Synthesis of 4-, 5- and 6-Benzoylated 7-Azaindoles

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Received 11 January 2008; revised 28 March 2008

Abstract: Efficient syntheses of 4-, 5- and 6-benzoyl-7-azaindoles are described. Two strategies were developed: i) formation of 4-lithio and 5-lithio-7-azaindole and reaction with aldehydes and ii) organomagnesium addition to 6-cyano-7-azaindole. Both methods should allow the introduction of a diverse range of acyl substituents.

Key words: 7-azaindole, acylation, 6-cyano-7-azaindole, fused-ring system, lithium–halogen exchange

7-Azaindole derivatives may be considered as useful indole bioisosteres in medicinal chemistry. An increasing number of pharmaceutically active compounds with application in various therapeutic areas contain the 7-azaindole (1-*H*-pyrrolo[2,3-*b*]pyridine) pharmacophore.[1] Functionalisation at C-2 and C-3 of the pyrrole moiety is well documented in the literature.[2] For example, the direct Friedel–Crafts acylation is known to preferentially take place at the C-3 position of the azaindole core.[3] However, the regioselective functionalisation of the electron-deficient pyridine ring of 7-azaindole remains a major challenge. A few approaches involve pyrrolo annelation into a preformed pyridine ring[1,2] and, more recently, some progress has been achieved starting from the *N*-oxide derivative.[4] In the course of our own program in medicinal chemistry, we required an efficient synthesis of 4-, 5- and 6-acylated 7-azaindole (Figure 1). In this paper, we wish to describe efficient methods with which to prepare acylated azaindole templates **1**–**3** (Figure 1, exemplified with R = phenyl).

6-Substituted 7-azaindoles have generally been prepared through ring closure of pyridine derivatives including the functional group.[1,2] Halogen and thiocyanato groups have been introduced onto position 6 of 7-azaindole via a Reissert–Henze salt. To permit the introduction of a wide range of acyl groups onto the 7-azaindole core, we envisaged the synthesis of azaindole **1** by addition of an organomagnesium compound on the cyano precursor **4** (Scheme 1).

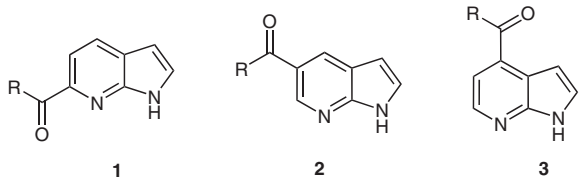
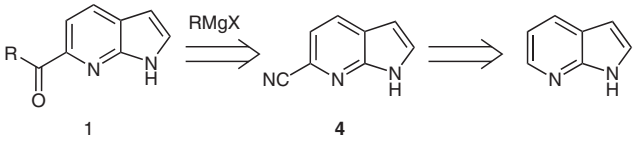
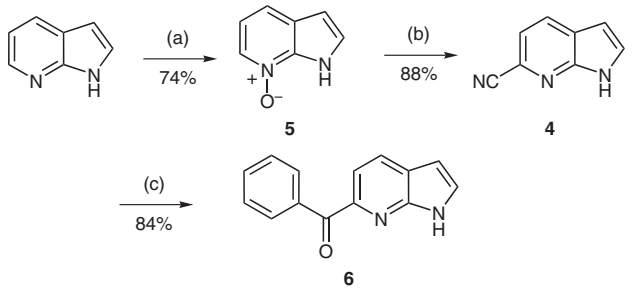


Figure 1 Target molecules



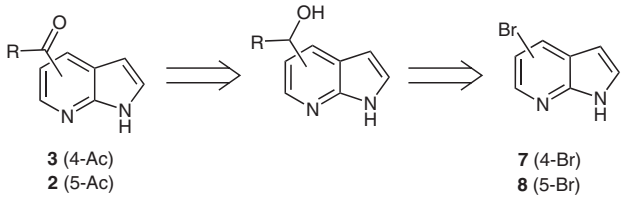
Scheme 1



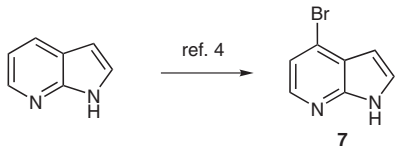
Scheme 2 *Reagents and conditions*: (a) *m*-CPBA, EtOAc, r.t., 1 h; (b) TMSCN, Et_3N, MeCN, reflux, 6 days; (c) (i) PhMgBr, TMSCl, THF, r.t., 15 h; (ii) H_2O.

