We, MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG

of Postfach 4119, D-6100 Darmstadt 1, Frankfurter StraBe 250, Germany

hereby apply for the grant of a Standard Patent for an invention entitled **Process for the Preparation of 1,2-disulfone Compounds**

which is described in the accompanying complete specification.

For a Convention application - details of basic application-

| Number | Country | Date of Application |
|---|---|---|
| P38 04 316.5 | Germany | 12th February, 1988 |

Our address for service is ARTHUR S. CAVE & CO., Patent and Trade Mark Attorneys, Level 10, 10 Barrack Street, Sydney, New South Wales, Australia 2000.

Dated this 10th day of February, 1989.

MERCK PATENT GESELLSCHAFT
MIT BESCHRÄNKTER HAFTUNG
By Its Patent Attorneys,
ARTHUR S. CAVE & CO.

HECTOR CUMMING, F.I.P.A.A.

To:
Commissioner of Patents

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

ASC 1

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 30.1.91

PATENT DECLARATION FORM (CONVENTION)
COMMONWEALTH OF AUSTRALIA
*Patents Act 1952*

Regulation 12 (2)

# DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

To be signed by the applicant(s) or in the case of a body corporate to be signed by a person authorised by the body corporate.

In support of the Convention application made for a patent for an invention entitled

(a) Insert title of invention.

(a) Process for the preparation of 1,2-disulfone compounds

(b) Insert full name(s) of declarant(s).

I/We (b) Brigitte Naumann
Jürgen Heumann

(c) Insert address(es) of declarant(s).

of (c) 250 Frankfurter Strasse,
D-6100 Darmstadt, Fed. Rep. of Germany

do solemnly and sincerely declare as follows:–

1. ~~I am/We are the applicant(s) for the patent~~

(OR, IN THE CASE OF AN APPLICATION BY A BODY CORPORATE.)

1. I am/We are authorised by MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG the applicant for the patent to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 of the Act was/were made in the following country or countries on the following date(s) namely:–

(d) Insert country in which basic application(s) was/were filed.
(e) Insert date of basic application(s).
(f) Insert full names of basic applicant(s).

in (d) Germany on (e) February 12, 1988
by (f) MERCK PATENT GMBH
in (d) ..... on (e) .....
by (f) .....
in (d) ..... on (e) .....
by (f) .....

~~3. I am/We are the actual inventor(s) of the invention referred to in the basic application.~~

(OR, WHERE A PERSON OTHER THAN THE INVENTOR IS THE APPLICANT)

(g) Insert full name(s) of actual inventor(s)
(h) Insert address(es) of actual inventor(s).

3. (g) Dr. Ekkehard Bartmann

of (h) 250 Frankfurter Strasse, D-6100 Darmstadt
Fed. Rep. of Germany

is/are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/are entitled to make the application are as follows:

(i) Set out how applicant(s) derive(s) title from actual inventor(s) i.e., assignee of the invention from the actual inventor(s).

(i) The applicant is the assignee of the invention from the actual inventors.

4. The basic application(s) referred to in paragraph 2 of this Declaration was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Attestation or legalization not required.

Declared at Darmstadt this 9th day of December 1988

To:

The Commissioner of Patents

Merck Patent Gesellschaft
mit beschränkter Haftung
ppa. ppa.
Naumann Heumann
principal officer principal officer

Signature of Declarant(s)

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

A.S.C.–4

(12) PATENT ABRIDGMENT (11) Document No. AU-B-29819/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 609246

(54) Title
PROCESS FOR THE PREPARATION OF 1,2-DISULFONE COMPOUNDS

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(57) In fact, it has been found that practically all the customary oxidizing agents are unsatisfactory or completely unsuitable for this reaction. It was found completely surprisingly, however, that concentrated nitric acid is an outstandingly suitable oxidizing agent for this reaction. It was particularly unexpected here that in addition to symmetric and unsymmetric diaryldisulfones, arylalkyldisulfones, dialkyldisulfones and variously substituted aryldisulfones and also heteroaromatic disulfones can also be prepared without problems with the aid of concentrated nitric acid.

