Environmentally Friendly Solvent Free Synthesis of Some [1,2-b]Pyrrole Derivatives at Room Temperature

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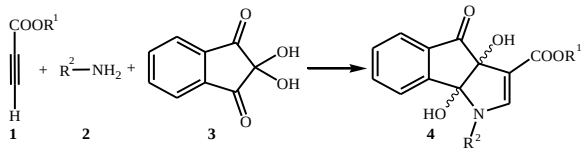
***Abstract*—The present study aimed to use a method for the synthesis of some tetrahydro-dihydroxy-oxoindeno[1,2-b]pyrroles. The question this study tried to answer was this reaction can be performed without solvent and catalyst or not. To find answer to the question, Some [1,2-b]pyrroles were synthesized, via condensation of amines, alkylpropiolates, and ninhydrin at room temperature without solvent and catalyst. Therefore we have synthesized this compounds with a novel method, which is eco_friendly, cost effective, environmentally friendly, acceptive yields, solvent Free and free catalyst was developed for the synthesis of some tetrahydro-dihydroxy-oxoindeno[1,2-b]pyrroles.**

***Index Terms*—Tetrahydro-dihydroxy-oxoindeno[1,2-b] pyrroles, free solvent, environmentally friendly, room temperature**

I. Introduction

Multicomponent reactions (MCRs) emphasize the development of environmentally friendly when synthesized of compounds without solvent and catalyst. 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 are 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]. Heterocycles with Five-membered are important building blocks of an extensive number of biologically active compounds [10]. Pyrroles are heterocycles of most importance because of their presence in numerous natural products like heme, chlorophyll, vitamin B12 , and various cytochrome enzymes [11]. Recently isolated some of the pyrrole-containing marine natural products [12]. They have biologically active compounds have emerged as chemotherapeutic agents. In addition, pyrrole derivatives are molecular frameworks with immense importance in material science [13]. They have been also employed as antioxidants, and antibacterial, antitumor, anti-inflammatory, and antifungal agents [14–19]. Moreover, they are a highly versatile class of intermediates in the synthesis of natural products as well as in heterocyclic chemistry [20]-[23]. In recent years, the direction of synthesis of organic compounds has been shifting more towards eco-friendly, natural product resources solvent Free and without catalyst or reusable catalysts. Although this reaction done previously in other conditions, [24]-[25] but herein we report in a different condition environmentally friendly, solvent Free, free catalyst, 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

II. Experimental

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.

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**.

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

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crystalline solid 87%, m.p. 139-140 °C, IR (KBr) (νmax, cm-1): 1647, 1736 (2C=O); 1H NMR(CDCl3, 300 MHz) δH: 1.24 (3H, t, 3J=7.2 Hz, CH3), 4.17 (2H, q, 3J=7.2 Hz O-CH2), 4.39, 4.56 (2H, 2 bs, 2OH), 4.63, 4.92 (2H, 2d, 3J=6.9, N-CH2), 7.03 (1H, s, C=CH), 7.22-7.91 (9H, m, Harom); 13C NMR(CDCl3, 75 MHz) δC: 14.89 (CH3), 48.31, 59.91(2CH2), 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 C21H19NO5: 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%, m.p. 142-143 °C, IR (KBr) (νmax, cm-1): 1652, 1719 (C=O); 1H NMR (CDCl3, 300 MHz) δH: 0.96, 1.27 (6H, 2t, 3J=7.14, 3J=7.50 Hz, 2CH3), 1.23-1.73 (4H, m, 2CH2butyl), 3.46, 3.72 (2H, m, N-CH2), 4.20 (2H, q, 3J=7.14, O-CH2), 4.26, 4.53 (2H, 2 bs, 2OH), 7.24 (1H, s, C=CH), 7.53-7.90 (4H, m, Harom); 13C NMR(CDCl3, 75 MHz) δC: 14.11, 14.94 (2CH3), 20.46, 32.46, 44.15, 59.78 (4CH2), 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 C18H21NO5: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.20; H, 6.25; N, 4.20.

