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Regioselective assembly of 3,4-dihydroisoquinoline derivatives

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ABSTRACT

A facile two-step sequence (**9**→**10**→**1**) of regioselective assembly of 3,4-dihydroisoquinoline derivatives **1** is reported. The halogen derivatives provide opportunity for Suzuki, Buchwald, and related coupling reactions useful for expanding the scaffold and lead optimization in drug discovery.

Alkaloids are an important class of natural products that are widely distributed in nature and produced by a large variety of organisms. The tetrahydroisoquinoline core is a structural centerpiece found in a number of biologically active synthetic and natural products with a wide spectrum of biological activities and for many years was used in folk medicines (Fig. 1).[1–7]

The importance of these natural products in inspiring drug discovery programs is proven and, therefore, their continued synthesis is of significant interest. The Bischler–Napieralski reaction is a commonly used strategy to achieve the synthesis of alkaloids and has been well documented.[8–12] For example in Scheme 1, the key intermediate 3,4-dihydroisoquinoline **1**, generated from **2** by the Bischler–Napieralski reaction, was reported to undergo dehydration to isoquinoline derivatives **3**,[9,13] and reduction to tetrahydroisoquinoline analogs **4**,[10,14] and condensation of **2** with alkyl vinyl ketone (MVK) to form β-keto-tertiary amine intermediates **5**[15] from which more complex alkaloids could be derived. Thus, the synthesis of the key intermediate 3,4-dihydroisoquinoline **1** is a cornerstone for the synthesis of many of these alkaloids.

In our ongoing drug discovery program, we needed to synthesize a series of the target molecules based on the isoquinolone scaffold with wide range of functional groups R_1 and R_2 (Scheme 1). The most direct route would be via the intermediates **1** and **5** using the Bischler–Napieralski reaction as a key step.

The Bischler–Napieralski reaction[16] is an intramolecular electrophilic aromatic substitution reaction that allows for the cyclization of β-arylethyl amides or β-arylethyl carbamates. Generally speaking, the reaction favors the β-arylethyl amides with electron-rich functional groups, such as alkoxy (**2**, R_1, R_2 = alkoxy), at the aromatic ring C6 and C7 positions. We were surprised to find that Bischler–Napieralski reactions bearing groups such as halogens in the aromatic ring at the C6 and C7 positions were, to the best of our knowledge, poorly precedented in the literature[17,18] despite their importance and potential utilities in construction of synthetic building blocks. We needed to explore structural–activity relationships (SAR) and to replace the metabolically labile 6-methoxy group[19] with metabolically stable functional groups. More importantly, we were interested in preparing the 6-bromo derivatives (**1**, R_1 = Br) as scaffolds to synthesize more complex compounds via Suzuki and Buchwald coupling or related reactions. Herein, we describe a facile two-step sequence of regioselective assembly of 3,4-dihydroisoquinoline derivatives **1** bearing groups positioned for further elaboration of this scaffold.

We commenced our initial exploration of Bischler–Napieralski reaction of the N-formyl compound **2** to the 3,4-dihydroisoquinoline **1** (R_1 = F, R_2 = OCH_3) (Scheme 1) under the standard literature reaction conditions (P_2O_5 or $POCl_3$, toluene).[20,21] Only black tar was obtained in many trials under a range of temperatures (80–120 °C). There was no desired product **1** (R_1 = F, R_2 = OCH_3) detected (LC/MS). When CH_3CN was used as the solvent and $POCl_3$ as the catalyst at lower temperature (80 °C, 25 h), a small amount of the desired product was isolated (**1**, R_1 = F, R_2 = OCH_3: <5% yield; **1**, R_1 = CH_3, R_2 = OCH_3: 20% yield) with the dimers, trimers, and tetramers (by LC/MS) as the major side products. We hypothesized that the polymerization could be avoided by masking the free-hydrogen on nitrogen of the β-arylethyl amine intermediate with a proper protecting group and then condense this material with formaldehyde to achieve cyclization. The protecting group could be removed and the imine functionality could be subsequently introduced to realize the desired 3,4-dihydroisoquinoline intermediate **1**

