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# One-Pot Synthesis of Benzo[4,5]imidazo[2,1-a]isoquinolines and

## Isoquinolino[3,4-b]quinoxalines via Tandem Cyclization Strategies

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**Abstract**: Two operationally-simple one-pot protocols have been developed for the synthesis of amino-functionalized benzo[4,5]imidazo[2,1-*a*]isoquinolines and isoquinolino[3,4-*b*]quinoxalines. Optimization data and substrate scope for these atom-economical transformations, which engage commercially available *o*-phenylenediamines and *o*-cyanobenzaldehydes, are discussed.

The extensive chemistry literature reflects both the intriguing structural features and the extensive pharmaceutical applications of heterocyclic compounds.<sup>1</sup> Indeed, the development of effective methodology to construct complex heterocyclic structures plays an important role in the drug discovery process<sup>2</sup> and these methods often enable the rapid generation of diverse small molecule libraries for high throughput screening.<sup>3</sup> In that context, one-pot tandem/domino reactions are powerful tools for the assembly of novel fused-ring systems from simple building

 blocks. These strategies employ atom and step-economical transformations to introduce structural complexity by allowing multiple bond forming events to occur in one transformative operation.<sup>4</sup> Recently, we and others have reported tandem reactions as novel routes to attractive heterocyclic scaffolds.<sup>5</sup> The targets of studies reported here are benzo[4,5]imidazo[2,1-*a*]isoquinoline and isoquinolino[3,4-*b*]quinoxaline cores as they appear in many bioactive compounds possessing anti-tumor, anti-cancer, antibacterial, anti-tuberculosis, and antimalarial activities.<sup>6</sup>

One representative example of a ring system embedding an isoquinolino[3,4-*b*]quinoxaline core, which was synthesized by relatively harsh conditions.<sup>7</sup> The synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinolines has previously been accomplished by transition metal-catalyzed cross coupling reactions.<sup>8</sup> These methods are interesting, but generally require pre-functionalization of precursors and often confront purification challenges in meeting rigorous limits for heavy metal impurities in drug research.<sup>9</sup> These limitations prompted our investigation into a more effective transition-metal-free method to construct the aforementioned heterocyclic motifs.

Recently, Cheon *et al.*<sup>10a</sup> and earlier Jiao *et al.*<sup>10b</sup> demonstrated convenient protocols for the synthesis of benzimidazoles (e.g., **2**) from *o*-phenylenediamines and aldehydes via a condensation/aerobic oxidation sequence. For example in the Cheon work, initial condensation of an aniline with benzaldehyde produced imine intermediate **1**, which subsequently underwent 5-*exo*-tet cyclization promoted by a nucleophilic catalyst (KI) to furnish benzimidazole **2** after aerobic oxidation (**Scheme 1**). Building on a 1987 report from Smith *et al.* who employed cyanide and *N-o*-nitrobenzylidene to give cinnoline 1-oxide analogs,<sup>11a</sup> Cheon *et al.*<sup>10a</sup>

employed *o*-phenylenediamines, aldehydes, and cyanide anion to produce 5-quinoxalin-2-amines (**5**).<sup>11</sup>



**Scheme 1**. Synthetic strategies toward benzo[4,5]imidazo[2,1*a*]isoquinolines and isoquinolino[3,4-*b*]quinoxalines.

Building on these strategies, we envisioned that appropriate methods could be developed for the synthesis of our target scaffolds (**Scheme 1**) when X = CN. Specifically, N-alkylation of **2a** with an RCH<sub>2</sub>X electrophile (R = EWG) followed by base-mediated cyclization was envisioned to transform **2a** into tetracycle **4**. Conversely, addition of the amino moiety of **5** to the electrophilic aryl nitrile (X = CN) would result in formation of the fused isoquinoline substructure **7**. Herein, we report one-pot routes to amino-functionalized benzo[4,5]imidazo[2,1-*a*]isoquinolines and isoquinolino[3,4-*b*]quinoxalines via the tandem annulation of *o*-cyanobenzaldehydes with *o*-phenylenediamines derivatives.

