PROCESSES FOR PREPARING RACEMIC AND ENANTIOMERIC 1-(PYRIDYL)-2-CYCLOHEXYLETHYLAMINE

TECHNICAL FIELD OF THE INVENTION

This invention relates to processes for the preparation of racemic and enantiomeric 1-(pyridyl)-2-cyclohexylethylamine and, in particular, the separation of (+)-(S)- or (-)-(R)-1-(2-pyridyl)-2-cyclohexylethylamine from a racemic mixture of 1-(R,S)-(2-pyridyl)-2-cyclohexylethylamine. According to this invention, the separation of a racemic mixture of 1-(pyridyl)-2-cyclohexylethylamine is carried out using 3-bromocamphor-8-sulfonic acid (BCSA). This invention also relates to a process for preparing a racemic mixture of 1-(pyridyl)-2-cyclohexylethylamine and free BCSA from readily available starting materials.

BACKGROUND OF THE INVENTION

1-(pyridyl)-2-cyclohexylethylamines constitute a class of important compounds. For example, 1-(2-pyridyl)-2-cyclohexylethylamine is a crucial intermediate in the preparation of leukotriene biosynthesis inhibitors, such as those described in US Patent 5,296,486, issued March 22, 1994 to E.S. Lazer et al. (the disclosure of which is encorporated herien by reference in its entirety).

One preparation scheme of racemic 1-(pyridyl)-2-cyclohexylethylamines is described in P. L. Pickard and T. L. Tolbert, Journal of Organic Chemistry, 93, p. 4886 (1961). This

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scheme includes a Grignard reaction using 2-cyanopyridine and an organometallic reagent, such as cyclohexylmethylmagnesium bromide to form a ketimine intermediate which is, in turn, reduced in situ. In another preparation scheme, Y. Wang et al. describe a process for preparing substituted-2-pyridyl methyl amines by condensing 2-(aminomethyl)pyridine with benzaldehyde, followed by alkylation with an alkyl halide in the presence of tetrabutylammonium bromide (Synthetic Communications, 22(2), pp. 265-269 (1992)). One ressolution method is described in US Patent 5,296,486, and also in Organic Preparation and Procedures International 24, p. 87 (1992), in which the separation of racemic 1-(pyridyl)-2-cyclohexylethylamine is accomplished via a diastereomeric amide. However, this separation procedure is cumbersome, requiring multiple processing steps and chromatographic separation, and is prohibitively expensive for use in large scale production.

Although each of the above-noted processes produce or can be modified to produce racemic mixtures of pyridyl cyclohexylethylamine, these methods suffer from a variety of disadvantages (including difficult reaction conditions, expensive and dangerous reagents, low yields and long reaction times). In addition, there were no efficient methods to recover a single desired isomer from those racemic mixtures. Accordingly, a need exists for an efficient and economical process for producing racemic mixtures of racemic 1-(pyridyl)-2-cyclohexylethylamine and for resolving such mixtures.

BRIEF DESCRIPTION OF THE INVENTION

This invention overcomes the above mentioned problems by providing a process for producing racemic mixtures of 1-(pyridyl)-2-cyclohexylethylamine comprising the steps of:

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(a) condensing a 2-(pyridylmethyl)amine with an aldehyde or ketone to produce an aldimine or ketimide;

(b) alkylating the aldimine or ketamine with a cyclohexylmethyl halide in the presence of a base and a phase transfer catalyst; and

(c) hydrolyzing the alkylated aldimine or ketimide to produce racemic 1-(2-pyridyl)-2-cyclohexylethylamine.

This invention also provides a process for producing (+)-S or (-)-R-1-(2-pyridyl)-2-cyclohexylethylamine comprising the steps of:

(a) admixing 1-(S,R)-(2-pyridyl)-2-cyclohexylethylamine with (+)- or (-)-3-bromocamphor-8-sulfonic acid to produce a crystalline addition product; and

(b) admixing a solution of an alkali metal hydroxide or ammonium hydroxide with the crystalline addition product to produce (+)-S or (-)-R-1-(2-pyridyl)-2-cyclohexylethylamine.

In another embodiment, this invention provides a process for producing a (+)- or (-)-3-bromocamphor-8-sulfonic acid comprising the steps of:

(a) reacting racemic bromocamphor sulfonic acid ammonium salt with a calcium hydroxide solution to form a hemi calcium salt;

(b) treating the hemi calcium salt with sulfuric acid to produce insoluble calcium sulfate;

(c) removing the insoluble calcium sulfate; and

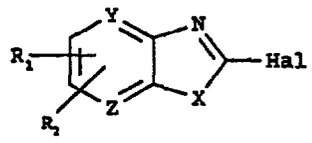
(c) recovering (+) or (-)-3-bromocamphor-8-sulfonic acid.

