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(54) Title: PROCESS FOR THE REDUCTION OF SULPHOXIDES TO SULPHIDES



(57) Abstract: The present application relates to a new process for the reduction of sulfoxides to sulfides, wherein said process provides the production of a sulfide compound of formula (I), by the reduction of a sulfoxide compound of formula (II): with oxalyl chloride, an alcohol and tertiary amine.

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PROCESS FOR THE REDUCTION OF SULPHOXIDES TO SULPHIDES

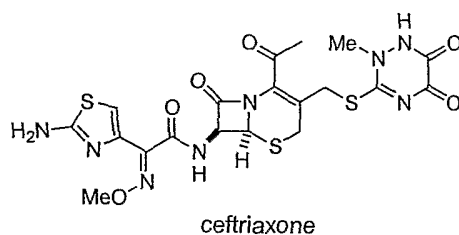
The present application relates to a new process for the reduction of sulfoxides to sulfides.

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The sulfide moiety occurs in many natural products of biological importance such as Ecteinasidin 743, Breynin A and (+)-Breynolide. It is also found to be present in compounds that occur in the mammalian system such as leukotriene C₄. The sulfide group also forms key architecture of many pharmaceutical drugs such as Zantac[®], Tagamet[®], Pepcid[®] and Axid[®]. The non-steroidal anti-inflammatory drug Clinoril[®]'s bioactive sulfide component arises from a reversible reduction of the sulfoxide moiety.

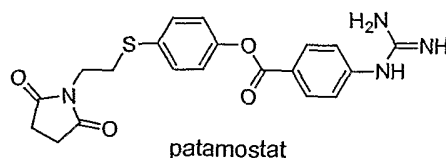
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The synthesis of biologically active compounds such as pharmaceutical drugs or natural products is complicated by the high proportion of functional groups within the molecular structure of the compound. Examples of drugs containing multiple functional groups in combination with a sulfide moiety include ceftriaxone produced by Hoffman-La Roche



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and patamostat mesylate produced by EISAI Co., Ltd.



Examples of natural products containing multiple functional groups in combination with a sulfide moiety include breynin A, ecteinascidin 743, leukotriene C₄ and biotin.

5 Thus in order to carry out the reduction of a sulfoxide to produce a molecule containing a sulfide group, it is necessary to consider the action of the reaction conditions on other functional groups in the molecule such as ketones, aldehydes, acids, amides, nitro groups etc. Furthermore, the required compounds may be susceptible to acidic or basic conditions required to afford
10 the reduction or to heat. It is also necessary to consider the susceptibility of a molecule containing multiple functional groups to the use of acidic or basic conditions and/or to the use of heat to afford the required reduction of the sulfoxide to the sulfide.

15 Methods for the reduction of sulfoxides to sulfides are known in the art and have been thoroughly reviewed by Drabowicz *et al* (*Org. Prep. Proc. Int.*, 1977, 9, 63; *Org. Prep. Proc. Int.*, 1984, 16, 171), Kukushkin (*Russ. Chem. Rev.*, 1990, 59, 844) and Madesclaire (*Tetrahedron*, 1988, 44, 6537). However, the known methods for the reduction of sulfoxides to sulfides
20 generally employ harsh reaction conditions, making the reduction of a sulfoxide moiety incompatible with the presence of sensitive functional groups within the same molecule.

A number of reagent systems/techniques are routinely employed for sulfoxide
25 reductions. These systems/techniques are summarised below.

Hydrogen halides and other halo-systems have been used to carry out the reduction of sulfoxides. Such systems include the use of HCl with ethanol or dioxane, HBr optionally with Br₂, HI, or reaction with KI and HCl, *t*-C₄H₉Br,

CHCl₃ or refluxing in cyanic chloride or fluoride in dioxane. However, the use of a hydrogen halide as a reductant involves the use of strongly acidic reaction conditions which are incompatible with a number of functionalities. The use of these conditions may also lead to the formation of undesirable byproducts e.g. products of oxidation or bromination with the free bromine produced during sulfoxide reduction. In some cases, such halide reagents involve the use of highly toxic cyanuric species, whose use is an unattractive proposition.

