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(34) Titre : PROCEDES DE PREPARATION DE SOLIFENACINE
(34) Title: INTERMEDIATES FOR PREPARING SOLIFENACIN

(57) Abrégé/Abstract:
Provided are new intermediates of solifenacin and methods for their preparation, as well as methods of preparing solifenacin and solifenacin succinate.
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PROCESSES FOR PREPARING SOLIFENACIN

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to United States Provisional Patent Application Nos. 60/753,236, filed December 21 2005; 60/835,802, filed August 3, 2006; 60/860,642, filed November 22, 2006; and 60/873,022, filed December 6, 2006, each of which is hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to new intermediates of solifenacin, methods for their preparation, and novel methods for preparing solifenacin and solifenacin succinate.

BACKGROUND OF THE INVENTION

(3R)-1-azabicyclo[2.2.2]oct-3-yl-(1S)-1-phenyl-3,4-dihydroisoquinoline-2-(1H)-carboxylate ((S)-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid 3(R)-quinuclidinyl ester) is known as solifenacin, also known as YM-905 (in its free base form) and YM-67905 (in its succinate form). Solifenacin has the molecular formula C_{23}H_{28}O_{2}, a molecular weight of 362.4647, and the following chemical structure:

![Chemical structure of solifenacin](image)

\[ C_{23}H_{28}N_{2}O_{2} \]

Exact Mass: 362.1994
Mol. Wt.: 362.4647
m/z: 362.1994 (100.0%), 363.2028 (25.6%), 364.2061 (3.1%)
C, 76.21; H, 7.23; N, 7.73; O, 8.83

Solifenacin succinate is a urinary antispasmodic, acting as a selective antagonist to the M(3)-receptor. It is used as treatment of symptoms of overactive bladder, such as urinary urgency and increased urinary frequency, as may occur in patients with overactive bladder syndrome (OAB), as reviewed in Chilman-Blair, Kim et al., Drugs of Today, 40(4):343 – 353 (2004). Its crystalline powder is white to pale yellowish-white and is freely soluble at room temperature in water, glacial acetic acid, DMSO, and methanol.
The commercial tablet is marketed under the trade name VESICARE®. As VESICARE®, it was approved by the FDA for once daily treatment of OAB and is prescribed as 5 mg and 10 mg tablets.

The drug was developed by Yamanouchi Pharmaceutical Co. Ltd. and disclosed in US. Patent No. 6,017,927 and its continuation, US. Patent No. 6,174,896. Disclosed therein are compounds whose general formula is:

![Chemical Structure](image)

The definitions of the various groups encompass solifenacin, including its salts, as well as pharmaceutical compositions. WO 2005/087231 and WO 2005/105795 more specifically disclose processes for the production of solifenacin and its salt to a high degree of purity for medicinal use.

There are two principal processes for synthesizing solifenacin disclosed in the art. Both use the following as key starting materials:

- HO
- (R)-(-)-Quinuclidinol
- 1-Phenyl-1,2,3,4-tetrahydroisoquinoline

![Scheme 1](image)

wherein the quinuclidinol reactant is available commercially. The overall synthesis as reported by Mealy, N., et al. in Drugs of the Future, 24 (8): 871-874 (1999) is depicted in Scheme 2:
U.S. Patent No. 6,017,927 discloses another process for the preparation of solifenacin, wherein 3-quinuclidinyl chloroformate monohydrochloride is admixed with (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline to obtain solifenacin, as seen below in Scheme 3:

There is a need in the art for additional processes for preparing solifenacin that employ shorter reaction times and less hazardous materials.

SUMMARY OF THE INVENTION

In one embodiment, the invention encompasses a haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate of the formula
wherein R is an alkyl and X is a halogen.

In another embodiment, the invention encompasses a process for preparing a haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate of the formula

comprising combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, a haloalkylhaloformate of the formula

and a base to obtain the haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate, wherein R is an alkyl and X is a halogen.

In another embodiment, the invention encompasses a process for preparing solifenacin comprising: combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, a haloalkylhaloformate of the formula

and a base to obtain a haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate of the formula
and converting the haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate into solifenacin, wherein R is an alkyl and X is a halogen.

