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Three-component process for the synthesis of some pyrrole derivatives under microwave irradiation

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We report a short and efficient 3-component reaction for synthesis of a series of [1,2-*b*]pyrrole derivatives from ninhydrin, alkyl propiolates, and simple primary amines under solvent free and microwave irradiation. This method provides a new route to produce pyrrole derivatives in good to excellent yields.

Key Words: Pyrrole derivatives, microwave irradiation, 3-component reaction.

Introduction

Synthesis of complex organic structures as efficient drugs is the dream of every chemist. Multicomponent reactions (MCRs) have manifested as a powerful tool for the rapid introduction of molecular diversity. The design and development of MCRs for the generation of heterocycles receives growing interest.[1]

Polyhydroxylated heterocycles have generated a great deal of synthetic interest in the past decade due to their structural resemblance to the sugar moiety of monosaccharides.[2] Because of their ability to mimic carbohydrates, they function as potent inhibitors of glycosidases; enzymes that are involved in a wide range of important biological processes.[3] The discovery that these sugar mimetics display considerable activity against cancer,[4] diabetes,[1] and viral infections (anti-HIV behavior) has led to an enhanced interest in them as potential therapeutic agents.[5] Presenting of novel structure leads that may be of use in designing new, potent, selective, and anticancer agents remains a major challenge for medicinal chemistry researchers.[6–9] There is substantial and continuing interest in artificial molecules that bind and interact with DNA. Most of these molecules have been studied with the purpose of developing novel antitumor lead compounds.[10–12] For example, the tetrahydro-

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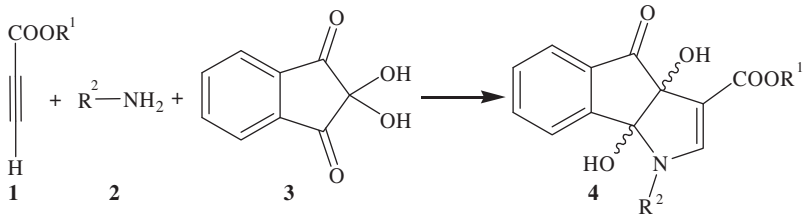
dihydroxy-oxoindeno[1,2-*b*]pyrrole system has been of interest in connection with the search for potential oral hypoglycemic agents.[13]

In our ongoing research prompted by our interest in multiple component reactions and as part of programs in the area of heterocyclic compounds containing nitrogen,[14] and due to the resultant pharmacological interest in compounds which belong to the polyhydroxylated alkaloids, although this reaction done previously in general conditions,[15] herein we report in a different condition using microwave irradiation, free solvent, a one pot reaction, a short time with high yields, easy separation of product, and a 3-component method for the construction of some new tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrroles, via condensation of amines, alkyl propiolates, and ninhydrin under microwave irradiation (Scheme 1).



Scheme 1. Condensation of amine, alkyl propiolate, and ninhydrin.

Experimental

All chemicals were obtained from Merck or Fluka. All reactions were carried out in a CEM MARS 5^{TM} microwave oven. Silica gel SILG/UV 254 plates were used for TLC. 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 Heracus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 Mass spectrometer operating at an ionization potential of 70 eV. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected.

Synthesis of Ethyl 1-benzyl-1, 3a, 4, 8b-tetrahydro-3a, 8b-dihydroxy-4-oxoindeno[1,2-b]pyrrole-3-carboxylate

Typical procedure for preparation of 1-benzyl-1, 3a, 4, 8b-tetrahydro-3a, 8b-dihydroxy-4-oxoindeno[1,2-*b*]pyrrole-3-carboxylate (**4a**): Montmorillonite K10 (0.3 g) was placed in a mortar followed by ethyl propiolate (0.098 g, 1 mmol), ninhydrin (0.178 g, 1 mmol), and benzyl amine (0.107 g, 1 mmol). These materials were then mixed using a pestle for ca. 4 min. The homogenized mixture was transferred to a beaker and irradiated with microwaves for 5 min. The progress of reaction was monitored by TLC. The mixture was extracted with 3 $\times$ 30 cm^3 CH_2Cl_2, filtered, and dried with anh. Na_2SO_4 sulfate. The solution was dried under high vacuum and the resulting solid residue recrystallized from ethanol to give the pure crystalline solid **4a**.

