

Chemistry Corner

Sulphur trioxide amine complexes: More than reagents

Dr Jörg Schrickel of [CABB](#) looks at the use of sulphur trioxide amine complexes in organic synthesis

Sulphur plays an important role in inorganic and organic molecules. Although it forms compounds in lower oxidation states, sulphur is mostly present in organic compounds in higher oxidation states as sulphonic acids, sulphonyl chlorides, sulphonamides, sulphones and derivatives thereof.

Commercially important sulphur-containing molecules are found throughout the chemicals industry. These include consumer applications in detergents, such as linear alkyl benzene sulphonates and fatty alcohol sulphates, ion exchange resins containing sulphonic acid functionalities, such as sulphonated styrene divinylbenzene complexes, dyes and pigments such as Mordant Yellow 20, as well as artificial sweeteners, like saccharin.¹⁻⁴

In APIs, a whole class of antibiotics is named sulphonamides - one prominent example is Sulfamethoxazol - while in agrochemicals sulphonyl ureas describe a class of pesticides, such as Cinesulfuron (Saliant).⁵ Other chemicals, like the methylating reagent dimethyl sulphate, can be prepared by the direct insertion of sulphur trioxide (SO₃) into dimethyl ether.⁶ Sulphonated synthetic polymers like DuPont's Nafion play an important role in many chemical and industrial processes.⁷

Sulphur oxides can be prepared in organic molecules in various different ways, most often by the oxidation of organic sulphides.⁸ Other methods include the radical substitution of alkanes with chlorine and sulphur dioxide to yield sulphonyl chlorides, or the reaction of aromatic compounds with chlorosulphonic acid to yield aromatic sulphonyl chlorides.⁹

The most straightforward reaction is the introduction of pure SO₃. However, due to the hazardous nature of this reagent, this route is generally only applicable for large volume reactions because special equipment is needed and SO₃ has to be generated *in situ*.

SO₃ itself is a liquid of high density (1.92 g/ml) with a melting point at 16.9°C and a boiling point of 45°C. It is aggressively hygroscopic and highly corrosive, which makes it difficult to handle. As a strong electrophilic reagent, SO₃ reacts with any organic molecule that contains an electron donor group. Due to the violent reaction and the heat evolution, most substrates are burned via the effect of concentrated sulphuric acid on organic compounds, resulting in the formation of black tar - as many chemists will have experienced personally in the laboratory.

SO₃ itself is not available on merchant markets in Europe and is only used captively by its producers. As an alternative, 'diluted', more convenient and transportable forms are available, such as oleum, sulphuric acid, chlorosulphonic acid and sulphamic acid (Figure 1).

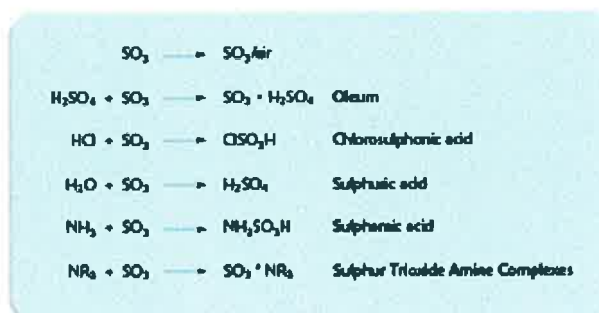


Figure 1 - SO_3 transfer reagents obtained as dilutions of SO_3

The reaction of SO_3 with amines, phosphines, oxygen-containing heterocycles and other Lewis bases leads to adducts of SO_3 .¹⁰⁻¹² Of these, only SO_3 amine complexes are of commercial interest due to their higher stability compared to the corresponding oxygen or phosphor adducts. Amongst these complexes, amines with aliphatic (trimethyl amine, triethylamine, dimethylethyl amine, dimethylformamide) or aromatic substituents (dimethylaniline) and nitrogen-containing heterocycles (pyridine) are used to obtain complexes with varying properties.^{14,10}

Properties, preparation & applications

The reactivity of SO_3 amine complexes is inversely proportional to the Lewis base strength of the amines, i.e. in terms of Lewis acid base strength, trimethylamine > triethylamine > pyridine > dimethyl aniline > dimethylformamide >> dioxane.¹⁰

The corresponding SO_3 complexes of trialkylamines are of low reactivity, whereas the pyridine sulphur trioxide (PSS) complex shows good stability in air and at room temperature but is still reactive enough for sulphonation of aromatic compounds.¹⁴ The dimethylformamide sulphur trioxide complex (DMFS) shows high reactivity but low stability. It is highly hygroscopic and decomposes at temperatures above 30°C.

