(51) International Patent Classification: Not classified

(21) International Application Number: PCT/IN2015/050003

(22) International Filing Date: 7 January 2015 (07.01.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
90/CHE/2014 8 January 2014 (08.01.2014) IN

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Declarations under Rule 4.17:
— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.17(i))
— if inventorship (Rule 4.17(iv))

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF TRANEXAMIC ACID

(57) Abstract: An improved process for the preparation of Tranexamic acid is disclosed. The process can be performed at moderate reaction conditions such as at moderate temperatures and moderate pressure for large scale manufacture of Tranexamic acid.
Published:
— without international search report and to be republished upon receipt of that report (Rule 48.2(g))
AN IMPROVED PROCESS FOR THE PREPARATION OF TRANEXAMIC ACID

FIELD OF THE INVENTION

The invention relates to an improved process for the preparation of tranexamic acid.

BACKGROUND OF THE INVENTION

Tranexamic acid is chemically known as trans-4-aminomethylcylohexanecarboxylic acid having the formula-1:

![Formula-I](image)

Tranexamic acid is an antifibrinolytic agent used for the treatment of cyclic heavy menstrual bleeding and is administered as oral tablet and injection form. Tranexamic acid is first disclosed in the patent US3950405. The process disclosed in US3950405 produces tranexamic acid from trans-4-cyanocyclohexane-l-carboxylic acid or its lower alkyl ester by hydrogenation at high pressure and temperature.

The US3449411 discloses a process for producing tranexamic acid from acetamidomethylbenzoic acid with heating about 120-200°C under 40-100 atm pressure for about 8-16 hours. The US3923879 discloses a process for the preparation of tranexamic acid from P-aminomethylbenzoic acid by hydrogenation at the temperature of 10-250 °C in hydrogene pressure from about 10-200 atm. The patent US3932497 discloses a process for the preparation of tranexamic acid from P-aminomethylbenzoic acid with ruthenium metal catalyst in the presence of hydrogen pressure 50-200 Kg/cm² and at a temperature 90 - 200 °C.
It is apparent that prior arts for the preparation of Tranexamic acid either employ elevated temperature or high pressure or both.

Hence, there exists a need of an improved process for the preparation of Tranexamic acid that could be done at moderate temperatures and/or moderate pressure for large scale manufacture.

**OBJECT OF THE INVENTION**

The primary object of the invention is to provide an improved process for the preparation of Tranexamic acid that could be performed at moderate temperatures and moderate pressure for large scale manufacture.

**SUMMARY OF THE INVENTION**

Accordingly, there is provided a process for preparation of Tranexamic acid at moderated temperature and pressure.

In one embodiment, the invention provides a process for the preparation of Tranexamic acid comprising the steps of:

(a) treating 4-Cyano benzylamine hydrochloride with sulfuric acid to obtain compound of formula II:

![Formula II](image)

(b) hydrogenating the compound of formula-II with Rhodium catalyst in presence of an acid, to obtain a compound of formula III:
(c) optionally, treating the compound of formula III with a mineral acid (HA) to obtain a compound of formula IV;

(d) treating the compound of the formula IV or formula III with an alkali base to obtain crude tranexamic acid; and

(e) optionally, crystallizing the tranexamic acid obtained in step (d) in a suitable solvent or by resin to obtain pure tranexamic acid.

In another embodiment, the invention provides a process for preparation of 4-methyl amino benzoic acid or its acid addition salts of the compound of the formula IIA:

wherein, HA is acid addition salt,
comprising the steps of:
(a) treating 4-Cyano benzylamine or its acid addition salts with an acid to obtain the compound of the formula IIA.

In another embodiment, the invention provides a process for preparation of 4-methyl amino cyclohexane or its pharmaceutical acid addition salt of the formula IIIA:

$$\text{HO} - \text{CONH}_2$$

Formula IIA

wherein, HA is acid addition salt,
comprising the steps of:
(a) treating 4-Cyano benzylamine or its acid addition salt with an acid to obtain compound of formula IIA,

$$\text{HO} - \text{CONH}_2$$

Formula IIA

(b) hydrogenating the compound of formula IIA obtained in the step (a) with Rhodium catalyst in the presence of an acid to obtain compound of formula IIIA.

