Iranian Journal of Organic Chemistry Vol. 4, No. 4 (2012) 931-934

An efficient synthesis of dihydroxy-tetrahydroindeno[2,1-b]pyrroles from ninhydrin, methyl acetoacetate, and primary amines

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Received: September 2012; Revised: October 2012; Accepted: October 2012

Abstract: An efficient synthesis of dihydroxy-tetrahydroindeno[2,1-*b*]pyrroles is described *via* a one-pot reactions between Ninhydrin, methyl acetoacetate, and Primary Amines.

Keywords: Methyl acetoacetate, Ninhydrin, MCRs, Amin.

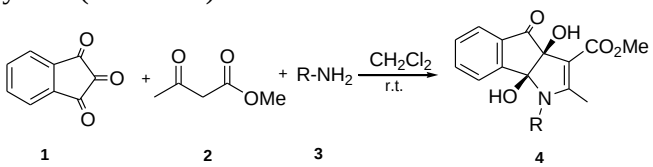
Introduction

Multicomponent reactions (MCRs), offer a straightforward route to generate complexity and diversity in a single operation [1]. MCRs are an extremely powerful tool in combinatorial chemistry and drug discovery [2]. However, only a few highly useful MCRs are available for applications [3,4], and rapid advances in this area lead to searches for new types of target molecules.

Nitrogen-containing heterocycles receive a considerable attention in the literature, as a consequence of their exciting biological properties [5]. Of these heterocycles, the synthesis, reactions and biological activities of pyrrole-containing molecules stands as an area of research in heteroaromatic chemistry and this structural motif appears in a large number of pharmaceutical agents and natural productes [6].

Results and discussion

As a part of our current studies on the development of new routes in heterocyclic synthesis [7-12], we report the results of our studies involving the reaction of ninhydrin (**1**), methyl acetoacetate (**2**) and primary amines (**3**) at room temperature, which constitutes a synthesis of highly functionalized dihydroxy-tetrahydroindeno[2,1-*b*]pyrrole derivatives (**4**) in good yields (Scheme **1**).



1 2 3 4

3, 4	R	Yield (%) of 4
a	Me	76
b	Et	80
c	Ph	84
d	Bn	90
e	4-MeOC$_6$H$_4$CH$_2$	87
f	4-MeC$_6$H$_4$CH$_2$	92
g	2-ClC$_6$H$_4$CH$_2$	85

Scheme 1: The one-pot synthesis of functionalized dihydroxy-tetrahydroindeno[2,1-*b*]pyrroles **4** from ninhydrin, methyl acetoacetate and primary amines.

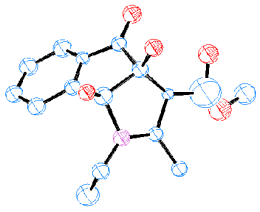


Figure 1: ORTEP diagram of **4b**.

Structures of compounds **4a-g** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H

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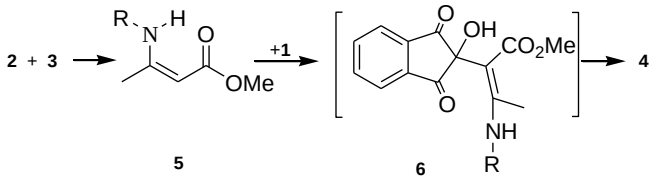
NMR spectrum of **4a** exhibited five sharp single lines for methyl (δ 2.17), Me-N (δ 3.19), methoxy (δ 3.62) and hydroxyl (δ 4.72 and 4.86) protons. The carbonyl groups resonances in the ^{13}C NMR spectrum of **4a** appear at δ 163.7 and 197.8. The mass spectra of **4a** displayed the molecular ion peak at the appropriate *m*/*z* values.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation (Scheme **2**). Presumably, the enaminoester intermediate **5** formed from the reaction of amine **3** with methyl acetoacetate is attacked by ninhydrin to produce **6**. Intermediate **6** can undergo cyclization under the reaction conditions employed to produce **4.**



Scheme 2: Plausible mechanism for the formation of functionalized dihydroxy-tetrahydroindeno[2,1-*b*]pyrroles **4**.