Ethyl 1-benzyl-1, 3a, 4, 8b-tetrahydro-3a, 8b-dihydroxy-4-oxoindeno [1,2-b]pyrrole-3-carboxylate (***4a***): light red crystalline solid 87%, mp 139-140 °C, IR (KBr) (ν_{max}, cm^{-1}): 1647, 1736 (2C=O); ^{1}H-NMR(CDCl$_3$, 300 MHz) δ_H: 1.24 (3H, t, ^3J=7.2 Hz, CH_3), 4.17 (2H, q, ^3J=7.2 Hz O-CH_2), 4.39, 4.56 (2H, 2 bs, 2OH), 4.63, 4.92 (2H, 2d, ^3J=6.9, N-CH_2), 7.03 (1H, s, C=CH), 7.22-7.91 (9H, m, H_{arom}); ^{13}C-NMR

($CDCl_3$, 75 MHz) δ_C: 14.89 (CH_3), 48.31, 59.91($2CH_2$), 84.62, 95.49 (2C-OH) 98.44, 124.55, 125.07, 128.55, 128.72, 129.40, 130.83, 135.58, 136.29, 136.57, 147.73, 149.03(Aromatic and alkene carbons), 165.27, 198.03 (2C=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***): yellow crystalline solid 77%, mp 142-143 °C, IR (KBr) (ν_{max}, cm^{-1}): 1652, 1719 (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ_H: 0.96, 1.27 (6H, 2t, ^3J=7.14,^3J=7.50 Hz, $2CH_3$), 1.23-1.73 (4H, m, $2CH_{2butyl}$), 3.46, 3.72 (2H, m, N-CH_2), 4.20 (2H, q, ^3J=7.14, O-$CH_{2)}$, 4.26, 4.53 (2H, 2 bs, 2OH), 7.24 (1H, s, C=CH), 7.53-7.90 (4H, m, H_{arom}); ^{13}C-NMR($CDCl_3$, 75 MHz) δ_C: 14.11, 14.94 ($2CH_3$), 20.46, 32.46, 44.15, 59.78 ($4CH_2$), 84.53, 95.44 (2C-OH), 97.27, 124.33, 125.03, 130.70, 135.59, 136,19, 147.79, 148.80 (Aromatic and alkene carbons), 165.39, 198.04 (2C=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***): light yellow crystalline solid 68%, mp 155-156 °C, IR (KBr) (ν_{max}, cm^{-1}): 1679, 1722 (2C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ_H: 1.37-2.18 (10H, CH_2-cyclohexyl), 3.72 (3H, s, O-CH_3), 3.80 (1H, m, N-CH), 4.24, 4.42 (2H, 2 bs, 2OH), 7.26 (1H, s, C=CH), 7.34-7.90 (4H, m, H_{arom}), ^{13}C-NMR ($CDCl_3$, 75 MHz) δ_C: 26.51, 31.32, 36.56, ($3CH_2$), 51.13 (CH), 53.94 (CH_3), 84.33, 95.69 (2C-OH), 96.76, 123.85, 125.08, 130.78, 135.25, 136.42, 147.04, 148.04 (Aromatic and alkene carbons), 165.69, 197.92 (2C=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***): yellow crystalline solid 70%, mp 147-148 °C, IR (KBr) (ν_{max}, cm^{-1}): 1679, 1722 (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ_H: 1.26 (3H, t, ^3J=6.90 Hz, CH_3), 1.36-2.17 (10H, CH_2-cyclohexyl), 3.87 (1H, m, N-CH), 4.17 (2H, q, ^3J=7.10, O- CH_2), 4.47, 4.78 (2H, 2 bs, 2OH), 7.33 (1H, s, C=CH), 7.51-7.88 (4H, m, H_{arom}); ^{13}C-NMR($CDCl_3$, 75 MHz) δ_C: 18.73 (CH_3), 26.51, 31.31, 34.41, 58.78 ($4CH_2$), 53.85 (CH), 84.31, 95.69 (C-OH), 96.70, 123.84, 124.14, 125.02, 130.72, 135.56, 136.35, 146.78 (Aromatic and alkene carbons), 165.40, 197.93 (2C=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-xoindeno[1,2-b]pyrrole-3-carboxylate(***4e***): light yellow crystalline solid 81%, mp 137-138 °C, IR (KBr) (ν_{max}, cm^{-1}): 1648, 1727 (2C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ_H: 3.66 (3H, s, O-CH_3), 4.52, 4.70 (2H, 2 bs, 2OH), 4.66, 4.88 (2H, 2d, ^3J=7.2, N-CH_2), 7.04 (1H, s, C=CH), 7.22-7.89 (9H, m, H_{arom}); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ_C: 48.36 (CH_2), 51.21 (CH_3), 48.31, 59.91 ($2CH_2$), 84.58, 95.50 (2C-OH), 98.17, 124.53, 125.14, 128.63, 128.78, 129.44, 130.87, 135.54, 136.36, 136.41, 147.70, 149.27 (Aromatic and alkene carbons), 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.