In yet a further embodiment, this invention provides a process for producing a leukotriene biosynthesis inhibitor, comprising the steps of

(a) reacting (+)-S or (-)-R-1-(2-pyridyl)-2-cyclohexylethylamine with a 2-halo-benzoxazole, 2-halo-oxazolopyridine, 2-halo-benzothiazole, or 2-halo-thiazolopyridine of formula I:

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(I)

wherein:

X is O or S;

Y is C or N;

Z is C or N;

with the proviso that Y and Z are not both N;

R_1 and R_2 are each, independently, hydrogen; C_1-C_6 alkyl; halo; CF_3; nitrile; C_1-C_6 alkoxy;

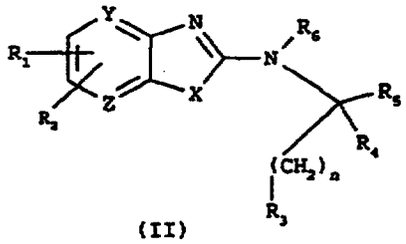
R_3 is cyclohexyl;

R_4 is a 2-, 3- or 4-pyridyl group;

R_5 and R_6 are each, independently, hydrogen or methyl; and

n is an integer 0, 1 or 2

to produce a compound of formula II:



(II)

wherein:

X is O or S;

Y is C or N;

Z is C or N;

with the proviso that Y and Z are not both N;

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R_1 and R_2 are each, independently, hydrogen; C_1-C_6 alkyl; halo; CF_3; nitrile; C_1-C_6 alkoxy; and Hal is Cl, Br, or I.

DETAILED DESCRIPTION OF THE INVENTION

According to the processes of this invention, enantiomerically pure or enriched 1-(pyridyl)-2-cyclohexylethylamine is produced from racemic 1-(pyridyl)-2-cyclohexylethylamine. The racemic 1-(pyridyl)-2-cyclohexylethylamine may be advantageously produced from commercially available 2-(aminomethyl) pyridines. Alternatively, the 2-(aminomethyl) pyridines may be prepared from commercially available starting materials using known techniques.

According to one embodiment of this invention, 2-(aminomethyl) pyridine is condensed with an aldehyde or ketone to produce a Schiff base. The condensation may be carried out in the presence of a solvent (such as methylene chloride or toluene) or without solvents to form an aldimine or ketimide (the Schiff base). Although it is possible to use any aldehyde or ketone that may be used to prepare Schiff bases, aromatic aldehydes are preferred in this process. Preferred aromatic aldehydes include benzaldehyde, salicylaldehyde, 3,5-dichlorosalicylaldehyde, p-nitrobenzaldehyde and 2-pyridine carboxaldehyde. Preferred ketones are aromatic ketones such as benzophenone, benzophenones substituted with branched or unbranched C_1 - C_6 (but preferably, C_1 - C_4) alkyl groups or halogens, and acetophenone. Reaction conditions for the condensation are those commonly used in the formation of Schiff bases and are well known to those of ordinary skill in the art.

The Schiff base is then deprotonated with a base such as potassium t-butoxide (preferably at room temperature) and alkylated using a cyclohexylmethyl halide, such as

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cyclohexylmethyl bromide, or cyclohexylmethyl methane sulfonate (which is easily prepared by reacting cyclohexyl methanol with methane sulfonyl chloride in the presence of triethylamine (J. Org. Chem., 35, p. 3195 (1970)). Using non-phase transfer catalysis conditions, the alkylation should be carried out in the presence of a base, such as potassium t-butoxide, in an aprotic solvent, such as toluene or tetrahydrofuran.

In an alternate (and preferred) embodiment of this invention, a phase transfer catalyst is employed in the alkylation reaction, i.e. a quaternary ammonium compound, such as tetrabutyl ammonium bromide, chloride or iodide. Preferably, the reaction mixture also contains a base, such as an alkali metal hydroxide (sodium hydroxide or potassium hydroxide being preferred). The reaction mixture may also contain solvents and other conventional alkylation reagents known to those of ordinary skill in the art. Phase transfer catalysis advantageously avoids the use of highly flammable solvents needed for Grignard reactions. In addition, the reaction conditions are scaleable and require no special equiptment for large-scale use in a production plant.

Follwoing alkylation, the alkylated Schiff base is then hydrolyzed in situ (e.g., with an acid such as hydrochloric acid) to produce a racemic mixture of a 1-(R,S)-(2-pyridyl)-2-cyclohexylethylamine. Hydrolysis conditions are well known by those of ordinary skill in the art.

