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A facile synthesis of 2,3-azaisoindoline

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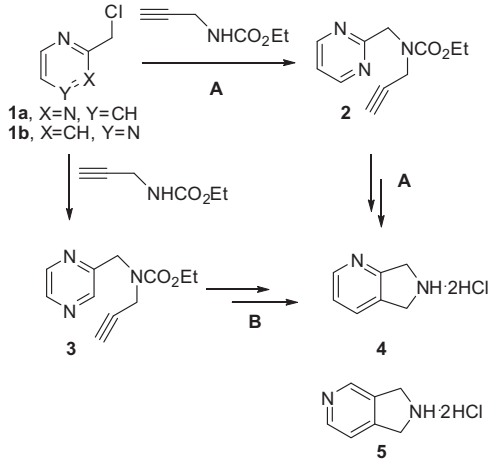
ABSTRACT

2,3-Azaisoindoline (**4**) was prepared via reaction of dichloride **11** with 2,4-dimethoxybenzyl amine followed by deprotection with trifluoroacetic acid and triethylsilane. Isolation of the unstable 2,3-azaisoindoline **4** was facilitated by conversion to the bis-HCl salt.

2,3-Azaisoindoline is an important intermediate used in the synthesis of pharmaceutical analogs to obtain desired properties of the target molecule.[1] Although it is available commercially, it is prohibitively expensive ($540–650/g). For our medicinal chemistry program, we required a synthetic route amenable to a large scale (50–1000 g) preparation of 2,3-azaisoindoline **4**. Compound **4** has been made on a small scale using the literature intramolecular Diels–Alder route shown in Scheme 1.[1b,c] However, route A was limited by the cost of starting material **1a** ($520–742/g) and route B gave isomeric products (**4** and **5**) in moderate yields.

An additional literature-based route looked attractive due to its simplicity and readily available starting materials (Scheme 2).[2] In addition, pthalimide had been shown to be easily reduced to the isoindoline with borane in moderate yield.[3] Thus, for our initial efforts, we prepared both the azapthalimide **6** and it is benzyl derivative **7** via literature-reported conditions (Scheme 2).[4]

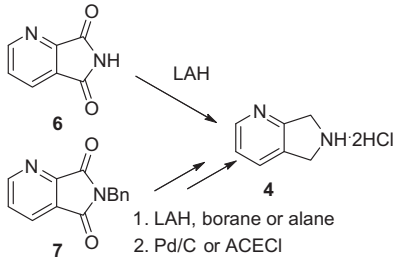


Scheme 1. Literature Diels–Alder approaches to **4**.

Attempted reduction of benzyl azapthalimide **6** with either LAH[2] or borane[3] resulted in over-reduction and/or incomplete reduction, resulting in variable yields (5–20%). Multiple attempts to repeat literature conditions used to reduce pthalimide failed to provide the desired product **4**.[2] Use of alane as the reducing agent (diethylether, room temp) gave about 20% yield of the corresponding benzyl-protected azaisoindoline intermediate. Unfortunately, the use of hydrogenolysis or carbamate exchange conditions with refluxing 1-chloro-ethyl chloroformate (ACE-Cl) failed to give pure azaisoindoline **4**. The catalytic hydrogenation conditions proceeded very slowly even upon heating and high pressure. Initial preparation of the mono hydrochloride salt of **7** not only helped the reduction progress but also led to side products resulting from reduction of the pyridine ring.

As an alternate, we pursued a route where the removal of the protecting group could be facilitated with an acid so the product could be isolated as a stable salt. For this approach, we envisioned preparing a suitably protected 2-azaisoindoline via the dimesylate **10** or the dichloride **11** intermediate[6] (Scheme 3).

Thus the commercially available, inexpensive diester **8** ($7.96/g for 25 g and $2.28/g for 2.5 kg) was reduced with sodium borohy-



Scheme 2. Azapthalimide route to prepare **4**.

