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Synthesis of 2,5-disubstituted-3-cyanoindoles

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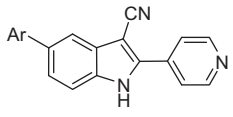
ABSTRACT

An efficient synthesis of 2,5-disubstituted-3-cyanoindoles is described. This approach utilizes a highly selective iodination together with the modified Madelung reaction to generate an intermediate which can be readily transformed to more fully elaborated 2,5-disubstituted-3-cyanoindole templates that were previously difficult to access. Detailed examples and utility of this approach are presented herein.

Indoles are of great interest among the medicinal chemistry community for their biological relevance.[1] One only has to do a search on the general indole substructure to find thousands of reports on their synthesis[2] and applications. More specifically, 3-cyanoindoles are known to be of biological significance for their use as aldosterone synthase modulators for cardiovascular disease,[3] factor Xa inhibitors for antithrombotics,[4] hepatitis C antivirals,[5] acetyl-CoA carboxylase inhibitors for type 2 diabetes,[6] and anticancer agents.[7] Thus an additional method by which 3-cyanoindoles and their derivatives could be prepared would be of great value and utility (vide infra).[8]

During the course of a medicinal chemistry effort, we required an efficient synthesis of 2-pyridyl-5-substituted-3-cyanoindoles **1** which would allow for the rapid preparation of analogs at the 5-position.



1

We initially planned to cyanate the 3-position of the corresponding 5-bromo-2-(4-pyridyl) intermediate **6**, and then couple the bromide with a variety of aryl boronic acids as the final step (Scheme 1). This approach would facilitate efficient analog preparation by introducing diversity as the final step in the synthesis. To achieve this, we investigated a variety of methods to prepare the required indole core. Preparation of the 5-bromoindole scaffold **6** was first attempted using the Fischer indole synthesis.[9] While treatment of hydrazone **2** on five gram scale with polyphosphoric acid (PPA) at high temperature afforded the indole **6** with good conversion, clean separation of the product from des-bromo and di-bromo side products on scale was difficult. An alternative approach using Sonagashira cross-coupling conditions to form 4-bromo-2-(pyridin-4-ylethynyl)aniline **5**, followed by ring closure with potassium tert-butoxide proceeded in good yield.[10] However, the cyanation reaction with chlorosulfonylisocyanate to form 5-bromo-2-(pyridin-4-yl)-1*H*-indole-3-carbonitrile **7a** was low yielding and poorly reproducible.[3] Protection of the indole N-1 nitrogen with a trimethylsilylethoxymethyl (SEM) group (**7b**) did not improve the outcome of this cyanation. Other cyanating reagents such as potassium ferrocyanide required protection of the N-1 nitrogen, and were found to be only slightly more effective.[11] Disappointingly, conversion of the bromide **7** to the coupled product was also poor. For example, compound **7a** was converted to 5-(isoxazol-4-yl)-2-(pyridin-4-yl)-1*H*-indole-3-carbonitrile **8a** in only 10% yield under standard Suzuki cross-coupling conditions. A similar result was observed when N-1 was SEM protected (**8b**). The low synthetic efficiency over multiple steps in this sequence, as well as the costly 4-ethynylpyridine starting material presented significant challenges to the synthesis of 2,5-disubstituted-3-cyanoindoles on larger scale. In addition, this route limited our ability to prepare diverse analogs due to the incorporation of the 2-position substituent at the beginning of the synthesis in the form of custom ethynyl starting materials.

The key requirements for an improved second generation synthesis were to avoid a separate cyanation step and to allow for ease of varying substituents at both the 2- and 5-positions. To address

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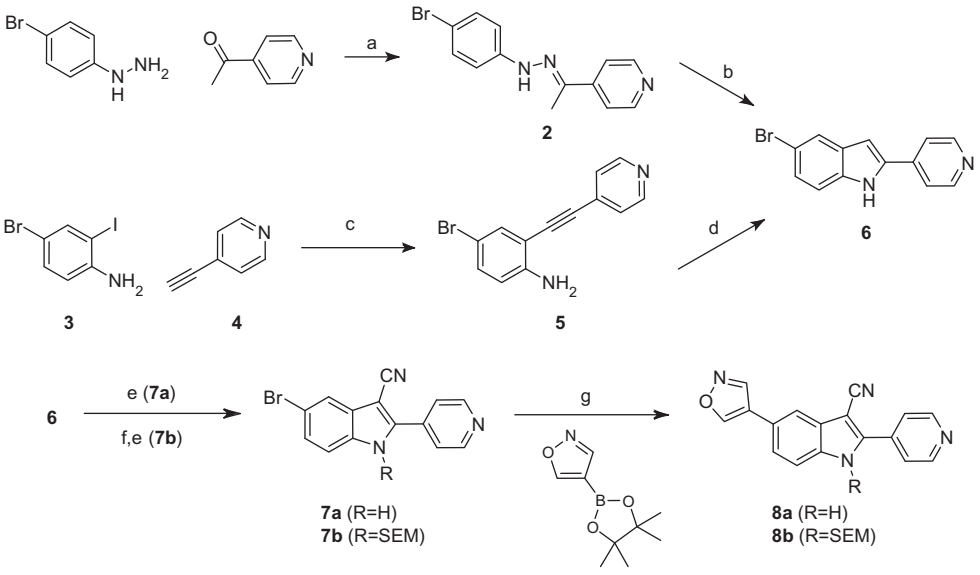


