F O R M 2

THE PATENTS ACT, 1970
(39 of 1970)
and
The Patents Rules, 2003
COMPLETE SPECIFICATION
(See section 10; rule 13)

1. Title of the invention.

NOVEL SYNTHESIS OF 5-(2-FLUOROPHENYL)-1H-PYRROLE-3-CARBALDEHYDE

2. Applicant(s)

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3. **PREAMBLE TO THE DESCRIPTION**

The following specification particularly describes the invention and the manner in which it is to be performed.

"NOVEL SYNTHESIS OF 5-(2-FLUOROPHENYL)-1H-PYRROLE-3-CARBALDEHYDE"

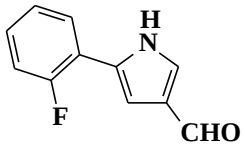
FIELD OF THE INVENTION

The present invention relates to a process for the preparation of 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde by using novel compound of formula (XIII) and (XIV).

BACKGROUND OF THE INVENTION

5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde as a key intermediate for the preparation of potassium ion-competitive acid blocker (P-CAB), this intermediate is also used in the preparation of Vonoprazan Fumarate, which is treated of gastroduodenal ulcer (including some drug-induced peptic ulcers) and reflux esophagitis.

5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde, is represented by structural Formula (I).

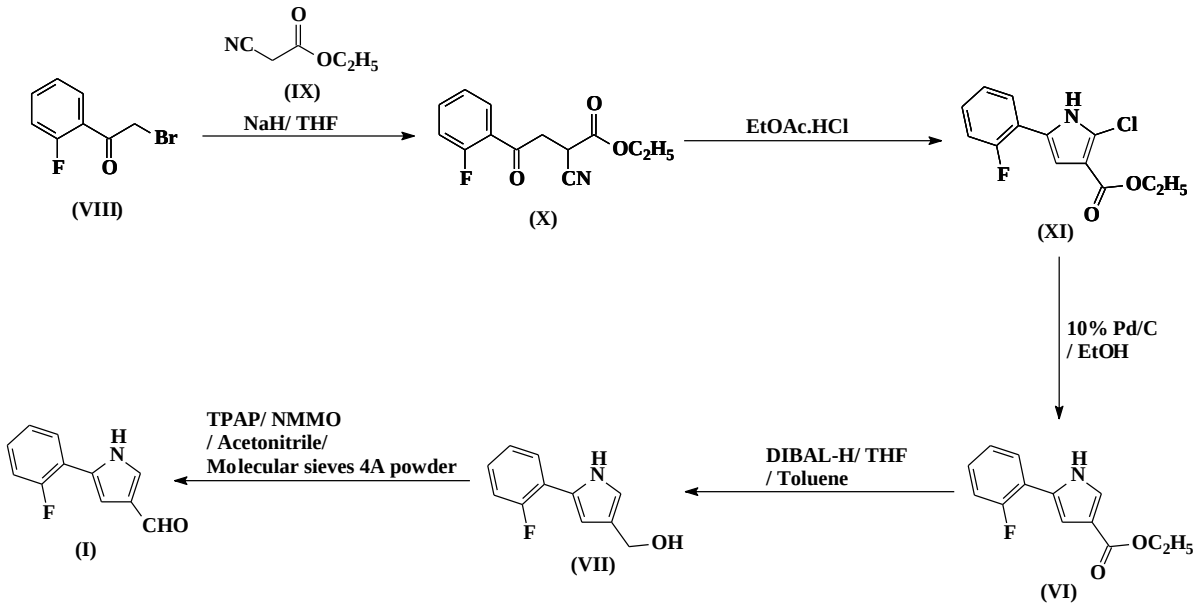


(I)

5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde of formula (I), which is a key intermediate for the preparation of Vonoprazan.

US 5122615, US 8048909 and US 7977488 discloses a process for the preparation of 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde of formula (I), which comprises compound of formula (VIII) is reacted with compound of formula (IX) in presence of sodium hydride (NaH)/ tetrahydrofuran (THF) to obtain the compound of formula (X). The compound of formula (X) is reacted with hydrogen chloride-ethyl acetate (EtOAc.HCl) to obtain the compound of formula (XI). The compound of formula (XI) is reacted with 10% Pd/C in presence of EtOH to obtain the compound of formula (VI). The compound of formula (VI) is reacted with diisobutylaluminum hydride (DIBAL-H)/ tetrahydrofuran (THF) in presence of toluene to obtain the compound of formula (VII). The compound of formula (VII) is reacted with tetrapropylammonium perruthenate (TPAP)/ N-methylmorpholine N-oxide (NMMO) in presence of acetonitrile (ACN) and molecular sieves 4A powder to obtain the compound of formula (I).

The above process is schematically shown as below:



The above processes disclose the preparation of the 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde is difficult for bulk manufacturing process commercially. Impurities are generated in the preparation process of the 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde, and the impurities affect the purity of the Vonoprazan Fumarate.

Hence, there is consequently a need development for new methods to sort out prior art existing methods. So, our inventors have developed a method for the preparation of 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde by using novel compound of formula (XIII) and (XIV). The present invention is providing a simple, cost effective and industrial applicable process.

