Xuwen Chen and Yunyun Liu*

Lactic acid-catalyzed fusion of ninhydrin and enamines for the solvent-free synthesis of hexahydroindeno[1,2-*b*]indole-9,10-diones

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Abstract: The lactic acid-catalyzed reactions of ninhydrin and secondary enaminones were conducted by solvent-free grinding at room temperature to yield polycyclic 4b,9b-dihydroxy-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*] indole-9,10-diones.

Keywords: enaminone; grinding; ninhydrin; polycyclic product; solvent-free.

Introduction

The synthesis of polycyclic organic molecules with fused heterocycles is of significant importance because of their structural resemblance with natural products [1, 2]. 4b,9b-Dihydroxy-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-diones (**3** in Scheme 1) are a class of heterocyclic molecules with fused indeno[1,2-*b*]indole polycyclic structure which are known to possess various biological activities [3–7]. Therefore, synthesis of such fused heterocyclic scaffolds has received significant attention in recent years. Currently, the synthesis of compounds **3** is predominantly accessed by the reaction of ninhydrin with amine derivatives of 1,3-dicarbonyl compounds [8] alkyl propiolates [9] dialkyl acetylenedicarboxylates [10] or 1,1-bis(methylthio)-2-nitroethene compounds [11]. Since a common feature of all these methods is the *in situ* generation of an enaminone (or enamino ester) intermediate product, the direct application of enaminones as the reaction partners of ninhydrin has also been developed [12]. Upon on our long-standing interest in developing environmentally benign synthesis and enaminone chemistry [13–15] we report herein a solvent-free protocol for the facile synthesis of products **3** by employing nontoxic and bio-available lactic acid (LA) as catalyst.

***Corresponding author: Yunyun Liu,** College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P.R. China, e-mail: chemliuyunyun@jxnu.edu.cn
Xuwen Chen: College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P.R. China

Results and discussion

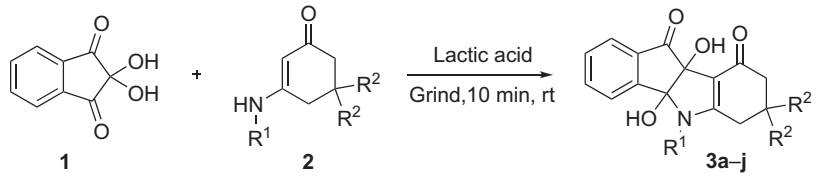
To start the exploration, the reaction of nihydrin (**1**) and secondary enaminone **2a** was selected. An attempted reaction of **1** and **2a** in the absence of any catalyst did not produce the desired product **3a**. On the other hand, compound **3a** was produced in a 41% yield in the presence of a catalytic amount of acetic acid and the yield was increased to 46% in the presence of a catalytic amount of lactic acid. Under optimized condition the amount of lactic acid was 50 mol% and this treatment furnished compound **3a** in an 87% yield. After the optimization of the reaction conditions, this solvent-free catalytic approach was then employed for the efficient synthesis of a variety of other ring-fused products **3b–j** (Scheme 1) (See also Supplemental Material).

Conclusions

A solvent-free method for the synthesis of hexahydroindeno[1,2-*b*]indole derivatives **3** via the reactions of nihydrin and secondary enaminones was developed. The environmentally benign feature of the method makes it useful in the sustainable synthesis of these important polycyclic scaffolds.

Experimental

Secondary enaminones **2** were synthesized following the literature procedure [1] and other chemicals were obtained from commercial sources and used directly without purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in DMSO-d_6. Melting points are not corrected.



R^1	R^2	Product
Ph	Me	**3a**
$PhCH_2$	Me	**3b**
H	Me	**3c**
Ph	H	**3d**
4-MeC_6H_4	H	**3e**
3-ClC_6H_4	H	**3f**
$PhCH_2$	H	**3g**
i-Pr	H	**3h**
$HO(CH_2)_2$	H	**3i**
H	H	**3j**

Scheme 1 Synthesis of indeno[1,2-*b*]indole derivatives **3a–j**.