Conclusion

In conclusion, we have described a convenient route to functionalized dihydroxy-tetrahydroindeno[2,1-*b*]pyrroles, from a three-component reaction of ninhydrin, methyl acetoacetate and primary amines. This method represents a simple procedure, uses mild reaction conditions and has fairly general applicability.

Experimental

General methods:

Mp: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H and ^{13}C NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp.; δ in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. All chemicals were used as-received from the appropriate suppliers.

General procedure for the preparation of compounds 4:

To a stirred solution of amine **3** (2 mmol) and 0.23 g of methyl acetoacetate (**2**, 2 mmol) in 10 mL of CH_2Cl_2, was added a solution of 0.32 g of ninhydrin (**1**, 2 mmol) slowly at r.t. After completion of the reaction (1-3h) as indicated by TLC (hexane/EtOAc 8:1), the solvent was evaporated from the reaction mixture under reduced pressure to leave a residue that was purified by column chromatography (SiO_2; hexane/EtOAc 8:1) to afford pure desired products **4**.

Methyl 3a,8b-dihydroxy-1,2-dimethyl-4-oxo-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrole-3-carboxylate (**4a**):

Yellow powder; m.p: 131-133 °C; yield: 0.66 g (76%). IR (KBr) (ν_{max}/cm^{-1}): 3415, 1739, 1716, 1686, 1575, 1442, 1150, 1124. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.17 (3 H, s, Me), 3.19 (3 H, s, MeN), 3.62 (3 H, s, MeO), 4.72 (1 H, s, OH), 4.86 (1 H, s, OH), 7.21 (1 H, d, ^2J = 7.7 Hz, CH), 7.67 (1 H, t, ^3J = 6.6 Hz, CH), 7.89 (1 H, t, ^3J = 7.4 Hz, CH), 8.05 (1 H, d, ^2J = 7.6 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.0 (Me), 31.6 (Me), 50.7 (MeO), 83.7 (C), 95.0 (C), 124.4 (CH), 124.7 (CH), 129.7 (CH), 133.6 (C), 136.0 (CH), 137.6 (C), 147.6 (C), 150.8 (C), 163.7 (C=O), 197.8 (C=O). EI-MS: *m/z* (%) = 289 (M$^+$, 20), 259 (32), 231 (65), 274 (15), 118 (90), 105 (33), 15 (100). Anal. Calcd for $C_{15}H_{15}NO_5$ (289.28): C, 62.28; H, 5.23; N, 4.84. Found: C, 62.4; H, 5.2; N, 4.8%.

Methyl 1-ethyl-3a,8b-dihydroxy-2-methyl-4-oxo-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrole-3-carboxylate **(4b)**:

Yellow powder; m.p: 129-132 °C; yield: 0.53 g (80%). IR (KBr): 1715, 1693, 1633, 1685, 1556, 1509, 1441, 1368, 1307, 1076. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.22 (3 H, t, ^3J = 7.0, Me), 2.21 (3 H, t, ^3J = 7.0, Me), 3.61 (2 H, d, CH_2), 3.68 (MeO), 4.72 (1 H, s, OH), 4.86 (1 H, s, OH), 7.52 (1 H, t, ^3J = 6.6 Hz, CH), 7.71 (1 H, t, ^3J = 7.4 Hz, CH), 7.79 (1 H, d, ^2J = 7.6 Hz, CH), 7.82 (1 H, d, ^2J = 7.9 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 12.8 (Me), 16.6 (Me), 36.7 (CH_2), 50.3 (MeO), 83.7 (C), 95.0 (C), 124.4 (CH), 124.7 (CH), 129.7 (C), 135.3 (CH), 136.0 (CH), 137.6 (C), 147.6 (C), 150.8 (C), 163.7 (C=O), 198.1 (C=O). EI-MS: *m/z* (%) = 303 (M$^+$, 22), 273 (35), 245(73), 274 (20), 118 (92), 105 (30), 29 (100). Anal. Calcd for $C_{16}H_{17}NO_5$ (303.31): C, 63.36; H, 5.65; N, 4.62. Found: C, 63.1; H, 5.6; N, 4.6%.

