A Practical, Efficient Synthesis of 5-Amino-7-azaindole

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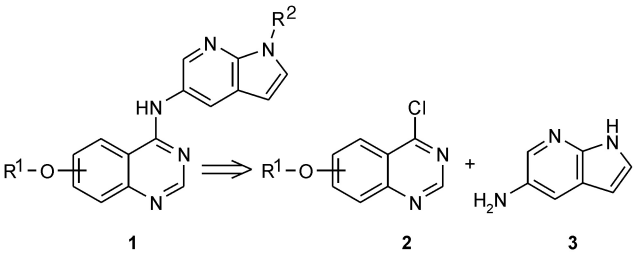
Abstract: A much improved, workable synthesis of 5-amino-7-azaindole is described in 66% overall yield starting from 2-amino-5-nitropyridine. The key stage involves a microwave promoted heteroannulation reaction of a pyridine alkyne.

Key words: azaindoles, alkynes, copper, cyclizations, microwaves

Our ongoing research programme investigating the use of 4-anilinoquinazolines as potential anticancer agents led us to consider compounds of type **1**. These compounds would be made from the reaction of an appropriately substituted 4-chloro-quinazoline **2** with 5-amino-7-azaindole (**3**) (Scheme 1). However, the key intermediate **3** is not easily accessible. There is only one previously reported literature synthesis,[1] giving the product in 21% overall yield in 4 steps from 7-azaindoline (**5**). A recent patent application by Bristol–Myers Squibb[2] describes the introduction of the 5-amino-7-azaindole moiety into a molecule indirectly, involving lithiation and protecting group chemistry. We herein report a much-improved synthesis of the title compound from the readily available 2-amino-5-nitropyridine.

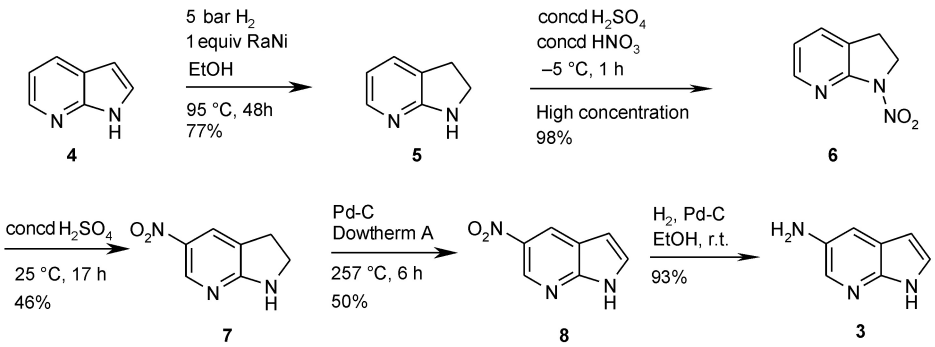
The 1959 Robison procedure (Scheme 2) starts from 7-azaindoline (**5**), which is not commercially available, and has to be prepared by reduction of 7-azaindole (**4**). In our hands, stoichiometric Raney Ni, 5 bar pressure of H_2, elevated temperature and an extended reaction time were required to effect this transformation. The nitration of **5** was



Scheme 1 Retrosynthetic strategy

accomplished by a 2-step procedure; reaction with a mixture of fuming HNO_3 and concentrated H_2SO_4 at –5 °C gives first 1-nitro-7-azaindole (**6**), which was rearranged to the desired 5-nitro- compound **7** by treatment with concentrated H_2SO_4. These two stages required highly concentrated solutions (1 g/mL of substrate) and careful monitoring of temperature otherwise yields were much reduced. Compound **7** was dehydrogenated with palladium on carbon at very high temperature to give 5-nitro-7-azaindole (**8**), a bright orange compound with very poor solubility in most solvents. A very dilute solution of this compound in EtOH was catalytically hydrogenated to give **3**. We found that this reaction gave a mixture of the desired product, nitroso compound and hydrogenated azaindole.