OBJECT OF THE INVENTION

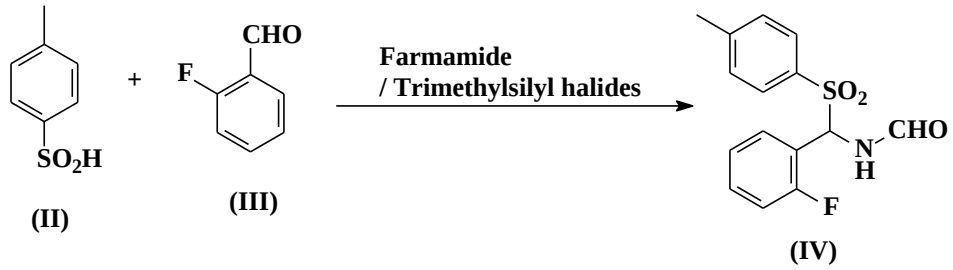
The present invention relates to a process for the preparation of 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde by using novel compound of formula (XIII) and (XIV).

SUMMARY OF THE INVENTION

The present invention relates to a process for the preparation of 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde with high yield and good purity by using novel compound of formula (XIII) and (XIV).

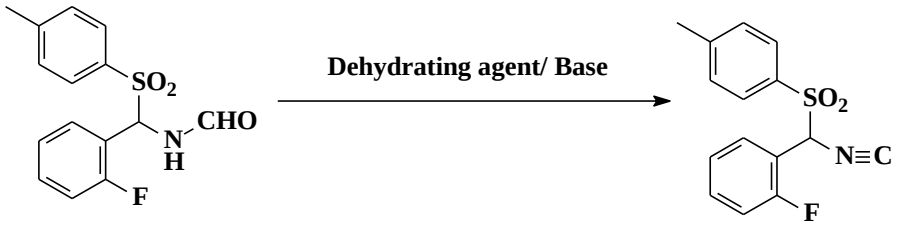
In one embodiment of the present invention provides a process for the preparation of 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde (I), comprising the steps of;

a) compound of formula (II) is reacting with compound of formula (III) in presence of farmamide and trimethylsilyl halides to obtain the compound of formula (IV),



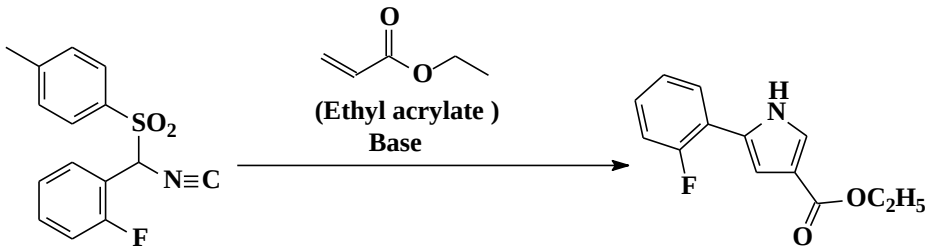
(II) (III) (IV)

b) compound of formula (IV) is reacting with dehydrating agent in presence of base to obtain compound of formula (V),



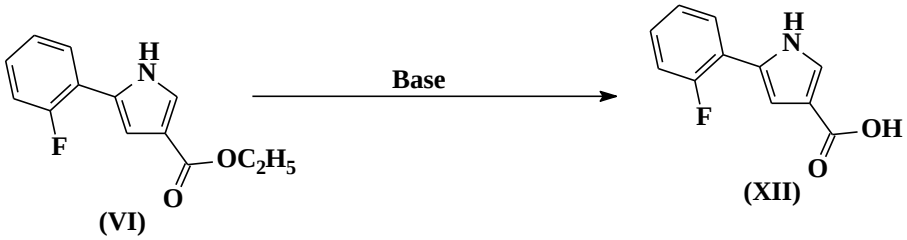
(IV) (V)

c) compound of formula (V) is reacting with ethyl acrylate in present of base to obtain compound of formula (VI),



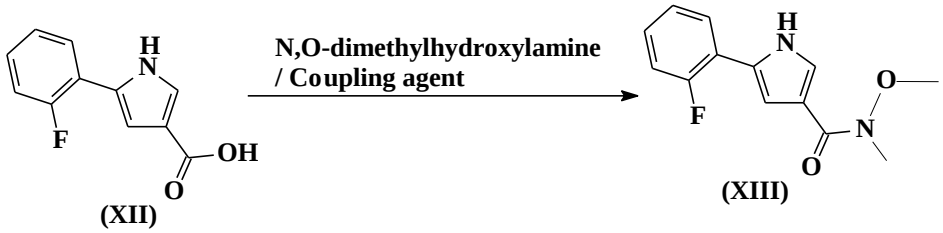
(V) (VI)

d) compound of formula (VI) is hydrolysing with base to obtain compound of formula (XII), and

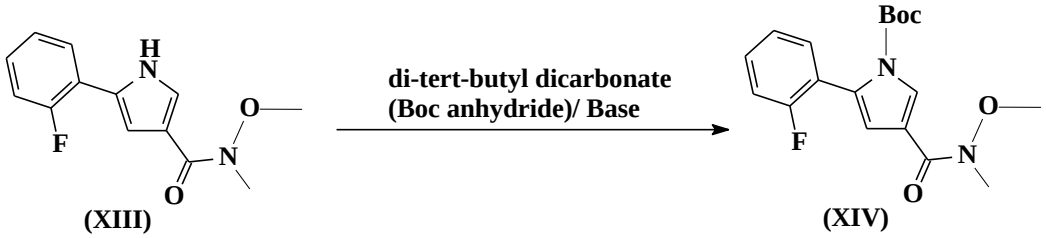


(VI) (XII)

