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(54) **Title:** IMPROVED PREPARATION OF AZAINDOLE COMPOUNDS

(57) **Abstract:** An improved method for making azaindoles and related compounds is disclosed.

# IMPROVED PREPARATION OF AZAINDOLE COMPOUNDS

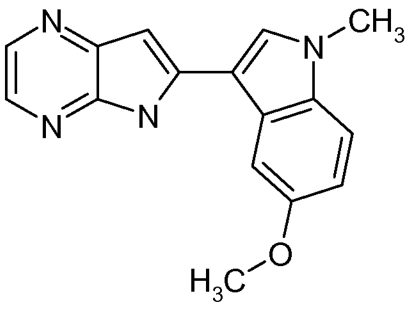
## FIELD OF THE INVENTION

This invention is directed to improved methods for preparing azaindole compounds and intermediates that are useful in the synthesis of the azaindole compounds.

## BACKGROUND OF THE INVENTION

A process for making certain azaindole compounds, or for making intermediates for preparing certain azaindole compounds, such as the compound of Formula I below, 6-(5-methoxy-1-methyl-1H-indol-3-yl)-5H-pyrrolo[2,3-b]pyrazine has been disclosed in United States Patent 6,770,643, issued August 3, 2004.

Formula I:



The compound of Formula I was prepared in the disclosure of that patent as follows. 6-(5-Methoxy-1-methyl-1H-indol-3-yl)-5H-pyrrolo[2,3-b]pyrazine was synthesized according to the following reactions. A stirred solution of diisopropylamine (59.9 mL) in tetrahydrofuran (1400 mL), at -15 degrees C. and under nitrogen, was treated with a solution of n-butyllithium in hexanes (131 mL, 1.6M) over 25 minutes, whilst maintaining the temperature below -10 degrees C. After stirring for 30 minutes the mixture was treated with methylpyrazine (26.8 g) over 15 minutes, then stirred for 1 hour and then treated with a solution of 5-methoxy-1-methyl-1H-indole-3-carbonitrile (53 g) in tetrahydrofuran (600 mL) over 1 hour, keeping the temperature below -10.degree. C. The reaction mixture was allowed to warm to room temperature over 2 hours, then stood overnight, then treated with water (100 mL). The tetrahydrofuran was removed in vacuo and the resultant mixture was partitioned between ethyl acetate (500 mL) and water (20 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organics were washed with water (500 mL) then evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of dichloromethane and methanol (19:1, v/v) to give the title compound (19.4 g) as a grey solid, m.p. 270-272.degree. C. MS: 279 (MH.sup.+).

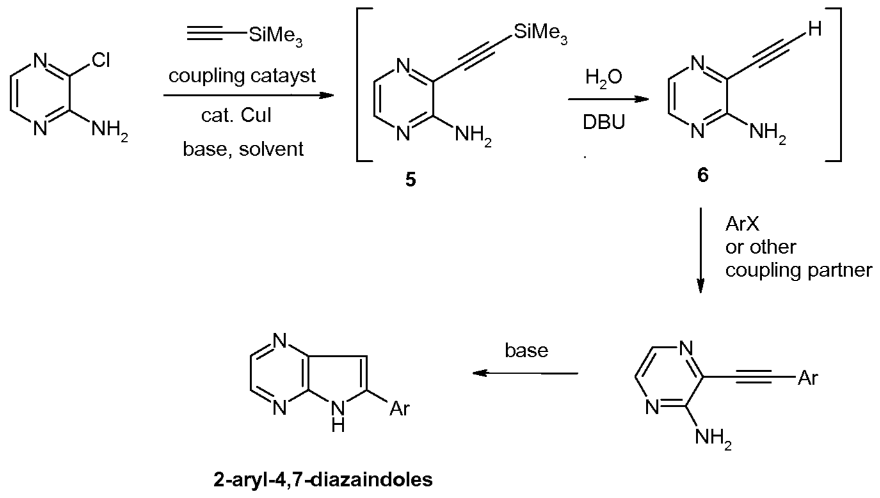
## SUMMARY OF THE INVENTION

The present invention is directed to an improved process for preparing a compound of Formula I or that is an intermediate useful in preparing a compound of Formula I.

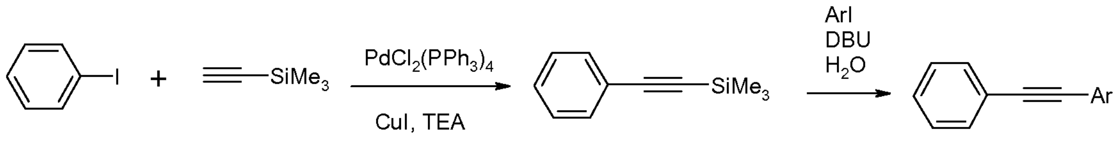
## DETAILED DESCRIPTION OF THE INVENTION

### ASPECT 1 OF THE INVENTION

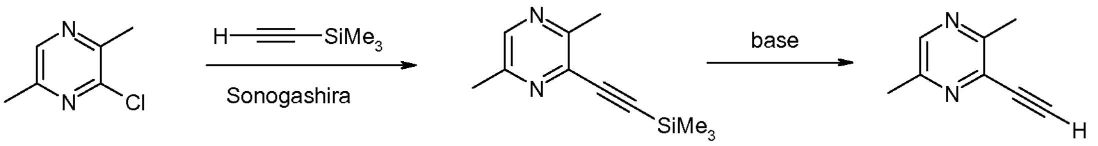
The improved process, according to a first aspect of the invention, comprises:



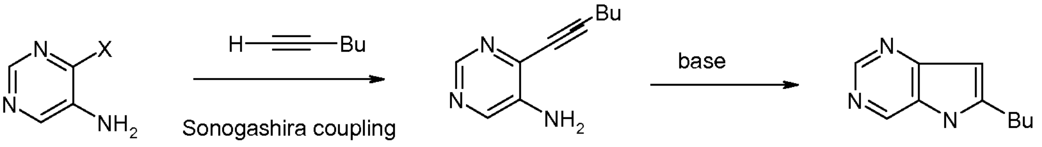
Sonogashira chemistry is well established in the literature to have application towards the preparation of bisarylethynes, which, when appropriately substituted, are important intermediates in the preparation of indoles. In addition, a recent paper describes the use of a one-pot, double Sonogashira protocol to prepare unsymmetrical alkynes. Grieco, P. A. et al. Org. Lett. 2002, 4(19), 3199-3232: described consecutive Sonogashira couplings in one-pot to prepare unsymmetrical bisarylethynes as follows:



Yamanaka, H. et al. Synthesis 1983, 312-314: showed that ethynylnitrogenheteroarenes can be readily prepared from the corresponding haloarenes and trimethylsilylacetylene:



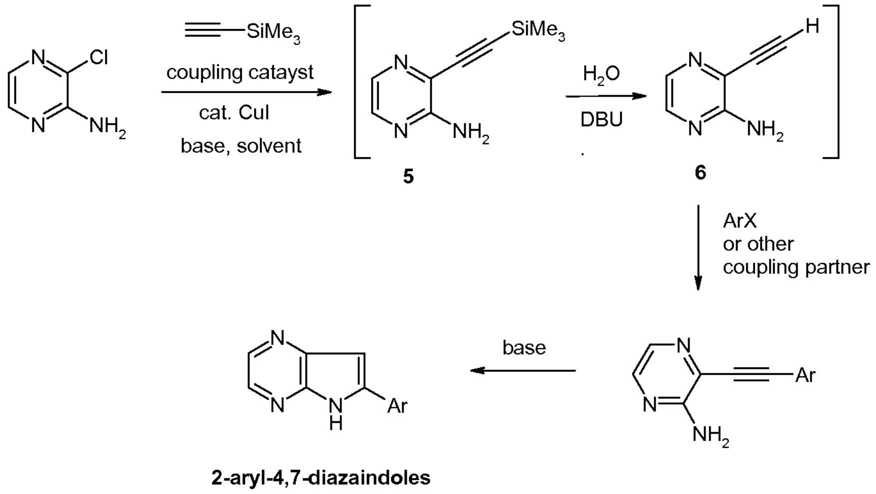
Knochel, P. et al. Angew. Chem. Int. Ed. 2000, 39 (14), 2488-2490: prepared 4,6-diazaindoles and 5,7-diazaindoles as follows:



These technologies were previously successfully adapted for the preparation of 2-(7-azaindol-2-yl)indoles. This is a further adaptation and novel utility of these technologies to prepare very generally 2-substituted-4,7-diazaindoles, generally (4,7-diazaindol-2-yl)indoles, and specifically a compound of Formula I as shown above.

