I.A.U. Karaj Branch

Journal of Applied Chemical Research, 9, 2, 15-19 (2015)

Journal of Applied Chemical Research
www.jacr.kiau.ac.ir

Three-component Process for the Synthesis of Some Substituted Pyrroles using Water as a Green Solvent

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(Received 18 Oct. 2014; Final version received 17 Dect. 2014)

Abstract

A novel, convenient and efficient three-component reaction for synthesizing substituted pyrroles from primary amines and electron deficient acetylenic compounds in the presence of ammonium thiocyanate in water leads to the formation of pyrroles in good yields.

Keywords**:** *Water, Primary amines, N-methyl imidazol, Pyrroles, Three-component reaction, Green Chemistry.*

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 B_{12}, 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 several methods for synthesis of pyrroles [11-16]. Of all the existing areas of chemistry, medicinal and pharmaceutical chemistry, with their traditionally large volume of waste/product ratio, are the most developed for 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).

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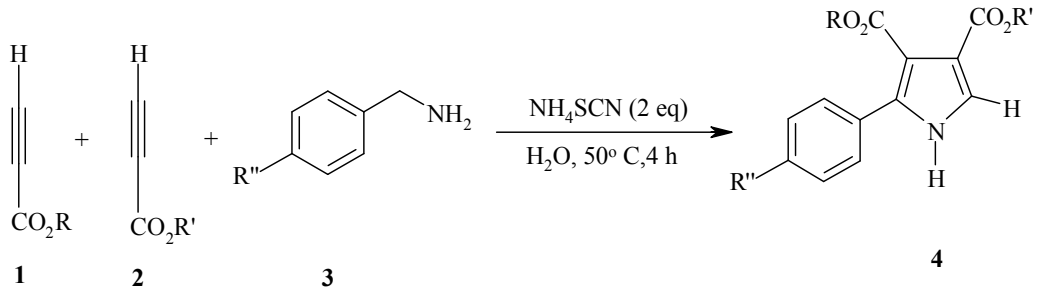


1 2 3 4

1, 2, 3, 4	R	R'	R"	Yield (%) of **4**
a	Me	Me	H	75
b	Me	Et	Me	87
c	Et	Me	MeO	70
d	Et	Et	Me	75

Scheme 1. Reaction of propiolate and benzyl amine in the presence of ammonium thiocyanate.

Experimental

Melting points were measured on an Electrothermal 9100 aparatus. 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. ^{1}H, and ^{13}C spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 respectively. 1H, and ^{13}C spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 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-d**

To a stirred mixture of amine **3** (2 mmol) and acetylenic ester **2** (2 mmol) in water (5 mL) was added mixture of NH_4SCN (2 mmol) and acetylenic ester **1** (2 mmol) in water at 50 ^{o}C. After completion of the reaction (4 h; TLC (AcOEt/hexane 1:5) monitoring), the residue was extracted by AcOEt and washed by cold diethyl ether to give pure product.

Dimethyl 2-phenyl-1H-pyrrole-3,4-dicarboxylate **(4a)**

Yellow oil; yield: 0.39 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1725, 1634, 1487. ^{1}H NMR (500.1 MHz, CDCl3): δ = 3.75 (3 H, s, MeO), 3.82 (3 H, s, MeO), 6.87 (1 H, s, CH), 7.12 (2 H, d, ^{3}J = 7.5 Hz, CH), 7.42 (3 H, m, CH), 9.32 (1 H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 51.2 (MeO), 51.8 (MeO), 112.4 (C), 125.8 (CH), 127.5 (2 CH), 128.4 (C), 128.7 (2 CH), 129.2 (CH), 132.0 (C), 143.4 (C), 162.4 (C=O), 163.8 (C=O) ppm. MS: *m/z*

(%) = 259 (M^+, 10), 228 (46), 91 (58), 77 (87), 31 (100). Anal. Calc. for $C_{14}H_{13}NO_4$ (259.26): C, 64.86; H, 5.05; N, 5.40; Found: C, 64.92; H, 5.14; N, 5.52.

