The present invention is directed to compounds of Formula III

\[
\text{Formula III}
\]

wherein the R1-R7 groups or substituents are defined herein.

The present invention also comprises improved methods in the preparation of oxazoles in which the compounds of Formula III are intermediates and which results in higher yields with less impurities and contaminants. Oxazoles constitute valuable intermediates in the synthesis of pharmacologically active substances such as, for example peroxisome proliferator activated receptor (PPAR) agonists which are pharmaceutical actives which can have a positive influence on both lipid and glucose metabolism.
NOVEL INTERMEDIATE COMPOUNDS
USEFUL IN THE PREPARATION OF
OXAZOLES AND PHARMACEUTICAL
ACTIVES FOR THE REGULATION OF LIPID
AND GLUCOSE METABOLISM

CROSS-REFERENCE TO RELATED
APPLICATIONS


FIELD OF THE INVENTION

[0002] The invention relates generally to intermediate compounds produced during the reaction sequence of a process for the preparation of pharmaceutical actives for the regulation of lipid and/or glucose metabolism. The intermediate compounds that are precursors to the final product are also useful in the improved methods for the preparation of oxazoles which results in higher yields with less impurities and contaminants. Oxazoles constitute valuable intermediates in the synthesis of pharmacologically active substances such as, for example peroxisome proliferator activated receptor (PPAR) agonists.

BACKGROUND OF THE INVENTION

[0003] The intermediate compounds of the present invention allow for the preparation of oxazoles in high yield and great purity. Oxazoles constitute valuable intermediates in the synthesis of pharmacologically active substances, for example PPAR agonists. Appropriate examples of PPAR agonists are described, inter alia, in WO 03/020269, WO 2004/075815, WO 2004/076447, WO 2004/076428, WO 2004/076426, WO 2004/076427, DE 102004035533.0, DE 102004035532.2, DE 102004039509.8, all of which are incorporated by reference herein. The latter are pharmaceutical actives which can have a positive influence both on lipid metabolism and on glucose metabolism.

[0004] The condensation of aromatic aldehydes with α-ketoimines to give N-oxides and the subsequent reaction with activated acid derivatives to give oxazoles is a reaction well known in the art.

[0005] For the conversion of the N-oxides to the oxazoles, the literature describes the reagents phosphorus (III) chloride (PCl₃) and phosphorus oxychloride (POCl₃) and, in one variant, acetic anhydride ((CH₃ COO)₂O) (Y. Goto, M. Yamazaki, M. Hamana, Chem Pharm Bull. 19 (1971) 2050, and literature cited there). These reagents are not widely applicable and often lead to no products or to highly contaminated products which can only be obtained in sufficient purity with low yields in a costly and inconvenient manner, for example by chromatographic processes.

[0006] The reaction conditions described require the isolation of the N-oxides. For N-oxides with exothermic decomposition potential, this constitutes a considerable safety risk and prevents the process from being practiced on the industrial scale.

[0007] It has now been found that, surprisingly, the transformation of the N-oxides to the halomethylxoxoazoles proceeds unexpectedly smoothly with high yield and great purity with inorganic thionyl halides or organic sulfonyl halides.

[0008] Although it was unexpected on the basis of the remarks in the literature, halomethyl-oxazoles in some cases precipitate cleanly directly out of the reaction mixture in the form of the free base or as salts.

[0009] Unexpectedly, for N-oxides with exothermic decomposition potential, it has been possible to achieve both safe preparation in dilute solution and the further direct reaction of the solution to give the halo-methylloxazoles.

SUMMARY OF THE INVENTION

[0010] The invention relates to chemical intermediates prepared during the process for the preparation of oxazoles by the condensation of aldehydes with α-ketoimines to give N-oxides in the form of their salts or as free bases. These compounds are then subsequently reacted with activated acid derivatives to give oxazoles in the form of their salts or free bases. More specifically, the present invention comprises a series of intermediate compounds produced during the condensation reaction between aromatic aldehydes and α-ketoimines followed by the reaction of inorganic thionyl halides or organic sulfonyl halides to produce higher, purer yields of chloromethylxoxoazoles.

DETAILED DESCRIPTION OF THE INVENTION

[0011] The present invention comprises intermediate compounds of formula III derived during the reaction steps of an improved process for the preparation of compounds of formula IV. This arises by means of conversion of aromatic aldehydes of the formula I using α-ketoimines of the formula II via N-oxides of the formula III to produce the halomethylxoxoazoles of the formula IV,
which comprises converting the aromatic aldehydes of the formula I using the α-ketoimines of the formula II

in which:

[0012] R¹ is selected from the group consisting of H, (C1-C6)-alkyl, F, Cl, Br, I, O—(C0-C8)-alkylene-H, CF₃, OCF₃, SF₅, OCF₂—CHF₂ and (C6-C10)-aryl, O—(C1-C4)-alkylene-(C6-C10)-aryl, NO₂, COOR¹, CONR¹R¹R¹, SH, or NR¹R¹R¹R¹, wherein aryl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl or CF₃;

[0013] wherein

[0014] R² is selected from the group consisting of H, Li, Na, K, ½Mg, ½Ca, ammonium ions which are un-substituted or mono-, di- or tri-substituted by (C1-C8)-alkyl, or is (C1-C8)-alkyl;

[0015] R⁰ and R¹ are each independently selected from the group consisting of H, (C1-C8)-alkyl, phenyl or CH₂-phenyl, wherein phenyl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl or CF₃;

[0016] or

[0017] R⁰ and R¹ together are (C4-C5)-alkylene, wherein one CH₂ group may be replaced by O, S, NH, N—CH₃ or N-benzyl;

