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A synthesis of dihydroimidazo[5,1-*a*]isoquinolines using a sequential Ugi–Bischler–Napieralski reaction sequence

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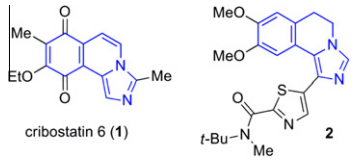
ABSTRACT

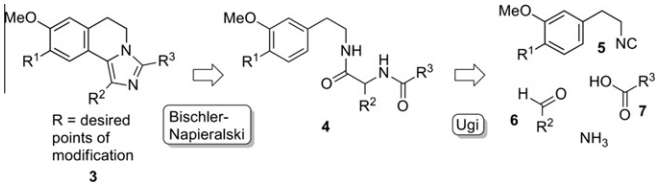
A flexible route to analogues of dihydroimidazo[5,1-*a*]isoquinolines is described. The synthesis hinges on a sequential Ugi coupling, followed by a Bischler–Napieralski reaction to form the imidazole isoquinoline core. This route facilitates the introduction of a range of substitutions throughout the carbon framework.

Cribrostatin 6 (**1**) is the first known naturally occurring example of an imidazole isoquinoline containing compound. In the course of several of our medicinal chemistry programs, we were interested in pursuing structures similar to compound **2**. The compounds contained a very similar carbon framework to cribrostatin 6 (blue). There have been several synthetic approaches to the imidazole isoquinoline core, including those that have led to the total synthesis of cribrostatin itself.[1] These synthetic approaches, although elegant, do not allow for the rapid introduction of different functional groups onto the core structure.

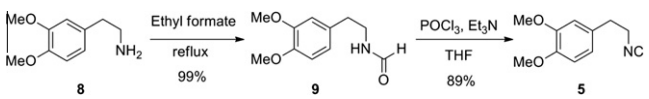


In our approach to the imidazole isoquinoline core, a key requirement would be the ability to rapidly create novel analogues for testing in biological assays. We were most interested in modifications to the imidazole ring, but also wanted a route that would still be amenable to modifications of the isoquinoline ring as well. We envisioned an Ugi multicomponent coupling[2] that would allow for the assembly of the different R group-containing fragments, followed by a Bischler–Napieralski[3] reaction to form the desired imidazole isoquinoline ring system (Scheme 1). It has been previously reported that the imidiazole isoquinoline ring system can be assembled via a Bischler–Napieralski reaction in low yield (11%).[4] We thought that we could improve the yield and efficiency of this reaction. Additionally, with careful selection of aldehyde **6**, acid **7**, and isonitrile **5** components for the Ugi coupling, we could assemble a large degree of chemical diversity in this tandem reaction sequence.

The desired isonitrile substrate for the Ugi coupling was routinely synthesized from the corresponding amine (Scheme 2). The amine was heated in neat ethyl formate to provide formamide **9**. The formamide was then cleanly converted to the desired



Scheme 1. Ugi–Bischler–Napieralski approach.



Scheme 2. Synthesis route for isonitriles.

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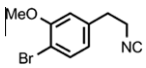
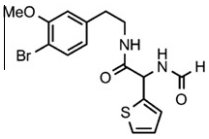
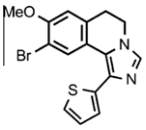
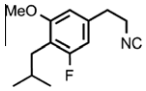
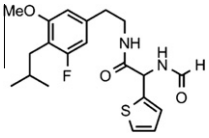
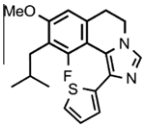
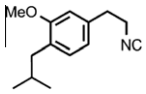
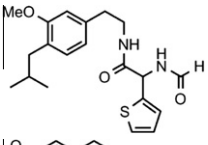
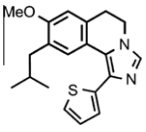
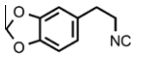
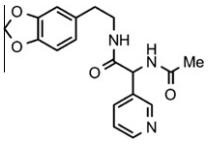
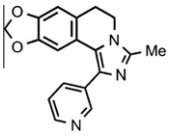
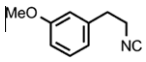
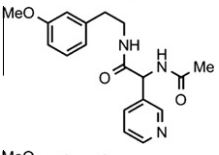
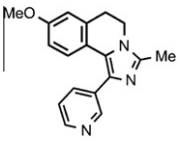
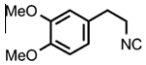
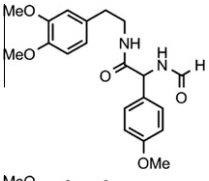
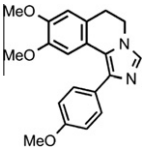
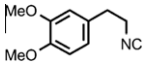
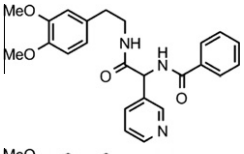
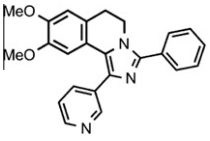
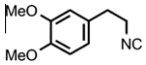
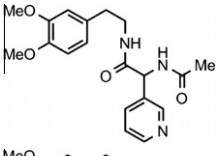
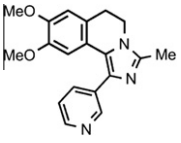
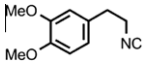
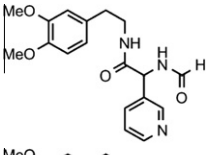
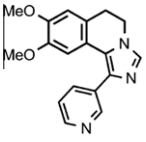
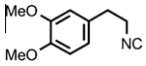
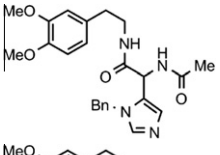
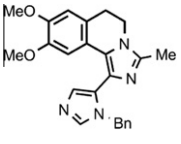
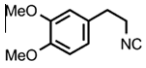
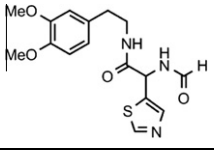
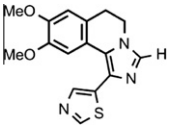
Table 1
Synthesis of dihydroimidazolisoquinones[5]

