

NOVEL PROCESS FOR THE PREPARATION OF ACID CHLORIDES

The present invention is directed to a process for the preparation of acid halides which are useful as intermediates in the preparation of pharmaceutically active compounds.

There is provided a process for the preparation of a compound of formula I



wherein

R¹ is hydrogen, C₁-C₈alkyl or C₂-C₈alkenyl which are unsubstituted or substituted by one or more substituents selected from C₁-C₈alkoxy and C₃-C₈cycloalkyl; and R² and R³ are combined with the carbon atom to which they are attached to form C₃-C₇-cycloalkyl or C₅-C₈cycloalkenyl;
comprising reacting a compound of formula II



wherein R¹, R² and R³ have the above meanings;

with thionylchloride in the presence of a tri-C₁-C₅alkylamine and an aliphatic hydrocarbon solvent.

In a first aspect, there is provided a process for the preparation of a compound of formula I



wherein

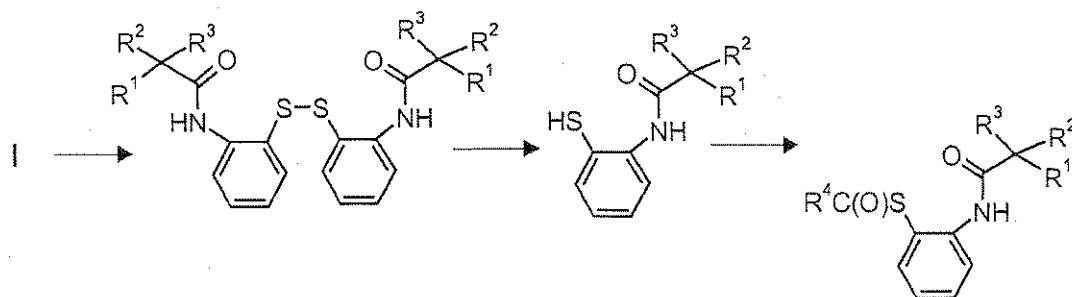
R¹ is hydrogen, C₁-C₈alkyl or C₂-C₈alkenyl which are unsubstituted or substituted by one or more substituents selected from C₁-C₈alkoxy and C₃-C₈cycloalkyl; and R² and R³ are combined with the carbon atom to which they are attached to form C₃-C₇-cycloalkyl or C₅-C₈cycloalkenyl;
comprising reacting a compound of formula II



wherein R¹, R² and R³ have the above meanings;
with thionylchloride in the presence of tributylamine and an aliphatic hydrocarbon solvent.

The compounds of formula I may be used as intermediates in the synthesis of valuable pharmaceutical compounds, e.g. those as described in e.g. EP 1,020,439.

Accordingly, in another embodiment the present disclosure provides a process comprising the synthetic steps represented in the following scheme:



wherein R¹, R² and R³ are as defined above and R⁴ is C₁-C₈alkyl. In particular, the process comprises reacting a compound of formula I with bis(2-aminophenyl)disulfide to acylate the amino groups of the (2-aminophenyl)disulfide, reducing the amino-acylated disulfide product with a reducing agent such as triphenylphosphine, zinc or sodium borohydride to yield the thiol product, and acylating the thiol group in the thiol product with R⁴C(O)Cl.

Hence, in a second aspect, there is provided the process for the preparation of a compound of formula I



wherein

R¹ is hydrogen, C₁-C₈alkyl or C₂-C₈alkenyl which are unsubstituted or substituted by one or more substituents selected from C₁-C₈alkoxy and C₃-C₈cycloalkyl; and R² and R³ are combined with the carbon atom to which they are attached to form C₃-C₇-cycloalkyl or C₅-C₈cycloalkenyl;

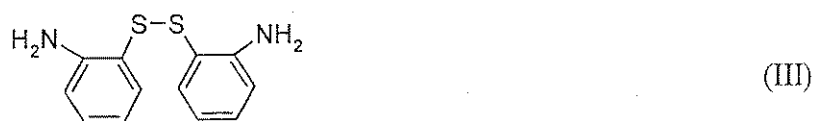
comprising reacting a compound of formula II



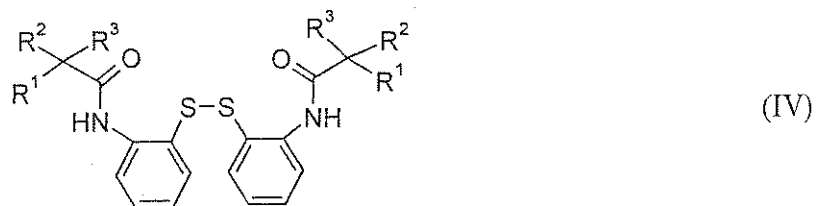
wherein R¹, R² and R³ have the above meanings;

with thionylchloride in the presence of tributylamine and an aliphatic hydrocarbon solvent

additionally comprising the step of acylating a compound of the formula III



with a compound of formula I to yield a compound of formula IV



wherein R¹, R² and R³ are as defined above.