Alternative reagents for this reduction are the use of sulfur and/or sulfur compounds including thiols such as H₂S, C₆H₅SH or Me₂S, L-cystein or N-phthaloyl cystein, and dithioacetic or dithiobenzoic acid. However, the use of many sulfur compounds is associated with problematic removal of P/S/Se-containing byproducts. The use of thiolacetic acid results in long reaction times and the use of thiols constitute the presence of objectionable odours being present.

Phosphorus compounds are also used as reagents for the reduction of sulfoxides. Such compounds include cyclic phospholanes, phosphorus, trihalides such as PCl₃, PBr₃ or PI₃, Ph₃P, [PS-P(Ph)₂], POCl₃, PSBr₃ and (Me₂N)₃P. Phosphorus compounds are often difficult to remove from the desired product. In addition, strong acidic conditions are employed by utilisation of the phosphorus trihalides. The use of reagents such as POCl₃ delivers unwanted chlorinated species. The use of PSBr₃ generates acidic POBr₃ as a byproduct, which can react further with many classes of compounds.

Silicon compounds such as HSiCl₃, Me₃SiCl or Me₃SiI, Si₂Cl₆, PhSeSiMe₃ or SiS₂ are employed in the reduction of sulfoxides. The use of SiS₂ leads to unwanted side products. Si₂Cl₆ is reported to generate a chlorinated species

from reaction with *p*-tolylsulfoxide. The employment of amine bases can lead to accompanying unwanted deprotonation reactions at ambient temperatures in certain susceptible systems.

5 Boron compounds including HBCl_2 , BF_3OEt_2 , Me_2BBr , BBr_3 , $\text{ThxBHCl-Me}_2\text{S}$, BH_3THF , catecholborane or selenoboranes are also used to reduce sulfoxides. Boranes however can reduce a number of different functionalities. Thus, there is a problem with the specificity of these reducing agents in highly functionalised molecules. Overreduction is a problem in sensitive systems
10 especially at ambient temperatures. Furthermore it is necessary to remove seleno-contaminants from the reduction products for example, compounds of pharmaceutical interest and such removal involves an extra purification step.

Metal hydrides are well known reducing agents and include LiAlH_4 , AlH_3 ,
15 Dibal-H, Redal and NaBH_4 . However, the use of metal hydrides will cause the unwanted reduction of various other functionalities that may be present in the molecule including aldehydes, ketones, amides, esters and epoxides.

Further reduction systems include the use of low-valent metal ions including
20 $\text{TiCl}_4/\text{metal hydride}$, TiCl_3 , VCl_2 , CrCl_2 , MoOCl_3 , SnCl_2 and $\text{K}_2\text{W}_2\text{Cl}_9$. However the use of low-valent metals is highly undesirable for the reduction of products such as pharmaceutical drug candidates as these low-valent metals must be fully removed from the product after the reduction step. Removal of the low-valent metals can be both difficult and time consuming. There is
25 further a problem with the specificity of such reagents as for example, TiCl_4 is also a good Lewis acid and can therefore react with other functionalities in the molecule.

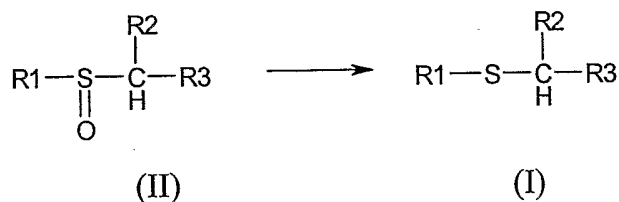
A number of miscellaneous reagents are also used to reduce sulfoxide functionalities. Such reagents include Zn powder, Fe and reduced pressure, Grignard reagent, Lawesson's reagent, n-BuLi and Pd/C. Metals such as Hg, Zn, Rh, Mo and Co are highly undesirable elements as impurities in compounds of potential therapeutic value and the use of these reagents is therefore not favoured. Reactions conducted at reduced pressures or with obnoxious smelling reagents such as Lawesson's Reagent, 1,3-dithiane or [CoO. MoO₃/Al₂O₃] presulfurised with H₂S have a number of obvious disadvantages. The use of Grignard reagents, alkyl lithiums or Pd/C will not be tolerated by many other functionalities that may be present in a molecule.

