



***Sulfur Trioxide Amine Complexes:
Versatile Reagents in Organic Synthesis***

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RSC Symposium Berlin 2010

Sulfur Trioxide Amine Complexes



Content

- Sulfur trioxide chemistry: Introduction
- Sulfur trioxide reagents: Overview and Properties
- Sulfur trioxide amine complexes: Products and Properties
 - *Reactivity*
 - *Selectivity*
 - *Sensitivity*
 - *Diversity*
- Summary

Sulfur Trioxide Amine Complexes



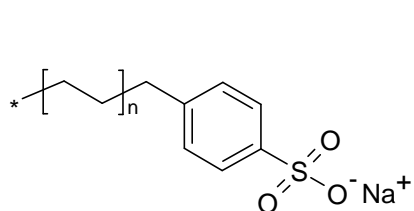
Sulfur trioxide chemistry: Introduction

- Exhibiting a similar reactivity as oxygen, sulfur forms thiols, thioethers, thioketones and others. More important are compounds, where sulfur is present in a higher oxidation level: sulfur trioxide derivatives.
- Sulfur trioxide is a high density liquid (1.92 g/ml) with a melting point of 16.9°C and a boiling point of 45°C. It is highly corrosive and aggressively hygroscopic.
- In Europe, sulfur trioxide is not commercially available in bulk quantities.
- To facilitate handling and to have sulfur trioxide in an available form, “dilutions” of sulfur trioxide are mainly used: chlorosulfonic acid, oleum, sulfuric acid, sulfamic acid.

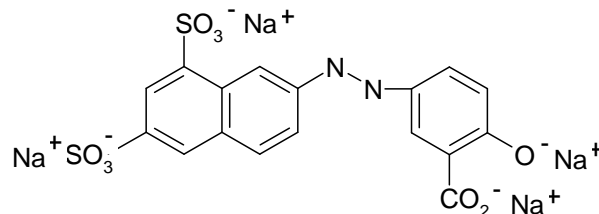
Sulfur Trioxide Amine Complexes

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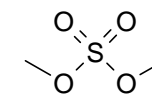
Sulfur trioxide chemistry: Introduction



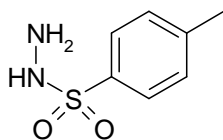
Linear Alkylbenzene sulfonate
Detergent



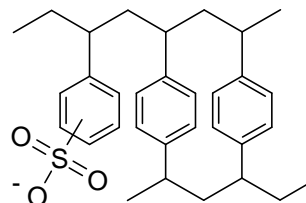
Mordant Yellow 20
Dye



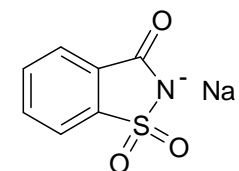
Dimethyl sulfate
Methylating agent



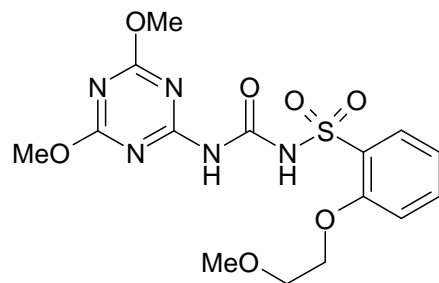
Toluenesulfonyl hydrazide
Blowing agent for rubber



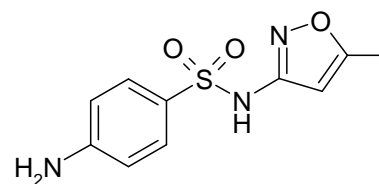
Sulfonated styrene divinylbenzene copolymers
Ion exchange resins