 We began our studies by examining the feasibility of the N-alkylation reaction between benzimidazole 2a and an RCH<sub>2</sub>X type electrophile, such as ethyl 2-bromoacetate. This alkylation would install an enolizable moiety on one of the benzimidazole nitrogens and deprotonation with added base would generate the corresponding enolate anion. Subsequent intramolecular attack of this enolate onto the nitrile of the benzonitrile would form an isoquinoline ring affording tetracyclic product **4**.

Indeed, treating *o*-phenylenediamine and *o*-cyanobenzaldehyde with a stoichiometric amount of KI in DMF at 80 °C cleanly delivered **2a** in excellent yield (**Scheme 1**).<sup>10,11</sup> Having this benzimidazole substrate in hand, the stage was set for a detailed study of the tandem N-alkylation/base-mediated cyclization of **2a** to **4a**. As summarized in **Table 1**, various reaction conditions were evaluated for the **2a**  $\rightarrow$  **4a** conversion. Surprisingly, the use of a strong base, NaH in acetone or THF at 0 °C, did





Entry	Solvent	Base	Conditions	Yield <sup>[a]</sup>
1	Acetone	NaH	0°C	NR <sup>[b]</sup>
2	THF	NaH	0 °C	NR <sup>[b]</sup>
3	Acetone	$K_2CO_3$	80°C	<10%
4	DMF	$K_2CO_3$	80 °C	54%

[a] Yield reported is the overall yield of **4a** from **2a**. [b] NR denotes no reaction occurred.

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not promote the transformation – rather resulting in the recovery of starting material (entries 1 and 2). However, a low yield of **4a** was observed with a weaker base:  $K_2CO_3$  in acetone at 80 °C (entry 3). Switching to the more polar solvent DMF and heating at the same temperature (entry 4) significantly improved the reaction, delivering the desired product in 54% yield. Interestingly, the uncyclized intermediate **3a** could not be isolated under any of these conditions suggesting its conversion to **4a** is rapid. The structure of tetracyclic product **4a** was unambiguously established by X-ray crystallographic analysis (see supporting information).<sup>12</sup>

The solvent compatibility of these two steps (e.g., DMF for both formation of **2a** and its subsequent conversion to **4a**) encouraged us to combine the efficient benzimidazole formation step with the subsequent tandem N-alkylation/base-mediated cyclization to give a one-pot synthesis of **4**. Once optimized conditions were in hand for this one-pot method, we set out to explore the generality and limitation of this method. As depicted in **Table 2**, the one-pot protocol effectively transformed a variety of *o*-phenylenediamines, electrophiles, and *o*-cyanobenzaldehyde into the corresponding tetracycles (**4a-e**) in moderate overall yields. The scope was, however, restricted to symmetrical *o*-phenylenediamines since the N-alkylation of unsymmetrical *o*-phenylenediamines results in an intractable mixture of products.





[a] Isolated yields. Products characterized by <sup>1</sup>H, <sup>13</sup>C NMR, IR, and HRMS.

As outlined in Scheme 1, formation of **2** proceeds via the cyclization of imine intermediate **1**. We thus envisioned that cyanide addition to imine **1a** followed by subsequent heterocyclization could lead to isoquinolino[3,4-*b*]quinoxalines **7** via the 3,4-dihydroquinoxalin-2-amine intermediate **5**. Our speculation leading into this study was that 2-aminoquinoxaline **5** (X = CN) would not be isolable because **5** would cascade on to **7** faster than it would undergo oxidation to **6** even though, when  $X \neq CN$ , oxidation of **5** does lead to **6**.<sup>11</sup> Proceeding with that idea, initial investigations centered on defining conditions to best provide imine intermediate **1a**, since the *o*-phenylene-

 diamine plus *o*-cyanobenzaldehyde going to imine reaction (see Scheme 1) is plagued by the imine undergoing cyclization to unwanted benzimidazole **2a**. As outlined in Table 3, we set out to address this question with optimization studies and we were pleased to find that the reaction run in THF under nitrogen led to an excellent conversion to imine **1a** (entry 3). Other solvent systems/conditions also produced **1a**, but together with variable amounts of benzimidazole **2a**.