Other techniques have been used to reduce sulfoxides. These include photochemical reduction, electrochemical reduction, enzymatic reduction and reduction by electron pulse radiolysis. However, none of these other techniques are viable on a diverse array of structures due to their limited applicability to only specific classes of sulfoxides.

The sulfide moiety is an important component of a number of biologically active molecules. The sulfide moiety is commonly introduced into a molecule in the form of a sulfoxide precursor which then undergoes reduction to provide the required sulfide. The use of the sulfoxide precursor is commonly used as part of a chiral auxillary in asymmetric synthesis. Sulfoxides are also commonly used where there is a need to increase the acidity of a proton alpha to the sulfur atom to form an alpha-carboanion, for example in carbon-carbon bond formation. Furthermore, the introduction of the sulfide moiety as a sulfoxide moiety or the temporary conversion of a sulfide moiety into a sulfoxide moiety allows the purification of complex products due to the increased polarity of the sulfoxides compared with the sulfides. There is therefore a need for a process for the reduction of a sulfoxide moiety to form a

sulfide moiety, wherein said process provides mild reaction conditions and can be used in the presence of other functionalities.

The first aspect of the present invention provides a process for the production of a sulfide compound of formula I,



by the reduction of a sulfoxide compound of formula II with oxalyl chloride, an alcohol and a tertiary amine wherein

R^1 , R^2 and R^3 are independently hydrogen, halogen, branched or unbranched alkyl (optionally interrupted by one or more of O-, -C(O)-, -N(R^2)-, -S(O)- or -S(O_2)-), alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, reduced arylalkyl, arylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, reduced aryl, reduced heterocyclyl, reduced heterocyclylalkyl or a substituted derivative of any of the foregoing groups, wherein the substituents are one or more independently of halogen, alkyl, halosubstituted alkyl, aryl, arylalkyl, heterocyclyl, reduced heterocyclyl, reduced heterocyclylalkyl, arylalkoxy, cyano, nitro, -C(O) R^6 , -CO $_2\text{R}^6$, -SOR 6 , -SO $_2\text{R}^6$, SONR $^7\text{R}^7$, NR $^7\text{SO}_2\text{R}^6$, NR $^7\text{CO}_2\text{R}^6$, -NR $^7\text{R}^7$, -OR 6 , -SR 6 , -C(O)CX $^1\text{X}^2\text{NR}^7\text{R}^7$, -C(O)N(OH) R^7 , -C(O)NR $^7\text{R}^7$, -NR $^7\text{C(O)R}^6$, -CR $^6(\text{NH}_2)\text{CO}_2\text{R}^6$, -NHCX $^1\text{X}^2\text{CO}_2\text{R}^6$, -N(OH)C(O)NR $^7\text{R}^7$, -N(OH)C(O) R^6 , -NHC(O)NR $^7\text{R}^7$, -C(O)NHN R^7R^7 , -C(O)N(OR 6) R^6 ,
 and where:-

R^6 is hydrogen, C $_{1-12}$ alkyl or aryl, optionally substituted by one or more of C $_{1-4}$ alkyl, halogen, C $_{1-4}$ haloalkyl, OR 8 , SR 8 , NO $_2$, CN, NR $^8\text{R}^8$, NR $^8\text{COR}^8$,

NR⁸CONR⁸R⁸, NR⁸COR⁸, NR⁸CO₂R⁸, CO₂R⁸, COR⁸, CONR⁸₂, S(O)₂R⁸, SONH₂, S(O)R⁸, SO₂ NR⁸R⁸, NR⁸S(O)₂R⁸, wherein the C₁₋₁₂ alkyl group optionally incorporates one or more insertions selected from the group consisting of -O-, -N(R⁸)-, -S(O)- and -S(O₂)-, wherein each R⁸ may be the same or different and is as defined below;