SO_3 complexes can be prepared according to standard literature methods.¹⁵ The direct reaction of SO_3 with the amine in an appropriate solvent or in the gas phase gives the best results without creating significant amounts of waste or by-products.

In situ preparation by reaction of the corresponding amine with chlorosulphonic acid in a chlorinated solvent is possible. However, this process is less atom-economical because two moles of amine have to be used; the second mole has to catch the released hydrochloride in the form of the amine hydrochloride salt.¹⁶ This leads to a low yield and the salt - if not filtered off - can have negative impacts on the reaction or on the final product.

The primary applications of SO_3 and its derivative reagents are in bond forming reactions sulphonation (C-S), sulphamation (N-S) and sulphation (O-S). The high reactivity of conventional reagents (SO_3 , oleum, sulphuric acid, chlorosulphonic acid, sulphamic acid, etc.) leads to reactions, even with unreactive substrates. However, controlled reaction conditions are necessary in order to obtain the desired product and to avoid oversulphation and poor regioselectivity.

The advantages of SO_3 amine complexes over conventional reagents are mainly their more moderate reactivity, which leads to less degradation, decomposition and discolouration.¹⁷ Their use allows higher reaction temperatures than with conventional reagents and makes it possible to obtain the desired degree of sulphation while keeping work-up procedures shorter.

The complexes are not acidic and can be used with acid-sensitive substrates like heterocycles and carbohydrates. No water is formed in the reaction, therefore the complexes do not lose their reactivity during a reaction.¹⁸

Sulphonation

The sulphonation of aromatic systems with conventional reagents leads to high degrees of sulphonation without regioselective control. With the use of SO₃ amine complexes, the degree of both sulphonation and regioselectivity can be controlled.

An example is an indene system that is used as optical brightener in liquid detergents.¹⁹ As shown in Figure 2a, the sulphonation does not take place at the aromatic rings. By reaction with SO₃ complexes, the adjacent cyclopentene ring is sulphonated in a regioselective way.

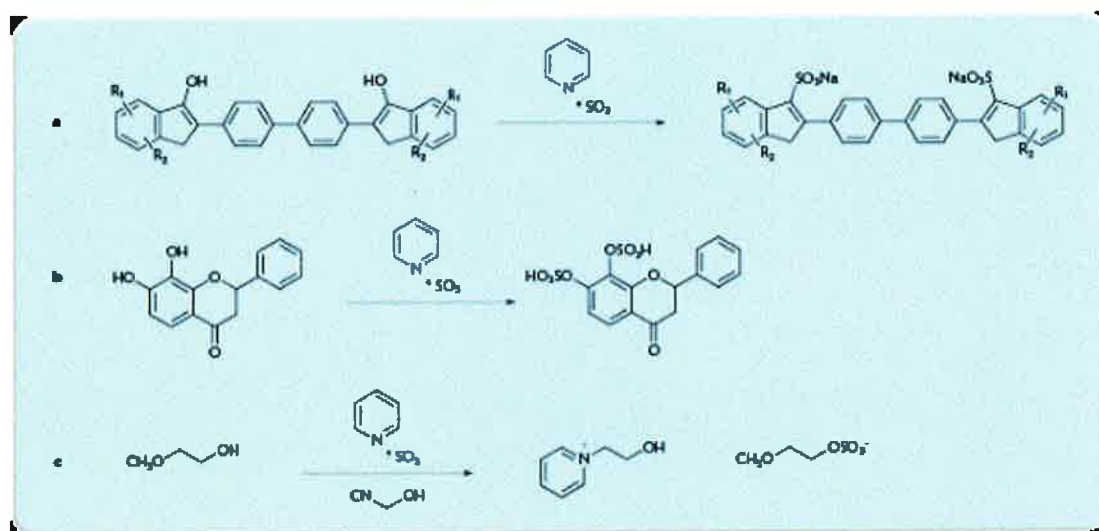


Figure 2 - Sulphated products obtained by reaction of SO₃ amine complexes of SO₃

Similarly, for the sulphonation of polymers, the degree of sulphonation depends on the reactivity of the reagent and the reaction conditions.²⁰ The compliance of the degree of sulphonation is often of high relevance for the properties of the final product. Here, conventional reagents often need low temperatures in order not to affect the substrates but then the degree of sulphonation cannot be obtained any more. SO₃ amine complexes lead to high degrees of sulphonation at ambient temperatures without destroying the substrate.²¹

