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Scalable synthesis and properties of 7-methyl-4-azaindole

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Abstract: An approach to the synthesis of 7-methyl-4-azaindole, which is a valuable building block for drug discovery programs, is described. The method relies on using a bromine atom as a 'place holding group' for one of the carbon atoms of the pyridine ring throughout the reaction sequence, and it is removed only upon the final reductive cyclization leading to the azaindole ring. Exhaustive hydrogenation of the target product proceeds in a diastereoselective manner and leads to a bicyclic conformationally restricted diamine derivative.

Keywords: catalytic hydrogenation; heterocycles; pyridine; pyrrole; pyrrolo[3,2-*b*]pyridine.

Introduction

In medicinal chemistry, building an effective structure-activity relationship (SAR) study requires the possibility of introducing substituents into every position of the molecule identified as an initial hit [1]. Even the smallest structural modification, such as a methyl group, can sometimes dramatically influence the biological properties of the compound when placed in a proper site of the molecular scaffold [2]. Pyrrolopyridines ('azaindoles') are scaffolds which have been widely used in drug discovery; the recently registered anti-cancer drugs venetoclax (**1**) and vemurafenib (**2**) [3], an anti-HIV agent BMS-378806 (**3**) [4], an anti-mycobacterial compound **4** [5] and a potential agent for the treatment of the cognitive impairments **5** [6] can be mentioned among the most prominent examples (Figure 1).

While the synthesis of various substituted azaindoles is generally well documented, some of the regioisomeric derivatives remain hardly accessible, in particular, 7-methyl-4-azaindole (**6**), a building block which was needed for our project on azaindole derivatives in multigram quantities. It was involved in the design of M_1 receptor positive allosteric modulators [6], muscarinic acetylcholine receptor modulators [7], decaprenylphosphoryl-β-D-ribose-2′-epimerase (DprE1) inhibitors [8] or HIV-1 attachment inhibitors [9]. However, all preparations of **6** reported so far (Scheme 1) were inefficient for the multigram preparation due to a dramatic yield drop at the key steps of Bartoli cyclization [10] and sp^2–sp^3 Suzuki coupling [8]) upon scale-up. In this work, we report an efficient method for the multigram synthesis of **6**, which in our opinion may also be useful for the preparation of other 7-substituted 4-azaindole derivatives.

Results and discussion

Our approach to the synthesis of compound **6** relied on the known reductive cyclization of 2-(3-nitropyridin-2-yl) acetonitriles of general formula **7** (Scheme 2) [11–13]. To the best of our knowledge, this method was not used for the preparation of 7-substituted 4-azaindole derivatives previously. The initial retrosynthetic approach to **6**, according to the selected strategy, led us to compound **8**. As there was no obvious way to assemble this 2,3,4-trisubstituted pyridine or any relevant synthetic precursor in a scalable manner (e.g., the related known compound **9** [14] is obtained via non-chemoselective nitration of amine **10**), we switched to the tetrasubstituted derivative **11** as a possible synthetic equivalent of **8**. The bromine atom was introduced into the molecule of **11** as a 'place holding group' for the sterically accessible C-5 position of the pyridine ring, which might be removed upon reductive conditions of the last step.

Our synthesis of compound **11** commenced from 2-amino-4-methylpyridine (**10**), which is readily available from commercial sources on a kilogram scale (Scheme 3). Compound **10** was transformed into 2,3,4,5-tetrasubstituted pyridine **12** using reported procedures [15–17]. Diazotation of **12** in the presence of HBr and Br_2 gave dibromide **13** (65%), which was purified by crystallization from hexanes. Reaction of **13** with *tert*-butyl cyanoacetate proceeded in a regioselective manner and the product **14**