In a third aspect, there is provided the process for the preparation of a compound of formula I



wherein

R^1 is hydrogen, C_1 - C_8 alkyl or C_2 - C_8 alkenyl which are unsubstituted or substituted by one or more substituents selected from C_1 - C_8 alkoxy and C_3 - C_8 cycloalkyl; and R^2 and R^3 are combined with the carbon atom to which they are attached to form C_3 - C_7 -cycloalkyl or C_5 - C_8 cycloalkenyl;
comprising reacting a compound of formula II



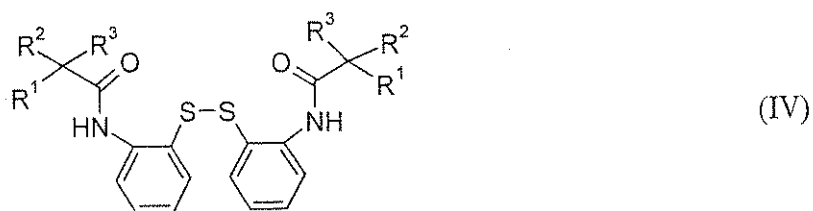
wherein R^1 , R^2 and R^3 have the above meanings;

with thionylchloride in the presence of tributylamine and an aliphatic hydrocarbon solvent

additionally comprising the step of acylating a compound of the formula III



with a compound of formula I to yield a compound of formula IV



additionally comprising the step of reducing the compound of formula IV with a reducing agent to yield a compound of formula V



wherein R^1 , R^2 and R^3 are as defined above.

In a fourth aspect, there is provided the process for the preparation of a compound of formula I



wherein

R^1 is hydrogen, C_1 - C_8 alkyl or C_2 - C_8 alkenyl which are unsubstituted or substituted by one or more substituents selected from C_1 - C_8 alkoxy and C_3 - C_8 cycloalkyl; and R^2 and R^3 are combined with the carbon atom to which they are attached to form C_3 - C_7 -cycloalkyl or C_5 - C_8 cycloalkenyl;
comprising reacting a compound of formula II



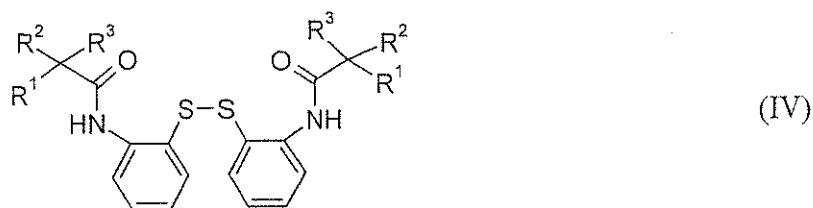
wherein R^1 , R^2 and R^3 have the above meanings;

with thionylchloride in the presence of tributylamine and an aliphatic hydrocarbon solvent

additionally comprising the step of acylating a compound of the formula III



with a compound of formula I to yield a compound of formula IV

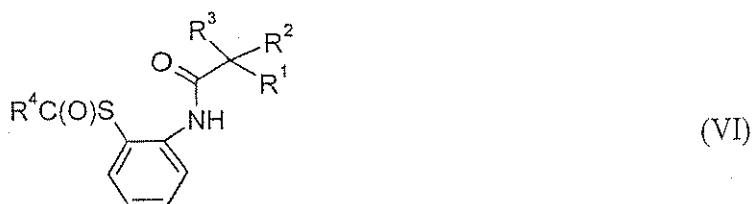


additionally comprising the step of reducing the compound of formula IV with a reducing agent to yield a compound of formula V



wherein R^1 , R^2 and R^3 are as defined above

additionally comprising the step of acylating the compound of formula V with $R^4C(O)Cl$ to yield a compound of formula VI



wherein R^1 , R^2 and R^3 are as defined above and R^4 is C_1 - C_8 alkyl.