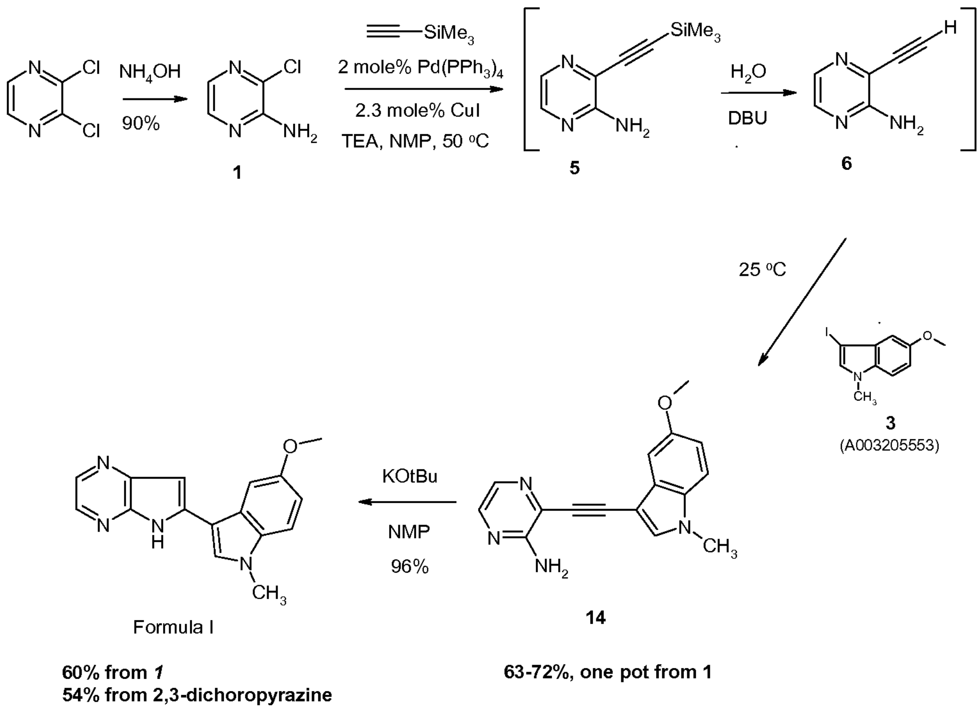
Performing the coupling sequences in one pot is advantageous because it avoids the need to isolate intermediate 6 indicated in the scheme above, which has been shown to be thermally unstable.

In a broad scope, this methodology can be used to prepare 2-substituted-4,7-diazaindoles where ArX represents aryl, heteroaryl and other suitable coupling partners as shown:

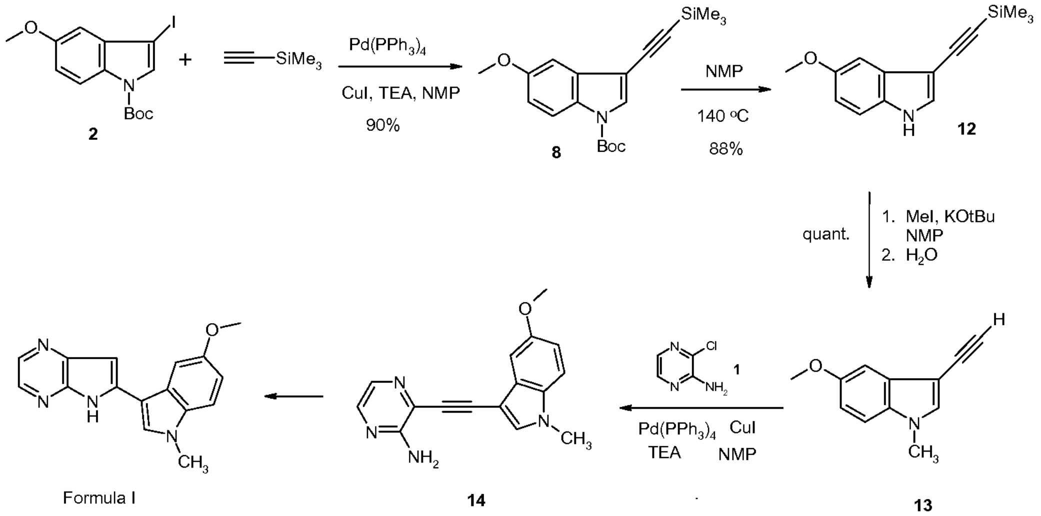


Reaction schemes useful for this aspect of the present invention are as follows.

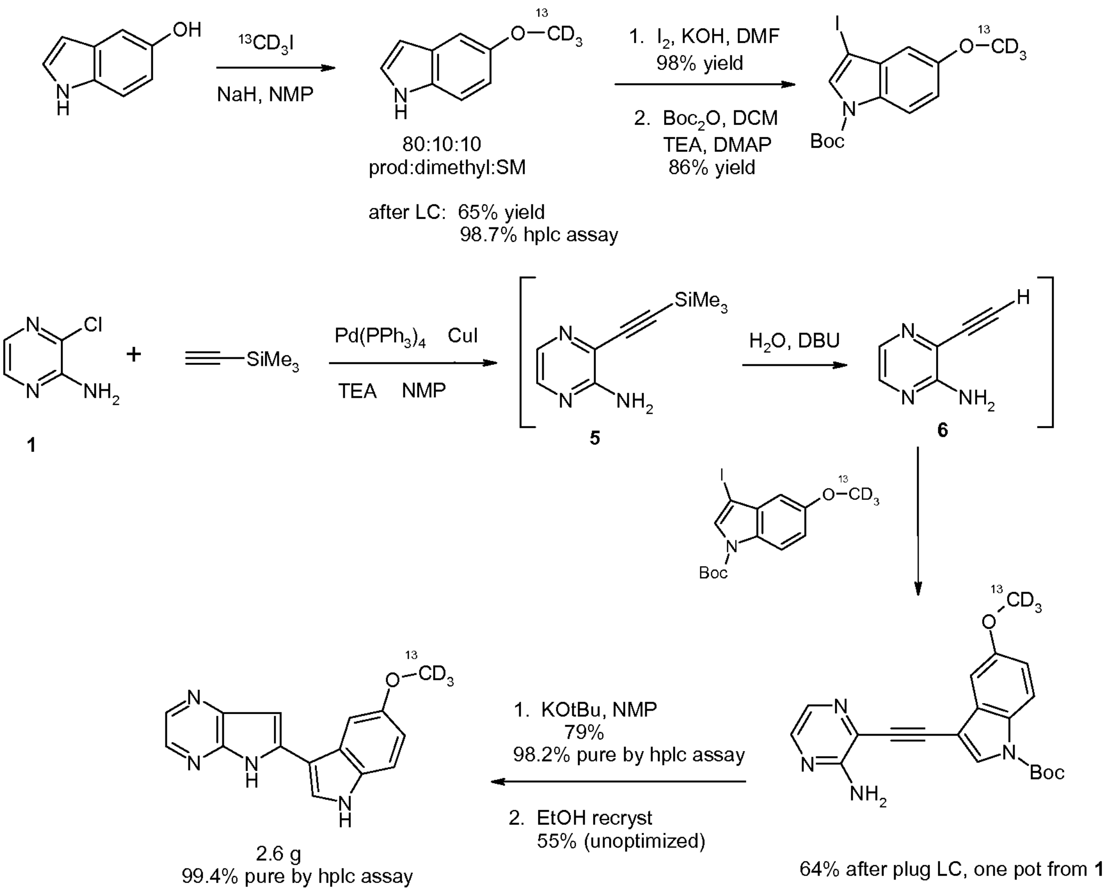
Scheme 1. Application to Preparation of a Compound of Formula I (preferred sequence)



Scheme 2. Application to Preparation of a Compound of Formula I (reversed sequence)



Scheme 3. Application to Preparation of an M+4 Metabolite of a Compound of Formula I

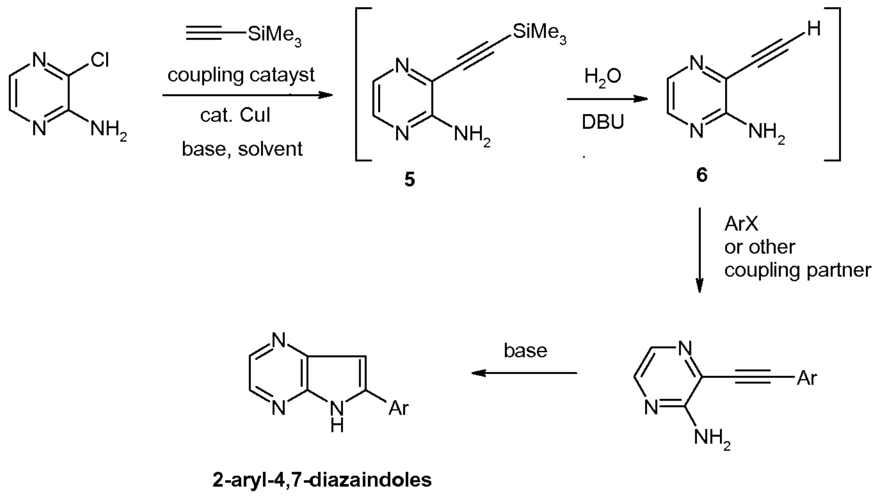


This technology represents a novel and facile way to prepare (generally) 2-substituted-4,7-diazaindoles with specific application to the preparation of the compound of Formula I and its metabolites.