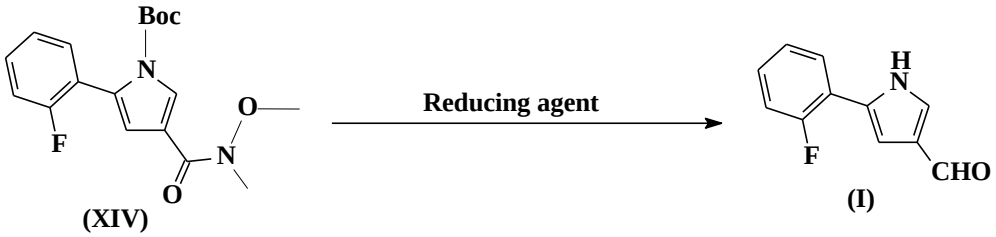
e) compound of formula (XII) is treating with N,O-dimethylhydroxylamine in presence of coupling agent to obtain compound of formula (XIII),



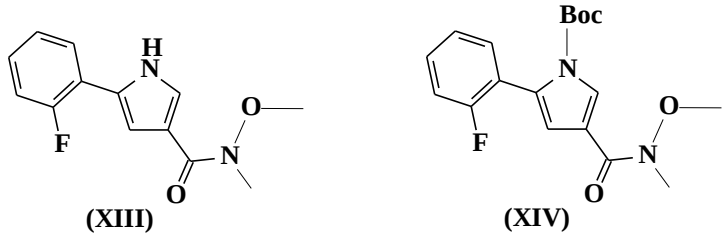
f) compound of formula (XIII) is protecting with di-tert-butyl dicarbonate (Boc anhydride) in presence of base to obtain compound of formula (XIV),



g) compound of formula (XIV) is reducing with reducing agent to obtain compound of formula (I).



In yet another embodiment of the present invention, a compound of formula (XIII) and (XIV).

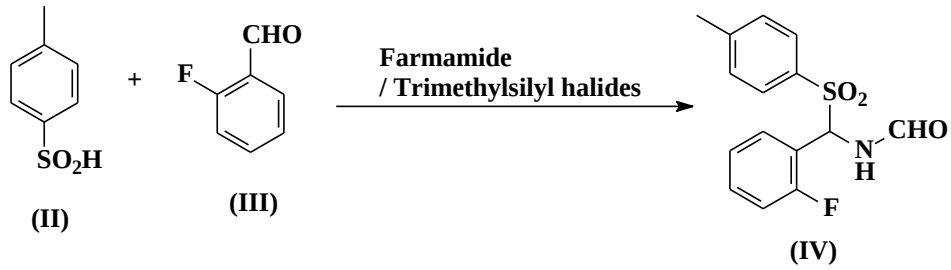


DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the preparation of 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde with high yield and good purity by using novel compound of formula (XIII) and (XIV).

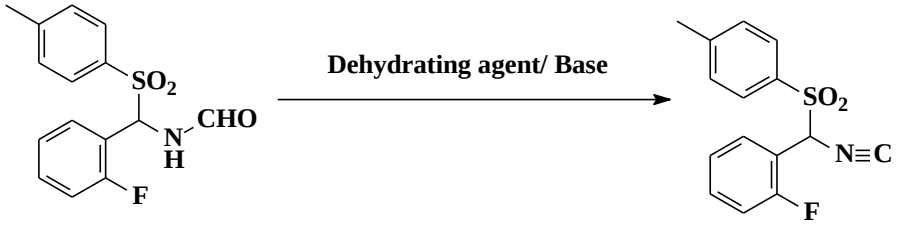
In one embodiment of the present invention provides a process for the preparation of 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde (I), comprising the steps of;

a) compound of formula (II) is reacting with compound of formula (III) in presence of farmamide and trimethylsilyl halides to obtain the compound of formula (IV),



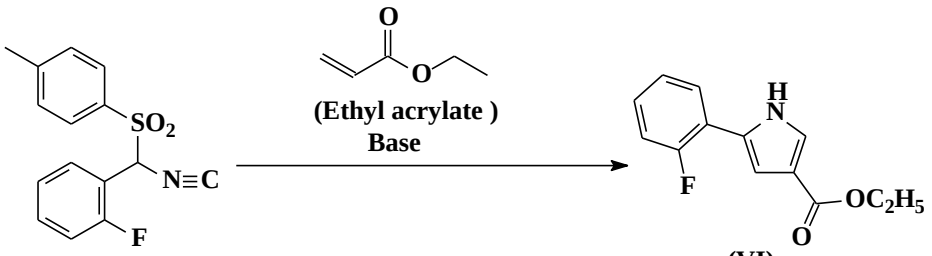
(II) (III) (IV)

b) compound of formula (IV) is reacting with dehydrating agent in presence of base to obtain compound of formula (V),



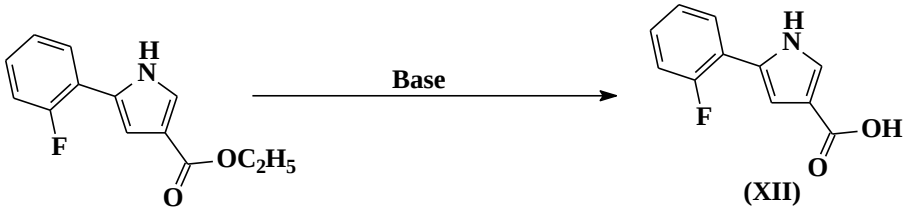
(IV) (V)

c) compound of formula (V) is reacting with ethyl acrylate in present of base to obtain compound of formula (VI),