In another embodiment, the invention provides a process for preparation of tranexamic
acid or its pharmaceutically acceptable salts, comprising the steps of:

(a) treating compound of formula IIIA with a base

\[ \text{HO} \quad \text{O} \quad \text{NH}_2 \quad \text{H} \quad \text{A} \]

Formula IIIA

to obtain a compound of formula V:

\[ \text{HO} \quad \text{O} \quad \text{NH}_2 \quad \text{N} \]

Formula V

(b) isomerizing the compound of formula V at 200-220°C to obtain tranexamic acid or its pharmaceutically acceptable salts.

In a further embodiment, the invention provides a process for the preparation of tranexamic acid or its pharmaceutically acceptable salts comprising the steps of:

(a) treating the compound of formula IIIA with an amine protecting group
Formula IIIA

\[
\text{Formula IIIA}
\]

to obtain the compound of formula VI

\[
\text{Formula VI}
\]

wherein "P" is amine protecting group;

(b) treating the compound of formula VI with cation ion exchange resin to obtain the tranexamic acid or its pharmaceutical salts.

**BRIEF DESCRIPTION OF THE DRAWINGS**

**Figure 1**: PXRD of tranexamic acid.

**Figure 2**: PXRD of sulfuric acid salt of the 4-methyl aminobenzoic acid

**Figure 3**: PXRD of sulfuric acid salt of the 4-methyl aminocyclohexane acid.

**DESCRIPTION OF THE INVENTION**

The present invention provides an improved process for the preparation of Tranexamic acid that could be done at moderate temperatures and moderate pressure for large scale manufacture from benzylamine or its acid addition salts.
In one embodiment, the invention provides a process for the preparation of Tranexamic acid comprising the steps of:

(a) treating 4-Cyano benzylamine hydrochloride with sulfuric acid to obtain compound of formula II;

(b) hydrogenating the compound of formula-II with Rhodium catalyst in presence of an acid to obtain a compound of formula III;

(c) optionally, treating the compound of formula III with a mineral acid (HA) to obtain a compound of formula IV;
(d) treating the compound of the formula IV or formula III with an alkali base to obtain crude tranexamic acid; and

(e) optionally, crystallizing the tranexamic acid obtained in step (d) in a suitable solvent or by resin to obtain pure tranexamic acid.

The acid employed in step (b) may be selected from the group comprising of formic acid, acetic acid, butyric acid, citric acid, lactic acid, malic acid, pyroglutamic acid, propionic acid, valeric acid, capronic acid, palmitic acid, succinic acid, hydrochloric, sulfuric acid, Nitric acid, Hydrofluoric acid, phosphoric acid and Hydrobromic acid. In a preferred embodiment the acid employed in step (b) is acetic acid.

The mineral acid (HA) employed in step (c) may be selected from the group comprising of hydrochloric acid, sulfuric acid, Nitric acid, Hydrofluoric acid, phosphoric acid and Hydrobromic acid. In a preferred embodiment the mineral acid (HA) selected in step (c) is Hydrochloric acid.

The alkali bases used in step (d) may be selected from the group comprising of alkali metals such as sodium, potassium, lithium; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate; alkali metal hydroxides such as sodium hydroxide, calcium hydroxide, potassium hydroxide. In a preferred embodiment, the alkali base employed in step (d) is sodium hydroxide (NaOH).

The solvent used in the step (e) is generally a polar organic solvent selected from the group comprising of methanol, ethanol, propanol, butanol, dichloromethane, tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide or mixtures thereof. In a preferred embodiment the solvent employed in step (e) is methanol.

In another embodiment, the invention provides a process for preparation of 4-methyl amino benzoic acid or its acid addition salts of the compound of formula IIA:
wherein, HA is acid addition salt, comprising the steps of:

(a) treating 4-Cyano benzylamine or its acid addition salts with an acid to obtain the compound of the formula IIA.

The acid employed in step (a) is selected from the group of organic or inorganic acids. The organic acid may be selected from the group comprising of C1-C6 carboxylic acid such as formic acid, acetic acid, butyric acid, citric acid, lactic acid, malic acid, pyroglutamic acid, propionic acid, valeric acid, capronic acid, palmitic acid, and succinic acid. Whereas, the inorganic acid may be selected from the group comprising of hydrochloric acid, sulfuric acid, Nitric acid, Hydrofluoric acid, phosphoric acid and Hydrobromic acid. In one preferred embodiment, the acid employed in step (a) is sulfuric acid.

