Facile Synthesis of the Isoquinoline Alkaloids Doryanine and Oxyhydrastinine

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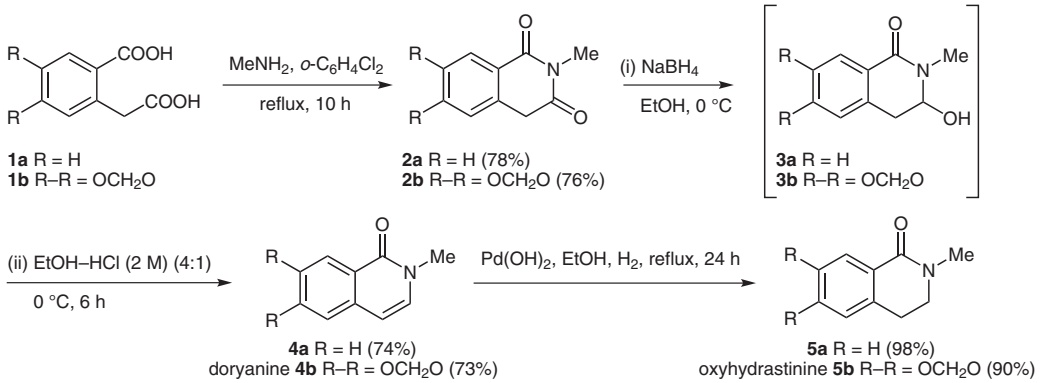
Abstract: Starting from 4,5-(methylenedioxy)homophthalic acid, a concise and efficient synthesis of the isoquinoline alkaloids doryanine and oxyhydrastinine is described via the corresponding homophthalimide utilizing a one-pot regioselective reductive dehydration and catalytic hydrogenation pathway.

Key words: homophthalic acid, homophthalimide, regioselective reduction, dehydration, isoquinoline alkaloids

The isoquinoline alkaloids are an important class of compounds and they exhibit a broad range of biological activity.[1] The alkaloid doryanine is isolated from *Cryptocarya chinensis*, *Doryphora sassafras*, and *Mitragyna speciosa* species.[2] The alkaloid oxyhydrastinine is wide spread in Nature and it is isolated from *Argemone mexicana*, *Hunnemania fumariaefolia*, *Hydrastis canadensis*, *Hypecoum erectum*, *Hypecoum leptocarpum*, *Fumaria agraria*, *Fumaria bastardii*, *Fumaria indica*, *Fumaria sepium*, and *Papaveraceae species*. It is known to possess antibacterial, antitubercular, and immunostimulant activity.[3] Several good synthesis of these two simple natural products are known in the literature.[4,5] They have been designed by employing several new C–C and C–N bond-forming reactions. Continuing our studies from the last two decades on cyclic anhydrides and their derivatives as bioactive natural products,[6] we reasoned that 4,5-(methylenedioxy)homophthalic anhydride[7] would be a potential precursor for the synthesis of doryanine and oxyhydrastinine. In this context, now we herein report a practical synthesis of the target compounds (Scheme 1).

The homophthalic acids **1a** and **1b** were initially stirred with excess 40% aqueous methylamine solution at 25 °C for few minutes to form the corresponding salt. The obtained dry salts on vigorous reflux in *o*-dichlorobenzene for 10 hours provided the corresponding precursor homophthalimides **2a** and **2b** in very good yields via amide formation followed by intramolecular dehydrative cyclization.[8] The regioselective sodium borohydride reduction of the more reactive unconjugated imide carbonyl group in imides **2a** and **2b** formed the corresponding geminal aminohydrin intermediates **3a** and **3b**. Herein the boron atom selectively complexes with an oxygen atom from the more electron-rich unconjugated imide carbonyl group resulting in complete regioselectivity. These aminohydrin intermediates exhibit ring-chain tautomerism and were prone to decomposition. During the course of the reduction we also noticed the formation of undesired acyclic overreduced product, which is in accordance with the observation of Cheng et al.[8b] Therefore, in situ dehydration with the periodic addition of a controlled amount of hydrochloric acid was performed to obtain the desired model compound **4a** and the natural product doryanine (**4b**) directly in nearly 75% yields. A similar protocol was earlier employed by Iida et al. en route to doryanine (**4b**), however the complete experimental details are not available;[4f] on completion of the sodium borohydride reduction reaction, they acidified the reaction mixture with 10% hydrochloric acid. In our studies, the periodic addition of hydrochloric acid to the reaction mixture is essential to ensure completion of the reaction and resolve yield issues. It also helps to avoid decomposition and the formation of



