated functional groups. Also, these products are the first evidence of our proposed mechanism since no chlorination of the double bond was observed nor did chlorination occur in the allylic position. α-deprotonation in compounds **a8** or **b8** might produce the corresponding allene, which was not observed. Aliphatic-aliphatic sulfoxides were easily reduced (products **b9**, **b10, b15, b16, b17 and b26**). Compound **b9** was obtained after the reduction of the bis-sulfoxide. It is noteworthy that approximately 10% of the doubly reduced product was observed. On the other hand, **b10** was obtained from the monosulfoxide.

We then turned our attention to more functionalized and potentially problematic substrates. Compatibility with commonly used protecting groups is illustrated with compounds **b11**-**b14** for nitrogen-protecting groups and **b15**-**b18** for oxygen-protecting groups; in all cases, the desired sulfide was obtained in good yield and no deprotection was observed, which is particularly important for labile acid functional groups, such as small silylated groups (TES in compound **b18**), in that case a small excess of triethylamine is use to neutralize the HCl. Chemoselective reduction of compounds **a19** and **a20** was accomplished without any particular issue. The aldehyde functional group showed null reactivity under the reaction conditions, as well as the ketone. Acetal **a21** required the addition of two equivalents of Et_3N since HCl is formed during the reaction; it cleaves the acetal, producing aldehyde **b22** in excellent yield. The addition of triethylamine resulted in the easy isolation of acetal **b21**. Potentially reactive functional groups such as free acids **a23**, free OH and NH_2 groups (sulfoxides **a24** and **a25**) were also tested. Free carboxylic acids may form the corresponding acyl chloride, making them incompatible with previous deoxygenations since the corresponding ester was isolated when low molecular weight alcohols were added to the reaction mixture. Nevertheless, product **b23** was isolated in excellent yield when using alcohol-free solvent. Free OH or NH_2 groups are vulnerable to acylation reactions when using acyl chlorides, so we were curious to see whether any by-product was obtained in those cases. The careful analysis of crude ^1H NMR showed some products issued from halogenation of the hydroxylated or aminated ring (as minor products). Nonetheless, the addition of a small excess of TMB (molar ratio 1.2:1:1) proved effective, affording the corresponding sulfides **b24** and **b25** in good yields. We then turned our attention to amino acid derivatives and found very good results (product **b26**). The use of sulfoxides without α-hydrogens was impossible with the previous use of oxalyl chloride; in our case, the reaction proceeded smoothly with compounds **a27**, **a28** and **a29**. With the use of an aromatic sulfoxide, compound **a27** was reduced to the corresponding sulfide, giving further evidence of our proposed mechanism; on the other hand, substrates **a28** and **a29** may be problematic since conjugated additions or vinylogous Pummerer reactions may be in competition. Fortunately, the sulfides **b28** and **b29** were obtained as the sole products and in good yields.



Scheme 4. Selective reduction of more complex sulfoxides. [a] The reaction was carried out in $CHCl_3$ as the solvent because of the low solubility of the substrate in CH_2Cl_2. [b]The reaction was performed at the 1 g scale.