Ethyl 1-methyl-1, 3a, 4, 8b-tetrahydro-3a, 8b-dihydroxy-4-oxoindeno [1,2-b]pyrrole-3-carboxylate(***4f***): light yellow crystalline solid 60%, mp 129-130 °C, IR (KBr) (ν_{max}, cm^{-1}): 1645, 1720 (2C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ_H: 1.28 (3H, t, ^3J=7.1 Hz, CH_3), 2.65 (3H, s, N-CH_3), 4.21 (2H, q, ^3J=7.1

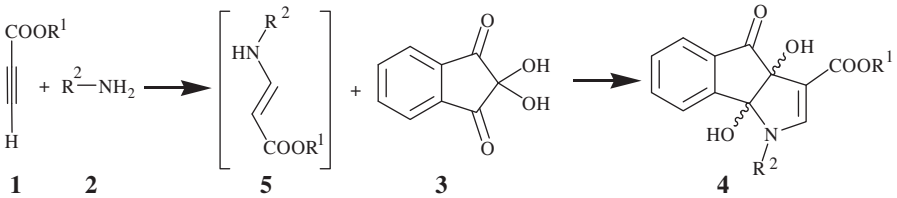
Hz O-CH_2), 4.23, 4.45 (2H, 2 bs, 2OH), 7.18 (1H, s, C=CH), 7.33-7.80 (4H, m, H_{arom}); ^{13}C-NMR($CDCl_3$, 75 MHz) δ_C: 14.25, 35.20 ($2CH_3$), 58.91(CH_2), 84.61, 89.90 (2C-OH) 98.63, 123.44, 125.66, 129.12, 129.83, 131.21, 132.65, 141.11 (Aromatic and alkene carbons), 166.65, 197.45 (2C=O); MS (m/z, %): 289 (M^+, 10), 274 (40), 199 (80), 74 (100), 16 (44). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.33; H, 5.20; N, 3.77.

