

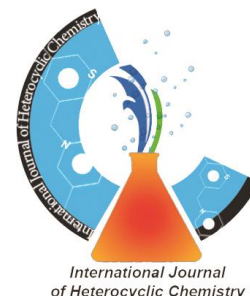
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## Research article

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# Solvent free synthesis of pyrrol derivatives using multicomponent reactions of 1,3- dicarbonyls, activated carbonyl compounds and primary alkylamines

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## Abstract

A one-pot synthesis of pyrrole derivatives via reaction between activated carbonyl compounds, primary amines and 1,3-dicarbonyls under solvent-free conditions is described.

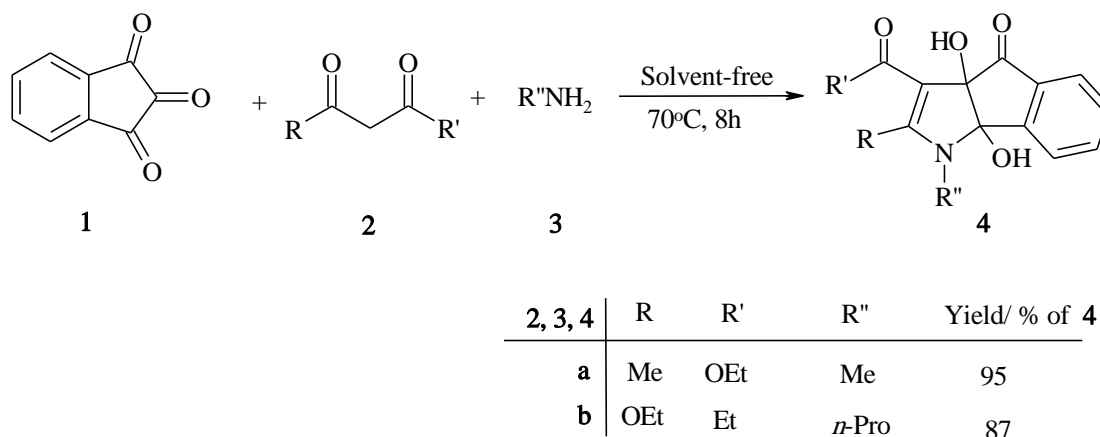
**Keywords:** One-pot reactions; 1,3-Dicarbonyl; pyrroles; Solvent-free; primary amines.

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## Introduction

Multicomponent reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion [1]. Five membered, nitrogen-containing heterocycles are important building blocks in an extensive number of biologically active

compounds [2]. Among them, pyrroles are heterocycles of great importance because of their presence in numerous natural products like heme, chlorophyll, vitamin B12, and various cytochrome enzymes [3]. Some of the recently isolated pyrrole-containing marine natural products have been found to exhibit considerable cytotoxicity and function as multidrug resistant reversal agents [4]. Many of these biologically active compounds have emerged as chemotherapeutic agents. In addition, polysubstituted pyrroles are molecular frameworks having immense importance in material science [5]. They have been also employed as antioxidants, antibacterial, ionotropic, antitumor, anti-inflammatory, and antifungal agents [6-11]. Moreover, they are a highly versatile class of intermediates in the synthesis of natural products as well as in heterocyclic chemistry [12]. As part of our current studies on the development of new routes in heterocyclic synthesis [13], we report an efficient procedure for direct synthesis of tetrahydroindeno [2,1-b]pyrrole-3-dicarboxylates (4) from the reaction of ninhydrin (1) and 1,3-carbonyl compounds 2 in the presence of primary amines (3) under solvent-free conditions at 70 °C (Scheme 1).

