Sulfur Trioxide Amine Complexes:

Versatile Reagents in Organic Synthesis

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Business Manager Specialities

RSC Symposium Berlin 2010

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- Sulfur trioxide reagents: Overview and Properties
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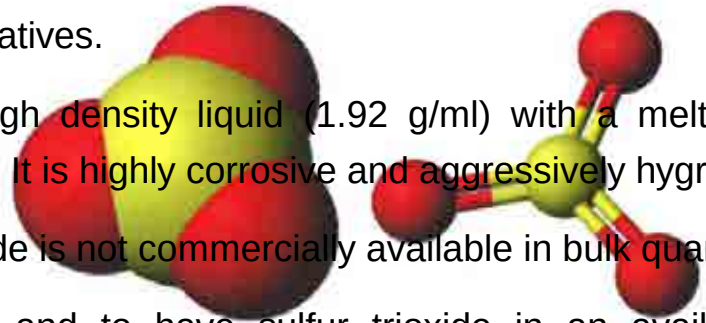
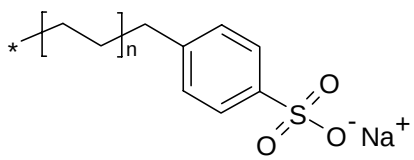
Sulfur trioxide chemistry: Introduction

- 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.

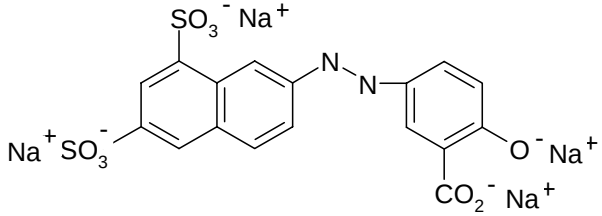


Sulfur Trioxide Amine Complexes

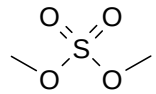
Sulfur trioxide chemistry: Introduction



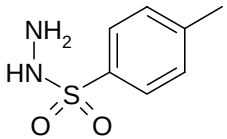
Linear Alkylbenzene sulfonate
Detergent



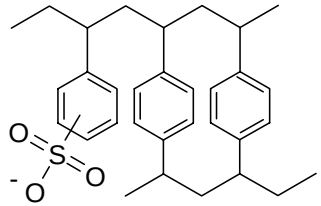
Mordant Yellow 20
Dye



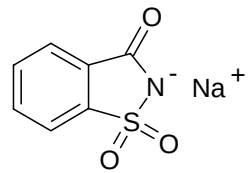
Dimethyl sulfate
Methylating agent



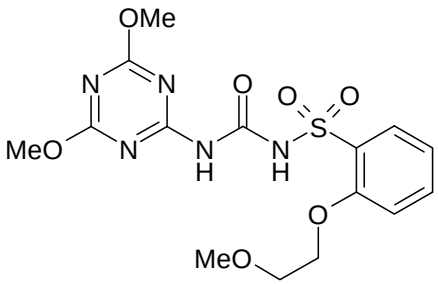
Toluenesulfonyl hydrazide
Blowing agent for rubber



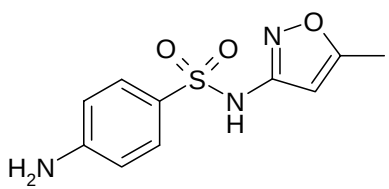
Sulfonated sytrene divinylbenzene copomylers
Ion exchange resins