We first attempted to modify the Robison procedure (Scheme 3). We found that reaction of 7-azaindoline with ferric nitrate nonahydrate[3] in refluxing EtOH gave selec-



Scheme 2 Original Robison synthesis of 5-amino-7-azaindole

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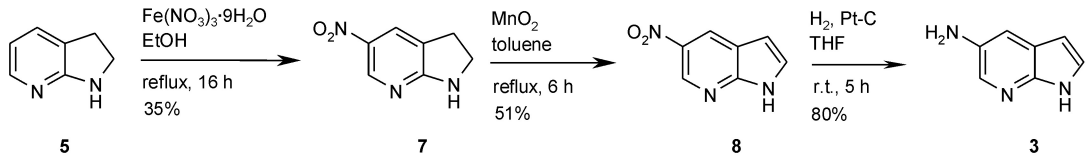


Scheme 3 Modified route from 7-azaindole

tive nitration of the 5-position in one step. Isolation of the product **7** was messy and cumbersome; we found it was somewhat unstable on silica. The dehydrogenation to give **8** could be accomplished using MnO_2; however, the insolubility and low polarity of **8** made its isolation problematic. Dry-loading onto silica and repeated chromatography was necessary to obtain material of adequate purity for the following step. The final reduction to **3** was found to proceed more reliably using 10% platinum on carbon with THF as solvent; this gave a cleaner product with no over-reduction observed.

This procedure allowed us to synthesise workable amounts of **3**, but was still far from ideal. The purifications at each stage were troublesome, and any attempt to carry through material without purification resulted in dramatically reduced yields.

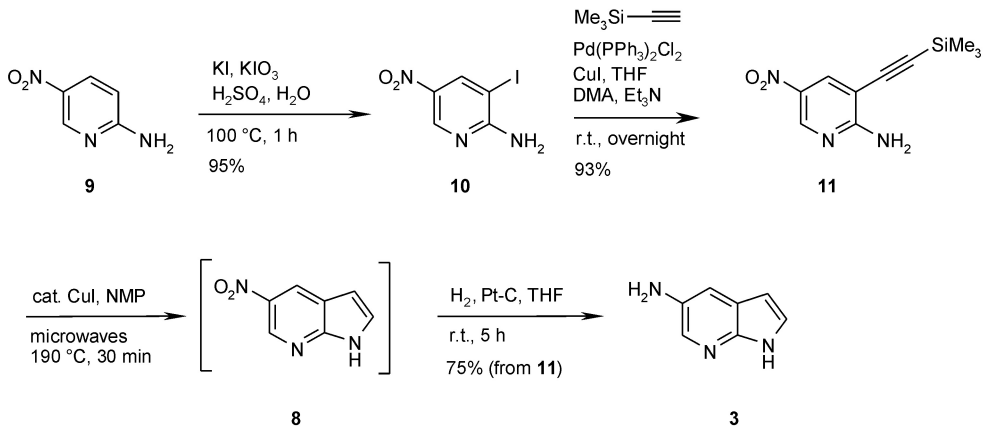
Indoles and azaindoles have been prepared by copper mediated cyclisation of aminopyridines bearing an *ortho*-alkyne group[4] although this methodology has not been previously used to prepare **3**. We decided to adopt this approach (Scheme 4); our starting point was 2-amino-5-nitropyridine (**9**), which was iodinated in the 3-position with a mixture of KI and KIO_3 according to the procedure of Batkowski.[5] A Sonogashira reaction of **10** with trimethylsilyl acetylene gave **11** in excellent yield. Cyclisation to the azaindole was achieved with catalytic copper (I) iodide either with thermal heating (reflux, 16 h, using DMF as solvent), or more conveniently with microwave irradiation. The CEM Explorer and Emrys Optimiser microwave synthesisers were both used for this procedure, and gave comparable results. We found that microwave heating gave cleaner products and shorter reaction times; the optimal reaction conditions being 30 minutes irradiation at 190 °C using NMP as solvent. Desilylation occurs under the reaction conditions to give **8**. The problems encountered in purifying and isolating **8** were solved by evaporating the reaction mixture directly onto diatomaceous earth; this was placed onto a short pad of silica and eluted with hot THF. This procedure removed copper residues and other insoluble impurities, which were found to poison the hydrogenation catalyst in the next stage. The product containing fractions were combined, cooled and hydrogenated directly under platinum on carbon catalysis to give **3**.