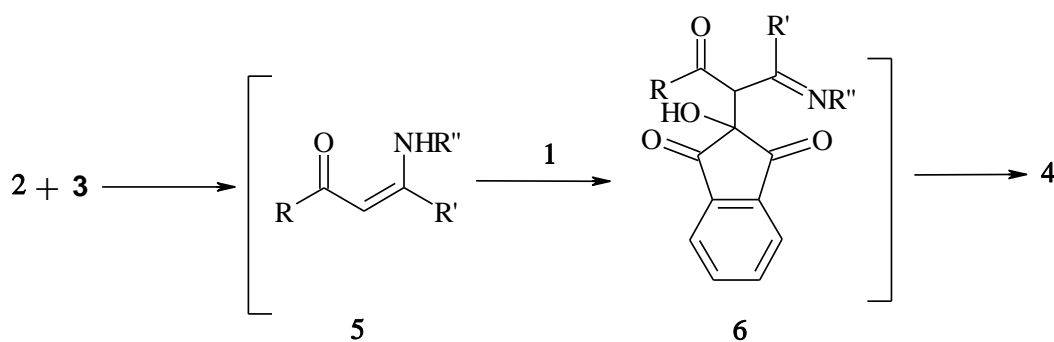


**fig1.** Three-component reactions of 1,3-dicarbonyls, ninhydrin and primary amines.

## Results and discussion

The Presence of two or more different heterocyclic moieties in a single molecule often enhances the biocide profile remarkably [14]. Therefore, we investigated a multicomponent reaction of ninhydrin 1 and 1,3-dicarbonyls 2 in the presence of primary amines 3 under solvent-free conditions which afforded pyrrole-3-carboxylate derivatives in good isolated yields (Scheme 1). The procedure was simple and easy to handle. Structures of compounds 4a–4b were assigned by IR, <sup>1</sup>HNMR, <sup>13</sup>CNMR and mass spectral data [15]. The <sup>1</sup>HNMR spectrum of 4a exhibited one triplet at  $\delta = 1.35$  ( $3J = 7.4$ ), two singlet at  $\delta = 2.21$  and 3.25 ppm for the methyl protons and two singlet at  $\delta =$

4.61 and 4.72 for OH protons, along with characteristic signals for aromatic protons at (7.56-7.87 ppm). The carbonyl group resonances in  $^{13}\text{C}$ NMR spectra of 4a appear at 165.7 and 190.1 ppm. The mass spectra of 4a displayed the molecular ion peaks at 303. A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that, the reaction involves the initial formation of enaminones 5 between 1,3-dicarbonyls 2 and primary amines 3. Enaminones that are formed under solvent-free conditions react with carbonyl group of 1 and produced 6. Cyclization of this intermediate leads to the compound 4.

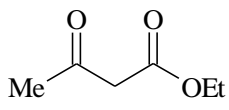
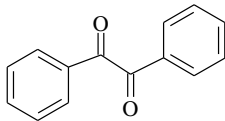
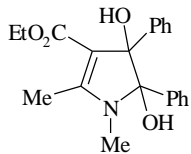
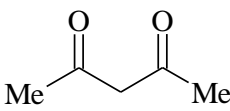
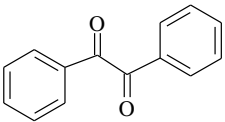
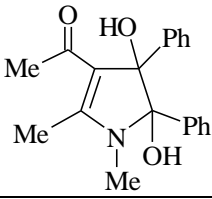
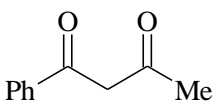
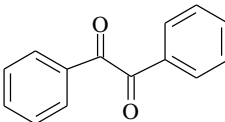
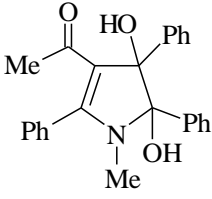
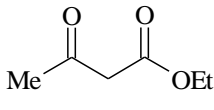
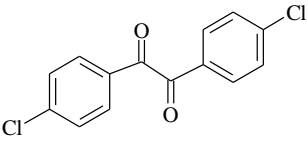
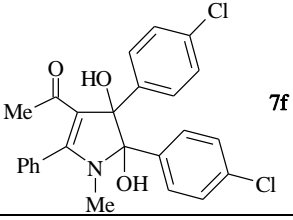


**fig 2.** Possible mechanism for the formation of products 4.

Under similar conditions, the reaction of 1,3-dicarbonyls 2 with another activated carbonyl compounds such as benzyl or acenaphthoquinone in the presence of methyl amine led to pyrrole derivatives in good yields (see Table 1).