R⁷ is C₁₋₁₂ alkyl or aryl, optionally substituted by one or more of C₁₋₄ alkyl, halogen, C₁₋₄ haloalkyl, OR⁸, SR⁸, NO₂, CN, NR⁸R⁸, NR⁸COR⁸, NR⁸CONR⁸R⁸, NR⁸COR⁸, NR⁸CO₂R⁸, CO₂R⁸, COR⁸, CONR⁸₂, S(O)₂R⁸, SONH₂, S(O)R⁸, SO₂ NR⁸R⁸, NR⁸S(O)₂R⁸, wherein the C₁₋₁₂ alkyl group optionally incorporates one or more insertions selected from the group consisting of -O-, -N(R⁸)-, -S(O)- and -S(O₂)-, wherein each R⁸ may be the same or different and is as defined below;

R⁸ is hydrogen, C₁₋₄ alkyl, or C₁₋₄ haloalkyl, aryl, or heterocyclyl;

X¹ and X² are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, arylalkyl, heterocyclylalkyl, reduced heterocyclyl or reduced heterocyclylalkyl.

20

In this text, 'reduced', in the context of 'reduced heteroaryl' and the like means fully or partially saturated.

For the purposes of this invention, "alkyl" means a straight chain or branched alkyl radical of 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms and most preferably 1 to 4 carbon atoms including but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl, hexyl, septyl, octyl, etc. The term "alkenyl" means a straight chain or branched alkylenyl radical of 2 to 12 carbon atoms, preferably 2 to 6 carbon atoms and most

preferably 2 to 4 carbon atoms, and containing one or more carbon-carbon double bonds and includes but is not limited to ethylene, n-propyl-1-ene, n-propyl-2-ene, isopropylene, etc. The term "alkynyl" means a straight chain or branched alkynyl radical of 2 to 12 carbon atoms, preferably 2 to 6 carbon atoms and most preferably 2 to 4 carbon atoms, and containing one or more carbon-carbon triple bonds and includes but is not limited to ethynyl, 2-methylethynyl etc. The term "cycloalkyl" means an saturated or partly unsaturated 3-12 membered cyclic alkyl group and includes but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl etc. Cycloalkyl groups may be optionally substituted or fused to one or more aryl, heterocyclyl or cycloalkyl group. "Heterocycloalkyl" means a 3-12 membered saturated or partly unsaturated cycloalkyl containing one or more hetero atom selected from N, S and O. "Haloalkyl" means an alkyl radical substituted with one or more halide atoms for example $\text{CH}_2\text{CH}_2\text{Br}$, CF_3 or CCl_3 .

"Aryl" means an aromatic 3-10 membered hydrocarbon containing one ring or being fused to one or more saturated or unsaturated rings including but not limited to phenyl, naphthyl, anthracenyl or phenanthracenyl; or partially saturated bicyclic rings such as tetrahydro-naphthyl. Examples of substituents which may be present on an aryl group include one or more of halogen, amino, nitro, alkyl, haloalkyl, alkoxy, phenoxy and phenoxy substituted by one or more of halo, alkyl or alkoxy.

"Heteroaryl" means an aromatic 3-10 membered aryl containing one or more heteroatoms selected from N, O or S and containing one ring or being fused to one or more saturated or unsaturated rings.

"Heterocyclyl" means a 3-10 membered ring system containing one or more heteroatoms selected from N, O or S and includes heteroaryl. The heterocyclyl

system can contain one ring or may be fused to one or more saturated or unsaturated rings; the heterocyclyl can be fully saturated, partially saturated or unsaturated and includes but is not limited heteroaryl and heterocarbocyclyl, e.g. cyclohexyl, phenyl, acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzoxazine, benzothiazole, carbazole, cinnoline, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyridopyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;. A reduced heteroaryl group or moiety may be for example a fully or partially saturated derivative of the aforementioned heteroaryl groups. Examples of reduced heteroaryl groups thus include pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl and piperidinyl. Suitable substituents include one or more of halogen, oxo, amino, nitro, alkyl, haloalkyl, alkoxy, phenoxy and phenoxy substituted by one or more of halo, alkyl, haloalkyl or alkoxy.

