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(54) **Title:** SELECTIVE PRODUCTION OF SULPHOXIDES

(57) **Abstract:** The invention pertains to a process for producing a sulphoxide compound, comprising oxidizing a thioether compound with an ozonide formed from a olefin and ozone, to obtain the corresponding sulphoxide compound, provided that the olefin is not ethene. The ozonide converts thio - ether compounds selectively, unlike its art - known oxidizing counterparts. The milder ozonide does not require manipulation of the stoichiometric amount of available oxidizing agent during the reaction, to prevent the formation of sulphones.

Selective production of sulphoxides

FIELD OF THE INVENTION

The invention pertains to a selective process for producing sulphoxides from thioethers.

BACKGROUND OF THE INVENTION

The selective production of sulphoxides represents an important task in getting access to basic materials for use in many fields. Many of those are listed as Active Pharmaceutical Ingredients (APIs).

One of the difficulties encountered in the preparation of sulphide compounds relates to the use of thio-ether precursors, and especially the difficulties in preventing overoxidation of such compounds, resulting in unwanted sulphones. This is reflected in the large number of patent publications related to the oxidation to sulphoxides as there as oxidizing agents, such as hydrogen peroxide, all or not in the presence of metal catalysts, peracids, peresters or ozone. Apart from the fact that many of the oxidizing agents are listed as hazardous and explosive, it still remains difficult to control the reaction selectivity. In practice, overoxidation is prevented by a proper adjustment of the reaction conditions and the reaction stoichiometry between the oxidizing agent and the substrate to be oxidized.

A good example is given in Bailey, *Ozonation in Organic Chemistry*, Academic Press, New York 1978, discussing ozone for the oxidation of sulphides. Here the selectivity, with respect to the easily oxidized products, is determined by the substitution pattern and thus by the reactivity of the sulphide with respect to the reaction material. However, the reaction between the gaseous oxidizing agent added and the substrate present in the solution makes determination of the exact stoichiometric conditions difficult and hard to implement on industrial scale. Hence, too often the harsh ozone realizes an overshoot, producing sulphones.

All so far published processes are characterized partially by the use of extreme reaction conditions or are based on the application of environmentally hazardous reagents that possess a potential toxicity for humans and the environment. Hence, there is a need for a cheap and efficient process for producing sulphoxides from thioethers, avoiding the formation of sulphones. The process strived for should be reliable, highly

selective, produce waste streams which are easily disposed of without causing harm to the environment, and produce a stable final product of high yield and purity. With such a new process, it should be possible to easily separate the thus generated oxidized sulphoxides by conventional separation techniques.

SUMMARY OF THE INVENTION

It is an object of the invention to provide a selective process to convert sulphides into sulphoxides without the aforementioned disadvantages, especially over-oxidation.

It is now found that excellent results are obtained using an ozonide as the oxidation agent. Ozonolysis, the process of forming ozonide from the reaction of an olefin with ozone, is well-known in the art. However, ozonide has presently found use in the reduction of olefins, converting unsaturated bonds to carbonyl groups. Ozonide has never been mentioned as an oxidizing agent, let alone a selective one. The benefits from its controlled manufacture and subsequent use in sulphoxide production are yet unknown.

The use of ozonide to convert a thio-ether over other oxidizing agents brings the advantage that sulphides may be formed without taking any measures to control the reaction selectivity, and still end up with a "sulphone-free environment". Ozonide appears not to react with the subsequently formed sulphoxide. Hence, unlike its art-known harsh and unselective oxidizing counterparts, the milder ozonide does not require manipulation of the stoichiometric amount of available oxidizing agent during the reaction, to prevent the formation of sulphones. Thus, ozonide makes a complete and selective conversion of thio-ether precursors into sulphoxides industrially feasible, provided that the total amount of ozonide is at least identical but preferably exceeds that of the sulphide moieties in the thio-ether precursor.The end-product is free from any sulphones.

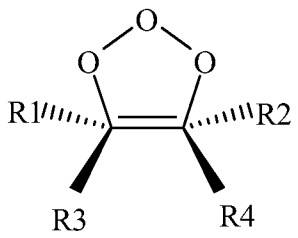
DETAILED DESCRIPTION OF THE INVENTION

The invention thus pertains to a process for producing a sulphoxide compound, comprising oxidizing a thioether compound with an ozonide formed from a olefin and ozone, to obtain the corresponding sulphoxide compound, provided that the olefin is

not ethene. Since it is unpractical to produce an ozonide from ethene and ozone, its use does not part of the invention.