In another embodiment, the invention provides a process for preparation of 4-methyl amino cyclohexane or its pharmaceutical acid addition salt of the formula IIIA:

wherein, HA is acid addition salt,
comprising the steps of:

(a) treating 4-Cyano benzylamine or its acid addition salt with an acid to obtain compound of formula IIA,

![Formula II A](image)

(b) hydrogenating the compound of formula IIA obtained in the step (a) with Rhodium catalyst in the presence of an acid to obtain compound of formula IDA.

The acid employed in step (a) may be selected from organic acid or inorganic acid. The organic acid may be selected from the group comprising of C1-C6 carboxylic acid such as formic acid, acetic acid, butyric acid, citric acid, lactic acid, malic acid, pyroglutamic acid, propionic acid, valeric acid, capronic acid, palmitic acid and succinic acid. The inorganic acid may be selected from the group comprising of hydrochloric, sulfuric acid, nitric acid, hydrofluoric acid, phosphoric acid and hydrobromic acid. In one preferred embodiment, the acid is sulfuric acid.

The acid employed in step (b) may be selected from the group comprising of formic acid, acetic acid, butyric acid, citric acid, lactic acid, malic acid, pyroglutamic acid, propionic acid, valeric acid, capronic acid, palmitic acid, succinic acid, hydrochloric, sulfuric acid, nitric acid, hydrofluoric acid, phosphoric acid and hydrobromic acid. In one preferred embodiment, the acid is acetic acid.

In another embodiment, the invention provides a process for preparation of tranexamic acid or its pharmaceutically acceptable salts, comprising the steps of:

(a) treating compound of formula IIIA with a base
to obtain a compound of formula V;

(b) isomerizing the compound of formula V at 200-220 °C to obtain tranexamic acid or its pharmaceutically acceptable salts.

The base employed in step (a) is selected from the group comprising of hydroxides such as sodium hydroxide, potassium hydroxide, caesium hydroxide, barium hydroxide, calcium hydroxide; carbonates such as sodium carbonate, potassium carbonate, caesium carbonate, barium carbonate, calcium carbonate; bicarbonates such as sodium bicarbonate, potassium bicarbonate, caesium bicarbonate, barium bicarbonate, calcium bicarbonate. In one preferred embodiment the base is calcium hydroxide.

In a further embodiment, the invention provides a process for the preparation of tranexamic acid or its pharmaceutically acceptable salts, comprising the steps of:

(a) treating the compound of formula IIIA with an amine protecting group
to obtain the compound of formula VI

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{\hspace{1cm}} & \text{HA} \\
\text{\hspace{1cm}} & \text{NMH}_2 \\
\text{Formula VI}
\end{align*}
\]

wherein "P" is amine protecting group;

(b) treating the compound of formula VI with cation ion exchange resin to obtain tranexamic acid or its pharmaceutical salts.

The amine protecting group "P" in step (a) is selected from the Carbobenzyloxy, p-Methoxybenzyl carbonyl, tert-Butyloxy carbonyl, 9-Fluorenylmethyloxycarbonyl, Acetyl, Benzoyl, Benzyl, Carbamate, p-Methoxy benzyl, 3,4-Dimethoxy benzyl, p-methoxyphenyl and Tosyl.

The following examples are provided to enable one skilled in the art to practice the invention and to merely illustrate the process of the invention. However, it is not intended in any way to limit the scope of the present invention which is further defined by the following claims.
EXAMPLES:

Example 1: Preparation of 4-aminomethyl benzoic acid sulfate of formula II

The compound 4-(Aminomethyl)benzonitrile hydrochloride (100 gm) was dissolved in a mixture of concentrated sulfuric acid (130 ml) and water (170 ml) and heated to 100 °C. The reaction mixture was stirred for about 12 hours at 100 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was cooled to 20-25 °C and slowly added water (165 ml) at temperatures below 30°C. The reaction mixture was maintained at a temperature of 25-30°C for 30 mints. The resultant solid was filtered, washed with water (100 ml) and dried at 80-85 °C in hot air oven for 10 hours. Yield: 135.0 g; Purity by HPLC: 96.87%.