Methyl 3a,8b-dihydroxy-2-methyl-4-oxo-1-phenyl-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrole-3-carboxylate (**4c**):

White powder; m.p: 127-130 °C; yield: 0.64 g (84%). IR (KBr) (ν_{max}/cm^{-1}): 3445, 1742, 1712, 1686, 1569, 1468, 1218, 1180. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.06 (3 H, s, Me), 3.80 (3 H, s, MeO), 4.73 (1 H, s, OH), 4.96 (1 H, s, OH), 7.33 (1 H, d, ^3J = 7.3 Hz, CH), 7.35 (1 H, d, ^3J = 7.4 Hz, CH), 7.38-7.68 (5 H, m, 5 CH), 7.76 (1 H, t, ^3J = 7.5 Hz, CH), 7.99 (1 H, t, ^3J = 8.0 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ =

14.3 (Me), 52.7 (MeO), 83.7 (C), 95.4(C), 95.4 (C), 124.5 (CH), 124.7 (CH), 127.8 (CH), 128.1 (2 CH), 128.5 (2 CH), 130.6 (CH), 135.2 (C), 136.1 (CH), 136.5 (C), 147.4 (C), 151.1 (C), 166.4 (C=O), 198.2 (C=O). EI-MS: *m/z* (%) = 351 (M^+, 25), 319 (30), 292 (70), 274 (15), 118 (95), 105 (35), 77 (100). Anal. Calcd for $C_{20}H_{17}NO_5$(351.35): C, 68.37; H, 4.88; N, 3.99. Found: C, 68.1; H, 4.8; N, 4.1%.

Methyl 1-benzyl-3a,8b-dihydroxy-2-methyl-4-oxo-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrole-3-carboxylate (**4d**):

Yellow powder; m.p: 128-130 °C; yield: 0.62 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 3445, 1742, 1712, 1686, 1569, 1468, 1218, 1180. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.20 (3 H, s, Me), 3.78 (3 H, s, MeO), 4.97(1 H, d, ^2J = 15.7 Hz, CH), 4.99 (1 H, s, OH), 5.25 (1 H, d, ^2J = 15.7 Hz, CH), 5.42 (1 H, s, OH), 7.21-7.34 (5 H, m, 5 CH), 7.59 (1 H, t, ^3J = 7.5 Hz, CH), 7.70 (1 H, t, ^3J = 8.1 Hz, CH), 7.76 (1 H, d, ^3J = 7.2 Hz, CH), 7.79 (1 H, d, ^3J = 7.3 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 35.2 (Me), 46.8 (CH_2N), 52.7 (MeO), 83.7 (C), 95.4 (C), 95.4 (C), 124.5 (CH), 124.7 (CH), 127.8 (CH), 128.1 (2 CH), 128.5 (2CH), 130.6 (CH), 135.2 (C), 136.1 (CH), 136.5 (C), 147.4 (C), 151.1 (C), 164.2 (C=O), 197.1 (C=O). EI-MS: *m/z* (%) = 365 (M^+, 19), 335 (28), 307 (75), 274 (20), 118 (93), 105 (35), 91 (100). Anal. Calcd for $C_{21}H_{19}NO_5$ (365.38): C, 66.03; H, 5.24; N, 3.83. Found: C, 66.2; H, 5.2; N, 3.8%.

Methyl 3a,8b-dihydroxy-1-(4-methoxybenzyl)-2-methyl-4-oxo-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrole-3-carboxylate (**4e**):

White powder; m.p: 122-126 °C; yield: 0.66 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 3450, 1742, 1713, 1665, 1573, 1466, 1205, 1179. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.93 (3 H, s, Me), 3.54 (3 H, s, MeO), 3.53 (3 H, s, MeO), 4.67 (1 H, d, ^2J = 15.8 Hz, CH), 4.88 (1 H, d, ^2J =15.8 Hz, CH), 4.99 (1 H, s, OH), 5.16 (1 H, s, OH), 6.65 (d, 2 H, ^3J = 8.6 Hz, 2 CH), 6.87 (d, 2 H, ^3J = 8.6 Hz, 2 CH), 7.32 (1 H, t, ^3J = 7.4 Hz, CH), 7.44 (1 H t, ^3J = 7.7 Hz, CH), 7.49 (1 H, d, ^3J = 7.8 Hz, CH), 7.66 (1 H, d, ^3J = 7.6 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.0 (Me), 44.9 (CH_2N), 50.2 (MeO), 53.5 (MeO), 83.7 (C), 95.2 (C), 124.4 (CH), 124.7 (CH), 128.0 (2 CH), 129.2 (2 CH), 130.7 (CH), 131.8 (C), 133.4 (C), 135.2 (C), 136.1 (CH), 137.7 (C), 147.4 (C), 151.1 (C), 164.1 (C=O), 197.0 (C=O). EI-MS: *m/z* (%) = 395 (M^+, 18), 365 (32), 337 (76), 274 (17), 118 (95), 105 (31), 122 (100). Anal. Calcd for $C_{22}H_{21}NO_6$ (395.40): C, 66.03; H, 5.24; N, 3.63. Found: C, 65.8; H, 5.2; N, 3.6%.

