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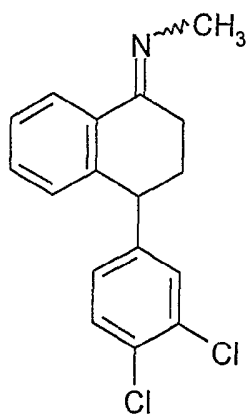
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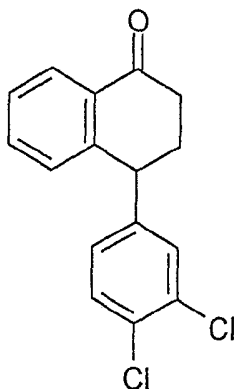
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(54) Title: PROCESS FOR THE PREPARATION OF AN IMINE INTERMEDIATE



(I)

(57) Abstract: The invention is directed to a process for the preparation of [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula (I) by reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)naphthalene-1-one of the Formula (II) with monomethyl amine which comprises carrying out the reaction in the presence of thionyl chloride in an ether-type solvent. The [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula I is a valuable pharmaceutical intermediate.



(II)



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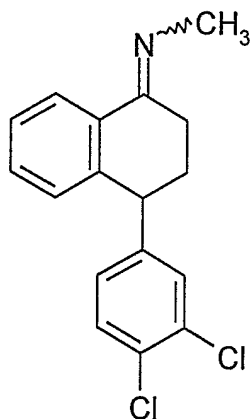
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Process for the preparation of an imine intermediate

BACKGROUND OF THE INVENTION

The invention relates to a new and improved process for the preparation of a ketimine compound which is a useful pharmaceutical intermediate. More particularly, the invention is directed to a new and improved process for the preparation of [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula



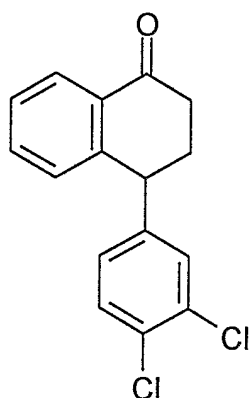
(I)

The compound of the Formula I is a valuable intermediate which can be used in pharmaceutical industry by the preparation of cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-

1,2,3,4-tetrahydro-1-naphthalene-amine-hydrochloride (INN sertraline) being a highly effective antidepressant.

STATE OF THE ART

The preparation of the compound of the Formula I was first described in US 4,536,518. According to this US patent 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one (tetralone) of the Formula



(II)

is coupled with methyl-amine in the presence of titan tetrachloride. Methyl-amine is used in a six-fold molar excess and the methyl-amine chlorohydrate and titan dioxide formed is removed by filtration from the reaction mixture. The disadvantage of this process is that titan tetrachloride is a highly corrosive product difficult to handle.

According to US 4,855,500 the reaction is carried out in an aprotic solvent in the presence of a molecular sieve under pressure. The reported yield is 87 %. However, this process is accompanied by the drawback that molecular sieve is very expensive and the reaction is rather slow. For the reason stated above the above process which uses a molecular sieve is unsuitable for the economical manufacture of the desired compound.

According to EP 1,047,666 tetralone is reacted with methylamine in a protic solvent at a temperature between 50°C and 110°C. Although high temperature and pressure are used, the conversion of the reaction is not higher than 95-98 %. The significant drawback of the process is that the reaction must be carried out in a special pressure-proof apparatus.

According to WO 00/26181 the reaction is carried out in a protic solvent, in the presence of a catalyst containing sulfonic acid or zeolite or silicate, in the presence of a dehydrating agent. The yield of the [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine obtained is between 66 % and 86 %.

According to the process described in WO 01/36377 a mixture containing 75-95 % of 4-(3,4-dichlorophenyl)-3,4-

dihydro-1(2H)-naphthalene-1-one and 25-5 % of 4-(2,3-dichlorophenyl)-3,4-dihydro-2H-naphthalene-1-one in a solvent is reacted with methyl-amine in the presence of a catalyst which contains sulfonic acid or zeolite or silicate or in the presence of a dehydrating agent under pressure at a temperature between 50°C and 70°C. A large number of solvents is enumerated. The product is purified by crystallization and the compound [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine is obtained in a purity above 99 %.

According to the process described in WO 02/096860 [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine is prepared by reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one with methyl-amine in an amide-containing solvent under the conditions of acid catalysis. Under such reaction conditions the reaction takes place rather slowly and requires 10 hours.

According to HU 98/01024 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one is reacted with methyl-amine in a lower alkanol to yield [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine. HU 98/01025 relates to a reduction process whereby [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-

naphthalene-1-ylidene]-methyl-amine is reduced to N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine preferably in an ether type solvent, particularly in tetrahydrofuran.

