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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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(54) **Title**: PROCESS FOR THE PREPARATION OF 3-(3-CHLORO-1*H*-PYRAZOL-1-YL)PYRIDINE

(57) **Abstract**: 3-(3-Chloro-1*H*-pyrazol-1-yl)pyridine is prepared by cyclizing 3-hydrazinopyridine-•dihydrochloride with acrylonitrile to provide 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine, by oxidizing to provide 3-(3-amino-1*H*-pyrazol-1-yl)pyridine, and by converting the amino group to a chloro group by a Sandmeyer reaction.

PROCESS FOR THE PREPARATION OF 3-(3-CHLORO-1*H*-PYRAZOL-1-YL)PYRIDINE

CROSS REFERENCE TO RELATED APPLICATIONS

This Application claims the benefit of the following U.S. Provisional Application: Serial No. 62/031,547, filed July 31, 2014, the entire disclosure of which is hereby expressly incorporated by reference into this Application.

BACKGROUND

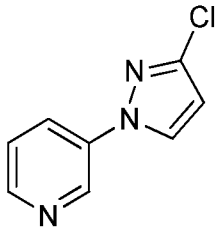
The present invention concerns an improved process for preparing 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine.

US 20130288893(A1) describes, *inter alia*, certain (3-halo-1-(pyridin-3-yl)-1*H*-pyrazol-4-yl)amides and carbamates and their use as pesticides. The route to prepare such compounds involved the preparation of 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine (5b) by the direct coupling of 3-bromopyridine with 3-chloropyrazole. The 3-chloropyrazole was prepared by a) treating 1*H*-pyrazole with 2-dimethylsulfamoyl chloride and sodium hydride to provide *N,N*-dimethyl-1*H*-pyrazole-1-sulfonamide, b) treating the *N,N*-dimethyl-1*H*-pyrazole-1-sulfonamide with perchloroethane and *n*-butyl lithium to provide 3-chloro-*N,N*-dimethyl-1*H*-pyrazole-1-sulfonamide, and c) removing the *N,N*-dimethylsulfonamide from 3-chloro-*N,N*-dimethyl-1*H*-pyrazole-1-sulfonamide with trifluoroacetic acid to give the 3-chloropyrazole.

The disclosed process produces low yields, relies on a starting material that is difficult to prepare (3-chloropyrazole) and provides a product that is difficult to isolate in a pure form. It would be desirable to have a process for preparing 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine that avoids these problems.

SUMMARY

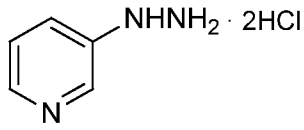
The present invention provides such an alternative by cyclizing 3-hydrazinopyridine-·dihydrochloride with acrylonitrile to provide 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine (9a), by oxidizing to provide 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a), and by converting the amino group to a chloro group by a Sandmeyer reaction. Thus, the present invention concerns a process for preparing 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine (5b),



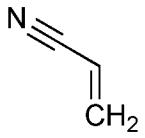
(5b)

which comprises

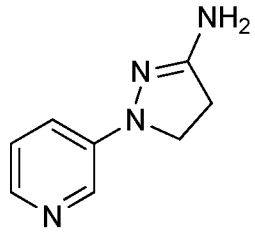
a) treating 3-hydrazinopyridine·dihydrochloride



with acrylonitrile

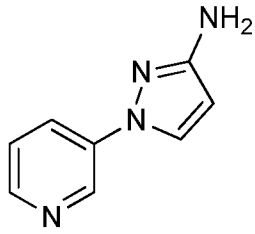


in a (C_1-C_4) aliphatic alcohol at a temperature of about 25 °C to about 100 °C in the presence of an alkali metal (C_1-C_4) alkoxide to provide 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine (9a)



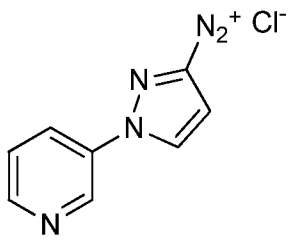
(9a);

b) treating the 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine (9a) with an oxidant in an inert organic solvent at a temperature of about 25 °C to about 100 °C to provide 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a)



(8a);

c) treating the 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a) in aqueous hydrochloric acid with sodium nitrite at a temperature of about 0 °C to about 25 °C to provide the diazonium salt (8b)



(8b); and

d) treating the diazonium salt (8b) with copper chloride at a temperature of about 0 °C to about 25 °C.