According to this invention, the separation of enantiomers from a racemic mixture of 1-(pyridyl)-2-cyclohexylethylamine is accomplished using 3-bromocamphor-8-sulfonic acid (BCSA) as the resolving agent. It was discovered that BSCA is the only agent capable of satisfactorily resolving racemic 1-(pyridyl)-2-cyclohexyl ethylamine. Various commercial methods exist for preparing (+)- or (-)-3-bromocamphor-8-sulfonic acid from the ammonium or calcium

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salt. This invention provides an improved process for producing (+)- or (-)-3-bromocamphor-8-sulfonic acid which is less expensive and less time consuming than the conventional processes. This process comprises the steps of :

(a) reacting racemic bromocamphor sulfonic acid ammonium or calcium salt with a calcium hydroxide solution to form a hemi calcium salt;

(b) treating the hemi calcium salt with sulfuric acid to produce insoluble calcium sulfate;

(c) removing the insoluble calcium sulfate; and

(c) recovering (+) or (-)-3-bromocamphor-8-sulfonic acid.

Free BCSA is conventionally prepared by treatment of the commercially available ammonium salt with an ion exchange resin. Using the process of this invention, the need for an expensive ion exchange resin is avoided. According to this process, treatment of the BCSA ammonium or calcium salt (preferably, the ammonium salt) with about a ½ equivalent of Ca(OH) gives a hemi calcium BCSA salt. Treatment of an aqueous solution of BCSA calcium salt with about a ½ equivalent of sulfuric acid results in the formation of insoluble $CaSO_4$, which may be readily filtered off. The filtrate containing free BCSA may be advantageously used without further purification.

The resolution process according to this invention is carried out by adding free BCSA (preferably produced by the above described process) to a solution of the racemic mixture of 1-(R,S)-(2-pyridyl)-2-cyclohexylethylamine (preferably, in ethyl acetate) and producing an enantiomerically enriched crystalline addition product. To obtain optical purity, the 2-pyridylcyclohexylalkylamine (R or S)-BCSA salt is crystallized from an organic solvent such as isopropanol. Depending on the reaction conditions, the salt of one enantiomer is cystallized while the other salt remains in solution. For example, under standard

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crystallization conditions, most of the S isomer of 1-(2-pyridyl)-2-cyclohexylethylamine cystallizes as the (+)-BSCA salt, while the R isomer remains in solution.

To produce, for example, crystals of the 1-(S)-(2-pyridyl) cyclohexylalkylamine, the (+)-BCSA salts are treated with a base such as ammonium hydroxide to recover the desired 1-(S)-(2-pyridyl)-2-cyclohexylalkylamine (and recover the resolution agent (BCSA-ammonium salt)) in high yields. By way of example, ammonium hydroxide may be added to an aqueous solution or suspension of the (+)BCSA salt. The insoluble free 1-(S)-(2-pyridyl)-2-cyclohexylalkylamine may then be extracted using a solvent such as methylene chloride or ethyl acetate. The BCSA ammonium salt remaining in the aqueous phase is recovered after concentration.

Advantageously, further amounts of the desired optical isomer can be obtained by treatment of the solution containing the R-isomer by refluxing with a catalytic amount of an aldehyde such as salicylaldehyde followed by crystallization. In this way the undesired isomer is re-racemized, forming additional amounts of the desired isomer. This sequence may be repeated with any recovered amounts of undesired , thereby producing greater amounts of the desired isomer. This so-called "crystallization-induced asymmetric transformation" will be familiar to those skilled in the art and is described in general by P. Reider *et al.* in Journal of Organic Chemistry 52, p. 956, (1987).

Importantly, the above-detailed resolution produces a single isomer of 1-(pyridyl)-2-cyclohexylethylamine, without needing to protect the terminal amine group. Protection of the amine group requires extra process steps, requires the use of expensive and /or hazardous materials, and produces a product that requires further purification (typically, chromatography). The process of the present invention avoids these disadvantages and as a result, is highly

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suitable for large scale production of enantiomerically enriched or enantiomerically pure 1-(pyridyl)-2-cyclohexyl ethylamine.

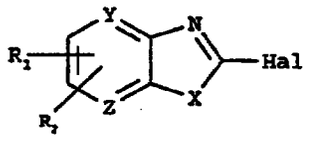
It should be noted that, although the various embodiments of this invention have been demonstrated with racemic mixtures, these reactions function equally well using mixtures with enhanced content of one or the other enantiomer. For example, essentially pure enantiomers (95%+, preferably 97%+ and more preferably 99%+) of (S)-amine may be isolated equally well from mixtures containing a ratio of (S)-amine to (R)-amine of 50:50 as from mixtures having ratios of 75:25 or 25:75. Preferably, the desired isomer is purified from a racemic mixture (50:50) or from a mixture enriched in the desired enantiomer.