The process of the present invention may be characterized as being "sulphone-free", meaning that no detectable amount of sulphone moieties is formed throughout the reaction process.

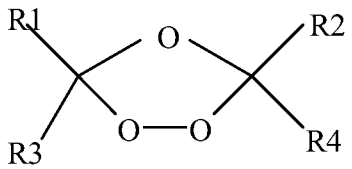
The term "ozonide" has its meaning as recognized in the art, i.e. the reaction product formed from olefin and ozone. The ozonide may schematically be represented by formula (I)



(I),

in which R1, R2, R3, R4 represent, independently, hydrogen or an organic component, and/or wherein two or more of R1, R2, R3, R4 maybe covalently interconnected, provided that R1-4 are not hydrogen simultaneously, thus excluding ethene.

In the literature, the ozonide is sometimes alternatively drawn up as:



(II),

R1 – R4 having the above meaning. However, the invention is not regarded being tied by the exact structural representation of the ozonide. Hence, where ozonide is mentioned in the context of the invention, it encompasses either of the above schematic representations, provided that the ozonide is formed from reacting an olefin with ozone, in the art referred to as "ozonolysis".

The molar ratio of the ozonide to the thio-ether compound is preferably at least 1, in order to complete the oxidation into sulphoxide. The molar ratio is calculated on the basis of the amount of thio-ether functionalities or sulphide moieties present in the precursor. Particularly good results can be obtained if the ratio is in the range of 1.1- 4, preferably 1.2 - 3. Advantageoulsy, high amounts of ozonide do not result in over-oxidation.

Theoretically, it may be possible to perform the selective oxidation process bringing the thio-ether precursor, olefin and ozone in direct contact with one another. However, it may be favorable to avoid direct contact between the sulphide moieties and ozone, since the ozone may oxidize the sulphide groups without forming the 'mild' ozonide oxidation agent. Hence, in a preferred embodiment the step of producing sulphoxides is free from ozone, i.e. contact between ozone and the sulphide groups is avoided.

To avoid over-oxidation, it is thus preferred that the ozonide is brought into contact with the thio-ether precursor only after ozonolysis. Hence, in the preferred embodiment thio-ether oxidation may be characterized as being "ozone-free", i.e. wherein ozone is not deliberately added and not present in detectable amounts. Thereto, ozonide may be produced separately.

Ozonide may be supplied to the thio-ether precursor batchwise or continuously, e.g. by dropwise addition. However, it is stressed once more that a continuous and controlled supply of ozonide is redundant from the perspective of avoiding over-oxidation.

Ozonolysis is a well-documented reaction route, albeit for a different intended use, and the skilled person will be readily able to determine the desired reaction conditions with general knowledge from the prior art. Nevertheless, few details are given here below.

Ozonolysis

Ozone may be produced using pure oxygen or mixtures of oxygen and inert gases in varying volumetric ratios to oxygen, preferably between 1 and 80 vol.%.

The gaseous ozone is then added to the reaction mixture containing the olefin. Therein, the ozone concentration in the gas supplied to the reaction mixture lies preferably within the range of 1 to 12 % by weight in relation to the total gas used. Especially preferred are ozone concentrations in the range of 4 to 8 % by weight.

Ozone can be introduced to the reaction mixture for olefin conversion in a molar range of 1 to 5, or preferably in the range of 1 to 3 and most preferably in the range of 1.1 to 2 molar equivalents, calculated on the molar amount of olefin. Under these conditions any undesired sideproducts of ozonolysis are minimized.

The olefin-containing reaction mixture preferably contains 2 to 50 % by weight, more preferably 4 – 25 wt%, most preferably 7.5 to 10 wt% of olefin, based on the total weight of the reaction mixture.

For the production of the ozonides, it is preferred to use oxidation-stable aromatic or non-aromatic solvents. The solvent must be suitable for use in an ozonolysis. Although the solvent should be inert in subsequent thio-ether conversion, it is found that the choice of solvent for ozonolysis is neither decisive nor critical for selectivity of the subsequent oxidation

Preferred solvents include substituted or non-substituted aromatic hydrocarbons or solvents which possess oxygen in the form of carbonyl, ether or alcohol functions. Halogenated aromatic and non-aromatic solvents have proved suitable for performing the reaction. Solvents with other oxidizable hetero-atoms (for example nitrogen) are likewise suitable, as a result of the high selectivity of the process. Because of the solubility of the reaction participants in toluene or alcohols, or mixtures of them, they are particularly preferred.

