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(54) **PROCESS FOR THE PREPARATION OF CYCLOPROPYL CARBOXYLIC ACID ESTERS AND DERIVATIVES**

VERFAHREN ZUR HERSTELLUNG VON CYCLOPROPYLCARBONSÄUREESTERN UND DEREN DERIVATEN

PROC D DE PREPARATION D'ESTERS D'ACIDE CARBOXYLIQUE CYCLOPROPYL ET DERIVES

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Description

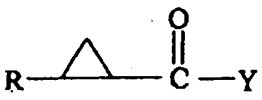
FIELD OF THE INVENTION

[0001] The present invention relates to a novel process for the preparation of certain cyclopropyl carboxylic acid esters and other cyclopropyl carboxylic acid derivatives; a novel process for the preparation of dimethylsulfoxonium methylide and dimethylsulfonium methylide; to the use of certain cyclopropyl carboxylic acid esters in a process for the preparation of intermediates that can be used in the synthesis of pharmaceutically active entities; and to certain intermediates provided by these processes.

[0002] The reaction of triethyloxosulphonium chloride or iodide with sodium hydride to give dimethyloxosulphonium methylide is described by E.J Corey et al, Journal the American Chemical Society, volume 87,1965, page 1353-1364. The reaction of dimethyloxosulphonium methylide with a, β-unsaturated ketones to form cyclopropyl ketones is also mentioned. The cyclopropanation of C=C couble bonds of α, β-enones using a ylide such as dimethyloxosulphonium methylide is also discussed by Bajgrowicz et al, US 5,929,291.

DESCRIPTION OF THE INVENTION

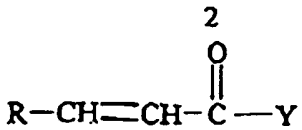
[0003] In a first aspect the invention provides a process for the preparation of a compound of formula (I):



(I)

wherein: R is phenyl substituted with one or more halogen; and Y is OR^1, where R^1 is a straight chain alkyl, branched alkyl, cycloalkyl, or a substituted bicycloheptyl group; which comprises:

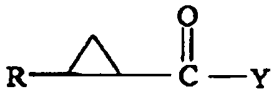
reacting a trimethylsulfoxonium salt with a solid metal hydroxide in dimethyl sulfoxide at ambient or an elevated temperature to produce dimethylsulfoxonium methylide; and, contacting compound of formula (II)



(II)

in which R and Y area s defined above, with the dimethylsulfoxonium methylide in the presence of a solvent at a temperature of -10°C -90°C.

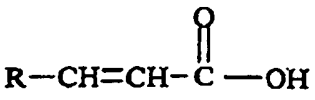
[0004] The present invention also provides a process for the preparation of a compound of formula (I):



(I)

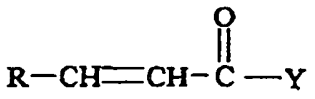
wherein: R is phenyl substituted with one or more halogen; and Y is OR^1, where R^1 is a straight chain alkyl, branched alkyl, cycloalkyl, or a substituted bicycloheptyl group; which comprises:

a. chlorinating a compound of formula (III)



(III)

by reaction with a chlorinating agent in the presence of an inert solvent and a catalyst at a temperature of 0-200°C; and then reacting the resulting solution with YH or Y, where Y is as defined in claim 1, at an elevated temperature to provide a compound of formula (II):



(II)

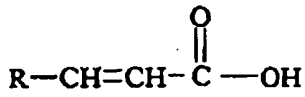
reacting a trimethylsulfoxonium salt with a solid metal hydroxide in dimethyl sulfoxide at ambient or an elevated temperature to produce dimethylsulfoxonium methylide; and, contacting the compound of formula (II) with the dimethylsulfoxonium methylide in the presence of a solvent at a temperature of -10°C - 90°C.

[0005] Suitably the solvent is a polar solvent, preferably dimethyl sulfoxide. Suitably, the reaction is carried out at -10°C - 90°C, preferably 25°C.

[0006] The dimethylsulfoxonium methylide can be prepared by reacting a trimethylsulfoxonium salt with a solid strong base which is a metal hydroxide, eg NaOH, LiOH, in solid form, in dimethyl sulfoxide at ambient or an elevated temperature. Preferably the base is sodium hydroxide.

