(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 January 2025 (02.01.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/003945 A1

(51) International Patent Classification:
C07C 253/14 (2006.01) *C07C 255/50* (2006.01)

(21) International Application Number:
PCT/IB2024/056261

(22) International Filing Date:
27 June 2024 (27.06.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
202321044177 30 June 2023 (30.06.2023) IN

(71) Applicant: **HIKAL LIMITED** [IN/IN]; 3A & 3B, International Biotech Park, Hinjewadi, Maharashtra, Pune 411 057 (IN).

(72) Inventors: **SHANKAR, Rama**; Hikal Limited, 3A & 3B, International Biotech Park, Hinjewadi, Maharashtra, Pune 411 057 (IN). **NIMESH CHANDRA, Misra**; Hikal Limited, 3A & 3B, International Biotech Park, Hinjewadi, Maharashtra, Pune 411 057 (IN). **LANDGE, Ravindra**; Hikal Limited, 3A & 3B, International Biotech Park, Hinjewadi, Maharashtra, Pune 411 057 (IN). **SAYYAD, Nisar**; Hikal Limited, 3A & 3B, International Biotech Park, Hinjewadi, Maharashtra, Pune 411 057 (IN). **PATIL, Rahul**; Hikal Limited, 3A & 3B, International Biotech Park, Hinjewadi, Maharashtra, Pune 411 057 (IN). **MORE, Monish**; Hikal Limited, 3A & 3B, International Biotech Park, Hinjewadi, Maharashtra, Pune 411 057 (IN).

(74) Agent: **SRINIWAS, Gopalan Deepak**; RAJESHWARI & ASSOCIATES, S-357, First Floor, Near HDFC Bank, Panchsheel Park, New Delhi 110017 (IN).

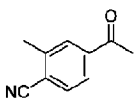
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2025/003945 A1

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF 4-ACETYL-2-METHYL-BENZONITRILE



(I)

(57) Abstract: The present invention relates to an improved process for the preparation of 4-acetyl-2-methyl- benzonitrile of formula (I). The present invention further provides an improved process for the preparation of isoxazoline derivatives using 4-acetyl-2-methyl-benzonitrile of formula (I) obtained by a process described herein.

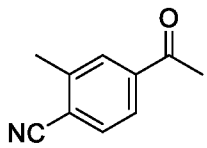
AN IMPROVED PROCESS FOR THE PREPARATION OF 4-ACETYL-2-METHYL-BENZONITRILE

RELATED APPLICATION

This application claims the benefit to Indian Provisional Application No. 202321044177, filed on June 30, 2023, the contents of which are incorporated by reference herein.

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of 4-acetyl-2-methyl-benzonitrile of formula (I). The present invention further provides an improved process for the preparation of isoxazoline derivatives using 4-acetyl-2-methyl-benzonitrile of formula (I) obtained by a process described herein.



(I)

BACKGROUND OF THE INVENTION

The 4-acetyl-2-methyl-benzonitrile is a key intermediate for preparing isoxazoline derivatives such as Fluralaner, Lotilaner, Afoxolaner and Fluxametamide.

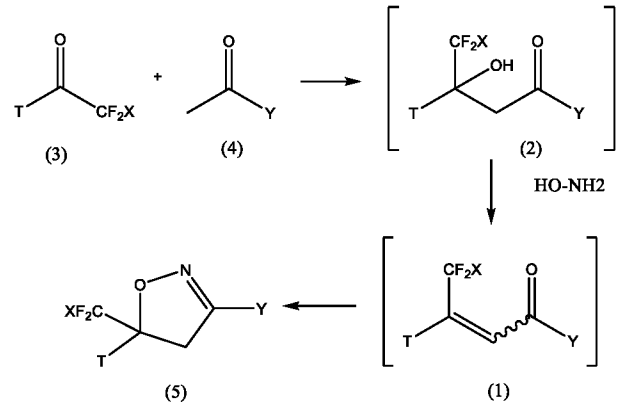
Several patent publications such as WO2011104089, WO2023012821, CN109553528 have disclosed the preparation of 4-acetyl-2-methyl-benzonitrile and its use in preparation of isooxazoline derivatives.

The synthetic process described in prior arts for the preparation of 4-acetyl-2-methyl-benzonitrile suffer from disadvantages mainly such as: i) use of expensive cyanide reagent such as potassium ferrocyanide; ii) use of phase transfer catalyst; iii) troublesome operation; iv) tedious workup and isolation technique; v) industrially non-accepted column chromatography for purification; v) excess polymerisation or degradation of compound; vi) low yield and purity.