Performing the coupling sequences in one pot is advantageous because it avoids the need to isolate intermediate 6 (Scheme 1), which has been shown to be thermally unstable.

In a broad scope, this methodology can be used to prepare 2-substituted-4,7-diazaindoles (Scheme 4) where ArX represents aryl, heteroaryl and other suitable coupling partners:

Scheme 4



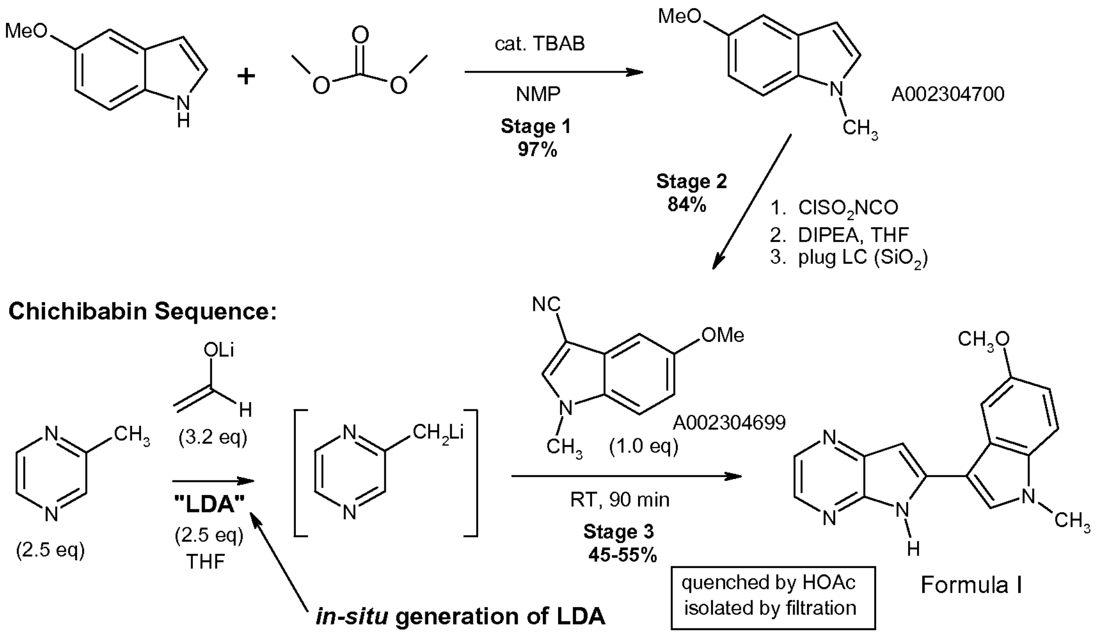
ASPECT 2 OF THE INVENTION

Intramolecular Chichibabin-type reactions are employed to prepare heterocycles such as pyrrolopyridine and pyrrolopyrazine, but generally proceed in low yield, especially for the synthesis of pyrrolopyrazines from 2-methylpyrazine (Wakefield, B. J., et al. Tetrahedron 1992, 48, 939; Meijer, L., et al, J. Med. Chem. 2003, 46, 222; see also: Leffler, M. Org. React., 1942, 1, 91; Kelly, T. R., et al. J. Org. Chem. 1997, 62, 2774).

We have adapted the literature procedure to synthesize samples of the compound of Formula I, a 2-substituted pyrrolopyrazine. During this effort, it was found that the yields of the Chichibabin step were on the order of 20-30% on a several-gram scale, but much lower and less reproducible (0-10%) on >10-g scale. The low yields were the result of several factors, including: 1) low reactivity of 2-methylpyrazine anion towards 5-methoxy-1-methyl-1H-indol-3-carbonitrile, 2) unfavorable Chichibabin cyclization of the imine anion, 3) competing deprotonation of 5-methoxy-1-methyl-1H-indol-3-carbonitrile at 2-position (leading to polymerize indol-nitrile).

An improved Chichibabin protocol towards the synthesis of the compound of Formula I, was by us developed by for the preparation of the compound of Formula I, and is shown in scheme below. This chemistry was used to prepare two lots (268 g and 790 g) of the compound of Formula I in three steps (40-45% overall) and with reproducible yields (50-60%) for the Chihibabin step (up to 600-g scale).

Scheme 5

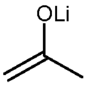
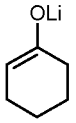
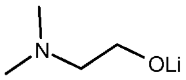
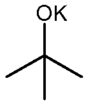


The improvements in the chemistry form the basis of this disclosure and are as follows:

Employment of additives:

Certain additives were found to promote the Chichibabin reaction. The best conditions employed acetoenolate (also known as lithium vinyloxide, LVO) as an in situ-generated additive (Jung, M. E. et al. Tetrahedron Lett. 1977, 18, 3791; Tidwell, T. T. et al. J. Org. Chem. 1990, 55, 3634). A summary of the role of LVO and a list of additives investigated are as follows:

Table 1

| **Additive** | **Scale (g)** | **yield** |
|---|---|---|
| | | |
| LVO (3.2 eq) | 600 | 57% |
| absence of LVO | 5 | 6% |
| | | |
| ***Amount of LVO*** | | |
| LVO (2.0 eq) | 5 | 47% |
| LVO (3.2 eq) | 5 | 61% |
| LVO (4.0 eq) | 5 | 57% |
| | | |
| ***Aging Time*** | | |
| LVO (3.2 eq, 2.5 day age) | 150 | 51% |
| LVO (3.2 eq, 19 h age) | 150 | 32% |
| | | |
| ***LVO<br>With/Without TMEDA*** | | |
| TMEDA (4.0 eq) | 5 | 59% |
| no TMEDA | 5 | 54% |
| | | |
| ***Other Additives*** | | |
|  (3.2 eq) | 5 | 39% |
|  (3.2 eq) | 5 | 42% |
|  (2.0 eq) | 5 | 8% |
|  (2.5 eq) | 5 | 7% |
| HMPA (2.5 eq) | 5 | 0% |

Temperature of addition (safe preparation of LVO)

Preparing LVO at elevated temperature (n-BuLi, by slow addition at 25 to 30 $^{0}$C) was found to be advantageous as both the exotherm and gas evolution (n-butane, ethylene) were thus addition-controlled. It was found that the methylpyrazine anion could be generated at temperatures up to –11 degrees C and with a prolonged addition (40 min to 120 min) without significantly affecting product yield or quality.

Stoichiometry

Maintaining an equivalent ratio of 1:1 of LDA to methylpyrazine: Excess LDA relative methylpyrazine leads to deprotonation at the 2-position of the nitrile and subsequent polymerization of the nitrile.

Equivalents of Anion

Increasing the equivalent amount of methylpyrazine anion from 1.0 to 2.5 equivalents improves the yield from about 30% to about 60%.

Volume Improvement

The volumes for the reaction (initially ~60/1, THF/nitrile) and the work-up (>30/1, acetone, MeOH/nitrile) were improved to ~20/1 and 2/1 (HOAc/nitrile), respectively, primarily by using 10 M n-BuLi rather than 2.5 M n-BuLi for both the LVO and pyrazine anion formation and by optimizing the work up.

Reaction Temperature

It was observed that the reaction could be conducted in high yield at room temperature (20 degrees C) (61%) than at higher or lower temperature (at 40 0C, 47%; at 0 $^0$C, 51%).

One-pot reaction

It was established that the process could be conducted as a one-pot procedure: LVO formation, addition of 2-methylpyrazine, addition of diisopropyl amine, addition of n-BuLi (i.e., *in situ* preparation of LDA), addition of nitrile as THF solution, addition of acetic acid, and addition of water, could be performed consecutively in the some pot.

Work up

The work up was simplified and consists of quenching with HOAc followed by: addition of $H_2O$ (1.3:1, $H_2O$/THF), filtration, then washing with THF/$H_2O$ (1.5:1), $H_2O$ and acetone. In experiments performed after the making of a 790 g sample of the compound of Formula I, the heptane addition was eliminated as it was found that it not only precipitated out additional compound of Formula I, it often precipitated out polymeric by-products, too. The improvement was offset somewhat by lower isolated yields (58% to 50%), but the new work-up gave a suspension that filtered more quickly (6 h to < 50 min) and afforded purer crude product (w/w% assay: 97%).

Recrystallization

A procedure to recrystallize the compound of Formula I from NMP/water that gives a complete solution (and provides opportunity for a polish filtration) and affords product in high recovery (>94%) and consistent quality (>98% w/w assay) was developed.