The aryl, heteroaryl or heterocyclyl group can be optionally fused to an unsaturated, partially saturated or fully saturated five to seven membered ring containing zero to three heteroatoms, each saturated carbon in the optional fused ring is further optionally and independently substituted by =O , =S , =NNHR^6 , NNR^6R^6 , =N-OR^6 , =NNHCOR^6 , $\text{=NNHCO}_2\text{R}^6$, $\text{=NNSO}_2\text{R}^6$, or =NR^6 , wherein each R^6 may be the same or different and is as defined above;

Each substitutable nitrogen atom in R is optionally substituted by R^7 , COR^6 , SO_2R^6 or CO_2R^6 , wherein each R^6 and R^7 may be the same or different and is as defined below;

5 Halogen means F, Cl, Br or I, preferably F.

The reduction conditions of the present invention comprise oxalyl chloride, an alcohol and a tertiary amine. For the purposes of the present invention, the alcohol is preferably a secondary alcohol such as isopropyl alcohol or isobutyl
10 alcohol, more preferably isopropyl alcohol. The tertiary amine is preferably triethylamine or an amine of equivalent basicity.

The reduction is preferably carried out at 0°C or below, more preferably between -78°C to -50°C , most preferably at approximately -70°C or below.

15

It will be noted that the process of the first aspect utilises the oxalyl chloride-isopropyl alcohol-triethylamine system. This system provides a number of benefits compared with conventional reduction systems or techniques. The reduction process of the present application provides extremely mild reaction
20 conditions, and the process can be carried out at temperatures as low as -78°C , allowing the reduction of unstable and temperature-labile molecules.

25

The by-products of the reduction reaction are innocuous and can be easily removed by standard aqueous work-up techniques which are routinely used and well-known to the person skilled in the art. The by-products are typically acetone, diisopropyl oxalate and inorganic salts. The process of the first aspect further provides an environmentally friendly procedure compared to current protocols (ie it does not involve the use of heavy metals etc.). The conditions

suitable for the described process are similar to those used commonly during the Swern oxidation of alcohols.

The process of the present invention provides the means to produce a wider and more varied array of sulfide containing molecules as the reaction conditions are tolerated by a wide range of functionalities including ethers in particular *p*-methoxybenzyl ether, acetal, nitro, alkene, alkyne, *t*-butoxycarbonylamino and others well known to those skilled in the art. The skilled person will appreciate that some functionalities for example alcohols and primary amines will require protection prior to the process of the present invention. In addition, the reaction reagents required for the process of the present invention are readily available and standard.

The second aspect of the invention relates to a product as produced by the process of the first aspect.

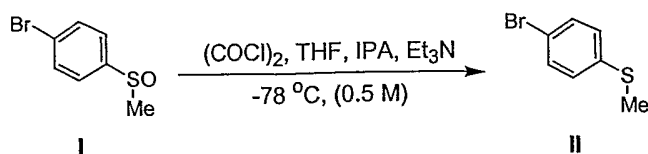
The present invention will now be illustrated by reference to the following non-limiting examples

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EXAMPLES

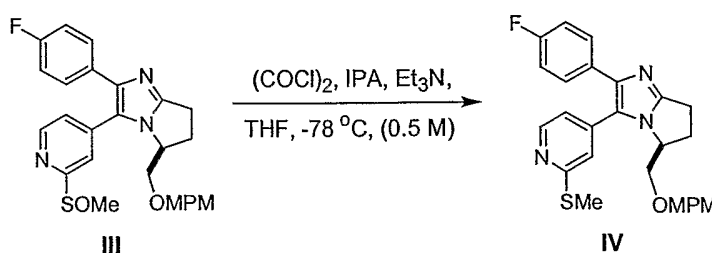
Deoxygenation of 1-bromo-4-methylsulfinyl-benzene (I; Table 1, entry 1)

