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Synthesis of functionalized 7-azaindoles via directed *ortho*-metalations ☆

Alexandre L'Heureux,* Carl Thibault and Réjean Ruel

Bristol-Myers Squibb, Institut de recherche pharmaceutique, 100 boul. de l'Industrie, Québec, Candiac, Canada J5R 1J1

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Abstract—Functionalization at C-5 of 4-fluoro- and 4-chloro-1-triisopropylsilyl-7-azaindole, **1** and **2**, respectively, leads to a variety of new substituted 7-azaindole derivatives. We also describe two approaches to introduce functionality at C-6.

7-Azaindole derivatives may be considered as useful indole bioisosteres in medicinal chemistry and functionalization at C-2 and C-3 of the 7-azaindole ring system is well described in the scientific literature. Substitution of the pyrrole ring has been effected either directly on the 7-azaindole core or, alternatively, by cyclization of a requisite pyridine precursor.[1] On the other hand, the limited number of examples of 4-, 5-, and 6-substituted 7-azaindoles reported thus far have been synthesized almost exclusively from functionalized pyridine precursors.[1] Consequently, we wish to describe herein efficient procedures for the functionalization at C-5 and C-6 of the 7-azaindole ring system. In addition, an application of this methodology yielding an improved synthesis of 5-hydroxy-7-azaindole (**6**) is described.

Table 1 summarizes the results we obtained when *N*-triisopropylsilyl-4-fluoro-7-azaindole (**1**)[2] and *N*-triisopropylsilyl-4-chloro-7-azaindole (**2**)[3] were submitted to directed *ortho*-metalation,[4] followed by the addition of an electrophile to the resulting anion to afford 4,5-disubstituted-7-azaindoles **3** and **4**, respectively (Scheme 1). The bulky silicon group prevents the lithiation at C-2 of the indole ring, therefore allowing metalation on the pyridine ring. Consequently, when *N*-silylated-4-fluoro-azaindole **1** was allowed to react with 1.5 equiv of *sec*-butyllithium at −78 °C for 1 h, followed by the addition of *N*-fluorobenzenesulfonimide (NFSI),[5] 4,5-difluoro-7-azaindole **3a** was obtained in 70% yield.[6] Introduction of chloride or bromide at C-5 was best carried out when hexachloroethane or carbon tetrabromide was used as electrophiles. In the latter case, the use of *N*-bromosuccinimide resulted in the isolation of bromide **3c** in only 26% yield (entry 4), along with 38% yield of the product resulting from bromination at C-3. Interestingly, this competitive electrophilic process was minor with 4-chloro-1-triisopropylsilanyl-7-azaindole (**2**) and bromide **4c** (entry 12) was isolated in 68% yield with NBS and 80% when CBr_4[7] was used as the electrophile. Control experiments without any added base showed rapid formation of the 3-bromo regioisomers in both the 4-fluoro and 4-chloro series.

The preparation of 5-hydroxy-4-fluoro-7-azaindole **3f** and 5-hydroxy-4-chloro-7-azaindole **4f** was best accomplished using camphorsulfonyloxaziridine[8] and Ti(*i*-PrO)$_4$/*t*-BuOOLi.[9] The former led to only 60% conversion to the alcohol **3f** and 58% isolated yield, while the latter led to complete conversion to the alcohol albeit in 50% isolated yield. In the case of 5-amino-7-azaindoles **3e** and **4e**, the preparation was accomplished using tosylazide[10] as the electrophile. The crude azide formed was then directly reduced to the amine by catalytic hydrogenation with palladium on charcoal in 30% and 41% overall isolated yield, respectively (entries 6 and 14). Finally, the anion derived from *N*-triisopropylsilyl-4-chloro-7-azaindole (**2**) was treated with triisopropylborate and the boronic acid was obtained in 47% yield after ester hydrolysis during the acidic work-up. This product was coupled under Suzuki condition[11] to afford **4h** (Scheme 1, E = Ph) in 41% yield.