The only known cyanation of 7-azaindole was performed at the 6-position by the treatment of its *N*-oxide with trimethylsilyl cyanide in the presence of benzoyl chloride.[5,6] The resulting 1-benzoyl-6-cyano-7-azaindole was obtained with low yield (39%) and the benzoyl group had to be removed by basic treatment.[7] Thus, the development of an improved cyanation of the *N*-oxide **5**[8] was undertaken. In reference to the pyridine chemistry, however, we found that treatment of compound **5** with trimethylsilanecarbonitrile and dimethylcarbamyl chloride in dichloromethane,[9] did not lead to the desired product. On the other hand, the one-step conversion of pyridine *N*-oxide into the α-cyano pyridine reported by Vorbrüggen and Krolikiewicz,[10] prompted us to evaluate the cyanation of the unprotected *N*-oxide **5** with trimethylsilyl cyanide (TMSCN) in acetonitrile in the presence of triethylamine[11] (Scheme 2). The expected 6-cyano-7-azaindole (**4**) was isolated in an excellent 88% yield. Although theoretically only three equivalents of trimethylsilyl cyanide are needed,[10] less than six equivalents led to lower yields. When phenylmagnesium bromide was added to compound **4** in the presence of trimethylsilyl chloride (TMSCl), the desired

SYNTHESIS 2008, No. 13, pp 2049–2054
Advanced online publication: 21.05.2008
DOI: 10.1055/s-2008-1067103; Art ID: T00508SS



Scheme 3



Scheme 4

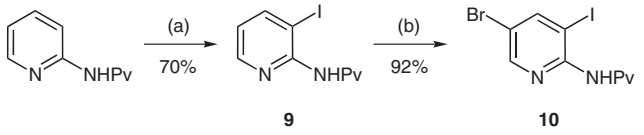
6-benzoyl-7-azaindole (**6**) was obtained in 84% yield (overall yield 55% in 3 steps from 7-azaindole).

To obtain analogues **2** and **3** acylated at positions C-5 and C-4, respectively, we envisaged a lithium–halogen exchange approach followed by treatment with an aldehyde as electrophile and further oxidation of the intermediate alcohol (Scheme 3).

Synthesis of the required 4-bromo-7-azaindole (**7**) was planned from commercially available 7-azaindole using a known procedure (Scheme 4).[4]

In the case of 5-bromo-7-azaindole (**8**), an alternative approach to the known synthesis described by Guillaumet and co-workers[12] from 7-azaindole was investigated. The strategy consisted of initial bromination of the pyridine, followed by pyrrole ring annelation.

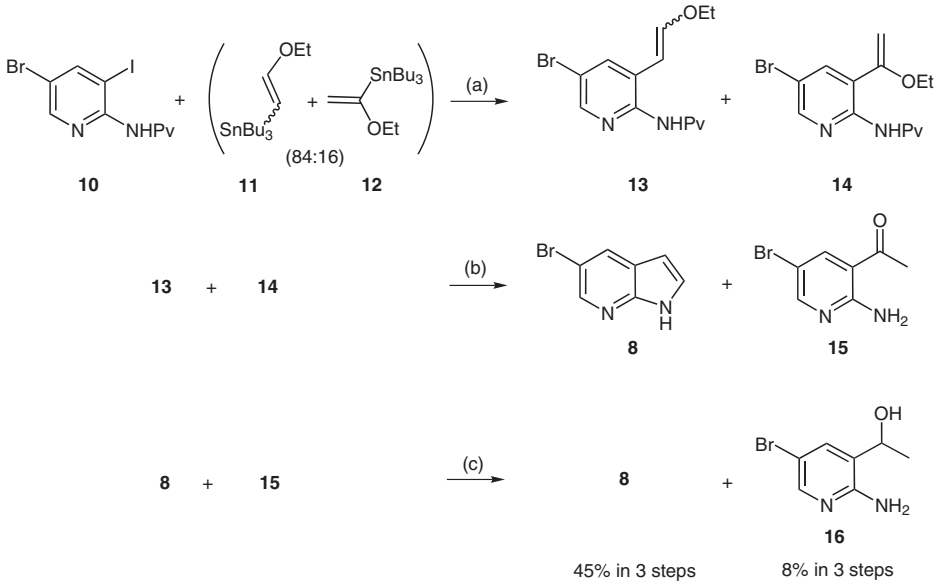
The *m*-bromopyridine intermediate **10** was prepared as shown in Scheme 5. The *ortho*-metallation of commercially available 2-(pivaloylamino)pyridine provided the iodo derivate **9**[13] in 70% yield, which was brominated in dimethylformamide to give the desired 5-bromo-3-iodopyridine (**10**). Stille cross-coupling was chemoselectively



Scheme 5 *Reagents and conditions*: (a) (i) *n*-BuLi, THF, –40 °C to –10 °C, 4 h; (ii) I_2, THF, –78 °C to r.t., 1 h; (b) Br_2, DMF, r.t., 24 h.

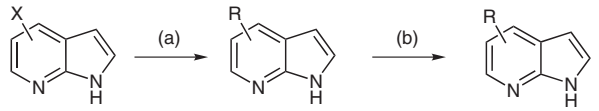
performed on the iodine atom of **10** with a mixture (84:16) of ethoxyvinylstannanes **11** and **12**[14] in the presence of dichlorobis(triphenylphosphine)-palladium and tetraethylammonium chloride in acetonitrile under reflux.[15] The resulting enol ethers **13** and **14** were directly heated in sulfuric acid (10%) to provide the desired azaindole **8** and the ketone **15**. In order to facilitate the purification by chromatography on silica gel, ketone **15** was reduced by treating the crude mixture with sodium borohydride. Thus, the resulting alcohol **16** was easily removed and 5-bromo-7-azaindole (**8**) was obtained in 45% yield over three steps (Scheme 6). This procedure was performed on a large scale (10 g) and required only one recrystallization and one purification by chromatography on silica gel from 2-(pivaloylamino)pyridine.