[0018] R² is selected from the group consisting of H, (C1-C6)-alkyl, F, Cl, Br, I, O—(C0-C8)-alkylene-H, CF₃, OCF₃, SF₅, OCF₂—CHF₂, (C6-C10)-aryl, O—(C1-C4)-alkylene-(C6-C10)-aryl, NO₂, COOR², CONR²R²R², SH, or NR²R²R²R², wherein aryl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl and CF₃;

[0019] wherein R⁰, R¹⁰ and R¹¹ are each as defined above;

[0020] R³ is selected from the group consisting of H, (C1-C6)-alkyl, F, Cl, Br, I, O—(C0-C8)-alkylene-H, CF₃, OCF₃, SF₅, OCF₂—CHF₂, (C6-C10)-aryl, O—(C1-C4)-alkylene-(C6-C10)-aryl, NO₂, COOR³, CONR³R³R³, SH, or NR³R³R³R³, wherein aryl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl or CF₃;

[0021] wherein

[0022] W is O, S or NR², if o=0;

[0023] or

[0024] R¹² is selected from the group consisting of H, (C1-C6)-alkyl, (C1-C6)-alkylamino, phenyl;

[0025] R⁴ is selected from the group consisting of H, (C1-C8)-alkyl, (C3-C8)-cycloalkyl, (C1-C3)-alkylene-(C3-C8)-cycloalkyl, phenyl, (C1-C3)-alkylene-phenyl, (C5-C6)-heterocarb, (C1-C3)-alkylene-(C5-C6)-heterocarboxyl or (C1-C3)-alkyl which is fully or partly substituted by F, or COOR⁴, CONR⁴R⁴R⁴;

[0026] wherein R⁴, R¹⁰ and R¹¹ are each as defined above;

[0027] R⁴ and R⁵ are each independently selected from the group consisting of (C1-C8)-alkyl, F, Cl, Br, I, O—(C0-C8)-alkylene-H, O—(C6-C10)-aryl, O—(C1-C4)-alkylene-(C6-C10)-aryl, COOR⁴, CONR⁴R⁴R⁴, SH and NR⁴R⁴R⁴R⁴;

[0028] wherein R⁴ and R⁵ are each as defined above;

or,

R⁵ and R⁶ together are selected from the group consisting of (C4-C5)-alkylene, in which one —CH₃ group may be replaced by O, S, NH, CH₂—CH₃ or N-benzyl;

R⁶ is selected from the group consisting of H or (C1-C8)-alkyl;

[0029] in the presence of one or more acids HX selected from the group consisting of HCl, HBr, H₂SO₄, H₃PO₄, HOOCCF₃, HOOCCH₂CH₂OH, HOOCCH₂CH₃, HO₂SC₂H₃, HO₂S—CH₂—CH₂—CH₃, HOOCCH₂Cl, to the N-oxides of the formula III

in which R¹¹ is 0, 1, ½ or ¾;
and wherein the latter is subsequently reacted with the reagent R²X² which is a compound selected from the group consisting of:

\[ \text{SOCl} \rightarrow \text{Cl}, \quad \text{SOBr} \rightarrow \text{Br}, \quad \text{CH}_2\text{SO}_2 \rightarrow \text{Cl}, \quad \text{CF}_3\text{SO}_2 \rightarrow \text{Cl}, \quad \text{C}_6\text{H}_5\text{SO}_2 \rightarrow \text{Cl}, \quad \text{p-CH}_3\text{C}_6\text{H}_4\text{SO}_2 \rightarrow \text{Cl}, \quad \text{CH}_3\text{SO}_2 \rightarrow \text{O}_x\text{SCH}_3, \quad \text{CF}_3\text{SO}_2 \rightarrow \text{O}_x\text{SCF}_3, \quad \text{C}_6\text{H}_5\text{SO}_2 \rightarrow \text{O}_x\text{SC}_6\text{H}_5, \quad \text{or} \quad \text{p-CH}_3\text{C}_6\text{H}_4\text{SO}_2 \rightarrow \text{O}_x\text{S-C}_6\text{H}_5-p-\text{CH}_3. \]

[0029] to give the halomethylaxoxoles of the formula IV

\[ \text{IV} \]

wherein R¹, R², R³, R⁴, R⁵, R⁶ and X² are each as defined above and

X³ is Cl, Br, CH₂SO₃, CF₃SO₃, C₆H₅SO₃ or p-CH₃C₆H₄SO₃ and

[0030] n₂ is 0 or 1.

[0031] Preferably, the invention relates to the compounds of the formula III in which:

W–CH and

[0032] o–1.

[0033] More preferably, the invention further relates to compounds of formula III in which:

[0034] R¹ is H;

[0035] R² is selected from the group consisting of H, (C₁–C₆)-alkyl, F, Cl, Br, I, O–(C₀-C₈)-alkylene-H, CF₃, OCF₃, SCF₃, SF₅, OCF₂-CHF₂, (C₆-C₁₀)-aryl, O–(C₆-C₁₀)-aryl, O–(C₁-C₄)-alkylene-(C₁-C₆)-aryl, NO₂, COOR², CONR¹O⁻R²⁻, SH, or NR¹²R⁴⁻, wherein ary is unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O–(C₁-C₄)-alkyl or CF₃;

[0036] wherein

[0037] R³ is selected from the group consisting of H, Li, Na, K, Mg, Ca, ammonium ions which are unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O–(C₁-C₄)-alkyl or CF₃;

[0038] R⁴ and R⁵ are each independently selected from the group consisting of H, (C₁-C₅)-alkyl, phenyl or CH₃-phenyl.