 Table 3. Imino aniline optimization studies.

Interestingly, DMF gave **1a** in high yield (Table 3, entry 4) and it was also the only solvent to promote subsequent annulation in the presence of added  $M^+CN^-$  to afford **7a** in a one-pot protocol (see Table 4); other polar aprotic solvent – such as MeCN, HMPA, and DMSO – resulted in no detectable formation of **7a**. Also, THF (the most efficient solvent for the formation of **1a**) with added  $M^+CN^-$  gave only a trace amount of **7a**. In all

cases, the only identified side product, together with unreacted starting materials, was benzimidazole **2a**.

### **Table 4**. One-pot Isoquinolino[3,4-b]quinoxaline (7a) optimization studies.



Entry	M⁺CN⁻	Solvent	Conditions <sup>[a]</sup>	Yield (%) <sup>[b]</sup>
1	KCN	DMF	under N <sub>2</sub> /NaCl	15
2	KCN	DMF	under N <sub>2</sub> /18-crown-6	28
3	KCN	DMF	under N <sub>2</sub> /none	31
4	KCN	MeCN	under N <sub>2</sub> /none	0
5	NaCN	DMF	under N <sub>2</sub> /none	37
6	NaCN	DMF	open air/none	36
7	NaCN	MeCN	under N <sub>2</sub> /none	0
8	NaCN	HMPA	under $N_2$ /none	0
9	NaCN	DMSO	under $N_2$ /none	0
10	NaCN	THF	under N <sub>2</sub> /Bu <sub>4</sub> NCI	trace <sup>[c]</sup>

[a] Conditions: under  $N_2$  or open to the air/additive.[b] Overall yield. [c] Trace; determined by LCMS of the crude reaction.

In light of these one-pot two-step results, we also examined a two-pot method (Scheme 2). Here, performing step one (imine formation) in THF, concentration under vacuum, and subsequent addition of NaCN in DMF delivered the targeted **7a**, but the overall yield (28%) was comparable to the one-pot method (see Table 4, entry 6). The inescapable conclusion of

 these one- and two-pot *o*-phenylenediamines plus *o*-cyanobenzaldehyde going to isoquinolino[3,4-*b*]quinoxalines studies is that (i) imine **1** is reluctant to react with cyanide (leading to recovered starting materials upon workup; the major issue when reactions are run at room temperature) and (ii) there is unwanted benzimidazole formation ( $\mathbf{1} \rightarrow \mathbf{2}$ ; this becomes a significant issue when reactions are heated to 80 °C). Together, these two issues deter the effectiveness  $\mathbf{1} \rightarrow \mathbf{5}$  – the key transformation required for isoquinolino[3,4-*b*]quinoxaline formation.



Scheme 2. Two-pot synthetic route to isoquinolino[3,4-*b*]quinoxaline 7a and 7b.

Finally, it is noteworthy that **7a** and **7b**are highly fluorescent, suggesting potential fluorophore applications. Despite their slight electronic differences, both **7b** and **7b** have  $\lambda_{max}^{excitation}$  bands of 292, 392, and 414 nm that do not vary in the solvents examined (chloroform, acetonitrile, acetone,

and ethanol; i.e. polar aprotic to polar protic solvents). Likewise, both isoquinolino[3,4-*b*]quinoxalines display similar emission profiles ranging from 430-460 nm, but these small changes do not result in a visual fluorescence change in the examined solvents. The UV-Vis and fluorescence spectra of **7b** and **7b** can be found in the accompanying Supporting Information.