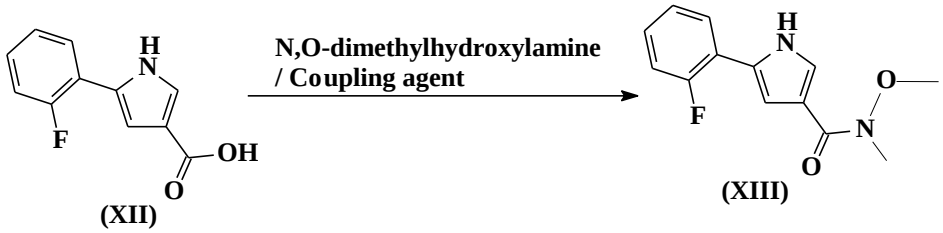
(V) (VI)

d) compound of formula (VI) is hydrolysing with base to obtain compound of formula (XII), and

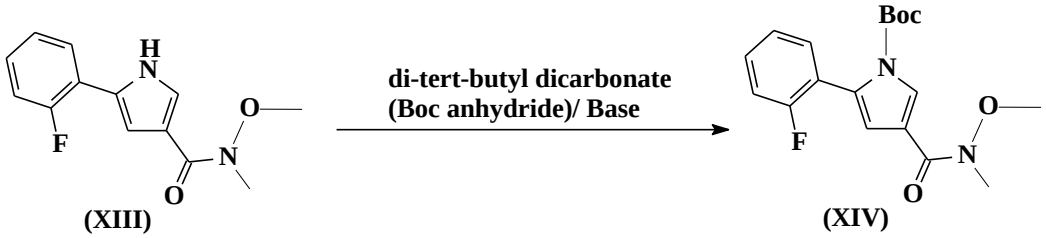


(VI) (XII)

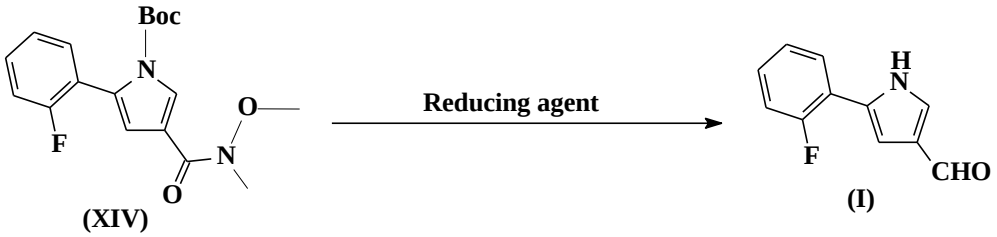
e) compound of formula (XII) is treating with N,O-dimethylhydroxylamine in presence of coupling agent to obtain compound of formula (XIII),



f) compound of formula (XIII) is protecting with di-tert-butyl dicarbonate (Boc anhydride) in presence of base to obtain compound of formula (XIV),



g) compound of formula (XIV) is reducing with reducing agent to obtain compound of formula (I).



According to embodiment of the present invention, compound of formula (II) is reacting with compound of formula (III) in presence of farmamide and trimethylsilyl halides and the reaction is carried out at 45-55°C for 14-16 hours to obtain the compound of formula (IV). The compound of formula (IV) is reacting with dehydrating agent in presence of base and the reaction is carried out at 08-12°C for 1-3 hours to obtain the compound of formula (V).

According to embodiment of the present invention, compound of formula (V) is reacting with ethyl acrylate in present of base and the reaction is carried out at 03-06°C for 1-3 hours to obtain the compound of formula (VI). The compound of formula (VI) is hydrolysing with base and the reaction is carried out at 55 to 70°C for 4-6 hours, followed by acidified pH 1-4 with conc. HCl to obtain the compound of formula (XII).

According to embodiment of the present invention, Compound of formula (XII) is treating with N, O-dimethylhydroxylamine (weinreb amine) in presence of coupling agent and the reaction is carried out at room temperature for 10-13 hours to obtain the compound of formula (XIII),

wherein preferably N, N′-Carbonyldiimidazole (CDI) is used as coupling agent in presence of hydroxybenzotriazole (HOBT).

According to embodiment of the present invention, Compound of formula (XIII) is protecting with di-tert-butyl dicarbonate (Boc anhydride) in presence of base and the reaction is carried out at room temperature for 10-13 hours to obtain the compound of formula (XIV), and compound of formula (XIV) reducing with reducing agent and the reaction is carried out at room temperature for 10-13 hours to obtain the compound of formula (I).

According to an embodiment of the present invention provides 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde (I) having HPLC purity ≥ 99.5%.

According to an embodiment of the present invention, wherein the trimethylsilyl halides is selected from trimethylsilyl chloride and trimethylsilyl iodide.

According to an embodiment of the present invention, wherein the dehydrating agent is selected from phosphorus oxychloride and (chloromethylene)dimethyliminium chloride (Vilsmeier reagent).