An initial attempt to affect the metal–halogen exchange of 5-bromo-7-azaindole (**8**) with three equivalents of *tert*-butyllithium was unsuccessful. Rapoport and co-workers[16] have demonstrated that, because the metal–halogen exchange was so rapid, it might effectively compete with abstraction of the indole NH. In order to prevent this problem, methyllithium was first used to remove the acidic pyrrole proton on **7** and **8**.[17] After complete deprotonation, two equivalents of *tert*-butyllithium were added to promote the bromine–lithium exchange. Benzaldehyde was then added to provide alcohols **17** and **18** in 73% and 90% yield, respectively. Finally, oxidation of the benzylic alcohols was carried out by *tert*-butyl hydroperoxide in the presence of catalytic amounts of chromium(VI) ox-



Scheme 6 *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, Et_4NCl, MeCN, reflux, 20 h; (b) H_2SO_4 (10%), reflux, 5 h; (c) $NaBH_4$, MeOH, r.t., 24 h.

ide,[18] to afford the desired 4- and 5-benzoyl-7-azaindoles **19** and **20** (Scheme 7).



7 X = 4-Br **17** R = 4-CH(OH)Ph 73% **19** R = 4-Bz 53%
8 X = 5-Br **18** R = 5-CH(OH)Ph 90% **20** R = 5-Bz 69%

Scheme 7 *Reagents and conditions*: (a) (i) MeLi (1 equiv), THF, –78 °C, 20 min; (ii) *t*-BuLi (2 equiv), –78 °C, 15 min; (iii) PhCHO, –78 °C to r.t., 16 h; (iv) H_2O; (b) CrO_3, *t*-BuOOH, CH_2Cl_2, r.t., 24 h.

An alternative synthesis of compound **20** was studied using the metallation chemistry developed by L'Heureux[19] on the protected 4-chloro-7-azaindole (**21**; Scheme 8). Thus, *ortho*-metallation of **21** with *sec*-butyllithium in tetrahydrofuran and treatment with benzaldehyde gave alcohol **22** in 93% yield. The success of this approach was dependent on the selective reduction of the C–Cl in comparison to the benzylic alcohol function. Numerous attempts under radical conditions, with zinc in acetic acid[20] or Pd hydrogenation with H_2 were ineffective or led to mixtures of compounds. Finally, the use of Pd/C in the presence of ammonium formiate in THF–water[21] furnished azaindole **23**. Oxidation with MnO_2 and removal of the silyl group afforded the benzoyl derivative **20**.

In conclusion, we have prepared 6-cyano-7-azaindole (**4**) and, after addition of phenylmagnesium bromide, 6-benzoyl-7-azaindole (**6**) in good yield. We have also developed a new synthesis of 5-bromo-7-azaindole (**8**) through a palladium-catalysed sequence. The efficient lithium–halogen exchange allowed the formation of the 4- and 5-benzoyl-7-azaindoles analogues. This methodology provides a powerful tool for the preparation of 4-, 5- and 6-benzoylated 7-azaindoles.

All chemicals were obtained from Aldrich or Acros and used without further purification. THF was distilled from sodium with benzophenone as indicator under argon prior to use. Experiments were performed under an anhydrous and oxygen-free argon atmosphere except were otherwise specially indicated. For TLC, aluminium sheets (Merck silca gel coated 60 F254) were used and the plates were visualized with UV light. Merck silica gel 40–70 μm (230–400 mesh) was used for flash chromatography. Melting points were determined on a Büchi apparatus and are uncorrected. ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were recorded on a Bruker Avance DPX250 spectrometer at 25 °C, using TMS as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are reported in Hertz (Hz). IR spectra were recorded on a Perkin–Elmer PARAGON 1000 PC spectrophotometer. HRMS (ESI-TOF) were performed on a Micromass LC TOF spectrometer.

1*H*-Pyrrolo[2,3-*b*]pyridine-7-oxide (5)

Prepared from commercially available 7-azaindole according to the procedure described by Benoît, Gringas and Soundara.[8]

1*H*-Pyrrolo[2,3-*b*]pyridine-6-carbonitrile (4)

To a stirred solution of 1*H*-pyrrolo[2,3-*b*]pyridine-7-oxide (**5**; 11.27 g, 84.02 mmol) in MeCN (450 mL) was added Et_3N (29.3 mL, 210.05 mmol) and TMSCN (50 g, 504.12 mmol) in 5 portions. The mixture was heated to reflux for 6 days then quenched with sat. $NaHCO_3$ (500 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 300 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain **4**. The analytical data were in accordance with literature values.[7]

Yield: 10.6 g (88%); white solid; mp 177–178 °C.

IR (KBr): 3407, 2228, 1580, 1412 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.65 (d, *J* = 2.9 Hz, 1 H, H-3), 7.50 (d, *J* = 8.0 Hz, 1 H, H-5), 7.72 (d, *J* = 2.9 Hz, 1 H, H-2), 8.08 (d, *J* = 8.0 Hz, 1 H, H-4), 11.40 (br s, 1 H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 101.8 (C-3), 118.8 (CN), 120.2 (C-5), 123.9 (C_q), 124.6 (C_q), 129.6 (C-4), 130.2 (C-2), 148.4 (C_q).

