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1-Methylimidazole-catalyzed reaction between tosylmethyl isocyanide and dialkyl acetylenedicarboxylates: An efficient synthesis of functionalized pyrroles

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Abstract

An efficient 1-methylimidazole-catalyzed synthesis of dialkyl 2-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylates is described. The reactive 1:1 zwitterionic intermediate formed by the addition of 1-methylimidazole to dialkyl acetylenedicarboxylates is trapped by tosylmethyl isocyanide (TOSMIC) to afford the title compounds in excellent yields.

Keywords: 1-Methylimidazole; Tosylmethyl isocyanide; Acetylenic esters; Pyrrole synthesis

Pyrroles, an important class of heterocyclic compounds, have attracted much synthetic attention. Some pyrroles are basic constituents of numerous natural products such as heme, chlorophyll, vitamin B12, and various cytochrome enzymes. Some pyrroles have been reported to possess antioxidant, antibacterial, ionotropic, antitumor, anti-inflammatory and antifungal activities. Furthermore, some pyrrole derivatives have been shown to be P38 kinase inhibitors, prolyl-4-hydroxylase inhibitors, poly (ADP-ribose) polymerase inhibitors, estrogen receptor β selective ligands, AT1-selective angiotensin II receptor antagonists, and minor groove recognition elements [1,2].

Classical methods including Knorr reaction, Paal–Knorr synthesis and Hantzsh synthesis [3] are still widely used for the preparation of substituted pyrroles [4]. There are several pyrrole syntheses from alkenes and isocyanides *via* pyrrolines. For example, a pyrrole synthesis has been reported based on the reaction between TOSMIC and electron-deficient alkenes [5]. Base-catalyzed reaction of nitroalkenes or β-nitroacetates with alkyl isocyanoacetates or TOSMIC afforded pyrrole-2-carboxylates [6] or 2-sulfonylpyrroles [7], respectively. However, only a few pyrrole syntheses are found in literature starting from acetylenes. In 1979, a pyrrole synthesis was reported *via* reaction between acetylenic esters and TOSMIC in the presence of DBU [8]. A direct synthesis of substituted pyrroles has been reported *via* cycloaddition of α-metalated isocyanides to acetylenic compounds [9]. Another synthesis of substituted pyrroles was reported *via* reaction of acetylenedicarboxylates with TOSMIC in the presence of triphenylphosphine [10]. However, most of these procedures have significant drawbacks such as long reaction times, low yields of the

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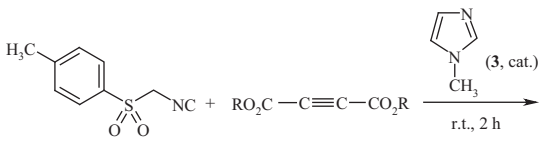


4	R	m.p. (°C) (lit) [11]	% Yield
a	Me	108–109 (107–108)	95
b	Et	159 (157–159)	93
c	*i*Pr	133–134 (132–134)	91
d	*t*Bu	143–144 (144–146)	90

Scheme 1.

products, use of highly basic conditions, use of expensive reagents or catalysts and low atom economy. Hence, development of simple and efficient methods for the preparation of substituted pyrroles is much desirable.

As part of our current studies on the development of efficient routes in heterocyclic synthesis [11], we would like to report herein a simple and mild method with higher atom economy for the preparation of highly functionalized pyrroles.

We found that a mixture of TOSMIC **1**, and a dialkyl acetylenedicarboxylate **2**, in the presence of a catalytic amount of 1-methylimidazole **3** undergo a smooth addition reaction in anhydrous CH_2Cl_2 at ambient temperature to afford 2,3,4-trisubstituted pyrroles **4** in 90–95% (Scheme 1).

The reactions were carried out by first mixing **1** and a catalytic amount of **3** in anhydrous CH_2Cl_2. Then, a solution of **2** in anhydrous CH_2Cl_2 was slowly added. The reaction proceeded smoothly at ambient temperature and was complete within a few hours to afford the functionalized pyrrole **4**. The ^{1}H NMR spectra of the crude products clearly indicated formation of pyrrole **4**. Any product other than **4** could not be detected by NMR spectroscopy.

The structure of compounds **4a–d** was deduced from their elemental analysis, and high-field ^{1}H- and ^{13}C NMR spectra. The mass spectrum of **4a** displayed the molecular ion (M^+) peak at m/z = 337, which was consistent with the 1:1 adduct of TOSMIC and dimethyl acetylenedicarboxylate. The ^{1}H NMR spectrum of **4a** exhibited four single sharp lines due to the methyl group (δ 2.36), two MeO functions (δ 3.77 and 3.91), and the pyrrole C5–H (δ 7.46). A fairly broad signal at δ 10.90 was observed for the pyrrole NH, along with characteristic signals for four aromatic H atoms. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 13 distinct resonances in agreement with the structure of the product.