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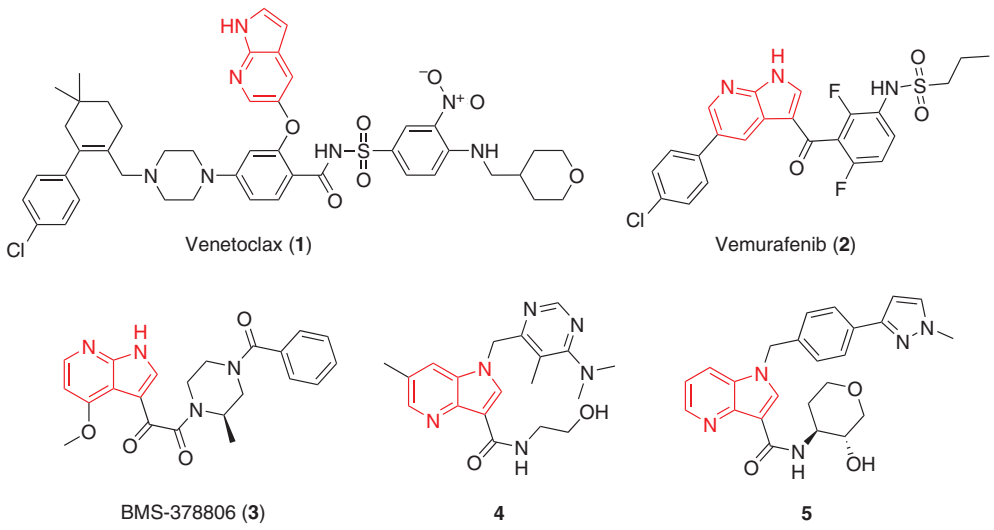
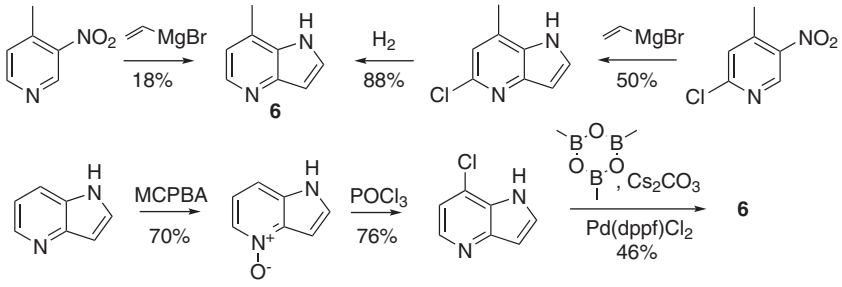
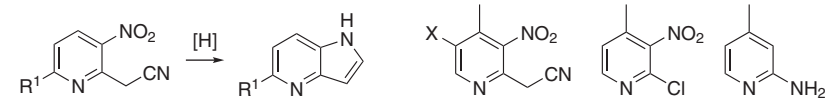


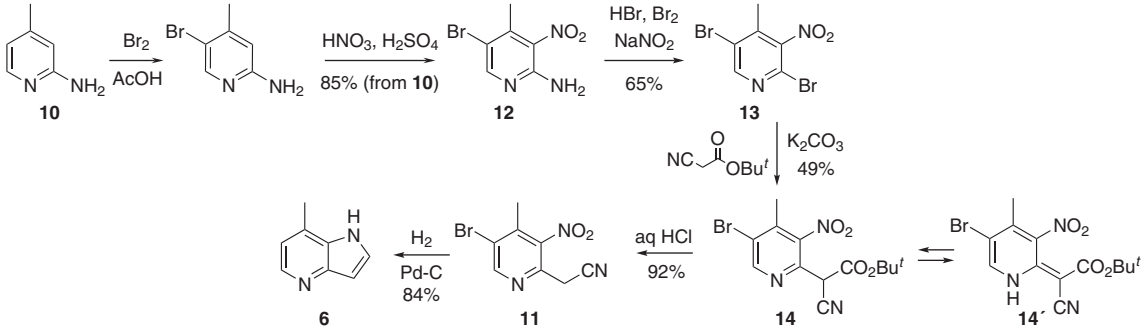
Figure 1 Some biologically active azaindoles.



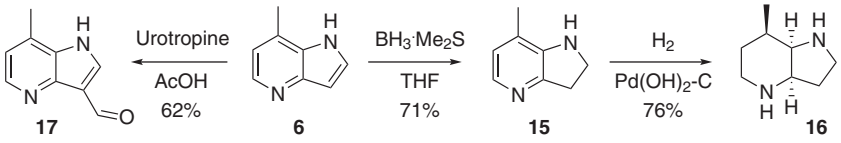
Scheme 1 The known syntheses of 7-methyl-4-azaindole (**6**).