[0039] where phenyl is unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O–(C₁-C₄)-alkyl or CF₃;

[0040] or

[0041] R⁴ and R⁵ together are (C₄-C₅)-alkylene, in which one CH₂ group may be replaced by O, S, NH, N–CH₃ or N-benzyl;

[0042] R⁶ is selected from the group consisting of H, (C₁-C₆)-alkyl, F, Cl, Br, I, O–(C₀-C₈)-alkylene-H, CF₃, OCF₃, SCF₃, SF₅, OCF₂-CHF₂, (C₆-C₁₀)-aryl, O–(C₆-C₁₀)-aryl, O–(C₁-C₄)-alkylene-(C₆-C₁₀)-aryl, NO₂, COOR⁶, CONR¹O⁻R²⁻, SH, or NR¹²R⁴⁻, wherein ary is unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O–(C₁-C₄)-alkyl or CF₃;

[0043] The invention even more preferably relates to the compounds of formula III in which:

R¹ is H;

[0045] R² is H;

[0046] R³ is selected from the group consisting of H, (C₁-C₆)-alkyl, F, Cl, Br, I, O–(C₀-C₈)-alkylene-H, CF₃, OCF₃, SCF₃, SF₅, OCF₂-CHF₂, (C₆-C₁₀)-aryl, O–(C₆-C₁₀)-aryl, O–(C₁-C₄)-alkylene-(C₆-C₁₀)-aryl, NO₂, COOR², CONR¹O⁻R²⁻, SH, or NR¹²R⁴⁻, wherein ary is unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O–(C₁-C₄)-alkyl or CF₃;

[0047] and wherein

[0048] R⁴ is selected from the group consisting of H, Li, Na, K, Mg, Ca, ammonium ions which are unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O–(C₁-C₄)-alkyl or CF₃;

[0049] R⁴ and R⁵ are each independently selected from the group consisting of H, (C₁-C₅)-alkyl, phenyl or CH₃-phenyl.

[0050] Wherein phenyl, the phenyl is unsubstituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O–(C₁-C₄)-alkyl or CF₃;

[0051] or

[0052] R⁴ and R⁵ together are (C₄-C₅)-alkylene, in which one CH₂ group may be replaced by O, S, NH, N–CH₃ or N-benzyl.

[0053] The invention even more preferably further relates to compounds of formula III, in which:

[0054] R¹, R², R³, R⁴, R⁵, R⁶ and X² are each independently selected from the group consisting of H, (C₁-C₆)-alkyl, F, Cl, Br, I, O–(C₀-C₈)-alkylene-H, CF₃, OCF₃, SCF₃, SF₅, OCF₂-CHF₂, (C₆-C₁₀)-aryl, O–(C₆-C₁₀)-aryl, O–(C₁-C₄)-alkylene-(C₆-C₁₀)-aryl, NO₂, COOR², CONR¹O⁻R²⁻, SH, or NR¹²R⁴⁻, wherein ary is unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O–(C₁-C₄)-alkyl or CF₃;

[0055] where

[0056] R⁴ is H, Li, Na, K, Mg, Ca, ammonium ions which are unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O–(C₁-C₄)-alkyl or CF₃;

[0057] R⁴ and R⁵ are each independently H, (C₁-C₅)-alkyl, phenyl or CH₃-phenyl.

[0058] Wherein phenyl is unsubstituted or mono-, di- or trisubstituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O–(C₁-C₄)-alkyl or CF₃;

[0059] or

[0060] R⁴ and R⁵ together are (C₄-C₅)-alkylene, in which one CH₂ group may be replaced by O, S, NH, N–CH₃ or N-benzyl.

[0061] The invention even more preferably also relates to a process for preparing the compounds of the formula III in which:

W–CH;

[0062] o–1;

R¹ is H;

R² is H, CH₃, OCH₃, Br or Cl;

R³ is H, CH₃, OCH₃, Br or Cl;

R⁴ is CH₃, CH₂CH₃ or CH(CH₃)₂;
R^5=H, CH_3, CH_2CH_3 or CH(CH_3)_2;
R^6=H, CH_3, CH_2CH_3 or CH(CH_3)_2;
X^3=Cl, CH_3SO_3 or p-CH_3-C_6H_4—SO_3

[0063] n2=0 or 1.

[0064] The un-substituted or substituted ammonium ions in the definition of R^2 are preferably each triethylammonium.

[0065] In particular, the invention relates to a process for preparing compounds of the formula VIII,

\[ R^1 \rightarrow R^2 \rightarrow R^3 \rightarrow R^4 \rightarrow R^5 \rightarrow R^6 \]

in which
R^1=H,
R^2=H or CH_3,
R^3=H or OCH_3,
R^4=CH_3 or CH(CH_3)_2,
W=CH_3
X^3=Cl or CH_3SO_3 and

[0066] n2=0 or 1.

[0067] The invention most preferably relates to a process in which the reagent R^2X^2 has the structure:

SOCl—Cl, SOb—Br, CH_3SO_3—Cl or p-CH_3—
C_6H_4—SO_3—Cl.

[0068] In particular, the invention relates to a process in which the reagent R^2X^2 has either the structure SOCl—Cl (formula IX) or CH_3SO_3—Cl (formula X).

[0069] The N-oxide (formula II) may either be isolated or further reacted directly in solution.

[0070] When the N-oxide (formula II) or the oxazolidine (formula IV) is obtained as the salt (n1=1 or n2=1), it can be converted to the corresponding free base by treatment with a base such as aqueous solutions of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate and potassium hydrogencarbonate, for example.

