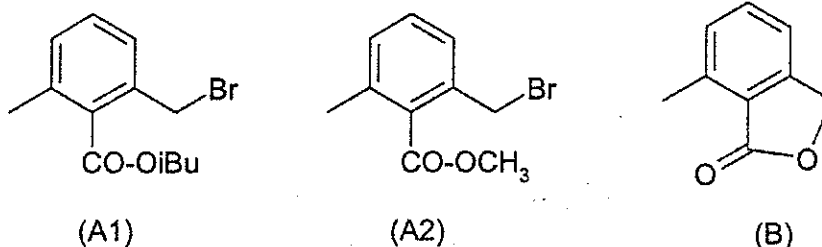


Description

Synthesis of 2-chloromethyl-6-methylbenzoic acid esters

- 5 2-Haloalkylbenzoic acid derivatives are used as building blocks for the synthesis of active pharmaceutical ingredients. For various reasons, it is desirable for the use to have storage-stable compounds which can additionally be prepared and purified in a simple manner. These reasons include, for example, the ensuring of a constant quality, the avoidance of frequent checks on the materials to record the product quality, the avoidance of the necessity of cold storage and/or cold transport, easy transfer to production plants and also simple cleaning of used vessels.

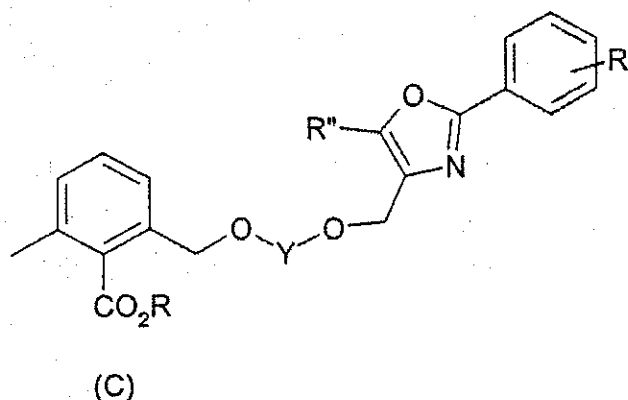
15 2-Bromomethyl-6-methylbenzoic esters (A1 and A2) are known, for example, from WO 00/64888 (R = iBu (A1)) and WO 00/64876 (R = Me (A2)). These compounds are not storage-stable at room temperature, since they cyclize spontaneously to the lactone (B) and in the process, as is well known, release mutagenic alkyl bromides as a by-product.



The use of these thermally labile substances on the industrial scale is therefore associated with occupational hygiene risks, difficulties and additional costs.

25 Among other uses, the 2-bromomethyl-6-methylbenzoic esters are of interest as starting materials for the preparation of PPAR agonists, as described, for example, in WO 00/64888, WO 00/64876 and WO 03/020269. Particular mention should be made here of the compounds of the formula (C):

30



where

- 5 R is H, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, C₆-C₁₂-aryl, C₁-C₄-alkyl-C₆-C₁₂-aryl or C₅-C₁₀-heteroaryl, where, in alkyl and cycloalkyl, one or more CH₂ groups may be replaced by -O- and alkyl, cycloalkyl and aryl may be substituted by halogen,
- Y is -(CH₂)₃-, 1,3-phenylene, 1,3-cyclohexanediyl;
- R' is H, F, Br, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, phenyl;
- 10 R'' is H, (C₁-C₆)-alkyl, (C₁-C₃)-alkylphenyl, (C₅-C₆)-cycloalkyl, phenyl, CF₃.

Preference is given to the compounds of formula (C) in which the phenyl ring is substituted by R' in the m- or p-position.

15

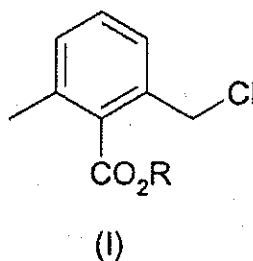
It is thus an object of the invention to find more stable compounds than (A1) and (A2) which do not have the above-outlined disadvantages. In addition, the compounds which can occur in a purity which is not yet sufficient when they are prepared even from a crude product should, in contrast to the compounds of the formulae (A1) and (A2), be purifiable.

20

This is achieved by the compounds of the formula (I) described below.