CLAIM

1. Process for the preparation of 1,2-disulfone compounds by oxidation of corresponding 1,2-disulfonylhydrazine compounds, characterized in that the oxidation is carried out with the aid of concentrated nitric acid as the oxidizing agent.

2. Process according to Claim 1, characterized in that the reaction partners are reacted with one another directly and at a temperature between -5 and +5°C.

AUSTRALIA

PATENTS ACT 1952

# 609246

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:
Related Art:

This document contains the amendments made under Section 49 and is correct for printing

TO BE COMPLETED BY APPLICANT

| | |
|---|---|
| Name of Applicant: | MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG |
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| Actual Inventor: | Dr Ekkehard BARTMANN |
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Complete Specification for the invention entitled Process for **the Preparation of 1,2-disulfone Compounds.**

The following statement is a full description of this invention including the best method of performing it known to me:-



ASC 49

# Process for the preparation of 1,2-disulfone compounds

The invention relates to a process for the preparation of 1,2-disulfone compounds.

1,2-Disulfone compounds have diverse potential uses. It is thus known, for example, from Bull. Chem. Soc. Jap. 45, 2906 (1972) (CA 78: 15196c) that diaryldisulfones are photoreactive and dissociate into radicals under the action of radiation. According to JP 58-83844 (CA 101: 63684a) such compounds are used as agents which produce free radicals in photosensitive compositions for photolithographic purposes. According to Makromol. Chem., Rapid Commun. 4, 539 (1983) (CA 99: 140979v) and JP 59-197422 (CA 102: 186029u), diaryldisulfones can be used as agents which crosslink by radiation for epoxy-functionalized acrylate polymers. 1,2-Disulfones are moreover useful reagents and synthesis intermediates, for example also in the synthesis of pharmaceutical active compounds.

No preparation process which can be used in the widest possible range in respect of the choice of substituents and is easy to carry out is as yet known for 1,2-disulfones with in principle any desired organic radicals. According to JP 58-83844, diaryldisulfones are accessible by reaction of alkali metal arylsulfinates with arylsulfonyl chlorides. This method is expensive, especially for unsymmetrically substituted disulfones. The product yields which can be achieved are moreover unsatisfactory.

A synthesis route which is simple in principle is described in Z. Naturforsch. 21b, 813 (1966). In this article, symmetric phenyl, p-tolyl and naphthyl disulfones were prepared by oxidation of corresponding disulfonyl hydrazines, and yields of between about 30 and 50% were achievable. Only mercury oxide and N-bromosuccin-

imide were used as oxidizing agents. The choice of these oxidizing agents, which are unusual because they are expensive and in the case of mercury oxide also problematical, and all in all are to be described as "exotic" suggests the conclusion that customary oxidizing agents did not lead to the aim in this reaction.

In fact, it has been found that practically all the customary oxidizing agents are unsatisfactory or completely unsuitable for this reaction. It was found completely surprisingly, however, that concentrated nitric acid is an outstandingly suitable oxidizing agent for this reaction. It was particularly unexpected here that in addition to symmetric and unsymmetric diaryldisulfones, arylalkyldisulfones, dialkyldisulfones and variously substituted aryldisulfones and also heteroaromatic disulfones can also be prepared without problems with the aid of concentrated nitric acid.

The invention thus relates to a process for the preparation of 1,2-disulfone compounds by oxidation of corresponding 1,2-disulfonylhydrazine compounds, the oxidation being carried out with concentrated nitric acid as the oxidizing agent.

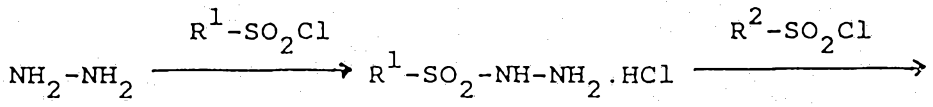
Diverse 1,2-disulfones with essentially any desired organic radicals can be prepared by the process according to the invention. These are, in particular, 1,2-disulfone compounds of the formula I

