



# Application of Green Procedure for the Synthesis of Substituted Pyrroles: Multi-component Reaction of Oxalyl Chloride

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(Received 12 Mar. 2015; Final version received 10 Jun. 2015)

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## Abstract

A novel, convenient and efficient approach to synthesis of pyrrole derivatives via the reaction of primary amines, alkyl propiolates and oxalyl chloride is described. The method offers several advantages including high yields of products and performing reaction in water as the solvent.

**Keywords:** Solvent-free condition, Primary amines, Pyrroles, Oxalyl chloride.

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## Introduction

Five membered, nitrogen-containing heterocycles are main building blocks in a broad number of biologically active compounds [1]. Among them, pyrroles are heterocycles of enormous importance because of their presence in several natural products like heme, chlorophyll, vitamin B12, and various cytochrome enzymes [2]. Some of the recently isolated pyrrole-containing marine natural products have been set up to display considerable cytotoxicity and function as multidrug resistant reversal agents [3]. Many

of these biologically active compounds have appeared as chemotherapeutic agents. In addition, substituted pyrroles are molecular skeleton having enormous importance in material science [4]. They have been also used as antioxidants, antibacterial, ionotropic, antitumor, anti inflammatory, and antifungal agents [5-10]. There are many methods for the synthesis of pyrroles [11-16]. Of all of the existing areas of chemistry, medicinal and pharmaceutical chemistry, with their traditionally large volume of waste/product ratio, are maybe the most developed for

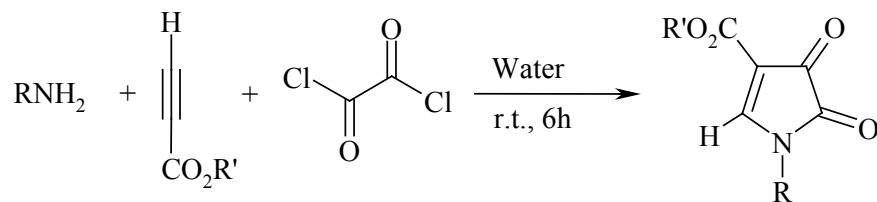
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greening [17].

As part of our current studies on the development of new routes in heterocyclic

synthesis, we report an efficient synthesis of pyrrole derivatives **4** in good yield (Scheme 1).



<b>1,4</b>	R	R'	Yield (%) of <b>4</b>
<b>a</b>	Bn	Me	85
<b>b</b>	4-MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	Me	80
<b>c</b>	n-Bu	Me	75
<b>d</b>	Et	Et	78
<b>e</b>	<sup>t</sup> Bu	Et	80

**Scheme 1.** Synthesis of compound **4** using primary amine, activated acetylenes and oxalyl chloride.

## Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for the C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. <sup>1</sup>H and <sup>13</sup>C spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 respectively. <sup>1</sup>H and <sup>13</sup>C spectra were obtained for solutions in CDCl<sub>3</sub> using TMS as internal standard or 85% H<sub>3</sub>PO<sub>4</sub> as external standard. All the chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and are used without further purification.

### General procedure for the preparation of compounds **4a-e**

To a mixture of primary amine **1** (2 mmol) and alkyl propiolate **2** (2 mmol) in water (5 mL) was added oxalyl chloride **3** (2.5 mmol) at room temperature. The reaction mixture was then stirred for 6 h. After completion of the reaction [TLC (AcOEt/hexane 1:7) monitoring], the reaction mixture was purified by flash column chromatography on silica gel (Merck 230–400 mesh) using n-hexane–EtOAc as eluent to afford pure compounds **4**.

### Methyl 1-benzyl-4,5-dioxo-4,5-dihydro-1H-pyrrole-3-carboxylate (**4a**)

White powder; 172–174 °C, yield 0.44 g (90%)  
IR (KBr) ( $\nu_{\max}$ /cm<sup>-1</sup>) = 1738, 1730, 1728,

1675, 1467, 1325  $\text{cm}^{-1}$ . - MS:  $m/z$  (%) = 245 ( $\text{M}^+$ , 15), 214 (70), 91 (96), 77 (64), 31 (100), Anal. Calcd. (%) for  $\text{C}_{13}\text{H}_{11}\text{NO}_4$  (245.23): C, 63.67; H, 4.52; N, 5.71. Found: C, 63.75; H, 4.63; N, 5.82.  $^1\text{H}$  NMR (500.1 MHz,  $\text{CDCl}_3$ ):  $\sigma$  = 3.75 (3 H, s, MeO), 4.84 (1 H, d,  $^2J$  = 11.7 Hz, CH), 5.15 (1 H, d,  $^2J$  = 11.7 Hz, CH), 7.12 (2 H, d,  $^3J$  = 7.4 Hz, 2 CH), 7.45 (1 H, t,  $^3J$  = 7.8 Hz, CH), 7.68 (2 H, t,  $^3J$  = 7.4 Hz, 2 CH), 8.65 (1 H, s, CH) ppm.  $^{13}\text{C}$  NMR (125.7 MHz,  $\text{CDCl}_3$ ):  $\sigma$  = 47.8 ( $\text{NCH}_2$ ), 52.2 (MeO), 112.2 (C), 128.5 (CH), 129.4 (2 CH), 129.8 (2 CH), 137.5 (C), 147.5 (CH), 162.4 (C=O), 163.5 (C=O), 165.7 (C=O) ppm.

