Synthesis of 5*H*-pyrrolo[1,2-*c*]imidazoles by Intramolecular Wittig Reaction

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Abstract: The intermediate phosphorus ylides which were prepared by reaction between triphenylphosphine and imidazole-4-carbaldehyde in the presence of acetylenic diesters produce dialkyl 5*H*-pyrrolo[1,2-*c*]imidazole-5,6-dicarboxylate derivatives *via* intramolecular Wittig reaction.

Keywords: Dialkyl 5*H*-pyrrolo[1,2-*c*]imidazole-5,6-dicarboxylates, imidazole-4-carbaldehyde, Acetylenic esters, Triphenylphosphine.

INTRODUCTION

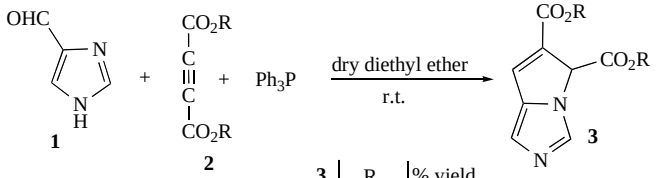
Imidazole-containing compounds have been widely reported in the mainstream as well as in the patent literature because of their potential such as anti-inflammatory, analgesic, antimicrobial and anti-fungicidal properties [1-4]. The interest in bicyclic 5:5 systems with one ring junction nitrogen atom between the five-membered rings and no extra heteroatoms, stems from the appearance of saturated and partially saturated pyrrolo[1,2-*c*]imidazole ring systems in many biologically active compounds [5-8]. For example, pyrrolo[1,2-*c*]imidazole-1,3-diones, imidazo[1,5-*a*]indole and pyrrolo[1,2-*c*]imidazol-5-one have anti-diabetic, aldose reductase inhibitory and immunosuppressive activity [9-11]. The Wittig reaction is a well known method for achieving alkenylation in these systems. Recently we have described the synthesis of many stable phosphorus ylides [12]. Now we report the preparation of pyrrolo[1,2-*c*]imidazole derivatives **3**, in the reaction of imidazole-4-carbaldehyde **1** and dialkyl acetylenedicarboxylates **2** in the presence of triphenyl-phosphine.

RESULTS AND DISCUSSION

The reaction between triphenylphosphine and imidazole-4-carbaldehyde **1** in the presence of the dialkyl acetylenedi-carboxylates **2** was carried out in dry diethyl ether and was completed at room temperature in a few hours to produce dialkyl 5*H*-pyrrolo[1,2-*c*]imidazole-5,6-dicarboxylate **3a-c** in high yields (see Scheme **1**).

Structures of compounds **3a-c** were characterized by their IR, ^{1}H- and ^{13}C-NMR and mass spectrometry data. The elemental analysis data are satisfactory favorable with calculated values.

The mass spectra of these compounds displayed molecular ion peak at appropriate *m/z* values. The IR spectrum of compound **3a** showed strong absorption peak at carbonyl region (1735 and 1685 cm^{-1}) in agreement with proposed structure. The ^{1}H NMR spectrum of **3a** exhibited six singlets for the methoxy (δ = 3.84 and 3.99 ppm) and methine (δ = 6.34, 6.67, 7.70 and 7.82 ppm) protons. The absence of methylene signal in the ^{1}H NMR spectrum of **3a** rules out structure **6** (see Fig. **1**). The ^{13}C-NMR spectrum of **3a** showed ten signals in agreement with the proposed structure. In this spectrum, the carbonyl groups were discernible at δ = 162.54 and 165.66 ppm. Partial assign-ments of these resonances are given in the experimental section. The ^{1}H- and ^{13}C-NMR spectra of **3b** and **3c** are similar to those of **3a**, except for the ester moieties, which exhibit characteristic signals at appropriate chemical shifts.



3	R	% yield
a	Me	95
b	Et	93
c	*t*-butyl	98

Scheme 1.

On the basis of the well established chemistry of trivalent phosphorus nucleophiles [6, 7, 13-18], it is reasonable to assume that zwitterionic specie **4** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by the NH compound **1**. Then the positively charged ion is attacked by the nitrogen atom of the conjugated base of the imidazolyl anion to form intermediate phosphoranes **5** (see Scheme **2**). A speculative mechanistic explanation for this reaction is provided in Scheme **2**.

The presence of three olefinic protons signals and methine proton signal in the ^{1}H NMR spectrum confirms the proposed structure **3**.

