Synthetic Methods

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In Situ Anionic Shielding for Regioselective Metalation: Directed *peri* and Iterative Metalation Routes to Polyfunctionalized 7-Azaindoles**

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Dedicated to Professor F. Marsais and Professor G. Quéguiner

Herein we report on a) the unusual *peri*(C4)-metalation[1] reactivity of N-unprotected 7-azaindole 3-tertiary amide and 3-sulfonamide dianion frameworks (**1**, Figure 1) using the new concept of anionic shielding of C2 and its generalization for the synthesis of 4-substituted derivatives, b) the use of the

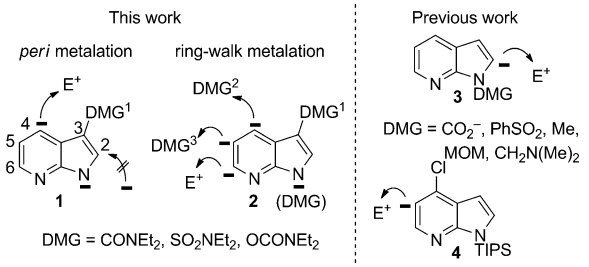

Figure 1. Metalation chemistry of 7-azaindoles.

thereby derived powerful directed metalation group (DMG) $CONEt_2$ on C4 for the directed *ortho* metalation (D*o*M) of C5, thus leading, through the linked Suzuki[2] and directed remote metalation (DreM)[3] chemistries, to new annulated heterocyclic systems, and c) the use of a ring-walk metalation platform (**2**) for the regioselective construction of polysubstituted 7-azaindoles. The reported results constitute, to the best of our knowledge, the first observation of *peri*-metalation of $CONEt_2$ and SO_2NEt_2 DMG systems,[4,5] demonstrate the advantages of multiple sequential D*o*M reactions, and offer a rational and general regioselective route to polysubstituted 7-azaindoles and the thereby derived, previously unknown, heterocycles of potential pharmaceutical significance.

Although first synthesized in 1927,[6] the azaindole (pyrrolopyridine) ring systems have attracted considerable attention from the synthetic chemistry community over the past decade because they represent promising building blocks with evolving potential and demonstrated value in pharmaceuticals and agrochemicals (Figure 2).[7,8] Among the four

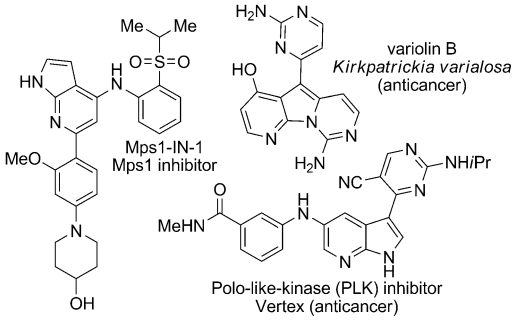

Figure 2. 7-Azaindole-containing pharmaceuticals and natural products.

isomeric systems, the commercially available 7-azaindole[9] systems have received the greatest synthetic attention because of their broad spectrum of biological activity.[7,10,11]

To date, the majority of synthetic methods for 7-azaindoles have provided N1-, C2-, or C3-substituted systems, with few procedures offering general solutions for pyridine ring functionalization.[12,13] To place into perspective with our work, the previous D*o*M synthetic chemistry of 7-azaindoles is based on the corresponding indole results[14] leading to the regioselective C2 functionalization (**3**; Figure 1)[15] with very limited examples of selective pyridine ring metalation and the requirement of circuitous, multistep sequences (**4**).[16]