[0071] For the reaction to form the N-oxides (formula I+formula II→formula III), useful reagents HX^1 are hydrogen halides, sulfurous acid and its acidic salt, phosphoric acid and its acidic salts, trifluoroacetic acid, trichloroacetic acid, trifluoromethanesulfonic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, formic acid and also HMOSO_3, HPO_3, HMPO_3, where M=Na, K, preference being given to hydrogen halides. In a particularly preferred embodiment, hydrogen chloride will be selected. In the case of sulfuric acid, hydrogen sulfates (n1=1) or sulfites (n1=1/2) can form; in the case of phosphoric acid, dihydrogen phosphates (n1=1), hydrogen phosphates (n1=1/2) or phosphates (n1=1/3) can form.

[0072] The reagent HX^1 can be used in stoichiometric amounts, based on the α-keoxime (formula II), up to a high excess. A preferred working range is the use of stoichiometric amounts up to a 7-fold excess. Particular preference is given to a 1 to 6-fold excess.

[0073] For the reaction to form the N-oxides (formula I+formula II→formula III), the solvents used may be protic polar solvents such as carboxylic acids, aprotic dipolar solvents such as sulfoxides, nitriles or ethers or polyethers, aprotic polar solvents such as halogenated aromatic and aliphatic hydrocarbons, or aprotic nonpolar solvents such as aromatic and aliphatic hydrocarbons, or a mixture of the solvent groups. For example, useful solvents are formic acid, glacial acetic acid, propionic acid, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrroldione, dimethyl sulfoxide, tetrahydrofuran, diethyl ether, diisopropyl ether, tert-butyl methyl ether, ethylene glycol dimethyl ether and higher homologs or dichloromethane and chlorobenzene or toluene, cyclohexane and n-heptane, in each case alone or in a mixture, in a preferred form, the reaction is carried out in glacial acetic acid, in a mixture of glacial acetic acid and ethylene glycol dimethyl ether, or in a mixture of glacial acetic acid and toluene.

[0074] The reaction temperatures for the formation of the N-oxides (formula I+formula II→formula III) can be varied within a wide range and depend upon factors including the solubility properties of the aldehydes (formula I) and α-keoximes (formula II) to be converted. Thus, in principle, reac-
tion temperatures of from minus 20°C to 150°C are possible, preference being given in general to reaction temperatures of from minus 10°C to 90°C. In a particularly preferred embodiment, reaction temperatures of from 0°C to 60°C will be selected.

[0075] The formation of the N-oxides (formula I = formula II = formula III) can be carried out either in a closed system under elevated pressure or else in an open system under standard pressure, i.e., for example, by introducing a hydrogen halide gas into the system open to the atmosphere or by using a hydrogen halide gas in an organic solvent.

[0076] When a further function such as COOR which can react with activated acid derivatives is present among the R₁ to R₅ radicals, the product can be obtained as the acid derivative COX₂ or, after preceding hydroslysis by processes known in principle, as the free acid COOH by acidic or alkaline hydrolysis.

[0077] The reagent RₓX is to be used in stoichiometric amounts, based on the intermediate N-oxide (formula II), up to a high excess. Preferably, the amount used is in stoichiometric amounts in a range that is the use of amounts up to 5-fold excess. Particular preference is given to a 1-4-fold excess. This introduces the X₀ moiety (of RₓX) in formula IV in covalently bonded form and converts Rₓ to Hₓ by hydrolysis.

[0078] For the reaction for the formation of the halomethylxoxazoles (formula III = formula IV), the solvents used may be aprotic dipolar solvents such as amides, sulfoxides, nitriles or ethers or polyethers, aprotic polar solvents such as halogenated aromatic and aliphatic hydrocarbons, or aprotic non-polar solvents such as aromatic and aliphatic hydrocarbons, or a mixture of the solvent groups. For example, useful solvents are N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, tetrahydrofuran, diethyl ether, disopropyl ether, tert-butyl methyl ether, ethylene glycol dimethyl ether and higher homologs, or dichloromethane and chlorobenzene or toluene, cyclohexane and n-heptane, in each case alone or in a mixture. In a preferred form, the reaction is carried out in dichloromethane or toluene. The reaction may also be carried out without solvent in an excess of the thionyl chloride or methanesulfonyl chloride reagents.

[0079] The reaction temperatures for the formation of the halomethylxoxazoles (formula III = formula IV) can be varied within a wide range and depend upon factors including the solubility properties for the aldehydes and α-ketoximes to be converted. Thus, in principle, reaction temperatures of from minus 20°C to 150°C are possible, preference being given generally to reaction temperatures of from 20°C to 120°C. In a particularly preferred embodiment, reaction temperatures of from 20°C to 80°C will be selected.

[0080] Halogen represents fluorine, chlorine, bromine or iodine, preferably fluorine, chloride, bromine, more preferably chlorine or bromine, and most preferably chlorine.

[0081] An aryl radical is understood to mean a straight-chain or branched hydrocarbon chain having from one to six carbons, for example methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, neopentyl, tert-butyl.

[0082] The alkyl radicals may be mono-, di- or trisubstituted by suitable groups, for example: F, Cl, Br, I, CF₃, NO₂, N₃, CN, COOH, COO(C₆H₄-alkyl), CONH₂, CONH(C₆H₄-alkyl), CON(C₆H₄-alkyl)₂, (C₅H₄-alkyl), (C₂H₅-alkyl), (C₆H₁₂-alkyl), O-(C₆H₅-alkyl), O-CO-(C₆H₅-alkyl), O-CO-(C₆H₁₂-alkyl).