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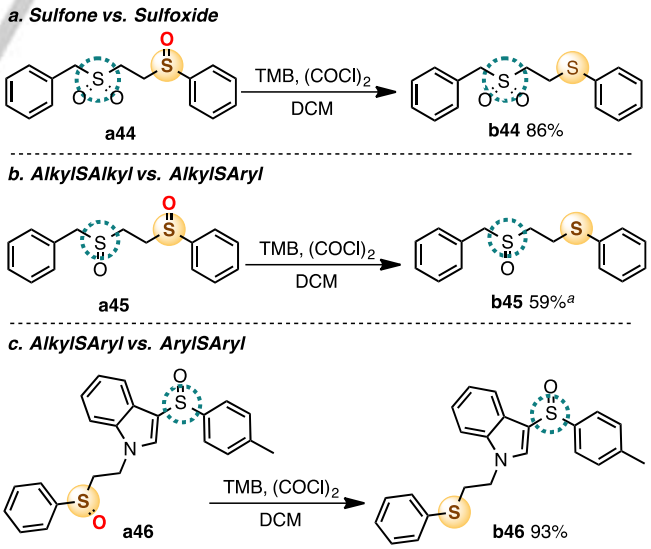
Oxalyl chloride has been used as an activator in Pummerer reactions.[15, 18] In these types of reactions, α-chlorinated sulfides were observed, demonstrating that they can react with Lewis acids or bases, leading to the formation of thionium ions or nucleophilic substitutions. According to careful analysis of the crude ^{1}H NMR spectra in all the cases described in Scheme 3, we hypothesize that the addition of TMB to the chlorosulfonium intermediate is so fast that the Pummerer reaction does not occur in this context. Nonetheless, even if we did not observe an α-chlorosulfide in any of the previous examples, we were curious to determine the behavior of our method with sulfoxides that can undergo a Pummerer cyclization reaction, that is, with substrates that can produce something more stable than chlorinated sulfides. On the other hand, it was also necessary to demonstrate the compatibly of the method with highly functionalized molecules and with asymmetric centers near the sulfur atom. Consequently, we performed the reduction on several sulfoxides issued from commercial drugs and some other sulfoxides described previously as suitable Pummerer substrates.

The results are summarized in Scheme 4. All the products showed great reactivity, and sulfoxides **a30**-**a43** were deoxygenated in good to excellent yields. Product **b30** was obtained without racemization, providing the third piece of evidence of our proposed mechanism since any alternative route should result in the loss of stereochemistry in the chiral center. Moreover, sulfoxides **a31** to **a35** have been described previously as being reactive in Pummerer reactions, producing oxazolines or chromanes and thus preventing alternative proposals for mechanisms *via* thionium ions. Product **b35** also proved the compatibility of this method with the Fmoc protecting group.

Proton pump inhibitors used for the treatment of gastroesophageal reflux, peptic ulcers and Zollenger-Ellison syndrome, such as **a36** and **a37** (omeprazole[19] and lansoprazole,[20] respectively), were reduced in very good yields, obtaining the corresponding sulfides **b36** and **b37**. These molecules, along with albendazole,[21] **b38**, a medicine used to treat parasitic infections, showed the compatibility of our method with nitrogen-heterocycles, small carbamates and basic functional groups.

The sulfoxide **a39** was obtained by the derivatization of podophyllotoxin,[22] a nonalkaloid natural toxin used in the treatment of genital warts and molluscum contagiosum. **a39** was reduced selectively over other oxygenated functional groups without affecting the highly activated aromatic rings. One of the most important issues in the reduction of sulfoxides is the use of expensive or highly toxic reagents or catalysts. Therefore, performing the reaction at a large scale (grams) is potentially problematic for the researcher and the environment. Also, if the molecule is highly functionalized, it can be very awkward from an economical point of view since most of the methods use strong reaction conditions. Keeping all these issues in mind, we performed the reduction of **a39** at the gram scale with comparable success to the reaction performed at the milligram scale, and negligible quantities of by-products were observed. We also obtained the testosterone derivative **a40**. Testosterone is the principal male sex hormone, it is used as a medication for the treatment of some types of breast cancer,[23] so analogues may have a potential as anticancer new drugs.[24] The reduction of **a40** proceeded smoothly yielding **b40** in excellent yield. Continuing with our exploration of late-stage reductions we used the losartan derivative **a41**; losartan[25] is a medication used to treat high blood pressure, in some cases for diabetic kidney disease and hearth failure; **a41** was reduced in very good yield. Quinine[26] modification afforded **a42,** and its reduction produced the corresponding sulfide **b42** as the sole product in excellent yield; quinine is an antimalaria used mainly for infections produced by *Plasmodium Falciparum* which is resistant to chloroquine or when other drugs are not available.[27] It is noteworthy that malaria is an infectious disease touching mainly the developing countries;[28] consequently, the production of synthetic analogues of commercial antimalarials seems a primary approach to partially address this important issue; also, quinine is an essential medicine worldwide and among the most effective and safest pharmaceuticals. Finally, we obtained **a43** from commercial lovastatin,[29] a medication from the statins group used to reduce the risk of cardiovascular diseases by reducing high cholesterol. The reduction of the synthetic analogue was accomplished with excellent results, yielding **b42**.