DETAILED DESCRIPTION

The present invention provides an improved process for preparing 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine (5b), by cyclizing 3-hydrazinopyridine·dihydrochloride with acrylonitrile to provide 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine (9a), by oxidizing to provide 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a), and by converting the amino group to a chloro group by a Sandmeyer reaction.

In the first step, 3-hydrazinopyridine·dihydrochloride is treated with acrylonitrile in a (C_1-C_4) aliphatic alcohol at a temperature of about 25 °C to about 100 °C in the presence of an alkali metal (C_1-C_4) alkoxide to provide 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine. While stoichiometric amounts of 3-hydrazinopyridine·dihydrochloride and acrylonitrile are required, it is often convenient to use about a 1.5 fold to about a 2 fold excess of acrylonitrile. The cyclization is run in the presence of an alkali metal (C_1-C_4) alkoxide base. It is often convenient to use about a 2 fold to about a 5 fold excess of base. The cyclization is performed in a (C_1-C_4) aliphatic alcohol. It is most convenient that the alkoxide base and the alcohol solvent be the same, for example, sodium ethoxide in ethanol.

In a typical reaction, 3-hydrazinopyridine·dihydrochloride and an anhydrous alcohol are introduced into a reaction vessel and the alkoxide base is gradually added. The mixture is stirred and the acrylonitrile is added. The mixture is stirred at about 60 °C until most of the 3-hydrazinopyridine has reacted. The mixture is allowed to cool and the excess base is neutralized with acid. The crude 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine (9a) is conveniently isolated and purified by standard techniques.

In the second step, 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine (9a) is treated with an oxidant in an organic solvent at a temperature of about 25 °C to about 100 °C to provide 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a). Suitable oxidants include manganese(IV) oxide, potassium ferricyanide(III), copper(I) chloride in the presence of oxygen, and iron(III) chloride in the presence of oxygen. Manganese(IV) oxide is preferred. It is often convenient to use about a 2 fold to about a 10 fold excess of oxidant. The oxidation is performed in a solvent that is inert to the oxidant. Suitable solvents include nitriles such as acetonitrile or halocarbons such as dichloromethane. With manganese(IV) oxide as the oxidant, acetonitrile is a preferred solvent.

In a typical reaction, 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine (9a) and solvent are mixed with the oxidant and the mixture is heated at about 60 °C until the reaction is completed. The 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a) is conveniently isolated and purified by standard techniques.

The 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a) is then converted to the desired 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine (5b) by treatment in aqueous hydrochloric acid with sodium

