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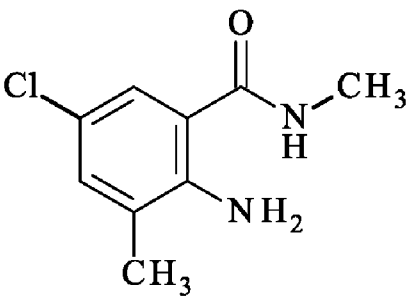
(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF INTERMEDIATES OF CHLORANTRANILIPROLE

(57) Abstract: The present invention relates to an improved process for the preparation of 2-Amino-5-chloro-3,*N*-dimethylbenzamide of Formula-I, which is an advanced intermediate of Chlorantraniliprole.



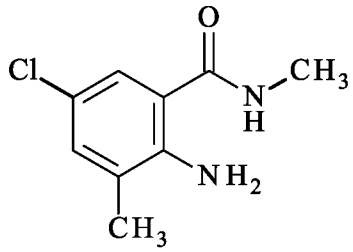
Formula-I

WO 2024/116196 A1

AN IMPROVED PROCESS FOR THE PREPARATION OF INTERMEDIATES OF CHLORANTRANILIPROLE

Field of the Invention

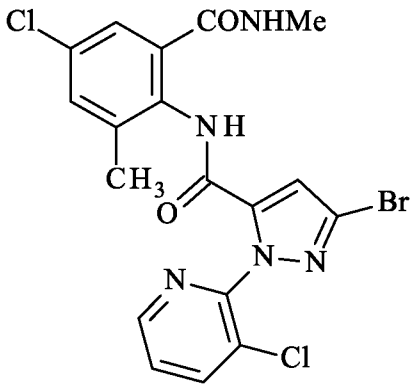
The present invention relates to an improved process for the preparation of 2-Amino-5-chloro-3,*N*-dimethylbenzamide of Formula-I, which is an advanced intermediate of Chlorantraniliprole.



Formula-I

Background of the Invention

Anthranilamide derivatives are a kind of novel insecticides with high efficacy and safety. 3-Bromo-*N*-(4-chloro-2-methyl-6-(methylcarbamoyl)phenyl)-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carboxamide is highly effective against insects, which is commercialized by DuPont, its generic common name is Chlorantraniliprole;



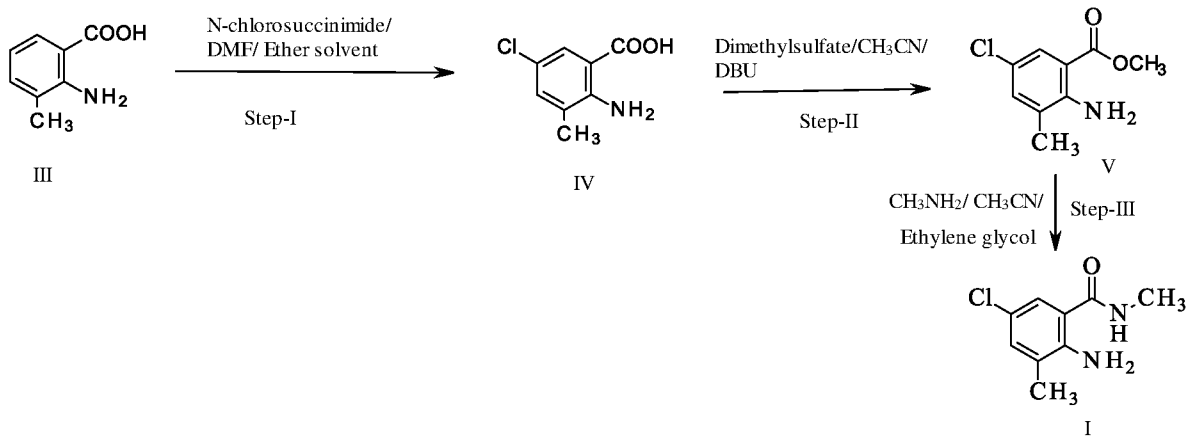
Chlorantraniliprole

There are number of methods reported for preparing phenylcarboxamides, for example:

WO03/015519 A1 discloses that 3-halo-1-(3-chloro-2-pyridyl)-1H-pyrazole-5-carboxylic acids reacts with substituted anthranilic acids, in the presence of methanesulfonyl chloride and pyridine as acid binding agent to give the benzoxazinones in 86%-92% yield. Then the product reacts with the alkylamine to yield the phenylcarboxamides. Calculated by 3-halo-1-(3-chloro-2-pyridyl)-1H-pyrazole-5-carboxylic acids, the total yield of the two-steps is 58%-65%. Bioorganic & Medicinal Chemistry Letters, 17 (2007), 6274-6279 discloses that 3-halo-1-(3-chloro-2-pyridyl)-1*H*-pyrazole-5-carbonyl chlorides react with isatoic anhydrides to give the benzoxazinones in 23% yield.

WO 2006062978 A1 discloses a process for the preparation of 2-amino-5-chloro-3,*N*-dimethylbenzamide of formula-I by chlorination of 2-amino-3-methylbenzoic acid of formula-III in the presence of *N*-chlorosuccinimide in DMF solvent to produce 2-amino-5-chloro-3-methylbenzoic acid of formula-IV, which undergoes further esterification in the presence of dimethylsulfate and DBU in acetonitrile solvent to obtain methyl 2-amino-5-chloro-3-methylbenzoate of formula-V. Further, compound of formula-V is reacted with methylamine in acetonitrile solvent to obtain 2-amino-5-chloro-3,*N*-dimethylbenzamide of Formula-I.

The synthetic procedure is illustrated in Scheme-I as below:

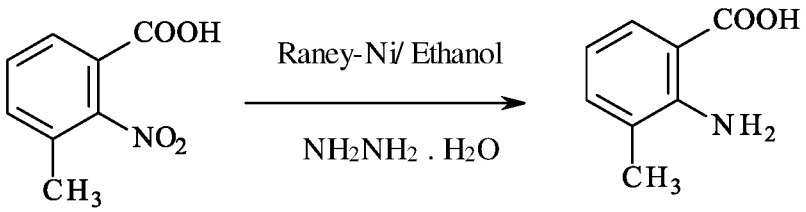


SCHEME-I

Bruce Guise (*Journal of the Chemical Society Perkin Transactions 1, Organic and Bio-Organic Chemistry (1972-1999), (8), 1637 -1648; 1982*) discloses a process for

the preparation of 2-amino-3-methylbenzoic acid of Formula-III by reduction of 2-nitro-3-methylbenzoic acid of Formula-II in the presence of Raney nickel catalyst and hydrazine hydrate in ethanol as solvent. Yield of the product is 66% by theory.

The synthetic procedure is illustrated in Scheme-II as below:

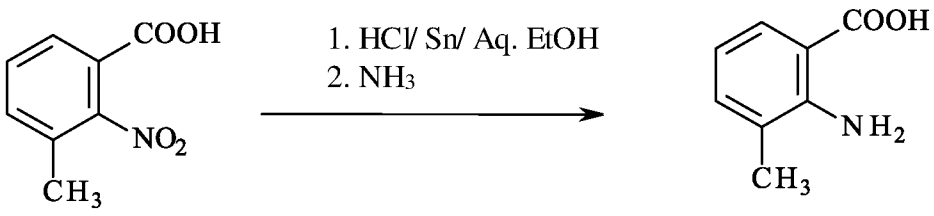


II III

SCHEME-II

Kano (*Bulletin of the Chemical Society of Japan, 1987, 60(10), 3659-62*) discloses a process for the preparation of 2-amino-3-methylbenzoic acid of Formula-III by reduction of 2-nitro-3-methylbenzoic acid of Formula-II in the presence of HCl and Tin (Sn) catalyst in aqueous ethanol solvent followed by addition of ammonia. Yield of the isolated product is 89%.