Phenyl(1*H*-pyrrolo[2,3-*b*]pyridine-6-yl)methanone (6)

To a stirred solution of phenylmagnesium bromide (1 M in THF, 25.2 mL, 25.2 mmol) in THF (7 mL) was added a solution of 1*H*-pyrrolo[2,3-*b*]pyridine-6-carbonitrile (**4**; 0.6 g, 4.2 mmol) and TMSCl (1.07 mL, 8.4 mmol) in THF (7 mL). After stirring overnight at r.t., the mixture was quenched with NH_4Cl (2 N, 20 mL) and acidified with aq HCl (10%) to pH 1. The resulting solution was stirred for 2 h at r.t. and basified with concentred ammonia solution to pH 9. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the organic layers were dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2 then CH_2Cl_2–MeOH, 99:1) to obtain the title compound.

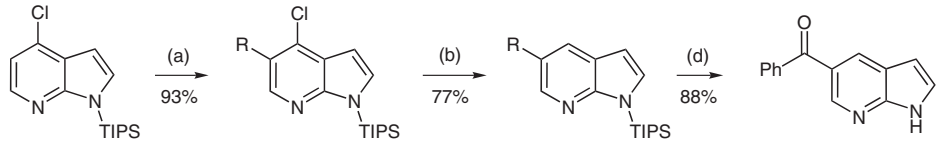
Yield: 784 mg (84%); yellow solid; mp 172–174 °C.

IR (KBr): 3407, 1657 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.50 (d, *J* = 1.2 Hz, 1 H, H-3), 7.25 (t, *J* = 2.8 Hz, 1 H, H-2), 7.47–7.60 (m, 3 H, ArH), 7.85 (d, *J* = 7.8 Hz, 1 H, H-5), 8.06 (m, 3 H, H-4 and ArH), 12.80 (br s, 1 H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 100.4 (C-3), 118.4 (C-5), 123.9 (C_q), 128.5 (CH_{Ph}), 128.7 (C-4), 130.8 (CH_{Ph}), 131.0 (C-2), 132.8 (CH_{Ph}), 137.9 (C_q), 146.6 (C_q), 148.2 (C_q), 195.0 (CO).

HRMS: *m/z* [M + H]$^+$ calcd for $C_{14}H_{11}N_2O$: 223.0871; found: 223.0865.



21 **22** R = CH(OH)Ph (c) **23** R = CH(OH)Ph, **24** R = Bz, 68% **20**

Scheme 8 *Reagents and conditions*: (a) (i) *s*-BuLi (2.2 equiv), THF, –78 °C; (ii) PhCHO, –78 °C to r.t., 16 h; (iii) H_2O; (b) Pd/C, HCO_2NH_4, THF–H_2O, r.t., 28 h; (c) MnO_2, toluene, reflux, 20 h; (d) TBAF, THF, r.t., 3 h.

N-(3-Iodopyridin-2-yl)-2,2-dimethylpropionamide (9)
To a stirred solution of *n*-BuLi (1.6 M in hexane, 210 mL, 337 mmol) was added dropwise at –40 °C a solution of 2,2-dimethyl-*N*-pyridin-2-yl-propionamide (20 g, 112 mmol) in THF (70 mL). After 4 h of stirring at –10 °C, the mixture was cooled to –78 °C and a solution of I_2 (60 g, 236 mmol) in THF (80 mL) was added via a dropping funnel. After 1 h, the reaction mixture was allowed to reach r.t., quenched with sat. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude product was recrystallised (CH_2Cl_2–pentane) to give the title compound. The analytical data were in accordance with literature values.[13]

Yield: 23.8 g (70%); white solid; mp 147–148 °C.

IR (KBr): 3298, 3044, 2974, 2934, 2874, 1670 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, 3 × CH_3), 6.84 (dd, *J* = 4.9, 7.8 Hz, 1 H, H-5), 7.92 (br s, 1 H, NH), 8.11 (dd, *J* = 1.5, 7.8 Hz, 1 H, H-4), 8.45 (dd, *J* = 1.5, 4.9 Hz, 1 H, H-6).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 27.5 (CH_3), 40.1 (C_q), 88.2 (C_q), 121.7 (C-5), 147.9 (C-4), 148.3 (C-6), 151.1 (C_q), 176.0 (C_q).

N-(5-Bromo-3-iodopyridin-2-yl)-2,2-dimethylpropionamide (10)
To a stirred solution of *N*-(3-iodopyridin-2-yl)-2,2-dimethylpropionamide (**9**; 12 g, 39.5 mmol) in DMF (54 mL) was added Br_2 (5.07 mL, 98.7 mmol) via a dropping funnel. After 24 h of stirring at r.t., the solvent was removed under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (50 mL) and washed with $Na_2S_2O_3$ solution (5%; 2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to give **10**.

Yield: 13.9 g (92%); white solid; mp 192–194 °C.

