WO 00/42851 A discloses the use of medetomidine for inhibition of marine biofouling on surfaces.

The known methods of preparation of medetomidine often use protecting groups, for example triphenylmethyl (trityl) residues, which entails high material consumption and the need for protection/deprotection steps. Consequently, these syntheses are long and expensive. Furthermore rather expensive and non-readily available starting materials are used.

There was a need for a synthetic route, which does not need protecting groups, starts with less expensive substrates, avoids large amounts of waste and has satisfying yields.

In the following text,

halogen means F, Cl, Br or I, preferably Cl, Br or I;

"alkyl" means linear, branched, cyclic or cyclo alkyl, preferably the commonly accepted meaning linear or branched alkyl if not otherwise stated. Examples of "alkyl" include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, and the like;

"cyclic alkyl" or "cyclo alkyl" are intended to include cyclo aliphatic, bicyclo aliphatic and tricycle aliphatic residues;

"alkane" means a linear, branched or cyclic alkane, preferably linear or branched alkane;

"alkanol" means a hydroxyalkane, with alkane having the meaning as defined above also with its preferred embodiments;

Ac	acetyl;
tBu	tertiary butyl;
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
DABCO	1,4-diazabicyclo[2.2.2]octane;
DIPEA	N-ethyl-N,N-diisopropylamine;
DMA	N,N-dimethylacetamide;
DMF	N,N-dimethylformamide;
EDTA-Na_2	ethylene diamine tetraacetic acid disodium;
hexanes	mixture of isomeric hexanes;
NMP	N-methyl-2-pyrrolidone;
OTf	trifluoromethanesulfonate, also known as triflate;

MPS $KHSO_5$, also known as potassium peroxymonosulfate or potassium monopersulfate, and marketed as a triple salt with the formula 2 $KHSO_5$ $KHSO_4$ K_2SO_4 under the trade names Caroat® and Oxone®, therefore $KHSO_5$ is often used in form of this triple salt;

salen ligand obtained from a condensation of salicylaldehyde or of a substituted salicylaldehyde derivative with ethylene diamine or with a substituted ethylene diamine;

sulfamic acid $HO\text{-}SO_2\text{-}NH_2$;

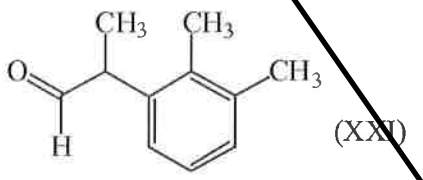
TEMPO 2,2,6,6-tetramethylpiperidine 1-oxyl;

THF tetrahydrofuran;

xylene 1,2-dimethylbenzene, 1,3-dimethylbenzene, 1,4-dimethylbenzene or a mixture thereof;

if not otherwise stated.

Subject of the invention is a method for preparation of medetomidine,
the method comprises a step (N) and a step (M1);
step (M1) comprises a reaction (M1-reac);
reaction (M1-reac) is a reaction between a compound of formula (XXI),



(XXI)

a reagent (M-reag) and a reagent (M-A) in a solvent (M-solv);

reagent (M-reag) is selected from the group consisting of p-toluenesulfonylmethyl isocyanide, trifluoromethanesulfonylmethyl isocyanide, methanesulfonylmethyl isocyanide, benzenesulfonylmethyl isocyanide, 4-acetamidobenzenesulfonylmethyl isocyanide and mixtures thereof;

reagent (M-A) is selected from the group consisting of ammonia, sulfamic acid, p-toluenesulfonamide, benzenesulfonamide, 4-acetamidobenzenesulfonamide,

can be done in the presence of an inert gas, the inert gas is preferably selected from the group consisting of nitrogen, a noble gas and carbon dioxide.

After reaction (N-reac), compound of formula (XXI) can be isolated by standard methods such as evaporation of volatile components, extraction, washing, drying, concentration, filtration, crystallization, distillation, chromatography and any combination thereof.

