

## Catalyst free synthesis of pyrrole derivatives using multicomponent reactions

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**Abstract:** A convenient and efficient procedure for the synthesis of substituted pyrroles has been reported based on three component reactions of primary amines and activated acetylenic compounds in the presence of *N*-formylmorpholine as a green solvent. The above synthetic procedure offers rapid access to novel and diversely substituted pyrrole derivatives.

**Keywords:** *N*-formylmorpholine, Primary amines, pyrrole, Three-component reaction, Green Chemistry.

### Introduction

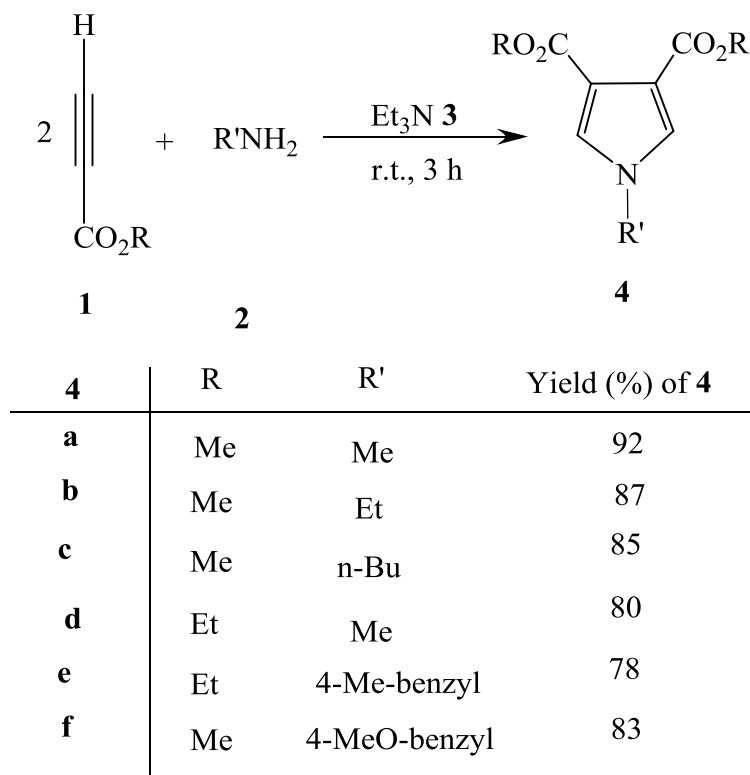
At the beginning of the new century, a move in importance in chemistry is obvious with the longing to extend environmentally gentle routes to a numerous of materials [1]. Green chemistry approaches hold out momentous potential not only for reduction of byproducts, a reduction in the waste produced, and lowering of energy costs but also in the development of new methodologies toward previously unobtainable materials, using existing technologies [2]. 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 greening [3]. Multicomponent reactions (MCRs) have been commonly employed by synthetic chemists as a too easy means to produce molecular diversity from bifunctional substrates that react successively in a intramolecular way [4]. Five membered, nitrogen-containing heterocycles are main building blocks in a broad number of biologically active compounds [5]. Among them, pyrroles are heterocycles of enormous importance because of their presence in several natural products like heme, chlorophyll, vitamin B<sub>12</sub>, and various cytochrome enzymes [6].

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 [7]. Many of these biologically active compounds have used as chemotherapeutic agents. In addition, substituted pyrroles are molecular skeleton having enormous importance in material science [8]. They have been also used as antioxidants, antibacterial, ionotropic, antitumor, anti inflammatory and antifungal agents [9-14]. There are many methods for the synthesis of pyrrole compounds [15-20]. In this research, we report the reaction of propiolates **1** and primary amines **2** in the presence of *N*-formylmorpholine **3** that produces pyrrole derivatives of **4** in excellent yield (Scheme 1).

### Results and discussion

The structures of compounds **4a-f** were assigned by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectral data. For example, in the <sup>1</sup>H NMR spectrum of **4a** exhibited one singlet for two methoxy protons at ( $\delta$  3.78 ppm), one singlet for N-Me protons at ( $\delta$  3.58 ppm) and one singlet for two methin groups at ( $\delta$  6.92 ppm). The <sup>13</sup>C NMR spectrum of **4a** exhibited 9 distinct resonances which further confirmed the proposed structure of **4a**.