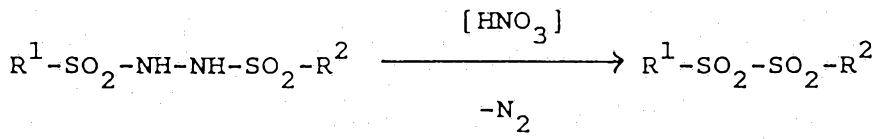
$$R^1\text{-}SO_2\text{-}SO_2\text{-}R^2 \qquad (I)$$

wherein $R^1$ and $R^2$ can be identical or different and are alkyl, cycloalkyl, aryl, aralkyl or heteroaryl having up to 12 C atoms and optionally substituted by one or more substituents from the group comprising halogen, cyano, nitro, carboxyl, alkyl, alkoxy, alkylthio, bisalkylamino, alkanoyl, alkanoyloxy, alkanoylamido, alkoxycarbonyl, alkylaminocarbonyl, alkylsulfoxy, alkylsulfonyl, aryloxy, arylthio, arylsulfoxy and arylsulfonyl having in each case up to 6 C atoms.

The 1,2-disulfonylhydrazine compounds to be used as starting substances are accessible in a simple manner by known methods by reaction of hydrazine with corresponding sulfonyl chlorides, it also being possible to obtain the unsymmetric 1,2-disulfonylhydrazine compounds by stepwise reaction.

The overall course of the reaction can be represented by the following equation:





The oxidation reaction to give the 1,2-disulfone is carried out according to the invention by adding concentrated nitric acid having a density of about 1.4 and a purity customary for synthesis purposes to the corresponding 1,2-disulfonylhydrazine compound, preferably while stirring and cooling. Since the reaction partners can be reacted with one another directly, the presence of a solvent can be dispensed with. The temperature of the reaction mixture during the addition and reaction is kept in the range from -5 to +5°C, preferably at about 0°C, for example by cooling the reaction vessel with ice. The reaction usually starts after a few minutes, with evolution of nitrogen. The product which has precipitated as a solid precipitate or is precipitated by addition of water after the end of the reaction can be purified by recrystallization as required.

In many cases, it is also possible to carry out the entire reaction sequence, that is to say the reaction of hydrazine to give 1,2-disulfonylhydrazine and the subsequent oxidation to the 1,2-disulfone, in a "one-pot reaction" without isolation of the disulfonylhydrazine

or, if appropriate, the monosulfonylhydrazine intermediate stage. This makes the process according to the invention particularly simple and economic.

A large number of widely differently substituted 1,2-disulfone compounds can be obtained in a form which is easy to isolate and in an outstanding to at least satisfactory yield using the oxidizing agent according to the invention. In contrast, with a large number of other customary oxidizing agents, such as, for example, hydrogen peroxide, potassium permanganate, potassium chlorate, chlorine or bromine, to single out only a few typical representatives, either no reaction was to be recorded or the reaction led to the disulfone to only a minor degree, if at all. Only with sodium hypochlorite was it possible in a very few cases, in particular in the case of disulfones of the formula I in which $R^1$ and $R^2$ are phenyl or p-tolyl, to obtain these in a moderate yield. In all other cases, this reagent also failed. The method of nitric acid oxidation is also particularly advantageous for the preparation of diaryldisulfones which carry sensitive substituents, that is to say substituents which tend to undergo secondary reactions, on the aryl radicals. Because of its comparatively mild conditions, the method is even compatible for many substituents which are rapidly oxidized or converted in other ways by other oxidizing agents. Thus, for example, sodium hypochlorite causes partial chlorination of i-propyl, acetamido and dimethylmaleimido radicals on the aromatic, whereas nitric acid leads to the corresponding 1,2-disulfone without problems in these cases.

Examples

A. General instructions for the preparation of 1,2-disulfones of the formula $R^1-SO_2-SO_2-R^2$ (I)

Concentrated nitric acid (density 1.4) is added dropwise to the corresponding 1,2-disulfonylhydrazine compound, while stirring and cooling with ice. After a few minutes, the reaction starts with evolution of nitrogen. When the reaction has subsided, the mixture is

stirred at 0°C for about 1 hour and the precipitate which has separated out is removed and recrystallized for purification.