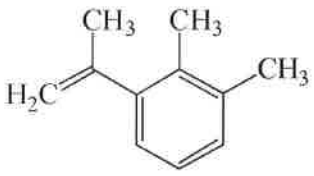
Compound of formula (XXI) can be obtained in step (N) as the aldehyde as depicted in formula (XXI), but also in form of its hydrate or hemiacetal. The hemiacetal of compound of formula (XXI), which can result as product from step (N), can be the product of an addition reaction between the aldehyde as depicted in formula (XXI) and an alcohol selected from the group consisting of tert-butanol and isopropanol, or between the aldehyde as depicted in formula (XXI) and any alcohol which is used during the isolation after reaction (N-reac). Also this hydrate and this hemiacetal can be directly used in step (M1).

When compound of formula (XXI) is obtained from reaction (N-reac) in form of its hydrate or of a hemiacetal, the hydrate or the hemiacetale can be converted into the aldehyde by standard reactions known to the person skilled in the art.

Preferably, compound of formula (XXII) is prepared in a step (O) or in two steps, the two steps are step (O1) and step (O2);

step (O) comprises a reaction (O-reac);

reaction (O-reac) is a reaction of compound of formula (XXIII) with a reagent (O-reag);



(XXIII)

reagent (O-reag) is selected from the group consisting of peracetic acid, trifluoroperacetic acid, perbenzoic acid, 3-chloroperbenzoic acid, monoperphthalic acid, dimethyldioxirane, tert-butylhydroperoxide, dibenzoyl peroxide, cumenehydroperoxide, oxygen, air, sodium hypochlorite, $KHSO_5$, Na_2O_2, aqueous H_2O_2, H_2O_2 dissolved in acetic acid, H_2O_2 dissolved in trifluoroacetic acid, and mixtures thereof;

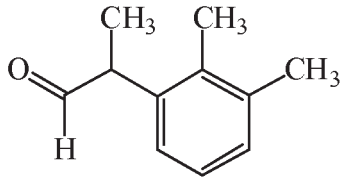
Claims

1. A method for preparation of medetomidine,

the method comprises a step (N) and a step (M1);

step (M1) comprises a reaction (M1-reac);

reaction (M1-reac) is a reaction between a compound of formula (XXI),



(XXI)

a reagent (M-reag) and a reagent (M-A) in a solvent (M-solv);

reagent (M-reag) is selected from the group consisting of p-toluenesulfonylmethyl isocyanide, trifluoromethanesulfonylmethyl isocyanide, methanesulfonylmethyl isocyanide, benzenesulfonylmethyl isocyanide, 4-acetamidobenzenesulfonylmethyl isocyanide and mixtures thereof;

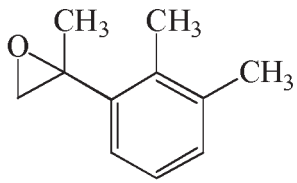
reagent (M-A) is selected from the group consisting of ammonia, sulfamic acid, p-toluenesulfonamide, benzenesulfonamide, 4-acetamidobenzenesulfonamide, tritylamine, formamide, urea, urotropine, ethyl carbamate, acetamide and mixtures thereof;

solvent (M-solv) is selected from the group consisting of N,N-dimethylformamide, C_{1-6} alkanol, formamide, 1,2-dimethoxyethane, NMP, toluene, acetonitrile, propionitrile, ethyl carbamate, N,N-dimethylacetamide, water, acetamide and mixtures thereof;

and wherein compound of formula (XXI) is prepared in the step (N);

step (N) comprises a reaction (N-reac);

reaction (N-reac) is a reaction of compound of formula (XXII) with a catalyst (N-cat);



(XXII)

catalyst (N-cat) is selected from the group consisting of acetic acid, formic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, HCl, HBr, H_2SO_4, HNO_3, H_3PO_4, $HClO_4$, BCl_3, BBr_3, BF_3OEt_2, BF_3SMe_2, BF_3THF, $MgCl_2$, $MgBr_2$, MgI_2, $AlCl_3$, $Al(O\text{-}C_{1\text{-}4}\ alkyl)_3$, $SnCl_4$, $TiCl_4$, $Ti(O\text{-}C_{1\text{-}4}\ alkyl)_4$, $ZrCl_4$, Bi_2O_3, $BiCl_3$, $ZnCl_2$, $PbCl_2$, $FeCl_3$, $ScCl_3$, $NiCl_2$, $Yb(OTf)_3$, $Yb(Cl)_3$, $GaCl_3$, $AlBr_3$, $Ce(OTf)_3$, LiCl, $Cu(BF_4)_2$, $Cu(OTf)_2$, $NiBr_2(PPh_3)_2$, $NiBr_2$, $NiCl_2$, $Pd(OAc)_2$, $PdCl_2$, $PtCl_2$, $InCl_3$, acidic inorganic solid substance, acidic ion exchange resin, carbon treated with inorganic acid and mixtures thereof.