Example 2: Preparation of 4-(aminoethyl)cyclohexane carboxylic acid sulfate of formula III
A mixture of the compound of formula II (100 gm), 1000 ml of acetic acid and Rhodium/Carbon (10 gm) was placed in sealed container and applied 5.0 Kg/cm2 of ¾ pressure. The sealed container containing the reaction mixture was heated to 70-75°C. The reaction mixture in the sealed container was maintained at a temperature of 70-75°C with a pressure of 5.0 Kg/cm2 for 12 hours. Then the reaction mixture was cooled to 25-30 °C and released pressure. The catalyst in the reaction mixture was filtered and washed with acetic acid (50 ml). The filtrate was distilled under vacuum at below 65°C to obtain a residue. The residue was dissolved in the acetone (250 ml) and maintained for 30 min at a temperature of 25-30 °C. The resultant solid was filtered, washed with acetone (100 ml) and dried at 55-60 °C under vacuum for 10 h. Yield: 92 gm; Purity by HPLC: Cis (59.67%) and Trans (37.53%)

**Example 3:** Preparation of Trans-4-(aminomethyl)cyclohexane carboxylic acid hydrochloride of formula IV

![Chemical structure](image)

Step-A: A mixture of the compound of formula III (100 gm), water (1000 ml) and Sodium hydroxide flakes (93 gm) was placed in sealed container and heated to 200-210°C. The reaction mixture in the sealed container was maintained at temperature of 200-210°C for 18 hours with the developed pressure. Then the reaction mixture was cooled to 25-30 °C and released the pressure. The reaction mixture was filtered and washed with water (20 ml). The filtrate distilled under vacuum at below 70 °C to obtain a solid residue. The residue was suspended in acetone (250 ml) and maintained for 30 minutes at 25-30°C. The resultant solid was filtered, washed with acetone (100 ml) and dried at 65-70 °C for 8 h. Yield: 122 g.
Step-B: A mixture of the dried solid (122 gm) obtained in step A and concentrated hydrochloric acid (230 ml) and heated to 105-110°C. The reaction mixture was maintained at 105-110°C for 12 hours and cooled to 25-30°C. The reaction mixture was filtered and the filtrate was distilled under vacuum at below 70°C to obtain a residue. The residue was mixed with acetone (200 ml) and maintained at 25-30°C for 30 minutes. The resultant solid was filtered, washed with acetone (50 ml) and dried at 65-70°C for 10 hours. Yield: 30 g.

Example-3(a): Preparation of tranexamic acid from the compound of formula-III

A mixture of the compound of Formula-III (100 gm), water (1000 ml) and Sodium hydroxide flakes (93.98 gm) was placed in sealed container and heated to 200-210°C. The reaction mixture in the sealed container was maintained at temperature of 200-210°C for 18 hours with the developed pressure. Then the reaction mixture was cooled to 25-30°C and released the pressure. The reaction mixture was filtered and washed with water (20 ml). The filtrate was passed through a resin column. The column was eluted with water (1000 ml) of 4% of ammonia solution. The eluate was distilled under vacuum at below 70°C to get a residue. The residue was mixed with methanol (300 ml) and stirred for 30 minutes at 25-35°C. The resultant precipitate was washed with methanol (30 ml) and dried at 80-85°C for 8 hours. Yield: 60 g.
Example 4: Preparation of tranexamic acid

The (30 g) compound obtained in the Example-3 was dissolved in water (90 ml) and cooled the contents to 10-15°C. The pH of the reaction mixture was adjusted to 7.00-7.50 with 10% Sodium hydroxide solution at 10-15 °C and stirred at 25-30°C for 30 min. The reaction mixture was distilled under vacuum at below 70 °C to obtain a residue. The obtained residue was mixed with acetone (60 ml) and stirred for 30 minutes at a temperature of 25-30°C. The resultant solid was filtered, washed with acetone (15 ml) and dried at 80-85°C for 4 hours. Yield: 32 g.

Example 5: Crystallization of Tranexamic acid

The 32 g of compound obtained in Example-4 was mixed with methanol (160 ml) and heated to reflux temperature. To the refluxed mixture, water (96 ml) was slowly added at 70-75°C and stirred for 15 min at the same temperature. The mixture was then cooled slowly to 25-30°C and maintained at the same temperature for 2 hours. The resultant solid was filtered, washed with methanol (15 ml) and dried at 100-105°C. Yield: 10 g.
Example 6: Process for the preparation of tranexamic acid.

