SOLVENT-FREE SYNTHESIS OF PYRROL DERIVATIVES USING MULTICOMPONENT REACTIONS OF 1,3-DICARBONYLS, ACTIVATED CARBONYL COMPOUNDS, AND PRIMARY ALKYLAMINES

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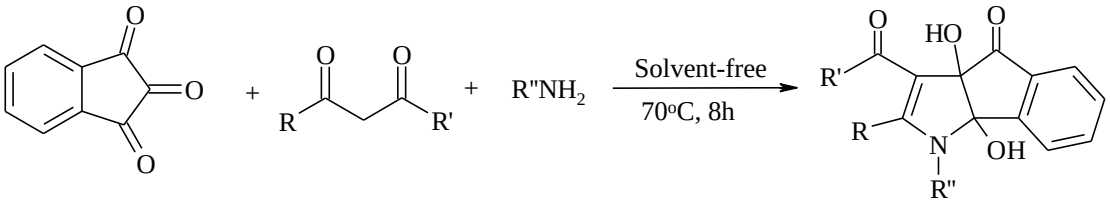
Abstract – A one-pot synthesis of pyrrole derivatives *via* reaction between activated carbonyl compounds, primary amines and 1,3-dicarbonyls under solvent-free conditions is described.

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

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).



1 **2** **3** **4**

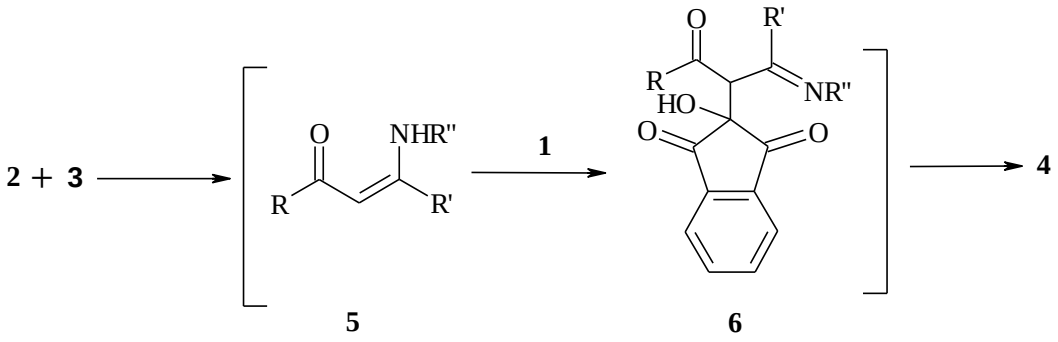
2, 3, 4	R	R'	R"	Yield/ % of **4**
a	Me	OEt	Me	95
b	OEt	Et	*n*-Pro	87

Scheme 1. 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, ^{1}HNMR, ^{13}CNMR and mass spectral data [15]. The ^{1}HNMR spectrum of **4a** exhibited one triplet at δ = 1.35 (^{3}J = 7.4), two singlet at δ = 2.21 and 3.25 ppm for the methyl protons and two singlet at δ = 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 13CNMR spectra of **4a** appear at 165.7 and 190.1 ppm. The mass spectra of **4a** displayed the molecular ion peaks at 303.

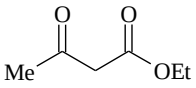
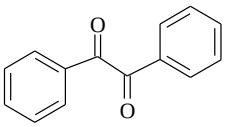
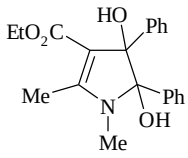
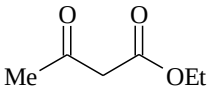
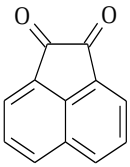
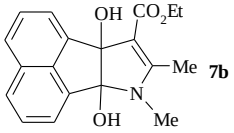
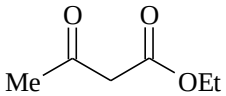
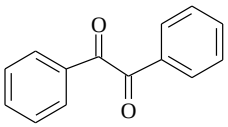
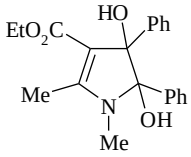
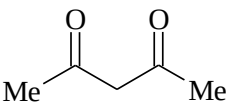
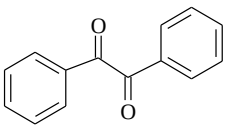
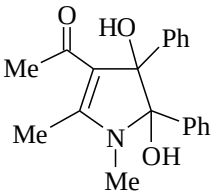
A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that, the reaction involves the initial formation of enaminones **5** between 1,3-dicarbonyls **2** and primary amines **3**. Enaminones that are formed under solvent-free conditions react with carbonyl group of **1** and produced **6**. Cyclization of this intermediate leads to the compound **4**.