In summary, we have developed one-pot two-step routes to novel benzo[4,5]imidazo[2,1-*a*]isoquinolines as well as novel isoquinolino[3,4-b]quinoxalines starting from the same substrates: *o*-phenylenediamines and *o*-cyanobenzaldehyde. The former proceeds via benzimidazole formation followed by *N*-alkylation/cyclization, whereas the latter involves nucleophilic addition of cyanide to the imine intermediate and subsequent annulation.

#### **Experimental Section**

General Methods: All solvents and reagents were purchased from commercial suppliers and used without further purification. Analytical thin layer chromatography was carried out on silica pre-coated glass plates (Silica gel 60 F254, 0.25 mm thickness) and visualized with UV light at 254 nm. Flash chromatography was performed with 60 Å, 35-70 µm particle-size silica gel. Concentration refers to rotary evaporation under reduced pressure. 1H NMR spectra were recorded on an NMR spectrometer **a** operating at 600 MHz at ambient temperature with CDCl<sub>3</sub> or DMSO-d6 as solvent. <sup>13</sup>C NMR spectra were recorded on an NMR spectrometer operating at 150 MHz at ambient temperature with CDCl<sub>3</sub> or DMSO-d6 as solvent. Data for <sup>1</sup>H NMR are recorded as follows: δ chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint., quintet; sext.,

sextet; m, multiplet; br, broad), coupling constant (Hz), integration. Chemical shifts are reported in parts per million relative to CDCl<sub>3</sub> (<sup>1</sup>H NMR: δ 7.26; <sup>13</sup>C NMR: δ 77.16), DMSO-d6 (<sup>1</sup>H NMR, δ 2.50; <sup>13</sup>C NMR, δ 39.52), or TMS (<sup>1</sup>H NMR,  $\delta$  0.00). Infrared spectra were recorded on an FT-IR spectrometer (with a Platinum ATR attachment) with the major peaks listed. Melting points were recorded on an automated melting point system. Liquid chromatography/mass spectrometry (LC/MS) data were obtained to verify molecular mass and analyze purity of products. The specifications of the LC/MS instrument are the following: electrospray (+) ionization, mass range of 100-1500 Da, 5V cone voltage, C18 column (2.1 mm x 50 mm x 3.5 µm), gradient mobile phase consisting of acetonitrile, water, and 0.1 % formic acid (FA) buffer, and a flow rate of 0.2 mL/min. High-resolution mass spectra were obtained on an orbitrap (ion trap) mass spectrometer equipped with an electrospray ionization source, operating in the positive or negative ion mode. Samples were introduced into the source via loop injection at a flow rate of 150  $\mu$ L/min, in a solvent system of 1:1 acetonitrile:water with 0.1% formic acid. The spectra were externally calibrated using the standard calibration mixture, and then further calibrated internally to <2ppm with the lock mass tool.

CCDC 1432428 (for **1a**; see **Table 3**) and CCDC 1432427 (for **4a**; see **Figure 1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif.

(*E*)-2-(((2-Aminophenyl)imino)methyl)benzonitrile (**1a**): *o*-Phenylenediamine (1 mmol, 108 mg) and *o*-cyanobenzaldehyde (1 mmol, 131 mg) were dissolved in THF (500 µL) at room temperature under N<sub>2</sub>. After 30 min, an orange precipitate was formed and stirring was continued until reaction was judged complete by thin layer chromatography (TLC). The resulting solid was collected by filtration and washed with minimal amounts of cold THF to afford **1a** (216 mg, 98%) as a yellow solid: m.p. 108-109 °C. IR (neat): vmax = 3451, 3348, 2223, 1602, 1491, 1322, 1261, 1152, 963, 766, 742 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, DMSO-d6):  $\delta$  = 8.85 (s, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 5.50 (s, 2H). <sup>13</sup>C NMR (151 MHz, DMSO-d6):  $\delta$  = 151.3, 145.4, 138.2, 134.7, 133.3, 133.1, 130.8, 130.7, 129.1, 118.9, 116.7, 116.0, 115.1, 109.1. HRMS calculated for [C<sub>14</sub>H<sub>11</sub>N<sub>3</sub> + H]<sup>+</sup>: 222.1031; found: 222.1014.