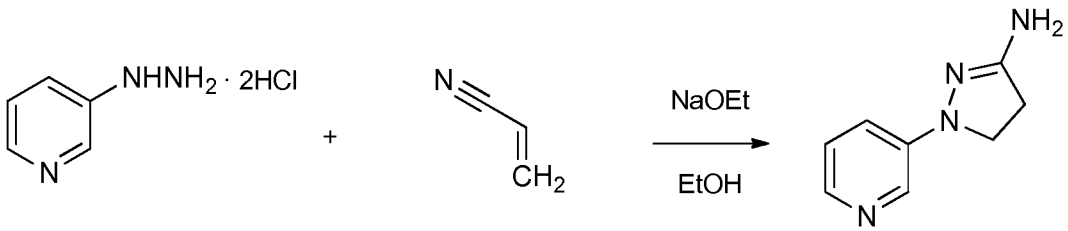
nitrite at a temperature of about 0 °C to about 25 °C to provide a diazonium salt followed by treatment of the diazonium salt with copper chloride at a temperature of about 0 °C to about 25 °C. While stoichiometric amounts of reagents are required, it is often convenient to use an excesses of reagents with respect to the 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a). Thus, aqueous hydrochloric acid is used in large excess as the reaction medium. Sodium nitrite is used in about a 1.3 fold to about a 2 fold excess. Copper chloride is used in about 5 mole percent to about 60 mole percent excess, preferably from about 15 mole percent to about 30 mole percent excess. The copper chloride may be either copper(I) chloride or copper(II) chloride. To suppress foaming during the reaction a water-immiscible organic solvent such as toluene or chloroform can be added during the treatment of the diazonium salt with copper chloride.

In a typical reaction, a mixture of 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a) and aqueous hydrochloric acid are mixed and cooled to about 0 °C. An aqueous solution of sodium nitrite is slowly added maintaining the temperature below about 5 °C. The suspension is stirred at about 0 °C for about 2 hours. In a separate vessel, a mixture of copper(II) chloride and toluene is cooled to about 0 °C and the chilled suspension of diazonium salt is added at a rate maintaining the temperature below about 5 °C. The mixture is allowed to warm to about ambient temperature. After completion of the reaction, the mixture is treated with aqueous sodium hydroxide to adjust the pH to about 8 to about 10. The resulting solution is extracted with a water-immiscible organic solvent. After removal of the solvent, the 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine (5b) can be used directly in the next reaction or further purified by standard techniques such as flash column chromatography or crystallization.

The following examples are presented to illustrate the invention.

Examples

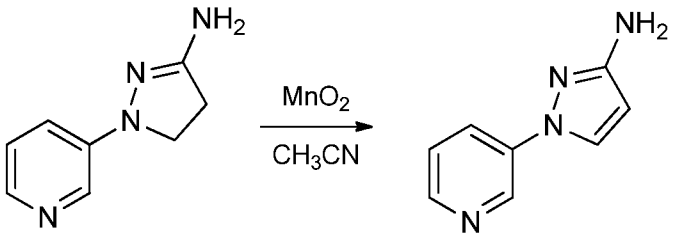
1. Preparation of 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine (9a)



To a 4-neck, round bottomed flask (250 mL) was charged sodium ethanolate (21 wt% in ethanol, 32 mL). 3-Hydrazinopyridine·dihydrochloride (5.00 g, 27.5 mmol) was added, causing an exotherm from 20 °C to 58 °C. The mixture was allowed to cool to 20 °C and acrylonitrile (2.91 g, 54.9 mmol) was added. The reaction was heated at 60 °C for 5 hours and cooled to 20 °C. The excess sodium ethanolate was quenched with hydrochloric acid (4 M in 1,4-dioxane, 6.88 mL, 27.5 mmol) at <20 °C. The mixture was adsorbed on silica gel (10 g) and the crude

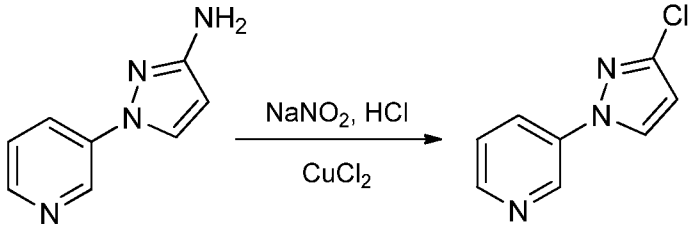
product was purified by flash column chromatography using 0–10% methanol/dichloromethane as eluent. The fractions containing pure product were concentrated to dryness to afford the title compound as a yellow solid (3.28 g, 74%): mp 156–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 2.8, 0.8 Hz, 1H), 8.01 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.22 (ddd, *J* = 8.4, 2.8, 1.5 Hz, 1H), 7.12 (ddd, *J* = 8.4, 4.6, 0.8 Hz, 1H), 4.20 (s, 2H), 3.70 (t, *J* = 9.3 Hz, 2H), 2.92 (t, *J* = 9.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.23, 144.78, 139.22, 135.08, 123.44, 119.44, 49.23, 32.74; ESIMS *m/z* 163 ([M+H]$^+$).