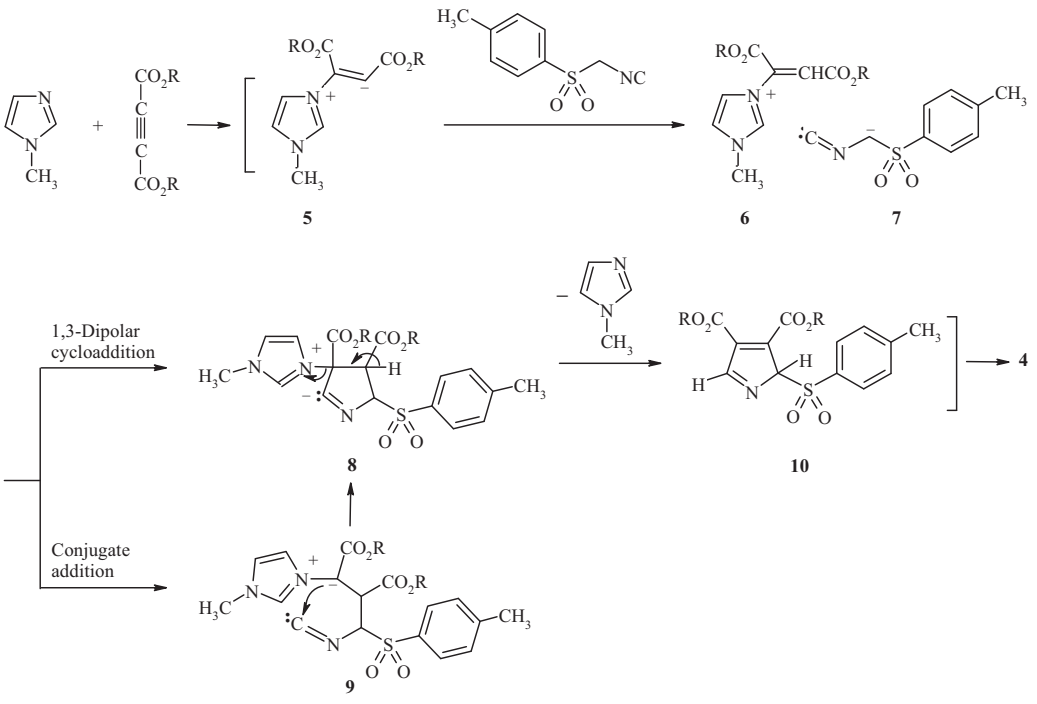
The mp values, elemental analyses, and spectral data of compounds **4b–d**, were also in good agreement with those of authentic samples [10].

A mechanistic rationalization of the reaction is provided in Scheme 2. The initially formed zwitterionic intermediate **5**, from nucleophilic addition of 1-methylimidazole on the acetylenic ester **2** [12], is protonated by TOSMIC. Then, the positively charged ion **6** and the conjugate base of TOSMIC **7** may undergo 1,3-dipolar cycloaddition to yield 1:1:1 adduct **8**. Alternatively, conjugate addition of **7** to **6** may form ylide **9**, which can cyclize to the adduct **8** under the reaction conditions. Then the catalyst, 1-methylimidazole **3**, may be removed from **8** to produce 2*H*-pyrrole intermediate **10**, which tautomerizes to afford the isolated 1*H*-pyrrole **4**.

In summary, we have found a simple and 1-methylimidazole-catalyzed reaction for the preparation of functionalized pyrroles. Excellent yields of the products, fairly fast reaction times, mild reaction conditions, use of simple and inexpensive catalyst, and high atom economy characterize this method. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but the substances have reacted without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.

1. Experimental

Dimethyl-, diethyl- and di(*tert*-butyl) acetylenedicarboxylates, 1-methylimidazole and tosylmethyl isocyanide were obtained from Merck and Fluka, and were used without further purification. Diisopropyl acetylenedicarboxylate was prepared according to the literature procedure [13]. 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 an Agilent Technologies (HP) 5973 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured with Bruker DRX-500 AVANCE (at 500.1 and 125.8 MHz) spectrometer using $CDCl_3$ solvent with TMS as an internal standard. Chromatography columns were prepared from Merck silica gel 60 mesh.



Scheme 2.

1.1. General procedure for the preparation of **4**

To a magnetically stirred solution of **1** (1 mmol) and **3** (0.2 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise a solution of **2** (1 mmol) in anhydrous CH_2Cl_2 (1 mL) at r.t. over 10 min. The mixture was stirred for 2 h. The solvent was removed and the residue was purified by column chromatography using *n*-hexane–EtOAc (3:1) as eluent. The solvent was removed and the product was recrystallized from 1:1 *n*-hexane–EtOAc.

1.2. Dimethyl 2-[(4-methylphenyl)sulfonyl]-1H-pyrrole-3,4-dicarboxylate (**4a**)

Yield: 0.32 g (95%). Colorless crystals. Mp 108–109; ^{1}H NMR ($CDCl_3$, 500.1 MHz): δ 2.36 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 7.26 (d, 2H, J = 8.2 Hz, 2CH), 7.44 (s, 1H, CH), 7.82 (d, 2H, J = 8.2 Hz, 2CH), 10.96 (br., 1H, NH). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 23.12 (CH_3), 53.41 and 54.49 ($2OCH_3$), 117.88 and 123.24 (2C), 128.73 and 129.16 (2CH), 130.06 (C), 131.44 (CH), 139.04 and 146.54 (2C), 164.41 and 165.97 (2C=O). EI-MS *m*/*z*: 337 (20, M^+). Anal. Calcd. for $C_{15}H_{15}NO_6S$ (337.34): C 53.41, H 4.48, N 4.15; found: C 53.37, H 4.52, N 4.01.

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