General procedure for the synthesis of indeno[1,2-*b*] indoles 3a–j

A mixture of ninhydrin **1** (0.3 mmol), enaminone **2** (0.3 mmol) and lactic acid (0.15 mmol) was thoroughly grounded using a pestle and mortar at room temperature for 10 min. Then the mixture was washed with saturated $NaHCO_3$ solution and water, filtered, and the crude product was crystallized from ethanol.

4b,9b-Dihydroxy-7,7-dimethyl-5-phenyl-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-dione (3a) White solid; yield 87%; mp 210–212°C (lit. [11] mp 211–212°C); ^{1}H NMR: δ 7.73 (d, 1 H, *J* = 6.8 Hz), 7.58–7.45 (m, 5 H), 7.30 (d, 2 H, *J* = 6.8 Hz), 7.26 (s, 1 H), 6.63 (d, 1 H, *J* = 6.4 Hz), 6.00 (brs, 1 H), 2.40 (d, 1 H, *J* = 17.2 Hz), 2.15 (d, 1 H, *J* = 15.6 Hz), 1.92 (d, 1 H, *J* = 15.6 Hz), 1.81 (d, 1 H, *J* = 17.2 Hz), 0.96 (s, 3 H), 0.89 (s, 3 H).

5-Benzyl-4b,9b-dihydroxy-7,7-dimethyl-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-dione (3b) White solid; yield 82%; mp 186–188°C (lit. [11] mp 188–189°C); ^{1}H NMR: δ 7.78 (d, 1 H, *J* = 7.6 Hz), 7.73–7.66 (m, 2 H), 7.56 (t, 1 H, *J* = 7.6 Hz), 7.32–7.22 (m, 5 H), 7.01 (brs, 1 H), 5.96 (brs, 1 H), 5.13 (d, 1 H, *J* = 16.8 Hz), 4.83 (d, 1 H, *J* = 16.8 Hz), 2.08–1.92 (m, 4 H), 0.84 (s, 3 H), 0.70 (s, 3 H).

4b,9b-Dihydroxy-7,7-dimethyl-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-dione (3c) White solid; yield 77%; mp 226–228°C (lit. [11] mp 229–230°C); ^{1}H NMR: δ 9.04 (s, 1 H), 7.79 (d, 2 H, *J* = 3.6 Hz), 7.65 (d, 1 H, *J* = 7.6 Hz), 7.55–7.52 (m, 1 H), 6.47 (s, 1 H), 5.49 (s, 1 H), 2.21 (d, 1 H, *J* = 17.2 Hz), 2.09 (d, 1 H, *J* = 17.2 Hz), 1.97–1.87 (m, 2 H), 1.01 (s, 3 H), 0.80 (s, 3 H).

4b,9b-Dihydroxy-5-phenyl-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-dione (3d) Pale yellow solid; yield 85%; mp 209–211°C (lit. [11] mp 212°C); ^{1}H NMR: δ 7.73 (d, 1 H, *J* = 6.8 Hz), 7.56–7.48 (m, 5 H), 7.33–7.28 (m, 3 H), 6.62 (d, 1 H, *J* = 7.2 Hz), 6.02 (s, 1 H), 2.47–2.39 (m, 1 H), 2.16–1.96 (m, 3 H), 1.81–1.77 (m, 2 H).

4b,9b-Dihydroxy-5-(p-tolyl)-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-dione (3e) White solid; yield 84%; mp; 228–231°C; ^{1}H NMR: δ 7.72 (d, 1 H, *J* = 7.2 Hz), 7.58–7.51 (m, 2 H), 7.29 (d, 2 H, *J* = 8.0 Hz), 7.21–7.17 (m, 3 H), 6.68 (d, 1 H, *J* = 7.2 Hz), 5.96 (s, 1 H), 2.38 (s, 4 H), 2.14–1.95 (m, 3 H), 1.78 (d, 2 H, *J* = 4.8 Hz); ^{13}C NMR: δ 197.6, 189.7, 164.8, 147.3, 137.4, 134.79, 134.71, 133.2, 130.1, 129.4, 129.2, 124.9, 123.2, 106.4, 96.3, 83.5, 37.1, 23.6, 21.7, 20.7. ESI-HR-MS. Calcd for $C_{22}H_{19}NNaO_4$ $[M+Na]^+$: *m/z* 384.1206. Found: *m/z* 384.1210.

