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(72) Feltaláló(k):
JIRMAN, Josef, 100 00 Praha 10 (CZ)
JUNEK, Richard, 104 00 Praha 10 (CZ)
LUSTIG, Petr, 530 03 Pardubice (CZ)
RICHTER, Jindrich, 530 12 Pardubice (CZ)
PLACEK, Lukas, 792 01 Bruntal (CZ)

(73) Jogosult(ak):
Zentiva, k.s., 102 37 Praha 10 (DO)

(74) Képviselő:
dr. Somfai Éva, Somfai és Társai Iparjogi Kft., Budapest

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VERFAHREN ZUR HERSTELLUNG VON SOLIFENACIN

PROCÉDÉ DE SYNTHÈSE DE SOLIFÉNACINE

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(73) Proprietor: **Zentiva, a.s.**
102 37 Praha 10 (CZ)

(72) Inventors:
- **JIRMAN, Josef**
  100 00 Praha 10 (CZ)
- **JUNEK, Richard**
  104 00 Praha 10 (CZ)
- **LUSTIG, Petr**
  530 03 Pardubice (CZ)
- **RICHTER, Jindrich**
  530 12 Pardubice (CZ)
- **PLACEK, Lukas**
  792 01 Bruntal (CZ)

(74) Representative: **Jirotkova, Ivana et al**
Rott, Ruzicka & Guttmann
Patent, Trademark and Law Offices
Vinohradskà 37
120 00 Praha 2 (CZ)

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EP-A- 0 801 067 **WO-A-2005/087231**

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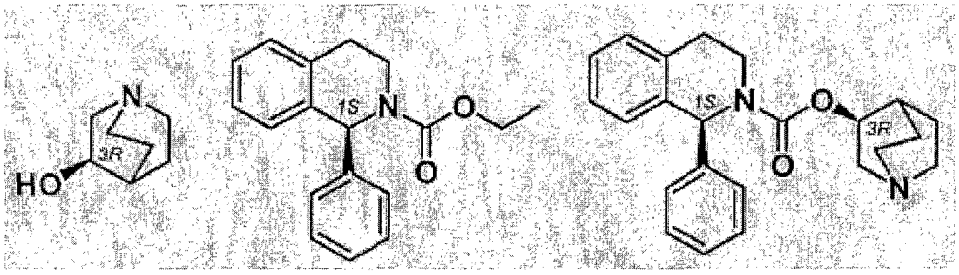
EP 2 029 587 B1

Description

TECHNICAL FIELD

[0001] The invention relates to a new process of conducting the condensation of 3-(R)-quinuclidol of formula I and (1S)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate of formula II to obtain (1S)-(3R)-1-azabicyclo[2.2.2.]oct-3-yl 3,4-dihydro-1-phenyl-2(1H)-isoquinoline carboxylate of formula III

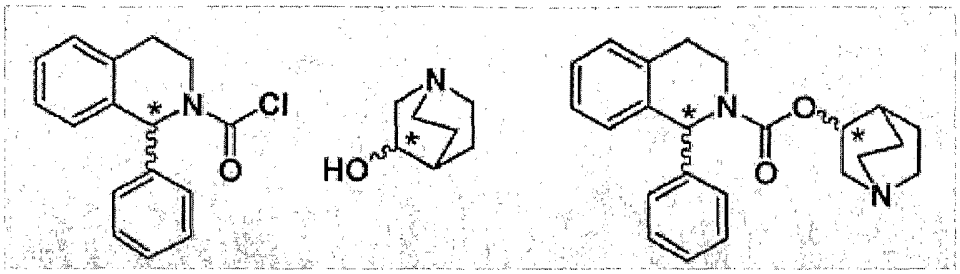


Formula I Formula II Formula III

BACKGROUND ART

[0002] Original patent literature (EP 0 801 067, WO 9620194) describes a procedure where (1S)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate is reacted with 3-(R)-quinuclidol, which is in about 290% theoretical amount, with sodium hydride, which is in about 156% theoretical amount, in a toluene suspension. The reaction mixture is refluxed, simultaneously distilling off the ethanol being formed, which leaves in the form of an azeotropic mixture with toluene. A reasonable degree of conversion is thereby attained. Nevertheless, the patent states that the yield is as modest as 56%.