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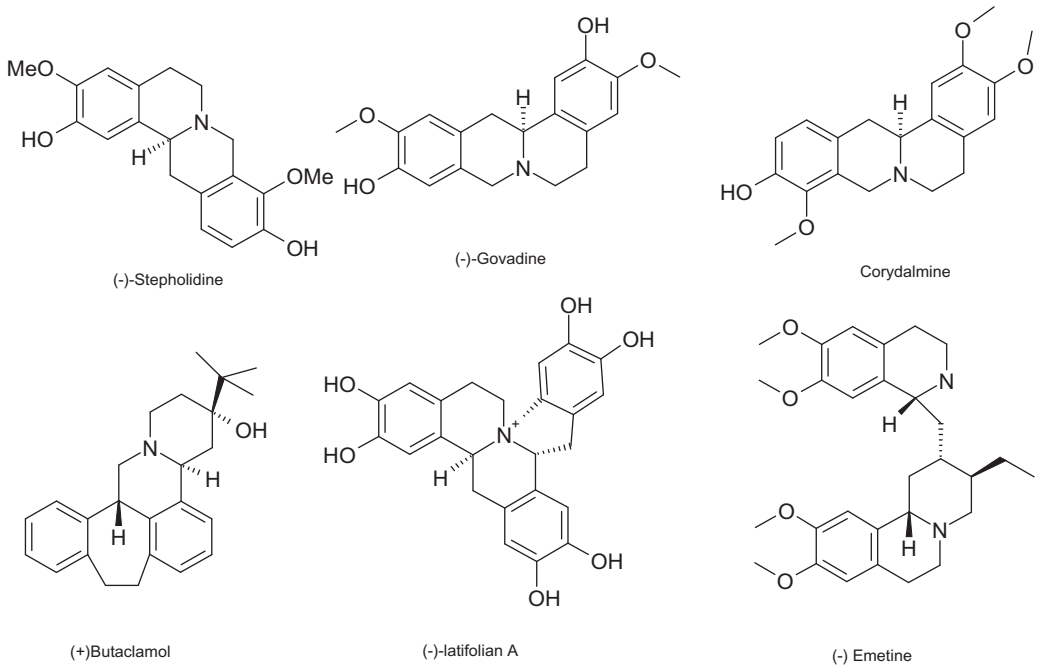


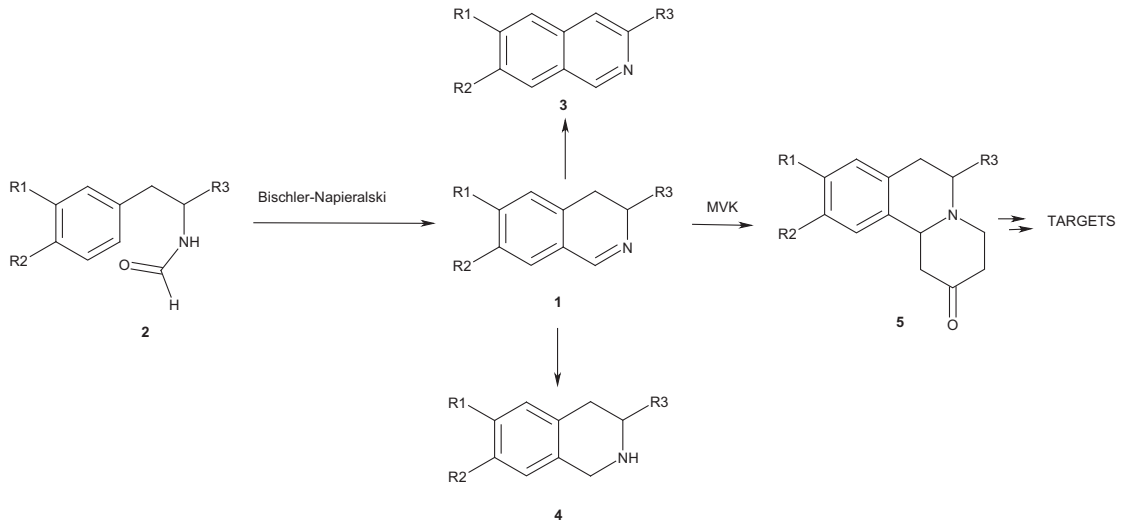
Figure 1. Natural products and bioactive drug candidates containing tetrahydroisoquinoline core structures.