In another embodiment, the invention encompasses a process for preparing solifenacin comprising: combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, a haloalkylhaloformate of the formula

\[ \text{XR} \quad \text{O} \quad \text{X} \]

and a first base to obtain a haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate of the formula

\[ \text{NR} \quad \text{O} \quad \text{RX} \]

and combining the haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate with (R)-3-quinuclidinol in the presence of a second base to obtain solifenacin.

In one embodiment, the invention encompasses a haloalkyl-quinuclidyl-carbonate of the formula

\[ \text{XR} \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{N} \]

wherein R is an alkyl and X is a halogen.

In another embodiment, the invention encompasses a process for preparing a haloalkyl-quinuclidyl-carbonate of the formula
comprising combining (R)-3-quinuclidinol, a haloalkylhaloformate of the formula

and a base to obtain the haloalkyl-quinuclidyl-carbonate, wherein R is an alkyl and X is a halogen.

In another embodiment, the invention encompasses a process for preparing solifenacin comprising: combining (R)-3-quinuclidinol, a haloalkylhaloformate of the formula

and a base to obtain a haloalkyl-quinuclidyl-carbonate of the formula

and converting the haloalkyl-quinuclidyl-carbonate into solifenacin, wherein R is an alkyl and X is a halogen.

In another embodiment, the invention encompasses a process for preparing solifenacin comprising: combining (R)-3-quinuclidinol, a haloalkylhaloformate of the formula

and a first base to obtain a haloalkyl-quinuclidyl-carbonate of the formula
and combining the haloalkyl-quinuclidyl-carbonate with (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline and a second base to obtain solifenacin, wherein R is an alkyl and X is a halogen.

In another embodiment, the invention encompasses a process for preparing solifenacin succinate comprising preparing solifenacin by one of the above-described processes, and converting the solifenacin into solifenacin succinate.

**DETAILED DESCRIPTION OF THE INVENTION**

As used herein, the term “room temperature” refers to a temperature of about 20°C to about 25°C.

The present invention provides new intermediates of solifenacin, and improved processes for the preparation of solifenacin succinate and solifenacin using (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (S-IQL), haloalkylhaloformate and (R)-3-quinuclidinol.

The present invention provides haloalkyl-IQL-carbamate. Preferably, the haloalkyl-IQL-carbamate is chloroethyl-IQL-carbamate.

The present invention provides a process for the preparation of haloalkyl-IQL-carbamate comprising combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (S-IQL), haloalkylhaloformate and a first base.

Preferably, the process further comprises adding a first organic solvent.

Preferably, the first organic solvent is selected from the group consisting of: dimethylformamide (DMF), tetrahydrofuran (THF), methyl-THF, dioxane, dimethylsulfoxide (DMSO), aromatic hydrocarbon, dichloromethane and mixtures of them with water. More preferably, the first organic solvent is selected from the group consisting of: aromatic hydrocarbon and THF. Preferably, the aromatic hydrocarbon is selected from the group consisting of toluene and xylene. Most preferably, the first organic solvent is toluene.

Preferably, the haloalkylhaloformate is selected from the group consisting of fluoroethylchloroformate, chloroethylbromoformate and bromoethylchloroformate, more preferably, chloroethylchloroformate.

Preferably, the process comprises: combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (S-IQL), a first organic solvent and a first base, and thereafter
combining the haloalkylhaloformate to obtain haloalkyl-IQL-carbamate. Preferably, the haloalkylhaloformate is added to the combination of the (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (S-IQL), the first organic solvent and the first base. Preferably, the haloalkylhaloformate is added dropwise. Preferably, prior to the haloalkylhaloformate addition, a cooling step is performed. Preferably, the cooling is to a temperature of about 0°C to about 25°C.

Preferably, the temperature during the process is from about 0°C to about 25°C.

Preferably, the first base is an organic base or carbonate. Preferably, the organic base is an amine. Preferably, the amine is selected from the group consisting of diisopropylamine and triethylamine. Preferably, the carbonate is selected from the group consisting of sodium carbonate, potassium carbonate, sodium bicarbonate, and potassium bicarbonate.

After combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (S-IQL), haloalkylhaloformate, and a first base, a reaction mixture is obtained. Preferably, the reaction mixture is maintained, preferably for about 1 hour to about 10 hours.

Preferably, the process further comprises separating the haloalkyl-IQL-carbamate. Preferably, the separation is by filtration. Optionally, the separation is isolation by extraction with water and evaporation of the solvent.

The present invention is also directed to the synthesis of solifenacin succinate by converting the haloalkyl-IQL-carbamate obtained by the above process to solifenacin succinate.