[0003] The patent mentions also possibility of the synthesis procedure is mentioned where 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carbonyl chloride of formula IV is reacted with 3-quinuclidol of formula V in dimethylformamide to obtain 1-azabicyclo[2.2.2.]oct-3-yl 3,4-dihydro-1-phenyl-2(1H)-isoquinoline carboxylate of formula VI.



Formula IV Formula V Formula VI

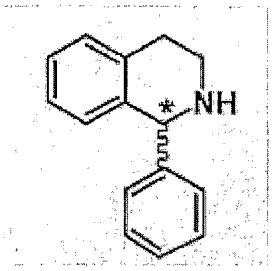
[0004] EP 0 801 067/WO 9620194 also report an arrangement where 3-(R)-quinuclidyl alkyl carbonate is allowed to react with 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline to give solifenacin.

[0005] Patent application WO 2005/087231 describes preparation of solifenacin by reacting (1S)-alkyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate (where the alkyl is a lower alkyl, preferably methyl, ethyl, or benzyl) in a toluene-dimethylformamide mixture with 3-(R)-quinuclidol, the reaction being catalyzed by a sodium alkoxide, the alkoxide being so selected that its alkyl is identical with the alkyl of the (1S)-alkyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate (hence, sodium methoxide, ethoxide, or benzyloxide).

[0006] We have found empirically that all the procedures published so far suffer from drawbacks. The procedure in EP 0 801 067 does not afford the product in a reasonably high yield and, in addition, uses a comparatively high excess of optically pure 3-(R)-quinuclidol which is rather costly.

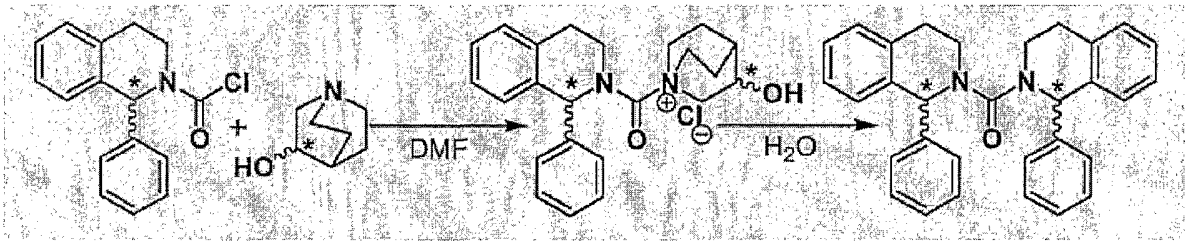
[0007] The other route - reaction of 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carbonyl chloride of formula IV with 3-quinuclidol of formula V in dimethylformamide, resulting in 1-azabicyclo[2.2.2.]oct-3-yl 3,4-dihydro-1-phenyl-2(1H)-isoquinoline carboxylate of formula VI - is mentioned in patent literature (EP 0 801 067) but no examples of the procedure are given. We have tested the procedure practically and found that, although the reaction between the two components, the carbamoyl chloride and quinuclidol, proceeds at a reasonably high rate without any additional catalysis (monitored

by HPLC), an intermediate seems to be formed, associated with acylation at the nitrogen giving a quaternary ammonium salt. This salt is hydrolyzed by water which is added within the product isolation step, and the acid formed is decarboxylated immediately. The forming 1-phenyl-1,2,3,4-tetrahydroisoquinoline of formula VIII



Formula VIII

reacts immediately with the residue of the acylation agent (intermediate) giving, in a nearly quantitative yield, an urea according to the following Scheme 1.