Absence of the methylen signal in the ^{13}C DEPT analysis confirms the structure **3** (Fig. **1**).

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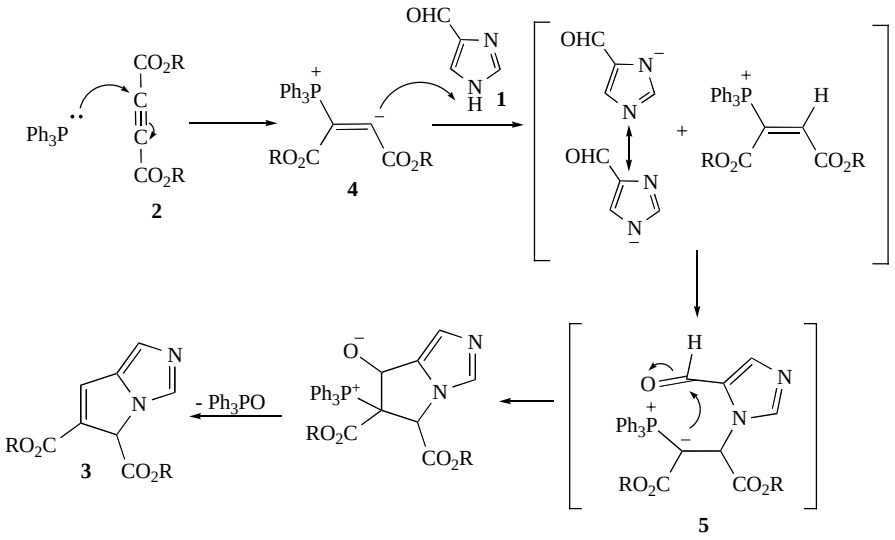


Scheme 2.

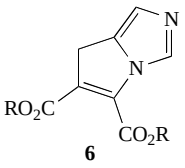


Fig. (1). Compound **6** was ruled out as a possible structure.

It is noticeable that when imidazol-2-carbaldehyde **7** was replaced instead of imidazol-4-carbaldehyde **1** at the same reaction (Scheme **3**) no reaction was observed.

In additional work, reaction carried out with other acetylenic esters such as methyl and ethyl propiolate **10** instead of acetylenic diesters **2**, but unfortunately other analogous of compound **3** were not obtained (see Scheme **4**).

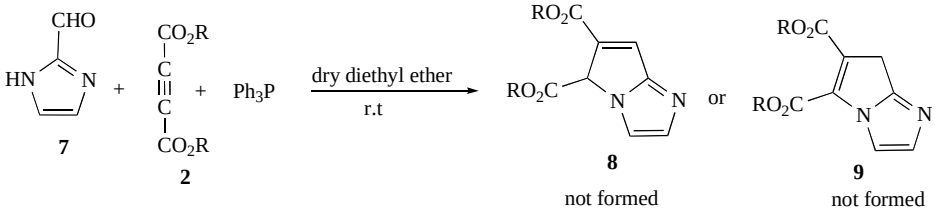
In summary, intramolecular Wittig reaction was employed for the preparation of dialkyl 5*H*-pyrrolo[1,2-*c*]imidazole-5,6-dicarboxylates under neutral condition at room temperature.

EXPERIMENTAL

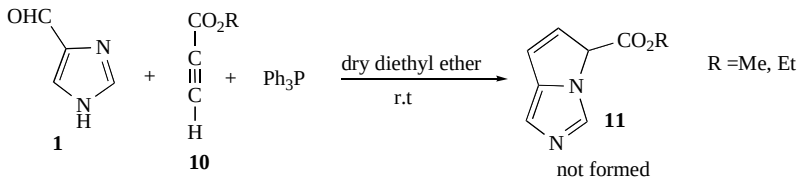
Melting points were taken on an Electrothermal 9100 apparatus and IR spectra of all compounds were recorded in a JASCO FT-IR spectrometer respectively. The ^{1}H- and ^{13}C-NMR spectra were measured with a Bruker DRX-300 AVANCE instrument with $CDCl_3$ as solvent at 300.1 and 75.5 MHz, respectively. The C, H and N elemental analyses were determined using a Heraeus CHN-O-Rapid analyzer. In addition, the mass spectra were recorded on a Shimadzu GCMS-QP5050A mass spectrometer operating at an ionization potential of 70 eV. All chemicals were purchased from (Fluka and Acros), and used without further purifications.