The present invention provides the compounds of formula (I)

25



where

5 R is H, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, C₆-C₁₂-aryl, C₁-C₄-alkyl-C₆-C₁₂-aryl or C₅-C₁₀-heteroaryl, and, in alkyl and cycloalkyl, one or more CH₂ groups may be replaced by -O-, and alkyl, cycloalkyl and aryl may be substituted by halogen.

10 Preference is given to the compounds of the formula (I) in which

R is C₁-C₈ alkyl, C₃-C₆-cycloalkyl or C₁-C₄-alkyl-C₆-C₁₂-aryl, each of which may optionally be substituted by halogen and in which one or two CH₂ groups may be replaced by -O-.

15 Particular preference is given to the compounds of the formula (I) in which

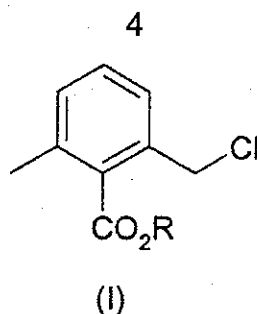
R is C₁-C₆ alkyl or C₁-C₄-alkyl-C₆-C₁₂-aryl, each of which may optionally be substituted by halogen and in which one CH₂ group may be replaced by -O-.

20 Very particular preference is given to the compounds of the formula (I) in which

25 R is methyl, ethyl, propyl, i-propyl, t-butyl, phenyl, 2-methoxyethyl or benzyl.

30 Alkyl may be branched or unbranched. Halogen is Cl, Br, I, preferably Cl. In this context, heteroaryl refers to 5- to 10 membered aromatic rings which contain from one to four identical or different heteroatoms from the group of N, O, S, for example pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, thiophene, oxazole, isoxazole, thiazole, isothiazole, triazole, tetrazole, triazine, tetrazine, preference is given to: pyrrole, imidazole, oxazole, thiazole and pyridine.

35 The present invention also provides a process for preparing the compounds of the formula (I)

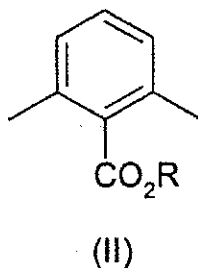


where

- 5 R is H, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, C₆-C₁₂-aryl, C₁-C₄-alkyl-C₆-C₁₂-aryl or C₅-C₁₀-heteroaryl, and, in alkyl or cycloalkyl, one or more CH₂ groups may be replaced by -O-, and alkyl, cycloalkyl and aryl may be substituted by halogen,

- 10 which comprises

reacting dimethylbenzoic esters of the formula (II)



15

where R is as defined above

- with a chlorinating reagent, for example sulfuryl chloride, N-chloro-succinimide (NCS), 1,3-dichloro-5,5-dimethylhydantoin (NDDH) or trichloro-isocyanuric acid [Org Process Research & Development 2002,6,384-393],
- 20 in an inert solvent, for example CCl₄, chlorobenzene, or without solvents above 40°C and subsequently optionally purifying.

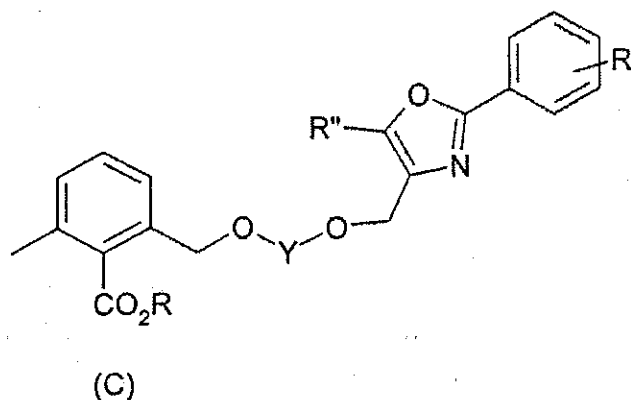
- Preference is given to carrying out the reaction at 60-90°C, while
- 25 chlorination on the aromatic ring is observed at lower temperatures than 40°C. The purification is preferably distillative or by a silica gel filtration.

- The chlorine compounds of the formula (I) are only obtainable very inefficiently, if at all, by a ring-opening chlorination of the lactones (B), since
- 30 the lactone structure is very stable. In addition, the 2-chloromethylbenzoic

acid derivatives can surprisingly be distilled, can be isolated by this method in excellent chemical purity and do not react spontaneously in the course of storage to give the lactones.