The synthetic procedure is illustrated in Scheme-III as below:

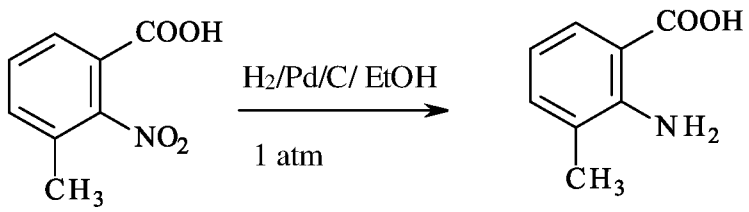


II III

SCHEME-III

Further, Jian-Feng (*Journal of Organic Chemistry, 2003, 68(23), 8918-8931*), discloses a process for the preparation of 2-amino-3-methylbenzoic acid of Formula-III by catalytic reduction of 2-Nitro-3-methylbenzoic acid of Formula (II) in the presence of palladium carbon in ethanol used as solvent medium. Yield of the product is 99% by theory.

The synthetic procedure is illustrated in Scheme-IV as below:

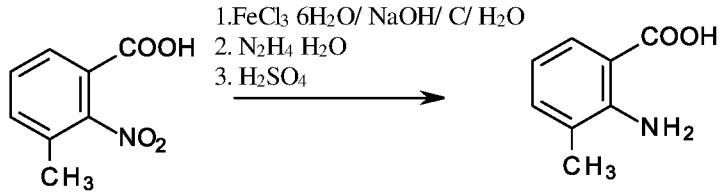


II III

SCHEME-IV

Jeon (*Jingxi Huagong Zhongjianti, 2010, 40(5), 17-19*) discloses a process for the preparation of 2-amino-3-methylbenzoic acid of Formula-III by reduction of 2-nitro-3-methylbenzoic acid of Formula II in the presence of $FeCl_3$ $6H_2O$/carbon/ NaOH in H_2O solvent followed by addition of hydrazine hydrate.

The synthetic procedure is illustrated in Scheme-V as below:

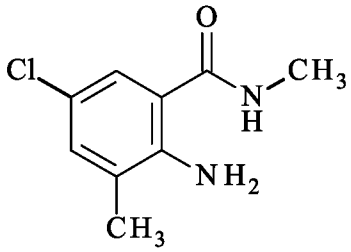


II III

SCHEME-V

Objective of the Invention

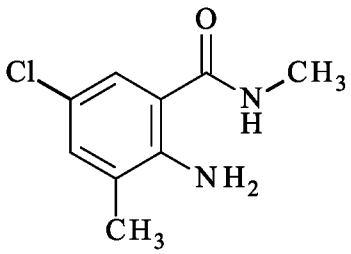
The main objective of the present invention is to provide a simple and cost effective and commercially viable processes for the preparation of 2-Amino-5-chloro-3,*N*-dimethylbenzamide of Formula-I , which is advanced intermediate of Chlorantraniliprole.



Formula-I

Summary of the Invention:

The present invention provides a process for preparation of 2-Amino-5-chloro-3,*N*-dimethyl benzamide of Formula-I,

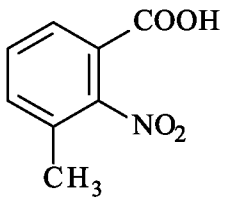


Formula-I

Formula-I

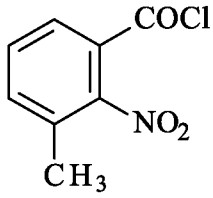
comprising the steps of:

a) reacting 2-Nitro-3-methylbenzoic acid of Formula-II



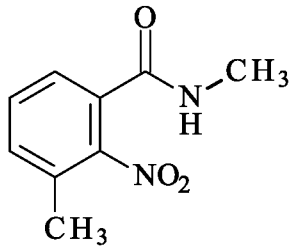
Formula-II

with chlorinating agent in a suitable solvent to produce compound of Formula-VI.