Silica chromatography (eluting with EtOAc–MeOH, 97:3) gave a pure sample of **3** as a colourless crystalline solid in 75% yield based on **11**. Pure samples of **3** were stored dry and in solution for months without decomposition.

We found it expedient to use freshly prepared samples of **3** without further purification in subsequent reactions. We were able to obtain our final products **1** in higher overall yield using this approach than we could by isolating **3**. However, crude unpurified samples of **3** were found to decompose over several days, giving polymeric material.

In summary, we now have an efficient practical route to 5-amino-7-azaindole which can be carried out on multigram scale[6] giving high quality material in 66% overall yield from 2-amino-5-nitropyridine.

All chemicals used were of reagent grade and used as supplied. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (2–500 mbar) with a bath temperature of up to 95 °C. Chromatography was carried out on silica; TLC was carried out on silica gel plates (Merck, Art. 5554). In general, the course of reactions was followed by TLC and/or analytical LC–MS. NMR



Scheme 4 Improved procedure from 2-amino-5-nitropyridine

spectra were obtained on a Bruker DPX-400 spectrometer at 400 MHz using DMSO-d_6 or $CDCl_3$ as solvent; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; v, very. Chemical shifts are expressed in ppm downfield from TMS, which was used as an internal standard. HRMS data were recorded by Madeleine Vickers, using Time of Flight (TOF), Electron Impact (EI+), or Electrospray (ES+) techniques. Values for *m*/*z* are given; the mass ion quoted is $[MH]^+$ which refers to the protonated mass ion; reference to M^+ is to the mass ion generated by loss of an electron.

Modified Route from 7-Azaindole

7-Azaindoline (5)

7-Azaindole (3.80 g, 32.2 mmol) was dissolved in EtOH (200 mL). Raney nickel (32.2 mmol) was added and the mixture hydrogenated at 90–95 °C for 48 h under 5 bar pressure of H_2. The reaction mixture was cooled and filtered through a bed of diatomaceous earth. The diatomaceous earth was washed with EtOH. The combined filtrates were concentrated in vacuo. The residue was purified by flash chromatography, eluting with 25–37% EtOAc in *i*-hexane to remove impurities, increasing to EtOAc then 5% MeOH in EtOAc to elute the product. Evaporation of the appropriate fractions gave the product as a white crystalline solid (3.0 g, 77%); mp 78–79 °C [Lit.[7] 78.5–79.5 °C].

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.94 (t, *J* = 8.3 Hz, 2 H), 3.44 (td, *J* = 8.3, 0.9 Hz, 2 H), 6.25 (br s, 1 H), 6.39 (dd, *J* = 7.0, 5.3 Hz, 1 H), 7.23 (dd, *J* = 7.0, 1.3 Hz, 1 H), 7.67 (dd, *J* = 5.3, 1.3 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): d = 27.4, 43.8, 112.4, 122.1, 131.1, 145.9, 165.4.

HRMS (TOF, EI+): *m*/*z* $[M]^+$ calcd for $C_7H_8N_2$: 120.0687; found: 120.0683.

5-Nitro-7-azaindoline (7)

7-Azaindoline (2.00 g, 16.7 mmol) was dissolved in EtOH (70 mL). Ferric nitrate nonahydrate (8.33 g, 20.6 mmol) was added, and the mixture stirred at ambient temperature for 1 h, increasing to 50 °C for 2 h, then at reflux for 16 h. The mixture was cooled and filtered through a pad of diatomaceous earth. The filtrate was evaporated onto diatomaceous earth; this was loaded onto a silica column which had been equilibrated with 25% EtOAc in *i*-hexane. The column was eluted with 25–50% EtOAc in *i*-hexane. Evaporation of the appropriate fractions gave 5-nitro-7-azaindoline as a light brown solid (950 mg, 35%); mp 155–160 °C [Lit.[1] 260.5–261.5 °C].