The compound of formula III (20gm) was dissolved in the (200 ml) water and added the calcium hydroxide (6 gm) to the above solution. The mass was stirred for 30 mints. The precipitate was filtered. The calcium hydroxide (5.8 gm) was added to the filtrate. The mass was heated at 200-210° C for the 12 hours. The pH of the reaction mass was adjusted to 4 - 7 with dilute sulfuric acid. Filter and costumer work up provided the tranexamic acid.

Example 7: Process for the preparation of tranexamic acid.

The compound of the formula III (20gm) was dissolved in 8 % NaOH solution. The reaction mass was heated for 200-210° C for 12 hours. The reaction mass was cooled to room temperature. The BOC anhydride (21 gm) was added to the above solution. The mass was stirred for 2 hours. The precipitate was filtered. The compound passed through the dry resin (ethyl acetate/ chloroform). The compound was eluted with methanolic ammonia to obtain the tranexamic acid.
I Claim:

1. A process for the preparation of Tranexamic acid comprising the steps of:

(a) treating 4-Cyano benzylamine hydrochloride with sulfuric acid to obtain compound of formula II;

(b) hydrogenating the compound of formula-II with Rhodium catalyst in presence of an acid, to obtain a compound of formula III;

(c) optionally, treating the compound of formula III with a mineral acid (HA) to obtain a compound of formula IV;
(d) treating the compound of the formula IV or formula III with an alkali base to obtain crude tranexamic acid; and

(e) optionally, crystallizing the tranexamic acid obtained in step (d) in a suitable solvent or by resin to obtain pure tranexamic acid.

2. The process as claimed in claim 1, wherein the acid employed in step (b) is selected from the group comprising of formic acid, acetic acid, butyric acid, citric acid, lactic acid, malic acid, pyroglutamic acid, propionic acid, valeric acid, capronic acid, palmitic acid, succinic acid, hydrochloric, sulfuric acid, Nitric acid, hydrofluoric acid, phosphoric acid and hydrobromic acid.

3. The process as claimed in claim 1, wherein the mineral acid (HA) employed in step (c) is selected from the group comprising of hydrochloric acid, sulfuric acid, nitric acid, hydrofluoric acid, phosphoric acid and hydrobromic acid.

4. The process as claimed in claim 1, wherein the alkali base employed in step (d) is selected from the group comprising of alkali metals, alkali metal carbonates, alkali metal bicarbonates and alkali metal hydroxides.

5. The process as claimed in claim 4, wherein the alkali metal is selected from sodium, potassium and lithium.

6. The process as claimed in claim 4, wherein the alkali metal carbonate is selected from sodium carbonate, potassium carbonate, cesium carbonate and lithium carbonate.

7. The process as claimed in claim 4, wherein the alkali metal bicarbonate is selected from sodium bicarbonate, potassium bicarbonate, lithium bicarbonate and cesium bicarbonate.

8. The process as claimed in claim 4, wherein the alkali metal hydroxide is selected from sodium hydroxide, cesium hydroxide and potassium hydroxide.

9. The process as claimed in claim 1, wherein the solvent used in step (e) is a polar organic
solvent selected from the group comprising of methanol, ethanol, propanol, butanol, dichloromethane, tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile and dimethyl sulfoxide or mixtures thereof.

10. A process for preparation of 4-methyl amino benzoic acid or its acid addition salts of formula IIA:

\[
\text{HO}_2\text{C-} \quad \text{HA}
\]

\[
\text{\text{NH}_2}
\]

Formula IIA

wherein, HA is acid addition salt,
comprising the steps of:
(a) treating 4-Cyano benzylamine or its acid addition salts with an acid to obtain the compound of formula IIA.

11. The process as claimed in claim 10, wherein the acid employed in step (a) is selected from organic acids and inorganic acids.

12. The process as claimed in claim 11, wherein the organic acid is selected from the group comprising of C1-C6 carboxylic acid such as formic acid, acetic acid, butyric acid, citric acid, lactic acid, malic acid, pyroglutamic acid, propionic acid, valeric acid, capronic acid, palmitic acid and succinic acid.

