Multi-Component Reaction of Amines, Alkyl Propiolates, and Ninhydrin: An Efficient Protocol for the Synthesis of Tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrrole Derivatives

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Received 4 July 2005; revised 14 September 2005

Abstract: A new protocol for the synthesis of a series of tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrrole from simple primary amines, alkyl propiolates, and ninhydrin was developed. The key step in the synthesis is an efficient three-component reaction of an amine with an alkyl propiolate to give a 3-amino acrylate derivative, which then reacts with ninhydrin.

Key words: tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrrole derivatives, multicomponent reaction, cyclization

Despite recent advances in molecular biology and the progress in combinatorial synthetic methodology, the rate of introduction of new pharmaceuticals has decreased markedly over the past two decades.[1a] Structural diversity in a focused collection of potential therapeutics is believed to increase the positive hit rate. Most pharmaceuticals in use are still small synthetic organic molecules that often contain a heterocyclic ring.[1a–c] However, the range of easily accessible and suitably functionalized heterocyclic building blocks for the synthesis of structurally diverse libraries is rather limited. The development of new, rapid, and clean synthetic routes toward focused libraries of such compounds is therefore of great importance to both medicinal and synthetic chemists.[1] Undoubtedly, the most efficient strategies involve multicomponent reactions (MCRs), which have become a powerful tool for the rapid introduction of molecular diversity.[2] Consequently, the design and development of MCRs for the generation of heterocycles have received increased interest.[2a]

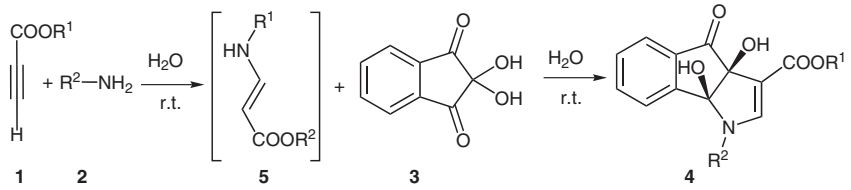
Polyhydroxylated alkaloids are interesting heterocycles that can act as powerful and selective inhibitors of glycosidases and exhibit bactericidal, antidiabetic, and antiviral activities,[3,4] making these compounds good lead compounds for the development of new drugs for the treatment of viral infections, cancer, and diabetes.[3,4] Consequently, the development of general and facile methods for the synthesis of such compounds is an active field of research.[4–7] For example the tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrrole system is of interest in connection with the search for potential oral hypoglycemic agents.[8]

As part of our general interest in MCRs,[9] our ongoing research programs in the area of heterocyclic compounds containing nitrogen,[9,10] and due to the resultant pharmacological interest in polyhydroxylated alkaloids, herein we report an efficient three-component method for the construction of new tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrroles, via condensation of amines, alkyl propiolates, and ninhydrin (Scheme 1).

In order to prove that β-aminoacrylates **5** exist as intermediates in this reaction, compound **5e** (*Z*/*E*, 6:4) was synthesized separately by the condensation of benzyl amine and methyl propiolate, and then reacted with **3**. The resulting product was identical to that formed in the three-component procedure.

The reaction was carried out by the simple addition of one equivalent of primary amine to one equivalent of alkyl propiolate in water, followed by the addition of one equivalent of ninhydrin; the reaction was complete within six hours at room temperature affording **4a–e** (Table 1).

The ^{1}H NMR spectra revealed only one diastereomer, for example, the ^{1}H NMR spectrum of **4a** exhibited one triplet



Scheme 1

SYNTHESIS 2006, No. 5, pp 0765–0767
Advanced online publication: 07.02.2006
DOI: 10.1055/s-2006-926327; Art ID: Z12805SS

Table 1 Three-Component Synthesis of Some Novel Tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrroles

Entry	R^1	R^2	Product	Yields (%)
1	Et	Bn	**4a**	96
2	Et	*n*-Bu	**4b**	89
3	Me	*c*-Hexyl	**4c**	82
4	Et	*c*-Hexyl	**4d**	85
5	Me	Bn	**4e**	87

at (1.24 ppm) and one quartet (4.17 ppm) corresponding to the ethyl group and two broad singlets (4.39 and 4.56 ppm) for the hydroxyl groups. On top of this, two doublets at 4.63 and 4.92 ppm are readily attributable to the methylene protons, along with multiplets at 7.03–7.91 corresponding to the alkene and aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 19 distinct resonances, in agreement with the proposed structure.

