A Regioselective Route to 5- and 6-Azaindoles

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Abstract: The synthesis of 4,7-dimethoxy 5- and 6-azaindoles, a structural unit that is present in recently developed anti-HIV-1 agents, was achieved in a regioselective manner. The developed strategy is based on the appropriate choice of a protecting group during a lithium-mediated formylation step, followed by thermal cyclization of azidoacrylates.

Key words: 5- and 6-azaindoles, pyridines, metalations, azides, regioselectivity

The indole nucleus is a prominent structural unit frequently found in numerous natural products and pharmaceutically active coumpounds.[1] Even if a wide variety of methodologies is known for the preparation of indoles,[2] a relatively small number of methods describes the preparation of azaindoles.[3] Furthermore, most of these approaches deals with the preparation of 7-azaindoles.[3b,d] Recently, 5- and 6-azaindoles have drawn considerable attention since 3-oxoacetyl-piperazino 6-aza derivatives (such as BMS-488043, Figure 1) have shown promising antiviral activities against HIV-1.[4] However, there is a lack of a general methodology for preparing 5- and 6-azaindoles: this prompted us to develop a new route to these nitrogen-containing rings.

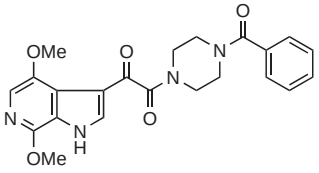


Figure 1

Looking for a regioselective access to dimethoxy 5- and 6-azaindoles **1**, we were interested in the preparation of both 3- and 4-formylpyridines **2** (Figure 2). Indeed, such compounds could be useful substrates for the preparation of the corresponding azidoacrylates **3**, precursors of the desired structures **1** via a Hemetsberger–Knittel reaction.[5]

We first investigated the formylation of 2,5-dimethoxypyridine **5**, a substrate which was easily prepared by methylation of 5-hydroxypyridine **4** under basic conditions (Scheme 1).[6] For this purpose, we used the lithium-based

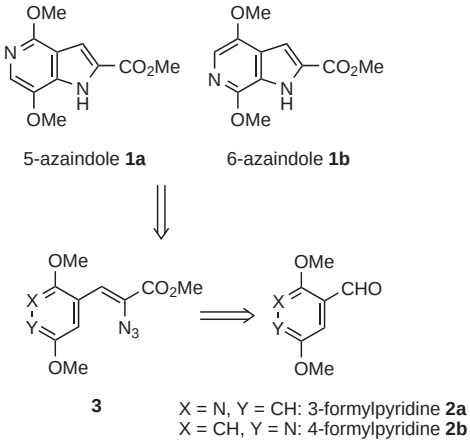
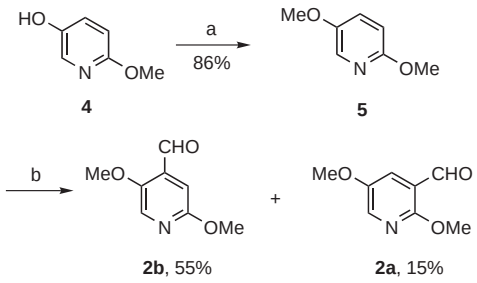


Figure 2

metalation procedure developed by Quéguiner and coworkers:[7] lithiation of **5** was performed at 0 °C by using methyllithium and a catalytic amount of diisopropylamine (DIPA), followed by electrophilic quench with *N*-formylpiperidine.[8] Although this method led to exclusive metalation at the 3-position on 2-methoxypyridine, with substrate **5** it gives a 81:19 mixture (determined from the ^{1}H NMR of the crude product) of 4- and 3-formyl derivatives in the favor of **2b** (55% isolated yield after flash chromatography, Scheme 1).



Scheme 1 *Reagents and conditions*: a) MeI 1.0 equiv, K_2CO_3 1.5 equiv, DMF, 50 °C, 3 h; b) 1) MeLi 1.8 equiv, DIPA 2 mol%, THF, 0 °C, 3 h; 2) *N*-formylpiperidine 1.8 equiv, –40 °C, 2 h.