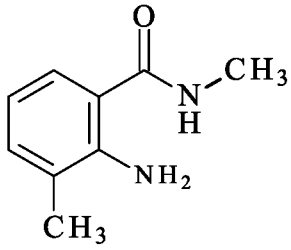
Formula-VI

b) reacting the compound of Formula-VI in-situ with methylamine in presence of a base in a suitable solvent to produce compound of Formula-VII.



Formula-VII

c) reducing the compound of Formula-VII in presence of Raney nickel catalyst and hydrogen in a suitable solvent to produce compound of Formula-VIII;



Formula-VIII

d) chlorinating the compound of Formula-VIII with HCl/ H_2O_2 in presence of a base in a suitable solvent to produce a compound of Formula-I.

Detailed Description of the Invention

The present invention provides a process for preparation of 2-Amino-5-chloro-3,*N*-dimethyl benzamide of Formula-I, comprising the steps of:

a) reacting 2-Nitro-3-methylbenzoic acid of Formula-II with chlorinating agent in a suitable solvent to produce compound of Formula-VI.

b) reacting the compound of Formula-VI in-situ with methylamine in presence of a base in a suitable solvent to produce compound of Formula-VII.

c) reducing the compound of Formula-VII in presence of Raney nickel catalyst and hydrogen in a suitable solvent to produce compound of Formula-VIII;

d) chlorinating the compound of Formula-VIII with HCl/ H_2O_2 in presence of a base in suitable solvent to produce compound of Formula-I.

In step a) of present invention, chlorinating agent is selected from thionyl chloride, oxalyl chloride, PCl_3, $POCl_3$.

In step a) of the present invention, a suitable solvent is selected from toluene,

acetonitrile, methylene chloride chloroform and xylene mixture thereof. Preferably toluene.

In step a) of the present invention, the reaction may be performed usually from 20°C to 100°C for 1 to 5 hours, preferably 30-65°C for 1 to 2 hours. The obtained compound of Formula-VI can be used in the next reaction without further purification.

In step b) of the present invention, the base is in-organic base comprising sodium hydroxide, potassium hydroxide, sodium carbonate and potassium carbonate. Preferably sodium carbonate.

In step b) of the present invention, the suitable solvent is selected from water, acetonitrile, *N,N*-dimethylformamide, toluene, dimethylsulphoxide. Preferably water.

In step b) of the present invention, the reaction may be performed usually from 20°C to 40°C for 1-10 hours, preferably 25-30°C for 1-2 hours. The obtained compound of Formula-VII may be used in next reaction with directly or optionally after further purification.

In step c) of the present invention, suitable solvent is selected from alcohol methanol, ethanol, propanol, isopropanol, n-butanol or mixture thereof. Preferably methanol.

In step c) of the present invention, the reaction may be performed usually from 20°C to 60°C boiling point of the solvent used for 1-10 hours, preferably 40-45°C for 2-3 hours. The compound of formula-VIII from step c) may be used in next reaction with directly or optionally after further purification.

The suitable solvent used in step d) of present invention is selected from acetonitrile, water, *N,N*-dimethylformamide, toluene, dimethylsulphoxide. Preferably water.

In step d) of the present invention, the reaction may be performed usually from 0°C

to 30°C for 2 to 24 hours, preferably 30-35°C for 5-6 hours. The compound of Formula-I from step (d) is isolated from reaction mass by distillation of solvent followed by quenching into water in >70% yield with purity > 97.0% by HPLC.

Advantages of present invention:

The present invention process involves less expensive and readily available reagents and solvents.