To test the notion that the formation of the N anion of 7-azaindole would constitute a protective measure against the normally favored C2 deprotonation and thereby lead to pyridine ring metalation, systematic experiments were carried out using the CD_3OD electrophile quench (Table 1). Metalation of **5a** in THF [0.07 M], using 2.5 equivalents of *s*BuLi/TMEDA at −78 °C and normal addition conditions, showed a clean reaction at C4 to yield **6a** in 95% yield ($D_1 = 80\%$; entry 1). Attempts to drive the metalation to completion (−40 °C, 1 h) resulted in higher D_1 incorporation (90%; entry 2) but also with the formation of by-products resulting from *s*BuLi and, surprisingly, THF addition to the amide (see the Supporting Information).[17] Through careful optimization, we found that after 5 minutes and 15 minutes of metalation time at −40 °C, clean but lower C4 deuterium incorporation of 65% and 80%, respectively (Table 1, entries 3 and 4) were achieved whereas longer reaction times at −40 °C led to the formation of by-products with a similar deuterium incorporation (entry 5). Consideration of the metalation time and observed insolubility of intermediate anionic species led to the establishment of optimized reaction conditions[18] (higher dilution [0.03 M] and inverse addition of

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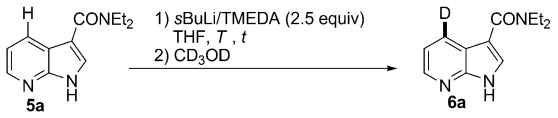
Table 1: Optimization of time and temperature in the metalation of azaindole **5a**.

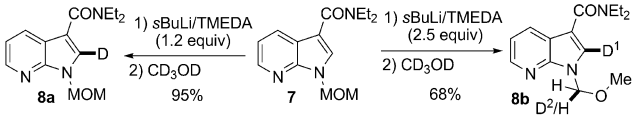


Entry	*T* [°C]	*t* [min]	D_1 [%][a]	Product
1	−78 °C	60	80[b]	**6a**
2	−40 °C	60	90[b]	**6a**[d]
3	−40 °C	5	65[b]	**6a**
4	−40 °C	15	80[b]	**6a**
5	−40 °C	30	85[b]	**6a**[d]
6	−40 °C	10	95[c]	**6a**

[a] D_1 incorporation at C4 determined by ^{1}H NMR spectroscopy. [b] Normal addition, [0.07 M]. [c] Inverse addition, [0.03 M]. [d] A side product was also obtained; see the Supporting Information.

2.5 equiv of *s*BuLi/TMEDA, −78 °C for 30 min then −40 °C, 10 min) which afforded the C4-deuterated product **6a** (D_1 = 95 %; entry 6).[19] For complete studies using CD_3OD and MeI quenches, see the Supporting Information.

To determine the effect of the N anion in the C4 deprotonation event, the N-MOM azaindole **7** was subjected to the −78 to −40 °C, inverse addition protocol using either 1.2 equivalents or 2.5 equivalents of *s*BuLi/TMEDA. When using 1.2 equivalents of *s*BuLi/TMEDA, the C2-deuterated product **8a** was obtained in 95 % yield (D_1 = 95 %; Scheme 1).

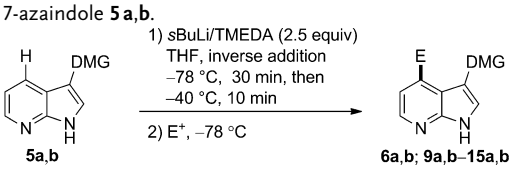


Scheme 1. Deuteration studies on the 7-azaindole **7**. The metalation was run at −78 °C for 30 min, then −40 °C for 10 min, with a subsequent CD_3OD quench at −78 °C.

In contrast, the use of 2.5 equivalents of *s*BuLi/TMEDA led to a complex mixture from which the main product **8b** was isolated in 68 % yield (C2 D_1 = 95 %, and MOM D_2 = 25 %). Significantly, the N-MOM C4-deuterated azaindole derivative was not detected. As a result of this stark contrast in selectivity between **5a** and **7**, we conclude that the C4 lithiation regioselectivity is driven by the N-anionic shielding effect (Table 1 and Scheme 1).

With the optimized inverse addition conditions in hand, the establishment of the scope of the *peri*(C4)-metalation reaction was undertaken for the azaindole **5a** and extended to the corresponding 3-SO_2NEt_2 derivative **5b** (Table 2). Thus, aside from deuterated products (**6a**,**b**), methylated (**9a**,**b**), carbinol (**10a**,**b**) and 4-formyl (**11a**) derivatives were obtained in both series in good to excellent yields. Noteworthy is the formation of the methylated derivatives **9a**,**b** to the complete exclusion of N-methylated products, most likely a result of the insolubility of intermediate anionic species (for details, see the Supporting Information). The difference in terms of yield between the two formylated products **11a** and

Table 2: Scope of C4 *peri*-metalation reaction of 3-$CONEt_2$ and 3-SO_2NEt_2 7-azaindole **5a**,**b**.