(Scheme 2). In order to test this hypothesis, the 6-bromo-7-methyoxyphenethylamine was protected as N-formyl, was then condensed with paraformaldehyde under Pictet–Spengler conditions.[21] The desired products were observed in good yield (97% collectively). Unfortunately, the formation of regioisomers **6** and **7** (2.5–1 by NMR) arose as a new issue (Scheme 2). To demonstrate the usefulness of this strategy for ultimate synthesis of intermediate **1**, the desired regioisomer **6** was isolated, and was then hydrolyzed (NaOH, EtOH, 80 °C, 10 h) to obtain the tetrahydroisoquinoline **8** in quantitative yield. Subsequently, **8** was transformed into imine **1** under known conditions.[22]

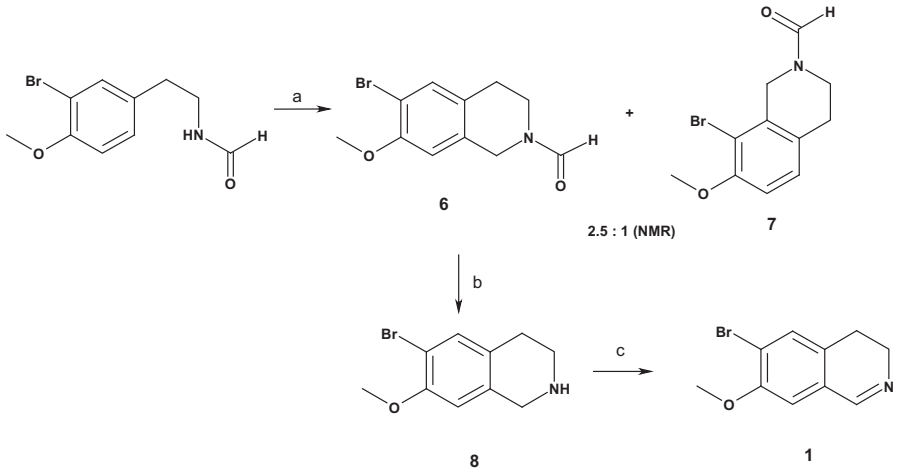
With these preliminary results in hand, we initiated optimization of the reaction conditions to improve the regioselectivity. We thought a bulkier protecting group might be able to direct the regiochemistry toward the desired regioisomer **6**. Tosyl was chosen as a N-protecting group and the reaction of **9**→**10** was conducted under our new conditions (paraformaldehyde, TFA, toluene, 60 °C). The reaction was very clean and provided **10** in 81% yield. None of the regioisomer was detected by LC/MS (Scheme 3).

The next task was to remove the tosyl protecting group. Under various conditions (KOH, EtOH, reflux overnight; KOBu^t, THF, reflux overnight), mainly starting material **10** was recovered with only a small amount of desired product **11** isolated along with a small amount of **1** detected (LC/MS). Clearly, **1** (R_1 = Br, R_2 = OCH_3) was generated via an elimination mechanism. This observation led us to explore a stronger base to promote elimination. LDA (−78 °C, THF, 10 min) was tried initially. The elimination reaction was readily achieved in 80—100% yield for variety of substrates (Table 1).