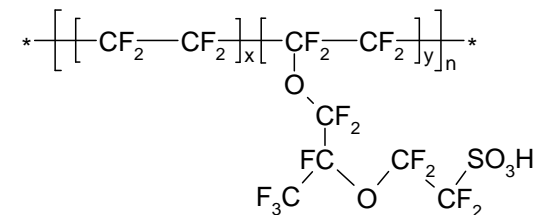
Saccharin
Artificial Sweetener



Cinesulfuron ("Sailant")
Sulfonylurea Herbicide



Sulfamethoxazole
Sulfonamide Antibiotic



NAFION™ (DuPont)
Sulfonated Polymer

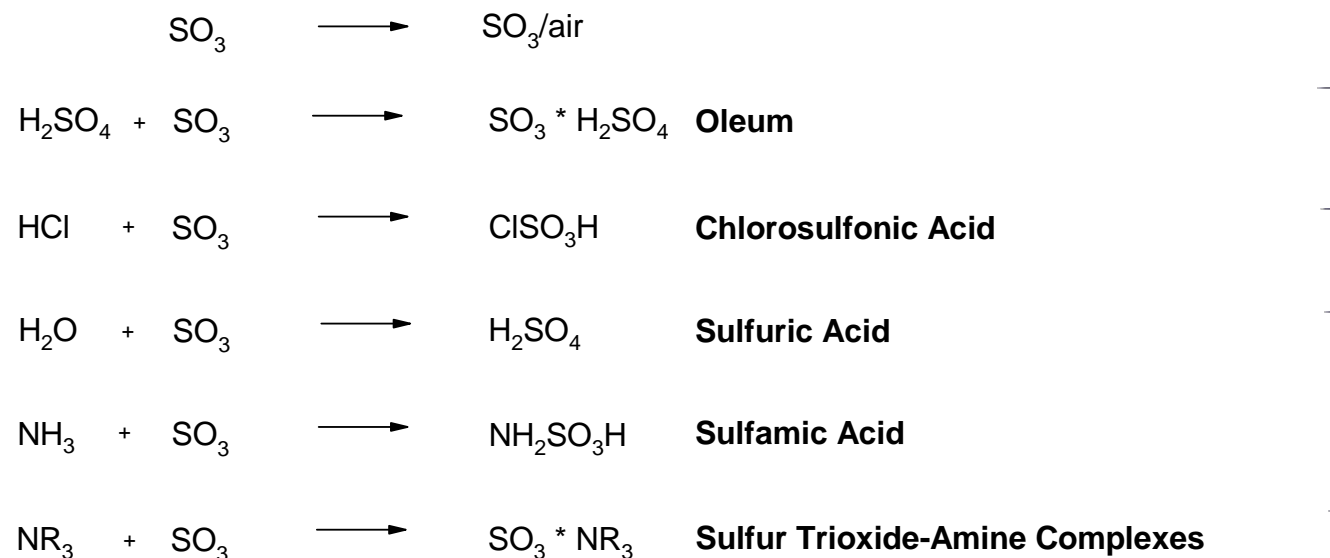
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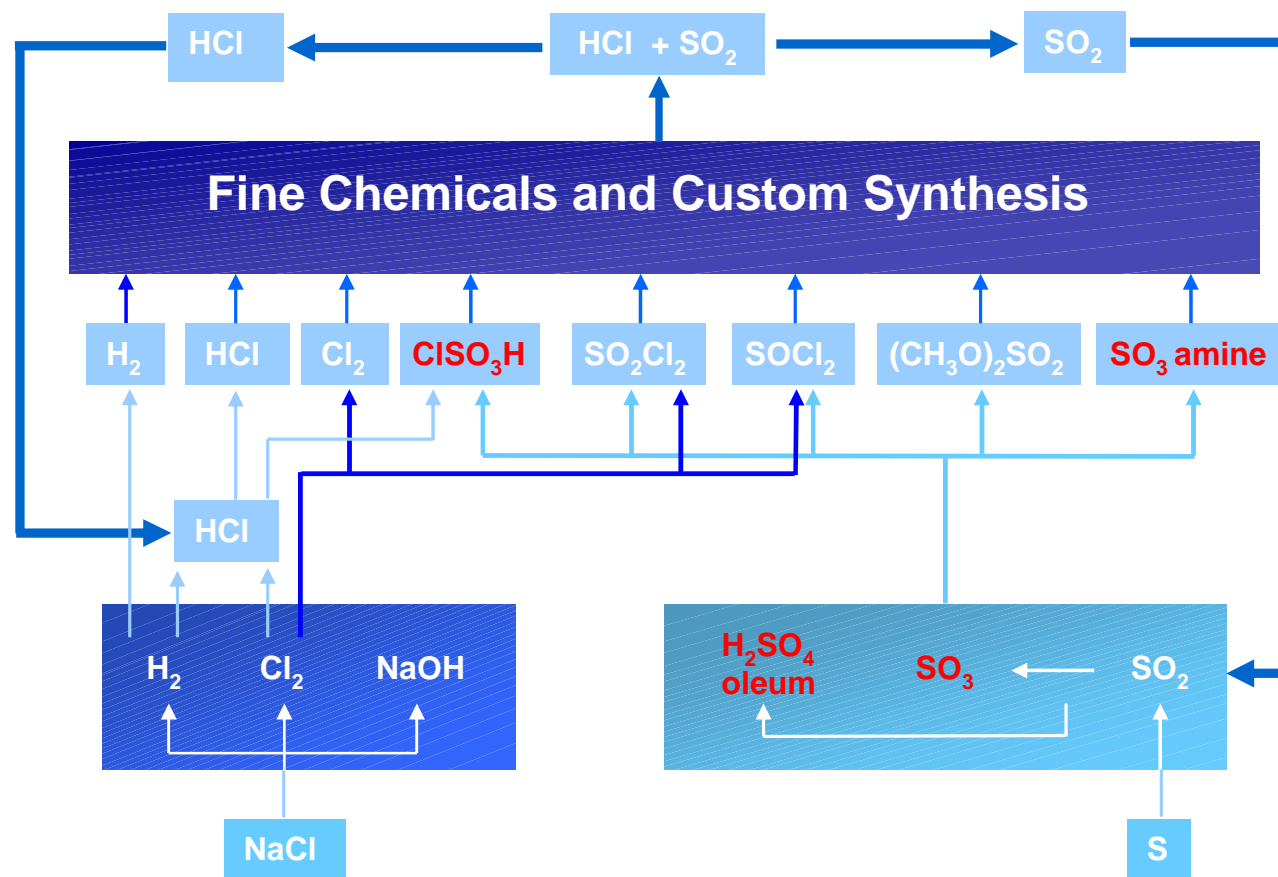
Sulfur trioxide reagents: Overview