IR (KBr): 3298, 1670 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.36 (s, 9 H, 3 × CH_3), 7.89 (br s, 1 H, NH), 8.22 (d, *J* = 2.1 Hz, 1 H, H-4), 8.48 (d, *J* = 2.1 Hz, 1 H, H-6).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 27.6 (CH_3), 40.3 (C_q), 88.1 (C_q), 115.8 (C_q), 149.2 (C-4), 149.3 (C-6), 149.9 (C_q), 176.0 (C_q).

HRMS: *m/z* [M + H]$^+$ calcd for $C_{10}H_{13}{}^{79}BrIN_2O$: 382.9256; found: 382.9263.

4-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine (7)
Prepared from commercially available 7-azaindole according to the procedure described by Thibault and co-workers.[4]

Preparation of Compound 8
A solution of pyridine **10** (1.0 g, 2.61 mmol), stannane mixture **11** and **12** (1.13 g, 3.13 mmol) and tetraethylammonium chloride (0.433 g, 2.61 mmol) in MeCN (20 mL) was degassed 3 times with argon. Dichlorobis(triphenylphosphine)palladium (0.073 g, 4 mol%) was added and the mixture was heated to reflux for 20 h. After cooling to r.t., sat. KF (10 mL) and EtOAc (10 mL) were added and this mixture was vigorously stirred for 30 min to precipitate the tin salts. After filtration through celite, the filtrate was extracted with EtOAc (2 × 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude oil, which appeared to be a mixture of **13** and **14**, was used without purification.

N-5-Bromo-3-[(*E*/*Z*)-2-ethoxyvinylpyridin-2-yl]-2,2-dimethylpropionamide (13)
^1H NMR (250 MHz, $CDCl_3$): δ = 1.32 (m, 24 H, CH_3 *cis* and *trans*), 3.86 (q, *J* = 7.0 Hz, 2 H, CH_2 *trans*), 4.02 (q, *J* = 7.0 Hz, 2 H, CH_2 *cis*), 5.03 (d, *J* = 7.0 Hz, 1 H, CH_{enol} *cis*), 5.54 (d, *J* = 12.8 Hz, 1 H, CH_{enol} *trans*), 6.36 (d, *J* = 7.0 Hz, 1 H, CH_{enol} *cis*), 6.90 (d, *J* = 12.8 Hz, 1 H, CH_{enol} *trans*), 7.71 (br s, 1 H, NH *cis*), 7.75 (d, *J* = 2.1 Hz, 1 H, H-4 *trans*), 7.93 (br s, 1 H, NH *trans*), 8.20 (d, *J* = 2.1 Hz, 1 H, H-6 *trans*), 8.27 (d, *J* = 2.1 Hz, 1 H, H-4 *cis*), 8.39 (d, *J* = 2.1 Hz, 1 H, H-6 *cis*).

N-5-Bromo-3-(1-ethoxyvinylpyridin-2-yl)-2,2-dimethylpropionamide (14)
^1H NMR (250 MHz, $CDCl_3$): δ = 1.35 (m, 12 H, CH_3), 3.92 (q, *J* = 7.0 Hz, 2 H, CH_2), 4.48 (s, 2 H, CH_2), 7.76 (d, *J* = 2.1 Hz, 1 H, H-4), 7.95 (br s, 1 H, NH), 8.48 (d, *J* = 2.1 Hz, 1 H, H-6).

The mixture of enol ethers **13** and **14** was dissolved in aq H_2SO_4 (10%; 75 mL) and heated to reflux for 5 h. The reaction was basified with NaOH to pH 9 and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to obtain a mixture of azaindole **8** and ketone **15**. To a solution of this crude mixture in MeOH (150 mL) was added, portionwise, $NaBH_4$ (0.360 mg, 9.5 mmol). The resulting solution was stirred for 24 h at r.t. then quenched with H_2O (15 mL). MeOH was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give the crude product, which was purified by flash chromatography on silica gel (PE–EtOAc–Et_3N, 3:2:1 then CH_2Cl_2–MeOH, 9:1) to give the desired product **8** and alcohol **16**. The analytical data were in accordance with literature values.[12]

5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine (8)
Yield: 231 mg (45% over 3 steps); white solid; mp 174–176 °C

IR (KBr): 3136 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 6.47 (d, *J* = 3.5 Hz, 1 H, H-3), 7.37 (d, *J* = 3.5 Hz, 1 H, H-2), 8.08 (d, *J* = 2.2 Hz, 1 H, H-4), 8.36 (d, *J* = 2.2 Hz, 1 H, H-6), 10.13 (br s, 1 H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 100.6 (C-3), 111.7 (C_q), 122.2 (C_q), 126.8 (C-2), 131.3 (C-4), 143.2 (C-6), 147.1 (C_q).