Ozonolysis is preferably performed at a temperature of -78°C to +30°C, in particular at -30°C to +10°C, and most preferably at -10°C to 0°C. Under these conditions secondary reactions of the ozonolysis and a potential hazard caused by exceeding the ignition temperature of one the reaction components can be avoided.

The final ozonlysis reaction mixture, containing the ozonide thus-formed, may be applied in the subsequent oxidation process without any intermediate isolation or purification steps. In principle, it is possible to perform the subsequent oxidation after ozonlysis as a “one-pot synthesis”, provided that the ozone throughput is conveniently stopped before introducing the thio-ether compound, i.e. contact between ozone and the sulphide groups is avoided. The skilled person can determine the time necessary for any traces of ozone to disappear from the ozonolysis reaction medium after bringing the ozone supply to a halt, depending on the actual ozone supply rate, the reactor build-up etc.

Ozonide

The structure of the ozonide of the present invention is determined by the conformation of the olefin bonding used for the synthesis.

In formula (I), R1, R2, R3 and R4 represent, independently, hydrogen or an organic component, independently (with preferably no more than 100 C-atoms), preferably a substituted component selected from the group comprising alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, cycloalkenyl, cycloalkenylalkyl, alkinyl, cycloalkylalkinyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, aryl, heteroaryl, arylalkyl, cycloalkylaryl, cycloalkenylaryl, cycloalkylheteroaryl, heterocycloalkylaryl, heterocycloalkenylaryl, heterocycloalkenylheteroaryl and heteroarylalkyl, and/or two or more of R1, R2, R3, R4 are covalently interconnected, provided that the olefin is not ethene.

If R1 – R4 are aromatically or non-aromatically substituted, the substituent(s) is/are preferably selected from the group consisting of:

- hydroxy,
- C_1-C_8-Alkyl, preferably Methyl, Ethyl, n-Propyl, iso-Propyl, n-Butyl, iso- Butyl, tert.- Butyl,
- C_3-C_{18}-Cycloalkyl, preferably Cyclopropyl, Cyclopentyl, Cyclohexyl, Cyclooctyl, Cyclododecyl, Cyclopentadecyl, Cyclohexadecyl,
- C_2-C_8-Alkinyl, preferably Ethinyl, Propinyl,
- C_1-C_8-Perfluoralkyl, preferably Trifluormethyl, Nonafluorbutyl,
- C_1-C_8-Alkoxy, preferably Methoxy, Ethoxy, iso-Propoxy, n-Butoxy, iso-Butoxy, tert.-Butoxy,
- C_3-C_{12}-Cycloalkoxy, preferably C_3-Cycloalkoxy, C_5-Cycloalkoxy, C_6-Cycloalkoxy, C_8-Cycloalkoxy, C_{12}-Cycloalkoxy, C_{15}-Cycloalkoxy, C_{16}-Cycloalkoxy,
- C_1-C_{20}-Alkoxyalkyl, in the 1 to 5 CH2-groups are replaced by oxygen
- -[-O-CH_2-CH_2-]$_v$-Q oder -[-O-CH_2-CHMe-]$_v$-Q, where Q may be OH or CH_3 and with can mean v = 1 bis 4,
- C_1-C_4-Acyl, preferably acetyl,
- C_1-C_4-Carboxy, preferably CO_2Me, CO_2Et, CO_2iso-Pr, CO_2tert.-Bu,
- C_1-C_4-Acyloxy, preferably Acetyloxy,

- halogen, preferably F or Cl,
- Si_1-Si_{10}-Silyl, and
- Si_1-Si_{30}-Siloxy or Polysiloxy.

If one or more of the components of R1, R2, R3, R4 contain nitrogen, then the nitrogen-containing component is preferentially stable with respect to oxidation.

Preferred oxidizing agents are ozonides are those given by formula (I), in which R1, R2, R3, R4 independently represent a substituted component selected from the group consisting of C_3-C_{25}-Aryl, C_2-C_{25}-Heteroaryl, C_4-C_{25}-Arylalkyl, C_8-C_{25}-Cycloalkylaryl, C_8-C_{25}-Cycloalkenylaryl, C_5-C_{25}-Cycloalkylheteroaryl, C_8-C_{25}-Heterocycloalkylaryl, C_8-C_{25}-Heterocycloalkenylaryl, C_8-C_{25}-Heterocycloalkenylheteroaryl and C_3-C_{25}-Heteroarylalkyl, provided that the ozonide structure lacks a symmetry axis, i.e. if not all of R1-R4 are the same.