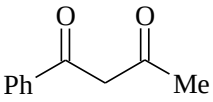
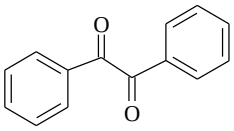
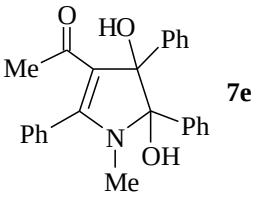
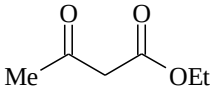
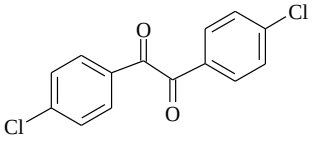
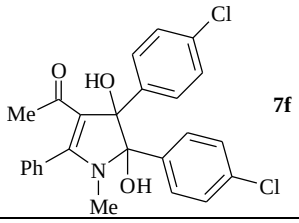


Scheme 2. Possible mechanism for the formation of products **4**.

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			 **7a**	95
2			 **7b**	89
3			 **7c**	95
4			 **7d**	80

5			 **7e**	65
6			 **7f**	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}H NMR and ^{13}C NMR spectra were obtained with a Bruker FT-500 spectrometer in chloroform-d1, 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 Nicollet 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 ±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-3carboxylate (4a)

Yellow crystal, mp 150-152˚C, yield: 0.57 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 3403, 1716, 1650, 1564, 1480, 1379, 1326, 1208 and 1140 cm^{-1}. ^1H NMR: 1.35 (3 H, t, $^3J_{HH}$ = 7.4 Hz, Me), 2.21 (3 H, s, Me), 3.25 (3 H, s, NMe), 4.26 (2 H, t, $^3J_{HH}$ = 7.4 Hz, OCH_2), 4.61 (1 H, s, OH), 4.72 (1 H, s, OH), 7.56 (1 H, t, $^3J_{HH}$ = 7.5 Hz, CH), 7.78 (2 H, d, $^3J_{HH}$ = 7.4 Hz, 2 CH), 7.87 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR: 14.1 (Me), 14.4 (Me), 28.5 (NMe), 58.6 (CH_2O), 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^+, 30), 271 (62), 243(92), 225 (97), 198 (30), 104(40),76 (30). Anal. Calcd for $C_{16}H_{17}NO_5$ (303.31): C, 63.36, H, 5.65, N, 4.62; Found: C, 63.42, H, 5.72, N, 4.75%.

Ethyl2-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) (ν_{max}/cm^{-1}): 3200,1772, 1726, 1514 and 1260 cm^{-1}. ^1H NMR: 0.92 (3 H, t, $^3J_{HH}$ = 7.2, Me), 1.28 (3 H, t, $^3J_{HH}$ = 7.2 Hz, Me), 1.32 (3 H, t, $^3J_{HH}$ = 7.3 Hz, Me), 1.69-1.72 (2 H, m, CH_2) ,2.52 (2 H, q, $^3J_{HH}$ = 7.3 Hz, CH_2), 3.39-3.41 (1 H, m, CH) ,3.62-3.64 (1 H, m, CH), 4.12 (2 H, q, $^3J_{HH}$ = 7.5 Hz, OCH_2), 4.56 (1 H, s, OH), 4.70(1 H, s, OH), 7.74 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.89(2 H, d, $^3J_{HH}$ = 7.4 Hz, 2 CH), 8.08 (1 H, t, $^3J_{HH}$ = 7.5 Hz, CH) ppm. ^{13}C NMR: 11.4 (Me), 14.1(Me), 14.5(Me), 24.4 (CH_2), 45.4 (CH_2) ,60.2 (OCH_2), 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^+,15), 301(60), 273 (88), 245 (78), 218 (25), 104 (50), 76 (33). Anal. Calcd for $C_{19}H_{23}NO_5$ (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-1*H*-pyrrole-2-carboxylate (7a)