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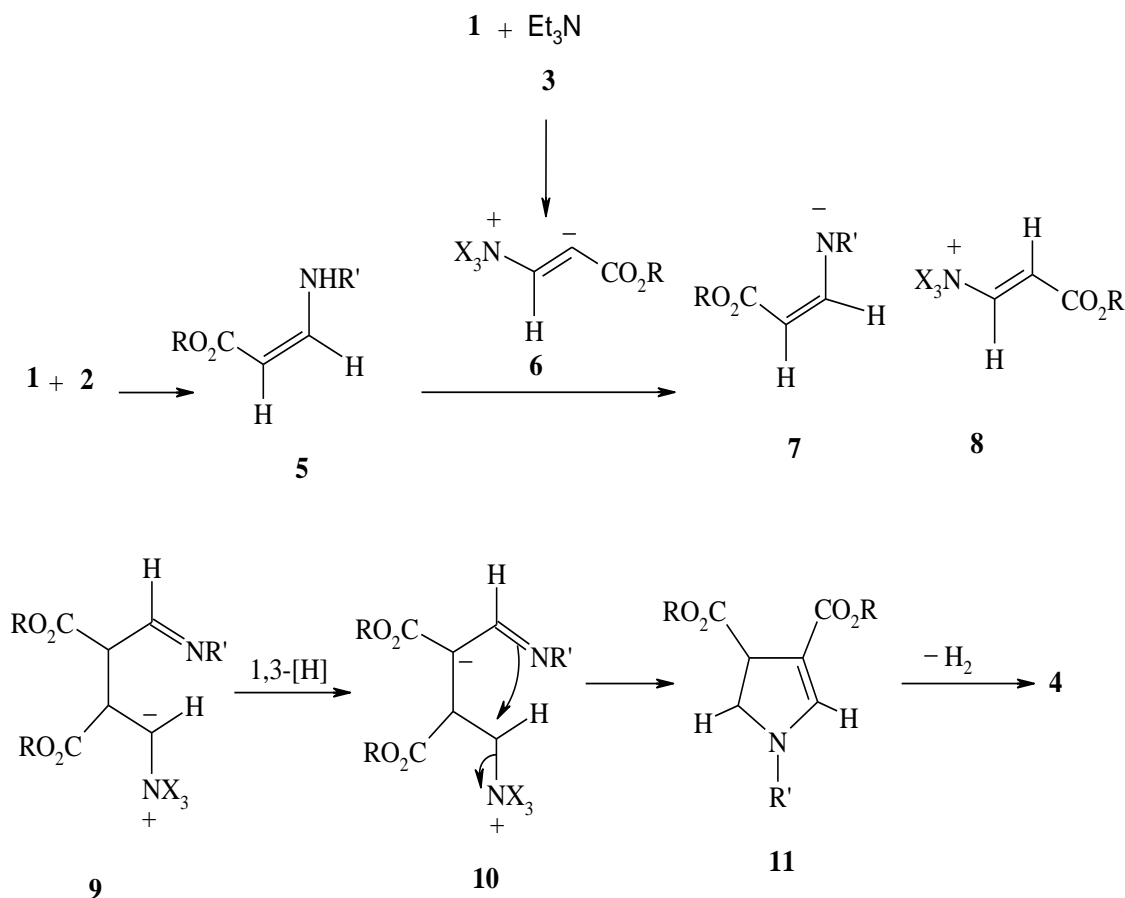
**Scheme 1:** Three-component reaction for synthesis of pyrrole derivatives.