The additional steps may be performed, e.g., according to the procedures described in Shinkai et al., J. Med. Chem. 43:3566-3572 (2000).

Examples for C_1 - C_8 alkyl include methyl, ethyl, straight and branched propyl, butyl, pentyl, hexyl, e.g. $CH_2CH(CH_2CH_3)_2$, heptyl and octyl. For R^1 , C_1 - C_8 alkyl is preferably $CH_2CH(CH_2CH_3)_2$. For R^4 , C_1 - C_8 alkyl is preferably isopropyl.

Examples for C_2 - C_8 alkenyl include unsaturated carbon chains containing one or more double bonds at any possible position, e.g. vinyl, allyl, butenyl, pentenyl, hexenyl, heptenyl and octenyl.

Examples for C_3 - C_7 cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Preferred is e.g. cyclohexyl. Examples for C_5 - C_8 cycloalkenyl include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl, cycloheptadienyl and cyclooctadienyl. Preferred are cyclopentenyl, cyclohexenyl and cycloheptenyl.

The term "tri- C_1 - C_5 alkylamine" denotes a compound of formula $R^4N(R^5)R^6$ wherein R^4 , R^5 and R^6 independently are a C_1 - C_8 alkyl, and includes triethylamine, tributylamine, diethyl-methylamine, dimethyl-ethylamine and methylethylbutylamine.

The term "aliphatic hydrocarbon" refers to a branched, straight or cyclic hydrocarbon chain, such as pentane, hexane, heptane, octane, cyclopentane, cyclohexane, or mixtures thereof. The most preferred aliphatic hydrocarbon is heptane.

The process may take place at a temperature in the range from 20 to 60°C, e.g. in a range
5 from 40 to 55°C.

The acylating steps of the present invention are preferably conducted in the presence of a base. Preferred bases include organic bases with N-Methylmorpholine being a preferred organic base.

The amount of thionylchloride in relation to the compound of formula II, in the reaction
10 mixture may be in the range from 1.0 to 2.0 equivalents of thionylchloride, e.g. from 1.0 to 1.2 equivalents, e.g. 1.2 equivalents.

The amount of the tri-C₁-C₅alkylamine in relation to the amount of the compound of formula II may be at a ratio of from 5 mol% to 0.1 mol%, e.g. from 0.3 mol% to 0.5 mol%, e.g. 0.3 mol%.

15 In another aspect the present invention provides a process for the preparation of a compound of formula I as above, comprising reacting a compound of formula II as above in the presence of a tri-C₁-C₅alkylamine and an aliphatic hydrocarbon solvent by continuously adding thionylchloride.

The term "continuously adding" denotes the addition of thionylchloride to a solution of
20 compound II in an aliphatic hydrocarbon solvent, during a period of time from 10 minutes to 5 hours, depending on the batch size. The solution of compound II is heated to the desired temperature prior to the addition of thionylchloride. This method is different from the batch mode where all components are mixed at RT and the mixture is heated to the desired temperature.

25 In one embodiment the present invention provides a process for the preparation of a compound of formula I wherein R¹ is -CH₂CH(CH₂CH₃)₂. In another embodiment the present invention provides a process for the preparation of a compound of formula I wherein the tri-C₁-C₅alkylamine is triethylamine or tributylamine. In a preferred embodiment the present invention provides a process for the preparation of a compound
30 of formula I wherein the tri-C₁-C₅alkylamine is tributylamine. When using tributylamine no precipitation of the hydrochloride salt of the tertiary amine occurs.

The compounds of formula II are commercially available or can be prepared by procedures known to the skilled person.

In general, the nomenclature used in this Application is based on AUTONOMTM v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. Chemical structures shown herein were prepared using ISIS[®] version 2.2. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen atom.

Example: Preparation of 1-(2-Ethyl-butyl)-cyclohexanecarbonyl chloride in the presence of 0.003 Eq. tributylamine and heptane as the solvent.