The most preferred ozonides are those according to formula (I), in which R1, R2, R3, R4 independently represent substituted groups selected from the group consisting of C_6-C_{20}-Aryl, C_3-C_{20}-Heteroaryl, C_7-C_{20}-Arylalkyl, C_8-C_{20}-Cycloalkylaryl, C_8-C_{20}-Cycloalkenylaryl, C_6-C_{20}-Cycloalkylheteroaryl, C_8-C_{20}-Heterocycloalkylaryl, C_8-C_{20}-Heterocycloalkenylaryl, C_8-C_{20}-Heterocycloalkenylheteroaryl and C_4-C_{20}-Heteroarylalkyl, in particular those selected from the group consisting of C_6-C_{20}-Aryl, C_3-C_{20}-Heteroaryl, C_8-C_{20}-Cycloalkylaryl, C_8-C_{20}-Cycloalkenylaryl, C_7-C_{20}-Cycloalkylheteroaryl, C_8-C_{20}-Heterocycloalkylaryl, C_8-C_{20}-Heterocycloalkenylaryl and C_8-C_{20}-Heterocycloalkenylheteroaryl.

Especially preferred are C_6-C_{20}-Aryl from the group consisting of Phenyl, 4-Methoxyphenyl, 2,4-Dimethoxyphenyl, 4-Methylyphenyl, 2,4-Dimethylphenyl, 3,5-Dimethylphenyl, 2-Tert.-butylphenyl, 4-Tert.-butylphenyl, 2,6-Di-tert.-butylphenyl, 4-CF_3-phenyl, 2,4-Di-CF_3-phenyl, 1-Naphthyl, 2-Naphthyl, 9-Anthacenyl, 9-Phenanthrenyl.

Alternatively or in addition thereto, C_3-C_{20}-Heteroaryl preferably comprise 2-Furfuryl, 3-Furfuryl, Imidazolyl.

Alternatively or in addition thereto, C_8-C_{20}-Cycloalkylaryl preferably comprise Indanyl, Fluorenyl.

Alternatively or in addition thereto, C_8-C_{20}-Cycloalkenylaryl is preferably Indenyl.

Especially preferred C_8-C_{20}-Heterocycloalkenylaryl is N-C_1-C_{16}-Alkyl- or N- C_1-C_8-Acyl-Indolyl.

Especially preferred C_6-C_{20}-Heterocycloalkylaryl is N-C_1-C_{16}-Alkyl- or N-C_1-C_8-Acyl-Indolinyl.

Thio-ether oxidation

Reaction during subsequent thioether oxidation is preferably in the range of -78 °C to +70 °C, in particular -30°C to +80°C and most preferably 20°C to 60°C. At these conditions fast and selective conversion of the thio-ether can be assured.

Obviously, in case ozonolysis and thioether oxidation are performed while all ozonolysis and oxidation precursors are in direct contact with one another, the reaction temperature is restricted to the mutual overlap between the aforementioned temperature trajects. However, taking into consideration that both reaction steps may perform optimally at different temperature conditions and ozone may hinder the selectivity of the reaction process, it is preferred to perform both steps separately, i.e. performing thio-ether oxidation after ozonolysis.

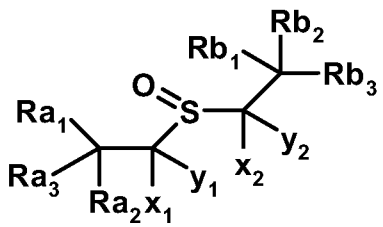
The choice of oxidation medium is already addressed under “ozonolysis”.

It is found that selectivity of the process is not affected by the order in which the components of the oxidation are mixed with one another. However, for sake of convenience, is preferred to add the oxidizing agent to the thio-ether precursor.

Thio-ether precursor – sulphoxide product

As evidenced in the accompanying examples, the thio-ether precursor is not particularly restricted to a certain group of thio-ethers. The ozonide has shown to be a successful tool in selectively converting each and everyone of the sulphide moieties investigated. Applicant’s interest particularly concern those thio-ethers known as API precursors, such as lanzoprazole, pantoprazole, omeprazole and rabeprazole.

