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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(ii))*

— *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-1H-pyrazol-1-yl)pyridine is prepared by coupling 3-bromopyridine with commercially available 3-aminopyrazole, purifying the 3-(3-amino-1*H*-pyrazol-1-yl)pyridine by crystallization, and 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. 62/031,557 filed Jul 31, 2014, the entire disclosure of which is hereby expressly incorporated by reference into this Application.

BACKGROUND

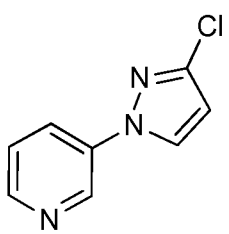
The present invention concerns an improved process for preparing 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine.

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 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 (5b) that avoids these problems.

SUMMARY

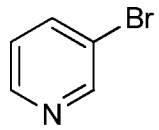
The present invention provides such an alternative by coupling 3-bromopyridine with commercially available 3-aminopyrazole, purifying the 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a) by crystallization, and converting the amino group to a chloro group by a Sandmeyer reaction. Thus, the present invention concerns a process for preparing 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine (5b),



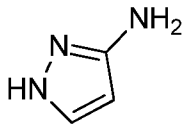
(5b)

which comprises

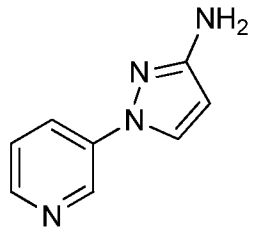
a) treating 3-bromopyridine



with 3-aminopyrazole



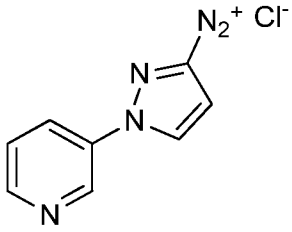
in a water-miscible polar aprotic organic solvent at a temperature of about 75 °C to about 155 °C in the presence of a catalytic amount of copper(I) chloride and a base to provide 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a)



(8a);

b) crystallizing the 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a) from water;

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 coupling 3-bromopyridine with commercially available 3-aminopyrazole, purifying the 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a) by crystallization, and converting the amino group to a chloro group by a Sandmeyer reaction.

In the first step, 3-bromopyridine is coupled with 3-aminopyrazole in a water-miscible polar aprotic organic solvent at a temperature of about 75 °C to about 155 °C in the presence of a catalytic amount of copper chloride and a base to provide 3-(3-amino-1*H*-pyrazol-1-

yl)pyridine (8a). While stoichiometric amounts of 3-bromopyridine and 3-aminopyrazole are required, it is often convenient to use an excess of 3-aminopyrazole. An excess from about 10 mole percent to about 50 mole percent 3-aminopyrazole is preferred. The coupling is run in the presence of about 5 mole percent to about 50 mole percent copper chloride, preferably from about 15 mole percent to about 30 mole percent copper chloride. The copper chloride may be either copper(I) chloride or copper(II) chloride. The coupling is also run in the presence of a base. While stoichiometric amounts of 3-bromopyridine and base are required, it is often convenient to use about a 1.5 fold to about a 2 fold excess of base. Alkali metal carbonates are preferred bases. The coupling is performed in a water-miscible polar aprotic organic solvent. Polar aprotic organic solvents that are soluble in water include nitriles such as acetonitrile, sulfoxides such as dimethyl sulfoxide, and amides such as *N*-methylpyrrolidinone, *N,N*-dimethylformamide, and *N,N*-dimethylacetamide. *N,N*-Dimethylformamide is particularly preferred.

In a typical reaction, copper(I) chloride, 3-aminopyrazole, potassium carbonate and *N,N*-dimethylformamide are introduced into a reaction vessel under a nitrogen atmosphere and 3-bromopyridine is gradually added. The mixture is heated at about 110 °C until most of the 3-bromopyridine has reacted. The mixture is allowed to cool and most of the solvent is removed under reduced pressure. The crude 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a) is conveniently isolated and purified by crystallization from water.

The purified 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 1.5 fold to about a 2 fold excess. Copper chloride is used in about 5 mole percent to about 50 mole percent excess, preferably from about 15 mole percent to about 30 mole percent excess. The copper chloride may be either copper(I) chloride, copper(II) chloride or copper powder. 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.

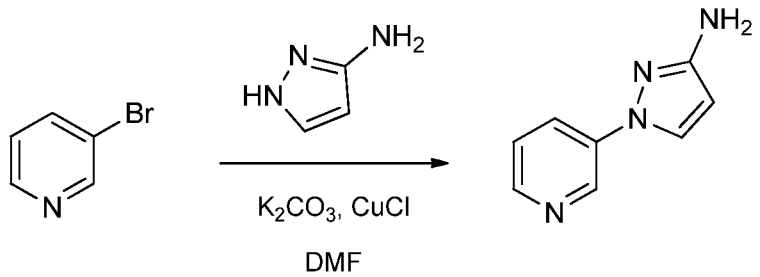
In a typical reaction, a mixture of 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a) and aqueous hydrochloric acid are mixed and cooled to about 0 °C. An aqueous solution of sodium nitrite is slowly added maintaining the temperature below about 5 °C. The suspension is stirred

at about 0 °C for about 2 hours. In a separate vessel, a mixture of copper(I) chloride and toluene are 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 step, or further purified by standard techniques such as flash column chromatography or crystallization.