SUMMARY OF THE INVENTION

The object of the invention is to eliminate the above disadvantages of the known processes and to provide an industrial scale new process for the preparation of [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula I.

The above object is achieved by the process of the present invention.

According to the present invention there is provided a process for the preparation of [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula I by reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one of the Formula II with monomethyl amine which comprises carrying out the reaction in the presence of thionyl chloride in an ether-type solvent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the surprising recognition that if the reaction is carried out without using an alcohol-type solvent, titan tetrachloride and molecular sieve as suggested according to the known methods, the compound of the Formula I can be prepared with a very short reaction time and in an excellent yield of 99.5 % by carrying out the reaction 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one of the Formula II and monomethyl amine in the presence of thionyl chloride in an ether-type solvent.

As ether type solvent preferably tetrahydrofurane, dioxane, diethyl ether, diisopropyl ether or methyl-tertiary butyl ether, particularly tetrahydrofurane can be used.

The reaction is carried out at a temperature between -30°C and +40°C, preferably between -10°C and +25°C.

The reaction can be performed under atmospheric pressure without heating. The reaction time is short even under such mild reaction condition and takes 0.5-5 hours, preferably 1-3 hours.

Monomethyl amine is used in an excess related to the compound of the Formula II, namely generally in a 5-15 molar excess, preferably 10-12 molar excess. Thionyl chloride is used in an amount of 1.1-5 mole, preferably 1.5-2 mole, related to 1 mole of the compound of the Formula II.

According to a form of realization of the present invention there is provided a process for the preparation of a mixture of the (+)- and (-)-enantiomers of the compound of the Formula I enriched in the (+)-enantiomer which comprises using as starting material a mixture of the (+)- and (-)-enantiomers of the compound of the Formula II enriched in the (+)-enantiomer.

The [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula I thus obtained can be converted into (+/-)-cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine (raceme sertraline) if desired by catalytic hydrogenation.

According to a further aspect of the present invention there is provided a process for the preparation of (+/-)-cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine which comprises reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one of the Formula II with monomethyl

amine in the presence of thionyl chloride in an ether-type solvent, and thereafter subjecting the [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula I thus formed to catalytic hydrogenation in the same solvent.

As ether-type solvent preferably tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether or methyl-tertiary butyl ether, particularly tetrahydrofuran can be used.

Catalytic hydrogenation can be carried out preferably in the presence of palladium-charcoal catalyst. One can proceed preferably under atmospheric pressure at room temperature.

The racemic sertraline thus obtained can be optionally converted into a pharmaceutically acceptable acid addition salt thereof, preferably into the hydrochloride.

According to a further aspect of the present invention there is provided a process for the preparation of cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine and pharmaceutically acceptable acid addition salts thereof, preferably the hydrochloride, which comprises reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one of the Formula II with monomethyl amine

in the presence of thionyl chloride in an ether-type solvent, subjecting the [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula I thus obtained to catalytic hydrogenation in the same solvent, and thereafter subjecting the (+/-)-cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine thus obtained to resolution and if desired converting the product into a pharmaceutically acceptable acid addition salt, preferably the hydrochloride thereof.

As ether-type solvent preferably tetrahydrofurane, dioxane, diethyl ether, diisopropyl ether or methyl-tertiary butyl ether, particularly tetrahydrofurane can be used.

Resolution of racemic sertraline is carried out in a known manner by a process described in prior art preferably by using optically active amygdalic acid.

The significant advantage of the above form of realization of the process of the present invention is that the compound of the Formula I prepared by the present invention can be directly converted into racemic sertraline by catalytic hydrogenation performed without solvent change in the same solvent, in the mixture obtained by the preparation thereof, thereafter the pharmaceutical active ingredient cis-(1S)(4S)-

N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine-hydrochloride can be prepared by resolution and salt formation carried out in a manner known per se.

Compared to the processes described in prior art the process of the present invention shows the following advantages:

- the formation of the ketimine of the Formula I and the catalytic reduction can be carried out in the same solvent;
- the reaction time is extremely short and this presents a valuable technological advantage from the point of view of capacity;
- the reaction can be carried out without using high pressure and high temperature;
- the conversion and the yield are extremely high;
- a product of high purity is obtained; and
- the process can be performed in a simple manner under industrial scale too.

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to said Examples.

Example 1**Process for the preparation of [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine**

9 g (30.8 mM) of 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one are dissolved in 140 ml of tetrahydrofurane. The solution is cooled to -10°C and 12.6 g (400 mM) of gaseous methyl amine are introduced. To the reaction mixture at -10°C 4.2 ml (60 mM) of thionyl chloride are added under stirring. The addition having been completed the reaction mixture is stirred at room temperature. The reaction is monitored by GC. The reaction mixture is worked up when the amount of the starting material is decreased below 0.3 %. The tetrahydrofurane phase is separated from the precipitated methyl amine hydrochloride, evaporated and the residue is suspended in 20 ml of cold methanol. The crystals obtained are dried under an infra lamp. Thus 8.7 g of the desired compound are obtained, yield 93 %. Mp.: 147-148°C.

