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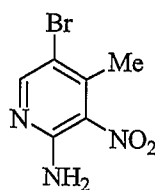
- as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))

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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF PREPARATION OF NITROAMINOPYRIDINE COMPOUNDS



(57) Abstract: A method of preparing an intermediate which is useful for the preparation of azaindole derivatives.

WO 2007/019259 A1

METHOD OF PREPARATION OF NITROAMINOPYRIDINE COMPOUNDS

CROSS- REFERENCE TO RELATED APPLICATIONS

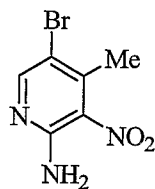
[0001] This application claims the benefit of U.S. Provisional Application Serial
5 Number 60/705,261 filed August 3, 2005.

FIELD OF THE INVENTION

[0002] The present invention provides a method of preparing an intermediate
useful for the preparation of azaindole derivatives.
10

SUMMARY OF THE INVENTION

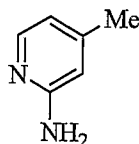
[0003] One aspect of the present invention provides a method of preparing a
compound of formula 4:



4

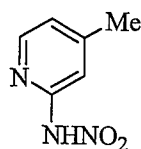
15 including the steps of:

(a) converting a compound of formula 1:



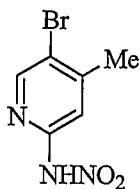
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[0004] to a compound of formula 2:



2

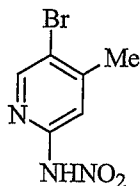
20 (b) brominating said compound of formula 2 to provide a compound of
formula 3:



3 ; and

(c) converting said compound of formula 3 to provide said compound of formula 4.

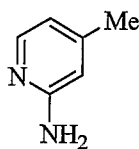
- 5 [0005] A further aspect of the present invention provides a method of preparing a compound of formula 3:



3

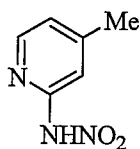
[0006] including the steps of:

- (a) converting a compound of formula 1:



1

[0007] to a compound of formula 2:



2

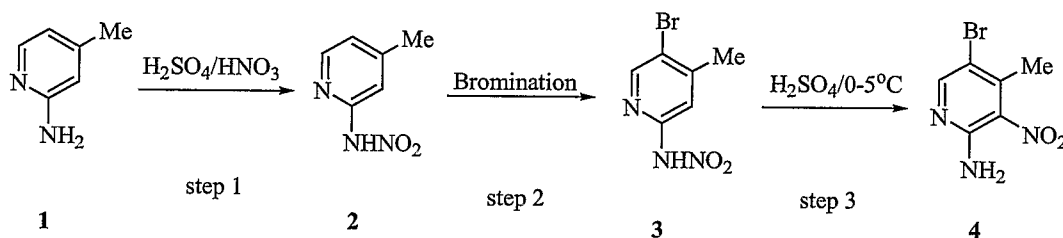
(b) brominating said compound of formula 2 to provide a compound of formula 3.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The present invention provides processes for the preparation of 2-amino,5-bromo,3-nitropicoline, otherwise referred to herein as the compound of formula 4.

- 5 This compound may be used, for example, as an intermediate useful in the preparation of azaindoles, such as those represented by the compound of formula 8. The compound of formula 8 is an azaindole derivative useful in the treatment of HIV. The present invention includes the preparation of the compound of formula 4 in addition to the preparation of intermediates as shown in the following scheme. Each
- 10 of the steps are shown below in more detail following the general Scheme.

SCHEME



- 15 [0009] Step 1 includes the conversion of the compound of formula 1 to the compound of formula 2, but the introduction of a nitro function to the amine. This is conducted with a strong acid such as sulfuric acid (H_2SO_4) followed by nitric acid (HNO_3).

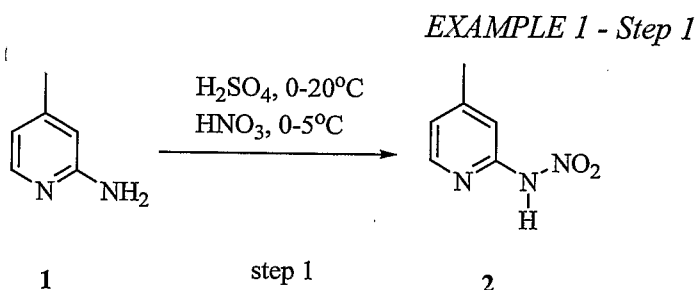
- 20 [0010] Step 2 is the bromination of the compound of formula 2 to a compound of formula 3, which may be performed by a variety of reaction conditions. The reaction may be conducted either at room temperature or with heating. One of the following combinations may also be included (i) acetic acid and sodium acetate followed by introduction of bromine and acetic acid, (ii) dichloro(m)ethane, acetonitrile and N-bromosuccinamide, (iii) acetic acid and potassium hydrogen phosphate followed by
- 25 the introduction of bromine and acetic acid, and (iv) dichloromethane, water and tetrabutylammoniumtribromide.