[0083] An aryl radical is understood to mean a phenyl, naphthyl, biphenyl, tetrahydroindenyl, alpha- or beta-tetralonyl, indanyl or indan-1-yl radical.

[0084] The aryl radicals may be mono-, di- or trisubstituted by suitable groups, for example: F, Cl, Br, I, CF₃, NO₂, SF₅, N₃, CN, COOH, COO(C₆H₄-alkyl), CONH₂, CONH(C₆H₄-alkyl), CON(C₆H₄-alkyl)₂, (C₅H₄-alkyl), (C₂H₅-alkyl), (C₆H₁₂-alkyl), O-(C₆H₅-alkyl), O-CO-(C₆H₅-alkyl), O-CO-(C₆H₁₂-alkyl).

[0085] A cycloalkyl radical is understood to mean a three- to eight-membered ring system which contains one or more rings and is present in saturated or partially unsaturated (with one or two double bonds) form which is composed exclusively of carbon atoms, for example cyclopropyl, cyclohexyl, cyclopentyl, cyclohexyl or adamantyl. The cycloalkyl radicals may be mono-, di- or trisubstituted by suitable groups, for example: F, Cl, Br, I, CF₃, NO₂, N₃, CN, COOH, COO(C₆H₄-alkyl), CONH₂, CONH(C₆H₄-alkyl), CON(C₆H₄-alkyl)₂, (C₅H₄-alkyl), (C₂H₅-alkyl), (C₆H₁₂-alkyl), O-(C₆H₅-alkyl), O-CO-(C₆H₅-alkyl), O-CO-(C₆H₁₂-alkyl).

[0086] A heteroaryl radical is understood to mean a C₅C₆-heterocycle which may contain from 1 to 4 heteroatoms from the group O, N, S. Examples include furan, thiophene, pyrrole, pyridine, pyrazine, pyrimidine, pyridazine, oxazole, isoxazole, isothiazole, furan, furazan, tetrazole.

[0087] The inventive compounds of the formula IV can be reacted, for example, according to DE 102004040736.3 further to give pharmacologically active substances, the PPAR agonists.

EXAMPLE 1

2-(3-Methoxyphenyl)-4,5-dimethoxylxazole 3-oxide
(formula XI)

[0088]

[0089] 15.2 g (0.150 mol) of 2,3-butanedioine monoxime were initially charged and 260 ml of toluene, 22.1 g (0.157 mol) of 3-methoxybenzaldehyde and 70 ml (73.4 g, 1.224 mol) of glacial acetic acid were added with stirring. 27.3 g (0.749 mol) of hydrogen chloride gas were introduced with cooling at such a rate that the internal temperature was <22°C. Subsequently, the mixture was stirred for up to 16 h. With stirring, the reaction mixture was added to 600 ml of water (exothermic reaction). The pH was adjusted to 10.6, for which 172 ml (1.930 mol) of 33% aqueous sodium hydroxide solution were required; the internal temperature was kept <32°C by external cooling. Two phases formed and were separated. The aqueous phase was extracted twice with 100 ml each time of toluene and subsequently discarded. The combined organic phases were concentrated under reduced pressure while distilling off 50 ml. The thus obtained toluenic solution (420 ml) was used directly for the synthesis of 4-chloroethyl-2-(3-methoxyphenyl)-5-methoxyxazole hydrochloride.

[0090] Yield: 32.9 g (100%) of 2-(3-methoxyphenyl)-4,5-dimethoxylxazole 3-oxide,
EXAMPLE 2
4-Chloromethyl-2-(3-methoxyphenyl)-5-methyloxazole hydrochloride (formula XII)

[0095]

EXAMPLE 3
4-Chloromethyl-2-(3-methoxyphenyl)-5-methyloxazole hydrochloride (formula XIII)

EXAMPLE 4
4,5-Dimethyl-2-p-tolyl oxazole 3-oxide hydrochloride (formula XIV)

EXAMPLE 5
4-Chloromethyl-5-methyl-2-p-tolyl oxazole (formula XV)

[0096] The entire toluene solution from Example 1 (420 ml) was allowed at 60°C. Dropwise with 54.2 g (0.456 mol) of thionyl chloride and stirred at <60°C for up to 22 h. Subsequently, the mixture was concentrated by distillation off 229 ml. The suspension was cooled to <20°C, and the product was isolated by filtration with suction, washed 3 times with 20 ml each time of toluene and dried at elevated temperature under reduced pressure.

[0097] Yield: 23.2 g (56%) of 4-chloromethyl-2-(3-methoxyphenyl)-5-methyl oxazole hydrochloride

EXAMPLE 5
4-Chloromethyl-5-methyl-2-p-tolyl oxazole (formula XV)

[0110] 10.1 g (0.037 mol) of 4-chloromethyl-2-(3-methoxyphenyl)-5-methyl oxazole hydrochloride were suspended in 100 ml of water and 75 ml of dichloromethane. With stirring, a pH of 12 was established in the water phase with 45 ml (0.023 mol) of aqueous sodium hydroxide solution. Subsequently, the phases were separated and the aqueous phase was discarded. The organic phase was concentrated by distillation completely under reduced pressure. The remaining oil crystallized through after the addition of seed crystals.

