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The Directed Metolation Group Dance. Regioselective Iterative Functionalization of 7-Azaindole by Controlled Annular Isomerism

Michael E. Dalziel[a], Jignesh J. Patel[a], Meagan K. Kaye[a], Jennifer L. Cosman[a], Matthew O. Kitching*[b], Victor Snieckus*[a]

Abstract: The regioselective functionalization of 7-azaindole by controlled annular directed metalation group isomerism is reported. The N-7 carbamoyl azaindoles 2a-b undergo regioselective metalation and electrophile quench to furnish C-6 substituted derivatives 3 which, in the presence of catalytic amount of CICONR₂ afford products 4 by an N-7 to N-1 carbamoyl group dance. A second directed metalation-electrophile quench sequence leads to a 2,6-substituted azaindole 5. Optimization of metalation conditions for C-2 and C-6, separately and iteratively, is presented. Using the directed metalation group dance strategy, a late-stage deuteriation of an antipsychotic drug is described. Overall, the controlled annular isomerism of a carbamoyl directing group allows multiple functionalization events of the bioactive azaindole scaffold.

Azaindoles occupy a prominent position in drug discovery research due to their diverse bioactivities, especially in the area of protein kinase inhibition for the development of anti-cancer therapies. Among the four isosteres, the 7-azaindole scaffold, also present in a rare class of natural products,[1] has emerged as the key heterocycle for structural modification for provision of new bioactive molecules (Figure 1, A).[2] Among the synthetic routes for 7-azaindole, metalation-based methodologies have achieved dominance over classical processes due to advantages of regioselectivity, multiple substitution and ready modification of the prototype nucleus.[3,4] In previous efforts, we have demonstrated the power of the directed ortho metalation (DoM) reaction in new halogen dance strategies,[5] anionic ortho-Fries rearrangement processes,[6] latent directed metalation group (DMG) protocols,[7] and, as demonstrated on the 7-azaindole framework, “walk-around-the-ring” sequences.[4a,4b,4c] Whilst synthetically powerful, these metalation based approaches involve several steps: DMG introduction, its use to direct the functionalization event, and its subsequent removal or modification.

Figure 1. A) 7-Azaindole in natural and bioactive molecules and drugs with azine and azole ring functionalization. B) Selective iterative functionalization through DMG controlled annular isomerization. C) Regioselective introduction and migration studies on 7-azaindole.

Inspired by the work of Sames on silyl migration,[9] we hypothesized that the N-7 DMG azaindole 2 would undergo DoM-mediated C-6 functionalization (Figure 1, B) and, by azine to azole ring DMG dance to the thermodynamically more stable
isomer (3→4), would allow C-2 functionalization to afford 2,6-
disubstituted azaindoles 5. Such a migration sequence

**Figure 2.** Regioselective synthesis of C-2 substituted 7-azaindoles. Reactions were performed on a 0.41 mmol scale. Reaction conditions: 6b (0.41 mmol, 1.0 equiv), LDA (0.90 mmol, 2.2 equiv), THF (0.10 M), −78 °C, 1 h, then E" (1.0−3.7 mmol, 2.5−9.0 equiv), −78 °C (1 h) to 23 °C (12 h). Yields of isolated products.

circumvents the removal and introduction of the DMG and would allow the same group to direct functionalization at a new, remote location. In continuing efforts to invent new DoM-founded chemistry,[10] we now report the successful attainment of the DMG dance concept (3→4), which establishes a regioselective route to 7-azaindoles bearing diverse C-2 (Table 1) and C-2 and C-6 (Figure 3) substitution patterns.

In order to test the DMG dance concept, the regioisomeric N-7 (2a,b) and N-1 (6a,b) carbamoyl azaindoles were prepared (Figure 1, C, for optimization see SI).[11] The choice of the CONR₂ as DMG was dictated by its previous efficacy in DoM chemistry.[40,12] Although N-1 DMG 7-azaindoles have been synthesized previously,[10,13] to the best of our knowledge, N-7 DMG-bearing 7-azaindole isomers are unknown. The identity of the two isomers was unambiguously confirmed by X-ray crystallography. To assess the expected thermodynamically driven DMG dance, compound 2b was subjected to a catalytic quantity of di-isopropyl carbamoyl chloride which led, under optimized conditions (see SI, Table 1), to the isomeric derivative 6b in 95% yield.