Keywords: *ortho*-Metalation; 7-Azaindole.
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* Corresponding author. Tel.: +1-450-4446132; fax: +1-450-4444166; e-mail: alexandre.lheureux@bms.com

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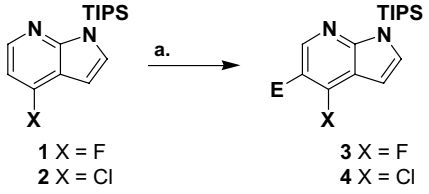
Table 1. Reactions of metalated azaindole with electrophile

Entry	Reactant	Electrophile	Product R (**3** or **4**)	Yield (%)
1	**1**	NFSI	F (**3a**)	70
2	**1**	C_2Cl_6	Cl (**3b**)	68
3	**1**	CBr_4	Br (**3c**)	63
4	**1**	NBS	Br (**3c**)	26
5	**1**	$ClCO_2Me$	CO_2Me (**3d**)	87
6	**1**	Tosylazide	NH_2 (**3e**)	30
7	**1**	Camphorsulfonyloxaziridine	OH (**3f**)	58
8	**1**	Ti(*i*-PrO)$_4$/*t*-BuOOLi	OH (**3f**)	50
9	**2**	NFSI	F (**4a**)	60
10	**2**	C_2Cl_6	Cl (**4b**)	86
11	**2**	CBr_4	Br (**4c**)	80
12	**2**	NBS	Br (**4c**)	68
13	**2**	$ClCO_2Me$	CO_2Me (**4d**)	79
14	**2**	Tosylazide	NH_2 (**4e**)	66
15	**2**	Camphorsulfonyloxaziridine	OH (**4f**)	65
16	**2**	Ti(*i*-PrO)$_4$/*t*-BuOOLi	OH (**4f**)	60
17	**2**	B(O-*i*-Pr)$_3$	$B(OH)_2$ (**4g**)	47

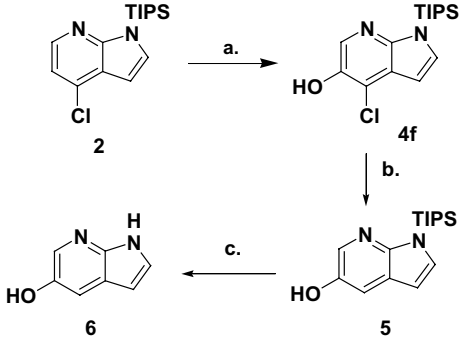


Scheme 1. Reagents and conditions: (a) (i) *sec*-BuLi, 1.5 equiv, THF, −78 °C, 1 h; (ii) electrophile (E).

In summary, the above reaction conditions resulted in clean *ortho*-metalations at C-5 without any sign of halogen scrambling,[12] pyridyne formation,[13] or competitive lithiation at C-2.[14]

The above methodology was also used to improve on the previously reported syntheses of 5-hydroxy-7-azaindole (**6**). The synthesis of alcohol **6** was first reported by Robinson et al., starting from 7-azaindoline-*N*-oxide[15] while the synthesis of the corresponding methyl ether was described by Viaud et al.[16] In the former synthesis, a nonregioselective N-oxide rearrangement with acetic anhydride was reported to give a mixture of 5- and 6-acetoxyazaindoline, while the latter approach involved an Ullman coupling of 5-bromo-7-azaindole. We obtained alcohol **6** in three steps and 26% overall yield starting from 4-chloro-1-triisopropylsilanyl-7-azaindole (**2**) (Scheme 2). Reduction of 4-chloro-5-hydroxy-1-triisopropylsilanyl-7-azaindole (**4f**) with zinc in EtOH/acetic acid gave 5-hydroxy-1-triisopropylsilanyl-7-azaindole (**5**) in 65% yield. The silicon group was then removed using TBAF to provide 5-hydroxy-7-azaindole (**6**) in 70% yield.

Iterative lithiation leading to 4,5,6-trisubstituted 7-azaindoles can also be carried out when an *ortho*-directing group is introduced at C-5 although alkyllithium bases could not be used due to aromatic nucleophilic substitutions of fluorine or chlorine at C-4. For example, 4-chloro-5-fluoro-1-triisopropylsilanyl-7-azaindole was deprotonated with lithium tetramethylpiperidide

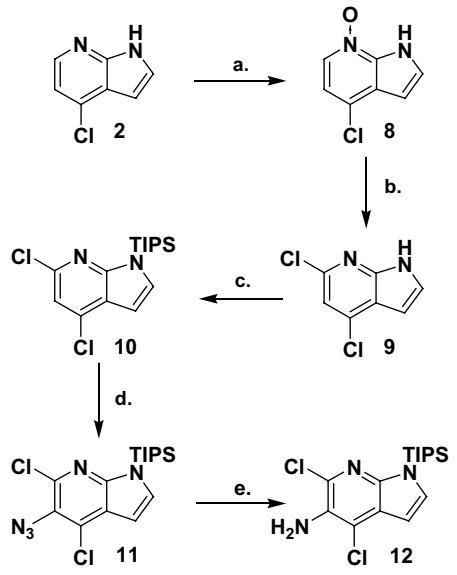


Scheme 2. Reagents and conditions: (a) *sec*-BuLi, THF, −78 °C, camphorsulfonyloxaziridine; (b) Zn, AcOH, EtOH; (c) TBAF, THF.