Generally, the efforts in achieving complete reaction conversion, non-degradation, and/or avoiding polymerization of desired compound along with good yield and purity is a challenge for an industry which remarkably affects the overall production cost. However, the inventors of the present invention developed a process which avoids the polymerization or degradation

of compound and leads to complete reaction conversion along with high purity and greater yield.

The application of intermediate of formula (I) which is obtained by the invented process is used for preparation of isooxazoline derivatives as shown below.

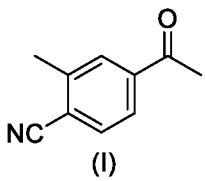


Wherein T and Y each independently represent a substituted aryl or a substituted heteroaryl, X represents a hydrogen atom or a halogen atom.

The inventors of instant invention have developed an improved process for the preparation of 4-acetyl-2-methyl-benzonitrile to overcome the limitations of the prior arts in cost effective and industrially convenient way in high yield (>73%) in less cycle time with greater chemical purity (99%). The instant process is performed on an industrial scale by using commercially available key raw materials such as 3-Methyl-4-fluoroacetophenone, sodium cyanide and a chelating agent such as citric acid. The instant process involves the simple reactions conditions, isolation, and purification technique to obtain desired compound in pale yellow solid with better yield and good purity. The 4-acetyl-2-methyl-benzonitrile obtained using said process is further utilized for the preparation of isoxazoline derivatives such as Fluralaner as disclosed in WO2013/021949 which is incorporated herein for reference.

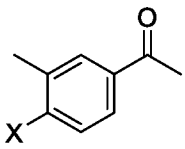
SUMMARY OF THE INVENTION

In one aspect of the present invention provides a process for the preparation of 4-acetyl-2-methyl-benzonitrile of formula (I)



(I)

by reacting 3-methyl-4-haloacetophenone, where halo is fluorine, chlorine, bromine, and Iodine with a solution consisting of sodium cyanide, chelating agent in a polar aprotic solvent.



(II)

X is halo

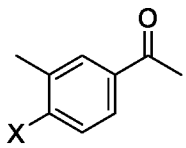
In another aspect, the present invention provides a 4-acetyl-2-methyl-benzonitrile having purity greater than 99%; more preferably greater than 99.5% as measured by HPLC.

In another aspect, the present invention relates to a process for the preparation of 4-acetyl-2-methyl-benzonitrile comprising the steps of:

i) preparing a solution of sodium cyanide, chelating agent in a polar aprotic solvent,

ii) heating a solution of step (a) at 65°C to 90°C,

iii) adding 3-methyl-4-haloacetophenone of formula (II)



(II)

where X is Cl, Br, I

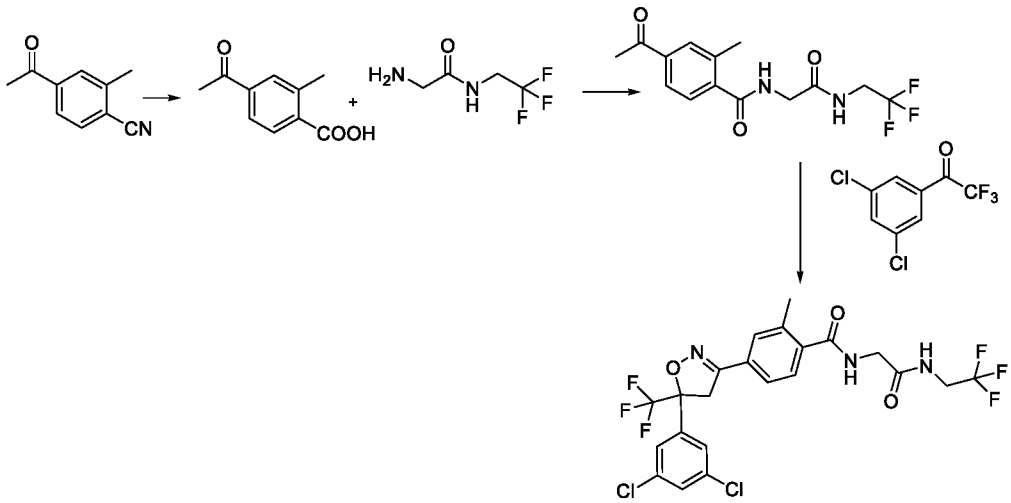
iv) heating the reaction mixture of step (iii) at 90°C to 120°C,

v) cooling the reaction mixture of step (iv),

vi) filtering, and

vii) recrystallisation the compound obtained in step (vi) using alcoholic solvent or hydrocarbon solvent.