[0011] Step 3 is the conversion from the compound of formula 3 to the compound of formula 4 is conducted with a strong acid such as sulfuric acid.

[0012] The features and advantages of the present invention are more fully shown by the following examples which are provided for purposes of illustration, and are not to be construed as limiting the invention in any way.

EXAMPLES

10



[0013] In a 500 mL 3-neck flask, equipped with a stirrer and an internal thermocouple probe (JKEM) was charged 116 mL of concentrated sulfuric acid (H₂SO₄) and allowed to cool between 0-5°C with an ice bath. Then 25g of the compound of formula 1 was charged, over a period of one hour, via an addition funnel.

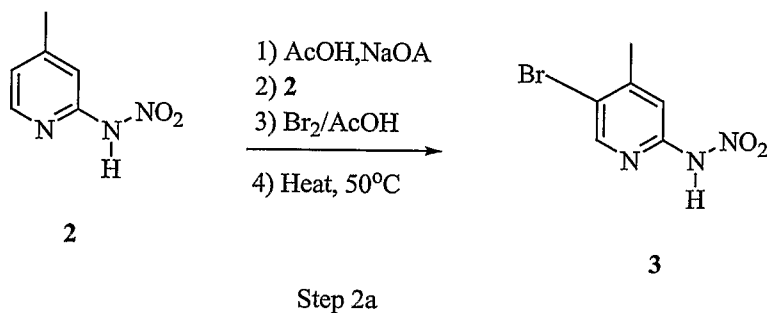
[0014] After one hour, 15.5mL (1 (eq.)) of concentrated nitric acid (69-71%) was added dropwise maintaining the reaction mixture between -3° to 0°C with external cooling (ice/methanol) over a period of 1.25 hours. The mixture was allowed to stir between 0-3°C for one hour, after which HPLC analysis revealed complete conversion of the compound of formula 1 to the compound of formula 2.

[0015] The solution was slowly quenched over 600g of we ice in a 1 L beaker. The ice was allowed to melt and the resulting white slurry was stirred at room temperature for 10 min. The slurry was vacuum filtered, dried in vacuo (5in Hg) at 50°C (overnight) giving 84% recovered yield of the compound of formula 2.

[0016] Analytical data: $^1\text{H-NMR}$ (CD_3OD) (δ , ppm): 2.50 (s, 3H), 7.20 (bd, 1H, $J = 6.6$ Hz, Ar-H), 7.30 (bs, 1H, Ar-H), 8.03 (d, 1H, $J = 6.6$ Hz, Ar-H); $^{13}\text{C-NMR}$ (CD_3OD) (δ , ppm): 21.00, 118.54, 119.91, 135.34, 144.00, 158.46; HRMS calcd for $\text{C}_6\text{H}_7\text{N}_3\text{O}_2$ 153.05383 found ($M+1$) 154.06166.

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EXAMPLE 2 - Step 2a



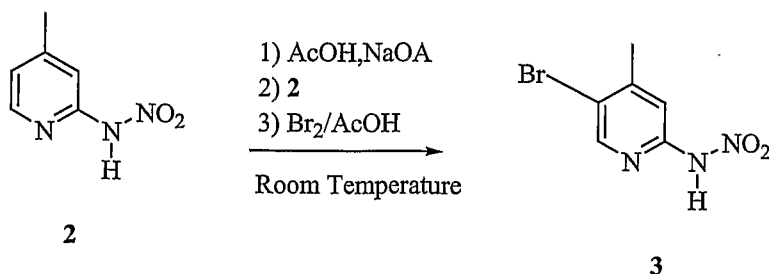
[0017] To a 50 mL single neck round bottom flask was charged 23 mL of acetic acid and 3.66g(8eq.) of anhydrous sodium acetate. The resulting mixture was heated to 40°C until complete dissolution of sodium acetate was achieved.