B. Compounds prepared

| No. | $R^1$ | $R^2$ | Recrystallized from | Melting point (°C) |
|---|---|---|---|---|
| 1 | Phenyl | Phenyl | Ethanol | 192 |
| 2 | " | 4-Methylphenyl | Methanol | 177 |
| 3 | " | 4-Methoxyphenyl | Acetone | 153 |
| 4 | " | 2-Naphthyl | Methyl t-butyl ether | 182 |
| 5 | " | Benzyl | Methyl t-butyl ether/acetone | 186 |
| 6* | " | 2-Nitro-3,5-dimethoxyphenyl | Acetone | 186 |
| 7 | " | 2,4,6-Trimethyl-phenyl | Toluene | 154 |
| 8 | " | 4-i-Propylphenyl | Glacial acetic acid | 92 |
| 9 | " | 4-Chlorophenyl | Toluene | 181 |
| 10 | " | 4-Bromophenyl | Acetone | 198 |
| 11 | 4-Methylphenyl | 4-Methylphenyl | Acetone/ether | 222 |
| 12 | " | 4-Chlorophenyl | Toluene | 206 |
| 13 | " | Benzyl | Methanol | 126 |
| 14 | " | 2-Naphthyl | Methyl t-butyl ether/methylene chloride | 186 |
| 15 | " | 4-Methoxyphenyl | Acetone | 173 |
| 16* | " | 2-Nitro-3,5-dimethoxyphenyl | Acetone | 182 |
| 17 | " | Methyl | Methyl t-butyl ether | 109 |
| 18 | " | 1-Naphthyl | Acetone | 201 |
| 19 | 1-Naphthyl | 1-Naphthyl | Acetone/dimethyl-formamide | 183 (decom-position) |
| 20 | 2-Naphthyl | 2-Naphthyl | Tetrahydrofuran | 226 (de-composi-tion) |

| | | | | |
|---|---|---|---|---|
| 21 | 4-Methoxy-phenyl | 4-Methoxyphenyl | Acetone | 194 (de-composi-tion) |
| 22 | 4-Nitrophenyl | 4-Nitrophenyl | Tetrahydrofuran | 224 (de-composi-tion) |
| 23 | 2-Methylphenyl | 2-Methylphenyl | Toluene | 160 |
| 24 | Benzyl | Benzyl | Glacial acetic acid | 183 (de-composi-tion) |
| 25 | Benzyl | n-Propyl | Methylene chloride/ n-pentane | 100 |
| 26 | n-Propyl | n-Propyl | (Water)** | 53 |
| 27 | n-Propyl | 4-Nitrophenyl | Methyl t-butyl ether | 111 |
| 28 | n-Propyl | 4-Methoxyphenyl | Petroleum ether | 83 |
| 29 | Phenyl | n-Propyl | Methyl t-butyl ether | 138 |
| 30 | " | 4-t-Butylphenyl | (Water)** | 128 |
| 31 | 4-Methylphenyl | n-Propyl | (Water)** | 86 |
| 32 | 4-i-Propylphenyl | Methyl | - | (oil) |
| 33 | 4-t-Butylphenyl | n-Propyl | Ether/petroleum ether | 110 |
| 34 | 1-Naphthyl | Methyl | Toluene | 157 |
| 35 | 1-Naphthyl | n-Propyl | (Water)** | 116 |
| 36 | 2-Naphthyl | Methyl | (Water)** | 146 |
| 37 | 2-Naphthyl | n-Propyl | Ether/petroleum ether | 67 |
| 38 | 4-Acetylamido-phenyl | n-Propyl | Glacial acetic acid | 189 |
| 39 | " | Phenyl | " | 208 |
| 40 | " | 4-Methylphenyl | " | 201 |
| 41 | " | 4-Methoxyphenyl | " | 204 |
| 42 | " | 4-Nitrophenyl | " | 198 (de-composi-tion) |
| 43 | 4-Phthalimido-phenyl | n-Propyl | " | 196 |
| 44 | " | Phenyl | Methylene chloride/ cyclohexane | 210 |
| 45 | " | 4-Methylphenyl | Glacial acetic acid | 214 |
| 46 | " | 4-Methoxyphenyl | " | 162 |