Isolation/Purification of A002304699 of Scheme 5

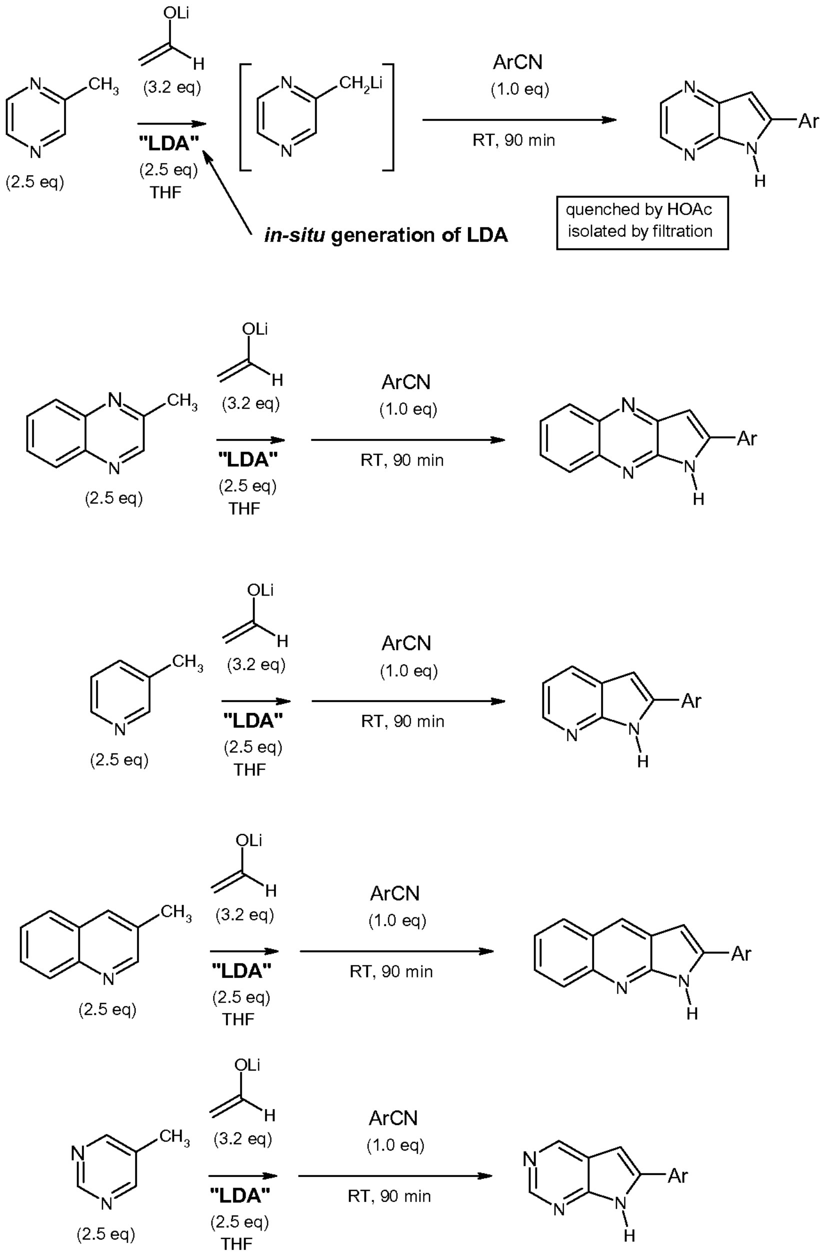
It was found that replacing TEA with DIPEA as base during the preparation of nitrile A002304699 from indole A002304700 simplified the work up and facilitated the isolation of the nitrile (TEAx$SO_3$ formed a neutral complex that was difficult to remove. The analogous DIPEAx$SO_3$¬ complex did not form).

This technology represents a novel, facile and reproducible way to prepare the compound of Formula I on large scales in high yields.

The Chichibabin reaction could be performed in one pot, which is advantageous for large-scale synthesis of the compound of Formula I.

In a broad scope, this methodology can be used to prepare various related heterocycles, including, substituted 2-indolyl-1H-pyrrolo[2,3-b]pyrazine, substituted 2-indolyl-1H-pyrrolo[2,3-b]quinoxaline, substituted 2-indolyl-1H-pyrrolo[2,3-b]pyridine, substituted 2-indolyl-1H-pyrrolo[2,3-b]quinoline, substituted 2-indolyl-1H-pyrrolo[2,3-b]pyrimidine, and substituted 2-Ar-1H-pyrrolo[2,3-b]pyrazine, substituted 2-Ar-1H-pyrrolo[2,3-b]quinoxaline, substituted 2-Ar-1H-pyrrolo[2,3-b]pyridine, substituted 2-Ar-1Hpyrrolo[2,3-b]quinoline, substituted 2-Ar-1H-pyrrolo[2,3-b]pyrimidine, where Ar represents aryl, heteroaryl and other suitable partners (see Scheme 5):

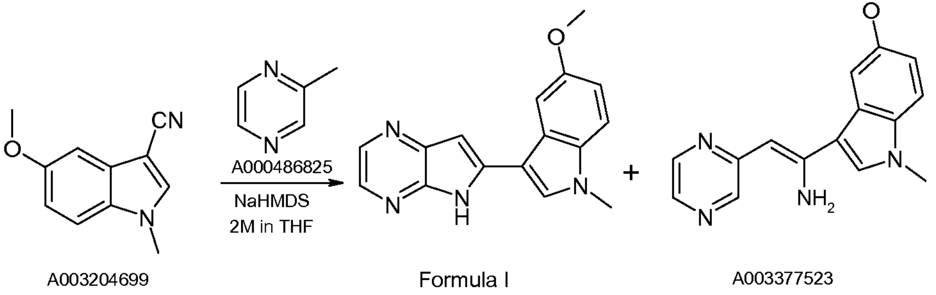
Scheme 5


OLi
H
(3.2 eq)
"LDA"
(2.5 eq)
THF
(2.5 eq)
N
CH3
CH2Li
ArCN
(1.0 eq)
RT, 90 min
Ar
H
*in-situ* generation of LDA
quenched by HOAc
isolated by filtration

ASPECT 3 OF THE INVENTION

Background: In earlier work, the conversion of A003204699 to the compound of Formula I had been accomplished by using BuLi/diisopropylamine (LDA generated in situ) as the base. This method was initially used and subsequently improved significantly by us to produce ~ 268 and 790 grams of the compound of Formula I. However, the method entailed the use of 10M BuLi. In perusing the literature, it was observed that the use of MHMDS bases to carry out this transformation was not reported. Specifically, the use of NaHMDS and KHMDS in this transformation had not considered been considered prior to this work.

Scheme 6



This work: The use of MHMDS bases offers a safer alternative to the use of BuLi bases which pose safe handling issues for scale-up. In addition, in this instance, the BuLi reactions tended to be capricious, with long cycle times (e.g. 5 days). By comparison, the procedure using NaHMDS as base was operationally much safer, simpler and the cycle time was one day. Hence, it offered several advantages for scale up work. In addition, at the time this procedure was being examined, the product produced using the BuLi based procedure was shown to have issues with polymeric impurities that were hard to remove. These impurities arise either from the polymerization of the two reactants or potentially from the polymerization of the acetaldehyde enolate. In addition because of the fine particle size of the product filtration of the batch would have been a problem in large scale synthesis.

In initial experiments, it was shown that LHMDS as base resulted in the formation of compound A003377523 (enamine) in good conversion (~ 89 A% by HPLC, see data below). However, it was not possible to convert the intermediate to the product without resort to additives. The influence of additives in this reaction is the subject of another aspect of this disclosure. Furthermore, even with additives, only partial conversion to the compound of Formula I was realized, offering only marginal improvement over the BuLi based process.

Conversion of A003204699 to A003377523 using LHMDS. 89 A% of A003377523 after workup:

Subsequently it was found possible that by using NaHMDS and KHMDS as bases to effect the formation of the compound of Formula I in up to 50 % conversion resulting in 35-40 % isolated yields using THF as solvent. It should be noted that these reactions do not need any additives and operationally are much easily adapted for scaleup. Based on additional considerations NaHMDS was chosen for further scaleup. Several Design of Experiments (DoE) studies were executed to optimize the conditions. These studies provided the following conditions as optimal for scaleup: 2.9 eq. of 2-Methylpyrazine, 3.6 eq. of NaHMDS, 50 °C.

Typical results from lab experiments are shown below.

Table 2

| Description | Result/Comments |
|---|---|
| Conversion of A003204699 to Formula I and A003377523 using NaHMDS. | 35 % yield of Formula I<br>Purity: 98.5 A%, Assay: 96.4 % |
| Conversion of A003204699 to Formula I and A003377523 using NaHMDS. | 39 % yield Formula I<br>Purity: 99.8 A%, Assay: 99.7 % |

| | |
|---|---|
| Conversion of A003204699 to Formula I and A003377523 using NaHMDS.<br>500 g scale | 37.4 % yield of Formula I<br>Purity: 99 A%, Assay: 94 % |
| Conversion of A003204699 to Formula I and A003377523 using KHMDS. | 20 % yield of Formula I<br>Purity: 98.4 A%, Assay: 89.5 % |

Solvent effect: Furthermore, it was found that using 1,4-dioxane or 1,3-dioxolane as solvents improved the yield by as much as 15 % in the lab. The observed solvent effect was quite unique to these two solvents among about 15 other solvents that were screened in this reaction. Some representative lab data is summarized in the table below.