The invention particularly relates to the formation of a sulphoxide compound which is represented by formula (II)



(II),

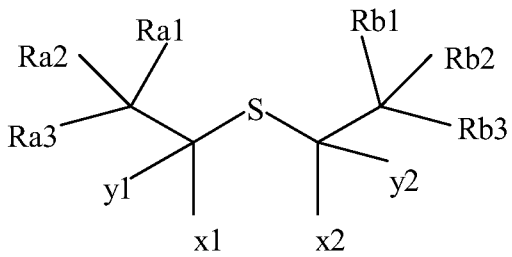
in which

Ra1, Ra2, Ra3, Rb1, Rb2 and Rb3 each represent, independently, H or an organic component (with preferably no more than 100 C-atoms), and preferably a substituted component selected from the group comprising alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, cycloalkenyl, cycloalkenylalkyl, alkinyl, cycloalkylalkinyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, aryl, heteroaryl, arylalkyl, cycloalkylaryl, cycloalkenylaryl, cycloalkylheteroaryl, heterocycloalkylaryl, heterocycloalkenylaryl, heterocycloalkenylheteroaryl and heteroarylalkyl,

in which two or all of Ra, and/or two or all of Rb may independently be covalently linked; and

x1, x2, y1 and y2 each represent, independently, H or C1-6 alkyl.

by oxidizing a corresponding thioether compound represented by formula (III):



(III)

under the above-mentioned controlled conditions.

Provided Ra and/or Rb are aromatic, these may be substituted with:

Hydroxy;

C_1-C_8-Alkyl, preferably Methyl, Ethyl, n-Propyl, iso-Propyl, n-Butyl, iso- Butyl, tert.-Butyl;

C_3-C_{18}-Cycloalkyl, preferably Cyclopropyl, Cyclopentyl, Cyclohexyl, Cyclooctyl, Cyclododecyl, Cyclopentadecyl, Cyclohexadecyl;

C_2-C_8-Alkinyl, preferably Ethinyl, Propinyl;

C_1-C_8-Perfluoralkyl, preferably Trifluormethyl, Nonafluorbutyl;

C_1-C_8-Alkoxy, preferably Methoxy, Ethoxy, iso-Propoxy, n-Butoxy, iso-Butoxy, tert.-Butoxy;

C_3-C_{12}-Cycloalkoxy, preferably C_3-Cycloalkoxy, C_5-Cycloalkoxy, C_6-Cycloalkoxy, C_8-Cycloalkoxy, C_{12}-Cycloalkoxy, C_{15}-Cycloalkoxy, C_{16}-Cycloalkoxy;

C_1-C_{20}-Alkoxyalkyl, wherein 1 to 5 CH_2 groups that are replaced by oxygen {?}, preferably -[-O-CH_2-CH_2-]$_v$-Q or -[-O-CH_2-CHMe-]$_v$-Q, in which Q = OH or CH_3, and v = 1,2, 3 or 4;

C_1-C_4-Acyl, preferably Acetyl;

C_1-C_4-Carboxy, preferably CO_2Me, CO_2Et, CO_2iso-Pr, CO_2tert.-Bu;

C_1-C_4-Acyloxy, preferably Acetyloxy;

Halogenid, preferably F or Cl;

Si_1-Si_{10}-Silyl; and/or

Si_1-Si_{30}-Siloxy or Polysiloxy.

Ra and Rb may independently be selected from the group consisting of C_3-C_{25}-Aryl, C_2-C_{25}-Heteroaryl, C_4-C_{25}-Arylalkyl, C_8-C_{25}-Cycloalkylaryl, C_8-C_{25}-Cycloalkenylaryl, C_5-C_{25}-Cycloalkylheteroaryl, C_8-C_{25}-Heterocycloalkylaryl, C_8-C_{25}-Heterocycloalkenylaryl, C_8-C_{25}-Heterocycloalkenylheteroaryl and C_3-C_{25}-Heteroarylalkyl.

Alternatively or in addition, Ra and Rb may independently be selected from the group consisting of C_6-C_{20}-Aryl, C_3-C_{20}-Heteroaryl, C_7-C_{20}-Arylalkyl, C_8-C_{20}-Cycloalkylaryl, C_8-C_{20}-Cycloalkenylaryl, C_6-C_{20}-Cycloalkylheteroaryl, C_8-C_{20}-Heterocycloalkylaryl, C_8-C_{20}-Heterocycloalkenylaryl, C_8-C_{20}-Heterocycloalkenylheteroaryl and C_4-C_{20}-Heteroarylalkyl.