13. The process as claimed in claim 11, wherein the inorganic acid is selected from the group comprising of hydrochloric acid, sulfuric acid, nitric acid, hydrofluoric acid, phosphoric acid and hydrobromic acid.

14. The process as claimed in claim 11, wherein the acid employed in step (a) is sulfuric acid.
15. A process for preparation of 4-methyl amino cyclohexane or its pharmaceutical acid
addition salt of formula IDA:

\[
\text{HO} \quad \text{O} \\
\text{HO} \quad \text{C} \\
\text{NH}_2
\]

Formula IIA

wherein, HA is acid addition salt,

comprising the steps of:

(a) treating 4-Cyano benzylamine or its acid addition salt with an acid to obtain
compound of formula IIA;

\[
\text{HO} \quad \text{O} \\
\text{HO} \quad \text{C} \\
\text{NH}_2
\]

Formula IIA

(b) hydrogenating the compound of formula IIA obtained in the step (a) with Rhodium
catalyst in the presence of an acid to obtain compound of formula IIIA.

16. The process as claimed in 15, wherein the acid employed in step (a) is selected from
organic acids and inorganic acids.

17. The process as claimed in claim 16, wherein the organic acid is selected from the
group comprising of C1-C6 carboxylic acid such as formic acid, acetic acid, butyric acid,
citric acid, lactic acid, malic acid, pyroglutamic acid, propionic acid, valeric acid,
capronic acid, palmitic acid and succinic acid.
18. The process as claimed in claim 16, wherein the inorganic acid is selected from the group comprising of hydrochloric, sulfuric acid, nitric acid, hydrofluoric acid, phosphoric acid and hydrobromic acid.

19. The process as claimed in claim 18, wherein the acid is sulfuric acid.

20. The process as claimed in claim 16, wherein the acid employed in step (b) is selected from the group comprising of formic acid, acetic acid, butyric acid, citric acid, lactic acid, malic acid, pyroglutamic acid, propionic acid, valeric acid, capronic acid, palmitic acid, succinic acid, hydrochloric, sulfuric acid, nitric acid, hydrofluoric acid, phosphoric acid and hydrobromic acid.

21. A process for preparation of tranexamic acid or its pharmaceutically acceptable salts, comprising the steps of:

(a) treating compound of formula IIIA with a base

\[
\text{HO} \cdot \text{C} = \text{O} \quad \text{HA} \\
\text{NH}_2
\]

Formula IIIA

to obtain a compound of formula V:

\[
\text{HO} \cdot \text{C} = \text{O} \quad \text{NH}_2
\]

Formula V
(b) isomerizing the compound of formula V at 200-220 °C to obtain tranexamic acid or its pharmaceutically acceptable salts.

22. The process as claimed in claim 21, wherein the base employed in step (a) is selected from the group comprising of hydroxides such as sodium hydroxide, potassium hydroxide, caesium hydroxide, barium hydroxide, calcium hydroxide; carbonates such as sodium carbonate, potassium carbonate, caesium carbonate, barium carbonate, calcium carbonate; bicarbonates such as sodium bicarbonate, potassium bicarbonate, caesium bicarbonate, barium bicarbonate, and calcium bicarbonate.

23. The process as claimed in claim 22, wherein the base is calcium hydroxide.

24. A process for preparation of tranexamic acid or its pharmaceutically acceptable salts, comprising the steps of:

(a) treating the compound of formula IIIA with an amine protecting group

(b) isomerizing the compound of formula V at 200-220 °C to obtain tranexamic acid or its pharmaceutically acceptable salts.
wherein "P" is amine protecting group;

(b) treating the compound of formula VI with cation ion exchange resin to obtain tranexamic acid or its pharmaceutical salts.

25. The process as claimed in claim 24, wherein the amine protecting group "P" in step (a) is selected from the Carbobenzyloxy, p-Methoxybenzyl carbonyl, tert-Butyloxy carbonyl, 9-Fluorenylmethyloxycarbonyl, Acetyl, Benzoyl, Benzyl, Carbamate, p-Methoxybenzyl, 3,4-Dimethoxy benzyl, p-methoxyphenyl and Tosyl.
Figure 1