IR (KBr): 1625, 1468, 1056, 764.

¹H-NMR (CDCl₃, i400): 8.20 (1H, dd, J₂=7.3 Hz, J₂=1.9 Hz), 7.3 m (2H), 7.19 (1H, d, J=2.0 Hz), 6.89 m (2H), 4.15 (1H,

dd, $J_1=4.5$ Hz, $J_2=6.8$ Hz), 3.17 s (3H), 2.52 m (2H), 2.28 m (1H), 2.13 m (1H).

Example 2

Preparation of (+/-)cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine

9 g (30.8 mM) of 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one are dissolved in 140 ml of tetrahydrofuran. The solution is cooled to -10°C and 12.6 g (400 mM) of gaseous methyl amine are introduced. To the reaction mixture 4.2 ml (60 mM) of thionyl chloride are added at -10°C under stirring. The addition having been completed the reaction mixture is stirred at room temperature. The reaction is monitored by GC. The reaction mixture is worked up when the amount of the starting material is decreased below 0.3 %. The tetrahydrofuran phase is made free of methyl amine by partial evaporation. To the residual tetrahydrofuran solution 6.5 ml of a 1:1 mixture of an aqueous solution of 52 ml of potassium chloride and methanol and thereafter 1 g of a palladium-charcoal catalyst (8 % Pd, 28 % C, 64 % H_2O) are added. The reaction mixture is flushed with nitrogen under stirring and thereafter hydrogenated under atmospheric pressure at room temperature. Hydrogenation is continued until the [4(S,R)-

(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine is consumed. After the termination of hydrogenation the reaction mixture is filtered and the filtrate is acidified with concentrated aqueous hydrochloric acid at room temperature. The precipitated crystals are filtered. Thus 8.6 g of the desired compound are obtained, yield 82 %.
M.p.: 280-283 °C.

IR (KBr): 3340, 3021, 1469, 1396, 878.

¹H-NMR (CDCl₃, i400): 10.03 (1H, s), 9.93 (1H, s), 7.77 (1H, d, J=7.4 Hz), 7.41 (1H, d, 1.9 Hz), 7.36 (1H, d, J=8.2 Hz), 7.2 (3H, m), 6.87 (1H, d, J=7.5 Hz), 4.3 (1H, kv, J=4.9 Hz), 4.00 (1H, dd, J1=5.4 Hz, J2=8.4 Hz), 2.58 (3H, t, J=5.4 Hz), 2.3 (2H, m), 2.1 (2H, m).

Example 3

Preparation of cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine-hydrochloride (sertraline hydrochloride)

From (+/-)-cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine-hydrochloride the base is set free and thereafter subjected to resolution with amygdalic acid. The sertraline base is set free and converted into the

hydrochloride. The desired compound is obtained with a yield of 46 %. Mp: 243-245°C.

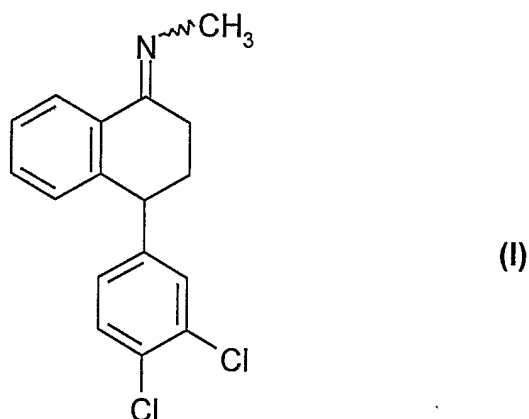
Optical rotation: $[\alpha]_D^{22} = +37,7$ (c=2, methanol).

IR (KBr): 3340, 3021, 1469, 1396, 878.

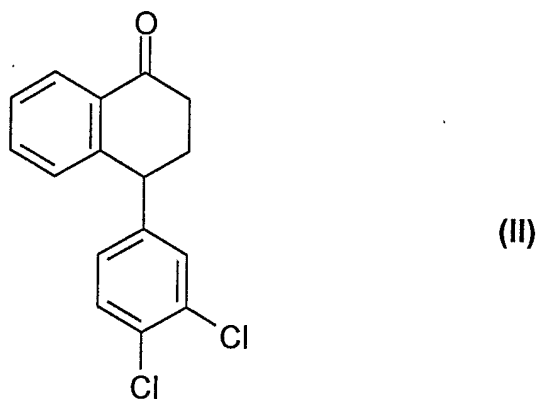
^1H -NMR (CDCl_3 , i400): 10.03 (1H, s), 9.93 (1H, s), 7.77 (1H, d, $J=7.4$ Hz), 7.41 (1H, d, 1.9 Hz), 7.36 (1H, d, $J=8.2$ Hz), 7.2 (3H, m), 6.87 (1H, d, $J=7.5$ Hz), 4.3 (1H, kv, $J=4.9$ Hz), 4.00 (1H, dd, $J_1=5.4$ Hz, $J_2=8.4$ Hz), 2.58 (3H, t, $J=5.4$ Hz), 2.3 (2H, m), 2.1 (2H, m).