[0007] Preferably, trimethylsulfoxonium iodide is stirred with sodium hydroxide powder in dimethyl sulfoxide (in the absence of a phase transfer catalyst), optionally under nitrogen, at 20-25°C for 90 minutes. Alternatively, the dimethylsulfoxonium methylide can be prepared from a trimethylsulfoxonium salt (preferably iodide or chloride) using sodium hydroxide in dimethyl sulfoxide with a phase transfer catalyst, for example tetrabutyl-n-ammonium bromide, or with other strong bases, such as alkali metal hydrides, in dimethyl sulfoxide.

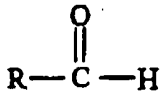
[0008] A compound of formula (II) can be prepared by reacting a compound of formula (III):



(III)

where R is as defined above, with a suitable chlorinating agent in the presence of an inert solvent and an optional catalyst at at a temperature of 0-200°C. Preferably Y is OR^1, the chlorinating agent is thionyl chloride, the inert solvent is toluene, and the catalyst is pyridine. Suitably the reaction temperature is 70°C. The resulting acid chloride is then reacted with YH or Y^-, (where Y^- is an anionic species of Y), Y is as defined above, optionally at an elevated temperature, such as 100°C.

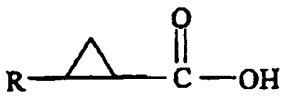
[0009] A compound of formula (III) can be prepared using standard chemistry, for example by contacting a compound of formula (IV):



(IV)

where R is as defined above, with malonic acid in the presence of pyridine and piperidine at an elevated temperature, preferably 50-90°C.

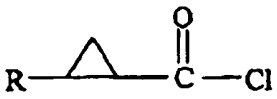
[0010] A compound of formula (I) can be hydrolysed using basic hydrolysis to yield a compound of formula (V):



(V)

where R is as defined above. For example, ester groups are preferably removed by basic hydrolysis using an alkali metal hydroxide, such as sodium hydroxide or lithium hydroxide, or quaternary ammonium hydroxide in a solvent, such as water, an aqueous alcohol or aqueous tetrahydrofuran, at a temperature from 10 - 100°C. Most preferably the base is sodium hydroxide, the solvent is ethanol, and the reaction temperature is 50°C.

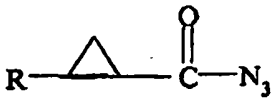
[0011] A compound of formula (V) can be used to generate a compound of formula (VI):



(VI)

where R is as defined above, by reaction with thionyl chloride or another suitable chlorinating agent in the presence of toluene, or another suitable solvent, and an optional catalyst, preferably pyridine, at 0-200°C. Preferably the temperature is to 65-70°C.

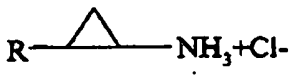
[0012] A compound of formula (VI) can be used in the synthesis of a compound of formula (VII):



(VII

where R is as defined above, by reaction with an alkali metal azide (preferably sodium azide) in the presence of a phase transfer catalyst (preferably tetra-*n*-butylammonium bromide), aqueous potassium carbonate and an inert solvent (preferably toluene). Preferably the reaction temperature is 0 - 10°C.

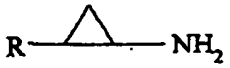
[0013] A compound of formula (VII) can be used in the synthesis of a compound of formula (VIII):



(VIII)

where R is as defined above, by rearrangement in toluene at temperatures between 0°C and 200°C, preferably at a reaction temperature of 90-100°C, after which the isocyanate intermediate is reacted with hydrochloric acid at elevated temperatures, preferably 85-90°C.

[0014] An unprotonated parent amine (free base) of formula (IX):



(IX)

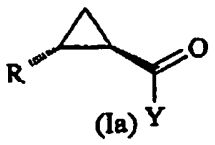
where R is as defined above, can be liberated by adjusting the pH of an aqueous solution of the salt of a compound of formula (VIII) to 10 or more. This can then be converted to other salts of organic acids or inorganic acids, preferably mandelic acid. The *R*-(-)-mandelic acid salt of a compound of formula (IX) can be generated by addition of *R*-(-)-mandelic acid at ambient or an elevated temperature to a solution of a compound of formula (IX) in a solvent, preferably ethyl acetate. Preferably the temperature is 20°C.

[0015] Suitably R is phenyl optionally substituted by one or more halogen atoms. Preferably, R is phenyl substituted by one or more fluorine atoms. More preferably R is 4-fluorophenyl or 3,4-difluorophenyl.

[0016] Preferably Y is D-menthoxy, or more preferably, L-menthoxy.

[0017] Compounds of formulae (I) to (IX) can exist in different isomeric forms (such as cis/trans, enantiomers, or diastereoisomers). The process of this invention includes all such isomeric forms and mixtures thereof in all proportions.