The resolution process of the present invention can be advantageously employed in the production of various substituted 2-benzoxazoles, 2-benzothiazoles, 2-oxazolopyridines and 2-thiazolopyridines which have the ability to inhibit leukotriene biosynthesis. Methods and processes for producing such compounds are referred to in U.S. Patent 5,296,486 (which in its entirety is incorporated herein by reference). In particular, compounds having leukotriene biosynthesis inhibitory properties may be produced by :

(a) reacting the (+)-S or (-)-R-1-(2-pyridyl)-2-cyclohexylethylamine with a 2-halo-benzoxazole, 2-halo-oxazolopyridine, 2-halo-benzothiazole, or 2-halo-thiazolopyridine of formula I:

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(I)

wherein:

X is O or S;

Y is C or N;

Z is C or N;

with the proviso that Y and Z are not both N;

R_1 and R_2 are each, independently, hydrogen; C_1-C_6 alkyl; halo; CF_3; nitrile; C_1-C_6 alkoxy;

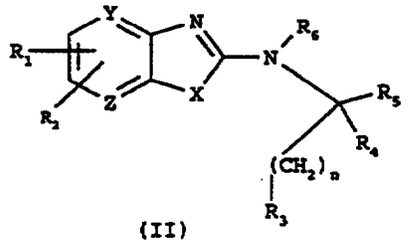
R_3 is cyclohexyl;

R_4 is a 2-, 3- or 4-pyridyl group;

R_5 and R_6 are each, independently, hydrogen or methyl; and

n is an integer 0, 1 or 2

to produce a compound of formula II:



(II)

wherein:

X is O or S;

Y is C or N;

Z is C or N;

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with the proviso that Y and Z are not both N; R_1 and R_2 are each, independently, hydrogen; C_1-C_6 alkyl; halo; CF_3; nitrile; C_1-C_6 alkoxy; and Hal is Cl, Br, or I.

The coupling reaction should be carried out in an inert solvent, such as methylene chloride, toluene, acetonitrile, diisopropyl ether or DMSO, and preferably, in the presence of a basic catalyst, such as triethylamine or an alkali metal hydroxide (eg. NaOH or KOH). The optimum choice of both solvent and catalyst will depend upon the nature of the reactants, as a person of ordinary skill in the art will readily appreciate.

Preferred compounds according to formula II are those wherein the R_1 substitutent is in the 5-position and is an C_1-C_3 alkyl group or halogen, R_4 is 2-pyridyl, the R_5 and R_6 substitutents are each hydrogen and n is 1. Other preferred compounds of formula II include those wherein X is O and Z is C and/or wherein R_1 and R_2 are each, independently, hydrogen or C_1 -C_6 alkyl (and more preferably, wherein R_1 is hydrogen and R_2 is 5-methyl). Accordingly, methods for producing these compounds are preferred.

The following examples are illustrative of the present invention.
These examples , however, are not to be construed as limiting the scope of the present invention, which scope is defined in the claims which follow. It will also be appreciated that the typical reaction conditions described in this application (including the Examples) may be readily modified to suit particular individualized requirements. Such modifications can be made without diverting from the teachings and spirit of this invention. Accordingly, such modifications are expressly included within the scope of this invention.

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EXAMPLE 1

Preparation of Racemic 1-(pyridyl)-2-cyclohexylethylamine

(Grignard Reaction)

To a refluxed stirred mixture of 1.34 kg (55.8 moles) of magnesium in 6L of t-butylmethyl ether (MTBE) and 4 g (0.016 moles) of iodine, a solution of 10 kg (55.9 moles) cyclohexylmethyl bromide in 22L (MTBE) was added slowly. After approximately 10% to 25% of the solution was added, heating was discontinued and the remainder of the solution was added at a rate to maintain refluxing temperature. After the addition, the reaction was refluxed for an additional 24 hrs, then cooled to 0° to 5°C and 3.903 kg (37.1 moles) of 2-cyanopyridine in 22L MTBE was added at 0° - 10°C. After the addition, the greenish thick suspension was stirred without cooling for 18 - 24 hrs. The Grignard reaction mixture was transferred with stirring to 40L of methanol at 10° to 15°C. To the clear solution was added 1.4 kg (36.8 moles) of sodium borohydride. The mixture was stirred at room temperature 18 hrs., then quenched by the addition of 16L of water and 36L of 4N hydrochloric acid. The organic solvents were removed under vacuum and the remaining aqueous solution was washed twice with 6 L of methylene chloride. The aqueous phase was basified with 15 L of ammonium hydroxide solution and extracted three times with 10 L of methylene chloride. The methylene chloride was dried over 6.5 kg of sodium sulfate and concentrated to yield 5.645 kg (75%) of 1-(R,S)-(2-pyridyl)-2-cyclohexylethylamine.