Scheme 1 Synthesis of isoquinoline alkaloids doryanine and oxyhydrastinine

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undesired overreduction product. Next, we performed the reduction of the C=C bond in heterocyclic ring B in compound **4a** using palladium-on-carbon in ethyl acetate and obtained the desired second prototypical compound **5a** in quantitative yield. Our above-specified hydrogenation reaction at room temperature under 2 bars of hydrogen pressure was very slow and it took almost three days to go to completion (monitored by ^{1}H NMR). The same reduction reaction with substrate **4b** was not feasible and the starting material remained completely unreacted. We also attempted the palladium-on-carbon catalyzed reduction of compound **4b** at room temperature in other solvents, such as methanol, ethanol, and petroleum ether, using a hydrogenation Parr shaker under 4.5 bars of hydrogen pressure. The results were not encouraging and we always ended up with isolation of the starting material. We feel that the cause for failure could be the relatively lower reactivity of substrate **4b** bearing the oxymethylene bridge. Finally, the palladium hydroxide induced hydrogenation of both compounds **4a** and **4b** under a balloon pressure hydrogen atmosphere in refluxing ethanol delivered the desired compound **5a** and natural product oxyhydrastinine (**5b**) in nearly quantitative yields. The analytical and spectral data obtained for synthetic **4b** and **5b** were in complete agreement with the reported data.[2–5] Thus starting from 4,5-(methylenedioxy)homophthalic acid, we completed the two-step synthesis of doryanine and three-step synthesis of oxyhydrastinine in decent overall yields.

In summary, we have described the well-organized synthesis of doryanine and oxyhydrastinine alkaloids. Our present approach to this isoquinoline class of compound is general in nature and will be useful to design a focused mini-library of their analogues and congeners for SAR studies.

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a 200 MHz NMR spectrometer. ^{13}C NMR spectra were recorded on a 200 NMR spectrometer (50 MHz) and 400 NMR spectrometer (100 MHz). MS were taken on an MS-TOF mass spectrometer. IR spectra were recorded on a FT-IR spectrophotometer. Column chromatographic separations used silica gel (60–120 mesh); petroleum ether = PE. Commercially available homophthalic acid, $MeNH_2$, *o*-dichlorobenzene, $NaBH_4$, Pd/C, and $Pd(OH)_2$ were used. 4,5-(Methylenedioxy)homophthalic acid (**1b**) was prepared by using known procedures.[7]

2-Methylisoquinoline-1,3(2*H*,4*H*)-dione (2a); Typical Procedure

To homophthalic acid (**1a**, 1.80 g, 10.00 mmol) was added 40% aq $MeNH_2$ (5 mL) and the mixture was stirred for 5 min. The mixture was then concentrated in vacuo and dried on a vacuum pump. To the obtained salt was added *o*-dichlorobenzene (20 mL) and the mixture was vigorously refluxed for 10 h. The mixture was allowed to cool to r.t. and subjected directly to column chromatographic (silica gel, EtOAc–PE) to give pure product **2a** as a white solid; yield: 1.36 g (78%); mp 119–121 °C.

IR ($CHCl_3$): 1710, 1664 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.38 (s, 3 H), 4.06 (s, 2 H), 7.28 (d, *J* = 8 Hz, 1 H), 7.45 (t, *J* = 8 Hz, 1 H), 7.60 (dt, *J* = 8, 2 Hz, 1 H), 8.23 (dd, *J* = 8, 2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.8, 36.3, 125.3, 127.1, 127.7, 129.1, 133.6, 134.0, 165.1, 170.2.

MS (ESI): *m*/*z* (%) = 175.89 (7) $[M + H]^+$.

6-Methyl[1,3]dioxolo[4,5-*g*]isoquinoline-5,7(6*H*,8*H*)-dione (2b)

Following the typical procedure for **2a** using acid **1b** gave the product as a faint yellow solid; yield: 1.33 g (76%); mp 142–144 °C.