- 5 A conversion of the chlorine compounds of the formula (I) to more reactive bromine or iodine compounds may likewise be advantageous, in order to increase the reactivity of this molecular building block in the further synthesis (for example to give PPAR agonists (C)). However, these compounds then have the "technical" disadvantages mentioned in the introduction. The conversion of the chlorine into the bromine or iodine
 10 compound is effected with alkali metal halides in inert solvents, preferably with sodium bromide or iodide in acetone under reflux. Alternatively, the transhalogenation and the further synthesis can also be carried out as a one-pot method with catalytical or stoichiometric amounts of alkyl halide,
 15 based on the chlorine compound used.

The present invention further provides a process for preparing the compounds of the formula (C)

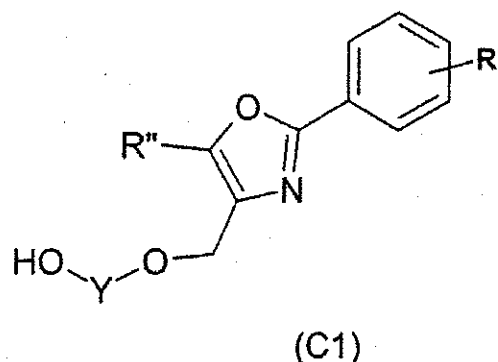


20

in which

- 25 R is H, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, C₆-C₁₂-aryl, C₁-C₄-alkyl-C₆-C₁₂-aryl or C₅-C₁₀-heteroaryl and, in alkyl and cycloalkyl, one or more CH₂ groups may be replaced by -O- and alkyl, cycloalkyl and aryl may be substituted by halogen,
 Y is -(CH₂)₃-, 1,3-phenylene, 1,3-cyclohexanediyl,
 R' is H, F, Br, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, phenyl;
 30 R'' is H, (C₁-C₆)-alkyl, (C₁-C₃)-alkylphenyl, (C₅-C₆)-cycloalkyl, phenyl, CF₃;

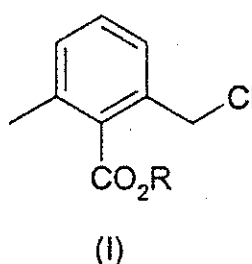
which comprises reacting compounds of the formula (C1)



5

where Y, R' and R'' are each as defined above

with compounds of the formula (I)



10

where R is as defined above

in toluene, NMP or other aprotic solvents, in the presence of a suitable
 15 base, preferably with potassium tert-butoxide, at from -78 to +50°C,
 preferably at from -30 to +20°C, and subsequently working up extractively
 and optionally crystallizing the end product.

The compounds of the formula (I) are notable for high stability compared to
 20 the corresponding bromine compounds. When the stability of methyl
 2-bromomethyl-6-methylbenzoate is compared to that of the analogous
 chlorine compound, the following result is obtained: methyl 2-chloromethyl-
 6-methylbenzoate can be distilled without decomposition at 66-77°C/0.1
 mbar, and only a bottom temperature of above 120°C leads to significant
 25 lactone formation. At room temperature, it can be stored stably over several
 months. The storage stability of methyl 2-bromomethyl-6-methylbenzoate
 differs distinctly from this. At room temperature, the content of the bromine

compound reduces sharply within a few days, within one week from 92.6 to 81.0%, within 2 weeks to 67.8% and within 2 months to 7.8%. At the same time, the lactone content rises from 1.9% via 13.9% after 1 week and 89.5% in 2 months.

5

The following examples are cited without restriction to them:

Example 1:

Synthesis of methyl 2-chloromethyl-6-methylbenzoate

10

11.9 g of methyl 2,6-dimethylbenzoate are initially charged in 50 ml of chlorobenzene admixed at room temperature with 8.2 g of sulfuryl chloride and 40 mg of AIBN. The mixture is stirred at 60-90°C for 2 h. Afterwards, the mixture is admixed with 80 ml of saturated NaHCO₃ solution. After the
15 phase separation, the organic phase is washed with 100 ml of 10% Na₂SO₃ solution, the organic phase is dried over magnesium sulfate and the chlorobenzene is distilled off in vacuo. 15.5 g of colorless liquid are obtained. The product is distilled under high vacuum (0.1 mbar, 66-77°C).
Yield: 10.2g (71% of theory; 95.2 area%).