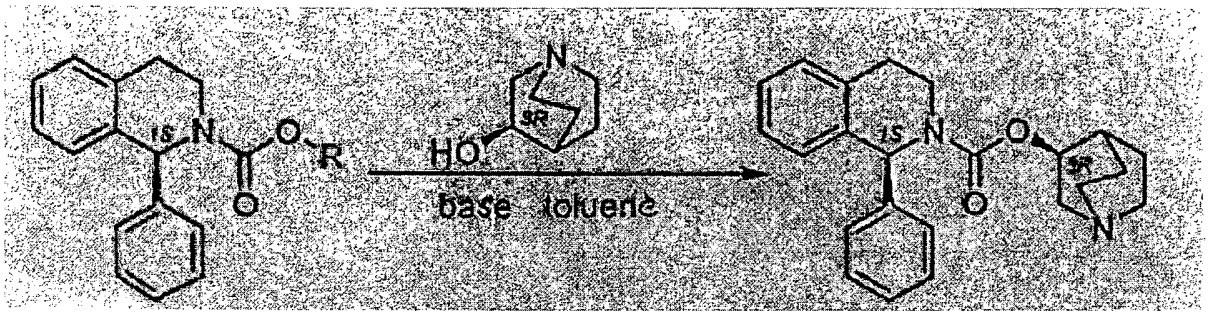


Scheme 1

[0008] Furthermore, we have found experimentally that catalysis using an unbranched sodium alkoxide, as described in WO 2005/087231, is inconvenient because the unbranched alkoxide acts not only as a base but also as a nucleophilic agent, whereupon an impurity is formed - solifenacin substituted by an alkyl group in position 2 at the quinuclidine backbone.

DISCLOSURE OF INVENTION

[0009] The invention consists in a new procedure to prepare (1S)-(3R)-1-azabicyclo[2.2.2.]oct-3-yl 3,4-dihydro-1-phenyl-2(1H)-isoquinoline carboxylate, known under the nonproprietary name solifenacin, by condensation of (1S)-alkyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate (where the alkyl is a primary C_1 - C_4 alkyl) with 3-(R)-quinuclidol, the reaction being catalyzed by a non-nucleophilic base (Scheme 2).



R – primary alkyl (C_1 - C_4)

Scheme 2

[0010] A non-nucleophilic base is a base whose nucleophilic substitution ability is limited significantly. Non-nucleophilic

bases include, in particular, sterically hindered alcoholates C_4 - C_6) or amines; lithium compounds; or a group of substances known as phosphazenes. Examples of non-nucleophilic bases are given in Table 1 below.

Table 1: An overview of non-nucleophilic bases

Abbreviation	Name
tBuLi	*tert*-Butyllithium
	Hexyllithium
KOtBu	Potassium *tert*-butoxide
NaOtBu	Sodium *tert*-butoxide
LDA	Lithium diisopropylamide
K-HMDS	Potassium hexamethyldisilazide
Na-HMDS	Sodium hexamethyldisilazide
Li-HMDS	Lithium hexamethyldisilazide
Li-TMP	Lithium tetramethylpiperidide
	2,6-Di-*tert*-butyl-4-methylpyridine
TED	1,4-Diazabicyclo(2.2.2)octane
MTBD	7-Methyl-1,5,7-triazabicyclo(4.4.0)dec-5-ene
PMDBD	3,3,6,9,9-Pentamethylpiperidin-2,10-diazabicyclo-(4.4.0)dec-1-ene
PMP	1,2,2,6,6-Pentamethylpiperidine
TMG	1,1,3,3-Tetramethylguanidine
TMP	2,2,6,6-Tetramethylpiperidine
TBD	1,5,7-Triazabicyclo(4.4.0)-dec-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
P_1-t-Bu base	N'-*tert*-butyl-N,N,N',N',N",N"-hexamethylphosphorimidetriamide
BTPP	*terc*-Butylimino-tris(pyrrolidino) phosphorane
P_1-t-Oct base	*tert*-Octylimino-tris(dimethylamino) phosphorane
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
P_2-t-Bu base	1-*terc*-Butyl-2,2,4,4,4-pentakis(dimethylamino)-2-Λ^5,4 Λ^5-catenadi(phosphazene)
P_2-Et base	1-Ethyl-2,2,4,4,4-pentakis(dimethylamino)-2-Λ^5,4 Λ^5-catenadi(phosphazene)
P_4-t-Bu base	1-*terc*-Butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2Λ^5,4Λ^5-catenadi(phosphazene)

[0011] The following non-nucleophilic base is used in the invention: potassium *tert*-butoxide. With this base the conversion is nearly complete within 3 hours and no impurities such as have been described, for instance, in WO 2005/087231, are formed.

[0012] The present approach is convenient in that the transformation of (1S)-primary alkyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate to solifenacin requires 3-(R)-quinuclidol in a small excess only. The excess is higher than or equal to the amount of the catalyst (non-nucleophilic base) employed to accelerate the reaction. In this setup the degree of conversion is sufficiently high and the degree of racemization of both the starting substances and the product is very low.