Table 3

| Description | Result/Comments |
|---|---|
| Conversion of A003204699 to Formula I and A003377523<br>100 gram scale, 1,3-Dioxolane as solvent, NaHMDS in THF as base. | 53.6 % yield of Formula I.<br>Purity: 99.4 A %, Assay: 97.9 % |
| Conversion of A003204699 to Formula I and A003377523<br>100 g scale, 1,3-Dioxolane as solvent, NaHMDS in THF as base. | 46 % yield after reslurry.<br>Purity: 100 A%, Assay: 98.6 % |
| Conversion of A003204699 to Formula I and A003377523 | 40 % yield of Formula I<br>Purity: 100 A%, Assay: 99.6 % |

| | |
|---|---|
| 100 g scale, 1,3-Dioxolane as solvent, NaHMDS in THF as base. | |
| Conversion of A003204699 to Formula I and A003377523<br>50g scale, 1,4-Dioxane as solvent, solid NaHMDS as base.<br>Use test of KOEI methylpyrazine and RMI nitrile. | 57 % yield corrected of Formula I<br>Purity: 99.6 A%, Assay: 88.3 % |
| Conversion of A003204699 to Formula I and A003377523<br>50g scale, 1,4-Dioxane as solvent, NaHMDS in THF as base with distillation of THF prior to addition of methylpyrazine and nitrile. | 57 % yield corrected of Formula I<br>Purity: 97.5 A%, Assay: 95.0 % |

Representative procedure: In a 3L Pignat jacketed reactor, equipped with a pitched blade hastalloy impeller, thermocouple, nitrogen blanket and a reflux condenser, charged 5-methoxy-1-methyl-1H-indole-3-carbonitrile (100 grams, 0.54 moles, 1 eq.), 1,3-dioxolane (1000ml) and 2-methylpyrazine (146.34 grams, 1.55 moles, 2.9 eq.). The mixture was stirred and heated to 51 °C at which point 2M NaHMDS was added in one portion (966.7 ml, 1.9 moles, 3.6 eq.). The temperature of the reaction fell from 51 °C to 48 °C over the addition. The reaction was then held 51 °C for 1 hour and sampled for HPLC (IPM-1: 21.3 A% enamine, 57.2 A % compound of Formula I, 0.7A% nitrile) At this point the reaction was cooled to 20 °C and a solution of 103.4 g of ammonium chloride in 1L of water was added over 75 min. between 20 and 52 °C. The mixture was stirred at 50 °C for 15 min. then cooled to 15 °C. Agitation was turned down to 50 rpm and the aqueous layer was allowed to separate over 30 min. This aqueous layer was removed and the organic layer containing the solids was filtered. The filter cake was washed with 2 x 250 ml of 84/16 ethanol/water at 20 °C. The filter cake was then placed in the oven over night at 50 °C and 50 mbar vacuum to yield 75 g of the compound of Formula I as a yellow solid (99.5A%, 90.9wt% pure, 50% yield).

On the basis that 1,4-dioxane had more issues (flash point < 200 °C, listed as a carcinogen) 1,3-dioxolane was chosen for scaleup in the plant. Results from the plant run are shown in the table below.

Table 4

| Scale | Result/Comments |
|---|---|
| Conversion of A003204699 to Formula I and A003377523<br>11.0 kg scale | 47 % yield of Formula I<br>Assay: 98.5 % |
| Conversion of A003204699 to Formula I and A003377523<br>11 kg scale | 43.8 % yield of Formula I<br>Assay: 98.8 % |
| Conversion of A003204699 to Formula I and A003377523<br>9.0 kg scale | 39. 4% yield of Formula I<br>Assay: 97.1 % |

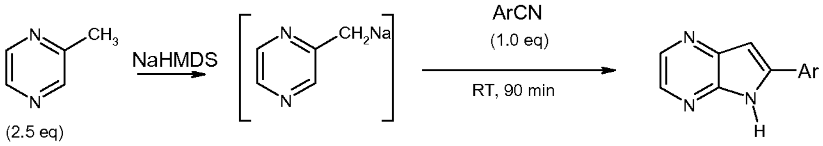
The initial lots of the compound of Formula I were prepared using a intramolecular Chichibabin type reaction using LDA (generated in situ from BuLi/diisopropyl amine) as base. For scaling up the synthesis of this compound it became necessary to use 10 M BuLi solution to carry out the reaction at a reasonable concentration. Some of the features of the reaction are still not well understood posing a scale-up risk. Further, scale-up in the pilot plant using 10 M BuLi posed serious handling issues as well.

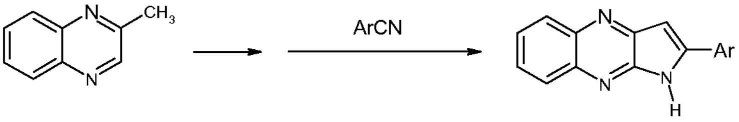
Use of the Sodiumhexamethyldisilazide was shown to have the desired features for scale up. Subsequently the reaction was scaled up to about an 11 kg scale.

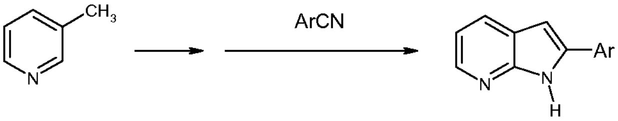
The synthesis disclosed here for this aspect of the invention offers several advantages over the art. These include use of a safer alternative to BuLi, lower cycle time, ease of purification of the final product, and increased product purity.

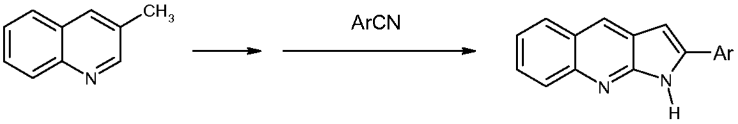
In a broad scope, this methodology can be used to prepare various related heterocycles, including, substituted 2-indolyl-1H-pyrrolo[2,3-b]pyrazine, substituted 2-indolyl-1H-pyrrolo[2,3-b]quinoxaline, substituted 2-indolyl-1H-pyrrolo[2,3-b]pyridine, substituted 2-indolyl-1H-pyrrolo[2,3-b]quinoline, substituted 2-indolyl-1H-pyrrolo[2,3-b]pyrimidine, and substituted 2-Ar-1H-pyrrolo[2,3-b]pyrazine, substituted 2-Ar-1H-pyrrolo[2,3-b]quinoxaline, substituted 2-Ar-1H-pyrrolo[2,3-b]pyridine, substituted 2-Ar-1H-pyrrolo[2,3-b]quinoline, substituted 2-Ar-1H-pyrrolo[2,3-b]pyrimidine, where Ar represents aryl, heteroaryl and other suitable partners (see Scheme 8 below). In addition, this methodology should be useful for the synthesis of enamines and ketones starting with 3-cyanoindoles (see Scheme 8 below).

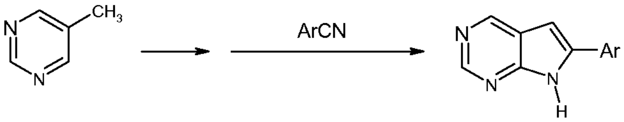
Scheme 8

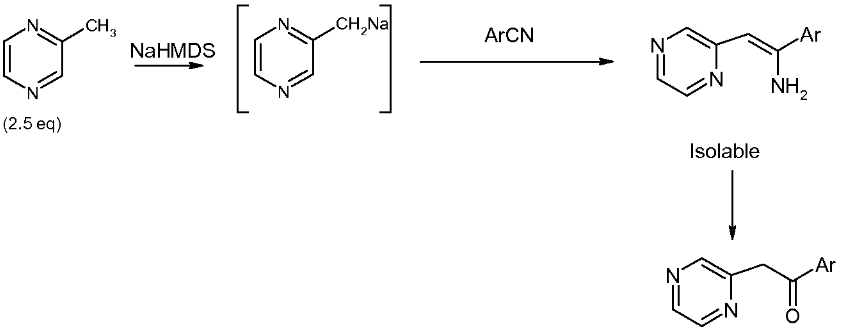

NaHMDS
(2.5 eq)
ArCN
(1.0 eq)
RT, 90 min


ArCN


ArCN


ArCN


ArCN

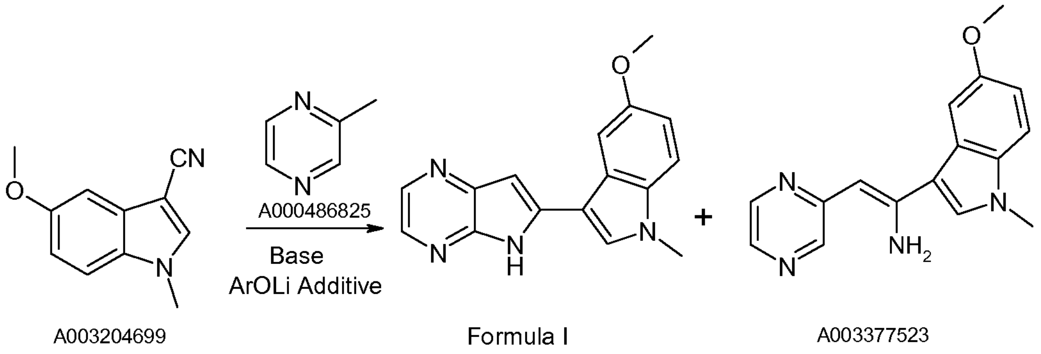

NaHMDS
(2.5 eq)
ArCN
Isolable

ASPECT 4 OF THE INVENTION

Following the unique discovery on the use of lithium vinyl oxide in the reaction of A003204699 and A00486825 under Chichibabin-type conditions, studies were undertaken to determine if other additives could be employed in this reaction. It was also found that LHMDS provided a cleaner (fewer side reactions) process, but provided an undesirable mixture of (9:91) of enamine A003377523 and the compound of Formula I. Thus, it was decided to screen additives to determine if this ratio could be impacted. After screening numerous additives, it was determined that the lithium phenoxide (LiOPh) system, having an "enolate" structure behaved in a similar manner to the enolates studied earlier.