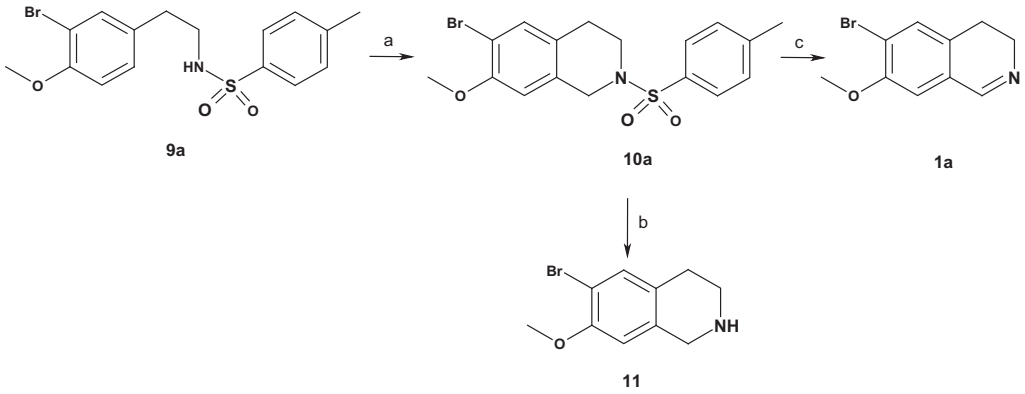
The cyclization reaction conditions were further refined by using dimethoxymethane instead of paraformaldehyde and dilute



Scheme 1. The Bischler–Napieralski reaction as a key step for alkaloid syntheses.

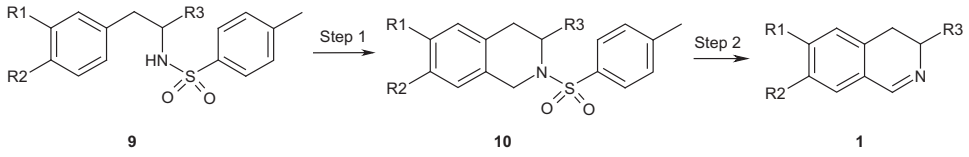


Scheme 2. Exploration of the Bischler–Napieralski reaction conditions. Reagents and conditions: (a) Paraformaldehyde, TFA, toluene, 60 °C, 97%; (b) NaOH, EtOH, 80 °C, 10 h, 100%; (c) NBS, DCM, rt, 15 min; NaOH, EtOH, rt, 4 h, 94%.



Scheme 3. Two-step sequence for construction of Bischler–Napieralski product. Reagents and conditions: (a) Dimethoxymethane, toluene, H_3PO_4 (85%, w/w), 60 °C, 25 h, 91%. (b) KOH, EtOH, reflux overnight; (c) LDA (1.0 equiv), THF, −78 °C, 10 min 92%.

Table 1
Reaction scope[a]



9 10 1

Product	R1	R2	R3	Step 1 reaction time (h)	Step 1 yield[b] (%)	Step 2 yield[b] (%)
1a	Br	MeO	H	25	91	92
1b	F	MeO	H	25	88	80
1c	Cl	MeO	H	12	86	88
1d	CH_3	MeO	H	12	100	95
1e	Et	MeO	H	12	100	95
1f	Br	H	H	15	90	70
1g	H	MeO	H	15	91	88
1h	OMe	F	H	12	87	85
1i	OMe	H	Et	15	65	72

[a] General procedure: To a solution of sulfonamide in toluene and dimethoxymethane (1:1, v/v) (1.6 ml/mmol of sulfonamide) was added 60% (w/w) sulfuric acid. The reaction was stirred at 50–60 °C for the time specified. The product was isolated by separating the two layers and extracting the aqueous layer with ether.
[b] Isolated yield.

