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(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **01.10.86**

(51) Int. Cl.⁴: **C 07 C 85/04**, C 07 C 87/28

(21) Application number: **83401429.2**

(22) Date of filing: **11.07.83**

ERRATUM

(SEITE, SPALTE, ZEILE)
(PAGE, COLUMN, LINE)
(PAGE, COLONNE, LIGNE)

DIE TEXTSTELLE: TEXT PUBLISHED: LE PASSAGE SUIVANT:			LAUTET BERICHTIGT: SHOULD READ: DEVRAIT ETRE LU:
The propargyl reaction	4	32	The propargylation reaction
$X-CH_2-CH \equiv CH$	(5	53)	
	(6	50)	$X-CH_2-C \equiv CH$
	(7	41)	
	(8	39)	
	(10	33)	
solvent is benene	6	14	solvent is benzene

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(21) Application number: **83401429.2**

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SEE ERRATA SLIP ATTACHED

(54) **New process for the preparation of propargyl amines.**

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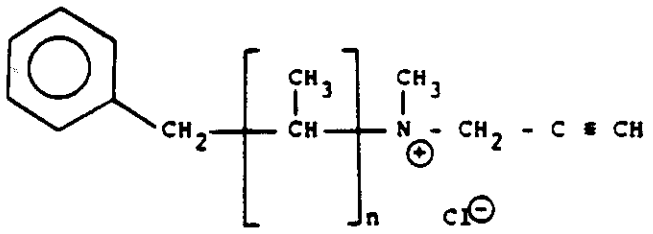
Description

This invention relates to a new process for the preparation of propargyl amines.

It is known that certain phenyl isopropyl amine derivatives possess valuable pharmaceutical properties and exhibit particularly useful MAO inhibiting and anti-parkinson effect.

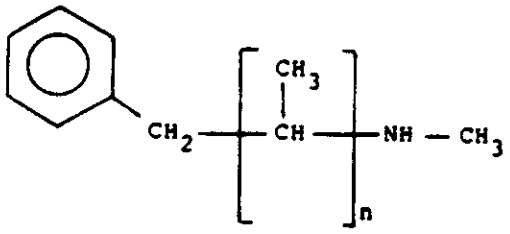
Several methods are known for the preparation of propargyl amines. Thus a bromo allyl amine derivative can be prepared by reacting the secondary amine with 0.5 mole of bromo allyl bromide [Ann *445*, 206 /1925/7]. This process is however complicated, lengthy, requires much labour and gives a yield of but 30—40%.

The invention relates to a new process for the preparation of propargyl ammonium chloride of the general Formula I



(I)

by alkaline decomposition of the d-tartarate of the l-isomer of an amine of the general Formula II



(II)

and subsequent reaction of the amine of the general Formula II with a halide of the general Formula III

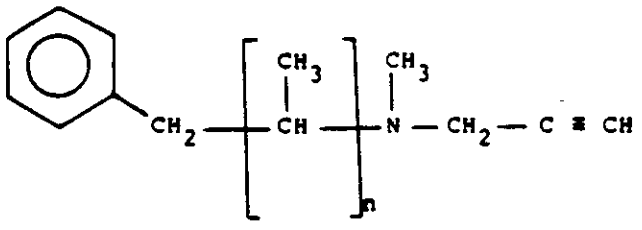
$$X—CH_2—C \equiv CH \qquad III$$

in the presence of an organic solvent, alkali and water/in which general Formulae

n is 1 or 0 and

X stands for halogen/

which comprises reacting the d-tartarate of the l-isomer of an amine of the general Formula II in aqueous suspension with an alkali, dissolving the base of the general Formula II, thus set free without isolation in a water non-miscible organic solvent and reacting the same in the said phase with a halide of the general Formula III, and thereafter — preferably after separating the aqueous layer — reacting the mixture which contains the amines of the general Formula II and IV



(IV)

in the inorganic phase in the presence of water with an organic acid or a solution which has a pH value of 1.5—6 and consists of an inorganic acid and water, thus dissolving in the two-phase mixture formed the salt of the amine of the general Formula II in the aqueous layer and selectively separating the amine of the general Formula II from the amine of the general Formula IV, and thereafter adding after the separation of the phases alcoholic hydrogen chloride or gaseous hydrogen chloride to the amine of the general Formula IV being in the organic phase and thus precipitating the salt of the general Formula I.