SO₃-transfer reactions can be carried out by a range of (commercially available) sulfur trioxide reagents. These have different grades of reactivity. CABB offers most of them.



Sulfur Trioxide Amine Complexes

Sulfur trioxide reagents: Overview

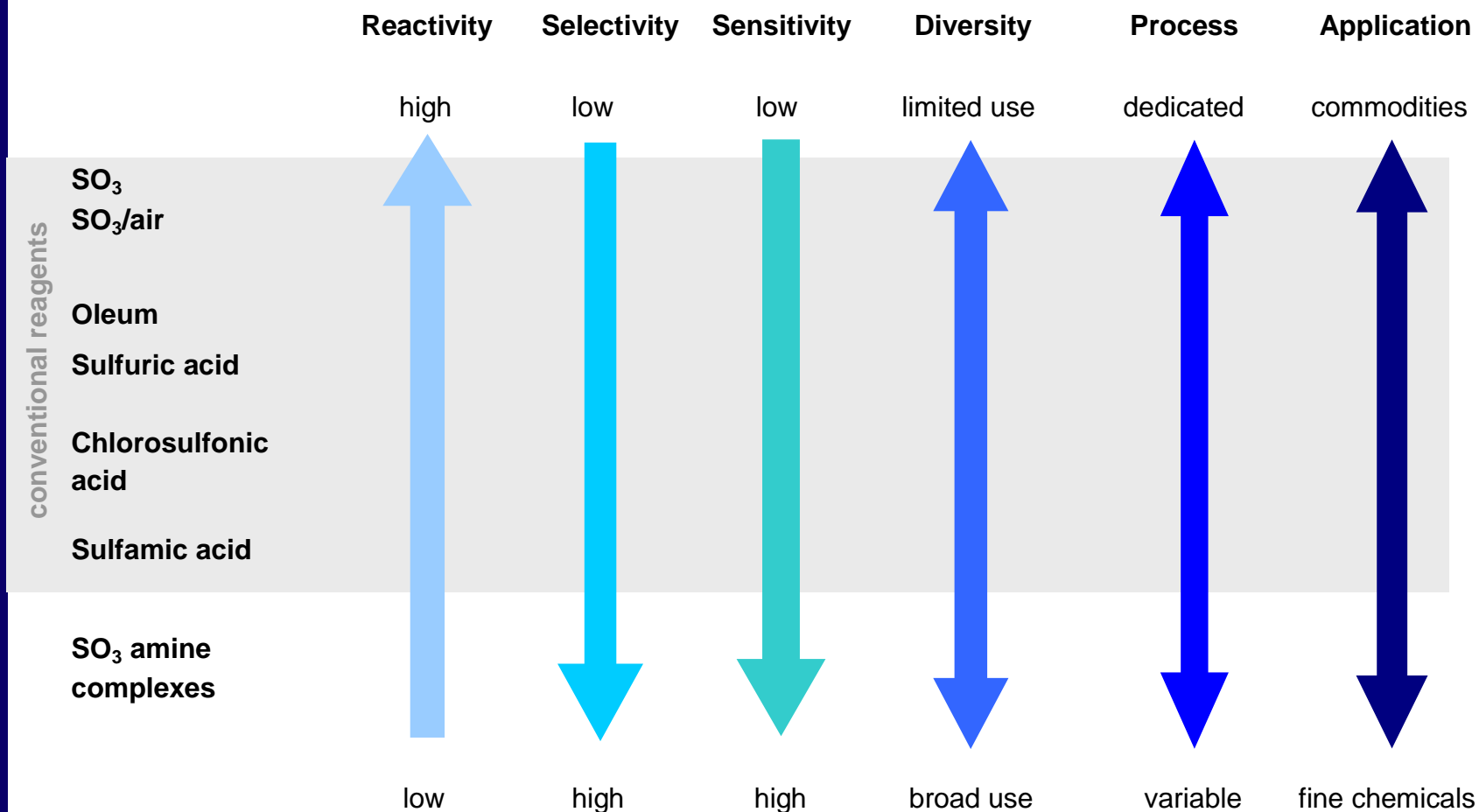


CABB produces in an integrated production system sulfur trioxide and derived reagents, for sales and captive use of downstream products.

Sulfur Trioxide Amine Complexes



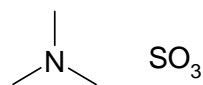
Sulfur trioxide reagents: Properties



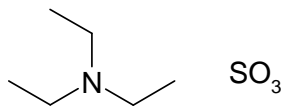
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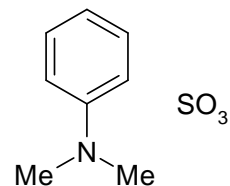
Sulfur Trioxide amine complexes: Products



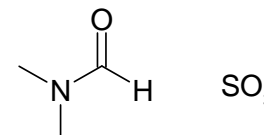
Trimethylamine SO₃
TMAS



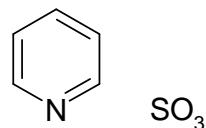
Triethylamine SO₃
TEAS



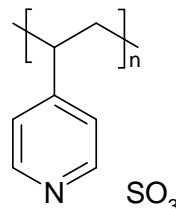
Dimethylaniline SO₃
DMAS



Dimethylformamide SO₃
DMFS



Pyridine SO₃
PSS



Polyvinylpyridine SO₃
PVPS

Lewis Base strength:

Trimethylamine > Triethylamine > Pyridine > Dimethyl aniline > Dimethylformamide >> Dioxane

Reactivity complexes:

TMAS < TEAS < PSS < DMAS < DMFS << DIOS

Sulfur Trioxide Amine Complexes



Sulfur Trioxide amine complexes: Properties

Reactivity:

- Moderated reactivity compared to conventional reagents
- Modification of reactivity with Lewis base strength of amines
- Cleaner reactions: better uniformity and reproducibility of end products

Selectivity:

- Controlled selectivity compared to conventional reagents
- Sulfation of carbohydrates with high regioselectivity
- Selective sulfation of O- or N- atoms

Sensitivity:

- Sulfonation reagents for acid sensitive compounds (e.g. heterocycles)
- Sulfation of polysaccharides without degradation of polymer backbone
- No cleavage of acid sensitive bonds