Scheme 2



Scheme 3



Scheme 4

was isolated in a 49% yield. It should be noted that **14** existed in equilibrium with its tautomer **14′**. Acidic hydrolysis of **14** was accompanied by decarboxylation and led to the target compound **11** in an excellent yield of 92%. The key step of the synthesis – reductive cyclization of **11** – proceeded smoothly using inexpensive and common 10% Pd-C as a catalyst. As expected, heterocyclization was accompanied by debromination and gave the target 4-azaindole **6** in a good yield of 84%. Notably, the reaction sequence described above allowed the preparation of up to 30 g of **6** in a single run. In our opinion, the developed method allows the preparation of even larger quantities of the target compound.

Some transformations were performed with azaindole **6** to demonstrate its chemical properties and potential for functionalization (Scheme 4). A partial reduction of the bicyclic system was achieved by treatment with $BH_3 \cdot Me_2S$, which furnished 2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine derivative **15** in a 71% yield. Further reduction of the pyridine ring was performed by catalytic hydrogenation; it occurred in a diastereoselective manner and gave (3a*R**,7*R**,7a*R**)-isomer **16** in a 76% yield, which was isolated as a sulfate salt. The relative stereochemistry of **16** · H_2SO_4 was established using the nuclear Overhauser effect spectroscopy (NOESY) experiment (Figure 2). It should be noted that direct hydrogenation of **6** to **16** was not successful. Compound **16** is a representative of bicyclic conformationally restricted diamines which are valuable building blocks in medicinal chemistry [18]. Finally, formylation of **6** with urotropine in aqueous AcOH gave 3-formyl derivative **17** in a 62% yield.

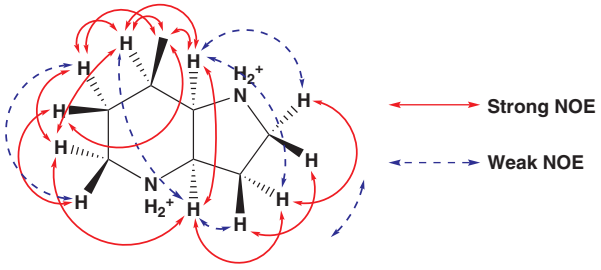


Figure 2 Significant correlations in the NOESY spectrum of **16** · H_2SO_4.

Conclusions

A convenient and scalable approach to 7-methyl-4-azaindole was developed. The method relies on using a bromine atom as a 'place holding group' for one of the carbon atoms of the pyridine ring throughout the reaction sequence, which is removed only upon the final reductive cyclization. The described reaction sequence can also be used for the synthesis of other substituted 4-azaindoles.

Experimental

The solvents were purified according to the standard procedures [19]. Compound **12** was prepared in a 85% yield from **10** using a reported method [15–17]. All other starting materials were purchased from commercial sources. Analytical thin-layer chromatography was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 spectrometer (at 400 MHz for ^1H and 101 MHz for ^{13}C). Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument using electrospray ionization (APESI).

2,5-Dibromo-4-methyl-3-nitropyridine (13)

Aqueous HBr (47%, 195 mL) and Br_2 (186 g, 1.17 mol, 60 mL) were added to compound **12** (90.0 g, 0.39 mol). A saturated solution of $NaNO_2$ (69.0 g, 1.00 mol) was added slowly to the mixture under mechanical stirring at 0–5°C. The mixture was stirred at 15°C for 2 h and then diluted with H_2O (1.5 L). The precipitate was filtered, washed with H_2O and dissolved in $CHCl_3$ (500 mL). The solution was washed with 15% aqueous $NaHSO_3$ (3×200 mL) and H_2O (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was crystallized from hexane; yield 74.3 g (65%) of orange solid; mp 76–77°C; ^1H NMR ($CDCl_3$): δ 8.55 (s, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 151.2, 148.5, 140.8, 130.2, 122.9, 18.2; MS (CI): *m/z* 295/297/299 (1:2:1, MH^+). Anal. Calcd for $C_6H_4Br_2N_2O_2$: C, 24.35; H, 1.36; N, 9.47. Found: C, 24.57; H, 1.72; N, 9.45.

tert-Butyl 2-(5-bromo-4-methyl-3-nitropyridin-2-yl)-2-cyanoacetate (14)