The present invention provides a process for the preparation of solifenacin, comprising of the steps:

(a) combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (S-IQL), haloalkylhaloformate, and a first base to obtain haloalkyl-IQL-carbamate; and

(b) combining the haloalkyl-IQL-carbamate with (R)-3-quinoclidinol in the presence of a second base to obtain solifenacin.

The above process may be illustrated in the following Scheme 4:
Preferably, step (a) further comprises adding a first organic solvent as described above.

Preferably, the haloalkylhaloformate is as described above.

Preferably, step (a) first comprises combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (S-IQL), a first organic solvent and a first base, and thereafter combining the haloalkylhaloformate to obtain haloalkyl-IQL-carbamate, as described above.

Preferably, the temperature in step (a) is as described above.

Preferably, the first base in step (a) is as described above.

After combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (S-IQL), haloalkylhaloformate, and a first base, a reaction mixture is obtained. Preferably, the reaction mixture is maintained, as described above.

Optionally, prior to step (b), the haloalkyl-IQL-carbamate of step (a) is separated. Preferably, the separation is by filtration. Optionally, the separation isolation is by extraction with water and evaporation of the solvent.

Preferably, step (b) further comprises adding a second organic solvent. Preferably, the second organic solvent in step (b) is selected from the group consisting of, dimethylformamide (DMF), tetrahydrofuran (THF), methyl-THF, dioxane, dimethylsulfoxide (DMSO), aromatic hydrocarbon, and mixtures thereof. More preferably, the second organic solvent in step (b) is selected from the group consisting of aromatic hydrocarbon and DMF. Preferably, the aromatic hydrocarbon is selected from the group consisting of toluene and xylene. Most preferably, the second organic solvent in step (b) is toluene.

Preferably, the temperature in step (b) is from about 10° to about 100°C. More preferably, the temperature in step (b) is from about 70° to about 90°C.
Preferably, the second base in step (b) is selected from the group consisting of: metal alkyls, metal alkoxydes and sodium hydride. More preferably, the second base in step (b) is sodium hydride.

Optionally, step (b) further comprises distilling the solvent.

After combining the haloalkyl-IQL carbamate with (R)-3-quinuclidinol in the presence of a second base, a reaction mixture is obtained. Preferably, the reaction mixture is maintained, preferably for about 1 hour to about 24 hours.

Preferably, the process further comprises a recovery step.

Preferably, the recovery comprises: extracting sulfinacin with a saturated NaCl solution, removing the aqueous layer, adding HCl solution to obtain a two phase system, separating the aqueous phase, basifying the aqueous phase with K₂CO₃ solution, extracting it with EtOAc and isolating. Preferably, the isolation is by filtering and evaporating the organic solvent.

The present invention provides haloalkyl-quinuclidyl-carbonate. Preferably, the haloalkyl-quinuclidyl-carbonate is chloroethyl-quinuclidyl-carbonate.

The present invention provides a process for the preparation of haloalkyl-quinuclidyl-carbonate, comprising combining (R)-3-quinuclidinol, haloalkylhaloformate and a first base.

Preferably, the process further comprises adding a first organic solvent. Preferably, the first organic solvent is selected from the group consisting of, dimethylformamide (DMF), tetrahydrofuran (THF), methyl-THF, dioxane, dimethylsulfoxide (DMSO), aromatic hydrocarbon, and dichloromethane. More preferably, the first organic solvent is selected from the group consisting of aromatic hydrocarbon and THF. Preferably, the aromatic hydrocarbon is selected from the group consisting of toluene and xylene. Preferably, the first organic solvent is toluene.

Preferably, the haloalkylhaloformate is selected from the group consisting of haloalkylbromoformate or haloalkylchloroformate, preferably fluoroethylchloroformate and chloroethylchloroformate, more preferably, chloroethylchloroformate.

Preferably, the temperature during the process is from about 0° to about 25°C.

Preferably, the first base is an organic base. Preferably, the organic base is an amine. Preferably, the amine is selected from the group consisting of diisopropylamine and triethylamine.

After combining (R)-3-quinuclidinol, haloalkylhaloformate and a first base, a reaction mixture is obtained. Preferably, the reaction mixture is maintained, preferably for about 1 hour to about 10 hours.
Preferably, the process further comprises separating the haloalkyl-quinuclidyl-carbonate. Preferably, the separation is by filtration.