[0018] Where Y is chiral, a compound of formula (I) will be a mixture of diastereoisomers and can be resolved to yield a diastereomerically-exuiched compound of formula (Ia):

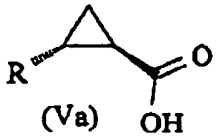


(Ia)

where R and Y are as defined above, by crystallisation or by chromatographic methods.

Preferably the crystallisation is carried out *in situ* following the synthesis of a compound of formula (I), as described above, by heating the crude reaction mixture until total or near-total dissolution is achieved, then cooling at an appropriate rate until sufficient crystals of the desired quality are formed. The crystals are then collected by filtration. Alternatively, the resolution can be carried out in any other suitable solvent, such as a hydrocarbon, eg heptane, by extracting a compound of formula (I) into a suitable amount of the solvent, heating the extracts until total dissolution is achieved, then cooling at an appropriate rate until sufficient crystals of the desired quality are formed. Optionally the organic extracts can be washed with water, dried over magnesium sulfate and filtered prior to the crystallisation described above.

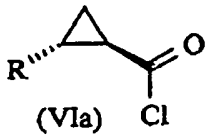
[0019] A compound of formula (Ia) can be hydrolysed to yield a compound of formula (Va):



(Va)

where R is as defined above, using the method described above for the hydrolysis of a compound of formula (I) to yield a compound of formula (V).

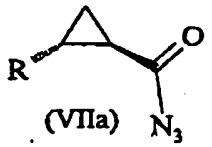
[0020] A compound of formula (Va) can be used to generate a compound of formula (VIa):



(VIa)

where R is as defined above, using the method described above for the conversion of a compound of formula (V) to yield a compound of formula (VI).

[0021] A compound of formula (VIa) can be used in the synthesis of a compound of formula (VIIa):



(VIIa)

where R is as defined above, using the method described above for the conversion of a compound of formula (VI) to yield a compound of formula (VII).

[0022] A compound of formula (VIIa) can be used in the synthesis of a compound of formula (VIIIa):

(VIIIa)

where R is as defined above, using the method described above for the conversion of a compound of formula (VII) to yield a compound of formula (VIII).

[0023] A compound of formula (VIIIa) can be used in the synthesis of a compound of formula (IXa):

(IXa)

where R is as defined above, using the method described above for the conversion of a compound of formula (VIII) to yield a compound of formula (IX).

[0024] The R-(-)-mandelic acid salt of a compound of formula (IXa) can be generated using the method described above for the generation of the mandelic acid salt of a compound of formula (IX).

Examples

[0025] The invention is illustrated by the following non-limiting examples.

Example 1.

[0026] This example illustrates the preparation of (E)-3-(3,4-difluorophenyl)-2-propenoic acid

[0027] A stirred mixture of pyridine (15.5 kg) and piperidine (0.72 kg) were heated to 90°C. Malonic acid (17.6 kg) was added, followed by slow addition, over 50 minutes, of 3,4-difluorobenzaldehyde (12.0 kg). The reaction mixture was stirred at 90°C for a further 4 hours and 36 minutes. Water (58.5 kg) was added and 32 litres of the pyridine/water mixture then was distilled out of the reactor under reduced pressure. The reaction mixture was acidified to pH 1 with 37% hydrochloric acid (6.4 kg) over a 40-minute period, then cooled to 25°C with strong stirring. The solids were collected by filtration, washed twice with 1 % hydrochloric acid (34.8 L per wash), once with water (61 L) and then deliquored thoroughly in the filter: The product was then dried under vacuum at 40°C for 24 hours and 40 minutes, affording 13.7 kg of the crystalline product.

Example 2.

[0028] This example illustrates the preparation of (*E*)-3-(3,4-difluorophenyl)-2-propenoyl chloride.

[0029] A stirred mixture of (*E*)-3-(3,4-difluorophenyl)-2-propenoic acid (8.2 kg), toluene (7.4kg) and pyridine (0.18kg) was heated to 65°C and then thionyl chloride (7.4kg) was added over 30 minutes. The reaction was stirred for a further 2h 15 minutes after the addition was complete, then diluted with toluene (8.7kg). Excess thionyl chloride, sulfur dioxide and hydrogen chloride were then distilled out, together with toluene (10 L), under reduced pressure, yielding a solution of the (*E*)-3-(3,4-difluorophenyl)-2-propenoyl chloride (approximately 9 kg) in toluene.

Example 3.

[0030] This example illustrates the preparation of (1*R*, 2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*E*)-3-(3,4-difluorophenyl)-2-propenoate.

