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A Facile and Convenient Synthesis of Tetrasubstituted *N*-Hydroxypyrroles via Intramolecular Wittig Reaction

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ABSTRACT: *Treatment of triphenylphosphine with dialkyl acetylenedicarboxylate leads to 1:1 adduct and concomitant protonation of late adduct by pentan-2,3,4-trione 3-oxime gave the reactive intermediate, vinyltriphenylphosphonium salts, which undergoes an intramolecular Wittig reaction to produce tetrasubstituted N-hydroxypyrroles in fairly high yields.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:100–103, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20382

INTRODUCTION

A five-membered ring system of pyrrole is one of the most ubiquitous throughout the plant and animal kingdoms because of its involvement as a subunit of haem and the chlorophylls. The biosynthetically related vitamin B_{12} is also a tetrapyrrole, as are the animal and plant bile pigments. Functionalized pyrroles are an important class of heterocycles, and many naturally occurring pyrroles are known to possess biological activities [1].

There are extensive studies on the synthesis and reactivity of pyrrole derivatives [2,3] specially designed pyrroles that have found application in pharmaceutical field [4] and also in polymer technology [5]. During the last decades, several methods have been developed for the preparation of pyrroles [6].

Multicomponent condensation reactions have become one of the most powerful methods for the synthesis of organic compounds [7,8].

Among the large family of pyrroles, several efforts have been focused on pyrrole carboxylates [9].

In continuation of our ongoing research to synthesize heterocyclic compounds [10,11], we report a one-pot and facile synthetic route to tetrasubstituted *N*-hydroxypyrroles such as **4**, using the intramolecular Wittig reaction [12,13]. Thus, the reaction of dialkyl acetylenedicarboxylate **2** with pentan-2,3,4-trione 3-oxime **3** in the presence of triphenylphosphine **1** leads to the corresponding *N*-hydroxypyrroles (see Scheme 1).

On the basis of the well-established chemistry of trivalent phosphorus nucleophiles [14–19], it is reasonable to assume that *N*-hydroxypyrroles **4** result from initial addition of triphenylphosphine to the acetylenic ester and concomitant protonation of the 1:1 adduct, followed by attack of nitrogen of the anion of pentan-2,3,4-trione 3-oxime to vinyltriphenylphosphonium cation **5** to generate yilid **6**. Attack of phosphorane **6** on the acetyl carbonyl in a normal intramolecular Wittig reaction would lead to the amine oxide **7**, which is a tautomer of **4** (see Scheme 2).

The essential structures of compounds **4a–c** were deduced from their elemental analyses and their ^1H and ^{13}C NMR spectra as well as from the IR spectra that exhibited strong OH band. The mass spectra of these compounds displayed molecular ion

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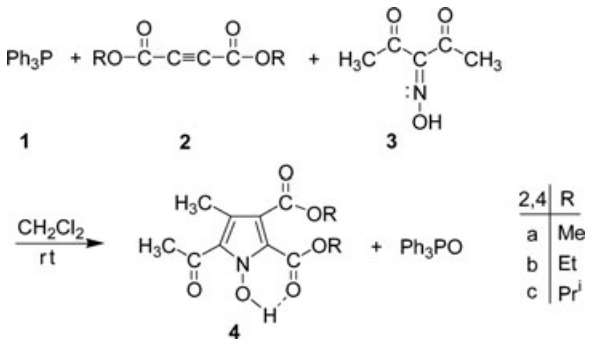


SCHEME 1 Synthesis of tetrasubstituted *N*-hydroxypyrrole via the intramolecular Wittig reaction.

peaks at *m/z* 255, 283, and 311 for **4a, 4b**, and **4c**, respectively. Initial fragmentations involve loss of the side chains that are characteristic for these compounds.

The ^{1}H NMR spectrum of **4a** displayed four single sharp lines arising from two methyl groups (2.59, s, 3H, CH_3-pyrrole ring) and (2.6, s, 3H, CH_3—C=O) and two methoxy groups (3.83, s, 3H) and (3.98, s, 3H, bonded to —OH) protons, along with a fairly broad band for the OH group at δ 14.2, indicating extensive intramolecular hydrogen-bond formation with the vicinal carbonyl group [20]. The ^{13}C NMR spectrum of **4a** displayed signals for methyl (δ 12.3 CH_3-pyrrole ring); (δ 29.17 CH_3 ketone) and methoxy (δ 51.78 and 53.15 bonded to —OH) groups, along with four signals (δ 110.93, 122.36, 124.18, and 126.56 pyrrole ring. C_s). The chemical shifts of the ester carbonyl groups at 160.11 and 163.65 are consistent with the unsymmetrical structure of **4a**. The signal for ketone carbonyl group appears at δ 193.62.