The present invention is also directed to the synthesis of solifenacin succinate by converting the haloalkyl-quinuclidyl-carbonate obtained by the above process to solifenacin succinate.

The present invention provides another process for the preparation of solifenacin, comprising of the steps:

(a) combining (R)-3-quinuclidinol, haloalkylhaloformate and a first base to obtain haloalkyl-quinuclidyl-carbonate; and

(b) combining the haloalkyl-quinuclidyl-carbonate with (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (S-IQL) and a second base to obtain solifenacin.

The above process may be illustrated in the following Scheme 5:

![Scheme 5 Image]

Preferably, step (a) further comprises adding a first organic solvent as described above.

Preferably, the haloalkylhaloformate is as described above.

Preferably, the temperature in step (a) is as described above.

Preferably, the first base in step (a) is as described above.

After combining (R)-3-quinuclidinol, haloalkylhaloformate and a first base, a reaction mixture is obtained. Preferably, the reaction mixture is maintained, as described above.

Optionally, prior to step (b), the haloalkyl-quinuclidyl-carbonate of step (a) is separated. Preferably, the separation is by filtration.

Preferably, step (b) further comprises adding a second organic solvent.
Preferably, the second organic solvent in step (b) is selected from the group consisting of: dimethylformamide (DMF), tetrahydrofuran (THF), methyl-THF, dioxane, dimethylsulfoxide (DMSO), aromatic hydrocarbon, and dichloromethane. More preferably, the second organic solvent in step (b) is selected from the group consisting of aromatic hydrocarbon and THF. Preferably, the aromatic hydrocarbon is selected from the group consisting of toluene and xylene.

Preferably, the temperature in step (b) is from about 10° to about 100°C. More preferably, the temperature in step (b) is from about 70° to about 90°C.

Preferably, the second base is selected from the group consisting of: metalalkyls, metal alkoxides and sodium hydride. More preferably, the second organic base is sodium hydride.

After combining the haloalkyl-quinuclidyl-carbonate with (S)-1-phenyl-1,2,3,4-tetrahydroisooquinoline (S-IQL) and a second base, a reaction mixture is obtained. Preferably, the reaction mixture is maintained, preferably for about 1 hour to about 24 hours.

Preferably, the process further comprises a recovery step. Preferably, the recovery comprises: extracting solifenacin with a saturated NaCl solution, removing the aqueous layer, adding HCl solution to obtain a two phase system, separating the aqueous phase, basifying the aqueous phase with K₂CO₃ solution, extracting it with EtOAc and isolating. Preferably, the isolation is by filtering and evaporating the organic solvent.

The present invention is also directed to the synthesis of solifenacin succinate by converting the solifenacin obtained by the above processes to solifenacin succinate. The conversion of the solifenacin to solifenacin succinate may be performed by any method known to one of skill in the art. Such methods include, but are not limited to, that disclosed in WO 2005/087231, hereby incorporated by reference.

Preferably, the conversion of the solifenacin to solifenacin succinate is performed by dissolving the solifenacin in EtOH and adding succinic acid to obtain a precipitate of solifenacin succinate. Optionally, the solution may be seeded with solifenacin succinate to induce the precipitation of the solifenacin succinate.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.
EXAMPLES

Example 1: Preparation of solifenacin succinate

A solution of (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (C_{13}H_{15}N) (16g), toluene (80ml), and diisopropylethylamine (DIPEA, 13.5g) was cooled to 0°C. Chloroethylchloroformate (C_{3}H_{4}Cl_{2}O_{2}) (CECF, 13.0gr) was added dropwise, keeping the temperature between 0°-20°C. After stirring at room temperature for 1.5 hours, the mixture was filtered.

The filtrate was added to solution of (R)-quinuclidin-3-ol (C_{7}H_{12}NO) (11.6g) in toluene (80ml), DMF (16ml), and NaH (60%, 5.5g) at 80°C during 1 hour, and stirred at 95°-100°C for 17 hours. The mixture was cooled to room temperature, and THF (small amount) was added. A saturated NaCl solution (300ml) was added, and the phases were separated. The organic phase was acidified with 10% HCl solution, and the phases were separated. The aqueous phase was basified with K_{2}CO_{3} solution and extracted with ethyl acetate (EtOAc). The organic phase was filtered and evaporated to obtain solifenacin (SLF) (21.25g). The residue was dissolved in ethanol (EtOH) (100ml) and succinic acid (7.0g) was added. Seeding with SLF-succinate was performed, and the mixture was stirred at RT for 16 hours. The product was isolated by vacuum filtration, washed with EtOH (3x20ml), and dried in vacuum oven at 50° over night to obtain SLF-succinate (10.46g).