[0031] A solution of L-menthol (7.1kg) in toluene (8.5kg) was added over a 20 minute period to the solution of (*E*)-3-(3,4-difluorophenyl)-2-propenoyl chloride (prepared as in Example 2) and pyridine (0.18kg, 2.28 mol) stirring at 65°C. The reaction mixture was stirred at 65°C for a further 4 hours and 40 minutes after the addition was complete, then cooled to 25°C and stirred for a 14 hours. The solution was diluted with toluene (16kg), washed with 5% aqueous sodium chloride (6.4kg), then 6% sodium hydrogen carbonate (6.47kg), then water (6.1kg). The solution was dried azeotropically by distillation of the solvent (20 L) under reduced pressure. Dimethyl sulfoxide (33.9 kg) was added and the remaining toluene was distilled off under reduced pressure, affording 47.3kg of a solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyelohexyl (*E*)-3-(3,4-difluorophenyl)-2-propenoate (approx. 13.3 kg) in dimethyl sulfoxide.

Example 4.

[0032] This example illustrates a method of preparing dimethylsulfoxonium methylide (dimethyl(methylene) oxo-λ^6-sulfane).

[0033] Sodium hydroxide powder (1.2kg), prepared by milling sodium hydroxide pellets in a rotary mill through a 1mm metal sieve, and trimethylsulfoxonium iodide (6.2kg) were stirred in dimethyl sulfoxide (25.2kg) under a nitrogen atmosphere at 25°C for 90 min. The solution was used directly in the preparation of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl) cyclopropanecarboxylate.

Example 5.

[0034] This example illustrates a method of preparing dimethylsulfonium methylide (dimethyl(methylene)-λ^4-sulfane).

[0035] Sodium hydroxide powder (970mg), prepared by milling sodium hydroxide pellets in a rotary mill through a 1mm metal sieve, and trimethylsulfonium iodide (4.66 g) were stirred in dimethyl sulfoxide (17 ml) under a nitrogen atmosphere at 20-25°C for 10 min. The solution was used directly in the preparation of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate.

Example 6.

[0036] This example illustrates the preparation of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate

[0037] A solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 3,4-difluorophenyl)-2-propenoate (approxi-

mately 8.6 kg) in dimethyl sulfoxide (approximately 27.9 kg) was added with stirring over 20 minutes to a mixture of dimethylsulfoxonium methylide (approximately 2.6kg, prepared as described above), sodium iodide ((*E*)-3-(approximately 4.2 kg), water (approximately 500 g) and sodium hydroxide (approximately 56 g) in dimethylsulfoxide (27.7 kg) at 25°C. The reaction mixture was stirred for a further 2 hours and 50 minutes at 25°C, then used directly for the preparation of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate.

Example 7.

[0038] This example illustrates the preparation of (1*R*, 2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl-*trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate

[0039] A crude solution of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate produced as described in example 6 was heated with stirring from 25°C to 50°C over a 1 hour period and the temperature was maintained for a further hour. The mixture was then cooled with stirring from 50°C to 35°C over 4 hours, kept at 35°C for 1 hour, then cooled to 26°C over 4 hours, kept at 26°C for 1 hour, then cooled to 19°C over 3 hours and kept at 19°C for 5 hours and 10 minutes. The product crystallised and was collected by filtration, affording a crystalline solid (2.7 kg) which was shown to contain a mixture of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate (1.99 kg) and (1*R*,2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*S*,2*S*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate (85 g).

Example 8.

[0040] This example illustrates an alternative method of preparing (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*, 2*R*)- 2-(3,4- difluorophenyl) cyclopropanecarboxylate

[0041] n-Heptane (82.5 L) was distilled under reduced pressure from a solution of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate (14.3 kg, 44.4 mol) in heptane (128.6 L). The mixture was then cooled from 34°C to 24°C over a period of 3 hours and 20 minutes. Seed crystals of (1*R*, 2*S*,5*R*)-2-isopropyl-5-methyleyclobexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate were then added and the mixture was cooled to 0°C over a period of 5 hours and 50 minutes. Filtration afforded the product as a crystalline solvent wet solid (7.05 kg) which was shown to contain a mixture of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate (4.7 kg) and (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*S*,2*S*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate (1.1 kg).

Example 9.

[0042] This example illustrates a method of preparing *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid.