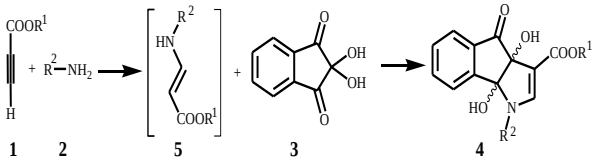
Methyl 1-cyclohexyl-1, 3a, 4, 8b-tetrahydro-3a,8b-dihydroxy-4-oxoindeno[1,2-b]pyrrole-3-carboxylate (4c): light yellow crystalline solid 68%, m.p. 155-156 ℃, IR (KBr) (νmax, cm-1): 1679, 1722 (2C=O); 1H NMR (CDCl3, 300 MHz) δH: 1.37-2.18 (10H, CH2-cyclohexyl), 3.72 (3H, s, O-CH3), 3.80 (1H, m, N-CH), 4.24, 4.42 (2H, 2 bs, 2OH), 7.26 (1H, s, C=CH), 7.34-7.90 (4H, m, Harom), 13C NMR (CDCl3, 75 MHz) δC: 26.51, 31.32, 36.56, (3CH2), 51.13 (CH), 53.94 (CH3), 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 C19H21NO5: 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%, m.p. 147-148 ℃, IR (KBr) (νmax, cm-1): 1679, 1722 (C=O); 1H NMR (CDCl3, 300 MHz) δH: 1.26 (3H, t, 3J=6.90 Hz, CH3), 1.36-2.17 (10H, CH2-cyclohexyl), 3.87 (1H, m, N-CH), 4.17 (2H, q, 3J=7.10, O- CH2), 4.47, 4.78 (2H, 2 bs, 2OH), 7.33 (1H, s, C=CH), 7.51-7.88 (4H, m, Harom); 13C NMR(CDCl3, 75 MHz) δC: 18.73 (CH3), 26.51, 31.31, 34.41, 58.78 (4CH2), 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 C20H23NO5: 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%, m. p. 137-138 ℃, IR (KBr) (νmax, cm-1): 1648, 1727 (2C=O); 1H NMR (CDCl3, 300 MHz) δH: 3.66 (3H, s, O-CH3), 4.52, 4.70 (2H, 2 bs, 2OH), 4.66, 4.88 (2H, 2d, 3J=7.2, N-CH2), 7.04 (1H, s, C=CH), 7.22-7.89 (9H, m, Harom); 13C NMR (CDCl3, 75 MHz) δC: 48.36 (CH2), 51.21 (CH3), 48.31, 59.91 (2CH2), 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 C20H17NO5: 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%, m.p. 129-130 °C, IR (KBr) (νmax, cm-1): 1645, 1720 (2C=O); 1H NMR(CDCl3, 300 MHz) δH: 1.28 (3H, t, 3J=7.1 Hz, CH3), 2.65 (3H, s, N-CH3), 4.21 (2H, q, 3J=7.1 Hz O-CH2), 4.23, 4.45 (2H, 2 bs, 2OH), 7.18 (1H, s, C=CH), 7.33-7.80 (4H, m, Harom); 13C NMR(CDCl3, 75 MHz) δC: 14.25, 35.20 (2CH3), 58.91(CH2), 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 C15H15NO5: 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%, m.p. 131-132 °C, IR (KBr) (νmax, cm-1): 1641, 1722 (2C=O); 1H NMR(CDCl3, 300 MHz) δH: 1.12 (3H, t, 3J=7.2 Hz, CH3), 1.25 (3H, t, 3J=7.2 Hz, CH3), 2.85 (2H, q, 3J=7.2 Hz N-CH2), 4.20 (2H, q, 3J=7.1 Hz O-CH2), 4.25, 4.48 (2H, 2 bs, 2OH), 7.28 (1H, s, C=CH), 7.25-7.93 (4H, m, Harom); 13C NMR(CDCl3, 75 MHz) δC: 14.65, 15.20 (2CH3), 35.8, 59.91(2CH2), 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 C15H15NO5: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.27; H, 5.70; N, 4.60.



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

III. 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.[26] The resulting product was identical to that formed in the three-component procedure (Scheme 2).

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 I.

TABLE I: THREE-COMPONENT SYNTHESIS OF SOME NOVEL TETRAHYDRO-DIHYDROXY-OXOINDENO[1,2-B]PYRROLES.

	R^1	R^2	Product	Yields (%)	m. p.	Time (hour)
1	-Et	benzyl	**4a**	77	139-140 ℃	24
2	-Et	n-butyl	**4b**	70	142-143 ℃	21
3	-Me	cyclohexyl	**4c**	65	155-156 ℃	29
4	-Et	cyclohexyl	**4d**	61	147-148 ℃	30
5	-Me	benzyl	**4e**	69	137-138 ℃	25
6	-Et	methyl	**4f**	53	129-130 ℃	27
7	-Et	ethyl	**4g**	55	131-132 ℃	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.

Herein, we wish to report on a novel synthesis of tetrahydro-dihydroxy-oxoindeno[1,2-*b*]pyrrole derivatives promoted by solvent Free and free catalyst at room temperature to acceptive yields. Therefore, we optimized this reaction Based on appropriate time, as shown in Table 2 for synthesis of Ethyl 1-benzyl-1, 3a, 4, 8b-tetrahydro-3a, 8b-dihydroxy-4-oxoindeno[1,2-b]pyrrole-3-carboxylate (**4a**). Surprisingly, a significant improvement was observed and the yield of 4a was dramatically increased to 77% after stirring; the mixture was stirred for only 24 h (Entry 1). With this optimistic result in hand, we further investigated the best reaction conditions using different times, when in the appropriate time was sufficient to synthesis the reaction effectively Because we did not want to use the solvent and catalyst.

In summary, the multicomponent reaction described herein provides a simple and direct entry into a number interesting novel synthesis of 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. Green chemists are trying to replace healthier chemical procedure with the current ones or by using better materials or performing the reactions under safer conditions , they can produce healthier products for the society. Some of them try to change chemistry closer to green chemistry, because biochemistry reactions have being done during millions of years and there have never been a problem for nor human being neither the ecosystem. Many of these reactions have being done under natural conditions and needn't high temperature or pressure. Their products as well are easily recyclable and their side products are useful for the livings. using the scheme of these reactions can reduce current health and environments problems.

IV. ACKNOWLEDGEMENTS

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