**Table 1. Tetrahydroindeno [1,2-b]pyrrole-3-carboxylate derivatives.**

Entry	1,3-dicarbonyl	Activated carbonyl compound	product	Yield (%)
1				95
2				89

3			 <b>7c</b>	95
4			 <b>7d</b>	80
5			 <b>7e</b>	65
6			 <b>7f</b>	80

In summary, the reaction of 1,3-dicarbonyls and activated carbonyl compounds such as ninhydrin, benzyl or acenaphthoquinone in the presence of primary amines under solvent-free conditions which afforded pyrrole derivatives in excellent yields. The advantages of our work are as follows: (1) the reaction is performed under solvent-free conditions and mild condition. (2) No catalyst is required for this reaction. (3) The simplicity of the present procedure makes it an interesting alternative to the complex multistep approaches.

## Experimental

All chemicals were obtained from commercial sources. Melting points were measured on a Kofler hot stage apparatus and are uncorrected.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were obtained with a Bruker FT-500 spectrometer in chloroform- $d_1$ , and tetramethylsilane (TMS) was used as an internal standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within  $\pm 0.4\%$  of the calculated values.

**General procedure for preparation of compounds 4a-b and 7a-f.**

A mixture of primary amines **3** (2 mmol) and 1,3-dicarbonyls **2** (2 mmol) was warmed at about 70 °C for 30 min. Then, activated carbonyl compounds **1** (2 mmol) was added slowly. The reaction mixture was stirred for 8 h at 70 °C, and then poured into 15 mL of water. The resulting precipitate was separated by filtration and using EtOH to afford the pure title compounds.

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

Yellow crystal, mp 150-152°C, yield: 0.57 g (95%). IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 3403, 1716, 1650, 1564, 1480, 1379, 1326, 1208 and 1140  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: 1.35 (3 H, t,  $^3J_{\text{HH}} = 7.4$  Hz, Me), 2.21 (3 H, s, Me), 3.25 (3 H, s, NMe), 4.26 (2 H, t,  $^3J_{\text{HH}} = 7.4$  Hz, OCH<sub>2</sub>), 4.61 (1 H, s, OH), 4.72 (1 H, s, OH), 7.56 (1 H, t,  $^3J_{\text{HH}} = 7.5$  Hz, CH), 7.78 (2 H, d,  $^3J_{\text{HH}} = 7.4$  Hz, 2 CH), 7.87 (1 H, t,  $^3J_{\text{HH}} = 7.6$  Hz, CH) ppm.  $^{13}\text{C}$  NMR: 14.1 (Me), 14.4 (Me), 28.5 (NMe), 58.6 (CH<sub>2</sub>O), 85.4 (C), 91.9 (C), 96.1 (C), 123.5 (CH), 124.8 (CH), 130.3 (CH), 135.5 (C), 135.9 (CH), 150.5 (C), 159.9 (C), 165.7 (C=O), 190.1 (C=O) ppm. EI-MS: 303 (M<sup>+</sup>, 30), 271 (62), 243(92), 225 (97), 198 (30), 104(40), 76 (30). Anal. Calcd for C<sub>16</sub>H<sub>17</sub>NO<sub>5</sub> (303.31): C, 63.36, H, 5.65, N, 4.62; Found: C, 63.42, H, 5.72, N, 4.75%.

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

Yellow powder, mp 195-197°C, yield: 0.60g (87%). IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 3200, 1772, 1726, 1514 and 1260  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: 0.92 (3 H, t,  $^3J_{\text{HH}} = 7.2$ , Me), 1.28 (3 H, t,  $^3J_{\text{HH}} = 7.2$  Hz, Me), 1.32 (3 H, t,  $^3J_{\text{HH}} = 7.3$  Hz, Me), 1.69-1.72 (2 H, m, CH<sub>2</sub>), 2.52 (2 H, q,  $^3J_{\text{HH}} = 7.3$  Hz, CH<sub>2</sub>), 3.39-3.41 (1 H, m, CH), 3.62-3.64 (1 H, m, CH), 4.12 (2 H, q,  $^3J_{\text{HH}} = 7.5$  Hz, OCH<sub>2</sub>), 4.56 (1 H, s, OH), 4.70 (1 H, s, OH), 7.74 (1 H, t,  $^3J_{\text{HH}} = 7.6$  Hz, CH), 7.89 (2 H, d,  $^3J_{\text{HH}} = 7.4$  Hz, 2 CH), 8.08 (1 H, t,  $^3J_{\text{HH}} = 7.5$  Hz, CH) ppm.  $^{13}\text{C}$  NMR: 11.4 (Me), 14.1 (Me), 14.5 (Me), 24.4 (CH<sub>2</sub>), 45.4 (CH<sub>2</sub>), 60.2 (OCH<sub>2</sub>), 82.4 (C), 95.2 (C), 109.1 (C), 122.7 (CH), 124.4 (CH), 129.2 (CH), 133.4 (C), 135.5 (CH), 136.6 (C), 140.2 (C), 160.2 (C), 165.4 (C=O), 183.2 (C=O) ppm. EI-MS: 345 (M<sup>+</sup>, 15), 301 (60), 273 (88), 245 (78), 218 (25), 104 (50), 76 (33). Anal. Calcd for C<sub>19</sub>H<sub>23</sub>NO<sub>5</sub> (345.39): C, 66.07, H, 6.71, N, 4.06; Found: C, 66.15, H, 6.82, N, 4.12%.