[0043] (1*R*, 2*S*, 5*R*)- 2- isoPropyl- 5- methylcyclohexyl *trans*-(1*R*, 2*R*)- 2-(3,4- difluorophenyl) cyclopropanecarboxylate (9.6 kg, 91.8% diastereomeric excess) was dissolved in ethanol (13.8 kg) and heated with stirring to 46°C. 45% Aqueous sodium hydroxide (3.1 kg) was added over a 20 minute period and the mixture was stirred for a further 2 hours and 27 minutes. Solvent (28 L) was distilled out of the mixture under reduced pressure, then the mixture was cooled to 24°C and diluted with water (29.3 kg), after which the liberated menthol was extracted into toluene (3 washes of 3.3 kg each).

[0044] The remaining aqueous material was acidified to pH 2 with 37% hydrochloric acid (3.3 L) and the product was extracted into toluene (8.6 kg, then 2 more washes of 4.2 kg and 4.3 kg). The combined toluene extracts were washed with 1% hydrochloric acid (4.9 L), then diluted with further toluene (4.2 kg) and azeotropically dried by distillation of the solvent (25 L) under reduced pressure. A final dilution with toluene (24.2kg) was followed by distillation of the solvent under reduced pressure (10 L) affording a solution containing *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid (approximately 3.45 kg) suitable for the production of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride.

Example 10.

[0045] This example illustrates a method of preparing *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride.

[0046] Pyridine (70 ml) was added to a solution of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid (approximately 3.45 kg) in toluene (approximately 12 -15 kg) prepared as described above,and the mixture was then heated to 65°C. Thionyl chloride (2.3kg) was added over a period of 1 hour and the mixture was stirred at 70°C for 3 hours. Thionyl chloride (0.5 kg) was added and the mixture was stirred a further 2 hours at 70°C. A final aliquot of thionyl chloride (0.5 kg) was added and the reaction mixture was stirred for 1 hour at 70°C, then cooled to 40°C. Periodic additions of toluene (45 kg, 3 additions of 15 kg each) were made during distillation of solvent (approximately 60 L) from the mixture under reduced pressure, then the solution of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride (approximately 3.8 kg) in toluene (approximately 6 - 9 L) was cooled to 20°C.

Example 11.

[0047] This example illustrates a method of preparing *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarb-

onyl azide.

[0048] A solution of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride (approximately 3.8 kg) in toluene (approximately 6 - 9 L) at 1°C was added over a period of 74 minutes to a mixture of sodium azide (1.24 kg), tetrabutylammonium bromide (56 g) and sodium carbonate (922 g,) in water (6.2 kg), stirring at 1.5°C. The mixture was stirred at 0°C for 1 hour and 55 minutes, then the aqueous layer was diluted with cold water (3.8 kg), stirred briefly, then separated. The toluene layer was washed once more at 0°C with water (3.8 kg), then with 20% aqueous sodium chloride (3.8 L), then stored at 3°C for further use.

Example 12.

[0049] This example illustrates a method of preparing *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropylamine.

[0050] A cold solution of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl azide prepared as described in Example 11 was added over a period of 41 minutes to toluene (6.0 kg) stirring at 100°C. The mixture was stirred for a further 55 minutes at 100°C, then cooled to 20°C and added over a period of 2 hours and 15 minutes to hydrochloric acid (3M, 18.2 kg) stirring at 80°C After 65 minutes the solution was diluted with water (34 kg) and cooled to 25°C. The toluene layer was removed and the aqueous layer was basified to pH 12 with 45% sodium hydroxide (3.8 kg) and the product was then extracted into ethyl acetate (31 kg) and washed twice with water (13.7 kg per wash), affording a solution containing *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyc1opropylamine (2.6 kg, 91.8% enantiomeric excess) in ethyl acetate (29.5 L).

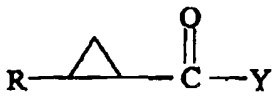
Example 13.

[0051] This example illustrates a method of preparing *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanaminium (2*R*)-2-hydroxy-2-phenylethanoate.

[0052] R-(-)-Mandelic acid (226 kg) was added to a solution containing *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl) cyclopropylamine (2.6 kg, 91.8% enantiomeric excess), stirring at 17°C in ethyl acetate (45.3 L). The mixture was stirred at 25°C for 3 hours and 8 minutes, then filtered and washed twice with ethyl acetate (13.8 kg total). The crystalline product was dried at 40°C under reduced pressure for 23 hours, affording *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanaminium (2*R*)-2-hydroxy-2-phenylethanoate (4.45 kg).