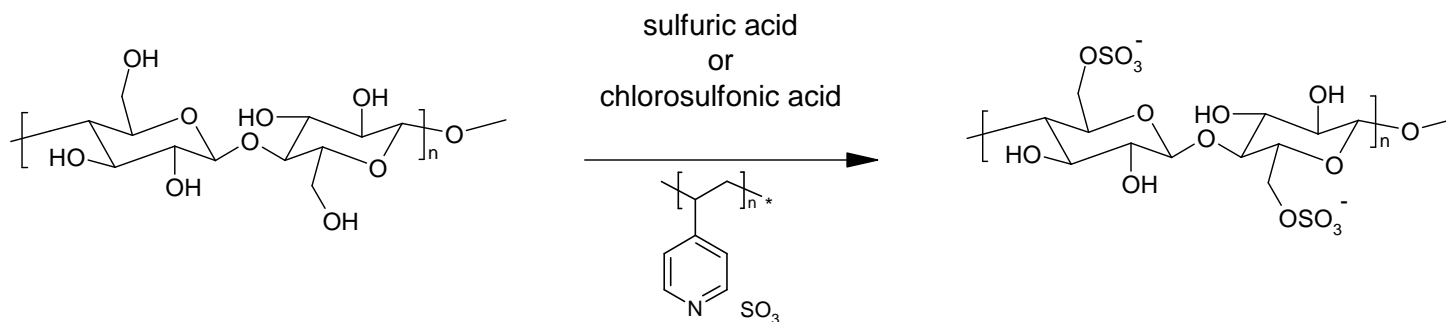
Diversity:

- Parikh-Doering oxidation with Pyridine sulfur trioxide
- Deoxygenation and dehydration as further reactions

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Reactivity: sulfation of carbohydrates



Use of conventional reagents for sulfation of polysaccharides:

- Chain cleavage
- Difficulty to control extent of reaction
- Discolored decomposition products
- Uniformity of products, nonreproducible viscosity
- Decreasing reactivity due to formation of water and dilution of the reaction mixture
- Difficulties with isolation and recovery of solvents
- Low yields of sulfated products

Advantages of Sulfur trioxide amine complexes:

- Reactivity of reagents maintained
- No chain cleavage, resulting in reproducible viscosity
- Superior uniformity of products
- Better control of reaction
- Discoloration can be prevented
- Good yield of sulfated products
- In case of polymeric pyridine SO₃ complex: no residual amines, ease of work up

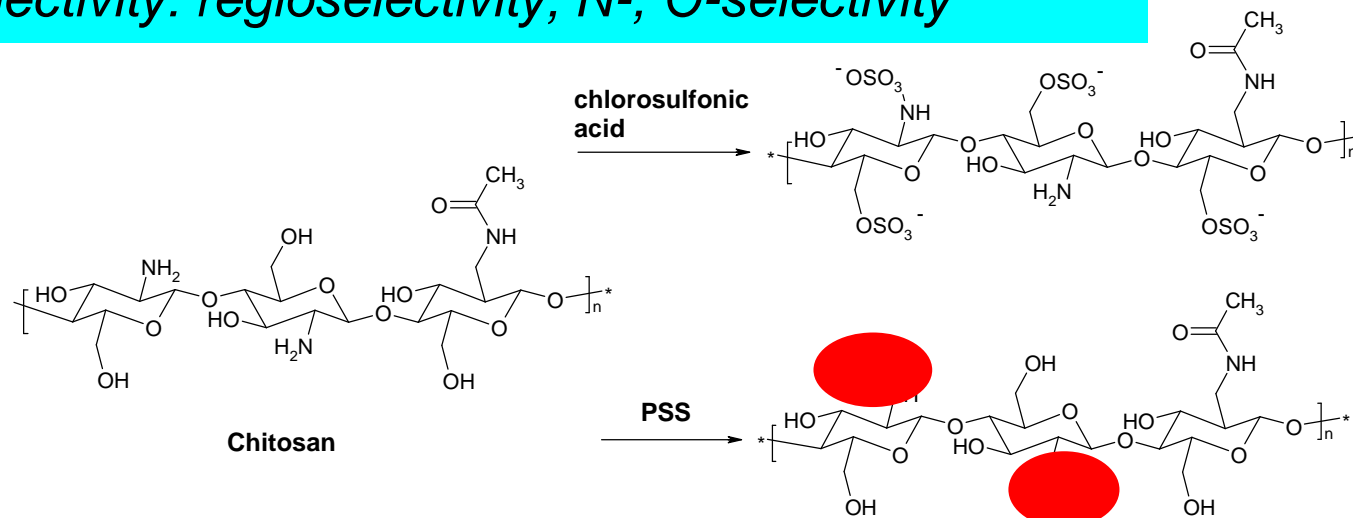
Literature:

US 3,057,855 (1962); US 4,814,437 (1989);
US 4,855,416 (1989); US 2009/0227537 (2009)
R.G. Schweiger, Carbohydr. Res. **1972**, 21, 219-228

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Selectivity: regioselectivity; N-, O-selectivity



Sulfation of chitosan:

- Chlorosulfonic acid in pyridine:
mixture of N-sulfated-O-sulfated chitosan or selective O-sulfation.
- Pyridine SO₃ complex:
selective N-sulfation

Regioselectivity can be achieved by the proper choice of the sulfur trioxide amine complex to obtain selective 2- or 6-sulfation in polysaccharides.