EXAMPLE 2

Preparation of Racemic 1-(pyridyl)-2-cyclohexylethylamine

(Aldehyde Condensation Reaction with Phase Transfer Catalysis)

Under a nitrogen atmosphere, 1.365 kg (12.86 moles) of benzaldehyde was added with stirring and cooling to 1.39 kg (12.86

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moles) of 2-(aminomethyl) pyridine maintaining the temperature <50°C. After stirring for 2 - 4 hours, the mixture was diluted with 13 L of t-butylmethyl ether (MTBE). To the clear solution was added 1.05 kg (27.72 moles) sodium hydroxide (flakes) and 2.375kg (6.43 moles) of tetrabutylammonium iodide. The suspension was stirred for 2 hrs., then 2.3kg (12.86 moles) of cyclohexylmethyl bromide was added. The reaction mixture was refluxed for 36-48 hrs. After cooling the mixture, it was diluted with 3 L of water followed by 12 L of 3N hydrochloric acid and stirred for 2-6 hours. The organic phase was separated and discarded. The aqueous phase was washed four times with 3 L of methylene chloride, then basified with 2.5 L of 0.5N ammonium hydroxide solution. The racemic amine was extracted three times from the aqueous phase with 4 L of methylene chloride. The extracts were dried over sodium sulfate and concentrated to dryness. The oily product was stirred with 2 L of hexane, filtered and concentrated to yield 1.14 kg (43.5%) of 1-(R,S)-(2-pyridyl)-2-cyclohexylethylamine.

EXAMPLE 3

Preparation of Racemic 1-(pyridyl)-2-cyclohexylethylamine

(Aldehyde Condensation Reaction without Phase Transfer Catalysis)

To 465 g (4.3 moles) of 2-(aminomethyl) pyridine was added with stirring 456 g (4.3 moles) of benzaldehyde. The temperature was increased to 70° - 80°C. The mixture was diluted with 2 L of MTBE and the water was removed by stirring the solution with 200 g of sodium sulfate overnight. The mixture was filtered and washed with 2 L of MTBE. To remove the remaining water, 100 g of molecular sieves were added. To the mixture was added 483 g (4.3 moles) potassium t-butoxide in portions followed by 842 g (4.38 moles) of cyclohexylmethyl methanesulfonate. After 10 - 20 hours, the mixture was hydrolyzed by the addition of 5 L water containing 720 mL of hydrochloric acid. The organic phase was separated and

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discarded. The aqueous phase was washed with 0.5 L of methylene chloride and basified with 0.5 L of ammonium hydroxide. The product was extracted with petroleum ether to yield 452 g of crude amine. The amine was purified by vacuum distillation at 88°C and 0.5 Torr to give 353 g (35%) of 1-(R,S)-(2-pyridyl)-2-cyclohexylethylamine.

EXAMPLE 4

Preparation of Racemic 1-(pyridyl)-2-cyclohexylethylamine

(Ketone Condensation Reaction with Phase Transfer Catalysis)

To a mixture of 21.6 g (0.2 mole) of 2-(aminomethyl) pyridine and 36.4 g (0.2 mole) benzophenone in 100 ml toluene was added 5.68 g (0.02 mole) of titanium (IV) isopropoxide and then it was heated to reflux using a water separator (Dean Stark distilling receiver) for 2 - 4 hours. After the theoretical amount of water was separated, the mixture was cooled and 16 g (0.4 mole) of sodium hydroxide followed by 36.9 g (0.1 mole) of tetrabutylammonium iodide and 35.4g (0.2 mole) cyclohexylmethyl bromide was added. The mixture was heated to reflux for 12 - 18 hours. Then the mixture was poured with stirring into 300 ml of water containing 100 ml of concentrated hydrochloric acid. The mixture was stirred at 30° - 50°C for one to two hours, cooled and the organic phase separated and discarded. The aqueous phase was basified by the addition of 200 ml of ammonium hydroxide. The product was extracted with 100 ml of hexane three times, dried over anhydrous magnesium sulfate, filtered and concentrated to yield 37 g (90%) of 1-(R,S)-(2-pyridyl)-2-cyclohexylethylamine.

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EXAMPLE 5

Preparation of Racemic 1-(pyridyl)-2-cyclohexylethylamine

(Aldehyde Condensation Reaction with Phase Transfer Catalysis)

A mixture of 2.16 g of 2-picolylamine (20 mmoles) and 2.12 g of benzaldehyde (20 mmoles) was stirred for 5 - 20 hours. The reaction mixture was diluted with 20 ml of toluene with stirring, then 1.12 g (20 mmoles) of potassium hydroxide added followed by the addition of 3.7 g of tetrabutylammonium iodide (10 mmoles) and 3.55 g of cyclohexylmethyl bromide (20 mmoles). The mixture was refluxed for 6 - 24 hours, then cooled and stirred with 10 ml of a 2N HCl for 2-6 hours. The organic phase was discarded, the aqueous acidic phase was washed with methylene chloride. The aqueous phase was basified with ammonium hydroxide and the racemic amine extracted with methylene chloride to yield 45% - 55% racemic 1-(2-pyridyl)-2-cyclohexylethylamine as a light yellow oil.