[0018] One gram of the compound of formula 2 was added at 40°C and the reaction was allowed to come to room temperature. A molecular bromine solution 1.005g (0.34mL/13mL acetic acid) was slowly added over a period of 30 minutes with an addition funnel and heated to 50°C for three hours.

[0019] The slurry containing the product was aged for 30 minutes at room temperature. The product was filtered in vacuo, washed with 5mL cold water, 2mL dichloromethane and dried under reduced pressure (8in Hg, 55°C) for one hour. The desired mono bromo derivative of formula 3 was obtained in 70% isolated yield (1.045g).

[0020] Analytical data: $^1\text{H-NMR}$ ($\text{CD}_3\text{OD}/\text{CDCl}_3$) (δ , ppm): 2.39 (s, 3H, -CH₃), 7.63 (s, 1H, Ar-H), 8.22 (s, 1H, Ar-H); $^{13}\text{C-NMR}$ (DMF-D_7) (δ , ppm): 19.46, 116.05, 116.44, 147.22, 147.80, 159.81; HRMS calcd for $\text{C}_6\text{H}_6\text{BrN}_3\text{O}_2$ 230.96434 found 231.97217.

EXAMPLE 3 - Step 2b



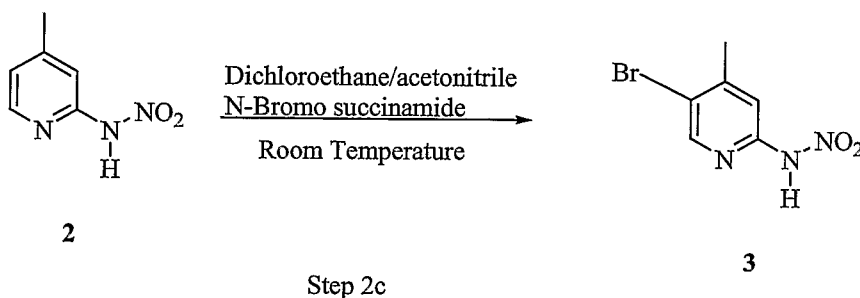
Step 2b

[0021] To a 250 mL single neck round bottom flask was charged 70mL of acetic acid and 8.23g (6eq.) of anhydrous sodium acetate. The resulting mixture was stirred at 40°C until complete dissolution of sodium acetate was achieved.

[0022] Three grams of the compound of formula 2 was added at 40°C under high stirring. This slurry was allowed to come to room temperature (15 minutes). A molecular bromine solution, 31.14g in 40mL acetic acid, was slowly added over a period of 30 minutes with an addition funnel and the mixture allowed to stir at room temperature for 24 hours.

[0023] The slurry containing the product was aged for an additional 6 hours at room temperature. The product was filtered in vacuo, washed with 5mL cold water, 2mL dichloromethane and dried under reduced pressure (8in Hg, 55°C) for one hour. The desired crude mono bromo derivative of formula 3 was obtained in 83% isolated yield (3.75g). See step 2a for analytical data.

EXAMPLE 4 - Step 2c

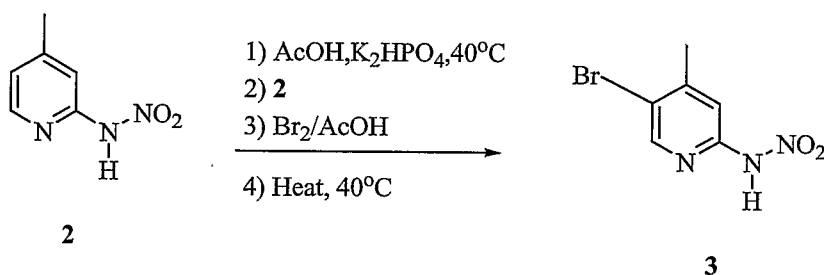


Step 2c

[0024] To a 250 mL single neck round bottom flask was charged 70mL of 1,2-dichloroethane and 20mL of acetonitrile. Then, 3.488g of N-Bromo Succinamide (NBS) (1eq.) was added at one time to this mixture and allowed to stir in the dark. Upon complete dissolution of the NBS, 3g of the compound of formula 2 was added at one time. This white slurry was allowed to stir at room temperature for a period of 15 hours.

[0025] After 15 hours, the brown slurry was filtered in vacuo, washed with 3mL dichloromethane and dried under reduced pressure (5in Hg, 50°C) to yield 2.99g of the crude product. See step 2a for analytical data.