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.26 (t, *J* = 7.9 Hz, 2 H), 4.14 (t, *J* = 7.9 Hz, 2 H), 8.66 (s, 1 H), 9.18 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 23.9, 46.3, 128.4, 131.1, 143.6, 145.1, 157.2.

HRMS (TOF, EI+): *m*/*z* $[M]^+$ calcd for $C_7H_7N_3O_2$: 165.0538; found: 165.0542.

5-Nitro-7-azaindole (8)

5-Nitro-7-azaindoline (1.90 g, 11.5 mmol) was suspended in toluene (125 mL), and the mixture was heated to reflux. Manganese dioxide (3.0 g, 34.5 mmol) was added and the mixture was heated at reflux. At intervals of 2 h and 4 h, manganese dioxide (3.0 g, 34.5 mmol) was added. After a total of 6 h at reflux, the mixture was filtered hot through a pad of diatomaceous earth. The diatomaceous earth was washed with MeOH–CH_2Cl_2 (1:1, 4 × 100 mL). The combined filtrates were evaporated onto silica; this was loaded onto a silica column, which had been equilibrated with CH_2Cl_2. The column was eluted with 0–2% MeOH in CH_2Cl_2. Evaporation of the appropriate fractions gave the pure product (300 mg), together with the material of inferior quality (1200 mg). Repeated chromatography with the above solvent system gave 5-nitro-7-azaindole as a pale orange solid (overall yield 950 mg, 51%); mp 279–281 °C [Lit.[1] 280 °C].

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.74 (dd, *J* = 3.5, 1.3 Hz, 1 H), 7.75 (dd, *J* = 3.5, 2.2 Hz, 1 H), 8.87 (d, *J* = 2.1 Hz, 1 H), 9.10 (br s, 1 H), 12.46 (br s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 103.1, 119.2, 125.0, 130.5, 138.9, 139.1, 150.6.

HRMS (TOF, ES+): *m*/*z* calcd $[MH]^+$ for $C_7H_5N_3O_2$: 164.0460; found: 164.0457.

5-Amino-7-azaindole (3)

5-Nitro-7-azaindole (950 mg, 5.82 mmol) was dissolved in THF (50 mL), and the solution was degassed and purged with N_2. Platinum on activated carbon (10%, 250 mg) was added, and the mixture was hydrogenated using a balloon filled with hydrogen for 5 h at r.t. The mixture was purged with N_2, and the catalyst removed by filtration. The filtrate was evaporated to give 5-amino-7-azaindole as an off white solid (620 mg, 80%); mp 118–121 °C [Lit.[1] 130.5–131.5 °C].

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.37 (br s, 2 H), 6.26 (dd, *J* = 3.3, 1.8 Hz, 1 H), 7.19 (d, *J* = 2.6 Hz, 1 H), 7.34 (dd, *J* = 3.3, 2.7 Hz, 1 H), 7.82 (d, *J* = 2.6 Hz, 1 H), 11.13 (br s, 1 H).

MS (ES+): *m*/*z* = 134.1.

Improved Procedure from 2-Amino-5-nitropyridine

2-Amino-3-iodo-5-nitropyridine (10)

2-Amino-5-nitropyridine (7.00 g, 50.0 mmol) was dissolved in H_2SO_4 (2 M, 100 mL). Potassium iodate (4.28 g, 20 mmol) was added portionwise at r.t. with stirring. The solution was heated to 100 °C under reflux. Potassium iodide (8.00 g, 48.2 mmol) was added dropwise over 1 h as a solution in water (20 mL). A brown solution resulted, with solid iodine collecting in the reflux condensor. Heating at reflux was continued for 30 min and the mixture was cooled to ambient temperature. The mixture was adjusted to pH 7 with the careful addition of solid $NaHCO_3$. The mixture was diluted with water (200 mL) and CH_2Cl_2 (250 mL) was added. Solid sodium thiosulfate was added with vigorous stirring until the iodine coloration had been discharged. A significant amount of yellowish solid remained out of solution; this was collected by filtration, washed with water and dried to give a yellow solid (10.5 g). The CH_2Cl_2 fraction was filtered through a silicone-treated filter paper and evaporated to give a yellow solid (2.4 g). The solids were combined to give 2-amino-3-iodo-5-nitropyridine (12.7 g, 95%); mp 228–231 °C [Lit.[5] 237 °C].