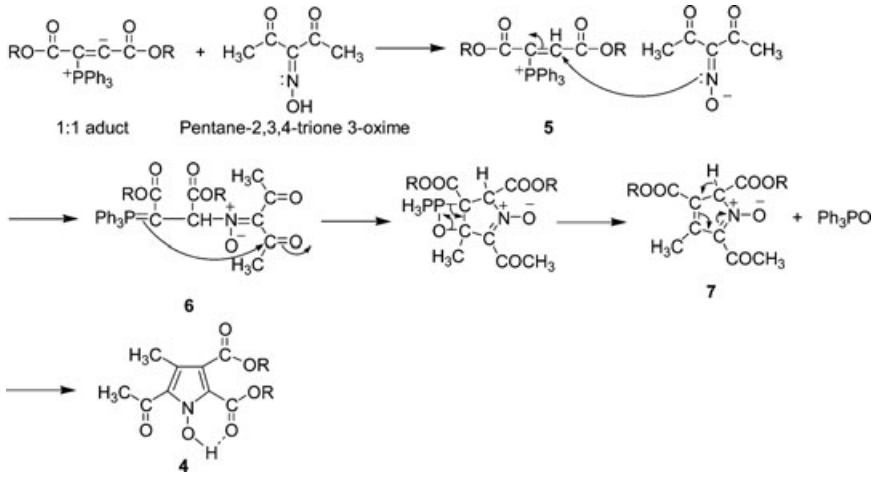
The ^{1}H and ^{13}C NMR spectra of **4b** and **4c** are similar to those of **4a**, except for the ester groups that exhibit characteristic signals with appropriate chemical shifts (see Experimental).

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analysis for C, H, and N was performed using a Heraeus CHN-O-Rapid analyzer; the results were in good agreement with the calculated values. IR spectra were recorded on a Philips PU 9800 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were measured with Bruker-AQS Avance-300 MHz. Mass spectra were obtained with a MS Agileni 5973 network mass selective detector operating at an ionization potential of 70 eV. Iminohydroxy ketone was prepared by the literature method [21]. Others chemicals were obtained from Merck and were used without further purification.

*Preparation of 5-Acetyl-1-hydroxy-4-methyl-1h-pyrrole-2,3-dicarboxylic Acid Dimethyl Ester (**4a**)*

General Procedure. To a magnetically stirred solution of triphenylphosphine (0.524 g, 2 mmol) and pentan-2,3,4-trione 3-oxime (0.23 g, 2 mmol) in CH_2Cl_2 (10 mL), a mixture of dimethyl acetylendicarboxylate (0.284 g, 2 mmol) in CH_2Cl_2 (2 mL) was added dropwise at –10°C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 24 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel (Merck silica gel 60, 230–400



SCHEME 2 Suggested reaction mechanism.

mesh) column chromatography using ethylacetate–hexane (1:2) as eluent. The solvent was removed under reduced pressure, and colorless crystals of **4a** (0.38 g, mp 84°C–86°C, 75%) were obtained. IR (KBr) (ν_{max}, cm^{-1}): 3452 (OH); 1724 (C=O ketone) and 1638 (C=O ester); 1418 and 1575 (C=C pyrr.); 1227 (C–O). ^{1}H NMR ($CDCl_3$) δ: 2.59 (3H, s, CH_3-pyrr.) and 2.6 (3H, s, CH_3 ketone); 3.83 (3H, s, OCH_3) and 3.98 (3H, s, OCH_3 bonded to –OH); 14.19 (1H, br s, O–H···O=C). ^{13}C NMR ($CDCl_3$) δ: 12.30 (CH_3-pyrr.); 29.17 (CH_3 ketone); 51.78 (OCH_3) and 53.15 (OCH_3 bonded to –OH); 110.93, 122.36, 124.18, and 126.56 (pyrrole, C_4, C_3, C_2, and C_5, respectively); 160.11 (C=O ester) and 163.65 (C=O ester bonded to –OH); 193.62 (C=O ketone). MS (*m/z*, %): 255 (M^+); 239 ($M^+ - O$); 224 ($M^+ - OCH_3$); 207 ($M^+ - OH - OMe$); 192 ($M^+ - OH - OMe - Me$); 176 ($M^+ - OH - 2\ OMe$); 121 ($M^+ - CO_2 - 2OMe - CO$). Analysis: Calcd for $C_{11}H_{13}NO_6$ (255.23): C, 51.76; H, 5.09; N, 5.49. Found: C, 51.77; H, 5.02; N, 5.27.