To a solution of *tert*-butyl cyanoacetate (33.8 g, 0.24 mol) in DMF (310 mL), K_2CO_3 (63.6 g, 0.46 mol) was added, followed by portion-wise

addition of compound **13** (50.4 g, 0.17 mol). The mixture was stirred overnight at 95°C, then cooled and poured in H_2O (1500 mL). The mixture was neutralized with 15% aqueous HCl and the resultant precipitate was filtered, washed with H_2O (2×250 mL) and hexanes (2×100 mL) and dried under reduced pressure. The crude product was taken up in $CHCl_3$/hexane (2:3, 1000 mL). The mixture was filtered and the filtrate was concentrated; yield 30.1 g (49%) of orange solid; mp 182–183°C; the compound exists as a 9:1 mixture of tautomers; ^{1}H NMR ($CDCl_3$), major tautomer: δ 8.86 (s, 1H), 5.15 (s, 1H), 2.52 (s, 3H), 1.50 (s, 9H); ^{1}H NMR ($CDCl_3$), minor tautomer: δ 15.63 (br s, 1H), 7.84 (d, J = 6.5 Hz, 1H), 2.38 (s, 3H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$), major tautomer: δ 160.6, 152.3, 141.3, 136.0, 124.8, 112.7, 86.1, 43.8, 28.1, 27.5, 18.8; MS (CI): *m/z* 356/358 (1:1, MH^+). Anal. Calcd for $C_{13}H_{14}BrN_3O_4$: C, 43.84; H, 3.96; N, 11.80. Found: C, 43.45; H, 3.81; N, 11.86.

2-(5-Bromo-4-methyl-3-nitropyridin-2-yl)acetonitrile (11)

To a solution of compound **14** (25.0 g, 70.2 mmol) in MeCN (500 mL), an aqueous solution of HCl (17%, 250 mL) was added. The mixture was heated under reflux for 2 h, then cooled and concentrated under reduced pressure. The residue was taken up in an aqueous saturated solution of $NaHCO_3$ (250 mL), and the product was extracted with EtOAc (4×300 mL). The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with hexanes/EtOAc (1:1) and crystallized from Et_2O/hexanes; yield 16.5 g (92%) of beige solid; mp 107–108°C; ^{1}H NMR ($CDCl_3$): δ 8.81 (s, 1H), 3.95 (s, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 152.2, 146.8, 140.8, 140.6, 123.9, 114.0, 23.6, 18.3; R_f 0.57 eluting with hexanes/EtOAc (1:1); MS (CI): *m/z* 256/258 (1:1, MH^+). Anal. Calcd for $C_8H_6BrN_3O_2$: C, 37.53; H, 2.36; N, 16.41. Found: C, 37.48; H, 2.06; N, 16.70.

7-Methyl-1*H*-pyrrolo[3,2-*b*]pyridine (6)

A mixture of compound **11** (14.0 g, 54.7 mmol) and 10% Pd/C (8.0 g) in aqueous 96% EtOH (400 mL) was hydrogenated under 50 bar of H_2 at room temperature for 30 h. The catalyst was filtered and the filtrate was concentrated under reduced pressure. Aqueous saturated $NaHCO_3$ was added to the residue to adjust to pH 8, and the mixture was concentrated. The residue was treated with hot *i*-PrOH (400 mL) filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with $CHCl_3$/MeOH (4:1); yield 6.07 g (84%) of beige solid; mp 185–187°C (dec); ^{1}H NMR (DMSO-d_6): δ 11.49 (br s, 1H), 8.20 (d, J = 4.7 Hz, 1H), 7.62 (s, 1H), 6.91 (d, J = 4.6 Hz, 1H), 6.55 (d, J = 2.3 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 145.3, 142.2, 129.1, 128.5, 128.4, 117.0, 101.6, 16.3; R_f 0.60 eluting with $CHCl_3$/MeOH (4:1); MS (CI): *m/z* 133 (MH^+). Anal. Calcd for $C_8H_8N_2$: C, 72.7; H, 6.10; N, 21.2. Found: C, 72.49; H, 6.13; N, 21.37.