2. Method according to claim 1, wherein reagent (M-reag) is selected from the group consisting of p-toluenesulfonylmethyl isocyanide, benzenesulfonylmethyl isocyanide and mixtures thereof.

3. Method according to claim 1 or 2, wherein reagent (M-A) is selected from the group consisting of ammonia, sulfamic acid, p-toluenesulfonamide, benzenesulfonamide, 4-acetamidobenzenesulfonamide, tritylamine, formamide and mixtures thereof.

4. Method according to one or more of claims 1 to 3, wherein solvent (M-solv) is selected from the group consisting of N,N-dimethylformamide, methanol, ethanol, n-propanol, isopropanol, butanol, pentanol, hexanol, water, formamide, 1,2-dimethoxyethane, NMP, toluene, acetonitrile, propionitrile, ethyl carbamate, N,N-dimethylacetamide, acetamide and mixtures thereof.

5. Method according to one or more of claims 1 to 4, wherein reaction (M1-reac) is done in the presence of a compound (M-comp), compound (M-comp) is selected from the group consisting of ammonia, tritylamine, NaCN, KCN, piperidine, DBU, DABCO, triethylamine, tributylamine, 4-dimethylaminopyridine, pyridine, tBuOK, tBuONa, $NaHCO_3$, Na_2CO_3, $(NH_4)HCO_3$, $(NH_4)_2CO_3$, $KHCO_3$, K_2CO_3, NaOAc, KOAc, NaOH, KOH, $Ca(OH)_2$, KF and mixtures thereof.

6. Method according to claim 5, wherein compound (M-comp) is selected from the group consisting of ammonia, tritylamine, NaCN, KCN, piperidine, tBuOK, tBuONa, KOH, K_2CO_3, Na_2CO_3, KF and mixtures thereof.

7. Method according to one or more of claims 1 to 6, wherein compound of formula (XXI) is first reacted with reagent (M-reag) and then reagent (M-A) added;

or

compound of formula (XXI) is first reacted with reagent (M-A) and then reagent (M-reag) added;

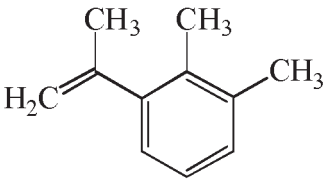
or

compound of formula (XXI) is simultaneously reacted with reagent (M-reag) and with reagent (M-A).

8. Method according to one or more of claims 1 to 7, wherein the catalyst (N-cat) is selected from the group consisting of acetic acid, formic acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, HCl, HBr, H_2SO_4, H_3PO_4, BCl_3, BF_3OEt_2, $MgCl_2$, $MgBr_2$, $AlCl_3$, $ZnCl_2$, $Cu(BF_4)_2$, aluminosilicates, acidic ion exchange resins, carbon treated with HCl, H_2SO_4 or HNO_3, and mixtures thereof.

9. Method according to one or more of claims 1 or 8, wherein reaction (N-reac) is done in a solvent (N-solv);
solvent (N-solv) is selected from the group consisting of water, tert-butanol, isopropanol, acetonitrile, propionitrile, THF, methyl-THF, NMP, dioxane, 1,2-dimethoxyethane, dichloromethane, 1,2-dichloroethane, chloroform, toluene, benzene, chlorobenzene, hexane, cyclohexane, ethyl acetate, acetic acid, formic acid, trifluoroacetic acid and mixtures thereof.