Therein:

- C_6-C_{20}-Aryl is preferably selected from Phenyl, 4-Methoxyphenyl, 2,4-Dimethoxyphenyl, 4-Methylyphenyl, 2,4-Dimethylphenyl, 3,5-Dimethylphenyl, 2-Tert.-butylphenyl, 4-Tert.-butylphenyl, 2,6-Di-tert.-butylphenyl, 4-CF_3-phenyl, 2,4-Di-CF_3-phenyl, 1-Naphthyl, 2-Naphthyl, 9-Anthacenyl, 9-Phenanthrenyl
- C_3-C_{20}-Heteroaryl preferably comprises 2-Furfuryl, 3-Furfuryl, Imidazolyl;
- C_8-C_{20}-Cycloalkylaryl is preferably Indanyl, Fluorenyl;
- C_8-C_{20}-Cycloalkenylaryl is preferably Indenyl;

- C_8-C_{20}-Heterocycloalkenylaryl is preferably N-C_1-C_{16}-Alkyl- or N-C_1-C_8-Acyl-Indolyl; and
- C_6-C_{20}-Heterocycloalkylaryl is preferably N-C_1-C_{16}-Alkyl- or N-C_1-C_8-Acyl-Indolinyl.

Provided one or more of the components of Ra and Rb contain oxidizable hetero-atoms, as for example nitrogen or phosphorous, it is not necessary for the conversion of the thio-ether to further protect them with an oxidation agent.

The invention further pertains to the use of an ozonide as described above as an oxidizing agent, in particular to selectively convert sulphide groups.

EXAMPLES

Example 1: Synthesis of di-noctylsolfoxide from di-n-octylsulfide

5.0 g of trans-stilbene (0.028 mol) suspended in 50 ml methanol at -20°C was supplied with 1.2 molar equivalents of ozone. A trans-stilbene-ozonide was produced, which was present as a clear, weakly yellow solution in methanol.

The solution of freshly produced ozonide wa s added drop-wise to a di-n-octylsulfide solution (7.2g / 0.028 mol) in 50 ml methanol, at 50°C. Conversion was completed after 2 hours, resulting in di-n-octylsulfoxide. The selectivity was 100 %, as determined with GC-MS.

Example 2: Synthesis of diphenylsulfoxide from Diphenylsulfide

A trans-stilbene ozonide was prepared using the recipe of example 1.

A cold solution containig 0.037 mol of the freshly produced ozonide was added drop-wise to a solution of diphenylsulfide (5.7g/0.031 mol) in 100 ml methanol at a reaction temperature of 50°C. Conversion was completed after 2 hours, resulting in diphenylsulfoxide. The selectivity was 100 %, as determined with GC-MS.

Example 3: Synthesis of Methylphenylsulfoxide from Thioanisole

A trans-stilbene ozonide was prepared using the recipe of example 1.

It was then added in an amount of 0.031 mol trans-stilbene-ozonide dropwise in 50 minutes to a boiling solution of thioanisole (3.8g/0.031 mol) in 100 ml methanol.

Conversion was completed after 2 hours, resulting in methylphenylsulfoxide. The selectivity was 100 %, as determined with GC-MS.

Example 4: Production of Benzylmethylsulfoxide

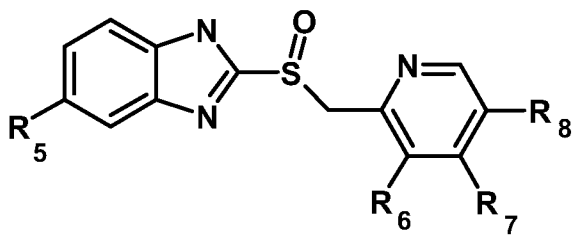
Example 3 was repeated, with the exception that the thio-ether in step b) was benzylmethylsulfide (4.3g/0.031 mol), and 0.062 mol trans-stilbene-ozonide was used.

Benzylmethylsulfoxide was thus prepared, with a selectivity of 100 %.

Example 6: Oxidation of Benzylimidazolyl-methyl-2-pyridylsulfide-derivatives with trans-Stilbene-ozonide

Trans-stilbene ozonide was prepared following the recipe of example 1, in an amount of 0.031 mol.