EXAMPLE 6

Resolution of 1-(2-pyridyl)-2-cyclohexylethylamine (+)-BCSA salt

To a solution of 1.176 kg (5.756 mole) of 1-(S,R)-(2-pyridyl)-2-cyclohexylethylamine and 6 L of ethyl acetate was added a suspension of 5.752 mole (+)-BCSA with stirring. The mixture was stirred overnight, filtered and washed with 1 L of ethyl acetate and washed twice with 0.5 L of ethyl acetate. The white crystals (1.22 kg) were dissolved in 12 L of 2-propanol at 75°C and cooled to ambient temperature overnight. The clear supernatant was decanted off and the remaining crystals dissolved in 8 L of hot 2-propanol. The solution was filtered hot and allowed to cool to ambient temperature overnight. The crystals were filtered and washed with 1.5 L of 2-propanol and dried under vacuum to yield

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726 g of white crystalline product (HPLC: 99% pure).

The original 2-propanol filtrate (12 L) was concentrated to 6 L, the resulting suspension was heated to 80°C and the clear solution was allowed to cool overnight to ambient temperature. The crystals were filtered and combined with the above 9.5 L of 2-propanol filtrate and washings and dissolved at 80°C. The clear solution was allowed to cool overnight to ambient temperature. The crystals were collected and dried under vacuum to give 294 g (91% pure by HPLC). The crystals were dissolved in 3 L of hot 2-propanol, allowed to ambient temperature, filtered and washed with 0.5 L 2-propanol to give 246 g (HPLC: 99.3% pure) of white crystals.

EXAMPLE 7

Recovery of (+)-S-1-(2-pyridyl)-2-cyclohexylethyl amine from amine (+)-BCSA salt

The combined crystals of (+)-BCSA salt [726g (HPLC: 99% pure) plus 246g (HPLC: 99.3% pure)] were suspended in 5 L of water. To this suspension was added 0.5 L of ammonium hydroxide and the alkaline mixture was stirred for 2 hours. The (+)-S-1-(2-pyridyl)-2-cyclohexylethyl amine was extracted with 4 L methylene chloride and then extracted four times with 1 L of methylene chloride. The methylene chloride phase was dried over magnesium sulfate (anhydrous) and concentrated to dryness to give 403 g of (+)-S-1-(2-pyridyl)-2-cyclohexylethylamine (34.2% recovery based on racemic amine).

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EXAMPLE 8

Recovery of (-)-R-1-(2-pyridyl)cyclohexylethylamine from amine (+)-BCSA salt

The original ethyl acetate filtrate and all 2-propanol mother liquors from the resolution of Example 6 were combined and concentrated to an oil. The oily residue was stirred with 14 L of water and 500 ml of amonium hydroxide. The enriched (-)-R-1-(2-pyridyl)-2-cyclohexylethylamine mixture was extracted four times with 1 L of methylene chloride. The methylene chloride extracts were dried over anhydrous magnesium sulfate and concentrated to dryness to give 864 g of (not completely dry) mostly (R)-(-)-amine (HPLC Ratio S/R = 25:75). If desired, the recovered (-)-R isomer can be racemized and used to produce additional amounts of (+)-(S)-isomer (as shown in Example 9).

EXAMPLE 9

Recovery of (+)-(S)- and (-)-(R)-1-(2-pyridyl)-2-cyclohexylethylamine from (+)-BCSA Salt and Racemization of Enriched (-)-(R)-Enantiomeric Mixtures and Methodology to Produce Additional Amounts of (+)-(S)-Isomer

The (+)-BCSA used in this example was prepared from [(1R)-(endo,anti)]-(+)-3-bromocamphor-8-sulfonic acid ammonium salt by treating an aqueous solution of the (+)-BCSA salt with Dowex 50 x $4H^+$ ion-exchange resin.