10. Method according to one or more of claims 1 to 9, wherein compound of formula (XXII) is prepared in a step (O) or in two steps, the two steps are step (O1) and step (O2);
step (O) comprises a reaction (O-reac);
reaction (O-reac) is a reaction of compound of formula (XXIII), with a reagent (O-reag);



(XXIII)

reagent (O-reag) is selected from the group consisting of peracetic acid, trifluoroperacetic acid, perbenzoic acid, 3-chloroperbenzoic acid, monoperphthalic acid, dimethyldioxirane,

tert-butylhydroperoxide, dibenzoyl peroxide, cumenehydroperoxide, oxygen, air, sodium hypochlorite, $KHSO_5$, Na_2O_2, aqueous H_2O_2, H_2O_2 dissolved in acetic acid, H_2O_2 dissolved in trifluoroacetic acid, and mixtures thereof;

step (O1) comprises a reaction (O1-reac);

reaction (O1-reac) is a reaction of compound of formula (XXIII) with water and with a compound (O1-comp);

compound (O1-comp) is selected from the group consisting of bromine, N-bromosuccinimide, chlorine, N-chlorosuccinimide, iodine, N-iodosuccinimide, IBr, BrCl, and mixtures thereof;

step (O2) comprises a reaction (O2-reac);

reaction (O2-reac) is a reaction of the reaction product from reaction (O1-reac) with a base (O2-base);

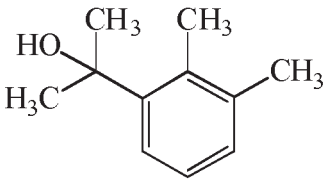
base (O2-base) is selected from the group consisting of sodium hydroxide, potassium hydroxide, calcium hydroxide and mixture thereof.

11. Method according to claim 10, wherein reagent (O-reag) is selected from the group consisting of peracetic acid, tert-butylhydroperoxide, oxygen, air, sodium hypochlorite, aqueous H_2O_2, H_2O_2 dissolved in acetic acid, H_2O_2 dissolved in trifluoroacetic acid, and mixtures thereof.

12. Method according to claim 10 or 11, wherein compound of formula (XXIII) is prepared in a step (P);

step (P) comprises a reaction (P-reac);

in reaction (P-reac) the compound of formula (XXIV) is exposed to a temperature (P-temp);

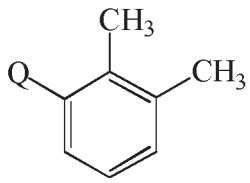


(XXIV)

temperature (P-temp) is from 0 to 300 °C.

13. Method according to claim 12, wherein compound of formula (XXIV) is prepared in three steps, the three steps are a step (Q1), a step (Q2) and a step (Q3);

step (Q1) comprises a reaction (Q1-reac) by a reaction of compound of formula (XXV) with a reagent (Q1-reag);



(XXV)

Q is Br, Cl, or I;

reagent (Q1-reag) is selected from the group consisting of lithium, magnesium, aluminum, zinc, calcium, isopropylmagnesium chloride, isopropylmagnesium bromide, butyllithium, sec-butyllithium and mixtures thereof;

step (Q2) comprises a reaction (Q2-reac);

reaction (Q2-reac) is a reaction of the reaction product of reaction (Q1-reac) with acetone;

in step (Q3) comprises a reaction (Q3-reac);

reaction (Q3-reac) is a reaction of the reaction product of reaction (Q2-reac) with a reagent (Q3-reag);

reagent (Q3-reag) is selected from the group consisting of water, methanol, ethanol, oxalic acid, citric acid, NH_4Cl, HCl, HBr, HNO_3, H_2SO_4, H_3PO_4, acetic acid, propionic acid, formic acid and mixtures thereof.

WO 00/42851 A discloses the use of medetomidine for inhibition of marine biofouling on surfaces.

The known methods of preparation of medetomidine often use protecting groups, for example triphenylmethyl (trityl) residues, which entails high material consumption and the need for protection/deprotection steps. Consequently, these syntheses are long and expensive. Furthermore rather expensive and non-readily available starting materials are used.

There was a need for a synthetic route, which does not need protecting groups, starts with less expensive substrates, avoids large amounts of waste and has satisfying yields.