In summary, the MCR described herein provides a simple and direct entry into a number of interesting novel tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrrole derivatives that may be of value in medicinal chemistry as oral hypoglycemic agents.

Mps were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-470 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker 300 DRX AVANCE instrument at 300 and 75 MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

Ethyl 1-Benzyl-1,3a,4,8b-tetrahydro-3a,8b-dihydroxy-4-oxoindeno[1,2-*b*]pyrrole-3-carboxylate (4a); Typical Procedure
$BnNH_2$ (0.107 g, 1 mmol) in H_2O (10 mL) was added to ethyl propiolate (0.098 g, 1 mmol). The mixture was stirred for 1 h, then ninhydrin (0.178 g, 1 mmol) was added and stirring was continued at r.t. for a further 6 h. The solid formed was removed by filtration and recrystallized (EtOH) to give **4a**.

Yield: 96%; light-red crystalline solid; mp 139–140 °C.

IR (KBr): 1647, 1736 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.24 (t, ^3J = 7.2 Hz, 3 H, CH_3), 4.17 (q, ^3J = 7.2 Hz, 2 H, OCH_2), 4.39, 4.56 (2 br s, 2 H, OH), 4.63, 4.92 (2 d, ^3J = 6.9 Hz, 2 H, NCH_2), 7.03 (s, 1 H, C=CH), 7.22–7.91 (m, 9 H, ArH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.89 (CH_3), 48.31, 59.91 (2 × CH_2), 84.62, 95.49 (2 × COH), 98.44, 124.55, 125.07, 128.55, 128.72, 129.40, 130.83, 135.58, 136.29, 136.57, 147.73, 149.03 (Ar, C=CH), 165.27, 198.03 (2 × C=O).

MS: *m*/*z* (%) = 365 (M^+, 4), 274 (20), 228 (80), 91 (100), 55 (44).

Anal. Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.10; H, 5.20; N, 3.75.

Ethyl 1-Butyl-1,3a,4,8b-tetrahydro-3a,8b-dihydroxy-4-oxoindeno[1,2-*b*]pyrrole-3-carboxylate (4b)
Yield: 89%; yellow crystalline solid; mp 142–143 °C.

IR (KBr): 1652, 1719 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.96 (t, ^3J = 7.14 Hz, 3 H, CH_3), 1.27 (t, ^3J = 7.50 Hz, 3 H, CH_3), 1.23–1.73 (m, 4 H, CH_2CH_2), 3.46, 3.72 (m, 2 H, NCH_2), 4.20 (q, ^3J = 7.14 Hz, 2 H, OCH_2), 4.26, 4.53 (2 br s, 2 H, OH), 7.24 (s, 1 H, C=CH), 7.53–7.90 (m, 4 H, ArH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.11, 14.94 (2 × CH_3), 20.46, 32.46, 44.15, 59.78 (4 × CH_2), 84.53, 95.44 (2 × COH), 97.27, 124.33, 125.03, 130.70, 135.59, 136.19, 147.79, 148.80 (Ar, C=CH), 165.39, 198.04 (2 × C=O).

MS: *m*/*z* (%) = 331 (M^+, 10), 285 (30), 258 (55), 186 (60), 105 (100), 77 (60), 41 (50).

Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.20; H, 6.25; N, 4.20.

Methyl 1-Cyclohexyl-1,3a,4,8b-tetrahydro-3a,8b-dihydroxy-4-oxoindeno[1,2-*b*]pyrrole-3-carboxylate (4c)
Yield: 82%; light-yellow crystalline solid; mp 155–156 °C.