1-(2-Amino-5-bromopyridin-3-yl)ethanol (16)
Yield: 40 mg (8% over 3 steps); mp 171–172 °C

IR (KBr): 3634, 3444, 3266–3158, 2970–2857, 1675, 1622 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.6 Hz, 3 H, CH_3), 3.84 (br s, 1 H, OH), 4.24 (q, *J* = 6.6 Hz, 1 H, C*H*OH), 5.19 (br s, 2 H, NH_2), 7.34 (d, *J* = 1.8 Hz, 1 H, H-4), 7.86 (d, *J* = 1.8 Hz, 1 H, H-6).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.4 (CH_3), 68.0 (*C*HOH), 107.7 (C_q), 124.9 (C_q), 136.9 (C-4), 146.9 (C-6), 155.6 (C_q).

HRMS: *m/z* [M + H]$^+$ calcd for $C_7H_{10}{}^{79}BrN_2O$: 216.9976; found: 219.9984.

Phenyl(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)methanol (17)
To a stirred solution of azaindole **7** (0.780 g, 3.96 mmol) in THF (9 mL) was added dropwise at –78 °C, MeLi (1.4 M in Et_2O, 4 mL, 5.54 mmol). The mixture was stirred for 20 min at –78 °C then *t*-BuLi (1.5 M in pentane, 6.6 mL, 9.9 mmol) was added. After stirring for 15 min at –78 °C, benzaldehyde (2 mL, 19.8 mmol) was added slowly. The mixture was allowed to warm slowly to r.t., stirred for 2 h then quenched with sat. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (PE–EtOAc, 1:1) to obtain the title azaindole **17**.

Yield: 0.648 g (73%); yellow solid; mp 68–69 °C.

IR (KBr): 1125, 1224, 3320 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 6.03 (br s, 2 H, CH and OH), 6.42 (d, *J* = 3.1 Hz, 1 H, H-3), 7.29–7.42 (m, 7 H, H-2, H-5 and ArH), 8.17 (d, *J* = 5.0 Hz, 1 H, H-6), 11.50 (br s, 1 H, NH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 72.4 (*C*HOH), 99.0 (C-3), 111.9 (C-5), 117.0 (C_q), 125.3 (C-2), 126.4 (CH_{Ph}), 126.9 (CH_{Ph}), 128.0 (CH_{Ph}), 142.5 (C-6), 144.5 (C_q), 145.7 (C_q), 148.7 (C_q).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O$: 225.1028; found: 225.1028.

Phenyl(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methanol (18)

To a stirred solution of azaindole **8** (3 g, 15.23 mmol) in THF (100 mL) was added dropwise at –78 °C, MeLi (1.4 M in Et_2O, 15.23 mL, 21.32 mmol). The mixture was stirred for 20 min at –78 °C then *t*-BuLi (1.6 M in pentane, 25.4 mL, 38.07 mmol) was added. After stirring for 15 min at –78 °C, benzaldehyde (6.2 mL, 60.92 mmol) was added slowly. The mixture was allowed to warm slowly to r.t., stirred for 16 h then quenched with sat. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (PE–EtOAc, 6:4 then 5:5) to obtain the desired azaindole **18**.

Yield: 3.07 g (90%); beige solid; mp 154–155 °C.

IR (KBr): 1216, 3616 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.00 (s, 1 H, C*H*OH), 6.45 (d, *J* = 3.4 Hz, 1 H, H-3), 7.27–7.45 (m, 6 H, H-2 and ArH), 7.93 (d, *J* = 1.9 Hz, 1 H, H-4), 8.29 (d, *J* = 1.9 Hz, 1 H, H-6).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 74.6 (*C*HOH), 101.0 (C-3), 120.4 (C_q), 125.9 (C-2 and C_q), 126.5 (CH_{Ph}), 127.6 (C-4), 127.7 (CH_{Ph}), 128.6 (CH_{Ph}), 142.1 (C-6), 144.0 (C_q), 147.7 (C_q).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O$: 225.1028; found: 225.1022.

Phenyl(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)methanone (19)

To a stirred mixture of chromium(VI) oxide (15 mg, 0.15 mmol) in CH_2Cl_2 (50 mL) was added, sequentially, commercial aq *tert*-butyl hydroperoxide (70%; 1.6 mL, 11.6 mmol) and alcohol **17** (0.650 g, 2.9 mmol). After stirring for 24 h at r.t. under an air atmosphere, the mixture was quenched with aq $Na_2S_2O_3$ (5%; 50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude material was purified by flash chromatography (PE–EtOAc, 1:1) to give the desired product **19**.

Yield: 0.342 g (53%); yellow oil.

IR (NaCl): 1680, 1130 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.42 (d, *J* = 3.2 Hz, 1 H, H-3), 7.30 (d, *J* = 4.7 Hz, 1 H, H-5), 7.47–7.53 (m, 3 H, H-2 and ArH), 7.60 (t, *J* = 7.4 Hz, 1 H, ArH), 7.87 (d, *J* = 7.4 Hz, 2 H, ArH), 8.48 (d, *J* = 5.0 Hz, 1 H, H-6), 11.40 (br s, 1 H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 101.4 (C-3), 116.5 (C-5), 119.0 (C_q), 127.6 (C-2), 128.6 (CH_{Ph}), 130.3 (CH_{Ph}), 133.3 (CH_{Ph}), 136.9 (C_q), 137.4 (C_q), 142.0 (C-6), 150.1 (C_q), 196.3 (C_q).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}N_2O$: 223.0871; found: 223.0884.