Ethyl 1-ethyl-1, 3a, 4, 8b-tetrahydro-3a, 8b-dihydroxy-4-oxoindeno [1,2-b]pyrrole-3-carboxylate (***4g***): light yellow crystalline solid 66%, mp 131-132 °C, IR (KBr) (ν_{max}, cm^{-1}): 1641, 1722 (2C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ_H: 1.12 (3H, t, ^3J=7.2 Hz, CH_3), 1.25 (3H, t, ^3J=7.2 Hz, CH_3), 2.85 (2H, q, ^3J=7.2 Hz N-CH_2), 4.20 (2H, q, ^3J=7.1 Hz O-CH_2), 4.25, 4.48 (2H, 2 bs, 2OH), 7.28 (1H, s, C=CH), 7.25-7.93 (4H, m, H_{arom}); ^{13}C-NMR($CDCl_3$, 75 MHz) δ_C: 14.65, 15.20 ($2CH_3$), 35.8, 59.91($2CH_2$), 86.75, 91.22 (2C-OH) 97.56, 124.85, 124.89, 129.45, 130.45, 132.38, 132.88, 145.38 (Aromatic and alkene carbons), 169.15, 198.56 (2C=O); MS (m/z, %): 303 (M^+, 10), 274 (33), 199 (75), 74 (100), 16 (20). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.27; H, 5.70; N, 4.60.

Results and discussion

In order to select the best solid support for this reaction we investigated the condensation of ninhydrin, alkyl propiolates, and simple primary amines on montmorillonite K-10, silica gel, acidic alumina, and zeolite HY under microwave irradiation. Under all conditions only the product **4a** (87%, 44%, 41%, and 31%) was separated. Thus we chose montmorillonite K-10 as the best yields were obtained using this solid support (Table 1). With zeolite HY the yields were lower. A probable explanation for this discrimination may be that the acidic Brønsted sites were partly occupied by the electron pairs of amine nitrogen atoms.

A rational mechanism for the reaction is depicted in Scheme 2, as it proceeds through intermediacy of the enamine **5**, followed by nucleophilic addition and substitution of this intermediate on ninhydrin, producing the product **4**. In numerous cases the presence of the β-aminoacrylates **5,** as an intermediate in this reaction, was synthesized separately by condensation of amine and propiolate, and then the reaction of **5** and **3** was examined.[16,17] The resulting product was identical to that formed in the 3-component procedure (Scheme 2).



Scheme 2. Mechanism of reaction through intermediacy of the enamine.

The multi-component diversity elements are introduced by simple addition of 1 equiv. of primary amine to 1 equiv. of alkyl propiolate and ninhydrin (1 equiv.); the reaction was complete within 4-8 min on solid support under microwave irradiation to afford **4a-g** (Table 1).

Table 1. Three-component synthesis of some novel tetrahydro-dihydroxy-oxoindeno[1,2-b]pyrroles.

Entry	R^1	R^2	Product	Yields (%)	mp	Time (min)
1	-Et	benzyl	**4a**	87	139-140 °C	5
2	-Et	n-butyl	**4b**	77	142-143 °C	8
3	-Me	cyclohexyl	**4c**	68	155-156 °C	7
4	-Et	cyclohexyl	**4d**	70	147-148 °C	7
5	-Me	benzyl	**4e**	81	137-138 °C	6
6	-Et	methyl	**4f**	60	129-130 °C	4
7	-Et	ethyl	**4g**	66	131-132 °C	4

These were characterized on the basis of their elemental analyses and IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra data. NMR spectra of products **4** have not shown the formation 2 diastereomers. For example, the ^{1}H-NMR spectrum of **4a** exhibited 1 triplet at (δ 1.24) and 1 quartet at (δ 4.17) for the ethyl group and 2 broad single lines at (δ 4.39 and 4.56) for the hydroxy groups. Two doublets at (δ 4.63 and 4.92) were readily recognized as arising from methylene protons as an AB system along with multiplets (δ 7.03-7.91) for 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 multicomponent reaction described herein provides a simple and direct entry into a number interesting novel tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrrole derivatives that may be of value in medicinal chemistry as oral hypoglycemic agents. This new method under microwave irradiation for the synthesis of [1,2-*b*]pyrroles has the advantages of high yield, high selectivity, short reaction time, ease of product isolation, being solvent free, and the catalyst as well as compliance with green chemistry protocols.

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