

Sulphur trioxide-pyridine complex: A versatile organic reagent

Dr Dirk Kusch, head of development at **SF-Chem**, looks at the use of the sulphur trioxide-pyridine complex in many applications

Sulphonation, sulphation and sulphamation (the formation of carbon-sulphur, oxygen-sulphur and nitrogen-sulphur bonds respectively (Figure 1)) are major industrial chemical processes. They are used to make a broad range of products, including dyes, pigments, detergents, pharmaceuticals, agrochemicals and organic intermediates.^{1,2}

In general, sulphonic acids formed by sulphonation are more stable molecules than sulphates, which are hydrolytically unstable and tend to decompose to sulphuric acid and the corresponding alcohol. The difference in stability among products obtained by reactions with sulphur trioxide (SO₃) has a significant impact on the choice of the process used to produce sulphonates, sulphates or sulphamates.

SO₃ is an extremely electrophilic reagent that rapidly reacts with any organic compound containing an electron donor group. Most organic compounds form a black tar on contact with pure SO₃, due to rapid reaction and heat evolution.² To adjust the reactivity of SO₃ for different types of reaction, various 'diluted' forms of SO₃ are available (Figure 2).

In addition, the use of 2.5-8% SO₃ in dry air is suitable for sulphonation and sulphation processes in large production volumes.² The reactivity of SO₃ can be controlled with solvents like liquid sulphur dioxide (SO₂) and its highly acidic character and reactivity can be moderated by the use of different nitrogen bases in order to form SO₃-amine complexes.

These complexes represent a very valuable and versatile class of reagents with mild and selective properties. They have multiple uses for the sulphonation of acid-sensitive heterocycles, aliphatic and aromatic hydrocarbons and for the sulphation of alcohols, as well as for sulphamation reactions.³

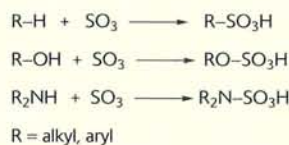


Figure 1 - Sulphonation, sulphation & sulphamation

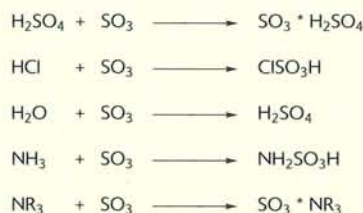


Figure 2 - 'Diluted' forms of sulphur trioxide

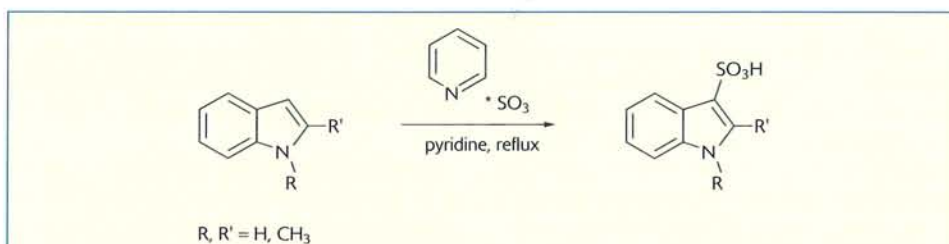


Figure 3 - Sulphonation of indoles with sulphur trioxide-pyridine complex

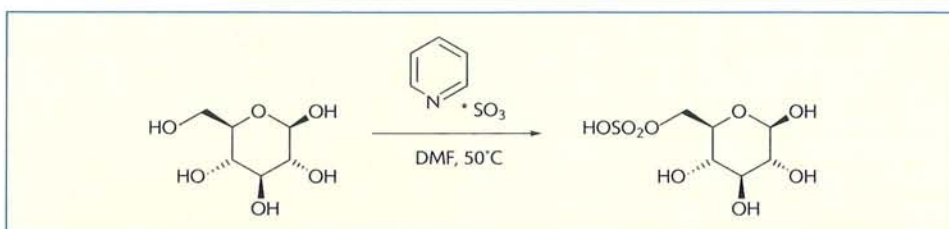


Figure 4 - Sulphation of glucose with sulphur trioxide-pyridine complex

The application of SO₃-amine complexes for the synthesis of sulphated polysaccharides as pharmaceutical intermediates is broadly used to provoke the cleavage of glycosidic bonds and other labile functions, such as amides, esters and even ethers.⁴ Recently, the regioselective sulphation of trimethylsilyl cellulose, using different SO₃-amine complexes, has also been described.⁵