4-ethyl-3-methyl 2-(4-methylphenyl)-1H-pyrrole-3,4-dicarboxylate **(4b)**

Pale yellow oil; yield: 0.49 g (87%). IR (KBr) (ν_{max}/cm^{-1}):, 1727, 1654, 1587, 1465. 1H NMR (500.1 MHz, CDCl3): δ = 1.24 (3 H, t, ^3J = 7.4 Hz, CH3), 2.42 (3 H, s, Me), 3.85 (3 H, s, MeO), 4.18 (2 H, q, ^3J = 7.4 Hz, CH2O), 7.12 (1 H, s, CH), 7.22 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.38 (2 H, d, ^3J = 7.8 Hz, 2 CH), 9.28 (1 H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.8 (CH_3), 22.5 (Me), 52.7 (MeO), 61.4 (CH_2O), 115.2 (C), 125.4 (CH), 126.5 (2 C), 129.4 (C), 130.4 (2 CH), 131.2 (2 CH), 144.7 (C), 162.3 (C=O), 163.8 (C=O) ppm. MS: *m/z* (%) = 287 (M^+, 15), 256 (45), 242 (58), 105 (100), 77 (86), 31 (100). Anal. Calc. for $C_{16}H_{17}NO_4$ (287.31): C, 66.89; H, 5.96; N, 4.88; Found: C, 66.93; H, 6.04; N, 4.92.

3-ethyl-4-methyl 2-(4-methoxyphenyl)-1H-pyrrole-3,4-dicarboxylate **(4c)**

Yellow oil; yield: 0.42 g (70%). IR (KBr) (ν_{max}/cm^{-1}): 1724, 1627, 1545, 1462, 1335, 1275. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.35 (3 H, t, ^3J = 7.4 Hz, CH_3), 3.75 (3 H, s, MeO), 3.94 (3 H, s, MeO), 4.32 (2 H, t, ^3J = 7.5 Hz, CH_2O), 6.94 (1 H, s, CH), 7.12 (2 H, d, ^3J = 7.8 Hz, CH), 7.46 (2 H, d, ^3J = 7.8 Hz, CH), 9.24 (1 H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.2 (CH_3), 51.6 (MeO), 55.6 (MeO), 62.4 (CH_2O), 114.7 (2 CH), 115.2 (CH), 120.4 (C), 123.6 (C), 130.2 (C),131.5 (2 CH), 141.7 (C), 160.2 (C), 161.7 (C=O), 164.5 (C=O) ppm. Anal. Calc. for $C_{16}H_{17}NO_5$ (303.31): C, 63.36; H, 5.65; N, 4.62; Found: C, 63.43; H, 5.74; N, 4.73.