20

Example 2:

Synthesis of isopropyl 2-chloromethyl-6-methylbenzoate

25

19.2 g of isopropyl 2,6-dimethylbenzoate are initially charged in 100 ml of carbon tetrachloride admixed at room temperature with 13.3 g of N-chlorosuccinimide and 200 mg of AIBN. The mixture is heated to reflux for 3 h. After the mixture has been cooled, it is filtered with suction and the succinimide is washed with 20 ml of carbon tetrachloride. The filtrates are combined and carbon tetrachloride is distilled off in vacuo. 21.8 g of color-
30 less liquid are obtained. The product is distilled under high vacuum (0.05 mbar, 94-97°C). Yield: 13.9 g (61% of theory; 93.6 area%).

Example 3:

Synthesis of 2-methoxyethyl 2-chloromethyl-6-methylbenzoate

35

10.4 g of 2-methoxyethyl 2,6-dimethylbenzoate are admixed at room temperature with 5.4 g of sulfuryl chloride and 40 mg of AIBN. The mixture is stirred at 60-90°C for 1-2 h. Afterwards, the mixture is admixed with 20 ml of water, the phases are separated and the organic phase is dried

over magnesium sulfate. The product is distilled under high vacuum (0.02 mbar, 95-103°C). Yield: 6.4 g (66% of theory; 91.8 area%).

Example 4:

5 Synthesis of benzyl 2-chloromethyl-6-methylbenzoate

12.0 g of benzyl 2,6-dimethylbenzoate are initially charged in 50 ml of carbon tetrachloride admixed at room temperature with 5.4 g of sulfuryl chloride and 40 mg of AIBN. The mixture is stirred at reflux for 4-5 h.
 10 Afterwards, it is admixed with 40 ml of saturated NaHCO₃ solution. After the phase separation, the organic phase is washed with 50 ml of 10% sodium sulfite solution and the organic phase is dried over magnesium sulfate. The product-containing solution is filtered through silica gel and washed again with 20 ml of carbon tetrachloride. After distilling off the
 15 solvent in vacuo, the product obtained is a bright yellow oil. Yield: 8.0 g (73% of theory; 88.4 area%).

Example 5:

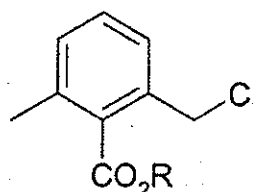
2-Methyl-6-[3-(2-phenyloxazol-4-ylmethoxy)propoxymethyl]benzoic acid

20

4.8 g of methyl 2-chloromethyl-6-methylbenzoate are dissolved at room temperature in 250 ml of acetone and admixed with 35 g of sodium iodide. The mixture is heated to reflux for 6 h. Subsequently, the solvent is removed at 0°C in vacuo. The residue is analyzed by means of LC-MS
 25 (87.7 area% of methyl 2-iodomethyl-6-methylbenzoate) and dissolved in 20 ml of toluene. The solution is added dropwise at -20°C within 10 min to a mixture of 5.0 g of 3-(2-phenyloxazol-4-ylmethoxy)propan-1-ol, 4.8 g of potassium tert-butoxide and 30 ml of toluene. Afterwards, the mixture is stirred at -20°C for 6 h and diluted with 100 ml of water, and the aqueous
 30 phase is removed. The organic phase is admixed with 40 ml of NMP and 10 ml of 32% sodium hydroxide solution and heated to reflux for 8 h on a water separator. Subsequently, the mixture is admixed with 100 ml of water and extracted twice with 25 ml of MTB ether each time. The aqueous phase is acidified with 5 ml of acetic acid and extracted twice with 50 ml of
 35 ethyl acetate each time. After the phases have been separated, the organic phase is dried over magnesium sulfate and the solvent is removed in vacuo. After the crystallization from diisopropyl ether, 4.2 g of 2-methyl-6-[3-(2-phenyloxazol-4-ylmethoxy)propoxymethyl]benzoic acid (50% of theory, 99.2 HPLC area%) are obtained.