phosphoric acid or sulfuric acid instead of TFA. The major advantage for using dimethoxymethane was a liquid biphasic reaction instead of a solid–liquid heterogeneous mixture. In addition, the product could be obtained simply by separation of the two layers and extraction. The typical reaction sequence[23] is shown in Scheme 3 in which the tosyl protected 6-bromo-7-methyoxyphenethylamine was heated (50–60 °C) with dimethoxymethane in toluene (1:1, v/v) and catalyzed by dilute sulfuric acid (60%, w/w) or

phosphoric acid (85%, w/w). The product obtained was treated with 1.0 equiv of LDA in THF at −78 °C for 10–15 min to yield the desired Bischler–Napieralski product **1a**.

With this preliminary protocol in hand, we explored the scope of the reaction starting from **9** with a variety of substituents in the aromatic ring. The reaction is tolerant of a range of substituents at different positions (Table 1).

In conclusion, we have developed a facile two-step sequence (**9**→**10**→**1**) to achieve the synthesis of 3,4-dihydroisoquinoline derivatives **1** in good yield bearing groups positioned for further elaboration of the scaffold. The functional groups at C*6*, especially 6-halogen analogs, offer opportunities for Suzuki, Buchwald, and related coupling reactions to open another dimension of diversity in medicinal chemistry lead optimization for drug discovery.