The present invention is based on the recognition that the propargyl halide should not be used in an excess, because this leads to the formation of polymeric by-products of tarry character. This risk is particularly involved on large scale production where it is also accompanied by the irritating effect of propargyl halides rising safety problems.

The invention is further based on the recognition that the separation of the tertiary amine [e.g. N-methyl-N-/2-pheyl-l-methyl/-N-propargyl amine/ being present in the reaction mixture from the secondary amine [e.g. N-methyl-N-/2-phenyl-l-methyl/-ethyl-amine] being also present in the reaction mixture and possessing very similar properties is very difficult and causes such serious problems in the working-up of the reaction mixture which already adversely effect the proper carrying out of the reaction.

It has been found that the pKA value of the tertiary base amounts to 6.2, while that of the secondary base is 9.8. The above difference can be used for making the reaction more selective and for separating the products, respectively.

In the first step of the reaction the d-tartarate of the l-isomer of the amine of the general Formula II is reacted in an aqueous suspension with an alkali and the base thus set free is dissolved without isolation in a water non-miscible organic solvent [e.g. preferably benzene, toluene, dichloroethane or diisopropyl ether].

The free base is reacted in the organic phase with a halide of the general Formula III; in the said organic layer both amines of the general Formulae II and IV are present. The said organic phase can be reacted with a solution which has a pH of 1.5—6 and consists of an inorganic acid and water. Thus the salt of the secondary amine formed with the added inorganic acid is obtained which goes over into the aqueous layer. As inorganic acid preferably hydrochloric acid, phosphoric acid or sulfuric acid can be used.

One may also proceed by reacting the organic layer which contains the amines of the general Formulae II and IV with an organic acid in the presence of water. For this purpose preferably mono- or polycarboxylic acids can be applied [e.g. acetic acid, propionic acid, formic acid, glycolic acid/or lactic acid]. The salt of the amine of the general Formula II formed with the organic carboxylic acid is obtained and dissolved in the aqueous layer. The secondary amine content of the organic phase of the two-phase mixture is decreased to such a low value that it no more effects in an adverse manner the isolation of the amine of the general Formula I. The end-product thus obtained is suitable for direct medical use.

The reaction mixture can be preferably worked up by adding alcoholic hydrogen chloride or gaseous hydrogen chloride to the organic layer which contains the compound of the general Formula IV.

The salts being present in the aqueous layer can be separated from the amines being in the organic phase on the basis of the principles of the separation of phases /e.g. sedimentation, decanting etc/.

Since the reactions are carried out in a multi-phase system, one may proceed preferably by reacting the compounds of the general Formulae II and III in the presence of a phase-transfer catalyst /e.g. N-benzyl-N,N,N-triethyl-ammonium-chloride/.

The propargyl reaction can be carried out advantageously at a temperature between 40°C and 70°C.

According to a further embodiment of the process of the present invention the propargyl halide and the aqueous alkali and optionally the phase-transfer catalyst are parallelly added to the secondary amine base or a solution thereof formed with a solvent.

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

Example 1

351.2 g of 1-N-methyl-/2-phenyl-1-methyl/-ethyl-amine-d-tartarate are suspended in 500 ml of water. The suspension is alkalised to the pH value of 13 by adding 700 ml. of 40% sodium hydroxide solution at room temperature. The solution is extracted with benzene. To the extract at 60°C 98 ml. of propargyl bromide and a solution of 46 g. of sodium hydroxide and 170 ml. of water are added. The reaction mixture is stirred at 60°C for 2 hours, whereupon the two phases are separated. The benzene phase is washed with water. To the benzene layer a solution of 100 ml. of water and 5 ml. of acetic acid is added /pH 6.5—7/.