General Procedure (Preparation of Compound 3a)

To a magnetically stirred solution of imidazole-4-carbaldehyde (0.096 g, 1 mmol) and triphenylphosphine (0.26 g, 1 mmol) in dry diethyl ether was added, dropwise, a mixture of dimethyl acetylenedicarboxylate (0.14 g, 1 mmol) in diethyl ether (3 mL) at -5 °C over 10 min. After



Scheme 3.



Scheme 4.

approximately 3 hours stirring at room temperature, the triphenylphosphinoxide was filtered off and then the liquid phase was concentrated and washed with a mixture of cold ethyl acetate and *n*-hexane (2:1) then the liquid phase was crystallized by slow evaporation and finally product was obtained as light yellow crystalline solids.

(3a) Dimethyl 5H-pyrrolo[1,2-c]imidazole-5,6-dicarboxylate

Light yellow crystal, yield (95%), m.p. 98-101°C. IR (KBr) (υ_{max},cm^{-1}): 1686 and 1735 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.84 and 3.99 (2s, 6 H, 2 OCH_3), 6.34 (s, 1 H, NCH), 6.67 (s, 1 H, CH), 7.70 (s, 1 H, CH), 7.82 (s, 1 H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 52.29 and 52.33 (2s, 2 OCH_3), 129.74 (NCH), 131.70 (C_{pyr}), 131.74 (CH_{pyr}), 132.38 (CH_{imi}), 133.12 (NC_{fus}), 133.40 (NCN), 165.37 and 165.66 (2 C=O); MS *m/z* (%): 222 (M^+, 1), 201 (25), 199 (27), 183 (28), 154 (7), 107 (8), 77 (40), 59 (14), 43 (100). Anal. Calcd for $C_{10}H_{10}N_2O_4$ (222.20): C, 54.05; H, 4.54; N, 12.61. Found: C, 54.21; H, 4.57; N, 12.69.

(3b) Diethyl 5H-pyrrolo[1,2-c]imidazole-5,6-dicarboxylate

Light yellow crystal, yield (93%), m.p. 69-72 °C, IR (KBr) (υ_{max},cm^{-1}): 1685 and 1735 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.28 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 1.30 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 4.22 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 4.24 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 6.23 (s, 1 H, NCH), 6.33 (s, 1 H, CH), 7.48 (s, 1 H, CH), 7.83 (s, 1 H, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ*C* 13.83 and 14.08 (2s, 2 OCH_2CH_3), 61.22 and 62.21 (2s, 2 OCH_2CH_3), 129.15 (NCH), 131.72 (C_{pyr}), 132.00 (CH_{pyr}), 132.67 (CH_{imi}), 133.10 (NC_{fus}), 133.61 (NCN), 164.99 and 165.25 (2 C=O); MS *m/z* (%): 250 (M^+, 2), 203 (3), 199 (100), 183 (17), 153 (6), 107 (5), 77 (19), 57 (3), 43 (2). Anal. Calcd for $C_{12}H_{14}N_2O_4$ (250.25): C, 57.60; H, 5.64; N, 11.20. Found: C, 57.71; H, 5.58; N, 11.23.

(3c) Di tert-butyl 5H-pyrrolo[1,2-c]imidazole-5,6-dicarboxylate

Pale white crystal, yield (98%), m.p. 122-125 °C, IR (KBr) (υ_{max},cm^{-1}): 1687 and 1734 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.49 and 1.50 (2s, 18 H, 2 $OCMe_3$), 6.05 (s, 1 H, NCH), 6.66 (s, 1 H, CH), 7.44 (s, 1H, CH), 7.67 (s, 1 H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 28.00 and 28.15 (2s, 2 $OCMe_3$), 81.64 and 81.76 (2s, 2 $OCMe_3$), 130.11 (NCH), 131.91 (C_{pyr}), 131.96 (CH_{pyr}), 132.01 (CH_{imi}), 132.94 (NC_{fus}), 134.56 (NCN), 164.40 and 164.46 (2 C=O); MS *m/z* (%): 308 (M^++2, 4), 306 (M^+, 13), 227 (6), 201 (36), 199 (43), 183 (39), 154 (7), 107 (5), 77 (100), 57 (70), 43 (83). Anal. Calcd for $C_{16}H_{22}N_2O_4$ (306.36): C, 62.73; H, 7.24; N, 9.14. Found: C, 62.78; H, 7.30; N, 9.22.

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