The thus-prepared ozonide was added drop-wise over 0.5h to a boiling solution of sulfide (0.031 mol) in 100 ml of methanol. The reaction solution is boiled for 3 hours under reflux conditions. The experiment was performed for a number of sulfides, generally represented by formula III. After 3 hours, the reaction mixtures were analyzed for conversion rate. The results are shown in table 1. In all cases, sulfoxide selectivity was 100%.



(III)

Table 1 – conversion thio-ether precursors

Sulfoxide	R5	R6	R7	R8	conversion
Lanzoprazol	H	CH_3	OCH_2CF_3	H	85%
Pantoprazol	OCF_2	OCH_3	OCH_3	H	100%
Omeprazol	OCH_3	CH_3	OCH_3	CH_3	67%
Rabeprazol	H	CH_3	$OC_3H_6OCH_3$	CH_3	70%

Example 7: Oxidation of Benzylimidazolyl-methyl-2-pyridylsulfide-derivatives with 1-Hexenozonide

21 g 1-Hexene (0.20 mol) in 500 ml of methanol at -15°C was converted with 1.2 molar equivalents of ozone, thus producing 1-hexen-ozonide. The ozonide was present as a clear solution in methanol.

The solution was used directly for the oxidation of the sulfides represented by formula III. Thereto, the ozonide was added dropwise over 0.5h to the boiling solution of the sulfide (0.20 mol) in 200 ml methanol. The reaction solution was refluxed for 3 hours. After 3 hours, the reaction mixtures were analyzed for conversion rate. The results are shown in table 2. In all cases, sulfoxide selectivity was 100%.

Table 2 – conversion thio-ether precursors

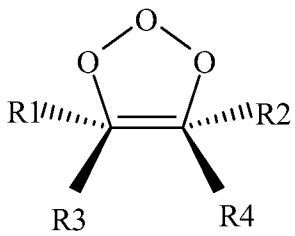
Name	R5	R6	R7	R8	Conversion
Lanzoprazol	H	CH_3	OCH_2CF_3	H	85%
Pantoprazol	OCF_2	OCH_3	OCH_3	H	100%
Omeprazol	OCH_3	CH_3	OCH_3	CH_3	65%
Rabeprazol	H	CH_3	$OC_3H_6OCH_3$	CH_3	70%

CLAIMS

1. A process for producing a sulphoxide compound, comprising oxidizing a thioether compound with an ozonide formed from a olefin and ozone, to obtain the corresponding sulphoxide compound, provided that the olefin is not ethene.

2. The process according to claim 1, wherein the molar ratio of said ozonide to sulphide moieties in said thio-ether compound is at least 1.

3. The process according to claim 1 or 2, wherein said ozonide is represented by formula (I)

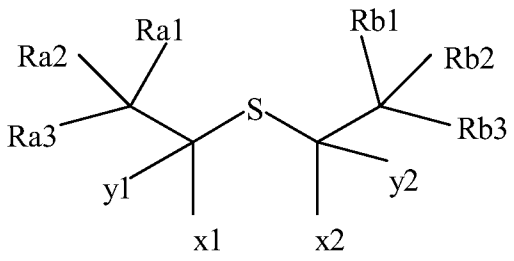


(I),

in which R1, R2, R3, R4 represent, independently, hydrogen or an organic component, and/or wherein two or more of R1, R2, R3, R4 maybe covalently interconnected,
provided that R1-4 are not hydrogen simultaneously.

4. The process according to any one of the preceding claims, wherein said

5. The process according to any one of the preceding claims, wherein said thio-ether compound is represented by formula (III)



(III),

in which

Ra1, Ra2, Ra3, Rb1, Rb2 and Rb3 each represent, independently, H or an organic component (with preferably no more than 100 C-atoms), and preferably a substituted component selected from the group comprising alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, cycloalkenyl, cycloalkenylalkyl, alkinyl, cycloalkylalkinyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, aryl, heteroaryl, arylalkyl, cycloalkylaryl, cycloalkenylaryl, cycloalkylheteroaryl, heterocycloalkylaryl, heterocycloalkenylaryl, heterocycloalkenylheteroaryl and heteroarylalkyl,
in which two or all of Ra, and/or two or all of Rb may independently be covalently linked; and
x1, x2, y1 and y2 each represent, independently, H or C1-6 alkyl.