[0102] Yield: 8.0 g (92%) of 4-chloromethyl-2-(3-methoxyphenyl)-5-methyl oxazole

EXAMPLE 3
4-Chloromethyl-2-(3-methoxyphenyl)-5-methyl oxazole hydrochloride (formula XIII)

EXAMPLE 4
4,5-Dimethyl-2-p-tolyl oxazole 3-oxide hydrochloride (formula XIV)

EXAMPLE 5
4-Chloromethyl-5-methyl-2-p-tolyl oxazole (formula XV)

[0106] 100 g (979 mmol) of butane-2,3-dione monoxide were initially charged and dissolved in 500 ml of acetic acid. 120 g (979 mmol) of 4-methylbenzaldehyde were added. 100 g (2.74 mol) of hydrogen chloride gas were introduced at such a rate that an internal temperature of 40°C was not exceeded. Subsequently, the mixture was stirred at 55-60°C for a further 3-3 hours. With intensive cooling, 2 l of tert-butyl methyl ether were added. The reaction mixture was stirred at 10°C for 1 hour. The product was isolated by filtration with suction, washed with tert-butyl methyl ether and dried at elevated temperature under reduced pressure.

[0107] Yield: 213 g (91%) of 4,5-dimethyl-2-p-tolyl oxazole 3-oxide hydrochloride

EXAMPLE 5
4-Chloromethyl-5-methyl-2-p-tolyl oxazole (formula XV)

EXAMPLE 5
4-Chloromethyl-5-methyl-2-p-tolyl oxazole (formula XV)

EXAMPLE 5
4-Chloromethyl-5-methyl-2-p-tolyl oxazole (formula XV)
[0111] 32.8 g (137 mmol) of 4,5-dimethyl-2-p-tolylloxazole 3-oxide hydrochloride were suspended in 165 ml of dichloromethane. 17.5 g (151 mmol) of methanesulfonyl chloride were added. The reaction was stirred at reflux up to full conversion (HPLC). Subsequently, 200 ml of ethylene glycol dimethyl ether were added, and the dichloromethane was distilled off under reduced pressure. The reaction mixture was cooled to 15°C and 250 ml of water were added. The mixture was stirred at 15°C for 1 hour. The precipitated product was isolated by filtration with suction, washed with water and dried at elevated temperature under reduced pressure.

[0112] Yield: 27.6 g (91%) of 4-chloromethyl-5-methyl-2-p-tolylloxazole

[0113] Melting point: 95°C.

[0114] 1H NMR (DMSO-D6, 500 MHz) 6 (ppm)=7.82 (d, J=8.1 Hz, 2H), 7.53 (d, J=8.1 Hz, 2H), 4.74 (s, 2H), 2.43 (s, 3H), 2.37 (s, 3H).

EXAMPLE 6
4-Methylpentane-2,3-dione 2-oxide (formula XVI)

[0115]

XVI

[0116] 100 g (948 mmol) of 2-methylpentan-3-one were dissolved in 400 ml of tert-butyl methyl ether. 50 g (274 mmol) of solution of hydrochloride in ethylene glycol dimethyl ether (20%) were added. Subsequently, a solution of 117 g (949 mmol) isoamyl nitrite in 150 ml of tert-butyl methyl ether was added dropwise within 60 minutes. The solvent was removed fully under reduced pressure. The residue was taken up in 300 ml of n-heptane and concentrated again under reduced pressure. After 200 ml of n-heptane had been added, extraction was effected with 522 ml of sodium hydroxide solution (2 molar). After phase separation, the aqueous phase was washed with n-heptane. The aqueous phase was acidified by adding conc. hydrochloric acid. The product was isolated by filtration with suction, washed with water and dried at elevated temperature under reduced pressure.

[0117] Yield: 61.1 g (50%) of 4-methylpentane-2,3-dione 2-oxide

[0118] Melting point: 94°C.

[0119] 1H NMR (DMSO-D6, 500 MHz) 6 (ppm)=12.3 (s, 1H), 5.34 (sept, J=6.9 Hz, 1H), 1.82 (2, 3H), 1.02 (s, 3H), 1.01 (s, 3H).

EXAMPLE 7
5-Isopropyl-2-(3-methoxyphenyl)-4-methyloxazole 3-oxide (formula XVII)

[0120]

XVII

[0121] 19.0 g (137 mmol) of 3-methoxybenzaldehyde were added to the solution of 20.0 g (137 mmol) of 4-methylpentane-2,3-dione 2-oxide in 30 g (99 mmol) of solution of hydrogen chloride in acetic acid (12%) at room temperature for 60 hours. The reaction was stirred at 30-55°C for 3 hours and at a pH of 3-4 was established by adding sodium hydrogen carbonate. After phase separation, the aqueous phase was extracted twice with 100 ml each time of tert-butyl methyl ether. The combined organic phases were washed with 4×100 ml of water and concentrated fully under reduced pressure.

[0122] Yield: 42.8 g (79% purity) (100%) of 5-isopropyl-2-(3-methoxyphenyl)-4-methyl oxazole 3-oxide

[0123] 1H NMR (DMSO-D6, 500 MHz) 6 (ppm)=8.12 (m, 1H), 7.86 (d, J=8.0 Hz, 1H), 7.48 (t, J=8.0 Hz, 1H), 7.06 (dd, J=2.4, 8.0 Hz, 1H), 3.82 (s, 3H), 3.16 (sept, J=7.0 Hz, 1H), 2.12 (s, 3H), 1.29 (d, J=7.0 Hz, 3H).

EXAMPLE 8
4-Chloromethyl-5-isopropyl-2-(3-methoxyphenyl) oxazole (formula XVIII)

[0124]

XVIII

[0125] 75 g (648 mmol) of methanesulfonyl chloride were added at a temperature of 20°C. To a solution of 135 g (435 mmol) of 5-isopropyl-2-(3-methoxyphenyl)-4-methyl oxazole 3-oxide in 500 ml of dichloromethane. The reaction was stirred at 40-45°C up to full conversion. 500 ml of tert-butyl methyl ether and 300 ml of water were added. Addition of 20% sodium hydroxide solution established a pH of 8. After
phase separation, the organic phase was washed with 3×200 ml of water. The organic phase was concentrated fully under reduced pressure.