2. Preparation of 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a)



To a 3-neck, round bottomed flask (100 mL) was charged 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine (1.00 g, 6.17 mmol) and acetonitrile (20 mL). Manganese(IV) oxide (2.68 g, 30.8 mmol) was added, causing an exotherm from 20 °C to 25 °C. The reaction was stirred at 60 °C for 18 hours, after which it was filtered through a Celite® pad and the pad was rinsed with acetonitrile (20 mL). Water (20 mL) was added to the combined filtrates and the resulting mixture was concentrated to 10 mL. Water (20 mL) was added and the resulting mixture was again concentrated to 10 mL. The resulting suspension was stirred at 20 °C for 18 hours and filtered. The filter cake was rinsed with water (2 × 5 mL) and dried to afford the title compound as a brown solid (0.68 g, 69%): mp 169–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 – 8.82 (m, 1H), 8.33 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.24 (d, *J* = 2.6 Hz, 1H), 8.00 (ddd, *J* = 8.4, 2.7, 1.4 Hz, 1H), 7.42 (ddd, *J* = 8.5, 4.6, 0.8 Hz, 1H), 5.80 (d, *J* = 2.6 Hz, 1H), 5.21 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.67, 144.68, 138.00, 136.22, 128.30, 123.95, 123.17, 97.08; ESIMS *m/z* 161 ([M+H]$^+$).

3. Preparation of 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine (5b)

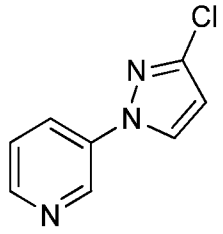


To a 3-neck round bottomed flask (250 mL) was charged 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (5.00 g, 31.2 mmol) and hydrogen chloride (37 wt%, 15 mL). The mixture was

cooled to 0 °C. A solution of sodium nitrite (4.31 g, 62.4 mmol) in water (15 mL) was added in portions at <1 °C over 20 minutes and the resulting brown solution was stirred at <0 °C for 2 hours. To a separate 3-neck round bottomed flask (250 mL) was charged copper(II) chloride (5.04 g, 37.5 mmol) and toluene (30 mL). It was cooled to 0 °C and the yellow solution was added in portions at <1 °C over 15 minutes. The resulting mixture was allowed to warm up, off-gassing was observed when the reaction temperature reached 18 °C. The reaction was stirred at 20 °C for 18 hours. The reaction was basified with 50 wt% sodium hydroxide to pH ~10. Celite® (10 g) was added and the resulting suspension was stirred for 10 minutes. The suspension was filtered through a Celite® pad (10 g) and the filter cake was rinsed with ethyl acetate (2 × 50 mL). The layers of the filtrates were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The organic layers were concentrated to dryness and the residue was purified by flash column chromatography using 0–60% ethyl acetate/hexanes as eluent. The fractions containing the desired product were concentrated to give the title compound as a white solid (3.80 g, 68%): mp 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 2.7 Hz, 1H), 8.57 (dd, J = 4.8, 1.4 Hz, 1H), 8.02 (ddd, J = 8.3, 2.7, 1.5 Hz, 1H), 7.91 (d, J = 2.6 Hz, 1H), 7.47–7.34 (M, 1H), 6.45 (d, J = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.01, 142.72, 140.12, 135.99, 128.64, 126.41, 124.01, 108.08; EIMS *m/z* 179 ($[M]^+$).