*5-Acetyl-1-hydroxy-4-methyl-1h-pyrrole-2,3-dicarboxylic Acid Diethyl Ester (**4b**)*

White crystals, mp 89°C–91°C. yield 84%. IR (KBr) (ν_{max}, cm^{-1}): 3456 (OH); 1738 (C=O ketone) and 1692 and 1656 (C=O ester); 1505 and 1582 (C=C pyrr.); 1221 (C–O). ^{1}H NMR ($CDCl_3$) δ: 1.32 (3H, t, $J = 7.12$, OCH_3) and 1.40 (3H, t, $J = 7.12$ Hz, OCH_3 bonded to –OH); 2.59 (3H, s, CH_3-pyrr.) and 2.60 (3H, s, CH_3 ketone); 4.29 and 4.44 (4H, q, $J = 7.12$ Hz, $2CH_2$); 14.14 (1H, br s, O–H···O=C). ^{13}C NMR ($CDCl_3$) δ: 12.23 (CH_3-pyrr.); 14.02 (OCH_3) and 14.14 (OCH_3 bonded to –OH); 29.17 (CH_3 ketone); 60.65 and 62.48 ($2CH_2$); 110.81, 122.28, 124.46, and 126.61 (pyrrole, C_4, C_3, C_2, and C_5, respectively); 159.82 (C=O ester) and 163.23 (C=O ester bonded to –OH); 193.47 (C=O ketone). MS (*m/z*, %): 283 (M^+); 266 ($M^+ - OH$); 238 ($M^+ - OEt$); 220 ($M^+ - OEt - H_2O$); 206 ($M^+ - OEt - OH - CH_3$); 192 ($M^+ - OEt - EtOH$); 179 ($M^+ - OEt - CO_2 - CH_3$); 165 ($M^+ - 2OEt - CO$); 148 ($M^+ - 2\ OEt - CO - OH$). Analysis: Calcd for $C_{13}H_{17}NO_6$ (283.29): C, 55.12; H, 6.05; N, 4.94. Found: C, 55.37; H, 6.13; N, 4.78.

*5-Acetyl-1-hydroxy-4-methyl-1h-pyrrole-2,3-dicarboxylic Acid Diisopropyl Ester (**4c**)*

White crystals, mp 40°C–42°C. yield 71%. IR (KBr) (ν_{max}, cm^{-1}): 3455 (OH); 1743 (C=O ketone) and 1715 and 1653 (C=O ester); 1503 and 1582 (C=C pyrr.); 1226 (C–O). ^{1}H NMR ($CDCl_3$) δ: 1.32 and 1.40 (12H, 2d, $J = 6.24$ Hz, $4CH_3$); 2.52 (3H, s, CH_3-pyrr.) and 2.57 (3H, s, CH_3 ketone); 5.19 and 5.28 (2H, m, $J = 6.24$ Hz, 2CH). ^{13}C NMR ($CDCl_3$) δ: 12.21 (CH_3-pyrr.); 21.69 and 21.85 ($4CH_3$, $2pr^i$); 29.16 (CH_3 ketone); 68.31 and 70.64 (2CH, $2pr^i$); 110.99, 122.17, 124.78, and 126.33 (pyrrole, C_4, C_3, C_2, and C_5, respectively); 159.50 (C=O ester) and 162.78 (C=O ester bonded to –OH); 193.23 (C=O ketone). MS (*m/z*, %): 311 (M^+); 269 ($M^+ - CH_3 - CH{=}CH_2$); 252 ($M^+ - O - CH_3CHCH_3$); 227 ($M^+ - 2CH_3{-}CH{=}CH_2$); 209 ($M^+ - OCH(CH_3)_2 - CH(CH_3)_2$); 192 ($M^+ - OCH(CH_3)_2 - CO - OH - Me$); 178 ($M^+ - 2\ OCH(CH_3)_2 - CH_3$); 165 ($M^+ - 2\ OCH(CH_3)_2 - CO$); 151 ($M^+ - 2\ OCH(CH_3)_2 - CO - CH_2$). Analysis: Calcd for $C_{15}H_{21}NO_6$ (311.17): C, 57.85; H, 6.8; N, 4.99. Found: C, 57.94; H, 6.68; N,4.94.

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