| | | | | |
|---|---|---|---|---|
| 47 | 4-(1,2-dimethylmaleimido)phenyl | n-Propyl | Methyl t-butyl ether | 143 |
| 48 | " | Phenyl | Methylene chloride | 222 |
| 49 | " | 4-Methylphenyl | Methylene chloride/ petroleum ether | 235 |
| 50 | " | 4-Methoxyphenyl | Glacial acetic acid | 162 |
| 51 | 4-Nitrophenyl | n-Propyl | Ether | 104 |

* The $NO_2$ group was introduced here during the nitric acid oxidation

** Already crystallizes out in a sufficient purity on addition of water

C. Comparative oxidation experiments

The suitability of other oxidizing agents for some of the 1,2-disulfone compounds prepared in B. was tested in comparison with the method of oxidation with concentrated nitric acid. The other oxidizing agents were used under the reaction conditions customary for them.

In the following Table 1, the symbols are as follows:

‡ disulfone can be isolated in a good yield

\+ disulfone can be isolated in a moderate yield

o disulfone detectable in a small amount but cannot be isolated

\- disulfone not detectable; other reaction products

= no reaction

Table 1: Comparative oxidation experiments

| Compound No. | 1 | 2 | 8 | 11 | 13 | 24 | 25 | 29 | 31 | 32 | 33 | 36 | 37 | 41 | 44 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $HNO_3$ | + + | + + | + + | + + | + | + | + | + + | + + | + + | + + | + + | + + | + + | + + |
| $NaOCl/H_2O$ | + | + | o | + | - | - | | o | o | - | o | - | - | - | + |
| $H_2O_2/Na_2WO_4$ | = | | | | | | | | | | | | | | |
| $K_2S_2O_8/H_2SO_4$ | | | | | | = | | | | | | | | | |
| N-Bromosuccinimide $/CH_2Cl_2$ | | | | | | - | | - | | | | | | | |
| $K_3Fe(CN)_6$ | | = | | | | | | | | | | | | | |
| Benzoyl peroxide/ -hlorobenzene | | | | = | | | | | | | | | | | |
| Bleaching powder | | | | = | | | | | | | | | | | |
| $Ce^{IV}/H_3O^+$ | - | | | | | | | | | | | | | | |
| $KClO_3/H_3O^+$ | = | | | | | | | | | | | | | | |
| $KMnO_4$/Acetone | | | | = | | | | | | | | | | | |
| $KMnO_4/CH_3CO_2H$ | | | | + | - | | | o | | | | | | | |
| m-Chloroperbenzoic acid/ $CH_2Cl_2$ | + | | | | | - | - | o | | | | | | | |
| $Cl_2/H_2SO_4$ | | | | - | | | | | | | | | | | |
| $Cl_2/CCl_4$ | | | | - | | | | - | | | | | | | |
| $Cl_2/C_2H_5OH$ | | | | o | | | | | | | | | | | |
| $Br_2/H_2SO_4$ | | | | | | - | - | | | | | | | | |
| $Br_2/CH_3CO_2H$ | - | | | o | - | - | - | | | | | | | | |
| $H_2O_2/HCl/H_2O$ | | | | = | | | | | | | | | | | |
| $H_2O_2/HCO_2H$ | = | | | | | | | | | | | | | | |
| $H_2O_2/CH_3CO_2H$ | | | | = | | | | | | | | | | | |

The Claims defining the invention are as follows:

1. Process for the preparation of 1,2-disulfone compounds by oxidation of corresponding 1,2-disulfonyl-hydrazine compounds, characterized in that the oxidation is carried out with the aid of concentrated nitric acid as the oxidizing agent.

2. Process according to Claim 1, characterized in that the reaction partners are reacted with one another directly and at a temperature between -5 and +5°C.

DATED this 24th day of January 1991.

MERCK PATENT GESELLSCHAFT
MIT BESCHRANKTER HAFTUNG
By Its Patent Attorneys,
ARTHUR S. CAVE & CO.