2-(1H-Benzo[*d*]imidazol-2-yl)benzonitrile (**2a**): *o*-Phenylenediamine (1 mmol, 108 mg), *o*-cyanobenzaldehyde (1 mmol, 131 mg), and KI (1 mmol, 166 mg) were dissolved in DMF (10 mL) and stirred at 80°C in an open flask for 22-24 h. Upon completion and cooling to room temperature, water (30 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 100 mL). The combined organics were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude material was purified by flash chromatography (gradient 25-50% EtOAc/hexane) to afford **2a** as a white solid (190 mg, 87% yield): m.p. 255-256 °C. IR (neat): vmax = 3062, 2677, 2226, 1621, 1455, 1433, 1401, 1371, 1316, 1284, 1229, 1137, 1080, 1007, 972, 765, 745 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, DMSO-d6):  $\delta$  = 10.35 (s, 1H), 8.59 (d, J = 7.7 Hz, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.56 (m, 2H), 7.34 (m,

2H). <sup>13</sup>C NMR (151 MHz, DMSO-d6):  $\delta$  = 151.3, 145.4, 138.2, 134.7, 133.3, 133.1, 130.8, 130.7, 129.1, 118.9, 116.7, 116.0, 115.1, 109.1. HRMS calculated for [C<sub>14</sub>H<sub>9</sub>N<sub>3</sub> + H]<sup>+</sup>: 220.0875; found: 220.0858.

Ethvl 5-Aminobenzo[4,5]imidazo[2,1-a]isoquinoline-6-carboxylate (**4a**): Benzo[d]imidazole 2a (1 mmol, 219 mg) was dissolved in DMF (10 mL) containing potassium carbonate (2 mmol, 276 mg) and ethyl 2bromoacetate (1.2 mmol, 200 mg); the resulting mixture was stirred at 80 °C for 24 h. Upon completion, water (30 mL) was added to the cooled mixture, which was subsequently extracted with ethyl acetate (3 x 100 mL). The combined organics were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The resulting crude material was purified by column chromatography and subsequent recrystallization from ethanol afforded 4a (200 mg, 66%) as a yellow solid: m.p. 182-183°C (recrystallized in EtOH). IR (neat): vmax = 3420, 3288, 2985, 1682, 1634, 1617, 1542, 1512, 1451, 1361, 1250, 1189, 1094, 1024, 753 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.81 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 6.07 (s, 2H), 4.51 (g, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H).  $^{13}$ C NMR  $(151 \text{ MHz}, \text{CDCl}_3)$ :  $\delta = 163.8, 144.9, 143.7, 139.6, 132.4, 131.0, 130.0,$ 126.1, 126.0, 125.7, 123.5, 122.1, 121.2, 119.8, 114.6, 105.0, 61.5, 14.4. HRMS calculated for  $[C_{18}H_{15}N_3O_2 + H]^+$ : 306.1243; found: 306.1231.

Benzo[4,5]imidazo[2,1-*a*]isoquinolines (**4a-e**) – General procedure A: The appropriate *o*-phenylenediamine (1 mmol), *o*-cyanobenzaldehyde (1 mmol, 131 mg), and KI (1 mmol, 166 mg) were dissolved in DMF (10 mL) and

stirred at 80°C in an open flask for 22-24 h. Potassium carbonate (2 mmol, 276 mg) and the appropriate alkylating agent ( $R^2CH_2Br$ ; 1.2 mmol) were added to the reaction vessel, the contents sealed, and mixture heated at 80 °C for 24 h. Upon completion and cooling, water (30 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 100 mL). The combined organics were then washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The resulting crude material was purified by column chromatography and the resulting product was recrystallized from ethanol to afford **4a-e**.