Claims

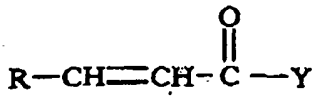
1. A process for the preparation of a compound of formula (I):



(I)

wherein: R is phenyl substituted with one or more halogen; and Y is OR^1, where R^1 is a straight chain alkyl, branched alkyl, cycloalkyl, or a substituted bicycloheptyl group; which comprises:

reacting a trimethylsulfoxonium salt with a solid metal hydroxide in dimethyl sulfoxide at ambient or an elevated temperature to produce dimethylsulfoxonium methylide; and,
contacting compound of formula (II)



(II)

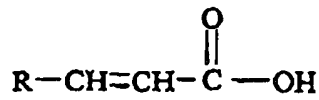
in which R and Y area s defined above, with the dimethylsulfoxonium methylide in the presence of a solvent at a temperature of -10°C - 90°C.

2. A process for the preparation of a compound of formula (I):

(I)

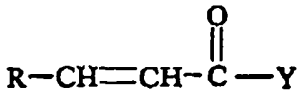
wherein: R is phenyl substituted with one or more halogen; and Y is OR^1, where R^1 is a straight chain alkyl, branched alkyl, cycloalkyl, or a substituted bicycloheptyl group; which comprises:

a. chlorinating a compound of formula (III)



(III)

by reaction with a chlorinating agent in the presence of an inert solvent and a catalyst at a temperature of 0-200°C; and then reacting the resulting solution with YH or Y^-, where Y is as defined in claim 1, at an elevated temperature to provide a compound of formula (II):



(II)

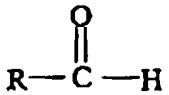
reacting a trimethylsulfoxonium salt with a solid metal hydroxide in dimethyl sulfoxide a ambient or an elevated temperature to produce dimethylsulfoxonium methylide; and, contacting the compound of formula (II) with the dimethylsulfoxonium methylide in the presence of a solvent at a temperature of -10°C - 90°C.

3. A process according to claim 1 or 2 in which the metal hydroxide is sodium hydroxide.

4. A process according to claim 1 in which a compound of formula (III) is reacted with thionyl chloride in the presence of an inert solvent and pyridine at a temperature of 0-200°C, and the resulting solution is then reacted with YH or Y^-, where Y is as defined in claim 1, at an elevated temperature.

5. A process according to any one of the preceding claims in which YH represents L-menthol.

6. A process according to any one of claims 1 to 5 in which a compound of formula (III) is prepared by contacting a compound of formula (IV):



(IV)

where R is as defined in claim 1, with malonic acid in the presence of pyridine and piperidine at elevated temperature.

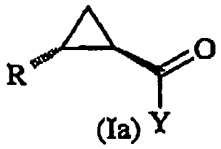
7. A process according to any one of the preceding claims in which R is phenyl substituted by one or more fluorine atoms.

8. A process according to claim 7 in which R is 3,4-difluorophenyl.

9. A process according to any one of the preceding claims in which Y is chiral.

10. A process according to claim 9 in which Y is L-menthoxy,

11. A process according to any one of claims 1 to 10 in which a compound of formula (I) is resolved to yield a compound of formula (Ia):

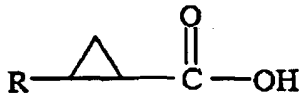


(Ia)

where R and Y are as defined above, by a crystallisation or chromatrographic method.

12. A process according to claim 11 in which the resolution is carried out by extracting a compound of formula (I) into heptane and then effecting crystallisation from the heptane extracts,

13. A process according to any one of claims 1 to 12 which includes the step of hydrolysing the compound of formula (I) using a base to yield a compound of formula (V).



(V)

Patentansprüche

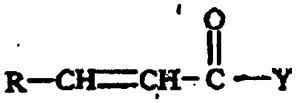
1. Verfahren zur Herstellung einer Verbindung der Formel (I):

(I)

worin R für durch ein oder mehrere Halogene substituiertes Phenyl steht und Y für OR^1, worin R^1 eine geradkettige Alkyl-, verzweigte Alkyl-, Cycloalkyl-

oder substituierte Bicycloheptylgruppe bedeutet, steht, bei dem man:

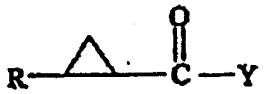
ein Trimethylsulfoxoniumsalz in Dimethylsulfoxid bei Umgebungstemperatur oder erhöhter Temperatur mit einem festen Metallhydroxid zu Dimethylsulfoxoniummethylid umsetzt und die Verbindung der Formel (II)



(II)

worin R und Y die oben angegebene Bedeutung besitzen, in Gegenwart eines Lösungsmittels bei einer Temperatur von -10°C bis -90°C mit dem Dimethylsulfoxoniummethylid in Berührung bringt.