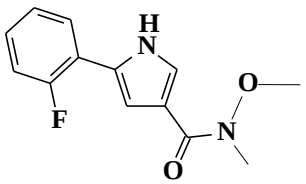
According to an embodiment of the present invention, wherein the base is selected from inorganic base or organic base; inorganic base is selected from alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium hydroxide; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and lithium carbonate; alkali metal bicarbonates such as sodium bicarbonate and potassium bicarbonate; alkali metal alkoxides such as sodium methoxide, potassium methoxide, sodium tertiary butoxide, potassium tertiary butoxide; alkali metal hydrides such as sodium hydride, potassium hydride, lithium hydride; ammonia; sodium sulphite; organic base is selected from triethylamine, triethanolamine, diisopropylethylamine, di-n-propylamine and 4-dimethylaminopyridine.

According to an embodiment of the present invention, wherein the coupling agents are N,N'-dicyclohexylcarbodiimide (DCC), N,N′-carbonyldiimidazole (CDI) and hydroxybenzotriazole (HOBt) and/or mixture thereof.

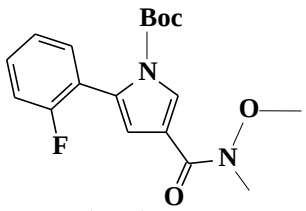
According to an embodiment of the present invention, wherein the reducing agent is selected from Red-Al (Vitride), diisobutylaluminum hydride (DIBAL-H), lithium aluminium hydride ($LiAlH_4$), sodium borohydride ($NaBH_4$), lithium borohydride ($LiBH_4$), potassium borohydride (KBH_4), calcium borohydride ($Ca(BH_4)_2$), sodium cyanoborohydride ($NaBH_3CN$), tetramethylammonium borohydride, tetraethylammonium borohydride, benzyltriethylammonium borohydride, tetrabutylammonium borohydride, tetramethylammonium triacetoxyborohydride, dithionates and thiosulfates.

According to an embodiment of the present invention, the reaction carried out suitable solvent is selected from tetrahydrofuran, toluene, water, acetone, acetonitrile, ethyl acetate, isopropyl alcohol, methanol, ethanol, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), isopropyl acetate and n-butyl acetate, methyl ethyl ketone, methyl isobutyl ketone, cyclohexanone, n-hexane, diethyl ether, diisopropyl ether, dioxane, 1,2-dimethoxyethane, dichloromethane (MDC), dichloroethane, carbon tetrachloride and chloroform, methyl tert-butyl ether (MTBE) and/or mixtures thereof.

In yet another embodiment of the present invention, a compound of formula (XIII) and (XIV).



(XIII)



(XIV)

The following examples illustrate the present invention, but should not be construed as limiting the scope of the invention.

EXAMPLES

Example 1:

Synthesis of sodium 4-methylbenzenesulfinate

Sodium bicarbonate (86 g, 1.02 mol) and sodium sulphite (123 g, 0.97mol) were dissolved in water (500 mL) and heated to 80-85^{o}C, followed by addition of P-toluene sulfonyl chloride (100g, 0.52 mol). The resultant mixture was stirred for 2 hrs at 80-85 ^{o}C, further it was slowly allow to cooled at 5-10^{o}C. The obtain solid was filtered and washed with ice cold water to afford sodium 4-methylbenzenesulfinate as an off-white solid.

Yield: 90.94 % (85 g).

HPLC Purity: ≥ 99 %

Example 2:

Synthesis of 4-methylbenzenesulfinic acid (II)

37% HCl (45 mL) was slowly added to a solution of sodium 4-methylbenzenesulfinate (85 g, 0.47 mol) in water (425 mL) and methyl tert butyl ether (425 mL) for 20 min, further the reaction mixture was stirred for 20 min. The layers were separated, the aqueous layers was further extracted with MTBE (200 ml). The combined organic layers were dried over sodium sulphate. The resultant product was filtered and concentrated into 80% n-heptane (100 mL). The obtain solid was filtered to afford 4-methylbenzenesulfinic acid as an off- white solid.

Yield: 70 % (75 g).

HPLC Purity: ≥ 99.2%

Example 3:

Synthesis of N-((2-fluorophenyl)(tosyl)methyl)formamide (IV)

2-Fluoro benzaldehye (39.7g, .32 mol) in acetonitrile (150 mL), toluene (150 mL) were added into formamide (36 g, 0.8 mol), trimethyl silyl chloride (51 g, 0.42 mol) and heated to 50-55^{o}C. The reaction mixture was stirred for 3h at same temperature, followed by addition of 4-methylbenzenesulfinic acid (75 g, 0.42 mol). The resultant mixture was stirred for 16h at 50-55^{o}C. The reaction was mixture was allowing to cooled at room temperature. The resultant reaction mixture was diluted with water (900 mL) and MTBE (150 mL). The obtained reaction mas was allow to cooled at 0^{o}C and stirred for 30 min. The afford solid was filtered to get N-((2-fluorophenyl)(tosyl)methyl)formamide as an off-white solid.

Yield: 60 % (58 g)

HPLC Purity: ≥ 99.2%

Example 4:

Synthesis of 1-fluoro-2-(isocyano(tosyl)methyl)benzene (V)

$POCl_3$ (63.7 g, 0.4 mol) was added to a solution of N-((2-fluorophenyl)(tosyl)methyl)formamide (64 g, 0.2 mol) in THF (300 mL) and stirred at room temperature for 15 min. The reaction mixture was allow to cooled at 5°C, followed by addition of trimethylamine (126 g, 1.24 mol). The resultant mixture was stirred for 2h at 10°C. The reaction was quenched with ice water (100 mL) and extracted with ethyl acetate (200 mL). The combined extracts were washed with 5% sodium bicarbonate solution (50 mL). The obtained product was dried over sodium sulphate and filtered to give a brownish sticky liquid. The resultant liquid was added into IPA (100 mL), stirred for 20 min at 0°C and filtered. The afford solid dried to get a 1-fluoro-2-(isocyano(tosyl)methyl)benzene as light brown solid.