Ethyl 5-aminobenzo[4,5]imidazo[2,1-*a*]isoquinoline-6-carboxylate (**4a**): Prepared according to general procedure A. The crude material was purified by flash chromatography (2.5% MeOH/DCM) to afford **4a** as a yellow solid (200 mg, 66% yield): see spectral data listed above.

(5-Aminobenzo[4,5]imidazo[2,1-*a*]isoquinolin-6-yl)(phenyl)methanone (**4b**): Prepared according to general procedure A. The crude material was purified by flash chromatography (2.5% MeOH/DCM) to afford **4b** as an orange solid (236 mg, 70% yield): m.p. 263-264 °C (recrystallized in EtOH). IR (neat): vmax = 3284, 3156, 1625, 1607, 1563, 1535, 1455, 1344, 1299, 1251, 1070, 923, 906, 846, 771, 733, 684 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, DMSOd6):  $\delta$  = 8.94 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.86 (m, 2H), 7.80 (t, J = 8.0 Hz, 1H), 7.55 (m, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.22 (m, 3H), 7.04 (d, J = 7.5 Hz, 1H), 6.93 (t, J = 8.0 Hz, 1H), 6.12 (s, 2H). <sup>13</sup>C NMR (151 MHz, DMSO-d6): δ = 187.3, 143.5, 143.1, 139.3, 138.3, 132.6, 131.2, 131.0, 130.3, 128.8, 128.5, 125.8, 125.3, 125.2, 124.3, 122.8, 121.1, 119.3,

113.0, 109.5. HRMS calculated for  $[C_{22}H_{15}N_3O + H]^+$ : 338.1293; found: 338.1285.

Ethyl 5-amino-9,10-dimethylbenzo[4,5]imidazo[2,1-a]isoquinoline-6-carboxylate (**4c**): Prepared according to general procedure A. The crude material was purified by flash chromatography (2.5% MeOH/DCM) to afford **4c** as a yellow solid (183 mg, 55% yield): m.p. 217-218 °C (recrystallized in EtOH). IR (neat): vmax = 3408, 3286, 3167, 2981, 2914, 1682, 1622, 1582, 1543, 1511, 1455, 1363, 1292, 1246, 1185, 1156, 1082, 1024, 895, 844, 757, 684 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.78 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.74 – 7.64 (m, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.30 (s, 1H), 6.02 (s, 2H), 4.51 (q, J = 7.2 Hz, 2H), 2.43 (s, 6H), 1.37 (t, J = 7.2 Hz, 3H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):  $\delta$  = 164.0, 144.4, 142.4, 139.3, 132.6, 131.0, 130.9, 130.3, 129.6, 126.4, 125.8, 125.4, 122.0, 119.7, 114.7, 105.3, 61.4, 21.0, 20.6, 14.4. HRMS calculated for [C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub> + H]<sup>+</sup>: 334.1556; found: 334.1543.

(5-Amino-9,10-dimethylbenzo[4,5]imidazo[2,1-*a*]isoquinolin-6-yl)(phenyl)methanone (**4d**): Prepared according to general procedure A. The crude material was purified by flash chromatography (gradient 30-50% EtOAc/hexane) to afford product **4d** as a red solid (180 mg, 46% yield): m.p. 220-221 °C (recrystallized in EtOH). IR (neat): vmax = 3283, 3155, 1627, 1565, 1537, 1448, 1343, 1290, 1248, 1176, 1090, 983, 913, 892, 829, 768, 714, 691 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.87 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.68 (ddd, J = 8.0, 7.5, 1.4 Hz, 1H), 7.57 (s, 1H), 7.54 (d, J = 7.5 Hz, 2H), 7.35 (td, J = 7.5, 1.4 Hz, 1H), 7.20 (t, J = 7.5 Hz, 2H), 6.76 (s, 1H), 6.10 (s, 2H), 2.27 (s, 3H), 2.06 (s, 3H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):  $\delta$  = 188.6, 143.7, 142.2, 138.4, 137.9, 132.8, 132.6, 131.1, 131.0, 130.1, 129.9, 128.9, 128.8, 126.3, 125.9, 125.6, 122.4, 119.5, 113.8, 113.7, 20.5, 20.4. HRMS calculated for  $[C_{24}H_{19}N_{3}O + H]^{+}$ : 366.1606, found: 366.1593.