2. Verfahren zur Herstellung einer Verbindung der Formel (I):

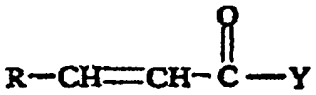


(I)

worin R für durch ein oder mehrere Halogene substituiertes Phenyl steht und Y für OR^1, worin R^1 eine geradkettige Alkyl-, verzweigte Alkyl-, Cycloalkyl- oder substituierte Bicycloheptylgruppe bedeutet, steht, bei dem man:
eine Verbindung der Formel (III)

(III)

durch Umsetzung mit einem Chlorierungsmittel in Gegenwart eines inerten Lösungsmittels und eines Katalysators bei einer Temperatur von 0-200°C chloriert und die erhaltene Lösung dann bei erhöhter Temperatur mit YH oder Y^-, worin Y die in Anspruch 1 angegebene Bedeutung besitzt, zu einer Verbindung der Formel (II):



(II)

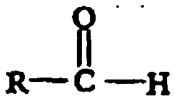
umsetzt, ein Trimethylsulfoxoniumsalz in Dimethylsulfoxid bei Umgebungstemperatur oder erhöhter Temperatur mit einem festen Metallhydroxid zu Dimethylsulfoxoniummethylid umsetzt und die Verbindung der Formel (II) in Gegenwart eines Lösungsmittels bei einer Temperatur von -10°C bis -90°C mit dem Dimethylsulfoxoniummethylid in Berührung bringt.

3. Verfahren nach Anspruch 1 oder 2, bei dem es sich bei dem Metallhydroxid um Natriumhydroxid handelt.

4. Verfahren nach Anspruch 1, bei dem man eine Verbindung der Formel (III) in Gegenwart eines inerten Lösungsmittels bei einer Temperatur von 0-200°C mit Thionylchlorid umsetzt und die erhaltene Lösung dann bei erhöhter Temperatur mit YH oder Y^-, worin Y die in Anspruch 1 angegebene Bedeutung besitzt, umsetzt.

5. Verfahren nach einem der vorhergehenden Ansprüche, bei dem YH für L-Menthol steht.

6. Verfahren nach einem der Ansprüche 1 bis 5, bei dem man eine Verbindung der Formel (III) herstellt, indem man eine Verbindung der Formel (IV)



(IV)

worin R die in Anspruch 1 angegebene Bedeutung besitzt, in Gegenwart von Pyridin und Piperidin bei erhöhter Temperatur mit Malonsäure umsetzt.

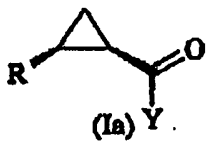
7. Verfahren nach einem der vorhergehenden Ansprüche, bei dem R für durch ein oder mehrere Fluoratome substituiertes Phenyl steht.

8. Verfahren nach Anspruch 7, bei dem R für 3,4-Difluorphenyl steht.

9. Verfahren nach einem der vorhergehenden Ansprüche, bei dem Y chiral ist.

10. Verfahren nach Anspruch 9, bei dem Y für L-Menthoxy steht.

11. Verfahren nach einem der Ansprüche 1 bis 10, bei dem man eine Verbindung der Formel (I) einer Spaltung nach einer Kristallisationsmethode oder chromatographischen Methode unterwirft, wobei man eine Verbindung der Formel (Ia):

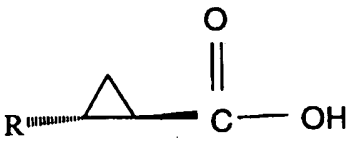


(Ia)

erhält, worin R und Y die oben angegebene Bedeutung besitzen.

12. Verfahren nach Anspruch 11, bei dem man die Spaltung durch Extraktion einer Verbindung der Formel (I) mit Heptan und nachfolgende Kristallisation aus den Heptanextrakten durchführt.

13. Verfahren nach einem der Ansprüche 1 bis 12, bei dem man die Verbindung der Formel (I) mit einer Base zu einer Verbindung der Formel (V) hydrolysiert.