(LiTMP) in THF at −78 °C and the resulting anion was trapped with methylchloroformate to yield 6-carbomethoxy-4-chloro-5-fluoro-1-triisopropylsilyl-7-azaindole (**7**) in 61% yield (Scheme 3).

Alternatively, functionalization at C-6 could also be carried out through a rearrangement involving an appropriate N-oxide. This strategy has the advantage of providing access to 4,6-disubstituted azaindoles, as well as 4,5,6-trisubstituted-7-azaindoles bearing non-*ortho*-directing functional groups at the 5-position. For example, 4-chloro-7-azaindole-*N*-oxide **8** was reacted with methanesulfonyl chloride to give 4,6-dichloro-7-azaindole (**9**) in 58% yield (Scheme 4). This product was then protected with triisopropylsilyl chloride to give 4,6-dichloro-1-triisopropylsilyl-7-azaindole (**10**) in 76% yield. *ortho*-Metalation with *sec*-butyllithium, followed

Scheme 3. Reagents and conditions: LiTMP, THF, −78 °C; $ClCO_2Me$.



Scheme 4. Reagents and conditions: (a) *m*-CPBA, $CHCl_3$; (b) $MeSO_2Cl$, DMF, 80 °C; (c) NaH, TIPSCl, THF, 80 °C; (d) *sec*-BuLi, THF, −78 °C, tosylazide; (e) H_2, Pd/C, EtOAc.

by addition of tosylazide to the resulting anion, gave 5-azido-4,6-dichloro-1-triisopropylsilanyl-7-azaindole (**11**) in 46% yield. This product can be reduced to 5-amino-4,6-dichloro-1-triisopropylsilanyl-7-azaindole (**12**) using catalytic hydrogenation in a quantitative yield.

In summary, we have demonstrated a new strategy for the functionalization of 7-azaindoles leading to substitution patterns difficult to obtain using existing methodology. We have also described the application of this new methodology in an improved synthesis of 5-hydroxy-7-azaindole (**6**).

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6. *Typical procedure*: A 10 mL oven-dried round-bottom flask was evacuated and backfilled with argon. The flask was charged with 4-fluoro-1-triisopropylsilanyl-1*H*-pyrrolo[2,3-*b*]pyridine (169 mg, 0.58 mmol), THF (4 mL) and the mixture was cooled to −78 °C. A *sec*-butyllithium solution (263 μL, 1.10 M in cyclohexane, 2.2 equiv) was added dropwise and after 30 min hexachloroethane (342 mg, 1.45 mmol) in THF (4 mL) was added rapidly. After 25 min, a solution of saturated ammonium chloride was added and the mixture was allowed to reach room temperature and it was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified using HPLC preparative reverse phase (RP): Primesphere® C-18-HC 21 × 100 mm column with solvent system: solvent A: 10% acetonitrile/90% water + 5 mM NH_4OAc; solvent B: 90% acetonitrile/10% water + 5 mM NH_4OAc, with 20–100% B. This procedure gave 136 mg (72%) of (**3b**) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.22 (1H, d, $J = 9.4$ Hz), 7.30 (1H, d, $J = 3.6$ Hz), 6.65 (1H, d, $J = 3.6$ Hz), 1.86 (3H, m), 1.13 (18H, d, $J = 7.6$ Hz). LCMS (solvent A: 10% acetonitrile/90% water + 5 mM NH_4OAc; solvent B: 90% acetonitrile/10% water + 5 mM NH_4OAc, with 50–100% B in 2 min gradient. Column Primesphere C4 4.6 × 30 mm, UV: 220 nm; Micromass ZMD 2000, ESI) m/z 327 ($M + H^+$), $t_R = 2.11$ min, purity = 100%. HPLC (solvent A: 10% acetonitrile/90% water + 0.05% TFA; solvent B: 90% acetonitrile/10% water + 0.05% TFA, with 50–100% B in 2 min gradient. Column Primesphere C4 4.6 × 30 mm, UV: 220 nm) $t_R = 2.28$ min, purity = 100%.
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11. (a) Conditions: **4g**, PhBr 1 equiv, $PdCl_2$ dppf 0.1 equiv, Cs_2CO_3 3 equiv, THF, 65 °C, 3 h, yield 41% yield of **4h** (E = Ph). (b) For an excellent review see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
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