What is claimed is:

1. A compound of the formula (I)



(I)

where

- R is H, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, C₆-C₁₂-aryl, C₁-C₄-alkyl-C₆-C₁₂-aryl or C₅-C₁₀-heteroaryl, and, in alkyl and cycloalkyl, one or more CH₂ groups may be replaced by -O-, and alkyl, cycloalkyl and aryl may be substituted by halogen.

2. A compound of the formula (I) as claimed in claim 1 in which

R is C₁-C₈ alkyl, C₃-C₆-cycloalkyl or C₁-C₄-alkyl-C₆-C₁₂-aryl, each of which may optionally be substituted by halogen and in which one or two CH₂ groups may be replaced by -O-.

3. A compound of the formula (I) as claimed in claim 1 or 2 in which

R is C₁-C₆ alkyl or C₁-C₄-alkyl-C₆-C₁₂-aryl, each of which may optionally be substituted by halogen and in which one CH₂ group may be replaced by -O-.

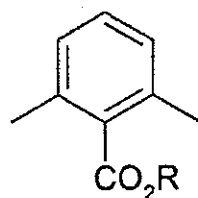
4. A compound of the formula (I) as claimed in claims 1 to 3 in which

R is methyl, ethyl, propyl, i-propyl, t-butyl, phenyl, 2-methoxy-ethyl or benzyl.

5. A process for preparing the compounds of the formula (I) as claimed in claims 1 to 4, which comprises

reacting dimethylbenzoic esters of the formula (II)

10



(II)

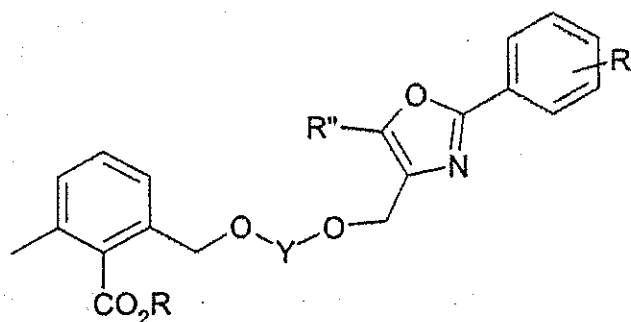
where R is as defined above

5

with a chlorinating reagent in an inert solvent or without solvents above 40°C and subsequently optionally purifying.

6. A process for preparing the compounds of the formula (C)

10



(C)

in which

15

R is H, C₁-C₁₂-alkyl, C₃-C₈-cycloalkyl, C₆-C₁₂-aryl, C₁-C₄-alkyl-C₆-C₁₂-aryl or C₅-C₁₀-heteroaryl and, in alkyl and cycloalkyl, one or more CH₂ groups may be replaced by -O- and alkyl, cycloalkyl and aryl may be substituted by halogen,

Y is -(CH₂)₃-, 1,3-phenylene, 1,3-cyclohexanediyl,

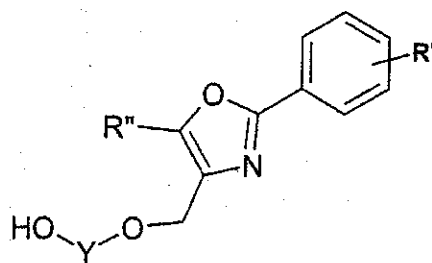
R' is H, F, Br, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, phenyl;

20

R'' is H, (C₁-C₆)-alkyl, (C₁-C₃)-alkylphenyl, (C₅-C₆)-cycloalkyl, phenyl, CF₃;

which comprises reacting compounds of the formula (C1)

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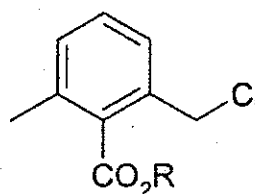


(C1)

where Y, R' and R'' are each as defined above

5

with compounds of the formula (I)



(I)

where R is as defined above

10

in toluene, NMP or other aprotic solvents, in the presence of a suitable base, at -78 to +50°C, and subsequently working up extractively and optionally crystallizing the end product.

15

7. The process for preparing the compounds of the formula (C) as claimed in claim 6, wherein the phenyl ring is substituted by R' in the m- or p-position.

20

8. The use of the compounds of the formula (I) as claimed in claims 1 to 4 for preparing PPAR agonists of the general formula (C).