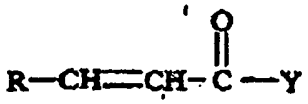
Revendications

1. Procédé de préparation d'un composé de formule (I) :

(I)

dans laquelle : R est phényle substitué avec un ou plusieurs halogènes ; et Y est OR^1, où R^1 est un alkyle à chaîne linéaire, un alkyle ramifié, un cycloalkyle ou un groupement bicycloheptyle substitué, comprenant :

la réaction d'un sel de triméthylsulfoxonium avec un hydroxyde métallique solide dans du diméthylsulfoxyde, à température ambiante ou à une température élevée pour produire le méthylure de diméthylsulfoxonium ; et, la mise en contact du composé de formule (II)



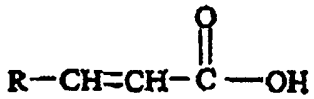
(II)

dans laquelle R et Y sont tels que définis ci-dessus, avec le méthylure de diméthylsulfoxonium en présence d'un solvant à une température de -10°C - 90°C.

2. Procédé de préparation d'un composé de formule (I) :

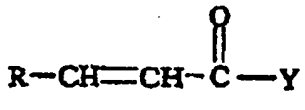
(I)

dans laquelle : R est phényle substitué avec un ou plusieurs halogènes ; et Y est OR^1, où R^1 est un alkyle à chaîne linéaire, un alkyle ramifié, un cycloalkyle ou un groupement bicycloheptyle substitué, comprenant : la chloration d'un composé de formule (III)



(III)

en le faisant réagir avec un agent de chloration en présence d'un solvant inerte et d'un catalyseur à une température de 0 - 200°C ; puis en faisant réagir la solution résultante avec YH ou Y^-, où Y est tel que défini dans la revendication 1, à une température élevée pour donner un composé de formule (II) :



(II)

la réaction d'un sel de triméthylsulfoxonium avec un hydroxyde métallique solide dans du diméthylsulfoxyde, à température ambiante ou à une température élevée pour produire le méthylure de diméthylsulfoxonium ; et, la mise en contact du composé de.formule (II) avec le méthylure de diméthylsulfoxonium en présence d'un solvant à une température de -10°C - 90°C.

3. Procédé selon la revendication 1 ou 2, **caractérisé en ce que** l'hydroxyde métallique est l'hydroxyde de sodium.

4. Procédé selon la revendication 1, **caractérisé en ce qu'**un composé de formule (III) est mis en réaction avec du chlorure de thionyle en présence d'un solvant inerte et de pyridine à une température de 0 - 200°C, et la solution résultante est alors mise en réaction avec YH ou Y^-, où Y est tel que défini dans la revendication 1, à une température élevée.

5. Procédé selon l'une quelconque des revendications précédentes, **caractérisé en ce que** YH représente le L-menthol.

6. Procédé selon l'une quelconque des revendications 1 à 5, **caractérisé en ce qu'**un composé de formule (III) est préparé par mise en contact d'un composé de formule (IV) :

(IV)

dans laquelle R est tel que défini dans la revendication 1, avec de l'acide malonique en présence de pyridine et de pipéridine à une température élevée.

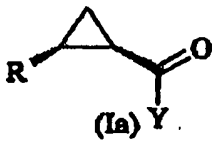
7. Procédé selon l'une quelconque des revendications précédentes, **caractérisé en ce que** R est phényle substitué par un ou plusieurs atomes de fluor.

8. Procédé selon la revendication 7, **caractérisé en ce que** R est 3,4-difluorophényle.

9. Procédé selon l'une quelconque des revendications précédentes, **caractérisé en ce que** Y est chiral.

10. Procédé selon la revendication 9, **caractérisé en ce que** Y est L-menthoxy.

11. Procédé selon l'une quelconque des revendications 1 à 10, **caractérisé en ce qu'**un composé de formule (I) est résolu pour donner un composé de formule (Ia) :

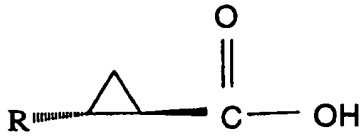


(Ia)

dans laquelle R et Y sont tels que définis ci-dessus, par une méthode de cristallisation ou chromatographique.

12. Procédé selon la revendication 11, **caractérisé en ce que** la résolution est effectuée par extraction d'un composé de formule (I) dans de l'heptane, puis par cristallisation à partir des extraits heptaniques.

13. Procédé selon l'une quelconque des revendications 1 à 12, **caractérisé en ce qu'**il inclut l'étape d'hydrolyse du composé de formule (I) à l'aide d'une base pour donner un composé de formule (V).



REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 5929291 A **[0002]**

Non-patent literature cited in the description

- **E.J COREY et al.** *Journal the American Chemical Society*, 1965, vol. 87, 1353-1364 **[0002]**