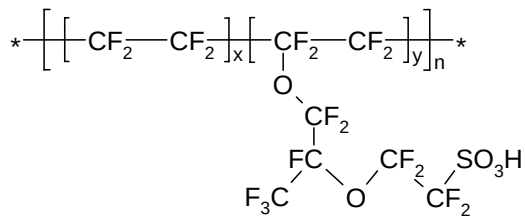
Saccharin
Artificial Sweetener



Cinesulfuron ("Sailant")
Sulfonylurea Herbicide



Sulfamethoxazol
Sulfonamide Antibiotic



NAFION™ (DuPont)
Sulfonated Polymer

Sulfur Trioxide Amine Complexes

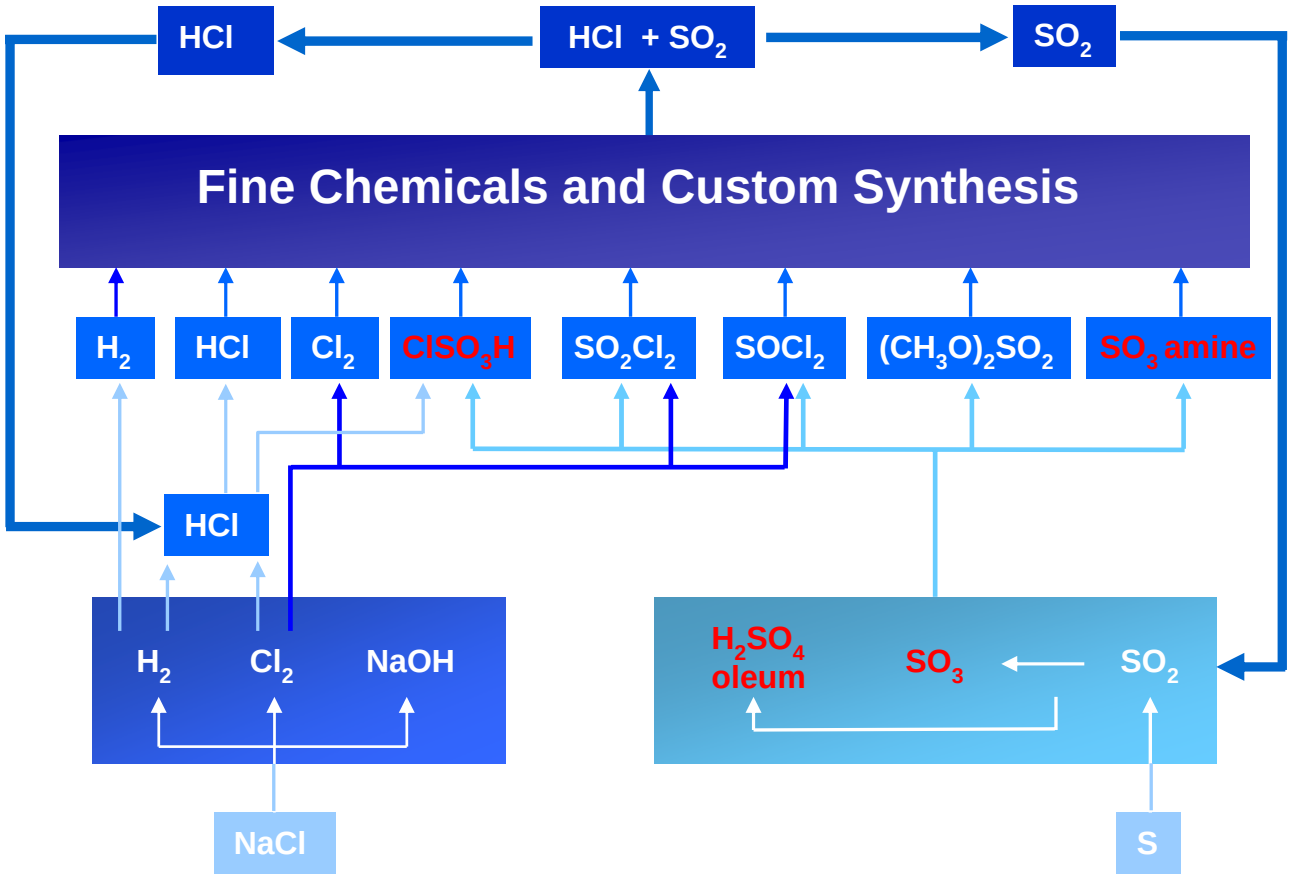
Sulfur trioxide reagents: Overview

SO_3-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.