**With conditions for the introduction and migration of the DMG in place, selective functionalization of each ring in the azaindole scaffold was undertaken. Firstly, the DoM route to 2-substituted 7-azaindoles 7 was investigated (Figure 2). After considerable optimization (see SI), treatment of 6b with LDA using an inverse addition protocol led to efficient C-2 metalation affording 7a (90% yield, by 1H NMR). A comprehensive study of the reaction scope was undertaken, leading to the preparation of a variety of carbon, halogen, sulfur, and phosphorus 2-substituted derivatives 7b-I. Of particular note is the oxidative conversion of the B(OR)₂ derivative into the azaindole 7f[14] and the availability of substrates for further useful metalation (7e, f, h, j) and cross-coupling (7b-d, g, i, j, l) chemistry.

With conditions for C-2 functionalization in hand, investigation of the C-6 metalation process was conducted (Table 1, A). Metalation of 2a using s-BuLi/TMEDA or LDA followed by CD₂OD quench resulted in product with undetectable d- incorporation, suggesting lower C-6 H acidity compared to that of the pyridine C-2 acidity.[15] Using Barbier conditions (LDA/THMCl)[16] led to quantitative conversion to 3 (E = TMS) by GC-MS analysis of crude product (entry 4) but normal aqueous work-up resulted in desilylation to starting material 2a. Switching to anhydrous work-up conditions resulted in formation of products 3 (E = TMS and Bpin) in excellent conversion by 1H NMR (entries 5 and 6) but subjection to normal work-up also resulted in isolation of starting material 2a, undoubtedly the result of ipso-protoprotonolysis and ipso-protoprotoprotonolysis.[17] In view of the limited electrophile-base compatible combinations for the Barbier and Martin procedures, we returned to examine C-6 metalation of 2b using inverse addition-electrophile quench procedures. Gratifyingly, 2.5 equiv of LDA under inverse addition conditions gave product 3a with modest d- incorporation (entry 7, 73% yield). Switching to the more stERICALLY hindered LiTMP and modification of reaction temperature improved the level of anion formation considerably (entries 8 and 9, 90% and 93% yield, respectively).

Under the optimized conditions, the C-6 DoM chemistry of 2b was generalized (Table 1, B). As shown, the methodology allows the synthesis of halogen containing 3b-d, carbon-based 3e-g, and heteroatom-based 3h azaindole derivatives. A potentially useful finding is the observation of controlled monob-siodation of 2b simply by modification of the L₁ stoichiometry (3c vs 3d). Although high levels of conversion (>92%) were observed in all cases (1H NMR analysis), yields of isolated products were compromised due to their instability to column chromatography. Fortunately, simple exposure of the crude reaction products to the optimized DMG dance conditions afforded 6-substituted azaindoles 4 which proved readily separable. In this manner, methyl, carbamoyl, carbino1, and sulfide substituted products 4a-h (Table 1, C) were readily accessible in good to excellent yields.

To fully establish the DMG dance strategy for general regioselective C-2 and C-6 functionalization of the 7-azaindole scaffold, C-2 DoM reactions of substrate 4 were undertaken. Application of the optimized C-2 metalation conditions on 4, followed by electrophile quench, afforded products
In summary, we have illustrated an application of this annular DMG isomer concept in the regioselective synthesis of deuterated antipsychotic agent L-745870, a result which may anticipate late-stage derivatization of other commercial drugs.