**Ethyl 4, 5-dihydroxy-1, 3-dimethyl-4, 5-diphenyl-4, 5-dihydro-1H-pyrrole-2-carboxylate (7a)**

Pale yellow powder, mp 118-120° C, yield: 0.67 g (95%). IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 3353, 3056, 2398, 1734, 1713, 1682, 1602, 1191 and 1088  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: 1.12 (3 H, t,  $^3J_{\text{HH}} = 7.2$  Hz,

Me), 2.37 (3 H, s, Me), 3.38 (3 H, s, NMe), 4.09 (2 H, q,  $^3J_{\text{HH}} = 7.2$  Hz, OCH<sub>2</sub>), 5.26 (2 H, s, 2 OH), 7.09-7.35 (10 H, m, 10 CH) ppm. <sup>13</sup>C NMR: 14.2 (Me), 19.3 (Me), 35.4 (NMe), 61.0 (OCH<sub>2</sub>), 93.4 (C), 98.2 (C), 113.2 (C), 123.3 (CH), 126.3 (2 CH), 127.1 (CH), 127.9 (2 CH), 128.3 (2 CH), 130.3 (2 CH), 136.5 (C), 138.3 (C), 151.7 (C), 170 (C=O) ppm. EI-MS: 353 (M<sup>+</sup>, 15), 321 (58), 293 (90), 275 (95), 248 (25), 171 (30), 76 (25). Anal. Calcd for C<sub>21</sub>H<sub>23</sub>NO<sub>4</sub> (353.42): C, 71.37, H, 6.56, N, 3.96; Found: C, 71.28, H, 6.47, N, 3.88 %.

#### **Ethyl 6b,9a-dihydroxy-7,8-dimethyl-7,9a-dihydro-6bH-acenaphtho[1,2-b]-pyrrole-9-carboxylate (7b)**

Yellow powder, mp 165-167°C, yield: 0.58 g (89%). IR (KBR) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3412, 1733, 1685, 1522, 1370, 1187, 1090 and 1014 cm<sup>-1</sup>. <sup>1</sup>H NMR: 1.48 (3 H, t,  $^3J_{\text{HH}} = 7.2$  Hz, Me), 2.23 (3 H, s, Me), 3.57 (3 H, s, NMe), 4.25 (2 H, q,  $^3J_{\text{HH}} = 7.2$  Hz, OCH<sub>2</sub>), 4.15 (1 H, s, OH), 4.45 (1 H, s, OH), 7.12-7.82 (6 H, m, 6 CH) ppm. <sup>13</sup>C NMR: 13.7 (Me), 17.5 (Me), 35.4 (NMe), 61.4 (CH<sub>2</sub>O), 90.4 (C), 95.0 (C), 110.3 (C), 116.1 (CH), 117.2 (CH), 124.7 (CH), 126.5 (CH), 127.5 (CH), 128.1 (CH), 130.2 (C), 131.4 (C), 132.3 (C), 140.0 (C), 144.1 (C), 166.7 (C=O) ppm. EI-MS: 325 (M<sup>+</sup>, 25), 293 (49), 265 (85), 247 (95), 220(33). Anal. Calcd for C<sub>19</sub>H<sub>19</sub>NO<sub>4</sub> (325.36): C, 70.14, H, 5.89, N, 4.30; Found: C, 70.23, H, 5.95, N, 4.42.