	SO_3	SO_3/air		
H_2SO_4 +	SO_3	$SO_3 * H_2SO_4$	**Oleum**	CABB
HCl +	SO_3	$ClSO_3H$	**Chlorosulfonic Acid**	CABB
H_2O +	SO_3	H_2SO_4	**Sulfuric Acid**	CABB
NH_3 +	SO_3	NH_2SO_3H	**Sulfamic Acid**	
NR_3 +	SO_3	$SO_3 * NR_3$	**Sulfur Trioxide-Amine Complexes**	CABB

Sulfur Trioxide Amine Complexes

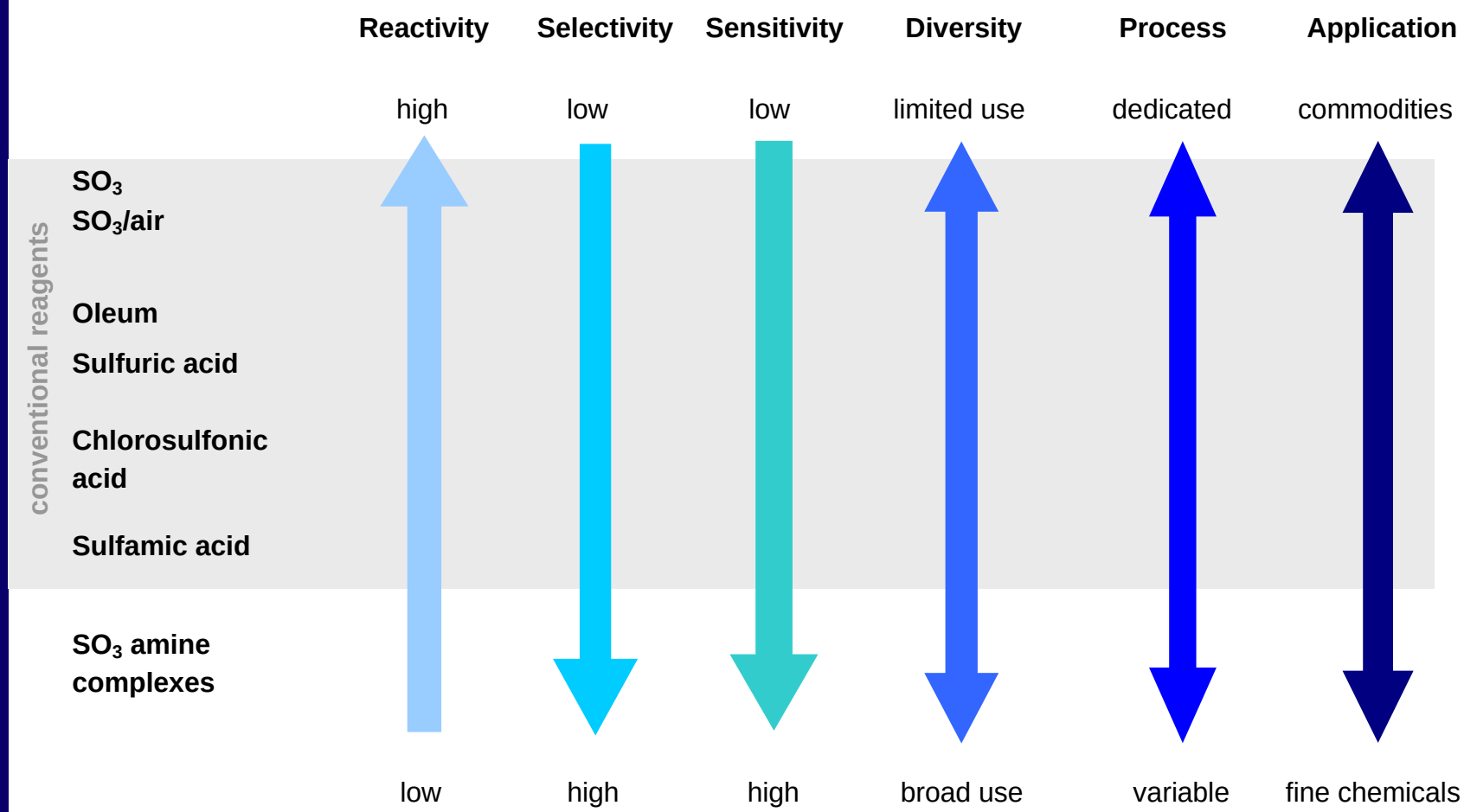
Sulfur trioxide reagents: Overview



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

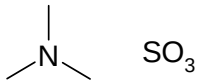
Sulfur Trioxide Amine Complexes

Sulfur trioxide reagents: Properties

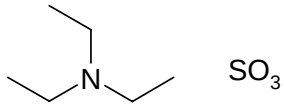


Sulfur Trioxide Amine Complexes

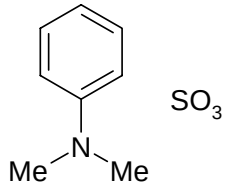
Sulfur Trioxide amine complexes: Products