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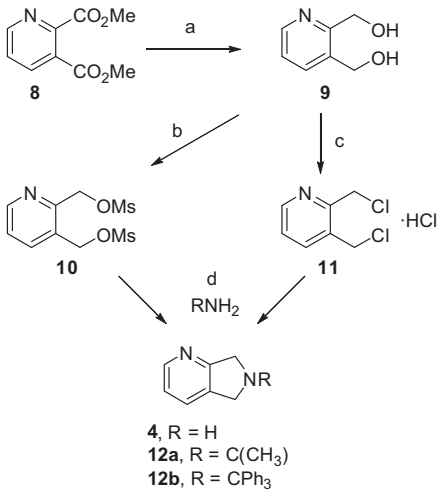
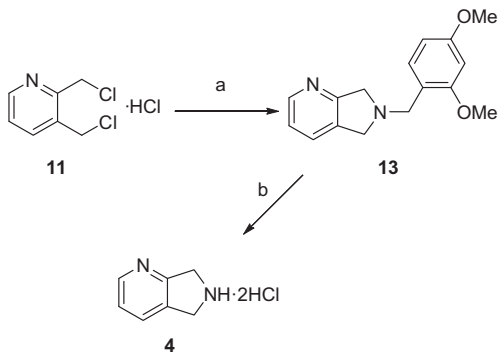


Scheme 3. Reagents and conditions: (a) $NaBH_4$, $CaCl_2$, EtOH, rt, 74%; (b) MsCl, iPr$_2$NEt, DCM, 48%; (c) $SOCl_2$, toluene, 100 °C, 93–96%; (d) For **12a**: tBuNH$_2$, Et$_3$N, DCM, 30%.



Scheme 4. Reagents and conditions: (a) 1.1 equiv 2,4-dimethoxybenzyl amine, 3.3 equiv iPr$_2$NEt, DCM, rt, 50%; (b) Et$_3$SiH, TFA, HCl/dioxane, 70%.

dride in the presence of calcium chloride to give the corresponding diol **9** in 74% yield (Scheme 3). Conversion to the dimesylate **10** proceeded in 48% yield.[5] Reaction of the diol with thionyl chloride, following available procedure,[6] gave the dichloride hydrochloride salt **11** in greater than 90% yield. Low yields with the dimesylate preparation are attributed to the instability of the dimesylate free base (formation of baseline by-products) whereas the dichloride is isolated as a stable salt.

Having secured the key intermediates, the initial idea was to convert dichloride **11** directly into 2,3-azaisoindoline **4** using ammonia (Scheme 3). Unfortunately, reaction with ammonia was rather messy (multiple spots on tlc, no product by LCMS) and did not yield any desired product. Next, we examined the double displacement of the dichloride with a suitably functionalized amine in which the substituent on the amine could serve as a protecting group that could be easily removed under acidic conditions. Reaction between dichloride **11** and t-butylamine or tritylamine gave the desired t-butyl- and triphenylmethyl azaisoindolines **12a** and **12b** in 30% and 3% yield, respectively (Scheme 3). We speculated that the low yields for these reactions were a result of the bulky amino groups used so we attempted the displacement with a less sterically demanding amine. To this end, reaction of dichloride **11** with 2,4-dimethoxybenzyl amine gave the suitably protected 2-azaisoindoline **13** in 50% yield (Scheme 4). It should be noted that reaction of the unstable dimesylate with dimethoxybenzylamine did provide **13** in 88% yield. Additionally, in our hands, attempted reactions with amide or sulfonamide protected amines ($BOCNH_2$, p-tolSO_2NH_2) failed to give the desired products ($BOCNH_2$)[7] or gave lower yields (p-tolSO_2NH_2, 30–40%).[1a]

Attempted removal of the t-butyl group of **12a** using TFA or HCl failed to give any desired product. However, the treatment of the 2,4-dimethoxybenzyl amine derivative **13** with TFA gave the desired product **4** as it is bis TFA salt but was difficult to purify. To provide clean reactions and facilitate isolation of the product, the deprotection reaction was performed in the presence of triethylsilane to trap the reactive dimethoxybenzyl cation generated from the TFA cleavage. This was followed by exchange of the resulting TFA salt with HCl which resulted in the formation of the desired product **4** as an easily filtered solid (Scheme 4). This reaction provided pure 2,3-azaisoindoline bis-hydrochloride **4** in 70% yield.[8]

In summary, we have demonstrated a four step synthesis of 2,3-azaisoindoline **4** in 25% overall yield. This approach is an improvement on previous methods as it uses the readily available and economic starting materials, can be performed on large scale, and allows facile isolation of the product as stable and easily handled solid.