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<th>Table 1. Optimization of C-6 metatllation, substrate scope and DMG migration from N-7 to N-1.</th>
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<td><strong>A</strong> Optimization of C-6 metatllation</td>
<td><strong>B</strong> C-6 metatllation substrate scope&lt;sup&gt;3,b&lt;/sup&gt;</td>
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<sup>a</sup> All % yields represent conversion as determined by 400 MHz H NMR analysis on the crude reaction mixture. B: Reaction conditions: 2b (0.41 mmol, 1.0 equiv), LiTMP (0.62 mmol, 1.5 equiv), THF (0.10 M), –78 °C (30 min) to –40 °C (10 min); then E+ (0.43–4.1 mmol, 1.05–10.0 equiv), –78 °C, 1.5 h. All % yields represent conversion as determined by 400 MHz H NMR on the crude reaction mixture. C: Reaction conditions: 2b (0.41 mmol, 1.0 equiv), LiTMP (0.62 mmol, 1.5 equiv), THF (0.10 M), –78 °C (30 min) to –40 °C (10 min); then E+ (0.43–4.1 mmol, 1.05–10.0 equiv), –78 °C, 1.5 h. After subsequent work-up: 3 (assumed 0.41 mmol, 1.0 equiv), CICONE<sub>2</sub>P<sub>3</sub> (0.10 mmol, 25 mol%), MeCN (0.04 M), 95 °C, 12 h. <sup>b</sup> All % yields are of isolated products over the two steps (i.e. from 2b).

5a–j in good yields (67–89%) (**Figure 3**). Of particular note, the presence of the powerful N-1 DMG overrides any competitive metatllation at C-5 aided by the potential DMGs present at C-6 (5k) including the powerful amide directing groups (5i). Given the prevalence of bioactive 2-arylated 7-azaizindole variants (e.g. GSK 1070916, **Figure 1, A**), we explored the feasibility of the cross-coupling of 5j with 4-nitrophenylboronic acid, two expectedly proficient coupling partners.<sup>16</sup> In a preliminary encouraging study, Suzuki-Miyaura coupling resulted in the formation of product 8 in good yield.

In consideration of the interest in deuterated molecules as new drug entities,<sup>19</sup> we undertook a deuteration study of the antipsychotic agent L-745870 (**Figure 4**). Thus, compound 10, prepared (see SI) and subjected to deuteration using the standard LDA protocol afforded 12 (88% yield, 74% <i>d</i>). Subjecting the isomeric N-7 carbanionyl derivative 11 to the LiTMP/D<sub>2</sub>O conditions as previously optimized (**Table 1, A**) followed by the catalytic DMG dance procedure afforded deuterated material 13 in 37% yield over two steps (79% <i>d</i>).

In summary, we have demonstrated a new DMG dance concept and developed it for a general and highly regioselective synthesis of 2- and 6- and combined 2,8-substituted 7-azaizindole derivatives. In addition, we have illustrated an application of this annular DMG isomer concept in the regioselective synthesis of deuterated antipsychotic agent L-745870, a result which may anticipate late-stage derivatization of other commercial drugs.
Aside from the viability of the DMG dance methodology for the construction of new and difficult to access 7-azaindoles, its adaption to similarly two-nitrogen related aza-heterocycles may be envisaged. Pertinent work is in progress and will be reported in due course.

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Keywords: Azaindole • DMG Dance • Iterative metalation • Regioselectivity • Lithiation

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Figure 3. Iterative C-6 and C-2 functionalization of 7-azaindole by DMG and DMG dance reactions. [a] yield from 4, [b] yield from 2b given in brackets over three step sequence. For 5h–5i (Oxidation), 5j–5k (Suzuki coupling), see SI.

Figure 4. Regioselective deuteration of antipsychotic agent L-745870.


The Directed Metalation Group Dance

A new Directed Metalation Group (DMG) dance concept is disclosed on the 7-azaindole framework. Azine selective (N-7) incorporation of the carbamoyl DMG allows C-6 functionalization via directed ortho metalation. The controlled annular DMG dance N-7 to N-1 generates the azole (N-1) DMG derivative. Second and iterative DoM reactions allow the synthesis of 2,6-substituted azaindoles in good yields. The DMG dance methodology is demonstrated in site selective deuteration of a drug scaffold.