6. Use of ozonide as an oxidizing agent for selective conversion of sulphide groups.

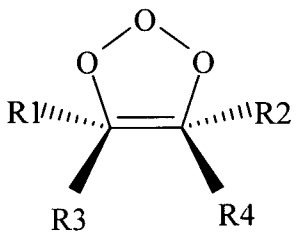
Amended Claims received by the International Bureau on 26 August 2008 (26.08.2008)

CLAIMS

1. A process for producing a sulphoxide compound, comprising oxidizing a thioether compound with an ozonide formed from a olefin and ozone, to obtain the corresponding sulphoxide compound, provided that the olefin is not ethene.

2. The process according to claim 1, wherein the molar ratio of said ozonide to sulphide moieties in said thio-ether compound is at least 1.

3. The process according to claim 1 or 2, wherein said ozonide is represented by formula (I)

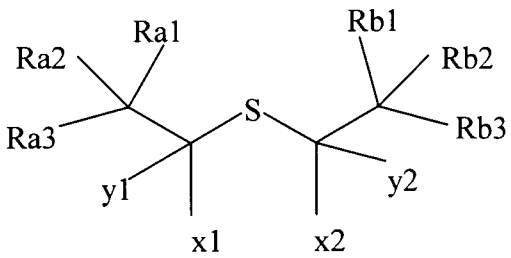


(I),

in which R1, R2, R3, R4 represent, independently, hydrogen or an organic component, and/or wherein two or more of R1, R2, R3, R4 maybe covalently interconnected,

provided that R1-4 are not hydrogen simultaneously.

4. The process according to any one of the preceding claims, wherein said thio-ether compound is represented by formula (III)



(III),

in which

Ra1, Ra2, Ra3, Rb1, Rb2 and Rb3 each represent, independently, H or an organic component (with preferably no more than 100 C-atoms), and preferably a substituted component selected from the group comprising alkyl, heteroalkyl,

cycloalkyl, cycloalkylalkyl, alkenyl, cycloalkenyl, cycloalkenylalkyl, alkinyl, cycloalkylalkinyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, aryl, heteroaryl, arylalkyl, cycloalkylaryl, cycloalkenylaryl, cycloalkylheteroaryl, heterocycloalkylaryl, heterocycloalkenylaryl, heterocycloalkenylheteroaryl and heteroarylalkyl,

in which two or all of Ra, and/or two or all of Rb may independently be covalently linked; and

x1, x2, y1 and y2 each represent, independently, H or C1-6 alkyl.

5. Use of ozonide as an oxidizing agent for selective conversion of sulphide groups.

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2008/050444

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C315/02 C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHERESHOVETS V V: "OXIDATION OF SULFIDES TO SULFOXIDES BY OPTICALLY ACTIVE PHOSPHITE OZONIDES" BULLETIN OF THE ACADEMY OF SCIENCES OF THE USSR. DIVISION OF CHEMICAL SCIENCE, CONSULTANTS BUREAU. NEW YORK, US, vol. 39, no. 9, 1 September 1990 (1990-09-01), pages 1943-1945, XP000219211 the whole document	6
A		1-5
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002464347 retrieved from XFIRE Database accession no. 1840511 abstract	6

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2008	19/08/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cooper, Simon

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& J. ORG. CHEM., vol. 49, no. 23, 1984, pages 4465-4470,	
X	US 3 637 768 A (SMETANA RICHARD D) 25 January 1972 (1972-01-25) the whole document	6
X	AKIRA MATSUURA ET AL: "Pd(II)-Mediated Oxidatin of Olefins Using the Transannular Ozonides of 9-tert-Butylanthracenes as an Oxygen Atom Source" J. ORG. CHEM., vol. 50, 1985, pages 5002-5004, XP002464357 the whole document	6
X	WO 2006/131040 A (XINJIANG TECHNICAL INST OF PHY [CN]; AILI WUMANJIANG [CN]; SUN ZICAI [ ) 14 December 2006 (2006-12-14) abstract	6
A	US 6 437 189 B1 (PRASAD VIDYANATHA A [US] ET AL) 20 August 2002 (2002-08-20) the whole document	1-6

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 4

Claim 4 is lacking text to such an extent that no guess could be made as to its intended content, rendering searching it impossible.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL2008/050444

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 4
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/NL2008/050444

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3637768 A	25-01-1972	NONE	
WO 2006131040 A	14-12-2006	CN 1709849 A	21-12-2005
US 6437189 B1	20-08-2002	CA 2254597 A1	12-06-1999