The IR spectrum of **4a** displayed characteristic C=O bands. The mass spectra of **4a** displayed the molecular ion peak at the appropriate *m/z*. Presumably, the zwitterionic intermediate **6**, formed from *N*-formylmorpholine ( $X_3N$ ) and alkyl propiolate **1** that is protonated by the enaminoester **5** was generated as in situ from primary amine **2** and alkylpropiolate **1**. Then by addition intermediate of **5** to **6** by proton transformation process, intermediates of **7** and **8** are resulted. In next step, by nucleophilic attack of the conjugate base of **7** to intermediate **8** leads to adduct **9**, which undergoes two proton shifts process to afford a new zwitterionic intermediate of **10**. Finally, by

intramolecular cyclization reaction of intermediate **10** and then by exiting of *N*-formylmorpholine group from that, affords compound **11**. Eventually in last step by elimination of  $H_2$  from compound **11** leads to the product of **4** (Scheme 2).

### Conclusion

In summary, we report a reaction which involving alkyl propiolates and primary amines in the presence of catalytic amount of *N*-formylmorpholine at room temperature which affords a new route to the synthesis of functionalized pyrroles.

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

## Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV.

IR spectra were measured on a Shimadzu IR-460 spectrometer.  $^1\text{H}$ , and  $^{13}\text{C}$  NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively.  $^1\text{H}$ , and  $^{13}\text{C}$ , spectra were obtained for solutions in  $\text{CDCl}_3$  using TMS as internal standard or 85%  $\text{H}_3\text{PO}_4$  as external standard.

### General procedure for preparation of compounds **4**

To a stirred mixture of alkyl propiolate **1** (2 mmol) and primary amine **2** (2 mmol) in water (5 mL) was added mixture of alkyl propiolate **1** and *N*-formylmorpholine **3** (5 mol%). The reaction mixture was then stirred for 3 h at room temperature. After completion of the reaction [1.5 h; TLC (AcOEt/hexane 1:4) monitoring], the solid residue was filtered and washed by cold diethyl ether to give pure product **4**.

### Dimethyl 1-methyl-1*H*-pyrrole-3,4-dicarboxylate (**4a**):

Pale yellow powder, Yield: 0.36 g (92%) IR (KBr): 1735, 1729, 1587, 1435, 1295, 1126  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: 3.58 (3 H, s, NMe), 3.78 (6 H, s, 2 MeO), 6.92 (2 H, s, 2 CH) ppm.  $^{13}\text{C}$  NMR: 35.8 (NMe), 51.8 (2 MeO), 137.2 (2 C), 138.3 (2 CH), 165.4 (2 C=O) ppm. EI-MS: 197 ( $\text{M}^+$ , 15), 135 (85), 79 (64), 31 (100). 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 5.74, N 7.22.

### Dimethyl 1-ethyl-1*H*-pyrrole-3,4-dicarboxylate (**4b**):

Yellow powder. Yield: 0.37 g (87%). IR (KBr): 1730, 1727, 1562, 1454, 12876  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: 1.23 (3 H, t,  $^3J = 7.4$  Hz, Me), 3.58 (2 H, q,  $^3J = 7.4$  Hz,  $\text{NCH}_2$ ), 3.82 (6 H, s, 2 MeO), 6.87 (2 H, s, 2 CH) ppm.  $^{13}\text{C}$  NMR: 14.2 (Me), 48.3 ( $\text{NCH}_2$ ), 52.4 (2 MeO), 137.5 (2 C), 139.0 (2 CH), 166.2 (2 C=O) ppm. EI-MS: 211 ( $\text{M}^+$ , 10), 121 (76), 79 (58), 45 (100). 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 56.74, H 6.14, N 6.52.

#### Dimethyl 1-butyl-1H-pyrrole-3,4-dicarboxylate (4c):

Pale yellow powder, Yield: 0.41 g (85%) IR (KBr): 1728, 1725, 1545, 1378, 1268, 1226  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: 0.92 (3 H, t,  $^3J = 7.3$  Hz, Me), 1.27 (2 H, m,  $\text{CH}_2$ ), 1.52 (2 H, m,  $\text{CH}_2$ ), 3.62 (2 H, t,  $^3J = 7.3$  Hz,  $\text{NCH}_2$ ), 3.75 (6 H, s, 2 MeO), 6.86 (2 H, s, 2 CH) ppm.  $^{13}\text{C}$  NMR: 13.2 (Me), 18.6 ( $\text{CH}_2$ ), 32.4 ( $\text{CH}_2$ ), 52.2 (2 MeO), 53.3 ( $\text{NCH}_2$ ), 135.4 (2 C), 137.6 (2 CH), 167.0 (2 C=O) ppm. EI-MS: 239 ( $\text{M}^+$ , 15), 208 (88), 31(100). Anal. Calcd for  $\text{C}_{12}\text{H}_{17}\text{NO}_4$  (239.27): C 60.24, H 7.16, N 5.85; Found: C 60.33, H 7.25, N 5.92.