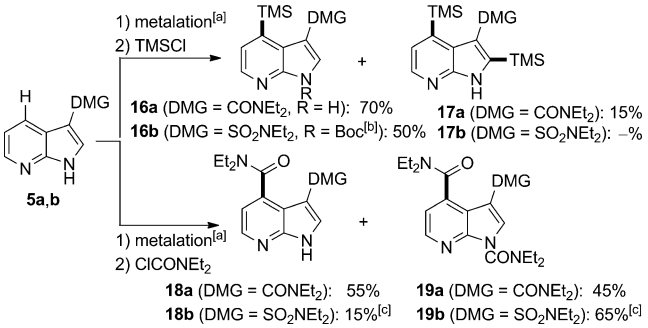
5a: DMG = $CONEt_2$, **5b**: DMG = SO_2NEt_2

Entry	E^+	Product (DMG, E)	Yield [%][a]
1	CD_3OD	**6a** ($CONEt_2$, D)	95
		6b (SO_2NEt_2, D)	85
2	MeI	**9a** ($CONEt_2$, Me)	94
		9b (SO_2NEt_2, Me)	87
3	*p*-$MeOC_6H_4CHO$	**10a** ($CONEt_2$, *p*-$MeOC_6H_4CHOH$)	95
		10b (SO_2NEt_2, *p*-$MeOC_6H_4CHOH$)	85
4	DMF	**11a** ($CONEt_2$, CHO)	94
		11b (SO_2NEt_2, CHO)	50[b]
5	*i*PrOBpin	**12a** ($CONEt_2$, Bpin)	54
		12b (SO_2NEt_2, Bpin)	73
6	*i*PrOBpin then H_2O_2	**13a** ($CONEt_2$, OH)	74
		13b (SO_2NEt_2, OH)	64
7	NFSI	**14a** ($CONEt_2$, F)	–
		14b (SO_2NEt_2, F)	72[b,c]
8	Cl_3CCCl_3	**15a** ($CONEt_2$, Cl)	85[d]
		15b (SO_2NEt_2, Cl)	45[d]

[a] Yield based on the isolated product after flash chromatography. [b] Yield based on ^{1}H NMR analysis of crude material after 2 steps. [c] To facilitate purification, the $PhSO_2$ derivative was prepared and purified by preparative HPLC. [d] The Boc derivative was prepared to facilitate purification. NFSI = *N*-fluorodibenzenesulfonimide, pin = pinacol.

11b is due to the difficulty in purification of the latter product (entry 4). The borylated derivatives **12a**,**b**, although formed quantitatively (^{1}H NMR), were isolated in modest yields presumably because of their instability to silica gel chromatography (entry 5). Nevertheless, their treatment with hydrogen peroxide[20] led to the interesting 4-hydroxy derivatives **13a**,**b** (entry 6). These structures were confirmed by nOe correlation, thus ruling out the possibility of the alternative pyridone tautomeric forms.

Although the reaction of dimetalated derivative **5a** with NFSI led only to the recovery of the starting material (95 %), the corresponding **5b** afforded the 4-fluoro azaindole **14b** (Table 2, entry 7).[21] Chlorination with Cl_3CCCl_3 proceeded well to afford the compounds **15a**,**b** in 45–85 % yields over two steps (entry 8). The structure of **10a** was confirmed by single-crystal X-ray structure determination (see the Supporting Information). Using TMSCl as an electrophile, both mono- and bis(silylated) products (**16a** and **17a**, respectively) were obtained (Scheme 2). To preclude the formation of the minor product **17a**, previously precedented to occur as an N- to C2 TMS migration in indoles,[22] the reaction mixture was maintained at −78 °C for 1 hour after addition of TMSCl and quenched with MeOH at the same temperature. In the case of **5b**, the optimum 70 % conversion (^{1}H NMR) into **16b** was achieved by maintaining the reaction temperature at −78 °C for 4 hours after the addition of TMSCl. Carrying out