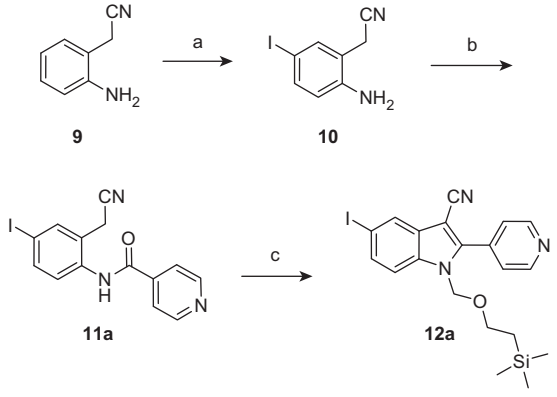
Scheme 1. Reagents and conditions: (a) EtOH, reflux, 2 h, 85% (b) PPA, 130 °C, 73% (c) $PdCl_2(PPh_3)_2$, Et_3N, reflux, 43%; (d) KOt-Bu, NMP, 53%; (e) $ClSO_2NCO$, CH_3CN, 0 °C; DMF; 17–28% **7a**; 0% **7b**; (f) NaH, SEMCl, DMF, 90%; (g) $PdCl_2(dppf)$, K_2CO_3, 1,4-dioxane/water (4:1), 100 °C, 5 h, 10% **8a**; <10% conversion after 16 h, **8b**.

the first of these goals, the synthesis of 3-cyanoindoles can be accomplished via application of the modified Madelung reaction[12] which incorporates the 3-cyano group at the beginning of the synthesis. This approach would also allow for the preparation of compounds with variation at the 2-position more easily from readily available acid chloride starting materials.

Additionally, a synthetic sequence which utilized a more reactive 5-iodoindole rather than the 5-bromoindole could be of significant benefit in subsequent aryl cross-coupling reactions. Gratifyingly, iodination of readily accessible (2-aminophenyl)acetonitrile **9** under the mild conditions of potassium iodide and 30% hydrogen peroxide in acetic acid[13] cleanly and exclusively afforded the desired *para* iodo intermediate **10** in 82% yield (Scheme 2). This material was then acylated with isonicotinoyl chloride to provide **11a** in 72% yield. Protection of **11a** with the SEM group, followed by ring closure with potassium tert-butoxide via the modified Madelung reaction delivered the desired iodide **12a** from **11a** in 52% yield in a one-pot sequence. To our knowledge, this is the first reported example of the preparation of a highly versatile 2-substituted-3-cyano-5-iodoindole.[14] Importantly, this sequence can be applied to the preparation of both aryl and alkyl motifs at the 2-position (**12a–g**) as shown in Table 1. Reactions with sterically hindered alkyl R groups (**12e–g**) were observed to be lower yielding than those with the methyl (**12d**) and aryl substituents (**12a–c**). We also investigated the application of this chemistry to the synthesis of 5-iodo-2-amino-3-cyanoindoles (Scheme 3). The desired product **12h** was not found, with the major product **14** resulting from oxidative hydrolysis of the nitrile.[15]

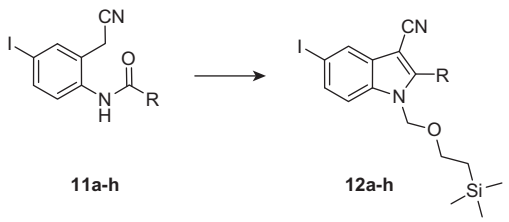
To demonstrate the utility of this route in preparing the desired 2,5-disubstituted-3-cyanoindoles, the iodo intermediate **12a** was coupled with a series of arylboronic acids to afford 2-pyridyl-5-aryl-3-cyanoindoles **15a–c** in 51–72% yield. The SEM group was subsequently removed using cesium fluoride in DMF to afford the final products **16a–c** in 37–58% yield (Scheme 4).[16,17]

In conclusion, we have devised an efficient synthesis of 2,5-disubstituted-3-cyanoindoles. This approach utilizes a highly selective and high yielding iodination followed by a one-pot modified Madelung reaction and protection sequence to generate the 2-substituted-3-cyano-5-iodoindole core. This protected intermediate can then be readily transformed to generate novel 5-substituted analogs which were previously difficult to access.