Using the procedure of Example 6, 3.389 mole of (+)-BCSA was added to a solution of 1.378 kg (6.745 mole) of racemic amine in 7 L of ethyl acetate. The resulting crystals of 1-(2-pyridyl)-2-cyclohexylethylamine-BCSA salt were collected and washed with ethyl acetate to give 1.364 kg S-enriched S:R ratio = 78:22 (by

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HPLC). The ethyl acetate supernatant containing the R-enantiomer as the major product, was heated and refluxed with 3.7 mole of HCl gas and 206 g of salicylaldehyde for 24 - 36 hours. The mixture was cooled and stirred with 4 L of water and 0.3 L of concentrated hydrochloric acid. The aqueous phase was separated, washed with ethyl acetate, and basified with ammonium hydroxide. The racemic amine was extracted with methylene chloride, dried and concentrated. The oil product was dissolved in 2.5 L of ethyl acetate and treated with 1.695 mole of (+) BCSA. The crystals were collected and washed with ethyl acetate to give an additional 540 g of S-enriched amine. Repeating the above sequence several times, resulted in approximately 2.4 kg of S-enriched amine (75-85% S-enantiomer).

EXAMPLE 10

Preparation of (+)-BCSA from (+)-BCSA-Ammonium Salt

A suspension of 311 g (0.95 mole) of [(1R)-(endo,anti)]-(+)-3-bromocamphor-8-sulfonic acid ammonium salt (CAS [14575-84-9]) in 500 ml water was added to 74.09 g (0.475 mole) of calcium hydroxide. The mixture was stirred at room temperature for 6 - 24 hours, then the solution was concentrated to a syrup. The resulting neutral solution of (+)-BCSA calcium salt was diluted with 0.5 L of water and treated with 46.6 g (0.475 mole) of sulfuric acid. The calcium sulfate was filtered off and the clear filtrate concentrated to a syrup and used without further purification in the above resolution processes as the source of (+)-3-bromocamphor sulfonic acid.

This same procedure is used to prepare [(1S)-(endo,anti)]-(-)-3-bromocamphor-8-sulfonic acid (CAS [55870-50-3]) in the same quantities.

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EXAMPLE 11
Fractional Crystallization of S-enriched Amine

The enriched S-amine of Example 9 (S-enantiomer = 75-85%, R-enantiomer =25-15%) and 23 L of 2-propanol were heated to reflux until a clear solution resulted. The solution was allowed to cool to room temperature. The supernatant was drained and the remaining crystals were recrystallized three times from 2-propanol to give +99% S-amine.

EXAMPLE 12
Racemization of Enriched R- Amine and Recovery of Additional S-Amine

The filtrates from Example 11 containing <50% S-enantiomer were racemized in ethyl acetate as the (+) BCSA-salt in the presence of salicylaldehyde. After cooling, S-enriched amine was collected by filtration. This crystallization-induced asymmetric transformation is carried out in the presence of (+) BCSA. The S-amine (+) BCSA-salt is removed from the system by virtue of its insolubility driving equilibrium (see J. Jacques, A. Collet, S. Wilen in Enantiomers, Racemates and Resolution; Wiley: N Y 1981; pp 369-377). All >99% (+) BCSA S-amine salt fraction obtained after racemization and additional crystallization in isopropanol were combined and suspended in 10 L of water and basified with 0.7 L of ammonium hydroxide to pH 9 - 10. The free pure S-amine was extracted with methylene chloride, washed with water, dried over sodium sulfate, filtered and concentrated to yield 697 g (45%) 1-(S)-(2-pyridyl)-2-cyclohexylethylamine. From the aqueous phase, the (+) BCSA ammonium chloride salt is recovered by concentration, cooling, filtration and drying in 88% - 100% yield.

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EXAMPLE 13
Production of
[(2-Cyclohexyl-1-(2-pyridyl)ethylamino]-5-methylbenzoxazole

To a solution of 132.8 g (0.65 moles) 1-(+)-(S)-(2-pyridyl)-2-cyclo-hexylethylamine in 550 mL methylene chloride was added 109 g (0.65 moles) 2-chloro-5-methylbenzoxazole followed by 168 g (1.3 moles) diisopropylethylamine. The reaction mixture was heated to reflux for 5 - 40 hours, cooled and concentrated under reduced pressure. The mixture was dissolved in 2 L of ethanol. Addition of 2 - 3L of water gave crude [(2-cyclohexyl-1-(2-pyridyl)ethylamino]-5-methylbenzoxazole. Recrystallization from ethanol/water gave 190 g (83%) as a hydrate; mp 80°-86°C.

While the present invention has been described with regard to a preferred embodiment thereof, the description is for illustrative purposes only and is not to be construed as limiting the scope of the invention. Various modifications and changes may be made by those skilled in the art without departing from the true spirit and scope of the invention as defined by the appended claims.

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What is claimed is:

1. A process for producing 1-(S,R)-(2-pyridyl)-2-cyclohexylethylamine comprising the steps of:

(a) condensing a 2-(pyridylmethyl)amine with an aldehyde or ketone to produce an aldimine or ketimide;

(b) alkylating the aldimine or ketimide with a cyclohexylmethyl halide in the presence of a base and a phase transfer catalyst; and

(c) hydrolyzing the alkylated aldimine or ketimide to produce racemic 1-(2-pyridyl)-2-cyclohexylethylamine.