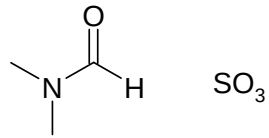
Trimethylamine SO_3
TMAS



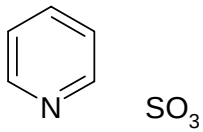
Triethylamine SO_3
TEAS



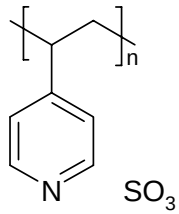
Dimethylaniline SO_3
DMAS



Dimethylformamide SO_3
DMFS



Pyridine SO_3
PSS



Polyvinylpyridine SO_3
PVPS

Lewis Base strength:

Trimethylamine > Triethylamine > Pyridine > Dimethyl aniline > Dimethylformamide

Reactivity complexes:

TMAS < TEAS < PSS < DMAS < DMFS

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

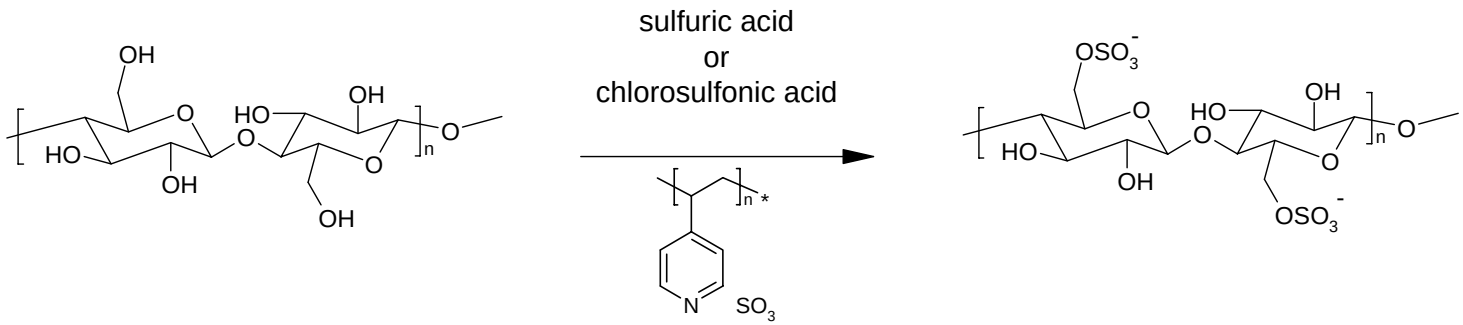
Selectivity:
- Controlled selectivity compared to conventional reagents
- Sulfation of carbohydrates with high regioselectivity
- Selective sulfation of O- or N- atoms

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

Sulfur Trioxide Amine Complexes

Reactivity: sulfation of carbohydrates



Use of conventional reagents for sulfation of polysaccharides:

- Chain cleavage
- Difficulty to control extend 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

