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Free solvent and free catalyst for the synthesis of some [1,2-b]pyrrole derivatives at Room Temperature

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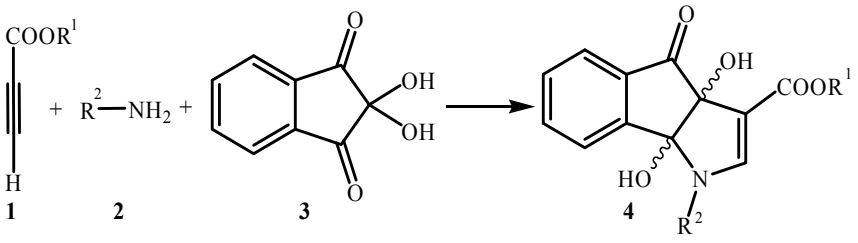
Abstract. A novel method, which is eco_friendly, cost effective, Free solvent and free catalyst was developed for the synthesis of some tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrroles, via condensation of amines, alkylpropiolates, and ninhydrin at room temperature.

Keywords: Tetrahydro-Dihydroxy-Oxoindeno[1,2-b]Pyrroles, Free solvent, free catalyst, Room temperature

1. Introduction

Multicomponent reactions (MCRs) have become more than two educts directly into their products by one-pot reaction. Synthesis of complex organic structures as useful drug is the dream of every chemist. MCRs as a powerful tool for the rapid introduction of molecular diversity is evident. The new compounds heterocycle synthesize by development MCRs. The development of efficient and mild methods for heterocyclic compound synthesis and application drugs represents a broad area of organic chemistry.[1,2] It is known that dihydroxy-oxoindeno[1,2-b]pyrroles exhibit a wide range of biological activities.[3-6] Pyrroles important classes of compounds with many medicinal activities.[7] For these reasons, many ways for the synthesis of substituted pyrroles are known.[8] In research prompted by our interest in multiple component reactions and as part of programmes in the area of heterocyclic compounds containing nitrogen,[9] and due to the resultant pharmacological interest in compounds which belong to the Polyhydroxylated alkaloids, Although this reaction done previously in other conditions, [10-11] but herein we report in a different condition using microwave irradiation, free solvent, one pot reaction, with high yields, easy separation of product and three-component method for the construction of some new tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrroles, *via* condensation of amines, alkyl propiolates and ninhydrin at room temperature (Scheme 1).



Scheme 1: condensation of amine, alkyl propiolate and ninhydrin

2. Experimental

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All chemicals were obtained from Merck or Fluka. 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 on ionization potential of 70 eV. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected.

2.1. 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): A mixture ethyl propiolate (1 mmol), ninhydrin (1 mmol) and benzyl amine (1 mmol) was stirred for 24h at room temperature. The progress of the reaction was monitored by TLC. 1), then end of reaction was purified by column chromatography (CC; SiO2 ; hexane/AcOEt 8 : 1) to afford the pure crystalline solid **4a**.

2.2. Ethyl 1-benzyl-1, 3a, 4, 8b-tetrahydro-3a, 8b-dihydroxy-4-oxoindeno [1,2-b]pyrrole-3-carboxylate *(4a):*

light yellow crystalline solid 87%, m.p. 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.

2.3. Ethyl 1-butyl-1, 3a, 4, 8b-tetrahydro-3a, 8b-dihydroxy-4-oxoindeno [1,2-b]pyrrole-3-carboxylate *(4b):*

yellow crystalline solid 77%, m.p. 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.

2.4. 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%, m.p. 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.

2.5. Ethyl 1-cyclohexyl-1, 3a, 4, 8b-tetrahydro-3a, 8b-dihydroxy-4-oxoindeno[1,2-b]pyrrole-3-carboxylate *(4d):*

yellow crystalline solid 70%, m.p. 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.

2.6. 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%, m. p. 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$_3$,

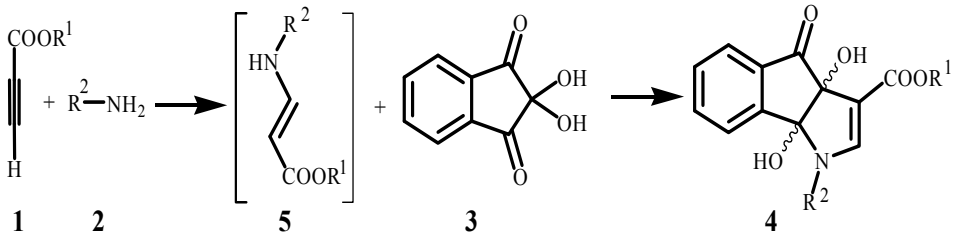
75 MHz) δ_C: 48.36 (CH_2), 51.21 (CH_3), 48.31, 59.91 ($2CH_2$), 84.58, 95.50 (2C-OH), 98.17, 124.53, 125.14, 128.63, 128.78, 129.44, 130.87, 135.54, 136.36, 136.41, 147.70, 149.27 (Aromatic and alkene carbons), 165.61, 148.04 (C=O); MS (m/z, %): 351 (M^+, 10), 260 (20), 228 (40), 91 (100), 76 (16), 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.

2.7. 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%, m.p. 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.

2.8. 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%, m.p. 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.

3. Results and Discussion

We investigated the condensation of ninhydrin, alkyl propiolates and simple primary amines at room temperature. Under all conditions only the product **4a,** (77%) was separated. Thus we obtained best yields at Room Temperature under Free solvent and free catalyst (Table 1). A rationale 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, compound **5** was synthesized separately by condensation of amine and propiolate, and then the reaction of **5** and **3** was examined previously.[12] The resulting product was identical to that formed in the three-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 20-30 hour at room temperature 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 (%)	m. p.	Time (hour)
1	-Et	benzyl	**4a**	77	139-140 °C	24
2	-Et	n-butyl	**4b**	70	142-143 °C	21

3	-Me	cyclohexyl	**4c**	65	155-156 °C	29
4	-Et	cyclohexyl	**4d**	61	147-148 °C	30
5	-Me	benzyl	**4e**	69	137-138 °C	25
6	-Et	methyl	**4f**	53	129-130 °C	27
7	-Et	ethyl	**4g**	55	131-132 °C	28

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 two diastereomers. For example, the ^{1}H NMR spectrum of **4a** exhibited one triplet at (δ 1.24) and one quartet at (δ 4.17) for ethyl group and two broad single lines at (δ 4.39 and 4.56) for hydroxy groups. Two doublets at (δ 4.63 and 4.92) 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 at Room Temperature for the synthesis of [1,2-*b*]pyrroles has the advantage of high yield, high selectivity, ease of product isolation, under Free solvent and free catalyst as well as compliance with green chemistry protocols.

4. Acknowledgements

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