To enhance the proportion of the 4-isomer further, we believed that the *ortho*-directing methoxymethyl (MOM) group would be of prime interest.[9] To this end, the MOM-protected pyridine **6** was synthesized by trapping the phenolate of **4** with MOM chloride (**CAUTION**: MOMCl is known to be a powerful carcinogenic alkylating reagent! Scheme 2). Metalation under the above conditions on

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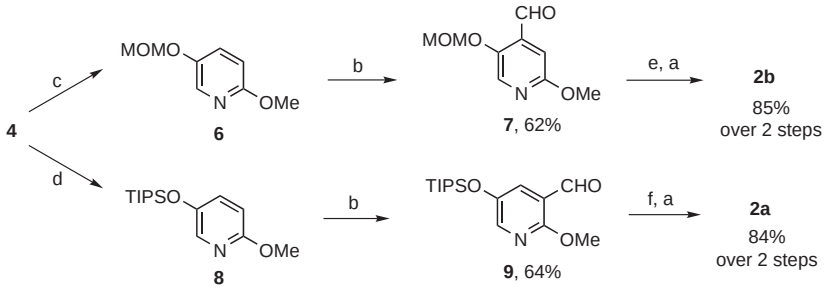
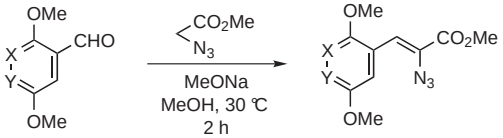


Scheme 2 *Reagents and conditions*: a) MeI 1.0 equiv, K_2CO_3 1.5 equiv, DMF, 50 °C, 3 h; b) 1) MeLi 1.8 equiv, DIPA 2 mol%, THF, 0 °C, 3 h; 2) *N*-formylpiperidine 1.8 equiv, –40 °C, 2 h; c) NaH 1.2 equiv, MOMCl 1.15 equiv, DMF, r.t., 3 h, 92%; d) TIPSCl 1.2 equiv, imidazole 2.1 equiv, DMF, r.t., 24 h, quantitative; e) 3 N aq HCl, THF, 50 °C, 3 h, 95%; f) TBAF 1.5 equiv, THF, 0 °C to r.t., 2 h, 87%.

substrate **6** led to the regioselective formation of 4-formylpyridine **7** with a 62% isolated yield.[10] Acidic cleavage of the MOM group followed by methylation afforded the 4-formylpyridine **2b**.

At the same time, we designed a selective synthesis of the other regioisomer **2a** using the sterically hindered triisopropylsilyl (TIPS) ether of common substrate **4**. Compound **8** was first prepared by silylation of **4** under classical conditions (TIPSCl, imidazole in DMF) and then submitted to the same metalation–electrophilic quench sequence. This resulted in the exclusive formation of the 3-formylpyridine **8** with a good 64% yield,[11] showing the utility of the bulky '*ortho*-repulsing' TIPS group. The dimethoxy compound **2a** was then obtained after deprotection of the silyl group with a fluoride source and subsequent methylation (Scheme 2).

With both regioisomers **2a** and **2b** in hand, we decided to prepare acrylates **3a** and **3b** by condensation of the latter with methyl azidoacetate[12] in the presence of sodium methoxide as a base. When the reaction was carried out at 30 °C, we observed the exclusive formation of the desired acrylates **3** albeit in moderate yields (Scheme 3).[13]

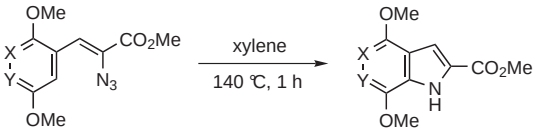


X = N, Y = CH: **2a**
X = CH, Y = N: **2b**

3a, 57%
3b, 51%

Scheme 3

The desired 5- and 6-azaindoles **1** were finally synthesized in moderate to good yields as solids by simply refluxing suspensions of the corresponding acrylates **3** in xylene during one hour followed by a slow cooling of the reaction mixture (Scheme 4).[14]



X = N, Y = CH: **3a**
X = CH, Y = N: **3b**

5-aza: **1a**, 82%
6-aza: **1b**, 52%

Scheme 4

In conclusion, we have described a regioselective synthesis of 4,7-dimethoxy 5- and 6-azaindoles **1** starting from 5-hydroxy 2-methoxypyridine **4**. Our strategy was based on the judicious choice of the protecting group (*ortho*-directing vs. *ortho*-repulsing) of this common substrate **4** during the formylation step. The reactivity of 5- and 6-azaindoles **1** is under investigation and will be reported in due course.