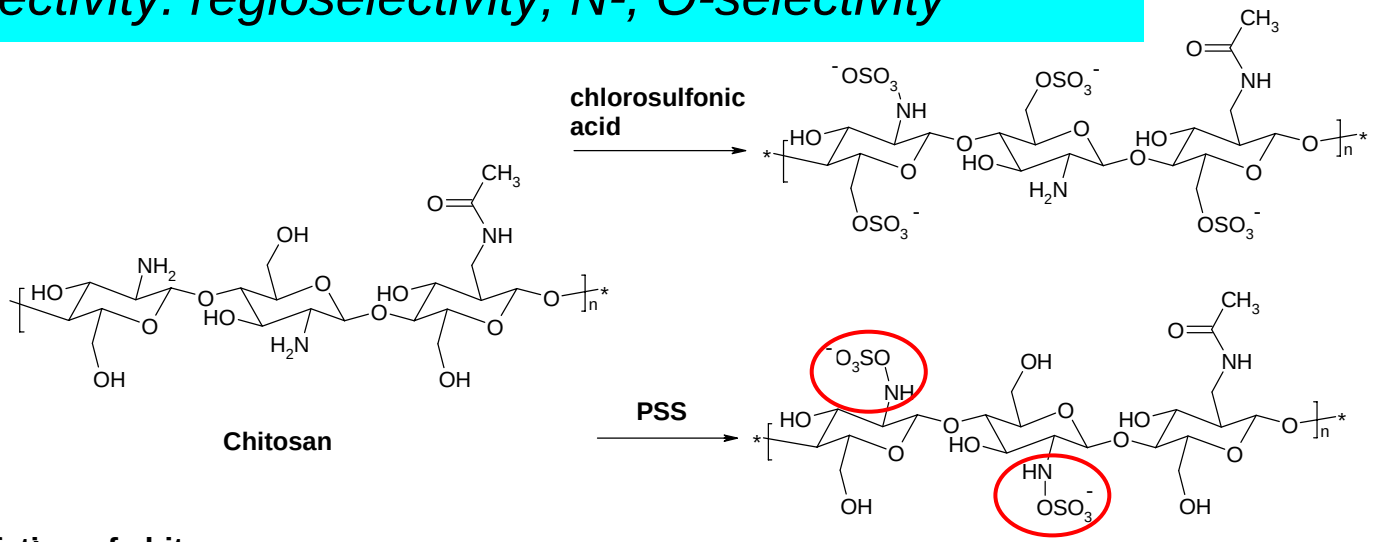
Advantages of Sulfur trioxide amine complexes:

- 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 SO_3 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, Carbohyd. Res. **1972**, *21*, 219-228

Sulfur Trioxide Amine Complexes

Selectivity: regioselectivity; N-, O-selectivity



Sulfation of chitosan:

Heparin:

- Naturally occuring sulfated polysaccharide
- Consists of alternating glucosamine and gluconic acid units
- Shows anticoagulant activity and is a “key player” in the regulatory network of the cell

Chitosan:

- Naturally occuring polyacetylglucosamine, present in crab shells
- Sulfation of chitosan will lead to products with similar structure as heparin

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.

- Chlorosulfonic acid in pyridine:
  mixture of N-sulfated-O-sulfated chitosan or selective O-sulfation.
- Pyridine SO_3 complex:
  selective N-sulfation

Literature:

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

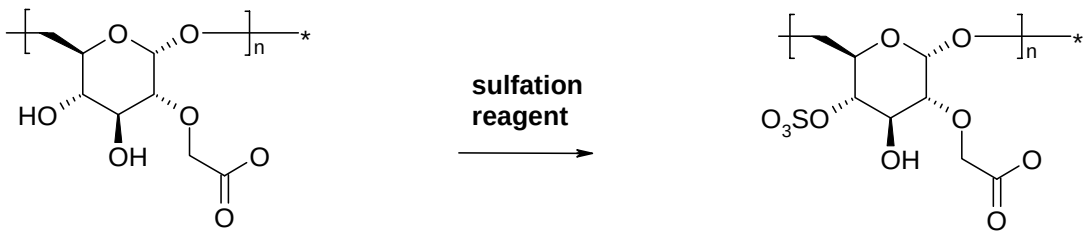
D.T. Warner; L.L. Coleman; J. Org. Chem. **1958**; *23*, 1133-1135

US 5874548 (**1999**)

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

Sulfur Trioxide Amine Complexes

Sensitivity: no degradation, no cleavage



Carboxymethyl modified dextrane

Carboxymethyl modified dextrane as an example for the sulfation of a modified polysaccharide. Dextran sulfate (in form of its sodium salt) has medical and pharmaceutical applications. It shows anti-coagulant properties, acts as anti-lipemic, anti-ulcerogenic and has demonstrated anti-HIV activity.