Example 2: Preparation of solifenacin succinate

Chloroethylchloroformate (CECF, 13.0g) is added dropwise to solution of (R)-quinuclidin-3-ol (11.6g) and diisopropylethylamine (DIPEA, 13.5g) in THF (150ml), keeping the temperature between 0°-20°C. The mixture is stirred at room temperature for several hours. Then (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (16g) is added and the solution is stirred at room temperature for another 16 hours. The solution is diluted with EtOAc (350ml) and washed with a saturated NaCl solution (300ml). The organic phase is acidified with 10% HCl solution, and the phases are separated. The aqueous phase is basified with K_{2}CO_{3} solution and extracted with EtOAc. The organic phase is filtered and evaporated to obtain SLF. The residue is dissolved in EtOH (100ml), and succinic acid (7.0g) is added. Seeding with SLF-succinate is performed, and the mixture is stirred at RT for 16 hours. The product is isolated by vacuum filtration, washed with EtOH (3x20ml), and dried in vacuum oven at 50° over night to obtain SLF-succinate.
Example 3: Preparation of solifenacin succinate

Chloroethylchloroformate (CECF, 13.0g) is added dropwise to solution of (R)-quinuclidin-3-ol (11.6g) and diisopropylethylamine (DIPEA, 13.5g) in Toluene (150ml), keeping the temperature between 0°-20°C. The mixture is stirred at room temperature for several hours and filtrated. Then (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (16g) is added followed by addition of sodium hydride (60%, 5.5g) and the mixture is stirred at reflux for another 16 hours. The solution is diluted with EtOAc (350ml) and washed with a saturated NaCl solution (300ml). The organic phase is acidified with 10% HCl solution, and the phases are separated. The aqueous phase is basified with K2CO3 solution and extracted with EtOAc. The organic phase is filtered and evaporated to obtain SLF. The residue is dissolved in EtOH (100ml), and succinic acid (7.0g) is added. Seeding with SLF-succinate is performed, and the mixture is stirred at RT for 16 hours. The product is isolated by vacuum filtration, washed with EtOH (3x20ml), and dried in vacuum oven at 50° over night to obtain SLF-succinate.
We claim:

1. A haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate of the formula

\[ \text{ORX} \]

\[ \text{ORX} \]

wherein \( R \) is an alkyl and \( X \) is a halogen.

2. The haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate of claim 1, wherein \( R \) is ethyl.

3. The haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate of claim 1 or 2, wherein \( X \) is chlorine.

4. A process for preparing the haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate of any one of claims 1 to 3, comprising combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, a haloalkylhaloformate of the formula

\[ \text{XR} \]

\[ \text{XR} \]

and a base to obtain the haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate, wherein \( R \) is an alkyl and \( X \) is a halogen.

5. A process for preparing solifenacin comprising:
   a) combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, a haloalkylhaloformate of the formula

\[ \text{XR} \]

\[ \text{XR} \]

and a first base to obtain a haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate of the formula
b) converting the haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate into solifenacin, wherein R is an alkyl and X is a halogen.

6. A process for preparing solifenacin comprising:
   a) combining (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, a haloalkylhaloformate of the formula

\[ XR - O - \backslash \text{halogen} \]

, and a first base to obtain a haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate of the formula

\[ \text{haloalkyl} - N - O - \text{halogen} \]

; and

b) combining the haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate with (R)-3-quinuclidinol in the presence of a second base to obtain solifenacin, wherein R is an alkyl and X is a halogen.

7. The process of claim 5 or 6, further comprising admixing the combination of step a) with a first organic solvent.

8. The process of claim 7, wherein the first organic solvent is selected from the group consisting of dimethylformamide, tetrahydrofuran, methyl-tetrahydrofuran, dioxane, dimethylsulfoxide, an aromatic hydrocarbon, dichloromethane, and mixtures thereof with water.
9. The process of claim 7 or 8, wherein the first organic solvent is an aromatic hydrocarbon or tetrahydrofuran.