Yield: 56 % (34 g)

HPLC Purity: ≥ 99.2%

Example 5:

Synthesis of ethyl 5-(2-fluorophenyl)-1H-pyrrole-3-carboxylate (VI)

Ethyl acrylate (13.8 g, 0.13 mol) was added to a solution of 1-Fluoro-2-(isocyano(tosyl)methyl)benzene (40 g, 0.14 mol) in DMF (200 mL) and it was allow to cooled at 5°C, followed by addition of sodium hydride (55% in paraffin oil, 11.06 g, 0.27 mol). The reaction mixture was stirred for 2h at 5°C. The resultant reaction mass was diluted with ice water to obtained solid. The obtained solid was filtered and washed with n-hexane to get ethyl 5-(2-fluorophenyl)-1H-pyrrole-3-carboxylate as a light brown solid.

Yield: 87% (28 g)

HPLC Purity: ≥ 99.2%

Example 6:

Synthesis of 5-(2-fluorophenyl)-1H-pyrrole-3-carboxylic acid (XII)

1N NaOH (50 mL) was added to a solution of ethyl 5-(2-fluorophenyl)-1H-pyrrole-3-carboxylate (40 g, 0.171 mol) in methanol (50 mL) at 0°C and heated to 60-65°C. The reaction mixture was stirred for 5h at 60-65°C. The reaction mixture was concentrated under reduce pressure. The resultant crude was dissolved in water (50 mL) and washed with ethyl acetate (50 mL). The aqueous layer was cooled to 0°C and acidified pH: 2-3 with conc. HCl. The obtained precipitated solid was filtered, washed with water and dried to obtain 5-(2-fluorophenyl)-1H-pyrrole-3-carboxylic acid as an off –white solid.

Yield: 67% (27g)

HPLC Purity: ≥ 99.2%

Example 7:

Synthesis of Synthesis of 5-(2-fluorophenyl)-N-methoxy-N-methyl-1H-pyrrole-3-carboxamide (XIII)

CDI (32g, 0.19 mol), HOBt (26.6 g, 0.19 mol) were added to solution of 5-(2-fluorophenyl)-1H-pyrrole-3-carboxylic acid (20 g, 0.13 mol) in DMF (100 mL) at 0^{o}C and stirred at same temperature for 15min, followed by added N,O-dimethylhydroxylamine (12.8 g, 0.13 mol), DIPEA (50.1g, 0.39 mol). The reaction mixture was stirred at room temperature for 12h. The reaction mixture was cooled to 0^{o}C and diluted with water (500 mL). The obtained precipitated solid was filtered and washed with water to give 5-(2-fluorophenyl)-N-methoxy-N-methyl-1H-pyrrole-3-carboxamide as an off-white solid.

Yield: 75% (18g)

HPLC Purity: ≥ 99.5%

1H-NMR (400 MHz, Dmso-d6, δ): 3.229 (s, 3H), 3.719 (s, 3H), 6.976 (s, 1H), 7.231-7.297 (m, 3H), 7.481 (s, 1H), 7.739-7.781 (m, 1H), 11.787 (bs, 1H).

13C-NMR (400 MHz, Dmso-d6, δ): 32.736, 60.710, 111.170, 116.096, 117.493, 119.740, 124.500, 124.728, 125.191, 126.603, 127.825, 156.907, 164.225.

Mass: 249.23 [M+H]+

Example 8:

Synthesis of tert-butyl 2-(2-fluorophenyl)-4-(methoxy(methyl)carbamoyl)-1H-pyrrole-1-carboxylate (XIV)

Di-tert-butyl dicarbonate (17.1g, 0.08mol) was added to solution of 5-(2-fluorophenyl)-N-methoxy-N-methyl-1H-pyrrole-3-carboxamide (13g, 0.05 mol) in THF (75 mL) at room temperature, followed by added triethyl amine (15.2g, 0.16 mol), DMAP (0.61 g, 0.005 mol). The reaction mixture was stirred at room temperature for 12h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with 1N HCl, water and brine solution. organic layer was dried over sodium sulphate and concentrated to obtain tert-butyl 2-(2-fluorophenyl)-4-(methoxy(methyl)carbamoyl)-1H-pyrrole-1-carboxylate as light brown liquid.

Yield: 92.8% (17.5 g)

HPLC Purity: ≥ 99.5%

1H-NMR (400 MHz, Dmso-d6, δ): 1.316 (s, 9H), 3.261 (s, 3H), 3.748 (s, 3H), 6.661-6.666 (d, 1H), 7.247-7.294 (m, 2H), 7.440-7.482 (m, 2H), 7.7890-7.895 (d, 1H).

13C-NMR (400 MHz, Dmso-d6, δ): 26.842, 32.632, 61.036, 84.902, 114.907, 115.643, 118.565, 121.077, 124.347,125.979, 127.648, 130.160, 130.798, 148.062, 158.283, 162.609.