**[0126]** Yield: 132 g (87% purity) (99%) of 4-chloromethyl-5-isopropyl-2-(3-methoxyphenyl)-oxazole

**[0127]** $^1$H NMR (DMSO-$d_6$, 500 MHz) δ (ppm): 7.55 (m, 1H), 7.45 (m, 2H), 7.10 (ddd, J=0.9, 2.7, 5.6 Hz, 1H), 4.77 (s, 2H), 3.85 (s, 3H), 3.55 (sept, 7.0 Hz, 1H), 1.30 (d, J=7.0 Hz, 6H).

What is claimed is:

1. The compounds of formula III,

\[
\text{III}
\]

wherein:

- $R^3$ is selected from the group consisting of H, (C1-C6)-alkyl, F, Cl, Br, I, O—(C6-C8)-alkylene-H, CF$_3$, OCF$_3$, SCF$_3$, SC$_3$F$_7$, OCF$_2$—CHF$_2$ (C6-C10)-aryl, O—(C6-C10)-aryl, O—(C1-C4)-alkylene-(C6-C10)-aryl, NO$_2$, COOR, CONH$_2$R, SH, or NR$_2$R, wherein aryl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl and CF$_3$; and
- $R^4$ is selected from the group consisting of H, Li, Na, K, ½Mg, ½Ca, ammonium ions which are un-substituted or mono-, di- or tri-substituted by (C1-C4)-alkyl, and is (C1-C8)-alkyl;
- $R^{10}$ and $R^{11}$ are each independently selected from the group consisting of H, (C1-C5)-alkyl, phenyl or CH$_2$-phenyl, wherein phenyl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl and CF$_3$;
- or $R^3$ and $R^{11}$ together are (C4-C5)-alkylene, in which one CH$_2$ group may be replaced by O, S, NH, N—CH$_3$, or N-benzyl;
- $R^5$ is selected from the group consisting of H, (C1-C6)-alkyl, F, Cl, Br, I, O—(C1-C8)-alkylene-H, CF$_3$, OCF$_3$, SCF$_3$, SC$_3$F$_7$, OCF$_2$—CHF$_2$ (C6-C10)-aryl, O—(C6-C10)-aryl, O—(C1-C4)-alkylene-(C6-C10)-aryl, NO$_2$, COOR, CONH$_2$R, SH, or NR$_2$R, wherein aryl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl and CF$_3$; wherein $R^5$, $R^{10}$ and $R^{11}$ are each as defined above;
- $R^6$ is selected from the group consisting of H, (C1-C6)-alkyl, F, Cl, Br, I, O—(C1-C6)-alkylene-H, CF$_3$, OCF$_3$, SCF$_3$, SC$_3$F$_7$, OCF$_2$—CHF$_2$ (C6-C10)-aryl, O—(C6-C10)-aryl, O—(C1-C4)-alkylene-(C6-C10)-aryl, NO$_2$, COOR, CONH$_2$R, SH, or NR$_2$R, wherein aryl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl and CF$_3$; wherein $R^6$, $R^{10}$ and $R^{11}$ are each as defined above;
- $W$ is O, S, NR$_2$, if o=0;
- o is 0 or 1;
- R$_{12}$ is H, (C1-C6)-alkyl, (C1-C6)-alkylene(phenyl, phenyl); R$_7$ is selected from the group consisting of H, (C1-C8)-alkyl, (C3-C8)-cycloalkyl, (C1-C3)-alkylene-(C3-C8)-cycloalkyl, phenyl, (C1-C3)-alkylene(phenyl, (C5-C6)-heteroaryl, (C1-C3)-alkylene-(C5-C6)-heteroaryl or (C1-C3)-alkyl which is fully or partly substituted by F, or COOR, CONH$_2$R, CONR$_{10}$R$_{11}$; wherein R$_8$, R$_{10}$ and R$_{11}$ are each as defined above;
- R$_7$ and R$_9$ are each independently selected from the group consisting of H, (C1-C8)-alkyl, F, Cl, Br, I, O—(C6-C8)-alkylene-H, O—(C6-C10)-aryl, O—(C1-C4)-alkylene-(C6-C10)-aryl, COOR, CONH$_2$R, CONR$_{10}$R$_{11}$, SH or NR$_2$R, wherein R$_8$, R$_{10}$ and R$_{11}$ are each as defined above;
- or, R$_7$ and R$_9$ together are (C4-C5)-alkylene, in which one CH$_2$ group may be replaced by O, S, NH, N—CH$_3$, or N-benzyl; R$_7$ is selected from the group consisting of H or (C1-C8)-alkyl and, wherein R$_1$, R$_2$, R$_3$, R$_4$, R$_5$, R$_7$ and X' are each as defined above and n1 is 0, ½ or ½;
- 2. The compounds of formula III as recited in claim 1, wherein:
- W=CH and o=1;
- 3. The compounds of formula III as recited in claim 2, wherein:
- R$_1$ is H;
- R$_3$ is selected from the group consisting of H, (C1-C6)-alkyl, F, Cl, Br, I, O—(C6-C8)-alkylene-H, CF$_3$, OCF$_3$, SCF$_3$, SC$_3$F$_7$, OCF$_2$—CHF$_2$ (C6-C10)-aryl, O—(C6-C10)-aryl, O—(C1-C4)-alkylene-(C6-C10)-aryl, NO$_2$, COOR, CONH$_2$R, SH, or NR$_2$R, wherein aryl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl or CF$_3$; wherein R$_3$ is selected from the group consisting of H, Li, Na, K, ½Mg, ½Ca, ammonium ions which are un-substituted or mono-, di- or tri-substituted by (C1-C4)-alkyl, or is (C1-C8)-alkyl, R$_{10}$ and R$_{11}$ are each independently H, (C1-C5)-alkyl, phenyl or CH$_2$-phenyl, wherein the phenyl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl and CF$_3$; or R$_{10}$ and R$_{11}$ together are (C4-C5)-alkylene, in which one CH$_2$ group may be replaced by O, S, NH, N—CH$_3$, or N-benzyl; R$_3$ is selected from the group consisting of H, (C1-C6)-alkyl, F, Cl, Br, I, O—(C6-C8)-alkylene-H, CF$_3$, OCF$_3$, SCF$_3$, SC$_3$F$_7$, OCF$_2$—CHF$_2$ (C6-C10)-aryl, O—(C6-C10)-aryl, O—(C1-C4)-alkylene-(C6-C10)-aryl, NO$_2$, COOR, CONH$_2$R, CONR$_{10}$R$_{11}$, SH or NR$_2$R, wherein aryl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl or CF$_3$; wherein R$_9$ is selected from the group consisting of H, Li, Na, K, ½Mg, ½Ca, ammonium ions which are un-substituted or mono-, di- or tri-substituted by (C1-C4)-alkyl, or is (C1-C8)-alkyl, R$_{10}$ and R$_{11}$ are each independently H, (C1-C5)-alkyl, phenyl or CH$_2$-phenyl, and wherein the phenyl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl or CF$_3$; or R$_{10}$ and R$_{11}$ together are (C4-C5)-alkylene, in which one CH$_2$ group may be replaced by O, S, NH, N—CH$_3$, or N-benzyl; R$_3$ is selected from the group consisting of H, (C1-C6)-alkyl, F, Cl, Br, I, O—(C6-C8)-alkylene-H, CF$_3$, OCF$_3$, SCF$_3$, SC$_3$F$_7$, OCF$_2$—CHF$_2$ (C6-C10)-aryl, O—(C6-C10)-aryl, O—(C1-C4)-alkylene-(C6-C10)-aryl, NO$_2$, COOR, CONH$_2$R, CONR$_{10}$R$_{11}$, SH or NR$_2$R, wherein aryl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C1-C4)-alkyl, O—(C1-C4)-alkyl or CF$_3$; wherein R$_{10}$ and R$_{11}$ are each as defined above.