10. The process of claim 8 or 9, wherein the aromatic hydrocarbon is selected from the group consisting of toluene and xylene.

11. The process of any one of claims 7 to 10, wherein the first organic solvent is toluene.

12. The process of any one of claims 5 to 11, wherein the haloalkylhaloformate is selected from the group consisting of fluoroethylchloroformate, chloroethylbromoformate and bromoethylchloroformate.

13. The process of any one of claims 5 to 12, wherein the haloalkylhaloformate is chloroethylchloroformate.

14. The process of any one of claims 7 to 13, wherein the (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, the first organic solvent, and the first base are combined, and the haloalkylhaloformate is added to the combination.

15. The process of claim 14, wherein the haloalkylhaloformate is added dropwise to the combination of the (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, the organic solvent, and the first base.

16. The process of claim 14 or 15, wherein the combination of the (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, the first organic solvent, and the first base is cooled before the addition of the haloalkylhaloformate.

17. The process of any one of claims 14 to 16, wherein the combination of the (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, the first organic solvent, and the first base is cooled to a temperature of about 0°C to about 25°C before the addition of the haloalkylhaloformate.

18. The process of any one of claims 5 to 17, wherein the first base is an organic base or carbonate.

19. The process of claim 18, wherein the organic base is an amine.

20. The process of claim 19, wherein the amine is selected from the group consisting of diisopropylamine and triethylamine.

21. The process of claim 18, wherein the carbonate is selected from the group consisting of sodium carbonate, potassium carbonate, sodium bicarbonate, and potassium bicarbonate.
22. The process of any one of claims 5 to 21, wherein the combination of step a) is maintained for about 1 hour to about 10 hours to obtain the haloalkyl-1,2,3,4-tetrahydroisoquinoline carbamate.

23. The process of any one of claims 5 to 22, wherein the combination of step a) is maintained at a temperature of about 0°C to about 25°C.

24. The process of any one of claims 5 to 23, further comprising admixing the combination of step b) with a second organic solvent.

25. The process of claim 24, wherein the second organic solvent is selected from the group consisting of dimethylformamide, tetrahydrofuran, methyl-tetrahydrofuran, dioxane, dimethylsulfoxide, an aromatic hydrocarbon, and mixtures thereof.

26. The process of claim 24 or 25, wherein the second organic solvent is selected from the group consisting of an aromatic hydrocarbon and dimethylformamide.

27. The process of claim 25 or 26, wherein the aromatic hydrocarbon is selected from the group consisting of toluene and xylene.

28. The process of any one of claims 24 to 27, wherein the second organic solvent is toluene.

29. The process of any one of claims 6 to 28, wherein step b) is performed at a temperature of about 10°C to about 100°C.

30. The process of any one of claims 6 to 29, wherein step b) is performed at a temperature of about 70°C to about 90°C.

31. The process of any one of claims 6 to 30, wherein the second base is selected from the group consisting of metal alkyls, metal alkoxides and sodium hydride.

32. The process of any one of claims 6 to 31, wherein the second base is sodium hydride.

33. The process of any one of claims 6 to 32, wherein the combination of step (b) is maintained for about 1 hour to about 24 hours to obtain solifenacin.

34. A haloalkyl-quinuclidyl-carbonate of the formula

\[
\text{XR} \quad \text{O} \quad \text{N}
\]

wherein R is an alkyl and X is a halogen.

35. The haloalkyl-quinuclidyl-carbonate of claim 34, wherein R is ethyl.
36. The haloalkyl-quinuclidyl-carbonate of claim 34 or 35, wherein X is chlorine.
37. A process for preparing the haloalkyl-quinuclidyl-carbonate of any one of claims
34 to 36 comprising combining (R)-3-quinuclidinol, a haloalkylhaloformate of the formula

\[
\text{XR} \overset{\circ}{\text{O}} \text{C} \overset{\circ}{\text{X}}
\]

and a base to obtain the haloalkyl-quinuclidyl-carbonate,
wherein R is an alkyl and X is a halogen.