In the following text,

halogen means F, Cl, Br or I, preferably Cl, Br or I;

"alkyl" means linear or branched alkyl; if not otherwise stated. Examples of "alkyl" include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, and the like;

"cyclic alkyl" or "cyclo alkyl" are intended to include cyclo aliphatic, bicyclo aliphatic and tricycle aliphatic residues;

"alkane" means a linear or branched alkane;

"alkanol" means a hydroxyalkane, with alkane having the meaning as defined above also with its preferred embodiments;

Ac	acetyl;
tBu	tertiary butyl;
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
DABCO	1,4-diazabicyclo[2.2.2]octane;
DIPEA	N-ethyl-N,N-diisopropylamine;
DMA	N,N-dimethylacetamide;
DMF	N,N-dimethylformamide;
EDTA-Na_2	ethylene diamine tetraacetic acid disodium;
hexanes	mixture of isomeric hexanes;
NMP	N-methyl-2-pyrrolidone;
OTf	trifluoromethanesulfonate, also known as triflate;

MPS $KHSO_5$, also known as potassium peroxymonosulfate or potassium monopersulfate, and marketed as a triple salt with the formula 2 $KHSO_5$ $KHSO_4$ K_2SO_4 under the trade names Caroat® and Oxone®, therefore $KHSO_5$ is often used in form of this triple salt;

salen ligand obtained from a condensation of salicylaldehyde or of a substituted salicylaldehyde derivative with ethylene diamine or with a substituted ethylene diamine;

sulfamic acid $HO\text{-}SO_2\text{-}NH_2$;

TEMPO 2,2,6,6-tetramethylpiperidine 1-oxyl;

THF tetrahydrofuran;

xylene 1,2-dimethylbenzene, 1,3-dimethylbenzene, 1,4-dimethylbenzene or a mixture thereof;

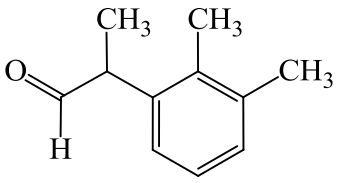
if not otherwise stated.

Subject of the invention is a method for preparation of medetomidine,

the method comprises a step (N) and a step (M1);

step (M1) comprises a reaction (M1-reac);

reaction (M1-reac) is a reaction between a compound selected from the group consisting of compound of formula (XXI), the hydrate of compound of formula (XXI) and a hemiacetal of compound of formula (XXI),



(XXI)

said hemiacetal of compound of formula (XXI) being the product of an addition reaction between the aldehyde as depicted in formula (XXI) and an alcohol selected from the group consisting of tert-butanol and isopropanol,

and a reagent (M-reag) and a reagent (M-A) in a solvent (M-solv);

reagent (M-reag) is selected from the group consisting of p-toluenesulfonylmethyl isocyanide, trifluoromethanesulfonylmethyl isocyanide, methanesulfonylmethyl isocyanide, benzenesulfonylmethyl isocyanide, 4-acetamidobenzenesulfonylmethyl isocyanide and mixtures thereof;

reagent (M-A) is selected from the group consisting of ammonia, sulfamic acid, p-toluenesulfonamide, benzenesulfonamide, 4-acetamidobenzenesulfonamide,

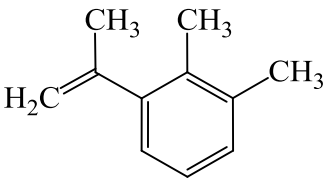
can be done in the presence of an inert gas, the inert gas is preferably selected from the group consisting of nitrogen, a noble gas and carbon dioxide.

After reaction (N-reac), compound of formula (XXI) can be isolated by standard methods such as evaporation of volatile components, extraction, washing, drying, concentration, filtration, crystallization, distillation, chromatography and any combination thereof.

Compound of formula (XXI) can be obtained in step (N) as the aldehyde as depicted in formula (XXI), but also in form of its hydrate or hemiacetal. The hemiacetal of compound of formula (XXI), which can result as product from step (N), can be the product of an addition reaction between the aldehyde as depicted in formula (XXI) and an alcohol selected from the group consisting of tert-butanol and isopropanol.
Also this hydrate and this hemiacetal can be directly used in step (M1).

When compound of formula (XXI) is obtained from reaction (N-reac) in form of its hydrate or of a hemiacetal, the hydrate or the hemiacetale can be converted into the aldehyde by standard reactions known to the person skilled in the art.