Atom selectivity is found in aminoalcohols, where sulfur trioxide amine complexes selectively sulfate the nitrogen whereas chlorosulfonic acid sulfates the hydroxyl groups.

Literature:

W.A. Reeves, J.D. Guthrie; J. Am. Chem. Soc. **1953**, 75, 4101

D.T. Warner; L.L. Coleman; J. Org. Chem. **1958**; 23, 1133-1135

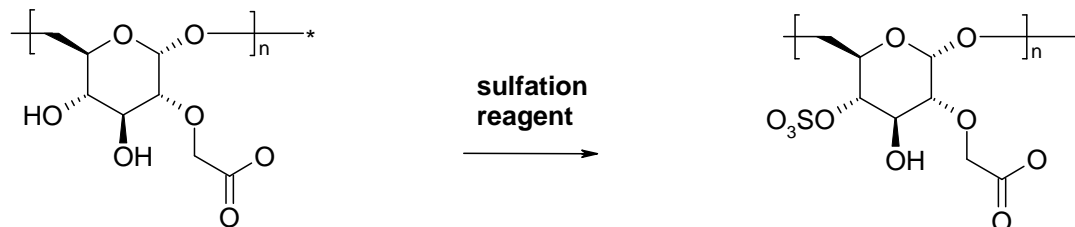
US 5874548 (**1999**)

P. Vongchan; W. Sajomsang; D. Subyen; P. Kongtawelert; Carbohydr. Res. **2002**, 337, 1239-1242

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Sensitivity: no degradation, no cleavage



Carboxymethyl modified dextrane

Sulfation of carboxymethyl dextrane may lead to three reactions: sulfation of hydroxyl groups with different degree of sulfation, cleavage of the carboxymethyl group, cleavage of the glycosidic bonds of the polymer backbone. The choice of the sulfation reagent influences degree of sulfation (dsS), degree of cleavage of carboxymethyl bond (dsCM) and the degradation of the polymer backbone (reduced sugars).

Reagent	equivalents	conditions	dsS	dsCM	reduced sugars
reference				0.56	1.03
ClSO ₃ H	2	22°C	0.35	0.37	12.71
ClSO ₃ H	2	4°C	0.14	0.50	4.04
DMFS	2	30°C	0.23	0.37	1.57
DMFS/2M2B	2	30°C	0.42	0.56	0.82

2M2B = 2-Methyl-2-butene (acid scavenger)

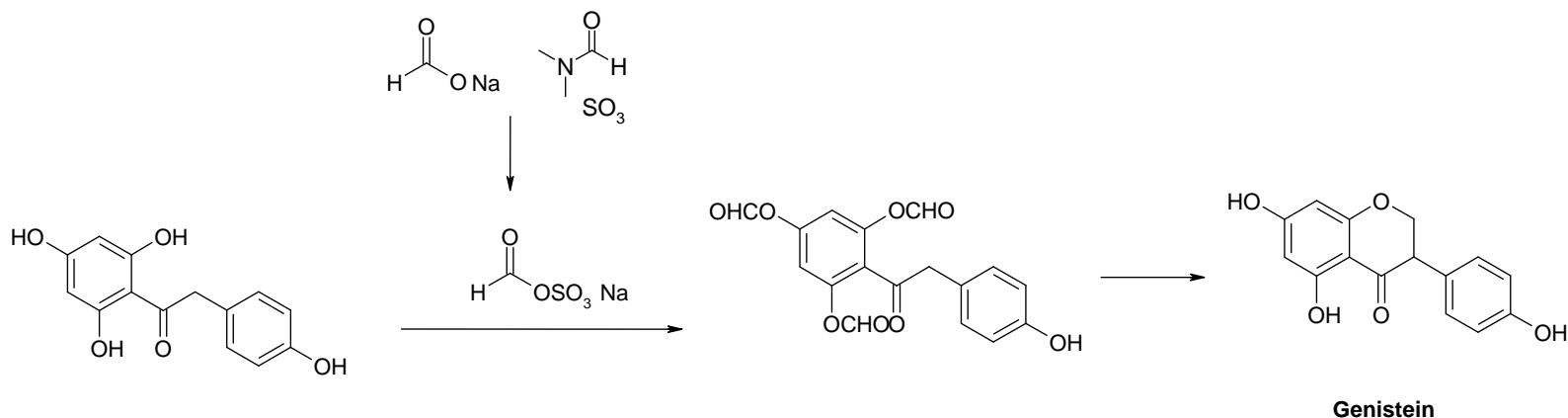
Literature:

E. Petit, et al, *Macromolecules*, **2005**, 38, 4647-4654
US 2004/0242801

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Diversity: Synthesis of Genistein



Possible methods for the synthesis of Genistein:

- Boron trifluoride: environmentally unfavorable, high temperatures, moderate yield (61%), activates the methylene group and deactivates the aromatic ring¹.
- Amine route: environmentally unfavorable amine waste and economically unfavorable (high temperatures, multistep synthesis, moderate yields)².

Synthesis of Genistein using DMFS³:

- Synthesis with modification/activation of formic acid
- Moderate reaction conditions
- Environmentally no concerns
- Recycling of DMF
- High yields (95%)

Literature:

¹ Synthesis **1978**, 843

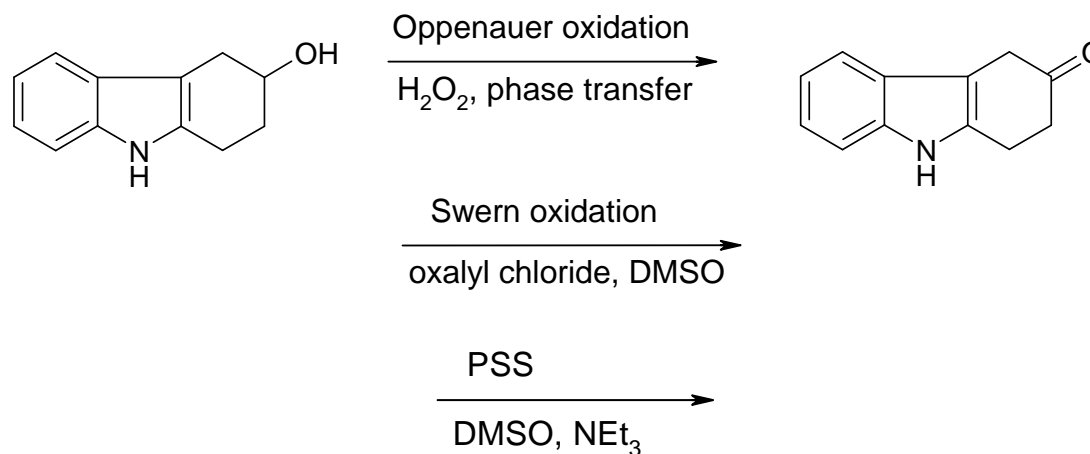
² J. Chem. Soc. **1953**, 1852-1860

³ US 2004/158082; WO 2004/009576

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Diversity: Parikh-Doering oxidation



Oxidation methods for primary and secondary alcohols¹:

- Oppenauer oxidation (H_2O_2 and phase transfer catalyst, poor yields)
- Swern Oxidation (oxalyl chloride and dimethyl sulfoxide, temperatures below 0°C , release of CO , CO_2 and dimethyl sulfide as off gases)

Parikh-Doering oxidation²:

- Excellent yields
- Excellent results with temperatures above 0°C
- Only Dimethyl sulfide as off gas.

Literature:

¹ K. v d Bruch, Chemistry Today, **2010**; 28, 48-50;

² J.P. Parikh, W.E. Doering, J. Am. Chem. Soc., **1967**, 89, 5505-5507

Summary

- Sulfur trioxide amine complexes exhibit a variety of advantages regarding sulfonation and sulfation reactions over conventional reagents
- Sulfur trioxide amine complexes allow further different reactions to sulfonation/sulfation which are not as easy accessible with other techniques
- **CABB offers:**
 - **most of the sulfation/sulfonation reagents**
 - **the support to carry out these reactions**
 - **the facilities and plants to perform these reactions**
 - **to optimise these reactions**



Thank you very much.

Please visit CABB at booth no. B15, hall 21

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