38. A process for preparing solifenacin comprising:
   a) comprising combining (R)-3-quinuclidinol, a haloalkylhaloformate of the formula

\[
\text{XR} \overset{\circ}{\text{O}} \text{C} \overset{\circ}{\text{X}}
\]

and a first base to obtain a haloalkyl-quinuclidyl-carbonate of the formula

\[
\text{XR} \overset{\circ}{\text{O}} \text{C} \overset{\circ}{\text{t}} \text{N} \overset{\circ}{\text{H}} \overset{\circ}{\text{H}} \overset{\circ}{\text{H}} \overset{\circ}{\text{H}} \overset{\circ}{\text{H}}
\]

; and

b) converting the haloalkyl-quinuclidyl-carbonate into solifenacin,
wherein R is an alkyl and X is a halogen.

39. A process for preparing solifenacin comprising:
   a) combining (R)-3-quinuclidinol, a haloalkylhaloformate of the formula

\[
\text{XR} \overset{\circ}{\text{O}} \text{C} \overset{\circ}{\text{X}}
\]

and a first base to obtain a haloalkyl-quinuclidyl-carbonate of the formula

\[
\text{XR} \overset{\circ}{\text{O}} \text{C} \overset{\circ}{\text{t}} \text{N} \overset{\circ}{\text{H}} \overset{\circ}{\text{H}} \overset{\circ}{\text{H}} \overset{\circ}{\text{H}} \overset{\circ}{\text{H}} \overset{\circ}{\text{H}}
\]

; and

b) combining the haloalkyl-quinuclidyl-carbonate with (S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline and a second base to obtain solifenacin,
wherein R is an alkyl and X is a halogen.
40. The process of claim 38 or 39, further comprising admixing the combination of step a) with a first organic solvent.

41. The process of claim 40, wherein the first organic solvent is selected from the group consisting of dimethylformamide, tetrahydrofuran, methyl-tetrahydrofuran, dioxane, dimethylsulfoxide, an aromatic hydrocarbon, and dichloromethane.

42. The process of claim 40 or 41, wherein the first organic solvent is selected from the group consisting of an aromatic hydrocarbon and tetrahydrofuran.

43. The process of claim 41 or 42, wherein the aromatic hydrocarbon is selected from the group consisting of toluene and xylene.

44. The process of any one of claims 40 to 43, wherein the first organic solvent is toluene.

45. The process of any one of claims 38 to 44, wherein the haloalkylhaloformate is selected from the group consisting of fluoroethylchloroformate, chloroethylbromoformate and bromoethylchloroformate.

46. The process of any one of claims 38 to 45, wherein the haloalkylhaloformate is fluoroethylchloroformate or chloroethylchloroformate.

47. The process of any one of claims 38 to 46, wherein the haloalkylhaloformate is chloroethylchloroformate.

48. The process of any one of claims 38 to 47, wherein the first base is an organic base.

49. The process of claim 48, wherein the organic base is an amine.

50. The process of claim 49, wherein the amine is selected from the group consisting of diisopropylamine and triethylamine.

51. The process of any one of claims 38 to 50, wherein the combination of step a) is maintained for about 1 hour to about 10 hours to obtain the haloalkyl-quinuclidyl-carbonate.

52. The process of any one of claims 38 to 51, wherein the combination of step a) is maintained at a temperature of about 0°C to about 25°C.

53. The process of any one of claims 39 to 52, further comprising admixing the combination of step b) with a second organic solvent.

54. The process of claim 53, wherein the second organic solvent is selected from the group consisting of dimethylformamide, tetrahydrofuran, methyl-tetrahydrofuran, dioxane, dimethylsulfoxide, an aromatic hydrocarbon, and dichloromethane.

55. The process of claim 53 or 54, wherein the second organic solvent is selected from the group consisting of an aromatic hydrocarbon and tetrahydrofuran.
56. The process of claim 54 or 55, wherein the aromatic hydrocarbon is selected from the group consisting of toluene and xylene.
57. The process of any one of claims 39 to 56, wherein step b) is performed at a temperature of about 10°C to about 100°C.
58. The process of any one of claims 39 to 57, wherein step b) is performed at a temperature of about 70°C to about 90°C.
59. The process of any one of claims 39 to 58, wherein the second base is selected from the group consisting of metal alkyls, metal alkoxides and sodium hydride.
60. The process of any one of claims 39 to 59, wherein the second base is sodium hydride.
61. The process of any one of claims 39 to 60, wherein the combination of step (b) is maintained for about 1 hour to about 24 hours to obtain solifenacin.
62. A process for preparing solifenacin succinate comprising:
   a) preparing solifenacin by the process of any one of claims 5 to 33 or 37 to 61; and
   b) converting the solifenacin into solifenacin succinate.