25



To a stirred and cooled (-78°C) solution of the sulfoxide **I** (497 mg, 2.27 mmol) in THF (4 mL) under a nitrogen atmosphere was added oxalyl chloride (0.26 mL, 2.95 mmol). After 1 h, 2-propanol (0.35 mL, 4.54 mmol) was added dropwise. The reaction mixture was stirred for a further 1 h, and then Et_3N (1.58 mL, 11.35 mmol) was added. After 3 min., the mixture was removed from the solid CO_2 /acetone bath and allowed to warm to room temperature, and then partitioned between CHCl_3 /brine. The aqueous layer was extracted with CHCl_3 (2x) and the combined organic extracts dried (MgSO_4), filtered and concentrated *in vacuo*. Analysis of the crude product revealed a 87:1 mixture of the sulfide and sulfoxide, respectively (based on integration of signals at δ 2.46 and 2.68 in the 400 MHz ^1H NMR spectrum). Purification by silica gel chromatography [hexanes-IPA (100:1)] afforded sulfide **II** (343 mg, 75 %).

Deoxygenation of (*S*)-2-(4-fluoro-phenyl)-3-(2-methanesulfinyl-pyridin-4-yl)-5-(4-methoxy-benzoyloxymethyl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**III**; Table 1, entry 7)



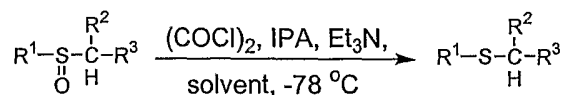
To a stirred and cooled (-78°C) solution of sulfoxide **III** (213.7 mg, 0.434 mmol) in THF (0.40 mL) under a nitrogen atmosphere was added a solution of oxalyl chloride (71.7 mg, 0.565 mmol) in THF (0.25 mL) dropwise to afford a pale yellow solution. After 1 h, a solution of 2-propanol (52.2 mg, 0.869 mmol) in THF (0.33 mL) was added to afford a yellow solution. Following a further 1 h stirring at -78°C , triethylamine (0.30 mL, 2.17 mmol) was added dropwise and the mixture stirred at -78°C for a further 3 min. Cooling bath was removed

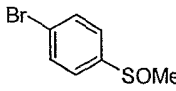
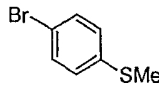
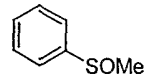
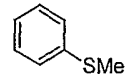
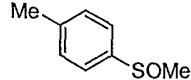
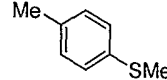
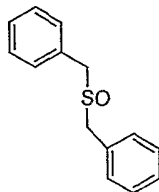
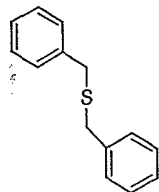
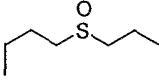
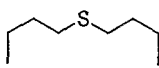
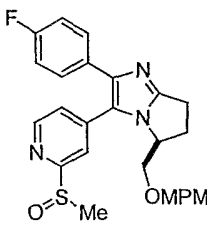
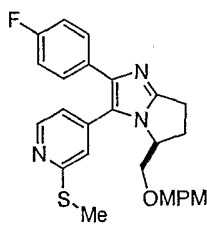
and the mixture was allowed to reach room temperature. The mixture was separated between CHCl_3 and saturated brine. The aqueous layer was extracted with CHCl_3 (2x) and the combined organic extracts dried (MgSO_4), filtered and evaporated to yield a 91.1:8.9 mixture of the sulfide **IV** and sulfoxide **III** (as judged by the integration of the signals at δ -115.45 and -114.70 ppm for the compounds **IV** and **III**, respectively in the ^{19}F NMR spectrum of the crude reaction mixture). The mixture was purified by flash column chromatography with hexanes:AcOEt as eluent in gradient (from 5:1 to 1:4, respectively) to afford sulfide **IV** as a viscous oil (111 mg, 54%). ^1H NMR (400 MHz; CDCl_3) δ 2.50-2.60 (m, 1H), 2.51 (s, 3H), 2.73-3.10 (m, 3H), 3.18 (dd, J = 10.0, 4.6 Hz, 1H), 3.33 (dd, J = 10.0, 2.7 Hz, 1H), 3.75 (s, 3H), 4.13 (d, J = 11.9 Hz, 1H), 4.26 (d, J = 11.9 Hz, 1H), 4.57 (bs, 1H), 6.76-6.82 (m, 3H), 6.93-7.03 (m, 5H), 7.46 (dd, J = 6.9, 6.4 Hz, 2H), 8.34 (d, J = 4.9 Hz, 1H). HR MS $\text{C}_{27}\text{H}_{26}\text{FN}_3\text{O}_2\text{S}$ (MH^+), Requires: 476.1808. Found: 476.1796690.