The invention involves adding lithium phenoxides (simple and substituted) in the reaction of nitrile A003204699 with methylpiperazine (A000486825) to enhance the performance of the reaction by providing higher yields of the compound of Formula I. Side product (A003377523) of this reaction is generated in higher levels without these additives. Most of the work used LiOPh as the additive and LiHMDS as the base, but other bases and ArOLi additives were demonstrated to have a similar effect in scouting experiments.

Scheme 9



The reaction was conducted in three ways. Method A used commercially available LiOPh as a solution in the reaction, Method B (the second less favorable method) used n-BuLi and PhOH to generate the LiOPh and Method C generated LiOPh using LiOMe (only done in scouting experiments). Typical experimentals are provided below. Note that the ratio of desired product and enamine are up to 80:20 under these conditions whereas the ratio is typically 7:93 without the phenoxide additive. Tables with explanations are provided to summarize the different conditions including different bases and additives.

Method A: Experimental for the compound of Formula I preparation using commercial grade 1M Lithium phenoxide. A 500 mL round-bottom flask was charged with 150 mL (150 mmol, 5.6 eq.) of 1M Lithium phenoxide in THF and concentrated on the rotary evaporator. The resultant light brown residue was taken up in 90 mL (90 mmol, 3.3 eq.) of 1M LHMDS in THF at room temperature with a nitrogen cover. The contents were transferred to a 500 mL 3-neck round-bottom flask equipped with mechanical stirrer, condenser, temperature probe, and nitrogen inlet. At room temperature, the flask was charged with 3.4 g (36 mmol, 1.3 eq.) of Methylpyrazine in one portion. The dark red mixture was stirred at room temperature under nitrogen for 15 min. Charged 5.0 g (26.9 mmol, 1.0 eq.) of the nitrile as a solid in one portion. The dark solution was warmed to 40 °C. After 5 hours at 40 °C the hplc showed 25 A% enamine, 59 A% the compound of Formula I, and 16 A% nitrile with a Formula I: enamine ratio of 68:32. The reaction was stirred at room temperature over the weekend to provide 30 A% enamine, 64 A% compound of Formula I, and 6 A% nitrile with 68:32 Formula I: enamine ratio. The reaction was treated with 7.1 g (118 mmol, 4.4 eq.) of glacial acetic acid keeping the reaction temperature less than 25 °C. Added 90 mL of water and stirred at room temperature for 2.5 hours. Filtered solids then washed cake twice with 25 mL of 1:1 THF/water followed by 25 mL of water. The cake was dried in a vacuum oven at 60 °C and 20 in Hg overnight to afford 3.23 g of a yellow solid of 91.6 A% purity and 92.9 w/w %, 40% yield corrected for assay.

Method B: Experimental for compound of Formula I preparation where Lithium phenoxide was generated using 10M n-BuLi. A 1 L jacketed reactor equipped with mechanical stirrer, condenser, thermocouple, and nitrogen bleed was charged with 30.3 g (322 mmol, 6 eq.) of Phenol and 100 mL of anhydrous THF. With the chiller set at –20 °C and the batch temperature of –17 °C, 32 mL (322 mmol, 6 eq.) of 10 M n-Butyllithium at a rate to keep the reaction temperature less than 5 °C. The total addition time was 40 min. The resultant yellow solution was warmed to 0 °C and held for 15 min. At 5 °C, 207 mL (269 mmol, 5 eq.) of 1.3 M LHMDS in THF was added over 20 min. At 1 °C, 12.6 g (134 mmol, 2.5 eq.) of methylpyrazine was added in one portion. The dark red reaction mixture was stirred at 0 °C for 15min. then 10 g (53.7 mmol, 1 eq.) of the nitrile was added as a solid in one portion. Warmed the reaction mixture to 40 °C. After 2.5 hours, hplc showed 21 A% enamine, 75 A% compound of Formula I, and 4.3 A% nitrile with Formula I: enamine ratio of 78:22. Cooled the mixture to 5 °C then added a solution of 150 mL ethanol and 16.9 mL (17.8 g, 296 mmol, 5.5 eq.) of acetic acid to the reaction keeping the temperature less than 25 °C. At 20 °C added 50 mL of water in one portion then stirred the mixture at room temperature overnight. Removed 330 mL of solvent by distillation with a jacket temperature of 85 °C, reaction temperature at 70 °C, and head temperature at 65 °C. Cooled the mixture to room temperature then added 30 mL of 2.5 N NaOH to adjust pH to 12 from 8-9. The mixture was cooled to 0 °C and held for 2 hours. The solids were filtered while cold over buchner funnel with 7 cm Whatman paper. The cake was washed twice with 50 mL of 3:1 ethanol: water followed by 50 mL of water to give 23.35 g of a wet yellow solid. The hplc of the cake showed phenol content so the cake was taken up in 100 mL of 1:1 2.5 N NaOH: water. The suspension was warmed to 40 °C, held for 20 min. then cooled to room temperature and filtered over buchner with 5.5 cm Whatman paper. The cake was washed twice with 50 mL of water then dried in the vacuum oven at 60 °C and 20 in Hg to afford 5.29 g of a yellow solid of 99.9 A% purity and 99.4 w/w%, 35% yield corrected for assay.

Method C: Procedure for the Preparation of compound of Formula I where Lithium Phenoxide was Prepared from Phenol and Lithium Methoxide. A 50 mL round-bottom flask with stir bar and nitrogen blanket was charged with 5.7 g (15.1 mmol, 5.6 eq.) of 10% Lithium methoxide in methanol. At room temperature the solution was treated with 1.9 g (20.5 mmol, 7.6 eq.) of Phenol and stirred for 1 hour. The solution was concentrated on the rotary evaporator, then the white residue was taken up in 10 mL of anhydrous THF and concentrated again to further dry the sample. The resultant white solid was treated at room temperature with 7.1 mL (9.2 mmol, 3.4 eq.) of 1.3 M LHMDS in one portion followed by 0.36 g (3.8 mmol, 1.4 eq.) of methylpyrazine, also added in one portion. The red solution was stirred at room temperature for 15 min., and then 0.5 g (2.7 mmol, 1.0 eq.) of the nitrile was added as a solid in one portion. The reaction was warmed to 40 °C and held for 3 hours to give 23 A% compound of Formula I, 16 A% enamine, and 61 A% nitrile with Formula I: enamine ratio of 60:40. The reaction was held at room temperature overnight to give 24 A%

compound of Formula I, 9 A% enamine, and 67 A% nitrile with Formula I: enamine ratio of 73:27.

Table 9 shows the effect of increasing the amount of LiOPh to the reatio of enamine and 0950, starting with no LiOPh (9:91) and increasing the amounts (Entries 3-6) from 1 to 5 eq. An effect is observed at 1 eq, but it seems to reach a maximum after 5 eq. Further studies were conducted with 3, 6 and 12 eq: 3 eq. LiOPh (56-73:44-27); 6 eq. LiOPh (32-33:68-67); 12 eq LiOPh (27-30:70-73). Thus, it appears that the amount of LiOPh needs to be preferably greater than 3 eq (equivalents), but not as much as 12 eq. The use of lithium vinyl oxide (Entry 2) and its impact to increase the ratio is also noteworthy.