Preferably, compound of formula (XXII) is prepared in a step (O) or in two steps, the two steps are step (O1) and step (O2);
step (O) comprises a reaction (O-reac);
reaction (O-reac) is a reaction of compound of formula (XXIII), with a reagent (O-reag);



(XXIII)

reagent (O-reag) is selected from the group consisting of peracetic acid, trifluoroperacetic acid, perbenzoic acid, 3-chloroperbenzoic acid, monoperphthalic acid, dimethyldioxirane, tert-butylhydroperoxide, dibenzoyl peroxide, cumenehydroperoxide, oxygen, air, sodium hypochlorite, $KHSO_5$, Na_2O_2, aqueous H_2O_2, H_2O_2 dissolved in acetic acid, H_2O_2 dissolved in trifluoroacetic acid, and mixtures thereof;

Claims

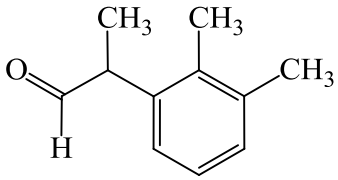
1. A method for preparation of medetomidine,

the method comprises a step (N) and a step (M1);

step (M1) comprises a reaction (M1-reac);

reaction (M1-reac) is a reaction between

a compound selected from the group consisting of compound of formula (XXI), the hydrate of compound of formula (XXI) and a hemiacetal of compound of formula (XXI),



(XXI)

said hemiacetal of compound of formula (XXI) being the product of an addition reaction between the aldehyde as depicted in formula (XXI) and an alcohol selected from the group consisting of tert-butanol and isopropanol,

and a reagent (M-reag) and a reagent (M-A) in a solvent (M-solv);

reagent (M-reag) is selected from the group consisting of p-toluenesulfonylmethyl isocyanide, trifluoromethanesulfonylmethyl isocyanide, methanesulfonylmethyl isocyanide, benzenesulfonylmethyl isocyanide, 4-acetamidobenzenesulfonylmethyl isocyanide and mixtures thereof;

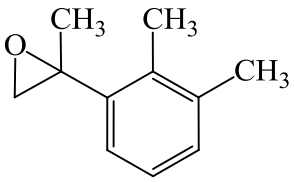
reagent (M-A) is selected from the group consisting of ammonia, sulfamic acid, p-toluenesulfonamide, benzenesulfonamide, 4-acetamidobenzenesulfonamide, tritylamine, formamide, urea, urotropine, ethyl carbamate, acetamide and mixtures thereof;

solvent (M-solv) is selected from the group consisting of N,N-dimethylformamide, C_{1-6} alkanol, formamide, 1,2-dimethoxyethane, NMP, toluene, acetonitrile, propionitrile, ethyl carbamate, N,N-dimethylacetamide, water, acetamide and mixtures thereof;

and wherein compound of formula (XXI) is prepared in the step (N);

step (N) comprises a reaction (N-reac);

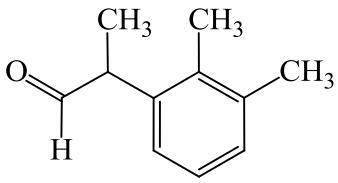
reaction (N-reac) is a reaction of compound of formula (XXII) with a catalyst (N-cat);



(XXII)

catalyst (N-cat) is selected from the group consisting of acetic acid, formic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, HCl, HBr, H_2SO_4, HNO_3, H_3PO_4, $HClO_4$, BCl_3, BBr_3, BF_3OEt_2, BF_3SMe_2, BF_3THF, $MgCl_2$, $MgBr_2$, MgI_2, $AlCl_3$, $Al(O\text{-}C_{1\text{-}4}\ alkyl)_3$, $SnCl_4$, $TiCl_4$, $Ti(O\text{-}C_{1\text{-}4}\ alkyl)_4$, $ZrCl_4$, Bi_2O_3, $BiCl_3$, $ZnCl_2$, $PbCl_2$, $FeCl_3$, $ScCl_3$, $NiCl_2$, $Yb(OTf)_3$, $Yb(Cl)_3$, $GaCl_3$, $AlBr_3$, $Ce(OTf)_3$, LiCl, $Cu(BF_4)_2$, $Cu(OTf)_2$, $NiBr_2(PPh_3)_2$, $NiBr_2$, $NiCl_2$, $Pd(OAc)_2$, $PdCl_2$, $PtCl_2$, $InCl_3$, acidic inorganic solid substance, acidic ion exchange resin, carbon treated with inorganic acid and mixtures thereof.