[0013] The reaction is conducted in toluene at a temperature of the reaction mixture of 90 °C to 120 °C, using 3-(R)-quinuclidol in a 0% to 50% molar excess with respect to (1S)-alkyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate, and using 0% to 50% mol. of the catalyst with respect to (1S)-alkyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate. Preferably, the molar amount of the catalyst is lower than the molar excess of 3-(R)-quinuclidol with respect to (1S)-alkyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate. Preferably, the primary C_1-C_4 alkyl is ethyl.

[0014] After the conversion is achieved, the reaction mixture is cooled and water is added. After phase separation, the aqueous phase is washed with toluene. The combined organic extracts are washed with water, brine, and water again. Subsequently, the toluene layer is evaporated to dryness. The crude evaporation residue is dissolved in methanol, and to the solution is added a solution of hydrochloric acid in methanol with the molar hydrogen chloride content equal to or slightly higher than the product content. Solifenacin HCl salt is isolated, which salt can be converted by conventional methods to any other organic or inorganic salt.

[0015] The principle of the invention is illustrated on the examples below.

EXAMPLES

Common features of Examples 1 through 6

[0016] To a solution of 1(*S*)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate (0.1 mol) in toluene (25 ml) is added 3(*R*)-quinuclidol (0.1 - 0.15 mmol). The system is heated at 90 °C, and after the two starting substances have dissolved completely, potassium *tert*-butanolate (0 - 0.05 mmol) is added to the constantly stirred mixture and the fine suspension formed is heated to boil. While the reaction proceeds, the azeotropic toluene-ethanol mixture is distilled off from the mixture. The reaction is terminated after reaching the appropriate degree of conversion.

[0017] The development of the reaction (conversion of the substances) was monitored by gas chromatography.

[0018] The optical purity of the product was determined by capillary electrophoresis.

[0019] The analytical results for the products prepared as specified in Examples 1 - 6 are given in the table below.

Batch	Starting substances (%)		Percent existing in															
			3 hours			4 hours			5 hours			6 hours			10 hours			
	Quin	tBOC	conv.	*R,R*	*S,S*	conv.	*R,R*	*S,S*	conv.	*R,R*	*S,S*	conv.	*R,R*	*S,S*	conv.	*R,R*	*S,S*
9-142	120	20	96.11	1.77	1.97	96.45	2.07	2.27	97.07	2.27	2.27	-	-	-	-	-	-
9-143	110	10	51.29	0.21	0.50	78.20	1.32	0.78	87.45	1.82	0.95	95.86	5.12	1.42	96.07	5.13	1.51
9-144	110	20	96.80	5.12	2.33	-	-	-	-	-	-	-	-	-	-	-	-
9-145	130	20	87.52	2.15	0.78	-	-	-	-	-	-	-	-	-	-	-	-
9-146	120	30	96.01	4.56	1.38	-	-	-	-	-	-	-	-	-	-	-	-
9-148	130	10	34.53	0.00	0.00	-	-	-	64.93	0.40	0.48	76.45	0.58	0.75	-	-	-

Example 7

[0020] To a solution of 1(5)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate (19.2 mol) in toluene (140 ml) was added 3(*R*)-quinuclidol (23.04 mmol). The system was heated at 90 °C, and after the two starting substances had dissolved completely, potassium *tert*-butanolate (3.84 mmol) was added to the constantly stirred mixture and the fine suspension formed was heated to boil. While the reaction proceeded, the azeotropic toluene-ethanol mixture was distilled off from the mixture. The reaction was terminated after 3 hours of boil, when GC indicated that a 97% degree of conversion had been reached. A volume of 50 ml of water was added and the mixture was stirred at room temperature for 20 minutes. The toluene layer was allowed to separate in a separating funnel and the aqueous layer was washed with toluene (2x 50 ml). The combined organic extracts were washed with 50 ml of water, 25 ml of brine, and 25 ml of water, and evaporated to dryness on a rotary vacuum evaporator. The crude evaporation residue was dissolved in methanol, a solution of hydrochloric acid in methanol was added, and the whole was evaporated to dryness in a rotary vacuum evaporator.

[0021] The product was obtained in the form of a white solid (4.54 g, 68.79% theory).