Table 9

| Entry | Conditions | Relative % nitrile remaining | Ratio of Enamine:095 |
|---|---|---|---|
| 1 | LHMDS, THF, 65 °C | <1%) | 9:91 |
| 2 | 2.5 eq. LHMDS, 3 eq. LVO, RT – 67 °C | < 1 A% nitrile (at both wavelengths) | 53:47 |
| 3 | 1eq LiOPh, 6eq LHMDS, 1 h | 55A% nitrile | 43:57 |
| 4 | 2eq LiOPh, 6eq LHMDS, 1 h | 53A% nitrile | 40:60 |
| 5 | 3eq LiOPh, 6eq LHMDS, 1 h | 51A% nitrile | 39:61 |
| 6 | 5eq LiOPh, 6eq LHMDS, 1 h | 57A% nitrile | 27:73 |
| 7 | 3eq LiOPh, 2.6eq LHMDS | 83A% nitrile | 73:27 |
| 8 | 3eq LiOPh, 7.6eq LHMDS | 28A% nitrile | 56:44 |
| 9 | 3eq LiOPh, 12.6 eq LHMDS | 8A% nitrile | 61:39 |
| 10 | 6 eq. LiOPh (conc), 5 eq. LHMDS | 1.5A% nitrile | 33:67 |
| 11 | 6 eq. LiOPh (conc), 5 eq. LHMDS, 1.5 eq. pyrazine | 3A% nitrile | 32:68 |
| 12 | 12 eq. LiOPh (conc), 2.5 eq. LHMDS | 19A% nitrile | 30:70 |
| 13 | 12 eq. LiOPh (conc), 5 eq. LHMDS | 5A% nitrile | 27:73 |

| | | | |
|---|---|---|---|
| 14 | 5g run, 5.6 eq. LiOPh (conc), 3.3 eq. LHMDS, 40°C, water w-up | 5 h 40°C 16A% nitrile<br>rt 6A% nitrile<br>slow filt'n, 43% crude yield, w/w = 92.9%, 91.6A%. | 5 h 40°C 30:7<br>rt on 32:68 |

Table 9 shows that LiOMe can be used to generate the LiPh with excess PhOH providing the highest ratio of (27:73).

Table 9

| Entry | Conditions | Relative % nitrile remaining | Ratio of Enamine:0950 |
|---|---|---|---|
| 15 | 5g run, 5.6 eq. LiOPh (syn from phenol/LiOMe), 3.3 eq. LHMDS, 40°C | 4 h 40°C 29A% nitrile<br>rt on 6A% nitrile<br>25% yield. | 4 h 40°C 49:51<br>rt on 53:47 |
| 16 | Repeat of B212i-85 to confirm result at 1g scale | 4 h 40°C 13A% nitrile<br>rt on 3A% nitrile | 4 h 40°C 43:57<br>rt on 46:54 |
| 17 | LiOPh (LiOMe syn w/xs phenol) | 67A% nitrile | 27:73 |
| 18 | LiOPh (LiOMe syn w/xs LiOMe) | 8A% nitrile | 52:48 |
| 19 | 5g run, 5.6 eq. LiOPh (syn from phenol/LiOMe), 3.3 eq. LHMDS, 40°C | 4 h 40°C 29A% nitrile<br>rt on 6A% nitrile<br>25% yield. | 4 h 40°C 49:51<br>rt on 53:47 |

Table 10 shows that different substituted phenols can be used in this process, but do not add much of an advantage. Note that generating the LiOPh using excess LHMDS was less favorable.

Table 10

| Entry | Conditions | Relative % nitrile remaining | Ratio of Enamine:0950 |
|---|---|---|---|
| 20 | 3eq phenol, LHMDS | | 71:28 |
| 21 | Phenol, BuLi | 22A% nitrile | 16:84 |
| 22 | 3eq p-Cl-phenol, LHMDS | 5A% nitrile | 77:23 |
| 23 | p-chlorophenol, BuLi | 3A% nitrile | 25:75 |
| 24 | 3eq p-MeO-phenol, LHMDS | 7A% nitrile | 72:28 |
| 25 | p-methoxyphenol, BuLi | Lots of impurities | |
| 26 | 3eq 2-MeO-4-me-phenol, LHMDS | 21A% nitrile | 75:25 |
| 27 | 2-methoxy-4-methylphenol, BuLi | 2A% nitrile | 46:54 |
| 28 | 3eq 4-Fl-phenol, LHMDS | 6A% nitrile | 76:24 |
| 29 | 4-Fluorophenol, BuLi | 2A% nitrile | 33:67 |
| 30 | 3eq Guaiacol, LHMDS | 95A% nitrile | 77:23 |
| 31 | Guaiacol, BuLi | 26:63:11 | 30:70 |

Table 11 shows that different bases can also be used, although the impact is not as great. Note that Lithium vinyl oxide also works with Li(bzl)TMS amide.

Table 11

| Entry | Conditions | Relative % nitrile remaining | Ratio of Enamine:0950 |
|---|---|---|---|
| 27 | 3 eq. Li vinyl ether, 4 eq. Li(bzl)TMS amide | 80A% nitrile | 20:80 |
| 28 | 4 eq. Li(bzl)TMS amide | 90A% nitrile | 50:50 |
| 29 | 3 eq. LiOPh, 4 eq. Li(bzl)TMS amide | 90A% nitrile | 25:75 |

Table 12 shows the impact of phenoxide when LDA was the base. Note that in this case, the conversion is more important than yield as mostly impurities and remaining starting material are observerd without LiOPh. Other phenoxides (used by generating in situ with excess LDA) were also demonstrated to be viable additives.

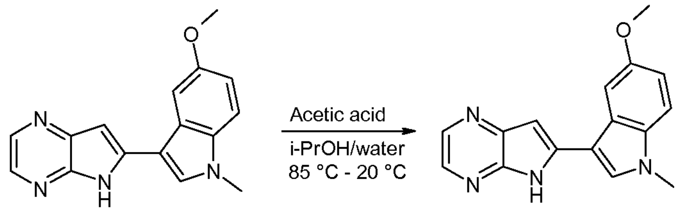
Table 12

| Entry | Conditions | Relative % nitrile remaining | Ratio of Enamine:0950 (tot A% of both) |
|---|---|---|---|
| 30 | 5.0eq LDA/pyrazine, 0eq LiOPh, -10C | 63A% nitrile | 29:71 (10%) |
| 31 | 2.5eq LDA/pyrazine, 1eq LiOPh, -10C | 51A% nitrile | 5:95 (48%) |
| 32 | 5.0eq LDA/pyrazine, 1eq LiOPh, -10C | 7A% nitrile | 4:96 (63%) |
| 33 | 10eq LDA/pyrazine, 1eq LiOPh, -10C | 8A% nitrile | 3:97 (65%) |
| 34 | 2.6eq LiOPh, 1.3 eq LDA, -20C | 9A% nitrile | <2:>98 (33%) |
| 35 | 12.6eq LiOPh, 1.3eq LDA, -20C | 39A% nitrile | 2:98 (49%) |
| 36 | 4eq pyrazine, 3eq LiOPh, 2.5eq LDA, 10C | 58A% nitrile | 8:92 (31%) |
| 37 | 5.5eq pyrazine, 3eq LiOPh, 4eq LDA, 10C | 33A% nitrile | 6:94 (39%) |
| 38 | 7eq pyrazine, 3eq LiOPh, 5.5eq LDA, 10C | 14A% nitrile | 5:95 (61%) |

| | | | |
|---|---|---|---|
| 39 | 3eq LiOPh, 3eq LDA | 39A% nitrile | 8:92 (41%) |
| 40 | 3eq p-Cl-phenol, LDA- overnight | 4.5A% nitrile | 10:90 (46%) |
| 41 | 3eq p-MeO-phenol, LDA- overnight | 4A% nitrile | 5:95 (45%) |
| 42 | 3eq 2-MeO-4-me-phenol, LDA- overnight | 12A% nitrile | 7:93 (58%) |
| 43 | 3eq Guaiacol, LDA- overnight | 31A% nitrile | 7:93 (43%) |
| 44 | 3eq 4-Fl-phenol, LDA - overnight | 6A% nitrile | 8:92 (57%) |
| 45 | 3eq phenol, LDA – 1h | 69A% nitrile | 7:93 (20%) |

This invention demonstrates the importance of additives in the Chichibabin reaction. This use of additives provides better yields of the desired product. These types of additives are unknown in the literature.

## ASPECT 5 OF THE INVENTION



Formula I Formula I

In a further aspect of the present invention, the compound of Formula I may be crystallized favorably by the procedure disclosed here.

Procedure:

The compound of Formula I (130 g, 0.467mole) was suspended in acetic acid (715 mL) in a jacketed reactor. The batch was stirred and heated to 85 °C until the solids had dissolved. The batch was then filtered while hot. The batch was returned to a jacketed reactor and reheated to 85 °C. A solution of 1:1 isopropanol (IPA):Water (1560 mL) was prepared and ca 22 wt% (328 mL) of this solution was added over 20-30 minutes. The batch was held at 85 °C, and was seeded with 0.3-wt% (0.4 g) of crystals of the compound of Formula I. After seeding, the batch was held at 85 °C for 30 - 45 minutes. The remainder of the IPA:Water mixture was then added over ca 2 hours and held for an additional 15 minutes. The batch was then cooled to 5 °C over 3 hours. After filtration, the batch was washed with 1:1IPA:water (2 x 250 mL). The solid was isolated and dried under vacuum at 80 °C to yield the compound of Formula I (112.7g, 87%).

This process has been used to recrystallize kilogram quantities of this compound. To date, the largest scale the process has been performed is 9.6 kg. The process has repeatedly produced material of high chemical purity and consistent physical quality.