In another aspect of the present invention provides an improved process for the preparation of Fluralaner using 4-acetyl-2-methyl-benzonitrile of formula (I) obtained by a process described herein, where the process for preparation of Fluralaner is followed by a skilled person as illustrated in WO2013021949.



DETAILED DESCRIPTION OF THE INVENTION

The present invention now will be described more fully hereinafter. As used herein, the terms "comprises," "comprising," "includes," "including," "has," "having," "contains" or "containing," or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, a composition, a mixture, process, method, article, or apparatus that comprises a list of elements is not necessarily limited to only those elements but may include other elements not expressly listed or inherent to such composition, mixture, process, method, article, or apparatus. Further, unless expressly stated to the contrary, "or" refers to an inclusive or and not to an exclusive. As used in the specification, and in the appended claims, indefinite articles "a" and "an" preceding an element or component of the invention are intended to be nonrestrictive regarding the number of instances (i.e., occurrences) of the element or component. Therefore "a" or "an" should be read to include one or at least one, and the singular word form of the element or component also includes the plural unless the number is obviously meant to be singular indicates otherwise.

The term 'solvent' used herein, refers to the single solvent or mixture of solvents.

The compound 4-acetyl-2-methyl-benzonitrile of formula (I) prepared by using the process described herein results purity having greater than 99%, preferably greater than 99.5%, and substantial percentage of known or unknown impurity as measured by HPLC.

The substantial percentage used herein refers to a maximum acceptable percentage by the regulatory authority for known or unknown impurity(es).

In accordance with the aspect of the present invention, the process for preparation of 4-acetyl-2-methyl-benzonitrile of formula (I), which comprises:

step (a) reacting a 3-methyl-4-haloacetophenone with a solution containing sodium cyanide, chelating agent such as citric acid in presence of polar aprotic solvent;
step (b) isolating; and
step (c) recrystallization in alcoholic solvent or hydrocarbon solvent or combination thereof resulting in good yield (>73%) and better purity (>99.5%).

In another embodiment of the present invention, wherein the use of chelating agent avoids impurity formation, polymerization, and degradation of reaction mass.

In another embodiment of the present invention, wherein chelating agent uses in catalytic amount, which is selected from citric acid, Ethylenedinitrilo-tetraacetic acid (EDTA), Nitrilotriacetic acid (NTA), meso-2,3-dimercaptosuccinic acid (DMSA), and Gluconic Acid.

In another embodiment of the present invention, wherein citric acid is used in 1 to 5 %w/w ratio with respect to 3-methyl-4-haloacetophenone.

In another embodiment of the present invention, wherein the reaction is performed at a temperature of 80°C to 120°C and for 10-20 hours.

In another embodiment of the present invention, wherein isolation step is performed by addition of water in reaction mixture, filtration, and subsequent purification by recrystallization.

In another embodiment of the present invention, wherein recrystallisation is performed using alcoholic solvent or hydrocarbon solvent or mixture thereof.

In another embodiment of the present invention, wherein recrystallisation process is comprising steps of:

i) adding compound of step (b) in an alcoholic solvent or hydrocarbon solvent or mixture thereof.
ii) heating the reaction mass till clear solution at 45 to 65°C for 1-2 hrs,
iii) gradually cooling the reaction solution to from 65°C to -5°C and maintaining for 1-2 hrs,

iv) filtering the compound to obtain 4-acetyl-2-methyl-benzonitrile.

In another embodiment of the present invention, wherein polar aprotic solvent is selected from ethyl acetate, acetonitrile, dimethylformamide, dimethyl sulfoxide and the like; preferably dimethyl sulfoxide.

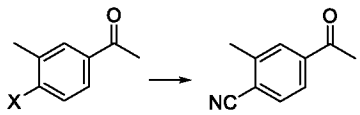
In another embodiment of the present invention, wherein alcoholic solvent is selected from methanol, ethanol, isopropanol, and the like.

In another embodiment of the present invention, wherein hydrocarbon solvent is selected from toluene, hexane, pentane, cyclohexane and the like.

The compound 4-acetyl-2-methyl-benzonitrile of formula (I) obtained by the process described herein is further used for the preparation of Fluralaner.

The preparation of the starting materials and reagents used in the present invention are well known in prior art.

The process for the preparation of 4-acetyl-2-methyl-benzonitrile of formula (I) is illustrated in the following synthetic scheme.



(II) (I)

where X is F, Cl, Br, I

The invention is further illustrated by the following examples, which should not be construed to limit the scope of the invention in anyway.