Reference example 8

[0022] To a solution of 1(*S*)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate (3.6 mol) in toluene (30 ml) was added 3(*R*)-quinuclidol (4.3.mmol). The system was heated at 90 °C, and after the two starting substances had dissolved completely, a 1.8M solution of lithium diisopropylamide in a THF-heptane-EtOH mixture (0.7 mmol) was added to the constantly stirred mixture, and the whole was heated to boil. While the reaction proceeded, the azeotropic toluene-ethanol mixture was distilled off from the mixture. The reaction was terminated after 6 hours of boil. The mixture was processed conventionally to obtain the product as the HCl salt. Yield of the white crystalline substance: 420 mg (29.2% theory).

Reference example 9

[0023] To a solution of 1(*S*)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate (3.6 mol) in toluene (30 ml) was added 3(*R*)-quinuclidol (4.3.mmol). The system was heated at 90 °C, and after the two starting substances had dissolved completely, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.7 mmol) was added to the constantly stirred mixture, and the whole was heated to boil. While the reaction proceeded, the azeotropic toluene-ethanol mixture was distilled off from the mixture. The reaction was terminated after 6 hours of boil. The mixture was processed conventionally to obtain the product as the HCl salt.

[0024] The yield of the white crystalline substance obtained was 400 mg (27.8 % theory).

Claims

1. A process for the preparation of (1S)-(3R)-1-azabicyclo [2.2.2]oct-3-yl 3,4-dihydro-1-phenyl-2(1H)-isoquinoline carboxylate by reacting (1S)-alkyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate with 3-(R)-quinuclidol in an inert solvent, **characterized in that** a primary alkyl ester of the carboxylate whose alkyl length is C_1-C_4 is used and the reaction is catalyzed by a non-nucleophilic base, wherein the non-nucleophilic base is potassium tert-butoxide.

2. The process as claimed in Claim 1, **characterized in that** the reaction is conducted in toluene at a temperature of the reaction mixture of 90 °C to 120 °C, using 3-(R)-quinuclidol in a 0% to 50% molar excess with respect to (1 S)-alkyl 1-phenyl-,2,3,4-tetrahydro-2-isoquinoline carboxylate, and using 0% to 50% mol. of the catalyst with respect to (1S)-alkyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate.

3. The process as claimed in Claim 2 **characterized in that** the molar amount of the catalyst is lower than the molar excess of 3-(R)-quinuclidol with respect to (1S)-alkyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate.

4. The process as claimed in Claims 1 through 3, **characterized in that** the ethyl ester is selected from the group of (1S)-alkyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylates.

Patentansprüche

1. Verfahren zur Herstellung von (1S)-(3R)-1-Aza-bicyclo[2.2.2]oct-3-yl-3,4-dihydro-1-phenyl-2(1H)-iso-chinolincarb-

oxylat durch Umsetzung von (1S)-Alkyl-1-phenyl-1,2,3,4-tetrahydro-2-isochinolincarboxylat mit 3-(R)-Chinuclidol in einem inerten Lösungsmittel, **dadurch gekennzeichnet, dass** ein primärer Alkylester des Carboxylats, dessen Alkyllänge C_1-C_4 beträgt, verwendet wird und die Reaktion durch eine nicht nucleophile Base katalysiert wird, wobei die nicht nucleophile Base Kalium-tert-Butoxid ist.

2. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, dass** die Reaktion in Toluol bei einer Temperatur des Reaktionsgemisches von 90 °C bis 120 °C durchgeführt wird, unter Verwendung von 3-(R)-Chinuclidol in einem molaren Überschuss von 0 % bis 50 %, bezogen auf (1S)-Alkyl-1-phenyl-1,2,3,4-tetrahydro-2-isochinolincarboxylat und unter Verwendung von 0 bis 50 Mol-% des Katalysators, bezogen auf (1S)-Alkyl-1-phenyl-1,2,3,4-tetrahydro-2-isochinolincarboxylat.

3. Verfahren nach Anspruch 2, **dadurch gekennzeichnet, dass** die molare Menge des Katalysators kleiner ist als der molare Überschuss an 3(R)-Chinuclidol, bezogen auf (1S)-Alkyl-1-phenyl-1,2,3,4-tetrahydro-2-isochinolincarboxylat.

4. Verfahren nach Ansprüchen 1 bis 3, **dadurch gekennzeichnet, dass** der Ethylester aus der Gruppe der (1S)-Alkyl-1-phenyl-1,2,3,4-tetrahydro-2-isochinolincarboxylate ausgewählt ist.