#### Diethyl 1-methyl-1H-pyrrole-3,4-dicarboxylate (4d):

Yellow powder, Yield: 0.36 g (80%) IR (KBr): 1735, 1730, 1587, 1345, 1347, 1252  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: 1.24 (6 H, t,  $^3J = 7.4$  Hz, Me), 3.64 (3 H, s, NMe), 4.28 (4 H, q,  $^3J = 7.4$  Hz,  $\text{CH}_2\text{O}$ ), 7.12 (2 H, s, 2 CH) ppm.  $^{13}\text{C}$  NMR: 13.7 (2 Me), 37.3 (NMe), 61.6 (2  $\text{CH}_2\text{O}$ ), 135.8 (2 CH), 136.4 (2 C), 164.5 (2 C=O) ppm. EI-MS: 225 ( $\text{M}^+$ , 15), 180 (68), 45 (100). 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 58.72, H 6.82, N 6.34.

#### Diethyl 1-(4-methylbenzyl)-1H-pyrrole-3,4-dicarboxylate (4e):

Yellow powder, Yield: 0.49 g (78%) IR (KBr): 1737, 1734, 1687, 1597, 1465, 1254  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR: 1.32 (6 H, t,  $^3J = 7.5$  Hz, Me), 2.38 (Me), 3.62 (3 H, s,  $\text{NCH}_2$ ), 4.34 (4 H, q,  $^3J = 7.5$  Hz,  $\text{CH}_2\text{O}$ ), 6.74 (2 H, s, 2 CH), 7.29 (2 H, d,  $^3J = 7.6$  Hz, 2 CH), 7.36 (2 H, d,  $^3J = 7.6$  Hz, 2 CH) ppm.  $^{13}\text{C}$  NMR: 14.1 (2 Me), 21.4 (Me), 61.4 (2  $\text{CH}_2\text{O}$ ), 61.7 ( $\text{NCH}_2$ ), 127.2 (2 CH), 128.4 (2 CH), 130.2 (C), 134.6 (C), 135.8 (2 CH), 136.2 (2 C), 167.3 (2 C=O) ppm. EI-MS: 315 ( $\text{M}^+$ , 15), 270 (87), 105 (100), 77 (46), 45(100). Anal. Calcd for  $\text{C}_{18}\text{H}_{21}\text{NO}_4$  (315.36): C 68.55, H 6.71, N 4.44; Found: C 68.62, H 6.84, N 4.53.

#### Dimethyl 1-(4-methoxybenzyl)-1H-pyrrole-3,4-dicarboxylate (4f):

Yellow powder, Yield: 0.53 g (83%) IR (KBr): 1733, 1728, 1694, 1587, 1486, 1375  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR:

3.68 (3 H, s,  $\text{NCH}_2$ ), 3.75 (6 H, s, 2 MeO), 3.84 (MeO), 6.65 (2 H, s, 2 CH), 7.15 (2 H, d,  $^3J = 7.5$  Hz, 2 CH), 7.23 (2 H, d,  $^3J = 7.5$  Hz, 2 CH) ppm.  $^{13}\text{C}$  NMR: 52.3 (2 MeO), 55.4 (MeO), 62.4 ( $\text{NCH}_2$ ), 114.2 (2 CH), 130.7 (2 CH), 132.8 (C), 134.8 (2 CH), 136.5 (2 C), 158.7 (C), 167.2 (2 C=O) ppm. EI-MS: 303 ( $\text{M}^+$ , 10), 272 (88), 121 (100), 31 (100). Anal. Calcd for  $\text{C}_{16}\text{H}_{17}\text{NO}_5$  (303.31): C 63.36, H 5.65, N 4.62; Found: C 63.45, H 5.72, N 4.74.

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