References and notes

1. (a) Kim, D. Y.; Lee, I. C.; Yoon, G. J. *J. Korean Chem. Soc.* **1998**, *42*, 102; b Petersen, U.; Krebs, A.; Schenke, T.; Grohe, K.; Bremm, K. D.; Endemann, R.; Grohe, K.; Bremm, K. D.; Endelman, R.; Metzger, K. G.; Zeiller, H. J. EP 92110043, 1992.; (c) Paget, S. D.; Foleno, B. D.; Boggs, C. M.; Goldschmidt, R. M.; Hlasta, D. J.; Weidner-Wells, M. A.; Werblood, H. M.; Wira, E.; Bush, K.; Macielag, M. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4173; (d) Paget, S. D.; Boggs, C. M.; Foleno, B. D.; Goldschmidt, R. M.; Hlasta, D. J.; Weidner-Wells, M. A.; Werblood, H. M.; Bush, K.; Macielag, M. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4537.
2. Bryans, J. S.; Johnson, P. S.; Roberts, L. R. WO2006123242(A1), 2006.
3. Gawley, R. E.; Chemburkar, S. R.; Smith, A. L.; Anklekar, T. V. *J. Org. Chem.* **1988**, *53*, 5381.
4. Carpino, L. A.; Xia, J.; El-Faham, A. *J. Org. Chem.* **2004**, *69*, 54.
5. Wang, Y.-X.; Mabic, S.; Castagnoli, N. *Bioorg. Med. Chem.* **1998**, *6*, 143.
6. Grimm, J. S.; Maryanoff, C. A.; Patel, M.; Palmer, D. C.; Sorgi, K. L.; Stefanick, S.; Webster, R. R. H.; Zhang, X. *Org. Proc. Res. Dev.* **2002**, *6*, 938.
7. Zwanenburg, D. J.; Wynberg, H. *J. Org. Chem.* **1969**, *34*, 333.
8. *Preparation of 6-(2,4-dimethoxybenzyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine* (**13**)
2,3-Bis(chloromethyl)pyridine hydrochloride (**10**·HCl, 17.89 g, 84.2 mmol) was placed in a dry flask with dichloromethane (350 ml). The flask was purged with argon and placed in a water bath (~15–20 °C. Diisopropylethylamine (46.1 ml, 278.9 mmol) was added dropwise over a 5 min period and the mixture was stirred for 10 min at room temperature. 2,4-Dimethoxybenzylamine (14 ml, 93.2 mmol) was added dropwise over a 7 min period and the mixture was stirred for 18 h at room temperature. Water (350 ml) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 175 ml). The combined organic layer was dried over sodium sulfate, was filtered, and was concentrated in vacuo yielding 31.22 g of a brown oil. Column chromatography over silica gel using 5% methanol in dichloromethane as the eluent gave 11.42 g (50%) of 6-(2,4-dimethoxybenzyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine (**13**) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 383 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 3.93 (s, 2H, CH_3OCCCH_2); 4.02 (s, 2H, NCH_2CCN); 4.07 (s, 2H, NCH_2CN); 6.48–6.52 (m, 2H, CH_3OCCH); 7.07 (dd, J = 7.6 Hz, J = 5.1 Hz, 1H, NCHCH); 7.30 (d, J = 8.9 Hz, 1H, $CH_3OCCHCH$); 7.46 (d, J = 6.6 Hz, 1H, NCCCH); 8.37 (d, J = 4.0 Hz, 1H, NCH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.87, 160.16, 158.62, 147.83, 133.85, 131.17, 129.92, 121.43, 118.90, 103.95, 98.52, 59.32, 56.95, 55.45, 55.32, 53.16; MS (*m*/*z*) 270.10 (M+); HRMS for $C_{16}H_{19}N_2O_2$ calcd 271.1441, found 271.1437.
6,7-Dihydro-5H-pyrrolo[3,4-b]pyridine dihydrochloride (**4**)
6-(2,4-Dimethoxybenzyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine (**13**, 9.43 g, 34.9 mmol) was placed in a dry flask under nitrogen. Trifluoroacetic acid (27 ml) and triethylsilane (6.0 ml) were added. The mixture was stirred and heated at 60 °C for 5 h. The volatiles were removed in vacuo resulting in a sticky oil. HCl (4 M in dioxane, 40 ml) was added to the residue followed by the addition of ethyl acetate (50 ml). Vigorous stirring at room temperature for ~1 h resulted in a precipitate. The solids were isolated by filtration and were washed with ethyl acetate (25 ml) and were dried in vacuo yielding 5.25 g (70%) 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride **4** as pale brown solid: ^{1}H NMR (300 MHz, CD_3OD) δ 4.71 (s, 2H, $NHCH_2CCN$); 4.78 (s, 2H, $NHCH_2CN$); 7.6 (t, J = 7.2 Hz, 1H, NCHCH); 8.10 (d, J = 7.6 Hz, 1H, NCCCH); 8.65 (d, J = 5.3 Hz, 1H, NCH). All other NMR data were compared with known compounds and were consistent with the structures.