Revendications

1. Un procédé pour la préparation de 3,4-dihydro-1-phényl-2(1H) isoquinoléine carboxylate de (1S)-(3R)-1-azabicyclo-[2.2.2]-oct-3-yl en faisant réagir 1,2,3,4 tétrahydro-2-isoquinoléine carboxylate de (1S)-alkyl 1-phényl avec le 3-(R)-quinuclidol dans un solvant inerte, **caractérisé en ce qu'**est utilisé un ester d'alkyle primaire du carboxylate avec un groupe alkyle en C_1-C_4 et **en ce que** la réaction est catalysée par une base non nucléophile, procédé dans lequel la base non nucléophile est le tert-butoxyde de potassium.

2. Le procédé selon la revendication 1, **caractérisé en ce que** la réaction est conduite dans du toluène à une température du mélange réactionnel de 90°C à 120°C, en utilisant le 3-(R)-quinuclidol en un excès molaire de 0% à 50% par rapport au 1,2,3,4 tétrahydro-2-isoquinoléine carboxylate de (1S)-alkyl 1-phényl, et en utilisant 0% à 50% en moles du catalyseur par rapport à 1,2,3,4 tétrahydro-2-isoquinoléine carboxylate de (1S)-alkyl 1-phényl.

3. Le procédé selon la revendication 2, **caractérisé en ce que** la quantité molaire du catalyseur est inférieure à l'excès molaire de l'acide 3-(R)-quinuclidol par rapport au 1,2,3,4 tétrahydro-2-isoquinoléine carboxylate de (1S)-alkyl 1-phényl.

4. Le procédé selon les revendications 1 à 3, **caractérisé en ce que** l'ester d'éthyle est choisi dans le groupe des 1,2,3,4 tétrahydro-2-isoquinoléine carboxylate de (1S)-alkyl 1-phényl.

REFERENCES CITED IN THE DESCRIPTION

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- EP 0801067 A **[0002] [0004] [0006] [0007]**
- WO 9620194 A **[0002] [0004]**
- WO 2005087231 A **[0005] [0008] [0011]**

Szabadalmi igénypontok.

1. Eljárás (1S)-(3R)-1-azabiciklo-[2.2.2]okt-3-il 3,4-dihidro-1-fenil-2(1H)-izokinolin-karboxilát előállítására (1S)-alkil 1-fenil-1,2,3,4-tetrahidro-2-izokinolin-karboxilát és 3-(R)-kinuklidinol inert oldószerben való reagáltatásával *azzal jellemezve, hogy* a karboxilát 1 – 4 szénatomos primer alkil-észterét használjuk és a reakciót egy nem-nukleofil bázissal katalizáljuk, ahol a nem-nukleofil bázis kálium-terc-butoxid.

2. Az 1. igénypont szerinti eljárás *azzal jellemezve, hogy* a reagáltatást toluolban végezzük el a reakcióelegy 90 ^{0}C - 120 ^{0}C közötti hőmérsékletén, a 3-(R)-kinuklidinolt [az (1S)-alkil 1-fenil-1,2,3,4-tetrahidro-2-izokinolin karboxilátra vonatkoztatott] 0% - 50% közötti moláris feleslegben használva és 0 - 50 mol% katalizátort használva az (1S)-alkil 1-fenil-1,2,3,4-tetrahidro-2-izokinolin karboxilátra vonatkoztatva.

3. A 2. igénypont szerinti eljárás *azzal jellemezve, hogy* a katalizátor moláris mennyisége kisebb, mint a 3-(R)-kinuklidinol moláris felesleg az (1S)-alkil 1-fenil-1,2,3,4-tetrahidro-2-izokinolin karboxilátra vonatkoztatva.

4. Az 1. – 3. igénypontok szerinti eljárás *azzal jellemezve, hogy* az (1S)-alkil 1-fenil-1,2,3,4-tetrahidro-2-izokinolin karboxilátok csoportjából az etilésztert alkalmazzuk.

A szabadalmas helyett
a meghatalmazott

Dr. Somfai Éva
szabadalmi ügyvivő

SOMFAI ÉS TÁRSAI
IPARJOGI KFT.
1137 Bp., Pozsonyi út 38.