4. The compounds of formula III as recited in claim 3 wherein:
- R$_1$ is H;
- R$_7$ is H;
R³ is H, (C₁-C₄)-alkyl, F, Cl, Br, I, O—(C₀-C₈)-alkylene, H, CF₃, OCTF₃, SCSF₅, OCF₂-CF₂, (C₆-C₁₀)-aryl, O—(C₆-C₁₀)-aryl, O—(C₁-C₄)-alkylene-(C₆-C₁₀)-aryl, NO₂, COOR³, CONR¹[R¹¹, SH, or NR²R¹¹] where aryl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O—(C₁-C₄)-aryl or CF₃;

wherein

R³ is H, Li, Na, K, ½Mg, ½Ca, ammonium ions which are un-substituted or mono-, di- or tri-substituted by (C₁-C₄)-alkyl, or is (C₁-C₄)-alkyl, wherein phenyl is un-substituted or mono-, di- or tri-substituted by F, Cl, Br, I, (C₁-C₄)-alkyl, O—(C₁-C₄)-aryl or CF₃;

or

R³⁰ and R¹¹ together form a (C₄-C₅)-alkylene, in which one CH₂ group may be replaced by O, S, NH, N—CH₃ or N-benzyl.

5. The compounds of formula III as recited in claim 4, wherein:

W=CH₂;
α=1;
R²=H;
R²=H, CH₃, OCH₃, Br or Cl;
R²=H, CH₃, OCH₂, Br or Cl;
R²=CH₂, CH₂CH₂, or CH(CH₃)₃;
R²=H, CH₃, CH₂CH₂, or CH(CH₃)₃;
R²=H, CH₃, CH₂CH₂, or CH(CH₃)₃;
X=Cl, CH₃SO₂ or p-CH₃—C₆H₄—SO₃ and n²=0 or 1.

6. The compounds of formula III

wherein:

R²=H;
R²=H or CH₃;
R²=H or OCH₃;
R²=CH₃ or CH(CH₃)₂, α;
W=CH₂;
X=Cl or CH₃SO₂, and n²=0 or 1.

7. A process for the preparation of compounds of formula III as recited in claim 1, wherein the reaction temperature for the formation of the N-oxides as depicted by formula III from the reaction of compounds of formulae I and II is between about −20° C. and +150° C.

8. The process for the preparation of compounds of formula III as recited in claim 7, wherein the reaction for the formation of the N-oxides as depicted by formula III is carried out in protic, polar, aprotic non-polar solvents or mixtures thereof.

9. The process for the preparation of compounds of the formula III as recited in claim 8, wherein the reaction temperature for the formation of the halomethyloxazoles as depicted by formula IV from compounds of the formula III is from about −20° C. to +150° C.

10. The process for the preparation of compounds of formula III as recited in claim 8 wherein one or more of the compounds of formula I and II are used in the preparation thereof.

11. The compound of formula XI.

Xl

12. The compound of formula XIV.

XIV

13. The compound of formula XVII.

XVII

* * * * *