Diethyl 2-(4-methylphenyl)-1H-pyrrole-3,4-tricarboxylate **(4d)**

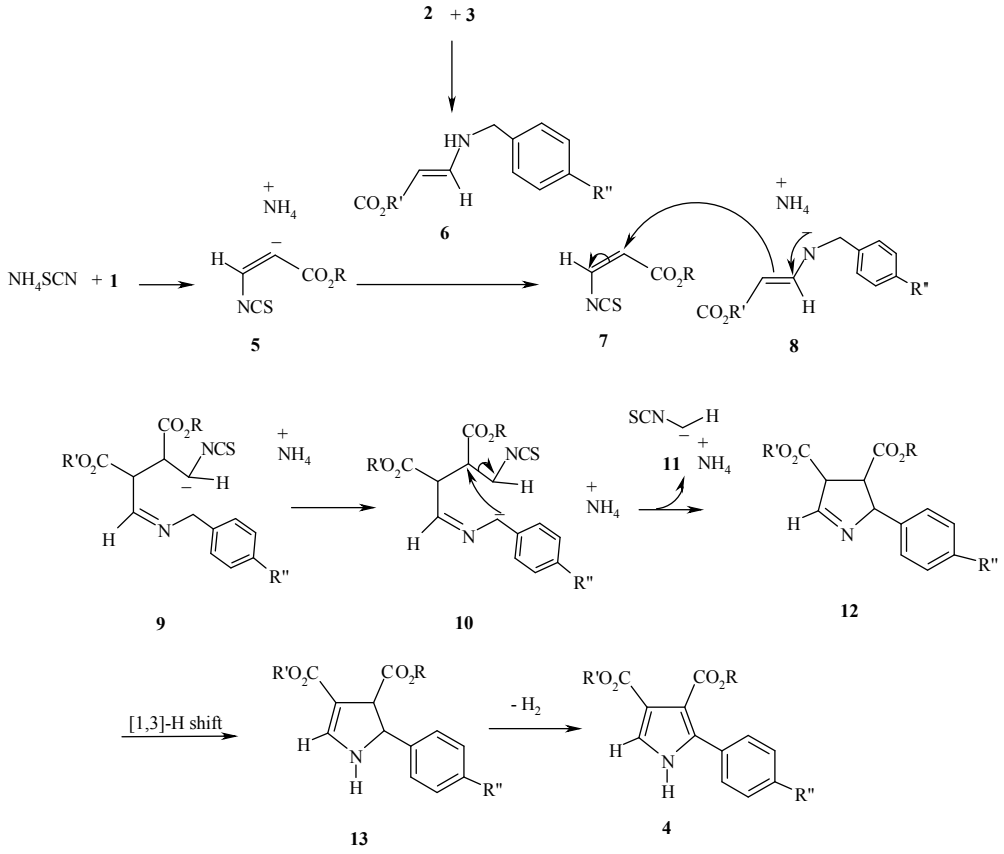
Yellow oil; yield: 0.45 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1728, 1637, 1587, 1465, 1346, 1237. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.27 (3 H, t, 3J = 7.2 Hz, CH3), 1.35 (3 H, t, ^3J = 7.5 Hz, CH3), 2.38 (3 H, s, Me), 4.22 (2 H, q, ^3J = 7.4 Hz, CH2O), 4.37 (2 H, q, ^3J = 7.5 Hz, CH_2O), 6.97 (1 H, s, CH), 7.26 (2 H, d, ^3J = 7.5 Hz, 2 CH), 7.43 (2 H, d, ^3J = 7.6 Hz, 2 CH), 9.23 (1 H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.4 (Me), 13.8 (Me), 20.4 (Me), 61.4 (CH_2O), 61.8 (CH_2O), 116.4 (CH), 121.8 (C), 128.3 (C),129.5 (2 CH), 130.2 (2 CH), 140.6 (C), 144.8 (C), 160.2 (C), 161.4 (C=O), 162.5 (C=O) ppm. Anal. Calc. for $C_{17}H_{19}NO_4$ (301.34): C, 67.76; H, 6.35; N, 4.65; Found: C, 67.83; H, 6.42; N, 4.74.

Results and discussion

The reaction of propiolates **1, 2** and benzyl amines **3** in the presence of ammonium thiocyanate produced the pyrrole derivatives **4** in excellent yield (Scheme 1). These reactions

had a very low yield with alkyl propiolate and wasn't performed with aliphatic primary amines.

Although, many scientific works were conducted and reported on the synthesis of pyrroles [11-16], the number of methods for synthesis of substituted pyrroles caused by benzylic oxidative cyclization, is restricted [18]. The structures of compounds **4** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, the ^{1}H NMR spectrum of **4a** exhibited two singlets for two methoxy protons at (δ 3.75 and 3.82 ppm) and one singlet for methin protons at (δ 6.87 ppm). The ^{13}C NMR spectrum of **4a** exhibited carbonyl resonance at 162.4 and 163.8 ppm which further confirmed the proposed structure. Probably, the first event includes protonation of the zwitter ionic intermediate **5** formed from NH_4SCN and **1**, by the enamine ester intermediate **6** generated *in situ* from the primary amine **3** and acetylenic ester **2** to produce intermediates 7 and **8**. Then, nucleophilic attack of the conjugate base **8** on intermediate **7** leads to adduct **9**, which undergoes intramolecular proton transfer reactions to afford **10**. Intermediate **10** undergoes intramolecular cyclization by elimination of salt **11** to generate the dihydropyrrol derivative **12**, which is converted to desired product **4** by [1,3]-H shift and air oxidation (Scheme 2).



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

Conclusions

In summary, we report a reaction involving alkyl propiolates and primary amines in the presence of catalytic amount of ammonium thiocyanate at 50 °C in water which affords a new route to the synthesis of functionalized pyrroles. The present procedure has the advantage that, not only is the reaction performed under neutral conditions, but also the reactants can be mixed without any prior activation or modification.

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