15

Experimental data for all the examples has been summarised in Table 1.

Table 1. Results of deoxygenation of selected sulfoxides using general method described above.



Entry	Sulfoxide	Sulfide	GC Analysis ^a			¹ H NMR analysis ^d
			Retention time/min sulfoxide	Retention time/min sulfide	% conv.	% conversion
1			30.21	25.70	99.7 ^b 99.9 ^c	99.8 97.1
2			25.25	19.84	99.3 ^b	Only product detected
3			27.70	21.80	99.7 ^b	Only product detected
4			38.26	33.56	- ^e	85.7
5			22.76	10.50	99.4 ^b	Only product detected
6			26.30	19.42	- ^e	87.5
7			- ^f	- ^f	- ^f	91.1 ^g

a - Perkin-Elmer 8500 gas chromatograph

G.C. column : 30M BPX5 0.32mm i.d. wide bore capillary column

Oven conditions : Initial 50 °C hold for 8 min, ramp 8 °C/min, final 250 °C hold for 12 min.

b - solvent is THF; c - solvent is DCM

d - ¹H NMR (400 MHz) of the crude reaction mixture in CDCl₃ or D₆-benzene, except stated otherwise

e - Not possible to calculate due to co-elution of interfering peaks

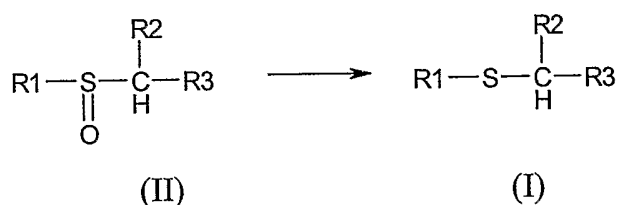
f - analysis not performed

g - ¹⁹F NMR (376 MHz) of the crude reaction mixture in CDCl₃

CLAIMS

1. A process for the production of a sulfide compound of formula I,

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- 10 by the reduction of a sulfoxide compound of formula II with oxalyl chloride, an alcohol and tertiary amine wherein

- 15 R^1 , R^2 and R^3 are independently hydrogen, halogen, branched or unbranched alkyl (optionally interrupted by one or more of O-, -C(O)-, -N(R^2)-, -S(O)- or -S(O₂)-, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, reduced arylalkyl, arylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, reduced aryl, reduced heterocyclyl, reduced heterocyclylalkyl or a substituted derivative of any of the foregoing groups, wherein the substituents are one or more independently of halogen, alkyl, halosubstituted alkyl, aryl, arylalkyl, heterocyclyl, reduced heterocyclyl, reduced heterocyclylalkyl, arylalkoxy, cyano, nitro, -C(O) R^6 , -CO₂ R^6 , -SOR⁶, -SO₂ R^6 , SONR⁷ R^7 , NR⁷SO₂ R^6 , NR⁷CO₂ R^6 , -NR⁷ R^7 , -OR⁶, -SR⁶, -C(O)CX¹X²NR⁷ R^7 , -C(O)N(OH) R^7 , -C(O)NR⁷ R^7 , -NR⁷C(O) R^6 , -CR⁶(NH₂)CO₂ R^6 , -NHCX¹X²CO₂ R^6 , -N(OH)C(O)NR⁷ R^7 , -N(OH)C(O) R^6 , -NHC(O)NR⁷ R^7 , -C(O)NHN⁷ R^7 , -C(O)N(OR⁶) R^6 ,