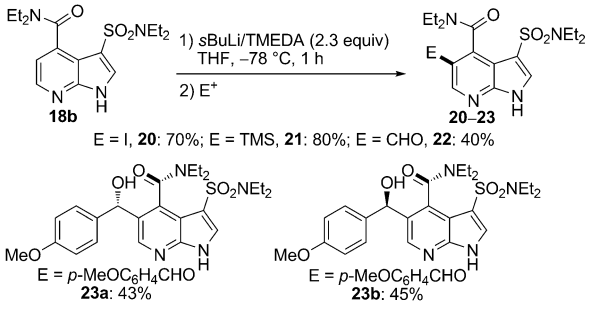


Scheme 2. Reaction of metalated **5a**,**b** with TMSCl and $ClCONEt_2$. [a] Metalation: *s*BuLi/TMEDA (2.5 equiv), inverse addition, THF [0.03 M], −78 °C, 30 min, then −40 °C, 10 min; and then E^+, −78 °C; [b] Boc Protection: Boc_2O (1.5 equiv), DMAP (cat.), CH_3CN, 12 h, RT. [c] The reaction performed on a 3 g scale gave similar yields. Boc = *tert*-butoxycarbonyl, DMAP = 4-(dimethylamino)pyridine, THF = tetrahydrofuram, TMS = trimethylsilyl, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylendiamine.

a quench with the important DMG-generating electrophile $ClCONEt_2$ (3.0 equiv) afforded a mixture of mono- and dicarbamoylated products (**18a**,**b** and **19a**,**b**, respectively; Scheme 2) in nearly quantitative yields. The difference in product ratios **18a**/**19a** and **18b**/**19b** may be a consequence of anion solubility (see the Supporting Information).

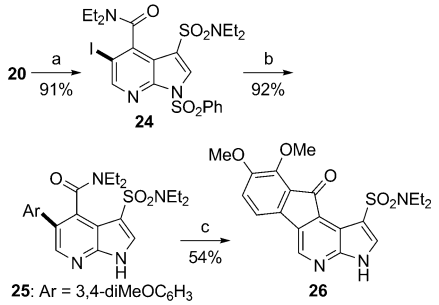
In the quest of iterative D*o*Ms on the azaindole scaffold, we selected the derivative **18b** (also obtained by N-decarbamoylation of **19b**[23]), bearing the potent DMG $CONEt_2$ on C4, to determine if C5 over C2 metalation would continue to prevail and thereby provide new routes to pyridine ring substituted 7-azaindoles. Following optimization conditions, selective C5 lithiation (2.3 equiv of *s*BuLi/TMEDA, −78 °C) of **18b** was achieved and quenching with several electrophiles at −78 °C afforded the 5-substituted azaindoles **20**–**23** in modest to very good yields (Scheme 3).

Interestingly, compound **23** was obtained as two separable diastereoisomeric atropoisomers in approximately a 1:1 ratio. The structure of the *syn* diastereoisomer was established by X-ray analysis (see the Supporting Information).[24] Furthermore, unambiguous confirmation of the atropoisomeric nature of the products was established through thermal interconversion which afforded approximately a 1:1 mixture of atropoisomers regardless of the diastereoisomer employed (for details, see the Supporting Information). Suzuki–Miyaura



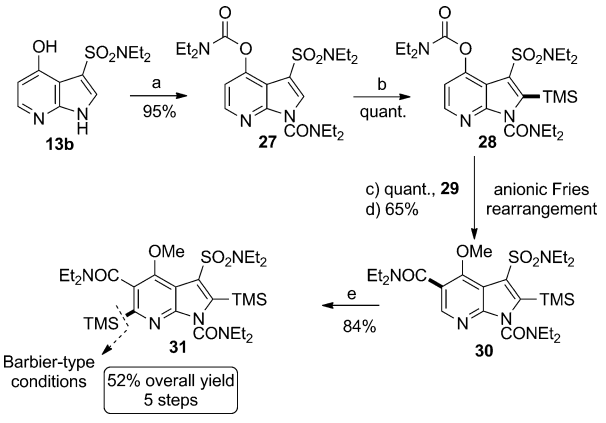
Scheme 3. D*o*M reaction at C5 of **18b**.