Numerous complexes of SO₃ with amines, such as trimethylamine, triethylamine, N,N-dimethylaniline, 2-methylpyridine or pyridine, are described in the literature.⁶ Complexes of SO₃ with other Lewis bases, such as dioxane, thioxane, dimethyl sulphide, dimethyl sulphoxide or N,N-dimethyl formamide are also known.⁷

The reactivity of these complexes is inversely proportional to their stability, which in turn varies directly according to the strength of base used.⁶ Different papers have described investigations into the sulphonation reactivity of different SO₃-amine and other SO₃-Lewis base complexes.^{7,8} Even the weakest complex is a much milder reagent than free SO₃. It is also possible to moderate the reactivity of SO₃ to any desired degree by the correct choice of a complexing Lewis base.⁶

Several methods have been described for the preparation of tertiary SO₃-amine complexes.⁹ The processes may be performed by the reaction of a tertiary amine (e.g. trimethylamine, triethylamine, N,N-dimethylaniline or pyridine) with SO₃ in the gaseous phase or in an organic solvent or by reaction with chlorosulphonic acid in a chlorinated organic solvent (e.g. 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane). By the use of chlorosulphonic acid, the tertiary amine

hydrochloride is formed as by-product.^{6,10}

The use of SO₂ as solvent is also described for the synthesis of SO₃-amine complexes. The reaction proceeds via the formation of a SO₂-amine complex as an intermediate. Complexes with ratios of SO₃ to tertiary amine other than 1:1 can also be prepared.^{6,11}

Using the reaction of a tertiary amine with SO₃ in a chlorinated organic solvent for the preparation of SO₃-amine complexes leads to the formation of chlorosulphates.¹²

Since these intermediates, which are formed by an insertion reaction of SO₃ with the chlorinated organic solvent, decompose under certain conditions, the reaction, work-up and isolation conditions have to be controlled carefully in order to avoid hazardous incidents.¹²

Due to its mild character, stability and relatively easy handling, the SO₃-pyridine complex is one of the most important SO₃-amine complexes used in organic synthesis for different kinds of reaction.¹³ It is a crystalline white solid with a melting point of 175°C, which can be prepared by using one of the methods described above.

The complex is a corrosive compound, which reacts quantitatively with hot water to give pyridine and sulphuric acid.¹³ Complexes with SO₃:pyridine molar ratios other than 1:1 (CAS 26412-87-3) can also be prepared: 2:1 (CAS 52922-34-6), 3:1 (CAS 52922-35-7) and 1:2 (CAS 82810-30-8).⁶

Any additional SO₃ in these complexes is much more reactive than the first equivalent. For instance, a complex with a SO₃:pyridine molar ratio of 2:1 can be used for the α -sulphonation of butyric acid. In general, however, the use of these complexes is very limited.^{3,6}

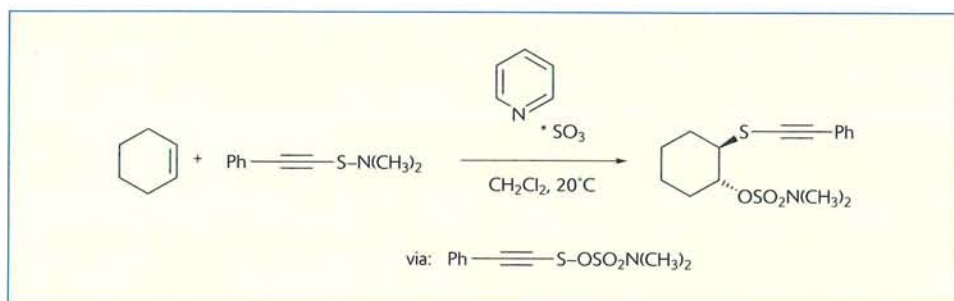


Figure 5 - Preparation of phenylethynylsulphenyl sulphamates with sulphur trioxide-pyridine complex

The SO_3 -pyridine complex can be used for the sulphonation of polycyclic compounds and acid-sensitive heterocycles, for example the synthesis of sulphonated indoles under mild reaction conditions (Figure 3).^{3,6,14} It is also broadly used for sulphonation of dyes, sterols, and especially for carbohydrates.^{3,6}