WHAT IS CLAIMED IS:

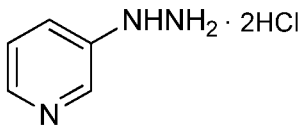
1. A process for preparing 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine (5b),



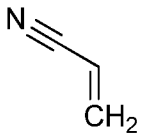
(5b)

which comprises

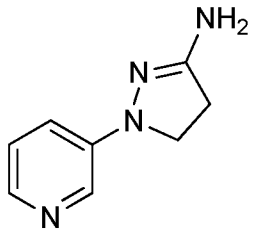
a) treating 3-hydrazinopyridine·dihydrochloride



with acrylonitrile

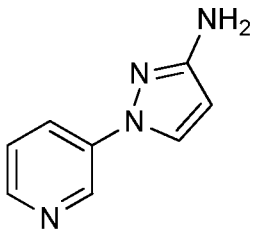


in a (C_1-C_4) aliphatic alcohol at a temperature of about 25 °C to about 100 °C in the presence of an alkali metal (C_1-C_4) alkoxide to provide1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine (9a)



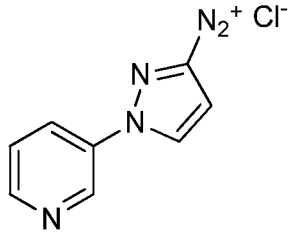
(9a);

b) treating the 1-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazol-3-amine (9a) with an oxidant in an organic solvent at a temperature of about 25 °C to about 100 °C to provide 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a)



(8a);

c) treating the 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a) in aqueous hydrochloric acid with sodium nitrite at a temperature of about 0 °C to about 25 °C to provide the diazonium salt (8b)



(8b); and

d) treating the diazonium salt (8b) with copper chloride at a temperature of about 0 °C to about 25 °C.

2. The process of Claim 1 in which the oxidant is manganese(IV) oxide, potassium ferricyanide (III), copper(I) chloride in the presence of oxygen, or iron(III) chloride in the presence of oxygen.

3. The process of Claim 2 in which the oxidant is manganese(IV) oxide.

4. The process of Claim 1 in which a water immiscible organic solvent is added in step d) to suppress foaming.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/61029

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 231/14; A01N 43/46; A61K 31/415 (2014.01)
CPC - C07D 403/04; C07D231/14
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)
IPC(8): C07D 231/14; A01N 43/46; A61K 31/415 (2014.01)
CPC: C07D 403/04; C07D231/14

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 548/364.1; 374.1; 514/406

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Thomson innovation (US Grant, AU Innov, CA App, US App, AU Grant, FR App, EP Grant, AU App, DE Util, EP App, GB App, DE Grant, WO App, CA Grant, DE App, JP App, KR Grant, KR App, Other, JP Util, KR Util , CN Util, JP Grant, CN Grant, CN App, VN Grant, MY Grant), Sureche, google, Pubwest. Terms: pyrazole, 3-(3-chloro-IH-pyrazol-1-yl)pyridine, acrylo

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,965,032 B2 (FREUDENBERGER) 15 November 2005 (15.11.2005) col 9, ln 63 - col 10, ln 7; col 12, ln 28-56; col 15, ln 13-42; col 19, ln 1-27; col 19, ln 61 - col 20, ln 21	1-4
A	US 2006/0167020 A1 (DICKERSON et al.) 27 July 2006 (27.07.2006) para [0132]-[0133]	1-4
A	US 2013/0109566 A1 (NIYAZ et al.) 02 May 2013 (02.05.2013) para [0110]-[0111], Scheme I; Scheme II; para [0164]-[0165], [0272]	1-4
A	US 2006/0287541 A1 (NISHINO et al.) 21 December 2006 (21.12.2006) para [0021], [0038], [0040], [0042]	1-4
A	US 2013/0288893 A1 (Buysse et al.) 31 October 2013 (31.10.2013) entire document	1-4
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☐ Further documents are listed in the continuation of Box C. ☐

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Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2014 (20.11.2014)	15 DEC 2014

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