If the pH value of the aqueous layer is higher than 7, a further amount of acetic acid is added and the two phases are repeatedly admixed.

Thereafter the benzene phase is separated from the aqueous layer containing the 1-N-methyl-/2-phenyl-1-methyl/-ethyl amine acetate, the organic layer is washed with water and dried.

From the benzene solution about 200 ml. of benzene are disillled off at a bath temperature of 50°C in vacuo /200 Hgmm/. The filtrate is clarified and acidified to the pH value of 1 by adding dropwise a 37% ethanolic hydrogen chloride solution. Thus 170 g of N-methyl-N-/2-phenyl-1-methyl-ethyl-N-propargyl-ammonium chloride are obtained, mp.: 141—143°C; $[\alpha]_D^{20} = -12°/c = 10$, water/.

From the mother-lye and the washing solution a further amount /20—50 g./ of the product can be isolated.

From the acetic acid washing liquid 30 g. of 1-N-methyl-/2-phenyl-1-methyl/-ethyl-amine base are recovered which can be used in the next batch.

Example 2

One proceeds according to Example 1 except that a solution of 121 g. of N-benzyl-N-methyl-amine in 850 ml. of benzene, 4.3 g. of N-benzyl-N,N,N-trimethyl-ammonium chloride, 84 ml. of propargyl bromide, an aqueous solution of 39 g. of sodium hydroxide in 145 ml. of water and acetic acid are used. Thus 159 g. of N-benzyl-N-methyl-propargyl-ammomium chloride are obtained.

Example 3

From 351.2 g of 1-N-methyl-/2-phenyl-1-methyl/-ethyl-amine-d-tartarate the base is set free with a 40% sodium hydroxide solution according to Example 1. To the base in benzen 5 g. of N-benzyl-N,N,N-triethyl-ammonium chloride are added, whereupon at 60°C 9.8 ml. of propargyl bromide and a solution of 46 g. of sodium hydroxide in 170 ml. of water are added. The reaction mixture is worked up as described in Example 1. Thus 167.0 g. of N-methyl-N-/2-phenyl-1-methyl/-ethyl-N-propargyl-ammonium chloride are obtained.

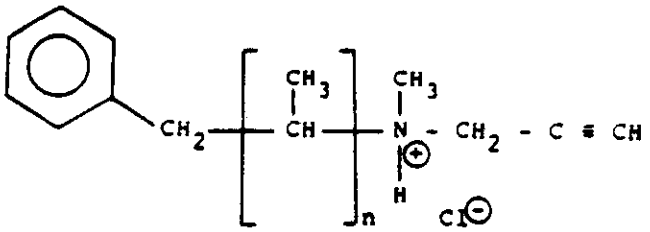
Example 4

One proceeds as described in Example 3 except that 351.2 g. of 1-N-methyl/2-phenyl-1-methyl/-ethyl-amine-d-tartarate, 91.8 ml. of propargyl bromide and a solution of 46 g. of sodium hydroxide in 170 ml. of water are used. Thus the benzene solution of N-methyl-N-/2-phenyl-1-methyl/-ethyl-N-propargyl-amine is obtained.

The pH of this solution is adjusted to 6.5—7 by adding 100 ml. of 5% hydrochloric acid. If the pH of the aqueous phase is higher /pH above 7/, a further amount of hydrochloric acid is added in order to adjust the pH to the desired value of 6.5—7. The benzene solution is separated and worked up as described in Example 1. Thus 155.0 g. of N-methyl-N-/2-phenyl-1-methyl/-ethyl-N-propargyl-ammonium chloride are obtained.