EXAMPLE 5 - Step 2d



Step 2d

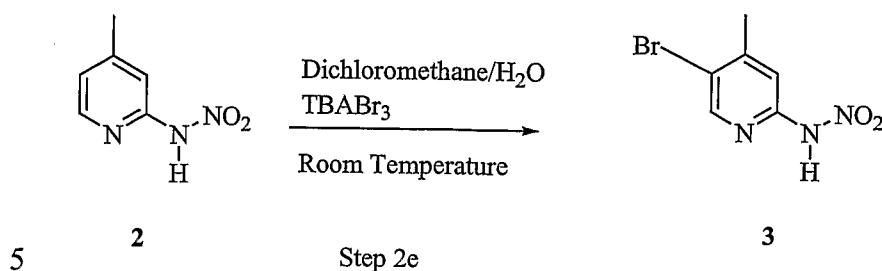
[0026] To a 50 mL single neck round bottom flask was charged 65mL of acetic acid and 4.5g (1eq.) of potassium hydrogen phosphate di basic (K_2HPO_4). The resulting mixture was heated to 40°C until complete dissolution of the potassium hydrogen phosphate di basic was achieved.

[0027] Then, 3g of the compound of formula 2 was added at 40°C and the reaction was allowed to come to room temperature. A molecular bromine solution, 3.137g (5.025mL/40mL acetic acid) was slowly added over a period of 30 minutes with an addition funnel at room temperature and heated to 40°C for 12 hours.

[0028] The slurry containing the product was aged for 30 min at room temperature. The product was filtered in vacuo, washed with 5mL cold water, 2mL dichloromethane and dried under reduced pressure (8in Hg, 55°C) for 3 hours to yield

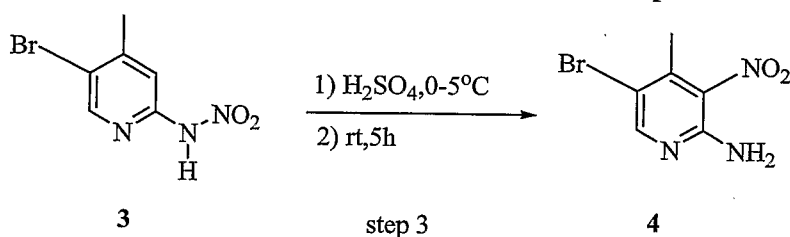
the desired mono bromo derivative of formula 3 in 65% isolated yield (corrected for purity, 2.867g). See step 2a for analytical data.

EXAMPLE 6 - Step 2e



[0029] To a 50 mL single neck round bottom flask was charged 30mL of dichloromethane and 3.15g (1.3eq.) of tetrabutylammoniumtribromide. Then, 1g of the compound of formula 2 was added at one time under stirring. After 10 minutes, 20mL of water was introduced under high stirring. The biphasic reaction mixture was allowed to stir for 48 hours, and aged for an additional one hour at room temperature. The desired mono bromo derivative was filtered, washed with 1 mL of dichloromethane and dried in vacuo (5in Hg, 50°C, 2hours) to yield 01.02g of the compound of formula 3 (65%, based on purity of the isolated solid). See step 2a for analytical data.

EXAMPLE 7 - Step 3



20 **[0030]** To a 50mL single neck flask equipped with a stirrer, an external cooling,
and an internal thermocouple probe, was added 10 mL of concentrated sulfuric acid.
The mixture was stirred between 0-5°C with an external ice bath. Then, 1 g of the
compound of formula 3 was added slowly to the solution. After one hour, the
reaction was allowed to come to room temperature and stirred for an additional 5
25 hours.

[0031] The reaction was quenched over 50g of wet ice and neutralized with 50%NaOH solution to pH 6.0 under constant stirring.

5 [0032] The desired compound of formula 4 was obtained as yellow slurry which was filtered and dried in vacuo (5in Hg, 50°C) for 3 hours. The product of formula 4 was recovered in 98% yield (0.98g).

[0033] Analytical data: m.p. 132 °C. IR (KBr, cm⁻¹): 1633, 1581, 1538, 1512, 1458, 1377, 1344, 1321, 1244, 869,779 . ¹H-NMR (CDCl₃) (δ, ppm): 2.55 (s, 3H),
10 5.85 (bs, 2H), 8.25 (s, 1H): ¹³C-NMR (CDCl₃) (δ, ppm): 20.81, 112.14, 144.49, 151.91, 153.78 (2C); HRMS: calcd for C₆H₆BrN₃O₂: 230.96434; found: (M+1): 231.97217.