*Methyl 1-(4-methylbenzyl)-4,5-dioxo-4,5-dihydro-1H-pyrrole-3-carboxylate (4b).*

White powder, 164-166  $^\circ\text{C}$ , yield 0.49 g (95%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ) = 1740, 1737, 1732, 1695, 1672, 1447, 1254, 1175  $\text{cm}^{-1}$ . MS:  $m/z$  (%) = 259 ( $\text{M}^+$ , 10), 153 (65), 105 (100), 77 (64), 31 (100). Anal. Calcd. (%) for  $\text{C}_{14}\text{H}_{13}\text{NO}_4$  (259.26): C, 64.86; H, 5.05; N, 5.40. Found: C, 64.92; H, 5.14; N, 5.53.  $^1\text{H}$  NMR (500.1 MHz,  $\text{CDCl}_3$ ):  $\sigma$  = 2.30 (3 H, s, Me), 3.84 (3 H, s, MeO), 4.75 (1 H, d,  $^2J$  = 12.4 Hz, CH), 5.23 (1 H, d,  $^2J$  = 12.4 Hz, CH), 7.24 (2 H, d,  $^3J$  = 7.9 Hz, CH), 7.32 (2 H, d,  $^3J$  = 7.9 Hz, 2 CH), 8.74 (1 H, s, CH) ppm.  $^{13}\text{C}$  NMR (125.7 MHz,  $\text{CDCl}_3$ ):  $\sigma$  = 20.7 (Me), 46.4 ( $\text{NCH}_2$ ), 52.3 (MeO), 111.4 (C), 128.5 (2 CH), 128.7 (2 CH), 130.2 (C), 133.5 (C), 161.4 (C=O), 162.3 (C=O), 165.4 (C=O) ppm.

*Methyl 1-(butyl)-4,5-dioxo-4,5-dihydro-1H-pyrrole-3-carboxylate (4c)*

White powder; 145-147  $^\circ\text{C}$ , yield: 0.63 g (95%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ) = 1742, 1740, 1735, 1694, 1425, 1324, 1236  $\text{cm}^{-1}$ . Anal. Calcd. (%) for  $\text{C}_{10}\text{H}_{13}\text{NO}_4$  (211.22): C, 56.86; H, 6.20; N, 6.63. Found: C, 56.92; H, 6.34; N, 6.73.  $^1\text{H}$  NMR (500.1 MHz,  $\text{CDCl}_3$ ):  $\sigma$  = 0.92 (3 H, t,  $^3J$  = 7.2 Hz,  $\text{CH}_3$ ), 1.27 (2 H, m,  $\text{CH}_2$ ), 1.43 (2 H, m,  $\text{CH}_2$ ), 3.74 (3 H, s, MeO), 3.82-3.93 (2 H, m,  $\text{NCH}_2$ ), 8.84 (1 H, s, CH) ppm.  $^{13}\text{C}$  NMR (125.7 MHz,  $\text{CDCl}_3$ ):  $\sigma$  = 13.4 ( $\text{CH}_3$ ), 18.7 ( $\text{CH}_2$ ), 28.6 ( $\text{CH}_2$ ), 42.5 ( $\text{NCH}_2$ ), 109.4 (C), 147.3 (CH), 161.2 (C=O), 162.5 (C=O), 164.2 (C=O) ppm.

*Ethyl 1-(ethyl)-4,5-dioxo-4,5-dihydro-1H-pyrrole-3-carboxylate (4d)*

White powder; 152-154  $^\circ\text{C}$  (decomp.); yield 0.35 g (90%). IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ) = 1738, 1735, 1728, 1425, 1229  $\text{cm}^{-1}$ . Anal. Calcd. (%) for  $\text{C}_9\text{H}_{11}\text{NO}_4$  (197.19): C, 54.82; H, 5.62; N, 7.10. Found: C, 54.93; H, 5.73; N, 7.18.  $^1\text{H}$  NMR (500.1 MHz,  $\text{CDCl}_3$ ):  $\sigma$  = 1.28 (3 H, t,  $^3J$  = 7.4 Hz,  $\text{CH}_3$ ), 1.36 (3 H, t,  $^3J$  = 7.5 Hz,  $\text{CH}_3$ ), 3.68-3.82 (2 H, m,  $\text{NCH}_2$ ), 4.25 (2 H, q,  $^3J$  = 7.5 Hz,  $\text{CH}_2\text{O}$ ), 8.74 (1 H, s, CH) ppm.  $^{13}\text{C}$  NMR (125.7 MHz,  $\text{CDCl}_3$ ):  $\sigma$  = 13.4 ( $\text{CH}_3$ ), 13.8 ( $\text{CH}_3$ ), 38.4 ( $\text{NCH}_2$ ), 61.4 ( $\text{CH}_2\text{O}$ ), 110.4 (C), 146.2 (CH), 161.5 (C=O), 162.3 (C=O), 164.7 (C=O) ppm.