Claims

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



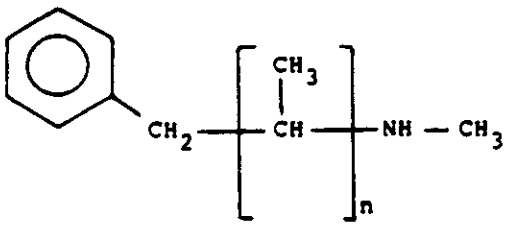
(I)

wherein

$n = 0$ or 1

characterized in that it comprises the steps of:

(a) dissolving a free base of the formula (II)

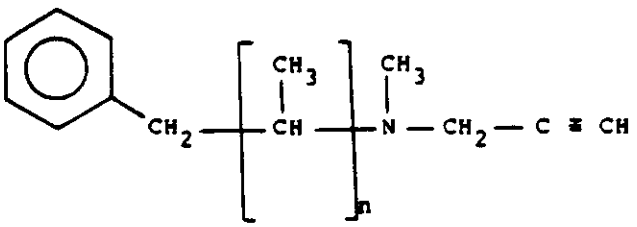


(II)

in a water, non-miscible organic solvent and propargylating said free base with a compound of the formula (III)

$$X—CH_2—C \equiv CH \qquad (III)$$

wherein X is halo, in the presence of an alkali and water to yield a mixture of the unreacted free base of the formula (II) and a free base of the formula (IV)



(IV)

in a two-phase system containing an organic phase and a first aqueous phase;

(b) separating the organic phase which contains the mixture of the free base of the formula (II) and the free base of the formula (IV) from the first aqueous phase;

(c) treating the organic phase containing the mixture of the free base of the formula (II) and the free base of the formula (IV) with water and an amount of acid sufficient to adjust the pH of the solution to 6.5 to 7 to selectively dissolve, in a second two-phase system thus formed, a salt of the compound of the formula (II) in the aqueous phase while the free base of the formula (IV) remains in the organic phase;

(d) separating the aqueous phase from the organic phase; and

(e) treating the organic phase containing the free base of the formula (IV) with hydrogen chloride to precipitate the salt of the formula (I).

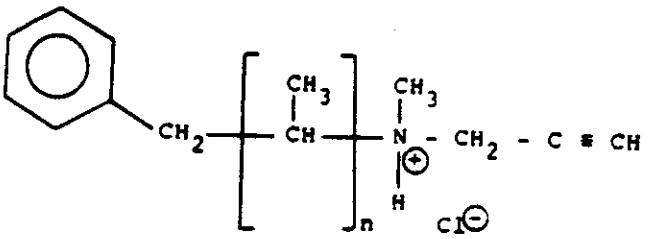
2. The process according to claim 1, characterized in that in step (a), the reaction of the compounds of the formulae (II) and (III) is carried out in the presence of a phase transfer catalyst.

3. The process according to claim 1, characterized in that in step (a), the water non-miscible organic solvent is benene, toluene, dichloroethane, or diisopropyl ether.

4. The process according to claim 2, characterized in that the phase transfer cataylyst is N-benzyl-N,N,N-triethyl-ammonium chloride.

5. The process according to claim 1, characterized in that in step (a), the propargylation is carried out at a temperature between 40—70°C.

6. A process for the preparation of a salt of the formula (I)



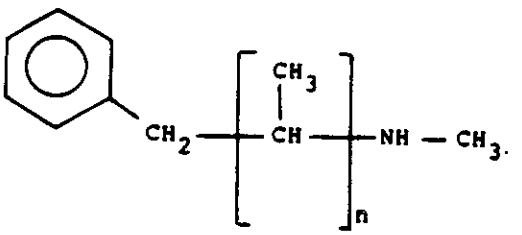
(I)

wherein

$n = 0$ or 1

characterized in that it comprises the steps of:

(a) alkali decomposing an aqueous suspension of the D-tartarate of the l-isomer of a compound of the formula (II)