2. A process for producing (+)-S or (-)-R-1-(2-pyridyl)-2-cyclohexylethylamine comprising the steps of:

(a) admixing 1-(S,R)-(2-pyridyl)-2-cyclohexylethylamine with (+)- or
(-)-3-bromocamphor-8-sulfonic acid to produce a crystalline addition product; and

(b) admixing a solution of an alkali metal hydroxide or ammonium hydroxide with the crystalline addition product to produce (+)-S or (-)-R-1-(2-pyridyl)-2-cyclohexylethylamine.

3. The process according to claim 2 in which the solution is an ammonium hydroxide solution.

4. The process according to claim 2, wherein the 1-(S,R)-(2-pyridyl)-2-cyclohexylethylamine is produced by reacting 2-(aminomethyl)pyridine with an aromatic aldehyde or ketone, followed by addition of a cyclohexylmethyl halide.

5. The process according to claim 4 in which the cyclohexylmethyl halide is cyclohexylmethyl bromide.

6. The process according to claim 2, further comprising the

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* C L M S *

steps of:

(a) racemizing the undesired enantiomer of 1-(2-pyridyl)-2-cyclohexylethylamine to produce 1-(S,R)-(2-pyridyl)-2-cyclohexylethylamine;

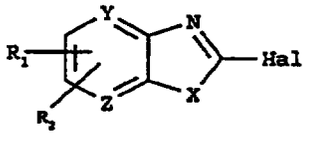
(b) admixing the 1-(S,R)-(2-pyridyl)-2-cyclohexylethylamine with (+)- or (-)-3-bromocamphor-8-sulfonic acid to produce a crystalline addition product; and

(c) admixing a solution of an alkali metal hydroxide or ammonium hydroxide with the crystalline addition product to produce (+)-S or (-)-R-1-(2-pyridyl)-2-cyclohexylethylamine.

7. The process according to any one of claims 1-6 in which (+)-S-1-(2-pyridyl)-2-cyclohexylethylamine is produced.

8. The process according to claim 2, further comprising the steps of:

(a) reacting the (+)-S or (-)-R-1-(2-pyridyl)-2-cyclohexylethylamine with a 2-halo-benzoxazole, 2-halo-oxazolopyridine, 2-halo-benzothiazole, or 2-halo-thiazolopyridine of formula I:



(I)

wherein:

X is O or S;

Y is C or N;

Z is C or N;

with the proviso that Y and Z are not both N;

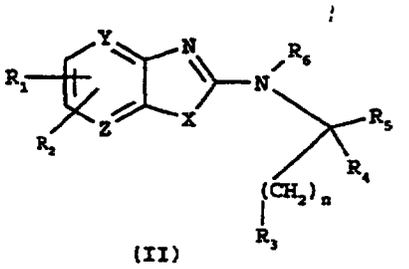
R_1 and R_2 are each, independently, hydrogen; C_1-C_6 alkyl; halo; CF_3; nitrile; C_1-C_6 alkoxy;

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R_3 is cyclohexyl;
R_4 is a 2-, 3- or 4-pyridyl group;
R_5 and R_6 are each, independently, hydrogen or methyl; and
n is an integer 0, 1 or 2

to produce a compound of formula II:



(II)

wherein:

X is O or S;
Y is C or N;
Z is C or N;
with the proviso that Y and Z are not both N;
R_1 and R_2 are each, independently, hydrogen; C_1-C_6 alkyl; halo; CF_3; nitrile; C_1-C_6 alkoxy; and
Hal is Cl, Br, or I.

9. The process according to claim 8 wherein X is O and Z is C.

10. The process according to claim 8 wherein R_1 and R_2 are each, independently, hydrogen or C_1 -C_6 alkyl.

11. The process according to claim 8 wherein R_1 is hydrogen and R_2 is 5-methyl.

12. A process for preparing a (+) or (-)-3-bromocamphor-8-sulfonic acid comprising the steps of:

(a) reacting racemic bromocamphor sulfonic acid ammonium

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or calcium salt with a calcium hydroxide solution to form a hemi calcium salt;

(b) treating the hemi calcium salt with sulfuric acid to produce insoluble calcium sulfate;

(c) removing the insoluble calcium sulfate; and

(c) recovering (+) or (-)-3-bromocamphor-8-sulfonic acid.

13. The process according to claim 12, wherein the (+) or (-)-3-bromocamphor-8-inorganic acid is (+) or (-)-3-bromocamphor-8-sulfonic acid.

14. The process according to claim 13 wherein the inorganic salt is an ammonium salt or a calcium salt, the hydroxide solution is a calcium hydroxide solution.

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