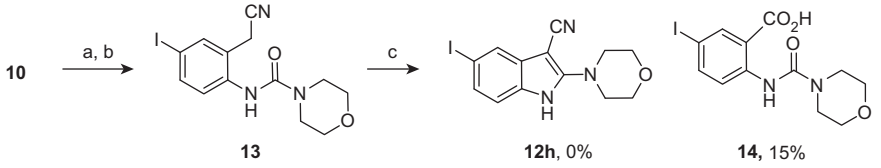


Scheme 2. Reagents and conditions: (a) KI, 30% H_2O_2, HOAc, 1 h, 82% (15 g scale); (b) isonicotinoyl chloride, DIEA, DCM, 72%; (c) NaH, SEMCl, THF, 30 min, then KOt-Bu, 30 min, 52%.

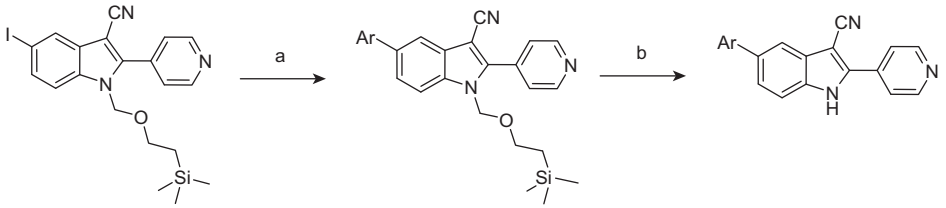
Table 1
Reaction yield for the conversion of compounds **11a–h** to **12a–h**



Compounds	R	Yield (%)
12a	4-Pyridyl	52
12b	3-Pyridyl	33
12c	4-CO_2Me-phenyl	43
12d	Methyl	47
12e	*iso*-Propyl	26
12f	*tert*-Butyl	24
12g	Cyclohexyl	4
12h	Morpholino	0



Scheme 3. Reagents and conditions: (a) $NaHCO_3$, DCM/water (1:1), phosgene (20% solution in toluene), 1 h, 92%; (b) morpholine, DCM, rt, 3 h, 79%; (c) NaH, TMSCl, THF, 30 min, rt, then KOt-Bu, 20 h, rt.



Scheme 4. Reagents and conditions: (a) $ArB(OH)_2$, $PdCl_2$(dppf), K_2CO_3, dioxane/H_2O, 100 °C μw, 1 h, 51–72%; (b) CsF, DMF, 125–130 °C, 2.5 h, 37–58%.

The useful synthetic approach reported herein can be applied to the synthesis of a variety of 2,5-disubstituted-3-cyanoindoles.