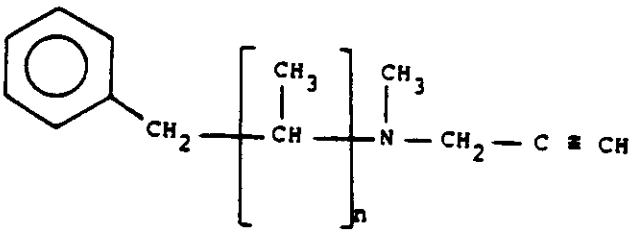
(II)

with an alkali, to obtain the free base of the formula (II) without isolation;

(b) dissolving the free base of the formula (II) in a water, non-miscible organic solvent and propargylating said free base with a compound of the formula (III)

$$X—CH_2—CH \equiv CH \qquad \text{(III)}$$

wherein X is halo, in the presence of an alkali and water to yield a mixture of the unreacted free base of the formula (II) and a free base of the formula (IV)



(IV)

in a two phase system containing an organic phase and a first aqueous phase;

(c) separating the organic phase which contains the mixture of the free base of the formula (II) and the free base of the formula (IV) from the first aqueous phase;

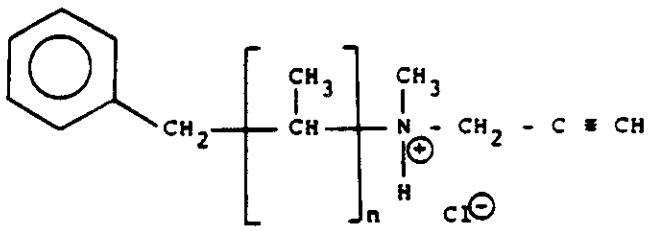
(d) treating the organic phase containing the mixture of the free base of the formula (II) and the free base of the formula (IV) with water and an amount of acid sufficient to adjust the pH of the solution to 6.5 to 7 to selectively dissolve, in a second two-phase system thus formed, a salt of the compound of the formula (II) in the aqueous phase while the free base of the formula (IV) remains in the organic phase;

(e) separating the aqueous phase from the organic phase; and

(f) treating the organic phase containing the free base of the formula (IV) with hydrogen chloride to precipitate the salt of the formula (I).

Patentansprüche

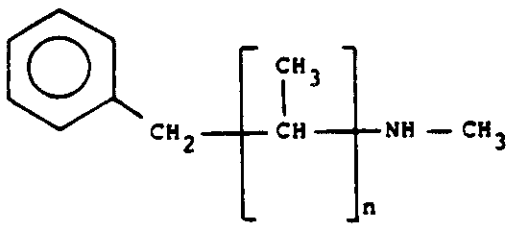
1. Verfahren zur Herstellung eines Salzes der Formel:



(I)

worin n = oder 1
dadurch gekennzeichnet, daß es folgende Stufen umfaßt:

(a) Auflösen einer freien Base der Formel:

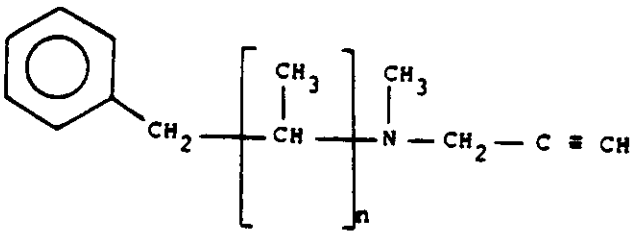


(II)

in einem mit Wasser nicht mischbaren organischen Lösungsmittel und Propargylieren der freien Base mit einer Verbindung der Formel:

$$X—CH_2—CH \equiv CH \qquad (III)$$

worin X für Halogen steht, in Gegenwart eines Alkalis und von Wasser zur Gewinnung eines Gemichs aus der nicht-umgesetzten freien Base der Formel (II) und einer freien Base der Formel:



(IV)

in einem Zweiphasensystem mit einer organischen Phase und einer ersten wäßrigen Phase;

(b) Abtrennen der das Gemisch aus der freien Base der Formel (II) und der freien Base der Formal (IV) enthaltenden organischen Phase von der ersten wäßrigen Phase;