IR ($CHCl_3$): 1708, 1665 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.34 (s, 3 H), 3.94 (s, 2 H), 6.06 (s, 2 H), 6.66 (s, 1 H), 7.59 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 36.4, 102.1, 106.4, 107.9, 119.4, 130.2, 147.8, 152.5, 164.5, 170.2.

MS (ESI): *m*/*z* (%) = 219.86 (80) $[M + H]^+$.

2-Methylisoquinolin-1(2*H*)-one (4a); Typical Procedure

To a stirred solution of imide **2a** (1.20 g, 6.85 mmol) in EtOH (20 mL) was added portionwise $NaBH_4$ (2.08 g, 54.80 mmol) at 0 °C. The mixture was stirred under argon at 0 °C with periodic addition of HCl–EtOH soln [EtOH (8 mL) and 2 M HCl (2 mL)] (2 drops) at 15 min intervals. At the end of 6 h, excess $NaBH_4$ was quenched at 0 °C by the addition of 2 M HCl–EtOH until the mixture became acidic. The solvent was removed in vacuo and the obtained residue was dissolved in EtOAc (25 mL). The organic layer was washed with H_2O (20 mL), brine (20 mL), and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by purification of the residue by column chromatography (silica gel, 40% EtOAc–PE) gave pure **4a** as a thick oil; yield: 806 mg (74%).

IR ($CHCl_3$): 1646, 1595 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.60 (s, 3 H), 6.47 (d, *J* = 8 Hz, 1 H), 7.06 (d, *J* = 8 Hz, 1 H), 7.40–7.67 (m, 3 H), 8.43 (d, *J* = 6 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 36.9, 105.9, 125.8, 126.0, 126.7, 127.6, 131.9, 132.3, 137.1, 162.6.

MS (ESI): *m*/*z* (%) = 159.93 (3) $[M + H]^+$.

6-Methyl[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (Doryanine, 4b)

Following the typical procedure for **4a** using imide **2b** gave the product as a faint yellow solid; yield: 812 mg (73%); mp 158–160 °C.

IR ($CHCl_3$): 1653, 1581 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.59 (s, 3 H), 6.07 (s, 2 H), 6.37 (d, *J* = 8 Hz, 1 H), 6.85 (s, 1 H), 6.99 (d, *J* = 8 Hz, 1 H), 7.78 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.0, 101.6, 103.6, 105.5, 105.8, 121.6, 131.2, 134.3, 147.8, 151.6, 161.8.

MS (ESI): *m*/*z* (%) = 226.06 (100) $[M + Na]^+$.

2-Methyl-3,4-dihydroisoquinolin-1(2*H*)-one (5a); Typical Procedure

To a stirred solution of lactam **4a** (636 mg, 4.00 mmol) in EtOH (20 mL) was added a catalytic amount of $Pd(OH)_2$ (25 mg, 0.20 mmol) and the mixture was refluxed under a balloon pressure H_2 atmosphere for 24 h. The mixture was allowed to cool to r.t. and then it was filtered through a pad of Celite to remove the catalyst and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 40% EtOAc–PE) to provide **5a** as a thick oil; yield: 631 mg (98%).

IR ($CHCl_3$): 1643, 1606 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.99 (t, *J* = 8 Hz, 2 H), 3.15 (s, 3 H), 3.56 (t, *J* = 8 Hz, 2 H), 7.16 (d, *J* = 8 Hz, 1 H), 7.25–7.45 (m, 2 H), 8.08 (dd, *J* = 8, 2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.7, 35.0, 48.0, 126.7, 126.8, 127.9, 129.2, 131.4, 137.8, 164.6.

MS (ESI): *m*/*z* (%) = 162.01 (4) $[M + H]^+$.

6-Methyl-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (Oxyhydrastinine, 5b)

Following the typical procedure for **5a** using **4b** gave the product as a crystalline solid; yield: 629 mg (90%); mp 95–97 °C.

IR ($CHCl_3$): 1641, 1605 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.91 (t, *J* = 8 Hz, 2 H), 3.13 (s, 3 H), 3.52 (t, *J* = 8 Hz, 2 H), 5.99 (s, 2 H), 6.61 (s, 1 H), 7.54 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 35.1, 48.2, 101.4, 106.8, 108.1, 123.5, 133.4, 146.8, 150.2, 164.5.

MS (ESI): *m*/*z* (%) = 227.85 (41) $[M + Na]^+$.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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