Acknowledgments

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References and notes

1. Cheng, J.; Fu, L.; Ling, C.; Yang, Y. *Heterocycles* **2010**, *81*, 2581.
2. Zhai, H.; Miller, J.; Sammis, G. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1557.
3. Dai, X.; Hu, R.; Sun, C.; Pan, Y. *J. Chromatogr., A* **2012**, *1226*, 18.
4. Jha, R. N. *J. Nepal Chem. Soc.* **2010**, *25*, 89.
5. Martin, F.; Grkovic, T.; Sykes, M. L.; Shelper, T.; Avery, V. M.; Camp, D.; Quinn, R. J.; Davis, R. A. *J. Nat. Prod.* **2011**, *74*, 2425.
6. Abbas, A. K.; Huang, F. S.; Li, R.; Ekstrom, J.; Wigstrom, H. *Brain Res.* **2011**, *1426*, 18.
7. Tacon, C.; Guantai, E. M.; Smith, P. J.; Chibale, K. *Bioorg. Med. Chem.* **2012**, *20*, 893.
8. Buyck, T.; Wang, Q.; Zhu, J. *Org Lett* **2012**, *14*, 1338.
9. Schrittwieser, J. H.; Resch, V.; Wallner, S.; Lienhart, W. D.; Sattler, J. H.; Resch, J.; Macheroux, P.; Kroutil, W. *J. Org. Chem.* **2011**, *76*, 6703.
10. Haning, H.; Giro-Manas, C.; Paddock, V. L.; Bochet, C. G.; White, A. J. P.; Bernardinelli, G.; Mann, I.; Oppolzer, W.; Spivey, A. C. *Org. Biomol. Chem.* **2011**, *9*, 2809.
11. Sotomayor, N.; Dominguez, E.; Lete, E. *J. Org. Chem.* **1996**, *61*, 4062.
12. Bergmeier, S. C.; Seth, P. P. *J. Org. Chem.* **1999**, *64*, 3237.
13. Shi, J.; Manolikakes, G.; Yeh, C.-H.; Guerrero, C. A.; Shenvi, R. A.; Shigehisa, H.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 8014.
14. Hajipour, A. R.; Mohammadpoor-Baltork, I.; Noroallhi, M. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2001**, *40B*, 152.
15. Maryanoff, B. E.; McComsey, D. F.; Taylor, R. J., Jr.; Gardocki, J. F. *J. Med. Chem.* **1981**, *24*, 79.
16. Stockigt, J.; Antonchick, A. P.; Wu, F.-R.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538.
17. Whaley, W. M.; Govindachari, T. R. *Org. React. (N.Y.)* **1951**, *VI*, 151.
18. Whaley, W. M.; Govindachari, T. R. *Org. React. (N.Y.)* **1951**, *VI*, 74.
19. Li, C. M.; Lu, Y.; Narayanan, R.; Miller, D. D.; Dalton, J. T. *Drug Metab. Dispos.: Biol. Fate Chem.* **2010**, *38*, 2032.
20. Brossi, A.; Dolan, L. A.; Teitel, S. *Org. Synth.* **1977**, *56*, 1–2.
21. Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev. (Washington, DC, U.S.)* **2004**, *104*, 3341.
22. Mohamed, M. A.; Yamada, K.-i.; Tomioka, K. *Tetrahedron Lett.* **2009**, *50*, 3436.
23. *Representative procedure for the synthesis of **1b***: (step 1) A solution of 4.12 g of *N*-[2-(3-fluoro-4-methoxy-phenyl)-ethyl]-4-methyl-benzenesulfonamide (**9b**), phosphoric acid (85% w/w, 7.3 g) in 20 mL of toluene, and 20 mL of dimethoxymethane was heated by an oil bath set at 60 °C externally with stirring under nitrogen for 15 h. The reaction was complete (LC/MS). The reaction mixture was cooled to rt and diluted with ether (50 mL). The two layers were separated and the aqueous layer was extracted with ether (25 mL). The combined ethereal solution was washed sequentially with water (15 mL), saturated sodium bicarbonate (15 mL), and brine (10 mL). The ethereal solution was then dried over anhydrous granular potassium carbonate, filtered, and concentrated in vacuo. The crude product, a solid after standing, was re-crystallized from ether (30 mL) and pentane (50 mL). The material was collected by suction filtration and dried under vacuum to give 3.75 g (88%) of the product **10b** as white crystalline solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.73 (d, J = 8.7 Hz, 2H,) 7.34 (d, J = 8.7 Hz, 2H), 6.80 (m, 1H), 6.61 (m, 1H), 4.18 (s, 3H), 3.82 (s, 3H), 3.32 (t, J = 6.0 Hz, 2H), 2.82 (t, J = 6.0 Hz, 2H,), 2.42 (s, 3H); LC: 3.22 min; MS m/z = 336. (step 2) Diisopropyl amine (3.42 g, 33.82 mmol) was weighted in a RBF. Anhydrous THF (44 mL) was introduced. The solution was cooled to −78 °C and the air was replaced with nitrogen by cooling-vacuum-nitrogen, three circles. To this cooled (−78 °C) solution was added butyl lithium (20 mL, 32 mmol). The almost colorless solution was stirred at −78 °C for 5 min; the ice-bath was removed and the stirring was continued for 5 min, then the reaction flask was submerged into an ice-water bath for 15 mins. To another flask was added sulfonamide **10b** (4.6 g, 14.22 mmol) and anhydrous THF (140 mL). The solution was cooled to −78 °C. To this solution was transferred LDA solution prepared above at −78 °C. The solution turned light yellow, then bright yellow, then orange, and finally reddish orange. This solution was stirred for 10 min TLC (DCM) showed that the reaction was complete. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (20 mL). The mixture was diluted with ethyl acetate (50 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (40 mL × 2). The combined ethyl acetate extracts were washed with sodium bicarbonate (20 mL) and brine (15 mL × 2), dried (anhydrous potassium carbonate), filtered, and concentrated in vacuo. The crude product was purified on a silica gel column, eluted with 3% MeOH in DCM to give **1b** as a colorless liquid (2.01 g, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.27 (br. s, 1H), 6.93 (s, 1H), 6.90 (d, J = 2.3 Hz, 1H), 3.92 (s, 3H), 3.75 (dt, J = 2.3 Hz, 7.8 Hz, 2H), 2.68 (t, J = 7.8 Hz, 2H); LC: 0.84 min; MS m/z = 180 ($M+H^+$).