7-Methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine (15)

To a stirred solution of compound **6** (1.98 g, 15.0 mmol) in dry THF (100 mL), $BH_3 \cdot Me_2S$ (16.0 g, 12.8 mL, 210 mmol) was added, and the mixture was heated under reflux for 11 h. After cooling, MeOH (25 mL) was added dropwise and the mixture was concentrated. MeOH (150 mL) and concentrated aqueous HCl (20 mL) were added to the residue. The mixture was stirred under reflux for 6 h, then cooled and concentrated under reduced pressure. An aqueous solution of NaOH (20%, 50 mL) was added to the residue, and the product was extracted with Et_2O (4×15 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with $CHCl_3$/MeOH (9:1); yield 1.43 g (71%) of white solid; mp 97–99°C; ^{1}H NMR ($CDCl_3$): δ 7.76 (d, J = 5.1 Hz, 1H), 6.71 (d, J = 5.1 Hz, 1H), 3.60 (t, J = 8.6 Hz, 2H), 3.60 (br s, 1H, NH), 3.12 (t, J = 8.6 Hz, 2H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 151.1, 143.6, 139.0, 125.2, 122.6, 45.1, 31.2, 16.2; R_f 0.28 eluting with $CHCl_3$/MeOH (9:1); MS (CI): *m/z* 135 (MH^+). Anal. Calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.43; H, 7.80; N, 20.64.

(3a*R**,7*R**,7a*R**)-7-Methyloctahydro-1*H*-pyrrolo[3,2-*b*] pyridine sulfate (16 · H_2SO_4)

A mixture of compound **15** (1.00 g, 7.50 mmol), 10% $Pd(OH)_2$-C (1.00 g), MeOH (50 mL) and concentrated aqueous HCl (1.5 mL) was hydrogenated at 35 bar of H_2 at 60°C for 24 h. The catalyst was filtered and the filtrate was concentrated under reduced pressure. An aqueous solution of NaOH (10%, 15 mL) was added to the residue, and the product was extracted with Et_2O (4×30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was dissolved in aqueous 96% EtOH (30 mL) and the solution was treated with concentrated H_2SO_4 to adjust to pH 4. The resultant diamine sulfate was filtered and crystallized from aqueous 96% EtOH (120 mL); yield 1.36 g (76%) of white solid; mp > 200°C (dec.); ^{1}H NMR (D_2O): δ 4.20 – 4.05 (m, 1H, 3a-C*H*), 3.98 (t, J = 4.7 Hz, 1H, 7a-C*H*), 3.85 – 3.70 (m, 1H, 1-C*H*H), 3.62 – 3.43 (m, 2H, 1-CH*H* and 5-CH*H*), 3.11 (td, J = 13.1, 3.0 Hz, 1H, 5-C*H*H), 2.67 (ddt, J = 15.1, 11.2, 7.5 Hz, 1H, 2-CH*H*), 2.48 – 2.25 (m, 2H, 7-C*H* and 2-C*H*H), 2.00 – 1.88 (m, 1H, 6-CH*H*), 1.88 – 1.67 (m, 1H, 6-C*H*H), 1.20 (d, J = 7.1 Hz, 3H, CH_3); N*H*s are exchanged with HDO; ^{13}C NMR (DMSO-d_6): δ 58.7, 52.7, 40.6, 40.1, 25.2, 24.8, 20.9, 14.3; MS (CI): *m/z* 141 (MH^+). Anal. Calcd for $C_8H_{18}N_2O_4S$: C, 40.32; H, 7.61; N, 11.76; S, 13.45. Found: C, 40.52; H, 7.81; N, 11.9; S, 13.26.

7-Methyl-1*H*-pyrrolo[3,2-*b*]pyridine-3-carbaldehyde (17)

A mixture of compound **6** (3.00 g, 22.7 mmol) and hexamethylenetetramine (4.91 g, 35.0 mmol) in a mixture of acetic acid (20 mL) and H_2O (50 mL) was heated under reflux for 6 h, then cooled and concentrated under reduced pressure. A saturated aqueous solution of $NaHCO_3$ (50 mL) was added to the residue, and the product was extracted with EtOAc (4×50 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with $CHCl_3$/MeOH (4:1); yield 2.25 g (62%) of light yellow solid; mp 210–212°C; ^{1}H NMR (CD_3OD): δ 10.12 (s, 1H), 8.33 (d, J = 4.9 Hz, 1H), 8.26 (s, 1H), 7.12 (d, J = 4.9 Hz, 1H), 2.57 (s, 3H); N*H* is exchanged with CD_3OD; ^{13}C NMR (CD_3OD): δ 187.2, 146.5, 144.4, 138.9, 134.6, 132.6, 121.5, 119.3, 17.4; R_f 0.56 eluting with $CHCl_3$/MeOH (4:1); MS (CI): *m/z* 161 (MH^+). Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.31; H, 5.43; N, 17.19.

Supplementary material

^{1}H and ^{13}C NMR spectra are available as online-only supplement.

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