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.60 (v br s, 2 H), 8.57 (d, *J* = 2.2 Hz, 1 H), 8.84 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 75.4, 135.1, 142.0, 146.1, 162.6.

HRMS (TOF, ES+): *m*/*z* $[MH]^+$ calcd for $C_5H_4N_3O_2I$: 265.9427; found: 265.9446.

2-Amino-5-nitro-3-[(trimethylsilyl)ethynyl]pyridine (11)

2-Amino-3-iodo-5-nitropyridine (2.00 g, 7.55 mmol) was dissolved in a mixture of Et_3N (50 mL), THF (8 mL) and DMA (16 mL), and the solution was degassed and purged with N_2 (3 ×). Trimethylsilylacetylene (1.60 mL, 11.3 mmol), copper(I) iodide (29 mg, 0.15 mmol) and bis(triphenylphosphino) palladium(II) chloride (106 mg, 0.15 mmol) were added. The mixture was degassed and purged with N_2 one more time, then stirred at ambient temperature for 16 h. A yellow solution containing a white precipitate resulted; the precipitate was removed by filtration, and the filtrate was concentrated in vacuo. The residue was redissolved in the minimum volume of CH_2Cl_2, and loaded onto a silica column which had been equilibrated with 15% EtOAc in *i*-hexane. The column was eluted with 15% EtOAc in *i*-hexane to remove impurities, increasing to 35% EtOAc

in *i*-hexane to elute the product. The appropriate fractions were evaporated, and the residue triturated with *i*-hexane to give 2-amino-5-nitro-3-[(trimethylsilyl)ethynyl]pyridine as a yellow solid (1.65 g, 93%); mp 200–202 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.29 (s, 9 H), 5.84 (br s, 2 H), 8.32 (d, *J* = 2.6 Hz, 1 H), 8.92 (d, *J* = 2.6 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 0.0, 97.8, 102.7, 104.0, 135.4, 136.4, 146.0, 162.1.

HRMS (TOF, ES+): *m*/*z* $[MH]^+$ calcd for $C_{10}H_{13}N_3O_2Si$: 236.0855; found: 236.0851.

5-Amino-7-azaindole (3) from 11

2-Amino-5-nitro-3-[(trimethylsilyl)ethynyl]pyridine (700 mg, 2.98 mmol) and copper(I) iodide (114 mg, 0.60 mmol) were dissolved in NMP (14 mL). The mixture was irradiated in an Emrys Optimiser focused microwave at 190 °C for 30 min. The mixture was evaporated (95 °C, 2 mbar) onto diatomaceous earth (5 g); the residue was placed onto a short pad of silica in a sinter funnel, and eluted with hot THF (ca 50 °C, 250 mL). The appropriate fractions (ca. 250 mL) were combined, and purged with N_2. Platinum on activated carbon (10%, 200 mg) was added, and the mixture hydrogenated using a burette filled with hydrogen for 6 h at ambient temperature. The mixture was purged with N_2, and the catalyst removed by filtration. The filtrate was concentrated and the residue chromatographed with 0–3% MeOH in EtOAc. The product containing fractions were evaporated, and the residue was triturated with Et_2O to give 5-amino-7-azaindole as a colourless crystalline solid (296 mg, 75%); mp 127–129 °C [Lit.[1] 130.5–131.5 °C].

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.59 (br s, 2 H), 6.14 (dd, *J* = 3.5, 2.0 Hz, 1 H), 7.07 (d, *J* = 2.5 Hz, 1 H), 7.21 (dd, *J* = 3.5, 2.4 Hz, 1 H), 7.69 (d, *J* = 2.5 Hz, 1 H), 11.00 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 100.0, 115.1, 121.0, 126.1, 133.6, 136.8, 144.6.

HRMS (TOF, EI+): *m*/*z* $[M]^+$ calcd for $C_7H_7N_3$: 133.0640; found: 133.0640.

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