Phenyl(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methanone (20)

Method A: To a stirred mixture of chromium(VI) oxide (31 mg, 0.31 mmol) in CH_2Cl_2 (140 mL) was added, sequentially, commercial aq *tert*-butyl hydroperoxide (70%; 3.43 mL, 24.99 mmol) and alcohol **18** (1.4 g, 6.25 mmol). After stirring for 21 h at r.t. under an air atmosphere, the mixture was quenched with aq $Na_2S_2O_3$ (5%; 100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude material was purified by flash chromatography (PE–EtOAc, 6:4 then 5:5) to give the desired product **20**.

Yield: 0.958 g (69%); white solid; mp 174–175 °C.

Method B: To a stirred solution of ketone **24** (0.250 g, 0.66 mmol) in THF (3 mL) under an argon atmosphere, was added TBAF (1M in THF, 1.45 mL, 1.45 mmol). The mixture was stirred 3 h at r.t. then quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (PE–EtOAc, 6:4 then 5:5) to provide the desired ketone.

Yield: 130 mg (88%); white solid; mp 174 °C.

IR (KBr): 1659 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.64 (d, *J* = 3.4 Hz, 1 H, H-3), 7.50–7.63 (m, 4 H, H-2 and ArH), 7.84 (d, *J* = 7.7 Hz, 2 H, ArH), 8.46 (s, 1 H, H-4), 8.90 (s, 1 H, H-6), 11.70 (br s, 1 H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 102.6 (C-3), 119.9 (C_q), 127.3 (C-2 and C_q), 128.6 (CH_{Ph}), 130.1 (CH_{Ph}), 132.0 (C-4), 132.5 (CH_{Ph}), 138.3 (C_q), 145.5 (C-6), 150.4 (C_q), 196.0 (C_q).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}N_2O$: 223.0871; found: 223.0872.

4-Chloro-1-triisopropylsilanyl-1*H*-pyrrolo[2,3-*b*]pyridine (21)

Prepared according to the procedure described by Benoît, Gringas and Soundara.[8]

(4-Chloro-1-triisopropylsilanyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-yl)phenylmethanol (22)

A round-bottom flask was evacuated and backfilled with argon. The flask was charged with 4-chloro-7-azaindole (**21**; 1.5 g, 4.86 mmol) and THF (50 mL) and the mixture was cooled to –78 °C. *s*-BuLi (1.3 M in hexane–cyclohexane, 8.2 mL, 10.69 mmol) was added dropwise and, after stirring for 30 min at –78 °C, benzaldehyde (1.3 mL, 12.15 mmol) was added rapidly. The mixture was stirred for 14 h at ambient temperature then sat. NH_4Cl (40 mL) was added. After extraction with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (PE–EtOAc, 98:2) to obtain the desired azaindole **22**.

Yield: 1.88 g (93%); colourless oil.

IR (NaCl): 758, 1216, 3620 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03–1.12 (m, 18 H, CH_3), 1.82 (sept, *J* = 7.6 Hz, 3 H, CH *i*-Pr), 2.67 (s, 1 H, OH), 6.35 (s, 1 H, C*H*OH), 6.63 (d, *J* = 3.5 Hz, 1 H, H-3), 7.23–7.47 (m, 6 H, H-2 and ArH), 8.33 (s, 1 H, H-6).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.3 (CH *i*-Pr), 18.2 (CH_3 *i*-Pr), 71.9 (*C*HOH), 101.9 (C-3), 121.6 (C_q), 126.7 (CH_{Ph}), 127.6 (CH_{Ph}), 128.4 (C_q), 128.5 (CH_{Ph}), 132.3 (C-2), 133.5 (C_q), 142.7 (C-6), 142.8 (C_q), 153.6 (C_q).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{32}N_2O^{28}Si^{35}Cl$: 415.1972; found: 415.1985.

Phenyl(1-triisopropylsilanyl-1*H*-pyrrolo[2,3-b]pyridine-5-yl)methanol (23)

To a solution of **22** (0.580 g, 1.40 mmol) in THF (24 mL), was added ammonium formate (0.325 g, 5.04 mmol), H_2O (8 mL) and Pd/C (5%; 0.232 g). The mixture was stirred under an argon atmosphere for 28 h at r.t., then filtered and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (PE–CH_2Cl_2, 5:5 then 0:10) to obtain the azaindole **23**.

Yield: 410 mg (77%); colourless oil.

IR (NaCl): 1021, 2868, 3610 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 7.5 Hz, 18 H, CH_3 *i*-Pr), 1.84 (sept, *J* = 7.5 Hz, 3 H, CH *i*-Pr), 2.28 (br s, 1 H, OH), 5.98 (s, 1 H, C*H*OH), 6.49 (d, *J* = 3.5 Hz, 1 H, H-3), 7.25–7.47 (m, 6 H, H-2 and ArH), 7.82 (d, *J* = 2.0 Hz, 1 H, H-4), 8.28 (d, *J* = 2.0 Hz, 1 H, H-8).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.4 (CH *i*-Pr), 18.3 (CH_3 *i*-Pr), 75.1 (*C*HOH), 103.2 (C-3), 122.2 (C_q), 126.6 (C-4), 126.5 (CH_{Ph}), 127.6 (CH_{Ph}), 128.6 (CH_{Ph}), 131.6 (C_q), 132.0 (C-2), 142.1 (C-6), 144.0 (C_q), 153.8 (C_q).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{33}N_2O^{28}Si$: 381.2362; found: 381.2378.