Mass: 349.31 [M+H]+

Example 9:

Synthesis of 5-(2-fluorophenyl)-1H-pyrrole-3-carbaldehyde (I)

Tert-butyl 2-(2-fluorophenyl)-4-(methoxy(methyl)carbamoyl)-1H-pyrrole-1-carboxylate (2 g, 0.005 mol) in Toluene (10 mL) at 0^{o}C, followed by added Vitride (80% in Toluene, 1.4 mL, 0.015 mol). The reaction mixture was stirred at room temperature for 12h. The reaction was quenched with 1 N HCl (20 mL) and stirred for 30 min. The reaction mass was filtered through celite bed and washed with toluene. The filtrate was taken, toluene layer was separated and washed with water, brine solution and dried over sodium sulphate. The obtain product filtered and concentrated. The obtain crude was triturated with ethyl acetate and hexane to give 5-(2-fluorophenyl)-1H-pyrrole-3-carbaldehyde a light brown solid.

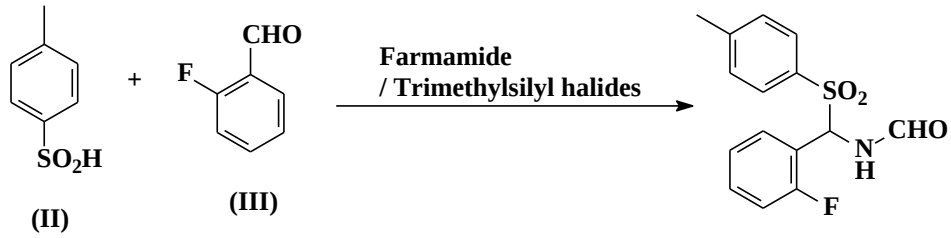
Yield: 60% (0.65 g)

HPLC Purity: ≥ 99.5%

We claim:

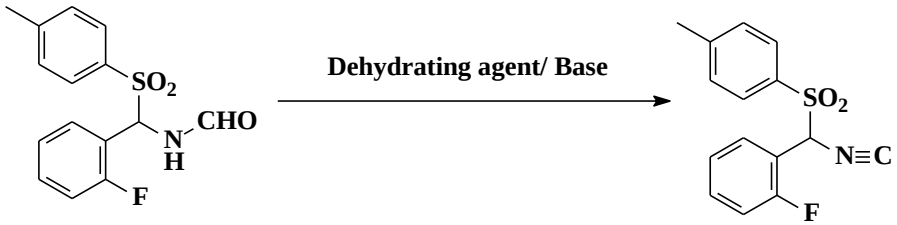
1. A process for the preparation of 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde (I), comprising the steps of;

a) compound of formula (II) is reacting with compound of formula (III) in presence of farmamide and trimethylsilyl halides to obtain the compound of formula (IV),



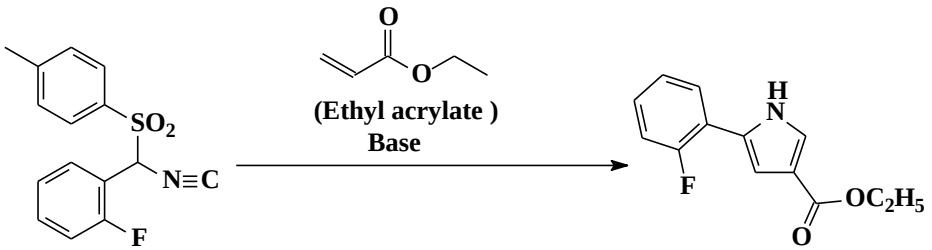
(II) (III) (IV)

b) compound of formula (IV) is reacting with dehydrating agent in presence of base to obtain compound of formula (V),



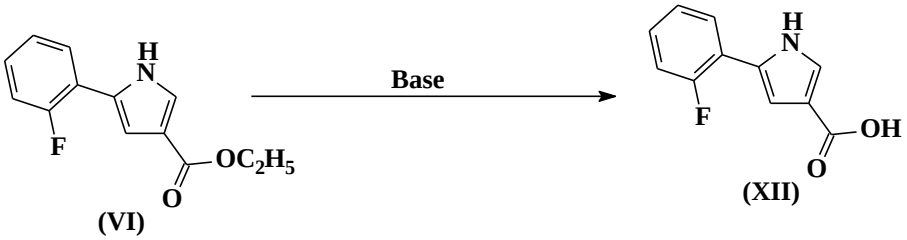
(IV) (V)

c) compound of formula (V) is reacting with ethyl acrylate in present of base to obtain compound of formula (VI),



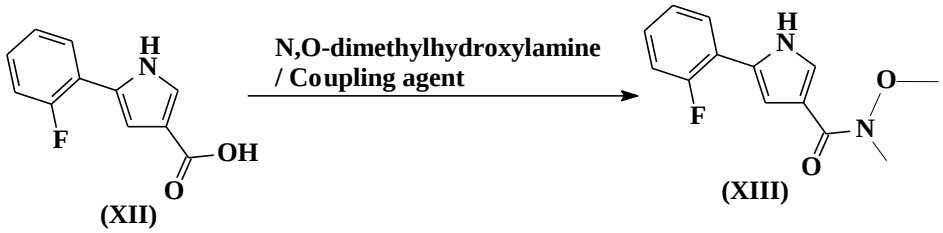
(V) (VI)

d) compound of formula (VI) is hydrolysing with base to obtain compound of formula (XII), and