- 10 A mixture of 6.0 kg (28.3 mol) 1-(2-ethyl-butyl)-cyclohexanecarboxylic acid and 20.6 mL tributylamine (0.085 mmol) in 10 L heptane was warmed to 50°C. 2.5 L (34.5 mol) of thionyl chloride was added during 40 minutes at a temperature of 40-50°C (reaction is endothermic, vigorous gas evolution) and the reaction mixture was kept at 53-55°C. An IPC-control after 60 minutes indicated complete conversion (0.04% 1-(2-ethyl-butyl)-
- 15 cyclohexanecarboxylic acid and no 1-(2-ethyl-butyl)-cyclohexanecarboxylic acid anhydride). After removing volatile components under reduced pressure (70°C bath, 13-8 mbar) 6.86 kg of the residue was obtained (assay 92.5% 1-(2-ethyl-butyl)-cyclohexanecarbonyl chloride, yield 97.2%)

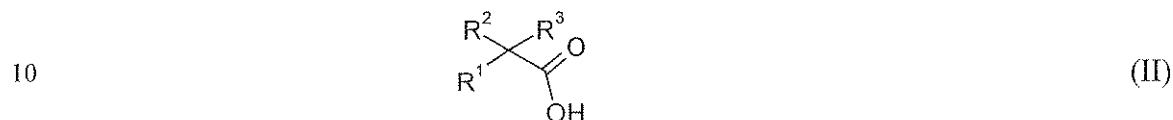
Claims

1. A process for the preparation of a compound of formula I



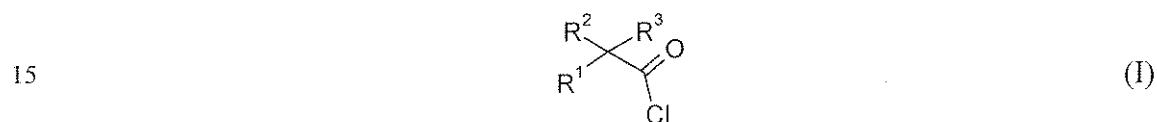
wherein

- 5 R^1 is hydrogen, C_1 - C_8 alkyl or C_2 - C_8 alkenyl which are unsubstituted or substituted by one or more substituents selected from C_1 - C_8 alkoxy and C_3 - C_8 cycloalkyl; and R^2 and R^3 are combined with the carbon atom to which they are attached to form C_3 - C_7 -cycloalkyl or C_5 - C_8 cycloalkenyl;
comprising reacting a compound of formula II



wherein R^1 , R^2 and R^3 have the above meanings;
with thionylchloride in the presence of tributylamine and an aliphatic hydrocarbon solvent.

2. The process for the preparation of a compound of formula I



wherein

- R^1 is hydrogen, C_1 - C_8 alkyl or C_2 - C_8 alkenyl which are unsubstituted or substituted by one or more substituents selected from C_1 - C_8 alkoxy and C_3 - C_8 cycloalkyl; and R^2 and R^3 are combined with the carbon atom to which they are attached to form C_3 - C_7 -cycloalkyl or C_5 - C_8 cycloalkenyl;
20 comprising reacting a compound of formula II



wherein R^1 , R^2 and R^3 have the above meanings;

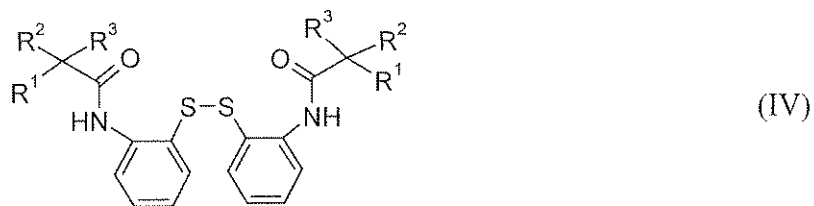
with thionylchloride in the presence of tributylamine and an aliphatic hydrocarbon solvent

additionally comprising the step of acylating a compound of the formula III

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with a compound of formula I to yield a compound of formula IV



wherein R¹, R² and R³ are as defined in claim 1.

3. The process for the preparation of a compound of formula I



wherein

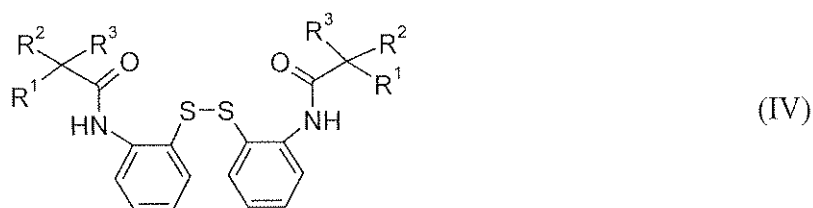
- R^1 is hydrogen, $\text{C}_1\text{-C}_8$ alkyl or $\text{C}_2\text{-C}_8$ alkenyl which are unsubstituted or substituted by one or more substituents selected from $\text{C}_1\text{-C}_8$ alkoxy and $\text{C}_3\text{-C}_8$ cycloalkyl; and R^2 and R^3 are combined with the carbon atom to which they are attached to form $\text{C}_3\text{-C}_7$ -cycloalkyl or $\text{C}_5\text{-C}_8$ cycloalkenyl;
- comprising reacting a compound of formula II