Sulphation

The sulphonation (O-S bond formation) of flavones, naturally occurring yellow plant dyes, yields products which show pharmaceutical and cosmetic activity in anti-inflammatory and anti-ageing applications.²² Sulphonation takes place in the 7- and 8-hydroxylated position of the aromatic ring of a flavone used as an intermediate in the synthesis of an antioxidant (Figure 2b). SO₃ amine complexes like PSS selectively react with the hydroxy functions, whereas more reactive conventional reagents also sulphonate the aromatic ring, yielding undesired benzene sulphonate by-products.

Certain classes of ionic liquids can also be prepared by the sulphonation of alcohols with PSS and subsequent reaction with acrylonitrile. In the first step, PSS reacts with methoxyethanol to yield pyridinium methoxyethylsulphate. Without isolation, this is further reacted with acrylonitrile to yield the protonated pyridinium compound 1-(2'-Cyanoethyl)pyridinium ethoxoyethyl sulphate (Figure 2c).²³

The sulphonation of chitosan is an example for the selectivity of sulphur trioxide complexes compared to conventional sulphonation reagents, in particular chlorosulphonic acid (CSA, Figure 3a). Chitosan is a naturally occurring polyacetylglucosamine with a similar structure to heparin, which shows anticoagulant properties. It is also an important regulator in the network of the cell.

The reaction of chitosan with CSA yields an unselective sulphonation of the N- and O-groups. In order to obtain the desired anti-coagulant properties, a high degree of N-sulphonation but no O-sulphonation is required. By using PSS (Figure 3b), a

selective N-sulphation can be obtained. This selectivity is also observed with monomeric amino alcohols. They can be selectively sulphated at the amine function with PSS, whereas CSA sulphates the hydroxyl group.²⁴

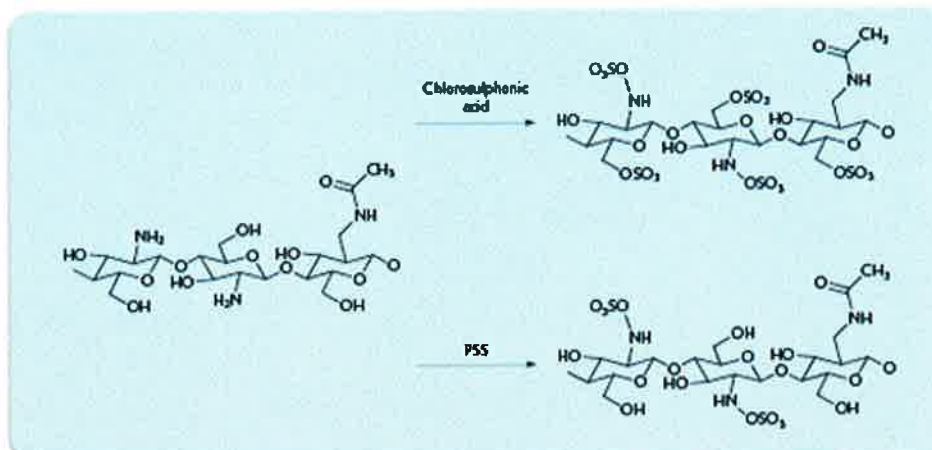


Figure 3 - Sulphonation of chitosan with a conventional reagent (a) & a SO₃ amine complex (b)

Parikh-Doering-oxidation

PSS is the most widely used SO₃ amine complex, with the broadest application possibilities. Apart from sulphonation, sulphation and sulphamation reactions, PSS also is used as an oxidising agent in the Parikh-Doering oxidation.

In this variation of the Swern oxidation, primary and secondary alcohols are oxidised to aldehydes and ketones respectively with PSS, in the presence of dimethyl sulphoxide (DMSO).²⁵ In a first step, dimethyl sulphide is activated by SO₃, which in a second step reacts with the alcohol under basic conditions to form the corresponding carbonyl compound (Figure 4).