This invention describes the process by which the compound of Formula I is recrystallized from an acetic acid, isopropyl alcohol and water mixture to afford crystalline compound. These solvents are ICH class 3 solvents (i.e. have no toxicological concerns and are preferred for the final active pharmaceutical ingredient). The previous crystallization process utilized N-methylpyrrolidinone (NMP), which is an ICH class 2 solvent. The crystalline form of the material produced consists of plates and rods. Previously, the existing process produced long needles. The material produced by the new process has better filtration characteristics, better flow characteristics and is more suitable for subsequent micronization. The identification of acetic acid was not obvious. The subject compound has very limited solubility in most other organic solvents but was found to have surprisingly good solubility in warm acetic acid.

This process is run using acetic acid. It is conceivable that acids of comparable pKa's could be used as substitutes although acetic acid is preferred from residual toxicity standpoint. Acids of higher strength are not suitable in that they provide acid salts of the subject compound and not the free base – the ability of acetic acid to act as a good recrystallization solvent to produce freebase of the subject compound rather than a salt derivative is another inventive (unexpected) aspect. Water:IPA is used as the antisolvent for this process. It is conceivable that other protic solvent could be used with similar results. It is expected that the crystallization could occur at different concentrations, temperatures or weight percentages of seeds.

## List of Abbreviations

As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

| | |
|---|---|
| ACN | acetonitrile |
| AIBN | 2,2'-azobisisobutyronitrile |
| BOC or Boc | tert-butyl carbamate |
| BOP | benzotriazol-1-yl-oxytris (dimethylamino) phosphonium |
| BuLi | n-Butyllithium |
| n-$Bu_3SnH$ | tri-n-butyltin hydride |
| t-Bu | tert-butyl |
| Cbz | benzyl carbamate |
| PTC | phase transfer catalyst |
| DAST | (diethylamino) sulfur trifluoride ($Et_2NSF_3$) |
| DCC | dicyclohexylcarbodiimide |
| DCM | dichloromethane ($CH_2CI_2$) |
| DIC | 1,3-diisopropylcarbodiimide |
| DIPEA | diisopropylethylamine |
| DMAP | 4-(N,N-dimethylamino)pyridine |
| DMP reagent | Dess-Martin Periodinane reagent |
| DMF | dimethylformamide |
| DMSO | dimethylsulfoxide |
| EA | elemental analysis |
| EDCI | 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide HCl |
| eq | equivalent(s) |
| Et | ethyl |

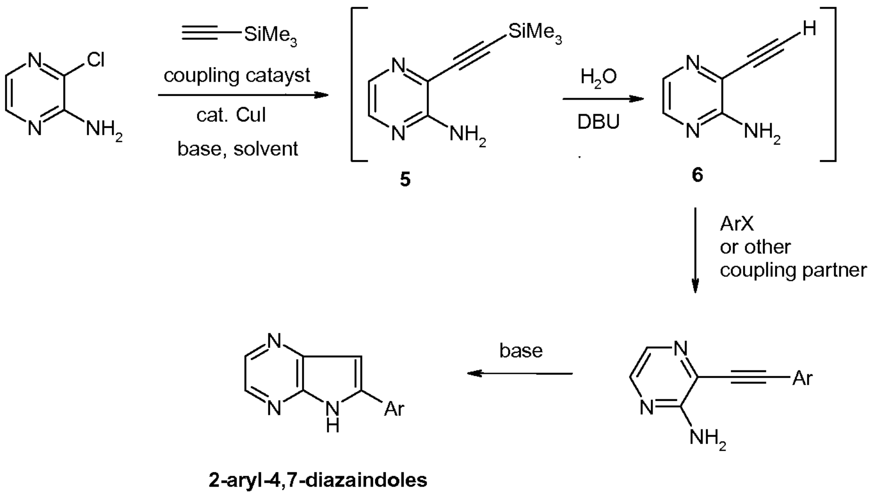
| | |
|---|---|
| $Et_2O$ | diethyl ether |
| EtOH | ethanol |
| EtOAc | ethyl acetate |
| FMOC | 9-fluorenylmethoxycarbonyl |
| HOAt | 1-hydroxy-7-azabensotriazole |
| HOBT | 1-hydroxybenztriazole |
| HOSu | N-hydroxysuccinamide |
| HPLC | high performance liquid chromatography |
| IPA | isopropanol |
| KHMDS | potassium hexamethyldisilazane |
| LAH | lithium aluminum anhydride |
| LDA | lithium diisoproploylamine |
| LHMDS | lithium hexamethyldisilazane |
| LiOPh | lithiumphenoxide |
| LVO | lithium vinyl oxide |
| Me | methyl |
| MeI | methyliodide |
| MeOH | methanol |
| MeOC(O) | methyl chloroformate |
| MHMDS | methyl hexamethyldisilazane |
| MOMCI | methoxymethylchloride |
| MOM | methoxymethyl |
| MS | mass spectroscopy |
| $NaBH_4$ | sodium borohydride |
| $Na_2C_4H_4O_6$ | sodium tartrate |
| NaHMDS | Sodium hexamethyldisilazane |
| NMP | N-methylpyrrolidinone |
| NMR | nuclear magnetic resonance |
| P | Polymer bond |
| PyBOP | benzotriazole-1-yl-oxytris-pyrrolidino-phosphonium hexafluorophosphate |

| | |
|---|---|
| TBD | 1,5,7-triazabicyclo[4.4.0]-dec-5-ene |
| RP-HPLC | reverse phase-high pressure liquid chromatography |
| TBSCI | tert-butyldimethylsilyl chloride |
| TCA | trichloroacetic acid |
| TEA | triethanolamine |
| TFA | trifluoroacetic acid |
| $Tf_2O$ | triflate anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyran |
| TLC | thin layer chromatography |

What is claimed is:

1. An improved method for making azaindoles, the improvement comprising:

carrying out a Sonogashira coupling according to the scheme:

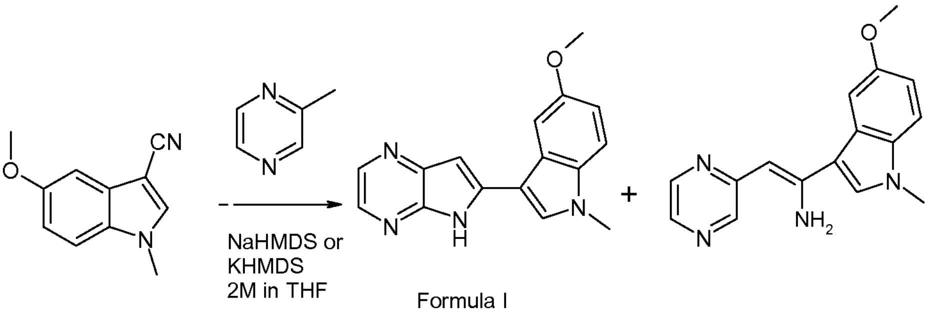


2. An improved synthesis for azaindoles, the improvement comprising:

carrying out a Chichibabin reaction with the additive lithium vinyloxide present.

3. An improved synthesis for azaindoles, the improvement comprising:

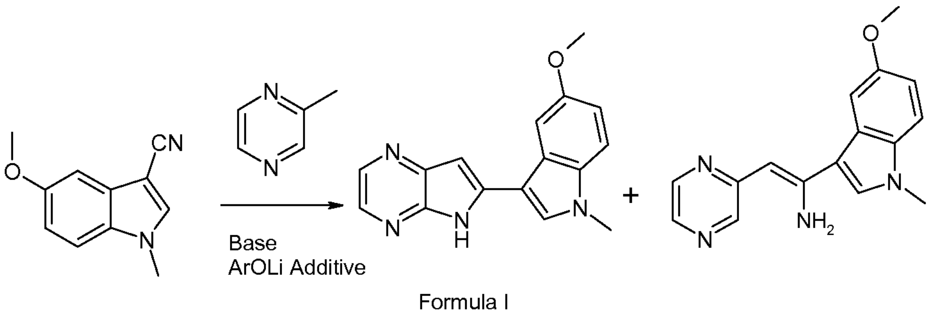
carrying out the reaction:



using sodium hexamethyldisilazane or potassium hexamethyldisilazane.

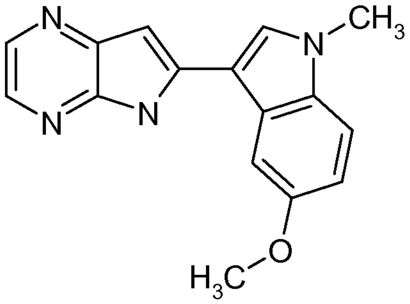
4. An improved synthesis for azaindoles, the improvement comprising:

carrying out the reaction:



using lithium pheoxide as an additive.

5. An improved method for crystallizing a compound of Formula I, comprising:



Formula I

crystallizing the compound by a) dissolving the compound in acetic acid, b) adding a solution of isopropanol/water, c) seeding with a crystal of the compound, and d) then adding additional isopropanol/water.