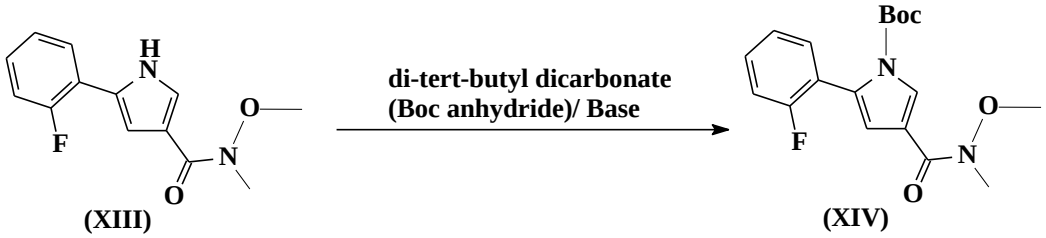


(VI) (XII)

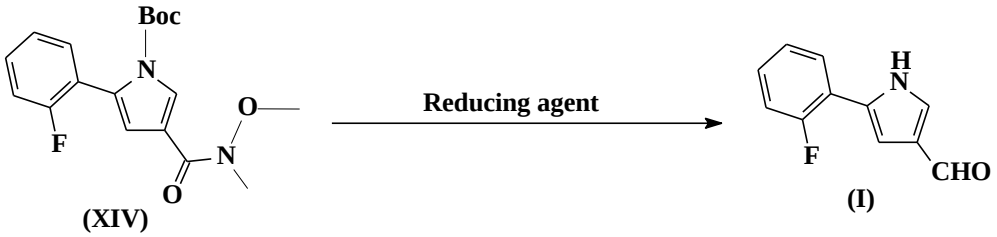
e) compound of formula (XII) is treating with N,O-dimethylhydroxylamine in presence of coupling agent to obtain compound of formula (XIII),



f) compound of formula (XIII) is protecting with di-tert-butyl dicarbonate (Boc anhydride) in presence of base to obtain compound of formula (XIV),



g) compound of formula (XIV) is reducing with reducing agent to obtain compound of formula (I).



2. The process as claimed in claim 1, wherein the trimethylsilyl halides is selected from trimethylsilyl chloride and trimethylsilyl iodide.

3. The process as claimed in claim 1, wherein the dehydrating agent is selected from phosphorus oxychloride and (chloromethylene)dimethyliminium chloride (Vilsmeier reagent).

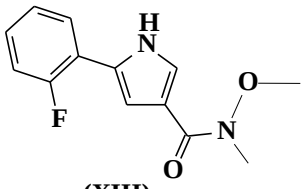
4. The process as claimed in claim 1, wherein the base is selected from inorganic base or organic base; inorganic base is selected from alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium hydroxide; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and lithium carbonate; alkali metal bicarbonates such as sodium bicarbonate and potassium bicarbonate; alkali metal alkoxides such as sodium methoxide, potassium methoxide, sodium tertiary butoxide, potassium tertiary butoxide; alkali metal hydrides such as sodium hydride, potassium hydride, lithium hydride; ammonia; sodium sulphite; organic base is selected from triethylamine, triethanolamine, diisopropylethylamine, di-n-propylamine and 4-dimethylaminopyridine.

5. The process as claimed in claim 1, wherein the coupling agents are N,N'-dicyclohexylcarbodiimide (DCC), N,N′-carbonyldiimidazole (CDI) and hydroxybenzotriazole (HOBt) and/or mixture thereof.

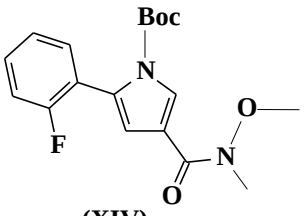
6. The process as claimed in claim 1, wherein the reducing agent is selected from Red-Al (Vitride), diisobutylaluminum hydride (DIBAL-H), lithium aluminium hydride ($LiAlH_4$), sodium borohydride ($NaBH_4$), lithium borohydride ($LiBH_4$), potassium borohydride (KBH_4), calcium borohydride ($Ca(BH_4)_2$), sodium cyanoborohydride ($NaBH_3CN$), tetramethylammonium borohydride, tetraethylammonium borohydride, benzyltriethylammonium borohydride, tetrabutylammonium borohydride, tetramethylammonium triacetoxyborohydride, dithionates and thiosulfates.

7. The process as claimed in claim 1, wherein the reaction carried out suitable solvent is selected from tetrahydrofuran, toluene, water, acetone, acetonitrile, ethyl acetate, isopropyl alcohol, methanol, ethanol, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), isopropyl acetate and n-butyl acetate, methyl ethyl ketone, methyl isobutyl ketone, cyclohexanone, n-hexane, diethyl ether, diisopropyl ether, dioxane, 1,2-dimethoxyethane, dichloromethane (MDC), dichloroethane, carbon tetrachloride and chloroform, methyl tert-butyl ether (MTBE) and/or mixtures thereof.

8. A compound of formula (XIII) and (XIV).



(XIII)



(XIV)

Dated this thirteenth (13th) day of July, 2023

Your Sincerely

Sridhar Prasangi (IN/PA 2608)
Associate vice president – IPM
Optimus Drugs Pvt Ltd.

ABSTRACT

“NOVEL SYNTHESIS OF 5-(2-FLUOROPHENYL)-1H-PYRROLE-3-CARBALDEHYDE”

The present invention relates to a process for the preparation of 5-(2-Fluorophenyl)-1H-pyrrole-3-carbaldehyde by using novel compound of formula (XIII) and (XIV).