IR (KBr): 1679, 1722 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.37–2.18 (m, 10 H, CH_2), 3.72 (s, 3 H, OCH_3), 3.80 (s, 1 H, NCH), 4.24, 4.42 (2 br s, 2 H, 2 × OH), 7.26 (s, 1 H, C=CH), 7.34–7.90 (m, 4 H, ArH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 26.51, 31.32, 36.56 (3 × CH_2), 51.13 (CH), 53.94 (CH_3), 84.33, 95.69 (2 × COH), 96.76, 123.85, 125.08, 130.78, 135.25, 136.42, 147.04, 148.04 (ArH, C=CH), 165.69, 197.92 (2 × C=O).

MS: *m*/*z* (%) = 343 (M^+, 10), 284 (20), 228 (100), 104 (66), 76 (60), 55 (100).

Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.40; H, 6.10; N, 4.05.

Ethyl 1-Cyclohexyl-1,3a,4,8b-tetrahydro-3a,8b-dihydroxy-4-oxoindeno[1,2-*b*]pyrrole-3-carboxylate (4d)
Yield: 85%; yellow crystalline solid; mp 147–148 °C.

IR (KBr): 1679, 1722 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.26 (t, ^3J = 6.90 Hz, 3 H, CH_3), 1.36–2.17 (m, 10 H, CH_2), 3.87 (s, 1 H, NCH), 4.17 (q, ^3J = 7.10 Hz, 2 H, OCH_2), 4.47, 4.78 (2 br s, 2 H, 2 × OH), 7.33 (s, 1 H, C=CH), 7.51–7.88 (m, 4 H, ArH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.73 (CH_3), 26.51, 31.31, 34.41, 58.78 (4 × CH_2), 53.85 (CH), 84.31, 95.69 (COH), 96.70, 123.84, 124.14, 125.02, 130.72, 135.56, 136.35, 146.78 (ArH, C=CH), 165.40, 197.93 (2 × C=O).

MS: *m*/*z* (%) = 365 (M^+, 10), 284 (24), 228 (100), 104 (66), 76 (60), 55 (100).

Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.15; H, 6.45; N, 3.90.

Methyl 1-Benzyl-1,3a,4,8b-tetrahydro-3a,8b-dihydroxy-4-oxoindeno[1,2-*b*]pyrrole-3-carboxylate (4e)
Yield: 87%; light-yellow crystalline solid; mp 137–138 °C.

IR (KBr): 1648, 1727 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.66 (s, 3 H, OCH_3), 4.52, 4.70 (2 br s, 2 H, OH), 4.66, 4.88 (2 d, ^3J = 7.2 Hz, 2 H, NCH_2), 7.04 (s, 1 H, C=CH), 7.22–7.89 (m, 9 H, ArH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 48.36 (CH_2), 51.21 (CH_3), 48.31, 59.91 (2 × CH_2), 84.58, 95.50 (2 × COH), 98.17, 124.53, 125.14, 128.63, 128.78, 129.44, 130.87, 135.54, 136.36, 136.41, 147.70, 149.27 (Ar, C=CH), 165.61, 148.04 (C=O).

MS: *m*/*z* (%) = 351 (M^+, 10), 260 (20), 228 (40), 91 (100), 76 (16), 50 (10).

Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.30; H, 4.80; N, 3.95.

(*E*/*Z*)-Methyl 3-(Benzylamino)acrylate (5e)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.60 (s, 3 H, *Z*-CH_3), 3.67 (s, 3 H, *E*-CH_3), 4.20 (d, ^3J = 5.70 Hz, 2 H, *Z*-CH_2), 4.30 (d, ^3J = 5.30 Hz, 2 H, *E*-CH_2), 4.53 (d, ^3J = 7.90 Hz, 1 H, *Z*-CH=CH), 4.75 (d, ^3J = 13.50 Hz, 1 H, *E*-CH=CH), 7.02 (dd, ^3J = 7.90, 7.30 Hz, 1 H, *Z*-CH=CH), 7.07 (dd, ^3J = 13.10, 7.50 Hz, 1 H, *E*-CH=CH), 7.22–7.45 (m, 5 H, *Z*/*E*-ArH), 7.65 (br s, 1 H, *Z*-NH), 7.50 (br s, 1 H, *E*-NH).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.01; H, 6.79; N, 7.20.

Acknowledgment

We gratefully acknowledge the financial support from the Research Council of Science and Research, Islamic Azad University.

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