Ethyl 5-Aminonaphtho[2',3':4,5]imidazo[2,1-*a*]isoquinoline-6-carboxylate (**4e**): Prepared according to general procedure A. The crude material was purified by flash chromatography (10% MeOH/DCM) to afford product **4e** as a yellowish tan solid (114 mg, 30% yield): m.p. 217.1-218.6 °C. IR (neat): vmax = 3282, 3166, 3132, 2200, 2138, 2066, 1666 cm<sup>-1</sup>. <sup>1</sup>H NMR (600MHz, CDCl<sub>3</sub>):  $\delta$  = 8.93 (d, J = 9.87 Hz, 1H), 8.40 (s, 1H), 8.05 (d, J = 8.63 Hz, 1H), 7.96 (m, 2H), 7.88 (d, J = 8.88 Hz, 1H), 7.82 (t, J = 15.05, 7.65 Hz, 1H), 7.77 (t, J = 15.29, 7.65 Hz, 1H), 7.44 (m, 2H), 6.05 (bs, 2H), 4.58 (q, J= 21.84, 7.85, 7.59 Hz, 2H), 1.35 (t, J = 14.17, 7.33 Hz, 3H). <sup>13</sup>C NMR (150MHz, CDCl<sub>3</sub>): δ = 163.7, 148.3, 143.5, 139.1, 132.9, 131.1, 130.9, 130.7, 129.1, 128.1, 127.9, 126.7, 126.6, 126.0, 124.0, 123.9, 122.0, 116.0, 110.9, 105.4, 61.5, 14.3. HRMS calculated for [C<sub>22</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub> + H]<sup>+</sup>: 356.1394, found: 356.1399.

Isoquinolino[3,4-*b*]quinoxalin-5-amine (**7a**) – one-pot protocol: *o*-Phenylenediamine (1 mmol, 108 mg) and *o*-cyanobenzaldehyde (1 mmol, 131 mg) were dissolved in THF (500  $\mu$ L) at room temperature. After 30 min, a precipitate was formed and stirring was continued until the reaction was judged complete by TLC. To this reaction mixture was added sodium cyanide (1.1 mmol, 54 mg) in DMF (10 mL) and the resulting mixture was stirred overnight at room temperature. Water (10 mL) was added to the reaction flask to afford a yellow precipitate, which was collected by filtration

and washed with cold chloroform to afford **7a** (91 mg, 37%) as a yellow solid: m.p. >400 °C. IR (neat): vmax = 3348, 3127, 2742, 1666, 1607, 1589, 1513, 1477, 1451, 1431, 1399, 1360, 1234, 1150, 1017, 913, 753 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, DMSO-d6):  $\delta$  = 9.10 (dd, J = 8.0, 1.3 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.17 (dd, J = 8.0, 1.3 Hz, 1H), 8.09 (s, 2H), 8.03 – 7.97 (m, 2H), 7.93 (td, J = 7.7, 1.3 Hz, 1H), 7.80 (ddd, J = 8.0, 6.6, 1.4 Hz, 1H), 7.72 (ddd, J = 8.0, 6.6, 1.4 Hz, 1H). <sup>13</sup>C NMR (151 MHz, DMSO-d6):  $\delta$  = 159.2, 149.7, 143.1, 138.5, 136.1, 133.1, 131.5, 130.5, 129.7, 128.5, 127.7, 127.0, 124.4, 124.2, 122.2. HRMS calculated for [C<sub>15</sub>H<sub>10</sub>N<sub>4</sub> + H]<sup>+</sup>: 247.0984; found: 247.0965.