25

and where:-

R^6 is hydrogen, C₁₋₁₂ alkyl or aryl, optionally substituted by one or more of C₁₋₄ alkyl, halogen, C₁₋₄ haloalkyl, OR⁸, SR⁸, NO₂, CN, NR⁸ R^8 , NR⁸COR⁸,

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$\text{NR}^8\text{CONR}^8\text{R}^8$, NR^8COR^8 , $\text{NR}^8\text{CO}_2\text{R}^8$, CO_2R^8 , COR^8 , CONR^8_2 , $\text{S(O)}_2\text{R}^8$,
 SONH_2 , S(O)R^8 , SO_2 NR^8R^8 , $\text{NR}^8\text{S(O)}_2\text{R}^8$, wherein the C_{1-12} alkyl group
 optionally incorporates one or more insertions selected from the group
 consisting of $-\text{O}-$, $-\text{N(R}^8)-$, $-\text{S(O)}-$ and $-\text{S(O)}_2-$, wherein each R^8 may be the
 5 same or different and is as defined below;

R^7 is C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl,
 halogen, C_{1-4} haloalkyl, OR^8 , SR^8 , NO_2 , CN , NR^8R^8 , NR^8COR^8 , $\text{NR}^8\text{CONR}^8\text{R}^8$,
 NR^8COR^8 , $\text{NR}^8\text{CO}_2\text{R}^8$, CO_2R^8 , COR^8 , CONR^8_2 , $\text{S(O)}_2\text{R}^8$, SONH_2 , S(O)R^8 , SO_2
 10 NR^8R^8 , $\text{NR}^8\text{S(O)}_2\text{R}^8$, wherein the C_{1-12} alkyl group optionally incorporates one
 or more insertions selected from the group consisting of $-\text{O}-$, $-\text{N(R}^8)-$, $-\text{S(O)}-$
 and $-\text{S(O)}_2-$, wherein each R^8 may be the same or different and is as defined
 below;

15 R^8 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl, aryl, or heterocyclyl;

X^1 and X^2 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl,
 cycloalkenyl, aryl, heterocyclyl, arylalkyl, heterocyclylalkyl, reduced
 heterocyclyl or reduced heterocyclylalkyl.

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2. A process as claimed in claim 1 wherein the alcohol is isopropyl alcohol.

3. A process as claimed in claim 1 or claim 2 wherein the tertiary amine is triethylamine.

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4. A process as claimed in any one of claims 1 to 3 where the process is carried out at -70°C or below.

5. A product as produced by a process as claimed in any one of claims 1 to 4.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/03402

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07B45/06 C07C319/14 C07C321/14 C07C321/20 C07C321/28
C07C323/09 C07D333/08 C07D487/04
//(C07D487/04,235:00,209:00)

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)

IPC 7 C07B C07C C07D

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, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A.J. MANCUSO, ET AL.: "Activated dimethyl sulphoxide: useful reagents for synthesis" SYNTHESIS, no. 3, March 1981 (1981-03), pages 165-185, XP002260590	1,3,5
Y	GEORG THIEME VERLAG, STUTTGART, DE page 179 - page 181; tables 13,14 ----- -/--	1-5

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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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

10 November 2003

Date of mailing of the international search report

27/11/2003

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INTERNATIONAL SEARCH REPORT

Internat. Application No

PCT/GB 03/03402

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A.J. MANCUSO, ET AL.: "Structure of the diemethyl sulphoxide-oxalyl chloride reaction product. Oxidations of heteroaromatic and diverse alcohols to carbonyl compounds" JOURNAL OF ORGANIC CHEMISTRY, vol. 44, no. 23, 9 November 1979 (1979-11-09), pages 4148-4150, XP002260591 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US	1,3,5
Y	the whole document -----	1-5
Y	G.A. OLAH, ET AL.: "Synthetic methods and reactions; part 56. Deoxygenation of sulphoxides with sodium iodide/oxalyl chloride and related acid chlorides" SYNTHESIS, no. 1, January 1979 (1979-01), pages 58-59, XP002260616 GEORG THIEME VERLAG, STUTTGART, DE the whole document -----	1-5