*Ethyl 1-(tert-butyl)-4,5-dioxo-4,5-dihydro-1H-pyrrole-3-carboxylate (4e)*

White powder; 148-150  $^\circ\text{C}$ , yield 0.43 g

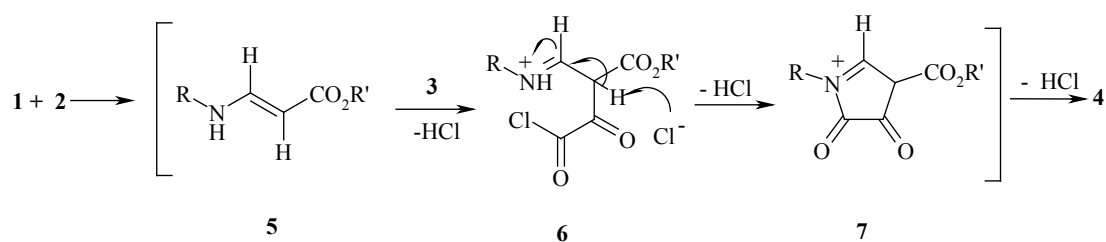
(95%). IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ) = 1745, 1740, 1738, 1462, 1430, 1347, 1232  $\text{cm}^{-1}$ . Anal. Calcd. (%) for  $\text{C}_{11}\text{H}_{15}\text{NO}_4$  (225.24): C, 58.66; H, 6.71; N, 6.22. Found: C, 58.75; H, 6.82; N, 6.34.  $^1\text{H}$  NMR (500.1 MHz,  $\text{CDCl}_3$ ):  $\sigma$  = 1.34 (3 H, t,  $^3J$  = 7.4 Hz,  $\text{CH}_3$ ), 1.48 (9 H, s,  $\text{Me}_3\text{C}$ ), 4.23 (2 H, q,  $^3J$  = 7.4 Hz,  $\text{CH}_2\text{O}$ ), 8.23 (1 H, s, CH) ppm.  $^{13}\text{C}$  NMR (125.7 MHz,  $\text{CDCl}_3$ ):  $\sigma$  = 13.7 ( $\text{CH}_3$ ), 26.5 ( $\text{Me}_3\text{C}$ ), 48.6 (NC), 61.4 ( $\text{CH}_2\text{O}$ ), 110.7 (C), 139.8 (CH), 162.9 (C=O), 163.4 (C=O), 165.7 (C=O) ppm.

## Results and discussion

Synthesis of pyrrole derivatives **4** using the reaction of primary amines **1** and dialkyl acetylenedicarboxylates **2** in the presence of oxalyl chloride **3** in water in good yields was investigated (Scheme 1).

Structures of compounds **4a–e** were determined on the basis of their IR,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra. The mass spectra of

these compounds display molecular ion peaks at the appropriate  $m/z$  values. For example, the  $^1\text{H}$  NMR spectrum of **4a** exhibits two singlets at  $\delta$  = 3.75 and 8.65 ppm for methoxy and methine protons respectively. Two doublet at  $\delta$  = 4.84 (d,  $^2J$  = 11.7 Hz) and 5.15 (d,  $^2J$  = 11.7 Hz) for  $\text{CH}_2$  protons along with signals for aromatic moiety. Although the mechanism of this reaction has not been established, a plausible rationalization can be advanced to explain product formation (Scheme 2). On the basis of the well established chemistry of amine nucleophiles it is reasonable to assume that pyrrole derivatives **4** results from the initial addition of primary amines to the alkyl propiolate and subsequent attack of the intermediate **5** to compound **3** and produce intermediate **6**. Intramolecular nucleophilic attack of the nitrogen to carbonyl group in compound **6** generates compound **7** that by elimination of HCl produce **4**.



**Scheme 2.** Proposed mechanism for the formation of **4**.

## Conclusion

In conclusion, we reported a novel method involving primary amines and alkyl propiolates in the presence of oxalyl chloride

for the synthesis of 1*H*-pyrrole derivatives. The advantages of our work are that the reaction is performed in water, without using a catalyst.

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