5-(3-Chlorophenyl)-4b,9b-dihydroxy-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-dione (3f) White solid; yield 80%; mp 223–226°C; ^{1}H NMR: δ 7.74 (d, 1 H, *J* = 7.2 Hz), 7.62–7.49 (m, 5 H), 7.34 (s, 1 H), 7.24 (d, 1 H, *J* = 6.8 Hz), 6.67 (d, 1 H, *J* = 7.6 Hz), 6.06 (s, 1 H), 2.46 (s, 1 H), 2.16–2.00 (m, 3 H), 1.82–1.77 (m, 2 H); ^{13}C NMR: δ 197.9, 190.5, 164.8, 147.5, 138.1, 135.5, 135.2, 133.6, 130.9, 130.8, 129.5,128.6, 128.4, 125.2, 123.8, 107.7, 97.0, 83.9, 37.6, 24.0, 22.2. ESI-HRMS. Calcd for $C_{21}H_{16}ClNNaO_4$ $[M+Na]^+$: *m/z* 404.0660. Found: *m/z* 404.0667.

5-Benzyl-4b,9b-dihydroxy-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-dione (3g) White solid; yield 86%; mp 207–208°C (lit. [11] mp 209–210°C]; ^{1}H NMR: δ 7.82 (d, 1 H, *J* = 7.6 Hz), 7.73–7.68 (m, 2 H), 7.57 (t, 1 H, *J* = 7.2 Hz), 7.33–7.24 (m, 5 H), 6.93 (s, 1 H), 5.79 (s, 1 H), 5.13 (d, 1 H, *J* = 16.8 Hz), 4.82 (d, 1 H, *J* = 16.8 Hz), 2.22–2.14 (m, 1 H), 2.03–1.96 (m, 3 H), 1.72–1.55 (m, 2 H).

4b,9b-Dihydroxy-5-isopropyl-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-dione (3h) White solid; yield 76%; mp 206–208°C (lit. [11] 205°C); ^{1}H NMR: δ 7.95 (d, 1 H, *J* = 7.6 Hz), 7.80 (t, 1 H, *J* = 7.2 Hz), 7.70 (d, 1 H, *J* = 7.6 Hz), 7.58 (t, 1 H, *J* = 7.6 Hz), 6.75 (s, 1 H), 5.69 (s, 1 H), 4.63–4.56 (m, 1 H), 2.71–2.67 (m, 1 H), 2.51–2.45 (m, 1 H), 2.04 (s, 2 H), 1.83–1.74 (m, 2 H), 1.45 (d, 3 H, *J* = 6.4 Hz), 1.24 (d, 3 H, *J* = 6.4 Hz).

4b,9b-Dihydroxy-5-(2-hydroxyethyl)-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-dione (3i) White solid; yield 77%; mp 208–209°C (lit. [11] mp 209–210°C); ^{1}H NMR: δ 7.93 (d, 1 H, *J* = 7.2 Hz), 7.79 (t, 1 H, *J* = 7.2 Hz), 7.70 (d, 1 H, *J* = 7.6 Hz), 7.58 (t, 1 H, *J* = 7.2 Hz), 6.68 (s, 1 H), 5.64 (s, 1 H), 4.93 (s, 1 H), 3.81–3.78 (m, 1 H), 3.62 (s, 3 H), 2.61–2.35 (m, 2 H), 2.04 (s, 2 H), 1.84–1.67 (m, 2 H).

4b,9b-Dihydroxy-4b,5,6,7,8,9b-hexahydroindeno[1,2-*b*]indole-9,10-dione (3j) White solid; yield 84%; mp 235–236°C (lit. [11] mp 237–238°C); ^{1}H NMR: δ 9.16 (s, 1 H), 7.81 (s, 1 H), 7.67 (d, 1 H, *J* = 7.6 Hz),

7.56 (m, 1 H), 6.53 (s, 1 H), 5.56 (s, 1 H), 2.40 (m, 1 H), 2.24–2.19 (m, 1 H), 2.02 (m, 2 H), 1.82–1.68 (m, 2 H).

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