#### **Ethyl 4,5-dihydroxy-2-methyl-4,5-diphenyl-4,5-dihydro-1H-pyrrole-3-carboxylate (7c)**

Pale yellow powder, mp 119-120°C, yield: 0.64 g (95%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3353, 3056, 2398, 1734, 1713, 1682, 1602, 1191, 1088, cm<sup>-1</sup>. <sup>1</sup>H NMR: 1.01 (t, 3 H,  $^3J_{\text{HH}} = 7.1$  Hz, Me), 2.37 (s, 3 H, Me), 3.55 (3 H, s, NMe), 4.09 (q, 2 H,  $^3J_{\text{HH}} = 5.7$  Hz, OCH<sub>2</sub>), 5.20 (s, OH), 7.09-7.3 (m, 10 H) ppm. <sup>13</sup>C NMR: 14.2 (Me), 30.3 (Me), 59.5 (OCH<sub>2</sub>), 35.2 (NMe), 61.1, 62.2, 113.2, 123.3, 126.3, 127.1, 127.9, 128.3, 128.4, 128.8, 128.9, 130.3, 131.1, 133.6, 136.3, 151.7, 170 (C=O) ppm.

#### **1-(4,5-dihydroxy-2-methyl-4,5-diphenyl-4,5-dihydro-1H-pyrrol-3-yl)-1-ethanone (7d)**

Yellow powder, mp 132-134°C, yield: 0.49 g (80%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3412, 1733, 1685, 1559, 1522, 1187, 1090, 830 cm<sup>-1</sup>. <sup>1</sup>H NMR: 1.87 (s, 3 H, Me), 2.37 (s, 3 H, Me), 4.12 (s, OH), 4.2 (s, OH), 3.25 (3 H, s, NMe), 7.09-7.62 (m, 10 H) ppm. <sup>13</sup>C NMR: 22.0 (Me), 30.6 (Me), 35.4 (NMe), 66.7, 80.6, 122.7, 123.3, 127.1, 127.2, 127.3, 127.6, 128.3, 128.9, 131.3, 131.2, 132.1, 135.7, 136.7, 151.2, 197.1 (C=O) ppm.

#### **1-(4,5-dihydroxy-2,4,5-triphenyl-4,5-dihydro-1H-pyrrol-3-yl)-1-ethanone (7e)**

Yellow powder, mp 140-142°C, yield: 0.48 g (65%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3319, 3180, 1911, 1594, 1570, 1324, 1261, 1092, 1025, 802 cm<sup>-1</sup>. <sup>1</sup>H NMR: 2.06 (s, 3 H, Me), 3.34 (3

H, s, NMe), 5.19 (s, OH ), 5.76 (s, OH), 7.25-7.91 (15H-Ar) ppm.  $^{13}\text{C}$  NMR: 23.3 (Me), 35.4 (NMe), 76.9 (COH), 92.7 (COH), 111.0, 118.2, 122.2, 124.3, 125.4, 126.1, 127.5 (3C), 127.7, 128.6 (3C), 128.7, 129.1, 130.0, 131.2 (3C), 140.5, 189.9 (C=O) ppm.

**Ethyl4,5-bis(4-chlorophenyl)-4,5-dihydroxy-2-methyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (7f)**

Yellow powder, mp 122-124 °C, yield: 0.65 g (80%). IR (KBR ) (  $\nu_{\text{max}}$  / $\text{cm}^{-1}$  ): 3412, 1733, 1685, 1522, 1370, 1187, 1090, 1014, 830  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: 1.19 (t, 3 H,  $^3J_{\text{HH}}=7.08$  HZ, Me ), 2.25 (s, 3H , Me), 3.42 (3 H, s, NMe), 4.04 (q, 2H,  $^3J_{\text{HH}} = 7.12$  HZ , $\text{CH}_2\text{O}$ ), 4.61 (s, 2OH), 7.18-7.35 (8 H-Ar) ppm.  $^{13}\text{C}$  NMR: 13.7(Me), 26.2 (Me), 35.7 (NMe), 59.1 ( $\text{CH}_2\text{O}$ ), 61.4 (COH), 114.1, 117. 2, 127.5, 128.01, 128.8, 129.06, 131.5, 132.1, 132.2, 132.9, 135. 6, 137.03, 150.1, 155.0, 165.1 (C=O), 169.5 (C=O) ppm.

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