cross-coupling of **24** gave the 5-aryl derivative **25**, which was converted by the DreM protocol[3] into the fused azafluorenone[25] **26** (54 %), which represents an important skeleton in medicinal chemistry (Scheme 4).[26]



Scheme 4. a) NaH, $PhSO_2Cl$, DMF, 70 °C; b) $[PdCl_2(dppf)]_2 \cdot CH_2Cl_2$ (8 mol %), K_2CO_3 (4 equiv), 3,4-di$MeOC_6H_3B(OH)_2$, 1,4-dioxane/H_2O (2:1), 100 °C; c) LDA (10 equiv), THF, 60 °C, 4 h. dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, DMF = *N*,*N*′-dimethyfomamide, LDA = lithium diisopropylamide.

In continuation of the iterative D*o*M path, we sought to functionalize the remaining C6 position, thus completing the exhaustive functionalization of 7-azaindole through a ring-walk metalation strategy (Scheme 5). In this quest, treatment of the 4-hydroxy azaindole **13b** with $ClCONEt_2$ in the presence of Hünig's base afforded the intermediate O,N-dicarbamoylated product **27** which, upon metalation with LiTMP (1.2 equiv) under Barbier in situ conditions,[27] afforded the TMS derivative **28** in quantitative yield, the structure of which was confirmed by X-ray crystallographic analysis (see the Supporting Information). Thus, the D*o*M reaction occurs synergistically between two DMGs as opposed to directed by the powerful $OCONEt_2$ DMG and



Scheme 5. Ring-walk metalation sequence to **31**. a) DIPEA (2.4 equiv), $ClCONEt_2$ (3.0 equiv), py, RT; b) LiTMP (1.2 equiv), TMSCl (1.2 equiv), THF, −78 °C, 1 h; c) *s*BuLi/TMEDA (1.3 equiv), THF, −78 °C to RT, 3 h; d) NaH (2.0 equiv), MeI (1.5 equiv), DMF, RT, 12 h; e) LiTMP (2.5 equiv), TMSCl (3.0 equiv), THF, −78 °C, 1 h. DIPEA = diisopropylethylamine, LiTMP = lithium 2,2,6,6-tetramethylpiperidide. **29** = 3-(*N*,*N*-Diethylsulfamoyl)-N^1,N^1,N^5,N^5-tetraethyl-4-hydroxy-2-(trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1,5-dicarboxamide (see the Supporting Information for the structure of **29**).

follows analogously to the C2 metalation result observed for the N-MOM azaindole **7**.

In the next step, the anionic *ortho*-Fries rearrangement[28] of **28** proceeded in quantitative yield to the amide **29** which, upon methylation, gave **30**, which was poised for the final D*o*M event. A second LiTMP/TMSCl in situ quench process afforded the richly functionalized **31** (for X-ray structure, see the Supporting Information), and completed the regioselective exhaustive elaboration of the azaindole core by a ring-walk metalation sequence.

In summary, we have demonstrated the regioselective *peri*(C4)-metalation of N-unprotected, powerful, and versatile[29] azaindoles **5a**,**b**, bearing a DMG on C3, through a new anionic C2 shielding concept, thus resulting in the first observation of *peri*-metalation of $CONEt_2$ and SO_2NEt_2 DMG systems. The reaction has been shown to be both robust and scalable.[30] The anionic shielding concept was extended to preferred C5 over C2 metalation to provide a general regioselective route to new azaindoles and fused derivatives. Importantly, we demonstrated by comparison of substrates **5a** and **7** that the N-anionic shielding effect is crucial to regioselectively lithiate the C4 position over the intrinsically favored C2 lithiation, thus allowing the first reported synthesis of the fully dressed azaindole **31** through a ring-walk metalation. The broader application of the derived synthetic chemistry may be anticipated.

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