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(6) Compound **4** was prepared in two steps from commercially available 2-methoxypyridine, following a literature procedure: Van de Poël, H.; Guillaumet, G.; Viaud-Massuard, M.-C. *Heterocycles* **2002**, *57*, 55.
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(8) After trying DMF as the electrophilic agent, we found that this reagent gave better results.
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(10) The ratio 4-formyl pyridine/3-formyl pyridine derivatives was determined by ^{1}H NMR on the crude product and estimated to be 95:5, respectively.
(11) No trace of the 4-formyl derivative was detected by ^{1}H NMR on the crude product. In this case, a small amount (less than 10%) of the starting material **8** was detected and separated from the desired product **9** by flash chromatography on silica gel.
(12) Methyl azidoacetate was prepared from methyl bromoacetate and sodium azide according to the following procedure: Moore, A. T.; Rydon, H. N. *Org. Synth.* **1965**, *45*, 47.
(13) **Typical Experimental Procedure for the Preparation of Acrylates 3.**
To dry MeOH (4 mL) at 0 °C was added Na (189 mg, 8.2 mmol) portionwise and the resulting mixture was stirred until complete consumption of the metal. The temperature was then raised to 30 °C and a solution of aldehyde **2a** (335 mg, 2.0 mmol) and methyl azidoacetate (875 mg, 7.6 mmol) in dry MeOH (6 mL) was added in one portion. After stirring during 2 h, the mixture was poured on ice (40 g) and placed at 4 °C during 1 h. The solid was then filtered on a sintered-glass funnel to afford acrylate **3a** as an off-white fine powder (299 mg, 57%); mp 123–124 °C (dec.). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.81 (3 H, s), 3.86 (3 H, s), 3.87 (3 H, s), 7.02 (1 H, s), 7.89 (1 H, d, *J* = 3.0 Hz), 8.12 (1 H, d, *J* = 3.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 53.3, 53.8, 56.2, 115.7, 116.0, 125.3, 127.3, 132.7, 150.4, 155.2, 163.0 ppm. HRMS (CI): *m*/*z* calcd for $C_{11}H_{13}N_4O_4$: 265.0937 [MH^+]; found: 265.0938.
Acrylate **3b** (yellow powder, 268 mg, 51%): mp 117–118 °C (dec.). ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.84 (3 H, s), 3.91 (3 H, s), 3.92 (3 H, s), 7.12 (1 H, s), 7.50 (1 H, s), 7.90 (1 H, s) ppm. ^{13}C NMR (75 MHz, acetone-d_6): δ = 53.6, 53.6, 57.2, 111.1, 116.1, 130.3, 130.5, 133.3, 149.3, 159.4, 164.0 ppm. HRMS (EI): *m*/*z* calcd for $C_{11}H_{12}N_4O_4$: 264.0859 [$M^{+\bullet}$]; found: 264.0856.
(14) **Typical Experimental Procedure for the Preparation of Azaindoles 1.**
To 13 mL of hot xylene (140 °C) was slowly added under vigorous stirring a suspension of acrylate **3a** (423 mg, 1.6 mmol) in 27 mL xylene. After addition, the mixture was stirred for 1 h at 140 °C and then slowly cooled down to r.t. overnight without stirring. Once the solid crystallized, the supernatant was removed and the solid dried under high vacuum to give 5-azaindole **1a** as pale pink crystals (310 mg, 82%). For the synthesis of 6-azaindole **1b** starting from acrylate **3b**, the crystallization occurred only at –20 °C. Additional purification of the supernatant by flash chromatography (silica gel, petroleum ether–EtOAc, 50:50) was necessary to recover all of **1b**, which is more soluble in xylene than its 5-aza analogue (compound **1a** is quantitatively recovered after crystallization at r.t.).
5-Azaindole **1a**: mp 192–193 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.84 (3 H, s), 3.90 (3 H, s), 3.92 (3 H, s), 7.10 (1 H, s), 7.47 (1 H, s), 12.57 (1 H, br s) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 51.9, 52.8, 56.4, 106.5, 113.0, 120.4, 127.5, 134.2, 140.0, 152.8, 160.9 ppm. HRMS (CI): *m*/*z* calcd for $C_{11}H_{13}N_2O_4$: 237.0875 [MH^+]; found: 237.0874.
6-Azaindole **1b** (pale yellow powder, 123 mg, 52%): mp 169–170 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.86 (3 H, s), 3.88 (3 H, s), 3.96 (3 H, s), 7.07 (1 H, s), 7.27 (1 H, s), 12.63 (1 H, br s) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 52.0, 52.8, 55.9, 104.9, 114.7, 123.0, 124.8, 129.0, 145.7, 146.4, 161.0 ppm. HRMS (EI): *m*/*z* calcd for $C_{11}H_{12}N_2O_4$: 236.0797 [$M^{+\bullet}$]; found: 236.0798.