Acknowledgment

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16. Experimental procedure for the synthesis of **16a:** (2-Aminophenyl)acetonitrile (**9**) (2.64 g, 20.0 mmol) was dissolved in 50 mL of acetic acid. KI (3.65 g, 22.0 mmol) was added followed by dropwise addition of 30% H_2O_2 (2.24 mL, 22.0 mmol). The reaction mixture was then stirred under nitrogen for 90 min, poured into 200 mL of 0.1 M sodium thiosulfate solution, and extracted with ethyl acetate (3 × 200 mL). The organic fractions were combined, washed with 0.1 M sodium thiosulfate (2 × 200 mL), satd sodium bicarbonate (2 × 200 mL) and brine (2 × 200 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Purification by automated flash chromatography (400 g silica gel, 25% ethyl acetate/hexanes) afforded **10** (3.5 g, 68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.41 (s, 2H), 6.53 (d, J = 8.34 Hz, 1H), 7.30 (dd, J = 8.59, 2.02 Hz, 1H), 7.39 (d, J = 2.02 Hz, 1H), NH_2 protons not resolved. (2-Amino-5-iodophenyl)acetonitrile (**10**) (258 mg, 1.0 mmol) was dissolved in 10 mL of DCM. 4-Pyridinecarbonyl chloride (178 mg, 1.0 mmol) was added, followed by DIEA (0.35 mL, 2.0 mmol). After 16 h at rt, the reaction mixture was concentrated in vacuo. Purification by automated flash chromatography (12 g silica gel, 2–10% MeOH in DCM, 40 min gradient) afforded **11a** as a grayish powder (260 mg, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 4.01 (s, 2H), 7.26 (d, J = 8.34 Hz, 1H), 7.78 (dd, J = 8.34, 2.02 Hz, 1H), 7.82–7.93 (m, 3H), 8.76–8.87 (m, 2H), 10.48 (s, 1H). *N*-[2-(Cyanomethyl)-4-iodophenyl]-4-pyridinecarboxamide (**11a**) (2.65 g, 7.3 mmol) was dissolved in 5 mL of THF and cooled to 0 °C. NaH (60% oil dispersion, 0.32 g, 8.0 mmol) was added. After 5 min, SEMCl (1.42 mL, 8.0 mmol) was added and the reaction mixture was allowed to stir for 30 min at room temperature. KOt-Bu (95%, 0.95 g, 8.0 mmol) was then added and the reaction mixture was stirred for another 30 min. The reaction was quenched with water (5 mL). The resulting mixture was stirred for 5 min and concentrated in vacuo to near dryness. The residue was taken up in ethyl acetate (400 mL), and washed with water (2 × 250 mL), satd NH_4Cl (2 × 250 mL), and brine (1 × 100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Purification by automated flash chromatography (200 g silica gel, 0–10% methanol/DCM, 50 min gradient) afforded **12a** (1.8 g, 52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: −0.15 to −0.11 (m, 9H), 0.71–0.78 (m, 2H), 3.37–3.44 (m, 2H), 5.60 (s, 2H), 7.73–7.79 (m, 4H), 8.08 (s, 1H), 8.84–8.89 (m, 2H). In a 5 mL microwave vial, 5-iodo-2-(4-pyridinyl)-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-indole-3-carbonitrile (**12a**) (100 mg, 0.21 mmol), 4-pyridinylboronic acid (38.8 mg, 0.32 mmol) and potassium carbonate (87 mg, 0.63 mmol) were taken up in 5 mL of 4:1 dioxane/water. The vial was flushed with nitrogen and $PdCl_2$(dppf) (15.4 mg, 0.02 mmol) was added and the vial capped. The reaction mixture was heated in the microwave at 100 °C for 1 h, then stirred with brine at rt. After 5 min, the dioxane layer was separated and concentrated in vacuo. Purification by automated flash chromatography (12 g silica gel, 0–10% MeOH in DCM, 40 min gradient) afforded **15a** (65 mg, 72%). ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm: 0.00 (s, 9H), 0.96 (t, 2H), 3.62 (t, J = 7.83 Hz, 2H), 5.51 (br s, 2H), 7.61–7.99 (m, 6H), 8.15 (br s, 1H), 8.60–9.04 (m, 4H). In a 2 dram teflon-capped vial, 2,5-di-4-pyridinyl-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-indole-3-carbonitrile (**15a**) (65 mg, 0.15 mmol) was dissolved in 1 mL of DMF and CsF (116 mg, 0.76 mmol) was added. The vial was capped and heated to 130 °C for 2.5 h. The reaction mixture was cooled to room temperature, filtered, and purified by automated reversed phase HPLC (Gilson, 5–55% ACN/water, 0.1% TFA, 7 min gradient) to afford **16a** as a bright yellow solid (47 mg, 58%). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm: 7.87 (d, J = 8.59 Hz, 1H), 8.05 (dd, J = 8.84, 1.77 Hz, 1H), 8.29 (br s, 2H), 8.44 (d, J = 1.26 Hz, 1H), 8.50 (d, J = 5.81 Hz, 2H), 8.75–9.19 (m, 4H), NH not resolved. Anal. calcd for $C_{19}H_{12}N_4{\cdot}2C_2HF_3O_2$: C, 52.68; H, 2.69; N, 10.68 . Found: C, 52.21; H, 2.42; N, 9.66 (di-TFA salt).
17. Our work in related areas has shown that incorporating a protecting group strategy could be critical to the success of utilizing this template for further elaboration using other metal-catalyzed cross-coupling reactions. For example, in a related series of 2-amino-3-cyano-6-bromo indole analogs, we observed that alkylation at N-1 was critical for the successful completion of 6-position coupling with alkyltrifluoroborates, as well as with amines. In these cases, no reaction was observed when the indole nitrogen was left unprotected, whereas good conversion was observed when the indole nitrogen was protected.