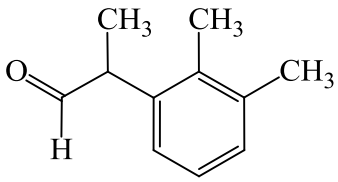
2. Method according to claim 1, wherein
reaction (M1-reac) is a reaction between
a compound of formula (XXI) or the hydrate of compound of formula (XXI),



(XXI)

and a reagent (M-reag) and a reagent (M-A) in a solvent (M-solv).

3. Method according to claim 1 or 2, wherein
reaction (M1-reac) is a reaction between
a compound of formula (XXI),



(XXI)

and a reagent (M-reag) and a reagent (M-A) in a solvent (M-solv).

4. Method according to one or more of claims 1 to 3, wherein reagent (M-reag) is selected from the group consisting of p-toluenesulfonylmethyl isocyanide, benzenesulfonylmethyl isocyanide and mixtures thereof.

5. Method according to one or more of claims 1 to 4, wherein reagent (M-A) is selected from the group consisting of ammonia, sulfamic acid, p-toluenesulfonamide, benzenesulfonamide, 4-acetamidobenzenesulfonamide, tritylamine, formamide and mixtures thereof.

6. Method according to one or more of claims 1 to 5, wherein solvent (M-solv) is selected from the group consisting of N,N-dimethylformamide, methanol, ethanol, n-propanol, isopropanol, butanol, pentanol, hexanol, water, formamide, 1,2-dimethoxyethane, NMP, toluene, acetonitrile, propionitrile, ethyl carbamate, N,N-dimethylacetamide, acetamide and mixtures thereof.

7. Method according to one or more of claims 1 to 6, wherein reaction (M1-reac) is done in the presence of a compound (M-comp), compound (M-comp) is selected from the group consisting of ammonia, tritylamine, NaCN, KCN, piperidine, DBU, DABCO, triethylamine, tributylamine, 4-dimethylaminopyridine, pyridine, tBuOK, tBuONa, $NaHCO_3$, Na_2CO_3, $(NH_4)HCO_3$, $(NH_4)_2CO_3$, $KHCO_3$, K_2CO_3, NaOAc, KOAc, NaOH, KOH, $Ca(OH)_2$, KF and mixtures thereof.

8. Method according to claim 7, wherein compound (M-comp) is selected from the group consisting of ammonia, tritylamine, NaCN, KCN, piperidine, tBuOK, tBuONa, KOH, K_2CO_3, Na_2CO_3, KF and mixtures thereof.

9. Method according to one or more of claims 1 to 8, wherein compound of formula (XXI) is first reacted with reagent (M-reag) and then reagent (M-A) added;

or

compound of formula (XXI) is first reacted with reagent (M-A) and then reagent (M-reag) added;

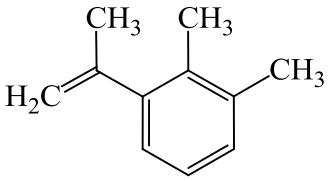
or

compound of formula (XXI) is simultaneously reacted with reagent (M-reag) and with reagent (M-A).

10. Method according to one or more of claims 1 to 9, wherein the catalyst (N-cat) is selected from the group consisting of acetic acid, formic acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, HCl, HBr, H_2SO_4, H_3PO_4, BCl_3, BF_3OEt_2, $MgCl_2$, $MgBr_2$, $AlCl_3$, $ZnCl_2$, $Cu(BF_4)_2$, aluminosilicates, acidic ion exchange resins, carbon treated with HCl, H_2SO_4 or HNO_3, and mixtures thereof.