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
$ClSO_3H$	2	22°C	0.35	0.37	12.71
$ClSO_3H$	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

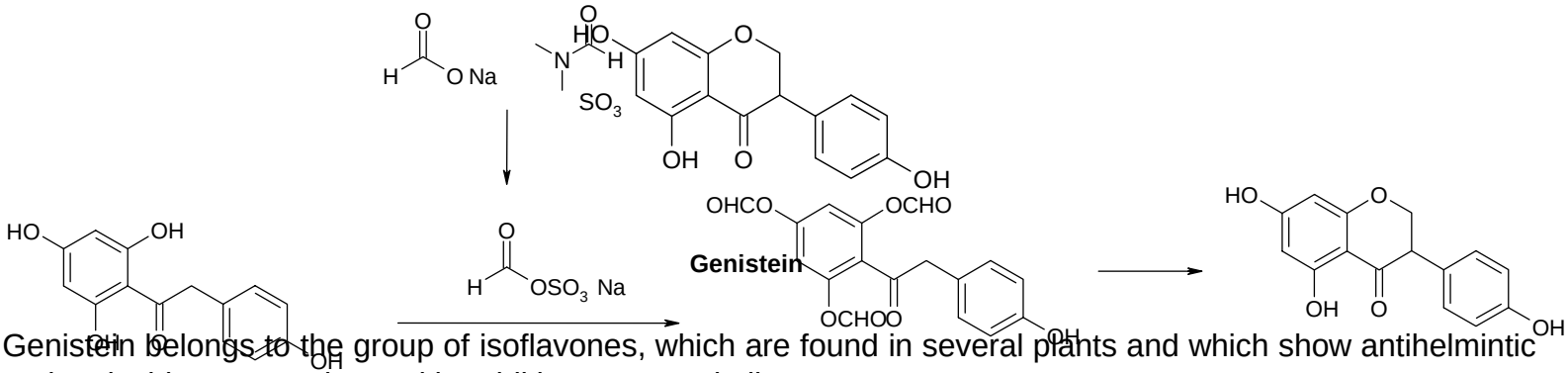
2M2B = 2-Methyl-2-butene (acid scavenger)

Literature:

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

Sulfur Trioxide Amine Complexes

Diversity: Synthesis of Genistein



Genistein belongs to the group of isoflavones, which are found in several plants and which show antihelmintic and antioxidant properties and in addition can act similar to estrogen.

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 ring[1].
- Amine route: environmentally unfavorable amine waste and economically unfavorable (high temperatures, multistep synthesis, moderate yields)[2].

Synthesis of Genistein using DMFS[3]:

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

Literature:

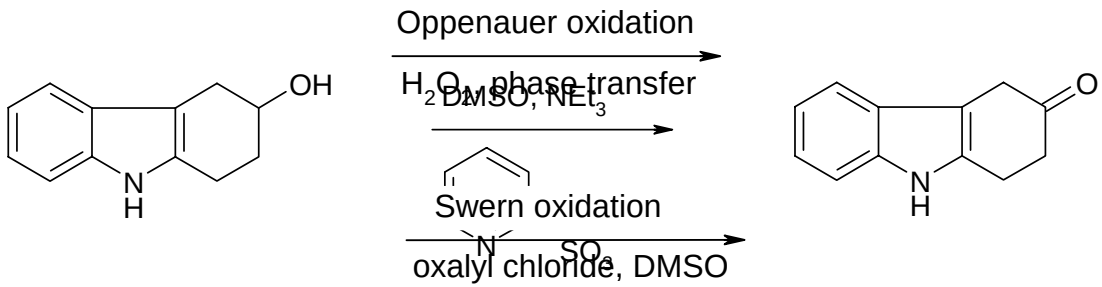
[1] Synthesis **1978**, 843

[2] J. Chem. Soc. **1953**, 1852-1860

[3] US 2004/158082; WO 2004/009576

Sulfur Trioxide Amine Complexes

Diversity: Parikh-Doering oxidation



Oxidation methods for primary and secondary alcohols[1]:

- 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 oxidation[2]:

- 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

Sulfur Trioxide Amine Complexes

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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