(c) Behandeln der das Gemisch aus der freien Base der Formel (II) und der freien Base der Formel(IV) enthaltenden organischen Phase mit Wasser und einer zur Einstellung des pH-Werts der Lösung auf 6,5—7 ausreichenden Säuremenge zum selektiven Auflösen in einem dabei gebildeten zweiten Zweiphasensystem eines Salzes der Verbindung der Formel (II) in der wäßrigen Phase, wobei die freie Base der Formel (IV) in der organischen Phase verbleibt;

(d) Abtrennen der Wäßrigen Phase von der organischen Phase und

(e) Behandeln der die freie Base der Formel (IV) enthaltenden organischen Phase mit Chlorwasserstoffsäure zur Ausfällung des Salzes der Formel (I).

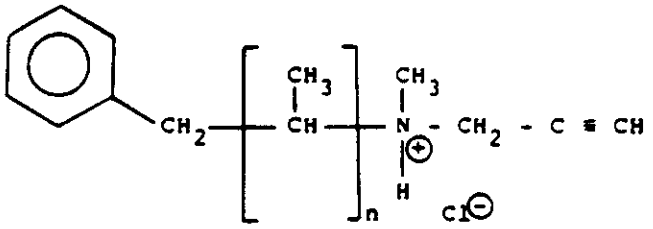
2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß in Stufe (a) die Umsetzung der Verbindungen der Formeln (II) und (III) in Gegenwart eines Phasentransfer-katalysators stattfindet.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß in Stufe (a) als mit Wasser nicht mischbares organisches Lösungsmittel Benzol, Toluol, Dichlorethan oder Diisopropylether verwendet wird.

4. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß der Phasentransferkatalysator aus N-Benzyl-N,N,N-triethylammoniumchlorid besteht.

5. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß in Stufe (a) die Propargylierung bei einer Temperatur zwischen 40°C und 70°C durchgeführt wird.

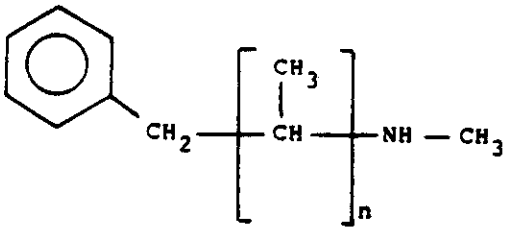
6. Verfahren zur Herstellung eines Salzes der Formel:



(I)

worin n = 0 oder 1,
dadurch gekennzeichnet, daß es folgende Stufen umfaßt:

(a) Zersetzen einer wäßrigen Suspension des d-Tartrats des 1-Isomeren einer Verbindung der Formel:



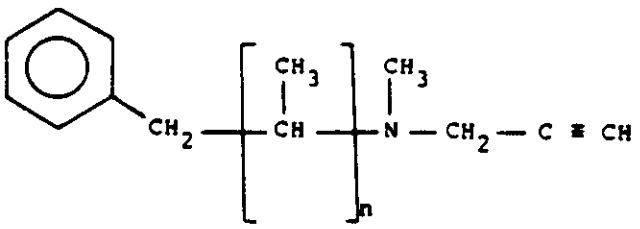
(II)

mit einem Alkali zur Bildung der freien Base der Formel (II), ohne Isolierung;

(b) Auflösen der freien Base der Formel (II) in einem mit Wasser nicht mischbaren organischen Lösungsmittel und Propargylieren der freien Base mit einer Verbindung der Formel:

$$X—CH_2—CH \equiv CH \qquad (III)$$

worin X für Halogen steht, in Gegenwart eines Alkalis und von Wasser zur Gewinnung eines Gemishs der nicht-umgesetzten freien Base der Formel (II) und einer Base der Formel:



(IV)

in einem Zweiphasensystem mit einer organischen Phase und einer ersten wäßrigen Phase;

(c) Abtrennen der das Gemisch aus der freien Base der Formel (II) und der freien Base der Formel (IV) enthaltenden organischen Phase von der ersten wäßrigen Phase;