Phenyl(1-triisopropylsilanyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-yl)methanone (24)

To a stirred solution of alcohol **23** (0.410 g, 1.08 mmol) in toluene (30 mL) under an argon atmosphere was added manganese dioxide (0.939 g, 10.80 mmol). The reaction mixture was stirred under reflux with a Dean–Stark trap for 20 h. After filtration through celite, the filtrate was evaporated under reduced pressure and the crude product was purified by flash chromatography (PE–CH_2Cl_2, 5:5 then 0:10) to provide the protected ketone.

Yield: 68%; colourless oil.

IR (NaCl): 1651, 2948 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 7.5 Hz, 18 H, CH_3 *i*-Pr), 1.88 (sept, *J* = 7.5 Hz, 3 H, CH *i*-Pr), 6.65 (d, *J* = 3.5 Hz, 1 H, H-3), 7.39 (d, *J* = 3.5 Hz, 1 H, H-2), 7.46–7.61 (m, 3 H, ArH), 7.84 (d, *J* = 7.9 Hz, 2 H, ArH), 8.36 (d, *J* = 2.2 Hz, 1 H, H-4), 8.78 (d, *J* = 2.2 Hz, 1 H, H-6).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.3 (CH *i*-Pr), 18.1 (CH_3 *i*-Pr), 104.4 (C-3), 121.5 (C_q), 126.1 (C-4), 128.3 (CH_{Ph}), 129.9 (CH_{Ph}), 130.6 (CH_{Ph}), 132.1 (C-2), 132.9 (C_q), 138.4 (C_q), 145.3 (C-6), 155.7 (C_q), 196.2 (C_q).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{31}N_2O^{28}Si$: 379.2206; found: 379.2219.

Acknowledgment

The Authors thank the ACI 'Molécules et cibles thérapeutiques' (CP) and Les Laboratoires Servier (CEB) for financial support.

References

(1) Mérour, J.-Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *5*, 471; and references cited therein.
(2) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031.
(3) Zhang, Z.; Yang, Z.; Wong, H.; Zhu, J.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *J. Org. Chem.* **2002**, 6226.
(4) Thibault, C.; L'Heureux, A.; Bhide, R. S.; Ruel, R. *Org. Lett.* **2003**, *5*, 5023.
(5) Minakata, S.; Komatsu, M.; Ohshiro, Y. *Synthesis* **1992**, 661.
(6) During the referee process, an alternative syntheses of 6-cyano-7-azaindole(**4**) was reported, see: Storz, T.; Bartberger, M.; Sukit, S.; Wilde, C.; Soukup, T. *Synthesis* **2008**, 201.
(7) An Minakata, S.; Hamada, T.; Komatsu, M. *J. Agric. Food Chem.* **1997**, *45*, 2345.
(8) Benoît, S.; Gringas, S.; Soundara, N. PCT Int. Appl. WO 2003082289, **2003**; *Chem. Abstr.* **2003**, *139*, 307795.
(9) Fife, W. K. *J. Org. Chem.* **1983**, *48*, 1375.
(10) Vorbrüggen, H.; Krolikiewicz, K. *Synthesis* **1983**, 316.
(11) It is noteworthy that using Et_3N stored on KOH, the reaction did not work.
(12) (a) Guillaumet, G.; Savelon, L.; Viaud, M. C.; Pavli, P.; Renard, P.; Pfeiffer, B.; Caignard, D. H.; Bizo-Espiard, J. G. Eur. Pat. Appl. EP 691339, **1996**; *Chem. Abstr.* **1996**, *124*, 261019p. (b) Mazéas, D.; Guillaumet, G.; Viaud, M. C. *Heterocycles* **1999**, *50*, 1065.
(13) Estel, L.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 2740.
(14) (a) Leusink, A. J.; Budding, H. A.; Drenth, W. *J. Organomet. Chem.* **1968**, *11*, 541. (b) Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365.
(15) Sakamoto, T.; Satoh, C.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1992**, *34*, 2379.
(16) Moyer, M.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.
(17) Brière, J.-F.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Heterocycles* **2000**, *52*, 1371.
(18) N'Ait Ajjou, A.; Muzart, J.; Savelon, L.; Guillaumet, G. *Synthesis* **1993**, 539.
(19) L'Heureux, A.; Thibault, C.; Ruel, R. *Tetrahedron Lett.* **2004**, *45*, 2317.
(20) Bourguignon, G.; Quéguiner, G. *J. Heterocycl. Chem.* **1989**, *26*, 1029.
(21) Bhupathy, M.; Conlon, D.; Wells, K.; Nelson, J.; Reider, P.; Rossen, K.; Sager, J.; Volante, R.; Dorsey, B.; Hoffman, J.; Joseph, S.; McDaniel, S. *J. Heterocycl. Chem.* **1995**, *32*, 1283.