The method can be used to minimise polysulphation, e.g. for the preparation of glucose-6-sulphate (Figure 4).¹⁵ Due to the fact that there are naturally occurring sulphated polysaccharides (e.g. heparin, bearing alternating glucosamine and glucuronic acid units), the use of SO_3 -pyridine complex is of general interest as a selective sulphonating reagent for amino groups in amino alcohols.¹⁶

The sulphated products can be used as intermediates for different subsequent reactions. For example, the pyridinium sulphate ester intermediates of substituted benzyl alcohols can be eliminated, to form substituted styrol compounds.¹⁷

Pyridinium sulphate esters can be used as intermediates for the deoxygenation of allylic and benzylic alcohols for substitution by hydride. This reaction is useful in reactions of allylic or benzylic alcohols which cannot be converted into halides.^{13,18}

The preparation of carboxylic acid amides from oximes can also be performed with the SO_3 -pyridine complex.¹⁹ Recent publications describe its use in the synthesis of sulphated alcohols as intermediates for the production of functionalised²⁰ and halogen-free ionic liquids.²¹ It can also be used for the manufacturing of pigment dispersions for the preparation of inkjet inks with specific properties.²²

The complex is suitable for sulphamation reactions of primary amines.^{3,13} Its use in the preparation of phenylethynylsulphenyl sulphamates from alkyne-sulphenamides can also be considered as a sulphamation reaction. Phenylethynylsulphenyl sulphamates can be used for the electrophilic addition to olefinic double bonds for the preparation of acetylenic sulphides (Figure 5).²³

The oxidation of primary alcohols to aldehydes and the oxidation of secondary alcohols to ketones by means of the SO_3 -pyridine complex and dimethyl sulphoxide in the presence of triethylamine

is known as Parikh-Doering oxidation.²⁴ This is broadly used for the synthesis of pharmaceutical intermediates, due to the mild reaction conditions it uses.²⁵

In the first step, dimethyl sulphoxide is activated by SO_3 , which in the second step reacts with an alcohol under basic conditions to form the corresponding carbonyl compound and dimethyl sulphide as a by-product (Figure 6).

Recently, unusual oxidation behaviour by a propargylic alcohol by Parikh-Doering oxidation was described. The aldehyde formed initially yields an α -

β -unsaturated- β -methylsulphenyl aldehyde, presumably formed by the addition of dimethyl sulphide.²⁶ The Parikh-Doering reaction with SO_3 -pyridine complex can also be performed on a large scale.²⁷

Dimethyl sulphide is formed as a by-product of the Parikh-Doering oxidation, using dimethyl sulphoxide. The general application of this side reaction is also described by using the SO_3 -pyridine complex along with sodium iodide for the deoxygenation of sulphoxides to sulphides at room temperature with high yields.²⁸

The activated dimethyl sulphoxide species formed by the reaction of SO_3 -pyridine complex with dimethyl sulphoxide as described above can also be used as a dehydrating agent to obtain nitriles from primary amides in excellent yields.²⁹

In conclusion, the SO_3 -pyridine complex represents a very valuable and versatile form of SO_3 and can be used for different types of reactions that have to be performed under mild conditions. SF-Chem produces it on a multi-tonne scale and has experience in the production and use of SO_3 -amine complexes for different kind of reactions.

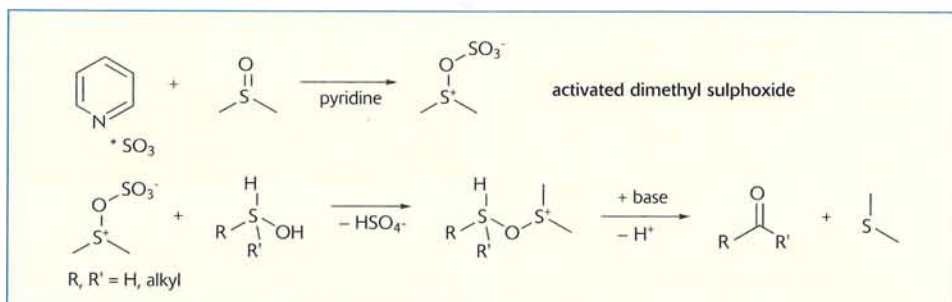


Figure 6 - Parikh-Doering oxidation of alcohols with sulphur trioxide-pyridine complex & dimethyl sulphoxide

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