11. Method according to one or more of claims 1 or 10, wherein reaction (N-reac) is done in a solvent (N-solv);
solvent (N-solv) is selected from the group consisting of water, tert-butanol, isopropanol, acetonitrile, propionitrile, THF, methyl-THF, NMP, dioxane, 1,2-dimethoxyethane, dichloromethane, 1,2-dichloroethane, chloroform, toluene, benzene, chlorobenzene, hexane, cyclohexane, ethyl acetate, acetic acid, formic acid, trifluoroacetic acid and mixtures thereof.

12. Method according to one or more of claims 1 to 11, wherein compound of formula (XXII) is prepared in a step (O) or in two steps, the two steps are step (O1) and step (O2);
step (O) comprises a reaction (O-reac);
reaction (O-reac) is a reaction of compound of formula (XXIII), with a reagent (O-reag);


(XXIII)

reagent (O-reag) is selected from the group consisting of peracetic acid, trifluoroperacetic acid, perbenzoic acid, 3-chloroperbenzoic acid, monoperphthalic acid, dimethyldioxirane, tert-butylhydroperoxide, dibenzoyl peroxide, cumenehydroperoxide, oxygen, air, sodium hypochlorite, $KHSO_5$, Na_2O_2, aqueous H_2O_2, H_2O_2 dissolved in acetic acid, H_2O_2 dissolved in trifluoroacetic acid, and mixtures thereof;

step (O1) comprises a reaction (O1-reac);
reaction (O1-reac) is a reaction of compound of formula (XXIII) with water and with a compound (O1-comp);
compound (O1-comp) is selected from the group consisting of bromine, N-bromosuccinimide, chlorine, N-chlorosuccinimide, iodine, N-iodosuccinimide, IBr, BrCl, and mixtures thereof;

step (O2) comprises a reaction (O2-reac);

reaction (O2-reac) is a reaction of the reaction product from reaction (O1-reac) with a base (O2-base);

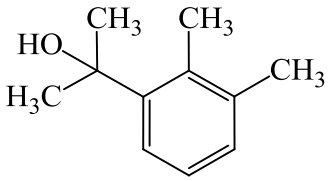
base (O2-base) is selected from the group consisting of sodium hydroxide, potassium hydroxide, calcium hydroxide and mixture thereof.

13. Method according to claim 12, wherein reagent (O-reag) is selected from the group consisting of peracetic acid, tert-butylhydroperoxide, oxygen, air, sodium hypochlorite, aqueous H_2O_2, H_2O_2 dissolved in acetic acid, H_2O_2 dissolved in trifluoroacetic acid, and mixtures thereof.

14. Method according to claim 12 or 13, wherein compound of formula (XXIII) is prepared in a step (P);

step (P) comprises a reaction (P-reac);

in reaction (P-reac) the compound of formula (XXIV) is exposed to a temperature (P-temp);

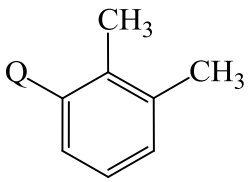


(XXIV)

temperature (P-temp) is from 0 to 300 °C.

15. Method according to claim 14, wherein compound of formula (XXIV) is prepared in three steps, the three steps are a step (Q1), a step (Q2) and a step (Q3);

step (Q1) comprises a reaction (Q1-reac) by a reaction of compound of formula (XXV) with a reagent (Q1-reag);



(XXV)

Q is Br, Cl, or I;

reagent (Q1-reag) is selected from the group consisting of lithium, magnesium, aluminum, zinc, calcium, isopropylmagnesium chloride, isopropylmagnesium bromide, butyllithium, sec-butyllithium and mixtures thereof;

step (Q2) comprises a reaction (Q2-reac);
reaction (Q2-reac) is a reaction of the reaction product of reaction (Q1-reac) with acetone;

in step (Q3) comprises a reaction (Q3-reac);
reaction (Q3-reac) is a reaction of the reaction product of reaction (Q2-reac) with a reagent (Q3-reag);

reagent (Q3-reag) is selected from the group consisting of water, methanol, ethanol, oxalic acid, citric acid, NH_4Cl, HCl, HBr, HNO_3, H_2SO_4, H_3PO_4, acetic acid, propionic acid, formic acid and mixtures thereof.