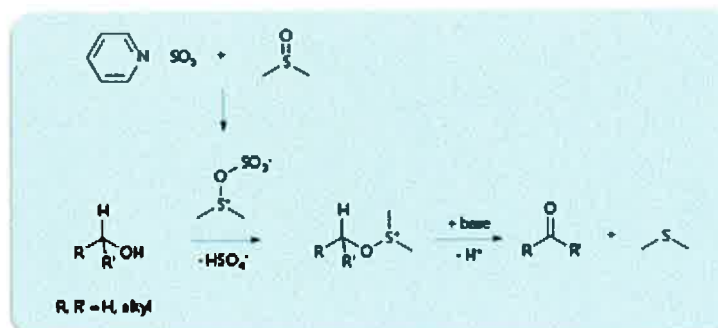


Figure 4 - Parikh-Doering oxidation of a secondary alcohol with PSS as active reagent

In the classical Swern oxidation (oxalyl chloride, dimethyl sulphide), temperatures below 0°C are required and CO, CO₂ and dimethyl sulphide are released as off gases. By contrast, with the Parikh-Doering oxidation excellent results can be achieved at temperatures above 0°C, without the formation of CO and CO₂. The Parikh-Doering oxidation is also applicable where the Oppenauer oxidation (of secondary alcohols to ketones in the presence of aluminium alcoholates) is limited or where other oxidation methods give lower yields or need more elaborous purification steps (Figure 5).²⁶

The release of dimethyl sulphide as an off-gas can be circumvented in an improved process where it is bound to a solid carrier. The activated sulphoxide oxidises the substrate and leaves the product along with a polymeric methylthioether, instead of the unpleasant smelling dimethyl sulphide.²⁷ This polymeric sulphide can be recovered and re-oxidised to give the active sulphoxide for further use - an advantage in times of green chemistry and increasing relevance of sustainability.

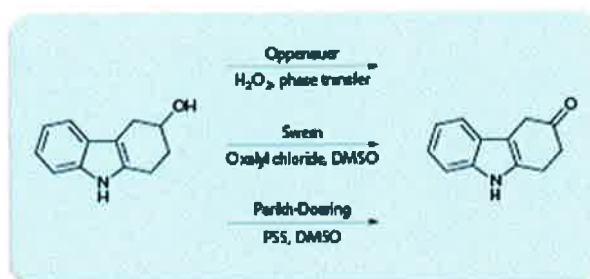


Figure 5 - Various oxidation methods of a carbazole derivative

Carrier-based reagents

SO_3 can be bound onto solid carriers, both organic and inorganic supports. In the case of organic polymeric carriers, suitable compounds with Lewis base characteristics like 4-polyvinylpyridine can be applied.²⁸ This polymeric reagent exhibits the same characteristics as PSS.

One of the advantages of solid SO_3 amine reagents is that no monomeric amine is formed during the reaction. After the sulphonation or sulphation, the polymeric amines remains solid and can be separated by simple filtration. In contrast, any monomeric amines used have to be removed from the final product by distillation.²⁹ The second advantage is the recyclability of the solid-supported reagent. The polymer can be reloaded again with SO_3 and reused in a next operation.

Polymer-bound SO_3 can also be used as a convenient transportable SO_3 reagent. SO_3 can easily be liberated from the carrier by applying heat, radiowaves or microwaves.³⁰ An example is the sulphonation of polymer surfaces in plastic containers, which leads to protection of the plastic against chemicals, oils, fuels, gases and other materials.

Summary

SO_3 amine complexes are versatile tools in organic synthesis. Due to their more moderate reactivity compared to pure SO_3 and conventional reagents, they are widely used for sulphonation, sulphation and sulphamation reactions in fine chemistry applications. Depending of the type of amine their reactivity can be adjusted. This graduated reactivity leads to increased regioselectivity or atom selectivity (N-, C- or O-atoms).

Their moderate reactivity makes SO_3 amine complexes preferred reagents for acid-sensitive substrates and for reactions with polymeric structures because they prevent degradation of the polymer backbone. Apart from sulphonation and sulphation, with the pyridine SO_3 complex the active reagent in the Parikh-Doering oxidation reaction can be prepared.

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