EXPERIMENTAL

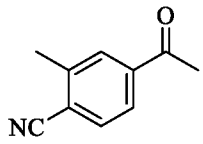
Preparation of 4-acetyl-2-methyl-benzonitrile (I)

To a solution of dimethyl sulfoxide (4-6V), citric acid (1-5%w/w), sodium cyanide (1-1.2eq) was added and heated at 70°C to 95°C for 1-2 hrs. To the above solution 3-methyl-4-fluoroacetophenone (1.0 eq) was added and the reaction mixture was heated at 100°C to 120°C for 10-20 hrs. The completion of reaction is monitored by HPLC. After completion, the reaction mixture was cooled to 15°C to 25°C and quenched by adding water. The solid compound was filtered to obtain crude compound with HPLC purity > 91%. To the crude compound ethanol

solvent was added and heated at 50°C to 60° for 1-2 hrs. The clear solution was gradually cooled to room temperature and further cooled to 0°C to -5°C and maintained for 1-2 hrs. The compound was filtered, dried to obtain 4-acetyl-2-methyl-benzonitrile (73% yield, HPLC purity: 99.5%, unknown impurities < 0.5%).

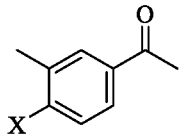
CLAIM:

1) A process for the preparation of 4-acetyl-2-methyl-benzonitrile of formula (I)



(I)

by reacting 3-methyl-4-haloacetophenone compound of formula (II)

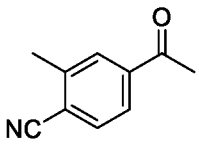


(II)

Wherein X is F, Cl, Br and I

with a solution consisting of sodium cyanide, chelating agent in a polar aprotic solvent.

2) The process for the preparation of 4-acetyl-2-methyl-benzonitrile of formula (I)



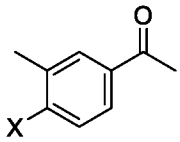
(I)

as claimed in claim 1 comprising the steps of:

i) preparing a solution of sodium cyanide, chelating agent in a polar aprotic solvent,

ii) heating a solution of step (a) at 65°C to 90°C,

iii) adding 3-methyl-4-haloacetophenone of formula (II)



(II)

where X is Cl, Br, I

iv) heating the reaction mixture of step (iii) at 90°C to 120°C,

v) cooling the reaction mixture of step (iv),

vi) filtering, and

vii) recrystallizing the compound obtained in step (vi) using alcoholic solvent or hydrocarbon solvent or mixture thereof.

3) The process as claimed in claim 1, wherein chelating agent is selected from citric acid, Ethylenedinitrilo-tetraacetic acid (EDTA), Nitrilotriacetic acid (NTA), meso-2,3-dimercaptosuccinic acid (DMSA), and Gluconic Acid.

4) The process as claimed in claim 1, wherein polar aprotic solvent is selected from ethyl acetate, acetonitrile, dimethylformamide, dimethyl sulfoxide; alcoholic solvent is selected from methanol, ethanol, isopropanol; and hydrocarbon solvent is selected from toluene, hexane, pentane, and cyclohexane.

5) The process as claimed in claim 1, wherein chelating agent is used in a 1-5% w/w.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2024/056261

A. CLASSIFICATION OF SUBJECT MATTER
C07C253/14,C07C255/50 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

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.
Y	WO 2011104089 A1 (SYNGENTA PARTICIPATIONS AG [CH], SYNGENTA LTD [GB]) 01 September 2011 (01-09-2011) See Example 10, step B	1-5
Y	WO 2023012821 A1 (ZENFOLD SUSTAINABLE TECH PRIVATE LIMITED [IN]) 09 February 2023 (09-02-2023) See Example 1, Step 1	1-5
Y	CN 109553528 A (JINGMEN INSTITUTE OF PHARMACEUTICAL INDUSTRY TECH; UNIV JINGCHU TECHNOLOGY) 02 April 2019 (02-04-2019) See Example 1	1-5
A	CN 116003293 A (BAYECAO HEALTH INDUSTRY RES INSTITUTE XIAMEN CO LTD; UNIV HUAQIAO) 25 April 2023 (25-04-2023) See Abstract, See claim 1	1-5

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08-10-2024	08-10-2024

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Somyajit Khan Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2024/056261

Citation	Pub.Date	Family	Pub.Date
WO 2011104089 A1	01-09-2011	EP 2539335 A1	02-01-2013
		BR 112012020983 A2	01-11-2016
		CN 102822168 A	12-12-2012