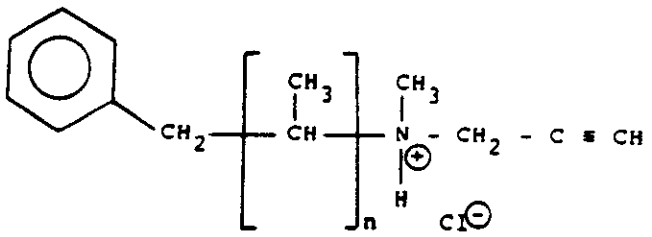
(d) Behandeln der das Gemisch aus der freien Base der Formel (II) und der freien Base der Formel (IV) enthaltenden organischen Phase mit Wasser und einer zur Einstellung des pH-Werts der Lösung auf 6,5—7 ausreichenden Säuremenge zum selektiven Auflösen in einem dabei gebildeten zweiten Zweiphasensystem eines Salzes der Verbindung der Formel (II) in der wäßrigen Phase, wobei die freie Base der Formel (IV) in der organischen Phase verbleibt;

(e) Abtrennen der Uäßrigen Phase von der organischen Phase und

(f) Behandeln der die freie Base der Formal (IV) enthaltenden organischen Phase mit Chlorwasserstoffsäure zur Ausfällung des Salzes der Formel (I).

Revendications

1. Un procédé pour la préparation d'un sel de formule (I)



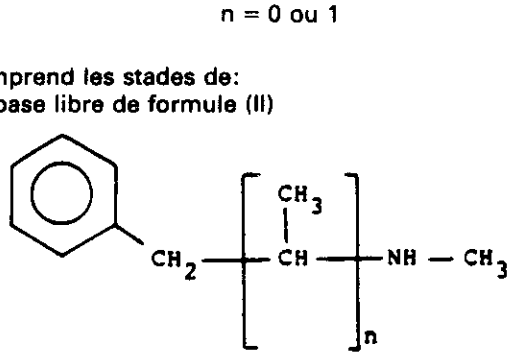
(I)

dans laquelle

$n = 0$ ou 1

caractérisé en ce qu'il comprend les stades de:

(a) dissolution d'une base libre de formule (II)

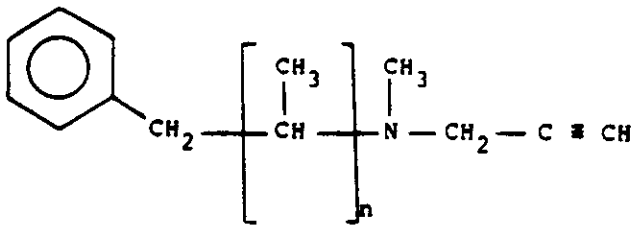


(II)

dans un solvent oganique non miscible à l'eau et la propargylation de ladite base libre avec in composé de formule (III)

$$X—CH_2—C\equiv CH \qquad (III)$$

dans laquelle X est un halogéno, en présence d'un alcali et d'eau pour fournir un mélange de la base libre n'ayant pas réagi de formule (II) et d'une base libre de formule (IV)



(IV)

dans un système à deux phases contenant une phase organique et une première phase aqueuse;

(b) séparation de la phase organique qui contient le mélange de la base libre de formule (II) et la base libre de formule (IV) d'avec la première phase aqueuse;

(c) traitement de la phase organique contenant le mélange de la base libre dr formule (II) et de la base libre de formule (IV) avec de l'eau et une quantité d'acide suffisante pour ajuster le pH de la solution entre 6,5 et 7 pour dissoudre sélectivement, dans un second système à deux phases ainsi formé, un sel du composé de formule (II) dans la phase aqueuse tandis que la base libre de formule (IV) demeure dans la phase organique;

(d) séparation de la phase aqueuse d'avec la phase organique; et

(e) traitement de la phase organique contenant la base libre de formule (IV) avec du chlorure d'hydrogène pour précipiter le sel de formule (I).