- Chlorinating reagents used in step-a of present invention process are thionyl chloride, oxalyl chloride which are very less expensive and readily available
- Solvents used in present invention were less expensive and can be recovered and reused.
- Product of present invention is directly isolated from the reaction mass without involving any laborious work-up processes. Therefore, the process of the present invention is suitable for commercial scale.
- Chlorinating reagents used in step-d of present invention process are hydrochloric acid, hydrogen peroxide which are very less expensive and readily available.

The following examples are provided to illustrate the invention and are merely for illustrative purpose only and should not be construed to limit the scope of the invention.

The following examples are provided to illustrate the invention and are merely for illustrative purpose only and should not be construed to limit the scope of the invention.

EXAMPLES:

Example-01: Preparation of N,3-dimethyl-2-nitro-benzamide Formula-VII

Charged 1000.0 ml of toluene lot-I and 500.0 g of 3-Methyl-2-nitro benzoic acid (2.76 moles, Formula-II) into a 3.0L 4N RB flask at 25-30°C and the resulting suspension was stirred for 5 min, after which N,N-Dimethylformamide (1.5 ml)

was added at 25-30°C and reaction mass (Suspension) was heated at 60-65°C. Thionyl chloride (459.4 g; 3.86 moles) was added to the reaction mass at 60-65°C and stirred for 2h. After completion of the reaction (by TLC), reaction mass was cooled to 25-30°C.

Into another 10.0 L, 4N RB flask charged 500.0 ml of toluene lot-II, 2750.0 ml of DM Water lot-I, 228.2 g of Sodium carbonate (2.15 moles) and 250.2 g of 40% Aqueous Mono methylamine solution (3.23 moles) and stirred the solution at 25-30°C for 10-15 min. The above acid chloride was slowly added to the reaction mass at 25±5°C and stirred for 1h. After completion of the reaction (by TLC), filtered the solid and washed with 500.0 ml of toluene then dried for 6h at 60-65°C to afford N,3-dimethyl-2-nitro-benzamide of Formula-VII as off-white coloured powder.

Weight of the product is 517.0g. (96.5% by theory). Purity by HPLC>99.0%.

Example-02: Preparation of 2-amino-N,3-dimethyl-benzamide of Formula-VIII

Charged 2500.0 ml of methanol and 500.0 g (2.57 moles) of Formula-VII into a 5.0 L hydrogenation Kettle at 25-30°C. Charged 100.0 g of Raney Nickel to reaction mass at 25-30°C. Reaction mass was heated at 40-45°C. Applied the hydrogen pressure to 80 psi. After completion of hydrogen consumption, the reaction mass was stirred at 40-45°C for 2h. After completion of the reaction (by TLC), filtered the reaction mass and washed with 500.0 ml of methanol. The solvent was distilled under vacuum at 60-65°C. Product was isolated from water to afford 2-amino-N,3-dimethyl-benzamide of Formula-VIII as light brown coloured powder. Weight of the product is 393.0g. (93.0% by theory). Purity by HPLC>99.0%.

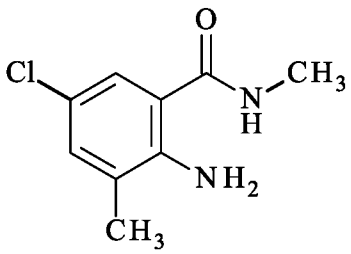
Example-03: Preparation of 2-amino-5-chloro-N,3-dimethyl-benzamide of Formula-I.

Charged 250.0 ml of aqueous hydrochloric acid and 50.0 g of Formula-VIII (0.609 moles) into a 1.0 L 4 N RB flask at 25-30°C. The reaction mass was stirred at 25-30°C for 5-10 min and heat the reaction mass to 30-35°C. 50% Hydrogen peroxide (33.2g) was added to reaction mass at 30-35°C over a period of 1h and stirred at

30-35°C for 5h. After completion of the reaction (by HPLC), reaction mass was cooled to 5-10°C, filtered, and filtrate was neutralized with sodium hydroxide solution. Solid was filtered and washed and dried to afford 2-amino-5-chloro-N,3-dimethyl-benzamide of Formula-I as solid. Weight of the product is 42.5g. (70.0% by theory). Purity by HPLC>99.0%.