What we claim is,

1. Process for the preparation of [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula



by reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one of the Formula



with monomethyl amine which comprises carrying out the reaction in the presence of thionyl chloride in an ether-type solvent.

2. Process according to Claim 1 which comprises using as ether-type solvent tetrahydrofurane, dioxane, diethyl ether, diisopropyl ether or methyl-tertiary butyl ether.
3. Process according to Claim 2 which comprises using tetrahydrofurane as ether-type solvent.
4. Process according to any of Claims 1-3 which comprises carrying out the reaction at a temperature between -30°C and +40°C.
5. Process according to Claim 4 which comprises carrying out the reaction at a temperature between -10°C and +25°C.
6. Process according to Claim 1 wherein the reaction time is between 0.5 hour and 5 hours.
7. Process according to Claim 6 wherein the reaction time is 1-3 hours.
8. Process according to Claim 1 which comprises using thionyl chloride in an amount of 1.1-5 moles, related to 1 mole of the compound of the Formula II.

9. Process according to Claim 8 which comprises using thionyl chloride in an amount of 1.5-2 moles, related to 1 mole of the compound of the Formula II.
10. Process according to any of Claims 1-9 for the preparation of a mixture of the (+)- and (-)-enantiomers of the compound of the Formula I enriched in the (+)-enantiomer which comprises using as starting material a mixture of the (+)- and (-)-enantiomers of the compound of the Formula II enriched in the (+)-enantiomer.
11. Process according to any of Claims 1-10 which comprises converging [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula I into (+/-)cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine (racemic sertraline) by catalytic hydrogenation.
12. Process according to any of Claims 1-11 for the preparation of (+/-)cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine which comprises reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one of the Formula II with monomethyl amine in the presence of thionyl chloride in an ether-type solvent,

and thereafter subjecting the [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula I thus formed to catalytic hydrogenation in the same solvent.

13. Process according to Claim 12 which comprises using as ether-type solvent tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether or methyl-tertiary butyl ether.

14. Process according to Claim 13 which comprises using tetrahydrofuran as ether-type solvent.

15. Process according to any of Claims 1-14 for the preparation of cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine and pharmaceutically acceptable acid addition salts, preferably the hydrochloride thereof which comprises reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one of the formula II with monomethyl amine in the presence of thionyl chloride in an ether-type solvent; subjecting the [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula I thus formed to catalytic hydrogenation in the same solvent; subjecting the (+/-)-cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine thus obtained to resolution and if desired

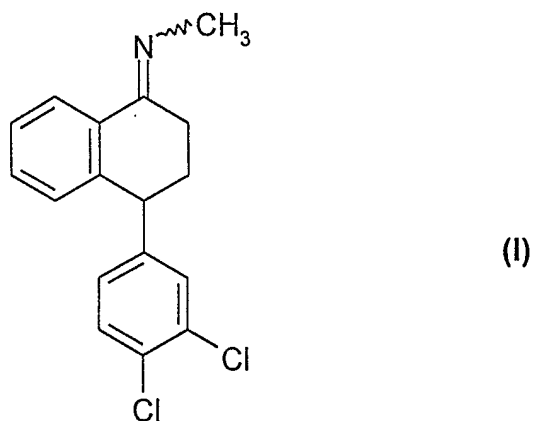
converting the (+/-)cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine into a pharmaceutically acceptable salt, preferably the hydrochloride thereof.

16. Process according to Claim 15 which comprises using as ether-type solvent tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether or methyl-tertiary butyl ether.

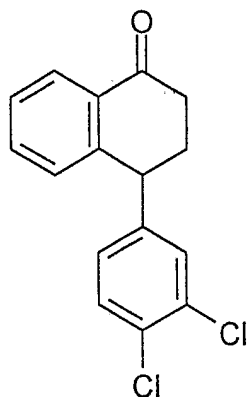
17. Process according to Claim 16 which comprises using tetrahydrofuran as ether-type solvent.

ABSTRACT

The invention is directed to a process for the preparation of [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula



by reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-one of the Formula



(II)

with monomethyl amine which comprises carrying out the reaction in the presence of thionyl chloride in an ether-type solvent.

The [4(S,R)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methyl-amine of the Formula I is a valuable pharmaceutical intermediate.