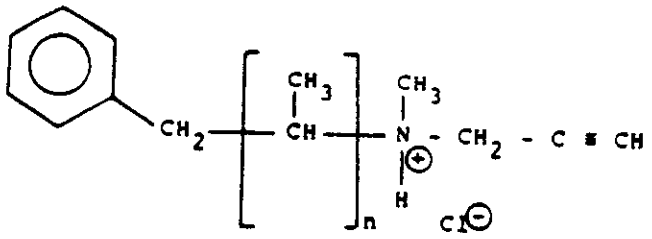
2. Le procédé selon la revendication 1, caractérisé en ce que dans le stade (a) la réaction des composés de formule (II) et (III) est effectuée en présence d'un catalyseur de transfert de phase.

3. Le procédé selon la revendication 1, caractérisé en ce que dans le stade (a) le solvant organique non miscible à l'eau est le benzène, le toluène, le dichloroéthane ou l'éther diisopropylique.

4. Le procédé selon la revendication 2, caractérisé en ce que le catalyseur se transfert de phase est le chlorure de N-benzyl-N,N,N-triéthylammonium.

5. Le procédé selon la revendication 1, caractérisé en ce que dans le stade (a) la propargylation est effectuée à une température entre 40 et 70°C.

6. Un procédé pour la préparation d'un sel de formule (I)



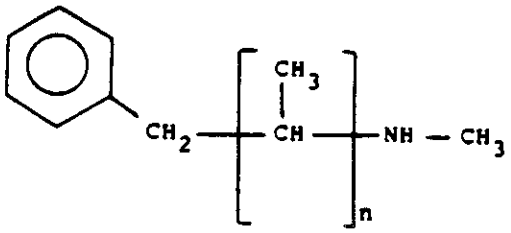
(I)

dans laquelle

$n = 0$ ou 1

caractérisé en ce qu'il comprend les stades de:

(a) décomposition alcaline d'une suspension aqueuse du d-tartrate de l'isomère 1 d'un composé de formule (II)



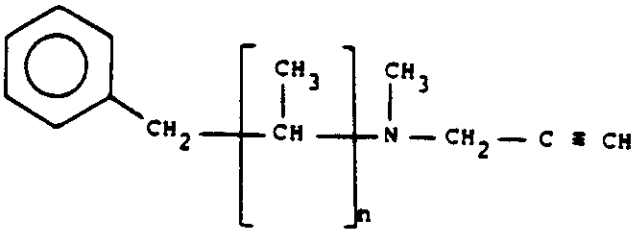
(II)

avec un alcali pour obtenir la base libre de formule (II) sans isolement;

(b) dissolution de la base libre de formule (II) dans un solvent oganique non miscible à l'eau et propargylation de ladite base libre avec un composé de formule (III)

$$X—CH_2— \equiv CH \qquad (III)$$

dans laquelle X est un halogéno, en présence d'un alcali et d'eau pour fournir un mélange de la base libre n'ayant pas réagi de formule (II) et d'une base libre de formule (IV)



(IV)

dans un système à deux phases contenant une phase organique et une première phase aqueuse;

(c) séparation de la phase organique qui contient le mélange de la base libre de formule (II) et de la base libre de formule (IV) d'avec la première phase aqueuse;

(d) traitement de la phase organique contenant le mélange de la base libre dr formule (II) et de la base libre de formule (IV) avec de l'eau et une quantité d'acide suffisante pour ajuster le pH de la solution entre 6,5 et 7 pour dissoudre sélectivement, dans un second système à deux phases ainsi formé, un sel du composé de formule (II) dans la phase aqueuse tandis que la base libre de formule (IV) demeure dans la phase organique;

(e)séparation de la phase aqueuse d'avec la phase organique: et

(f) traitement de la phase organique contenant la base libre de formule (IV) avec du chlorure d'hydrogène pour précipiter le sel de formule (I).

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