Pale yellow powder, mp 118-120˚ C, yield: 0.67 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 3353, 3056, 2398, 1734, 1713, 1682, 1602, 1191 and 1088 cm^{-1} .^1H NMR: 1.12 (3 H, t, $^3J_{HH}$ = 7.2 Hz, Me), 2.37 (3 H, s, Me), 3.38 (3 H, s, NMe), 4.09 (2 H, q, $^3J_{HH}$ = 7.2 Hz, OCH_2), 5.26 (2 H, s, 2 OH), 7.09-7.35 (10 H, m, 10 CH) ppm. ^{13}C NMR: 14.2 (Me), 19.3 (Me), 35.4 (NMe), 61.0 (OCH_2), 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^+, 15), 321 (58), 293 (90), 275 (95), 248 (25), 171 (30), 76 (25). Anal. Calcd for $C_{21}H_{23}NO_4$ (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) (ν_{max} /cm^{-1}): 3412, 1733, 1685, 1522, 1370, 1187, 1090 and 1014 cm^{-1} .^{1}H NMR: 1.48 (3 H, t, $^3J_{HH}$ = 7.2 Hz, Me), 2.23 (3 H, s, Me), 3.57 (3 H, s, NMe), 4.25 (2 H, q, $^3J_{HH}$ = 7. 2 Hz, OCH_2), 4.15 (1 H, s, OH), 4.45 (1 H, s, OH), 7.12 -7.82 (6 H, m, 6 CH) ppm.^{13}C NMR: 13.7 (Me), 17.5 (Me), 35.4 (NMe), 61.4 (CH_2O), 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^+, 25), 293 (49), 265 (85), 247 (95), 220(33). Anal. Calcd for $C_{19}H_{19}NO_4$ (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-1*H*-pyrrole-3carboxylate (7c)

Pale yellow powder, mp 119-120˚ C. yield: 0.64 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 3353, 3056, 2398, 1734, 1713, 1682, 1602, 1191, 1088, cm^{-1} .^{1}H NMR: 1.01 (t, 3 H, $^3J_{HH}$ = 7.1 Hz, Me), 2.37 (s, 3 H, Me), 3.55 (3 H, s, NMe), 4.09 (q, 2 H, $^3J_{HH}$ = 5.7 Hz, OCH_2), 5.20 (s, OH), 7.09-7.3 (m, 10 H) ppm. ^{13}C NMR: 14.2 (Me), 30.3 (Me), 59.5 (OCH_2), 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-1*H*-pyrrol-3yl)-1-ethanone (7d)

Yellow powder, mp 132-134 ˚C, yield: 0.49 g (80%). IR (KBr) (ν_{max}/cm^{-1}): 3412,1733, 1685, 1559, 1522, 1187, 1090, 830 cm^{-1}. ^{1}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. ^{13}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-1*H*-pyrrol-3yl)-1-ethanone (7e)

Yellow powder,mp 140-142 ˚C, yield: 0.48 g (65%). IR (KBr) (ν_{max}/cm^{-1}): 3319, 3180, 1911, 1594, 1570, 1324, 1261, 1092, 1025, 802 cm^{-1} .^{1}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}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) (ν_{max} /cm^{-1}): 3412, 1733, 1685, 1522,1370,1187, 1090, 1014, 830 cm^{-1} .^{1}H NMR: 1.19 (t, 3 H, $^{3}J_{HH}$ =7.08 HZ, Me), 2.25 (s, 3H , Me), 3.42 (3 H, s, NMe), 4.04 (q, 2H, $^{3}J_{HH}$ = 7.12 HZ ,CH_2O), 4.61 (s, 2OH), 7.18-7.35 (8 H-Ar) ppm.^{13}C NMR: 13.7(Me), 26.2 (Me), 35.7 (NMe), 59.1 (CH_2O), 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.

ACKNOWLEDGEMENTS

We gratefully acknowledge financial support from the Research Council of Islamic Azad University, Zahedan Branch.

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