Finally, we turned our attention to competition experiments. During the course of our research, we observed that, even if the common reaction time was 10 min, some substrates were completely consumed in shorter reaction times. Consequently, we performed three experiments to determine the selectivity between different kinds of sulfoxides and between sulfoxides and sulfones. The results of these experiments are summarized in Scheme 5; as expected, the reaction is completely selective to sulfoxides over sulfones (product **b44**). This was easily predictable since sulfones are less nucleophilic than sulfoxides, and their reduction usually requires metallic hydrides[30] (Scheme 5a). The competition between dialkyl sulfoxides and alkyl-aryl sulfoxides proved slightly difficult. Clearly, alkyl-aryl sulfoxide reacts faster than dialkyl sulfoxide (see product **b45**); however, approximately 15% of the doubly reduced product was observed. On the other hand, the reaction of alkyl-aryl sulfoxides over diaryl sulfoxides is much faster and completely selective (product **b46**). These results also indicate that dialkyl sulfoxides react faster than diaryl sulfoxides.



Scheme 5. Competition experiments [a] Approximately 15% of the doubly reduced product was observed.

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Conclusion

In summary, we describe a simple, inexpensive and highly chemoselective method for the deoxygenation of sulfoxides. The method is compatible with many other reducible functional groups and can be applied at any stage of synthesis, including late stages. The most important result of this investigation is the use, for the first time, of a tandem sulfoxide activation and an electrophilic aromatic substitution as the reduction reaction. The oxidized functional group, in this case, is a chlorinated aromatic that can be easily separated from the reaction mixture. The efficiency of this method was illustrated with more than 45 examples, including commercial drugs as substrates and as precursors. The uniqueness of this method might facilitate its application in other deoxygenations in both industry and academia as well as in the development of new halogenation reactions. Related studies are currently ongoing in our laboratory.

Experimental Section

General procedure for deoxygenation of sulfoxides: To a solution of the corresponding sulfoxide (1 equiv.) in dry DCM (0.15 M) at 0°C, trimethoxybenzene (0.8 equiv.) and oxalyl chloride (1.2 equiv.) were added. The mixture was stirred at the same temperature for around 10 minutes (complete conversion was checked by TLC). The reaction was neutralized with NaOH (1M). The aqueous layer was extracted with DCM (3 x 15 mL), the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified using flash chromatography to afford the pure product. The products were obtained with yields between 61 and 97%.

Acknowledgements

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Conflict of Interest

There are no conflicts to declare.

Keywords: Chemoselectivity • Deoxygenation • sulfides • Sulfonium salts • sulfoxides

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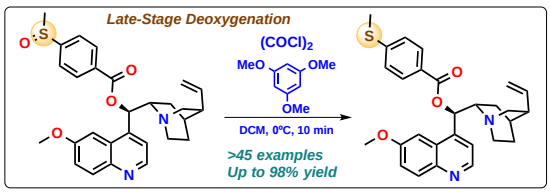

A highly chemoselective late-stage deoxygenation of sulfoxides is described; this is a new process using chlorosulfonium salts generated *in situ* from sulfoxides. The reaction is easy to handle, economic and showed great functional-group tolerance. It is appropriate for poly-functionalized molecules, as demonstrated with more than 45 examples, including commercial drugs and some analogues.

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