Entry	Isonitrile	Ugi coupling product	Yield[a] (%)	Bischler–Napieralski coupling product	Yield[a] (%)
1			52		74
2			50		77
3			58		46
4			99		48
5			62		56
6			82		43
7			84		45
8			58		62
9			64		68
10			65		64
11			46		40

[a] Isolated yield.

isonitrile **5** using $POCl_3$. With the isonitrile in hand, we could attempt the desired Ugi–Bischler–Napieralski sequence (Table 1).

Methanol was an acceptable solvent for the Ugi coupling; however, optimal results were obtained by pre-forming the imine in

trifluroethanol, then adding the isonitrile.[6] A variety of modifications were tolerated on the phenyl ring (entries 1–6). Electron-withdrawing (entry 1) and electron-donating (entries 3–6) groups were well tolerated. Trisubstitution on the aryl ring (entry 2) did not hinder the reaction. It was interesting to note that in the case of entry 5, the Bischler–Napieralski cyclization gave only the less sterically hindered product. The coupling-cyclization sequence also tolerated a variety of aromatic and heteroaromatic aldehydes (**6**) including thiophene (entries 1–3), pyridine (entries 4, 5 and 7–9), phenyl (entry 6), imidiazole (entry 10), and thiazole (entry 11). Additionally, the reaction sequence was tolerant of modifications of the acid coupling partner (**7**) with Me (entries 4, 5, 8 and 10) and phenyl (entry 7) being well tolerated.

In summary, we have optimized a new two step Ugi–Bischler–Napieralski sequence for the synthesis of biologically active dihydroimidiazoleisoquinolines. These conditions have been applied on a large scale to provide gram quantities of the desired products. Future efforts will focus on expanding the scope of the reaction to new substrate classes.

References and notes

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3. For a review, see: Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903.
4. Nagarajan, K.; Rodrigues, P. J. *J. Chem. Res.* **1993**, 336.
5. Representative procedure (entry 8): 3-Pyridine carboxaldehyde (1.00 mL, 10.6 mmol) was dissolved in trifluroethanol (18 mL). Ammonium acetate (1.63 g, 21.2 mmol) was added in one portion and the solution was heated to 60 °C for 30 min. Isonitrile **10** (2.23 g, 11.7 mmol) was added in one portion at 60 °C and the resulting solution was stirred for a further 4 h at 60 °C. The reaction mixture was cooled to room temperature and concentrated. The residue was purified via column chromatography on silica gel (0–10% MeOH/DCM) to provide 2.17 g (58%) of the desired product as a white solid. TLC R_f = 0.33 (5% MeOH/DCM); mp = 151–152 °C; ^{1}H NMR 400 MHz ($CDCl_3$) δ 8.54 (m, 1H), 8.49 (m, 1H), 7.62 (m, 1H), 7.23 (m, 1H), 7.09 (m, 2H), 6.72 (d, J = 8 Hz, 1H), 6.65 (m, 1H), 6.60 (m, 1H), 6.52 (d, J = 8 Hz, 1H), 5.45 (d, J = 7.2 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.56 (m, 1H), 3.47 (s, 3H), 3.41 (m, 1H), 2.68 (m, 2H), 1.99 (s, 3H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 170.2, 169.4, 148.9, 148.8, 148.6, 147.5, 134.8, 134.3, 131.0, 123.8, 120.6, 111.7, 111.2, 55.8, 54.5, 50.4, 41.1, 34.9, 22.9; LC–MS (ESI+) 97.6% [M+H] = 358. P_2O_5 (4.31 g, 30.4 mmol) was added to methanesulfonic acid and heated to 75 °C for 30 min, at which time all of the P_2O_5 had dissolved. The Ugi coupling product (2.17 g, 6.07 mmol) was added in one portion at 75 °C and the reaction was stirred for 4 h to consume all of the starting material (TLC). The reaction was cooled to room temperature and poured slowly into solid $NaHCO_3$. Ice water was slowly added and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to a yellow oil that was purified via column chromatography on silica gel (0–5% MeOH/DCM/NH_3) to provide 1.18 g (62%) the desired product as a white solid. TLC R_f = 0.40 (5% MeOH/DCM_3/NH); mp = 170–171 °C ^{1}H NMR 400 MHz ($CDCl_3$) δ 8.95 (m, 1H), 5.52 (m, 1H), 8.01 (m, 1H), 7.32 (m, 1H), 6.96 (s, 1H), 6.75 (s, 1H). 3.98 (m, 2H), 3.88 (s, 3H), 3.57 (s, 3H), 3.05 (m, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.6, 148.1, 148.0, 144.5, 143.5, 135.6, 131.8, 131.7, 125.0, 124.1, 123.1, 120.3, 111.3, 106.7, 56.0, 55.7, 41.2, 29.3, 13.0. LC–MS (ESI+) 99.9% [M+H] = 322.
6. Isaacson, J.; Gilley, C. B.; Kobayashi, Y. *J. Org. Chem.* **2007**, *72*, 3913.