EXAMPLE 8 - Step 3

15 [0034] The procedure in Example 7 was repeated using 72 mL of sulfuric acid which was maintained between 0-5°C. Then, 11.28g of the compound of formula 3 was added over a period of 20 minutes and stirred for an additional 20 minutes. The reaction mixture was allowed to come to room temperature and stirred for an additional one hour.

20

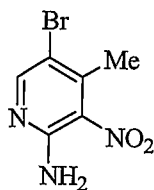
[0035] The reaction was quenched over 300 of wet ice and aged for 30 minutes. This cold solution was neutralized with 200 ml of 50% sodium hydroxide to pH 5.2. The resulting yellow slurry was filtered and dried in vacuo (5in Hg, 40°C, 10 hours) to yield 9.53g of the compound of formula 4 as a yellow solid in 93% recovery. See
25 Example 7 for analytical data.

[0036] While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of
30 the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

CLAIMS

What is claimed is:

1. A method of preparing a compound of formula 4:

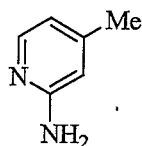


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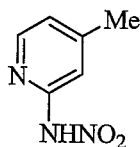
comprising the steps of:

- (a) converting a compound of formula 1:



1

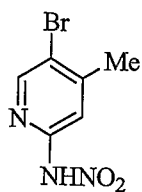
to a compound of formula 2:



2

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- (b) brominating said compound of formula 2 to provide a compound of formula 3:

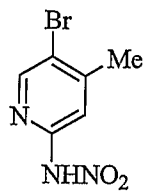


3 ; and

- (c) converting said compound of formula 3 to provide said compound of formula 4.

15

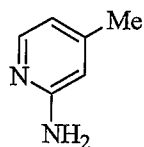
2. The method of claim 1, wherein said converting said compound of formula 1 to said compound of formula 2 is conducted by reaction with sulfuric acid followed by the introduction of nitric acid.
- 5 3. The method of claim 1, wherein said brominating said compound of formula 2 is conducted at room temperature.
4. The method of claim 1, wherein said brominating said compound of formula 2 is conducted with heating.
- 10 5. The method of claim 3, wherein said brominating further comprises steps of combining the compound of formula 2 with acetic acid and sodium acetate followed by introduction of bromine and acetic acid.
- 15 6. The method of claim 4, wherein said brominating further comprises steps of combining the compound of formula 2 with acetic acid and sodium acetate followed by introduction of bromine and acetic acid.
- 20 7. The method of claim 3, wherein said brominating is conducted in the presence of dichloroethane, acetonitrile and N-bromosuccinamide.
8. The method of claim 3, wherein said brominating further comprises steps of combining the compound of formula 2 with acetic acid and potassium hydrogen phosphate followed by introduction of bromine and acetic acid.
- 25 9. The method of claim 4, wherein said brominating is conducted in the presence of dichloromethane, water, and tetrabutylammoniumtribromide.
10. The method of claim 1, wherein said converting said compound of formula 3 to said compound of formula 4 is conducted in the presence of sulfuric acid.
- 30 11. A method of preparing a compound of formula 3:



3

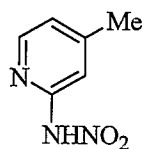
comprising the steps of:

(a) converting a compound of formula 1:



1

5 to a compound of formula 2:



2

(b) brominating said compound of formula 2 to provide a compound of formula 3.

10

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/030347

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/76

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)

C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 530 524 A1 (ICHIKAWA GOSEI KAGAKU KK [JP]) 10 March 1993 (1993-03-10) page 2, line 50 - page 5, line 51 page 10; examples 8,10 claim 1	1-11
Y	----- H. RITTER ET. AL.: "Synthesis and Reactions of Dinitrated Amino and Diaminopyridines" JOURNAL OF HETEROCYCLIC CHEMISTRY. DEC 1971, vol. 32, no. 2, March 1995 (1995-03), pages 585-590, XP002412572 ISSN: 0022-152X page 1 -----	1-11

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

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Date of the actual completion of the international search

21 December 2006

Date of mailing of the international search report

22/01/2007

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Authorized officer

Bissmire, Stewart

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/030347

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP 0530524	A1	10-03-1993	DE 69232916 D1	13-03-2003
			DE 69232916 T2	11-09-2003
			JP 5201981 A	10-08-1993