WE CLAIM:

1. A process for preparation of 2-Amino-5-chloro-3,*N*-dimethyl benzamide of Formula-I,

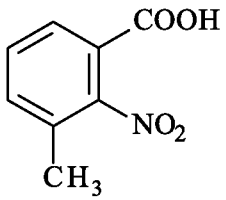


Formula-I

Formula-I

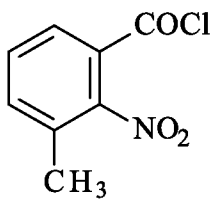
comprising the steps of:

a) reacting 2-Nitro-3-methylbenzoic acid of Formula-II



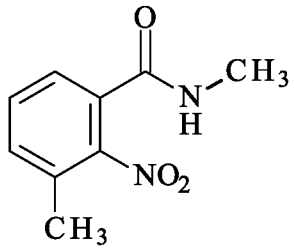
Formula-II

with chlorinating agent in a suitable solvent to produce compound of Formula-VI.



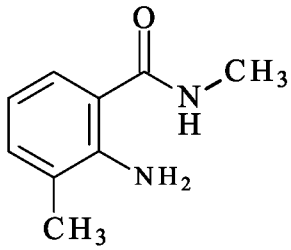
Formula-VI

b) reacting the compound of Formula-VI in-situ with methylamine in presence of a base in a suitable solvent to produce compound of Formula-VII.



Formula-VII

c) reducing the compound of Formula-VII in presence of Raney nickel catalyst and hydrogen in a suitable solvent to produce compound of Formula-VIII;



Formula-VIII

d) chlorinating the compound of Formula-VIII with HCl/ H_2O_2 in presence of a base in a suitable solvent to produce a compound of Formula-I.

2. The process as claimed in claim 1, a suitable solvent used in step a) is selected from toluene, acetonitrile, methylene chloride chloroform and xylene mixture thereof.

3. The process as claimed in claim 1, wherein the base used in step b) is selected from sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate.

4. The process as claimed in claim 1, wherein the suitable solvent used in step c) is selected from alcohol methanol, ethanol, propanol, isopropanol, n-butanol or mixture thereof.

5. The process as claimed in claim 1, wherein the suitable solvent used in step-d) is selected from acetonitrile, *N,N*-dimethylformamide, toluene, dimethylsulphoxide.

6. The process as claimed in claim 1, wherein the compound of Formula-I is used in the preparation of Chlorantraniliprole.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2023/051093

A. CLASSIFICATION OF SUBJECT MATTER
C07C237/30,C07C231/02,C07C205/57,C07D401/04 Version=2024.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C,C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021033172 A1 (EUROFINS ADVINUS LIMITED) 25 FEB 2021 (25-02-2021) Abstract; Claims 1-6; Scheme 9; [FAMILY: NONE]	1-6
X	CN 101492387 A (ZHEJIANG UNIVERSITY ZJU) 29 JULY 2009 (29-07-2009) Abstract; Claims 1-9 (Espacenet English translation) ; [FAMILY: NONE]	1-5
X	IN202141049445 (LAURUS LABS LIMITED) 30 NOV 2021 (30-11-2021) Abstract; Claims 1-11; Examples 1-4; [FAMILY: NONE]	1-6
X	IN202141035921 (LAURUS LABS LIMITED) 27 AUG 2021 (27-08-2021) Abstract; Claims 1-9; Examples 1-3; [FAMILY: NONE]	1-6
X	An Improved Synthesis of 2-Amino-5-chloro-N,3-dimethylbenzamide Author(s): LIU Jian-hua, DU Xiao-hua, Catalytic Hydrogenation Research Center, Zhengjiang University of Technology Pages: 793-795+811	1-6

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INTERNATIONAL SEARCH REPORT

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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