Methyl 3a,8b-dihydroxy-1(4-methylbenzyl)-4-oxo-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrole-3-carboxylate (**4f**):

Yellow powder; m.p: 126-129 °C; yield: 0.66 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 3445, 1742, 1712, 1662, 1569, 1468, 1240, 1180. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.98 (3 H, s, Me), 2.25 (3 H, s, MeO), 3.69 (3 H, s, MeO), 4.81 (1 H, d, ^2J = 15.5 Hz, CH), 5.01 (1 H, d, ^2J = 15.5 Hz CH), 5.30 (1 H, s, OH), 5.41 (1 H, s, OH), 6.94 (2 H, d, ^3J = 7.9 Hz, 2 CH), 7.06 (2 H, d, ^3J = 7.9 Hz, 2 CH), 7.48 (1 H, t, ^3J = 7.4 Hz, CH), 7.50 (1 H, t, ^3J = 7.7 Hz, CH), 7.59 (1 H, d, ^3J = 8.0 Hz, CH), 7.83 (1 H, d, ^3J = 7.6 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.7 (Me), 31.8 (Me), 45.3 (CH_2N), 50.5 (MeO), 83.8 (C), 95.3 (C), 114.0 (2 CH), 124.5 (CH), 124.7 (CH), 128.4 (C), 129.5 (2 CH), 130.6 (CH), 135.2 (2 C), 136.2 (CH), 147.4 (C), 151.1 (C), 159.4 (C), 164.2 (C=O), 197.1 (C=O). EI-MS: *m/z* (%) = 379 (M^+, 19), 349 (30), 321 (70), 274 (15), 118 (95), 105 (35), 91 (100). Anal. Calcd for $C_{22}H_{21}NO_5$ (379.41): C, 69.65; H, 5.58; N, 3.69. Found: C, 69.8; H, 5.6; N, 3.7%.

Methyl 1-(2-chlorobenzyl)-3a,8b-dihydroxy-2-methyl-4-oxo-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrole-3-carboxylate **(4g)**:

White powder; m.p: 130-133 °C; yield: 0.66 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1725, 1720, 1687, 1545, 1432,1254,1100. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.05 (3 H, s, Me), 3.71 (3 H, s, OMe), 4.54 (1 H, s, OH), 4.68 (1 H, s, OH), 4.84 (1 H, d, ^2J = 15.6 Hz, CH), 4.97 (1 H, d, ^2J=15.6 Hz, CH), 7.07 (1 H, d, ^3J = 8.3 Hz, CH), 7.18 (1 H, t, ^3J = 8.3 Hz, CH), 7.24 (1 H, t, ^3J = 7.5 Hz, CH), 7.36 (1 H, d, ^3J = 7.5 Hz, CH), 7.52-7.56 (2 H, m, 2 CH), 7.62 (1 H, t, ^3J = 7.8 Hz, CH), 7.87 (1 H, d, ^3J = 7.5 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.1 (Me), 44.1 (CH_2N), 52.9 (MeO), 83.6 (C), 95.4 (C), 124.4 (CH), 124.7 (CH), 126.8 (CH), 128.9 (CH), 129.0 (CH), 129.4 (CH), 129.7 (C), 130.7 (CH), 132.6 (C), 134.2 (C), 135.1 (C), 136.2 (CH), 147.3 (C), 151.1 (C), 161.8 (C=O), 196.9 (C=O). EI-MS: *m/z* (%) = 365 (M^+, 25), 369 (29), 341 (68), 274 (16), 118 (96), 105 (29), 91 (100). Anal. Calcd for $C_{21}H_{18}ClNO_5$ (365.60): C, 63.08; H, 4.54; N, 3.50. Found: C, 63.4; H, 4.5; N, 3.5%.

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