The following examples are presented to illustrate the invention.

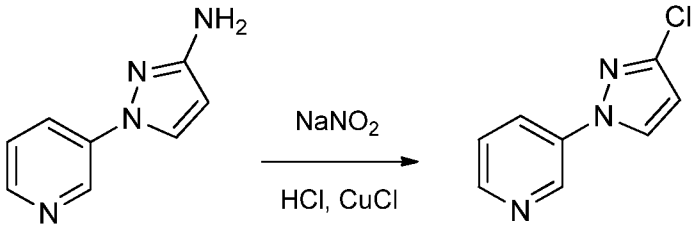
Examples

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



A 4-neck round bottomed flask (500 mL) was charged with copper(I) chloride (2.51 g, 25.3 mmol), 1*H*-pyrazol-3-amine (15.8 g, 190 mmol), potassium carbonate (35.0 g, 253 mmol), and *N*,*N*-dimethylformamide (100 mL). The mixture was stirred under nitrogen for 10 minutes and 3-bromopyridine (12.2 mL, 127 mmol) was added. The mixture was heated at 110 °C for 18 hours, at which point HPLC analysis indicated that ~15.5% 3-bromopyridine remained. The reaction was allowed to cool to 20 °C and concentrated to give a brown residue. Water (200 mL) was added and the resulting suspension was stirred at 20 °C for 2 hours and filtered. The solid was rinsed with water (2 × 50 mL) and dried to afford a pale green solid. The solid was suspended in water (200 mL) and the resulting suspension was heated at 90 °C for 2 hours and was filtered hot through a Celite® pad. The pad was rinsed with hot water (50 mL). The combined filtrates were allowed to cool to 20 °C to afford a yellow suspension, which was stirred at 20 °C for 2 hours and filtered. The solid was rinsed with water (2 × 50 mL) and air dried to afford the desired product as a light yellow crystalline solid (11.6 g, 57%): 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]$^+$).

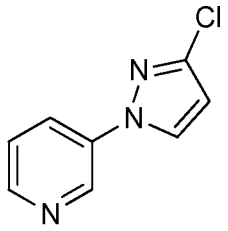
2. Preparation of 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine (5b)



To a 3-neck round bottomed flask (100 mL) was charged 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (0.500 g, 3.12 mmol) and hydrochloric acid (37 wt%, 3 mL). The mixture was cooled to 0 °C and a solution of sodium nitrite (0.431 g, 6.24 mmol) in water (3 mL) was added in portions at <5 °C. The resulting yellow suspension was stirred at 0 °C for 2 hours. To a separate 3-neck round bottomed flask (100 mL) was charged copper(I) chloride (0.371 g, 3.75 mmol) and toluene (3 mL). It was cooled to 0 °C and the yellow suspension was added in portions at <5 °C. The resulting mixture was allowed to warm to 20 °C and stirred for 18 hours. It was basified with 50% sodium hydroxide to pH 10 and extracted with ethyl acetate (2 × 20 mL). The organic layers were concentrated to dryness and the residue was purified by flash column chromatography using 0–10% ethyl acetate/hexanes as eluent. The fractions containing the desired product were concentrated to give the title compound as a white solid (0.340 g, 61%): mp 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 27 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:

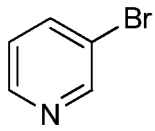
1. A process for preparing 3-(3-chloro-1*H*-pyrazol-1-yl)pyridine (5b)



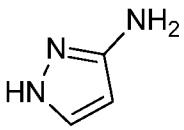
(5b)

which comprises

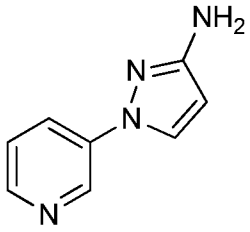
a) treating 3-bromopyridine



with 3-aminopyrazole



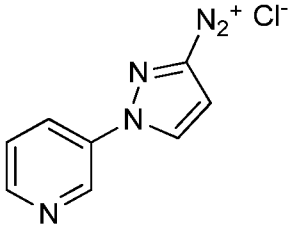
in a water-miscible polar aprotic organic solvent at a temperature of about 75 °C to about 155 °C in the presence of a catalytic amount of copper chloride and a base to provide 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a)



(8a);

b) crystallizing the 3-(3-amino-1*H*-pyrazol-1-yl)pyridine (8a) from water;

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

2. The process of Claim 1 in which the water-miscible polar aprotic organic solvent is acetonitrile, dimethyl sulfoxide, *N*-methylpyrrolidinone, *N,N*-dimethylformamide or *N,N*-dimethylacetamide.

3. The process of Claim 2 in which the water-miscible polar aprotic organic solvent is *N,N*-dimethylacetamide.

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 14/61023

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, pyrazo

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
A	US 4,407,803 A (HAVIV et al.) 04 October 1983 (04.10.1983) entire document especially col 2, ln 55-64; col 4, ln 50-56	1-4

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"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
20 November 2014 (20.11.2014)	15 DEC 2014

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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