- wherein R^1 , R^2 and R^3 have the above meanings;
- with thionylchloride in the presence of tributylamine and an aliphatic hydrocarbon solvent
- additionally comprising the step of acylating a compound of the formula III



- with a compound of formula I to yield a compound of formula IV



additionally comprising the step of reducing the compound of formula IV with a reducing agent to yield a compound of formula V



- wherein R^1 , R^2 and R^3 are as defined in claim 1.

4. The process for the preparation of a compound of formula I



wherein

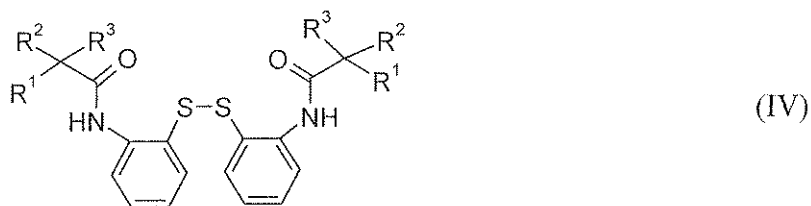
- R^1 is hydrogen, C_1 - C_8 alkyl or C_2 - C_8 alkenyl which are unsubstituted or substituted by one or more substituents selected from C_1 - C_8 alkoxy and C_3 - C_8 cycloalkyl; and R^2 and R^3 are combined with the carbon atom to which they are attached to form C_3 - C_7 -cycloalkyl or C_5 - C_8 cycloalkenyl;
- comprising reacting a compound of formula II



- wherein R^1 , R^2 and R^3 have the above meanings;
- with thionylchloride in the presence of tributylamine and an aliphatic hydrocarbon solvent
- additionally comprising the step of acylating a compound of the formula III



- with a compound of formula I to yield a compound of formula IV

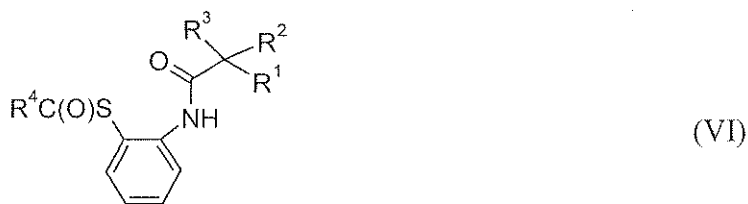


additionally comprising the step of reducing the compound of formula IV with a reducing agent to yield a compound of formula V



- wherein R^1 , R^2 and R^3 are as defined in claim 1

additionally comprising the step of acylating the compound of formula V with $R^4C(O)Cl$ to yield a compound of formula VI



wherein R^1 , R^2 and R^3 are as defined in claim 1 and R^4 is C_1 - C_8 alkyl.

- 5 5. The process according to claim 4 wherein R^4 is isopropyl.
6. The process according to claims 1 to 4 wherein the thionyl chloride is present in the range from 1.0 to 2.0 equivalents of thionylchloride in relation to the compound of formula II.
7. The process according to claims 1 to 4 wherein the amount of the tributylamine in
10 relation to the amount of the compound of formula II is at a ratio of from 5 mol% to 0.1 mol%.
8. The process according to claims 1 to 4 wherein thionylchloride is continuously added.
9. The process according to claims 1 to 4 wherein in formula I, R^2 and R^3 are combined with the carbon atom to which they are attached to form C_3 - C_7 cycloalkyl.
- 15 10. The process according to claims 1 to 4 wherein in formula I, R^1 is $CH_2CH(CH_2CH_3)_2$ and R^2 and R^3 are combined with the carbon atom to which they are attached to form cyclohexyl.

11. The process according to claims 2 and 4 wherein the acylating steps are performed in the presence of a base.
12. The process according to claim 11 wherein the base is an organic base.
13. The process according to claim 12 wherein the organic base is N-methylmorpholine.