9,10-Dimethylisoquinolino[3,4-*b*]quinoxalin-5-amine (**7b**) one-pot protocol: 4,5-Dimethylbenzene-1,2-diamine (1 mmol, 136 mg) and ocyanobenzaldehyde (1 mmol, 131 mg) were dissolved in THF (500 µL) at room temperature. After 30 min, a precipitate was formed and stirring was continued until reaction completion as was judged by TLC. To this reaction mixture was added sodium cyanide (1.1 mmol, 54 mg) in DMF (10 mL) and the resulting mixture was stirred overnight at room temperature. Water (10) mL) was added to the reaction flask to afford a yellow precipitate, which was collected by filtration and washed with cold chloroform to afford 7b (82) mg, 30%) as a yellow solid: m.p. 333-334 °C. IR (neat): vmax = 3506, 3403, 3314, 3174, 1640, 1617, 1585, 1517, 1446, 1408, 1358, 1214, 1004, 869, 767, 729, 674 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, DMSO-d6):  $\delta$  = 9.03 (d, J = 8.0 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.09-7.93 (m, 3H), 7.91-7.85 (m, 2H), 7.75 (s, 1H), 2.46 (s, 6H). <sup>13</sup>C NMR (151 MHz, DMSO-d6):  $\delta$  = 158.9, 149.1, 142.2, 140.6, 138.0, 137.6, 135.2, 133.6, 131.8, 130.4, 127.6, 126.7,

124.7, 124.2, 122.0, 20.1, 19.8. HRMS calculated for  $[C_{17}H_{14}N_4 + H]^+$ : 275.1297; found: 275.1281.

Isoquinolino[3,4-*b*]quinoxalin-5-amine (**7a**) – two-step protocol: *o*-Phenylenediamine (1 mmol, 108 mg) and *o*-cyanobenzaldehyde (1 mmol, 131 mg) were dissolved in THF (500  $\mu$ L) at room temperature. After 30 min, a precipitate was formed and stirring was continued until the reaction was judged complete by TLC. THF was removed *in vacuo* resulting in an orange oil. To this oil was added sodium cyanide (1.1 mmol, 54 mg) in DMF (10 mL) and the resulting mixture was stirred overnight at room temperature. Water (10 mL) was added to the reaction flask to afford a yellow precipitate, which was collected by filtration and washed with cold chloroform to obtain **7a** (69 mg, 28%): see spectral data above.

9,10-Dimethylisoquinolino[3,4-*b*]quinoxalin-5-amine (**7b**) – two-step protocol: 4,5-Dimethylbenzene-1,2-diamine (1 mmol; 136 mg) and *o*cyanobenzaldehyde (1 mmol, 131 mg) were dissolved in THF (500  $\mu$ L) at room temperature. After 30 min, a precipitate had formed and stirring was continued until the reaction was judged complete by TLC. THF was removed *in vacuo* resulting in an orange oil. To this oil was added sodium cyanide (1.1 mmol, 54 mg) in DMF (10 mL) and the resulting mixture was stirred overnight at room temperature. Water (10 mL) was added to the reaction flask to afford an off-yellow/orange precipitate, which was collected by filtration and washed with cold chloroform to afford **7b** (82 mg, 30%) as a yellow-brown solid: see spectral data above.

# **Associated Content:**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

<sup>1</sup>H- and <sup>13</sup>C-NMR spectra (**1a**, **2a**, **4a**, **4b**, **4c**, **4d**, **4e**, **7a**, and **7b**), UV-Vis and fluorescence data, and X-ray crystallographic data (**1a** and **4a**).

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[12] Compound **3a** crystallized in the monoclinic space group p21/c with a final R1 value of 4.59%. Note the slight occupancy disorder due to the degrees of freedom of the ethyl chain of the carboxylate moiety.