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Synthesis of tetrasubstituted *N*-alkoxypyrroles from reaction of α-oximino ketones, dialkylacetylendicarboxylates and trialkylphosphites via intramolecular Wittig reaction

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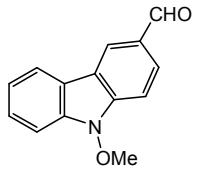
Abstract: The protonated reactive 1:1 adduct generated from reaction of dialkyl acetylendicarboxylates and trialkylphosphites by α-oximinoketones leads to vinyltrialkoxy phosphonium salts, which endure intramolecular Wittig reaction to produce dialkyl 1-alkoxypyrrole dicarboxylates in good yields.

Keywords: Dialkyl acetylendicarboxylate, α-oximinoketone, Intramolecular, Vinyl trialkoxy phosphonium salt, Wittig reaction.

Introduction

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications to biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important [1]. For example natural alkaloid 9-methoxycarbazole-3-carbaldehyde **1** isolated from *Murraya euchrestifolia Hayata* [2] is an inhibitor. Pyrroles are an important class of N-heterocyclic compounds and many naturally occurring pyrroles are known to own biological activity. The biosynthetically related vitamin B_{12} is also a tetrapyrrole, as are the



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animal and plant bile pigments [3].
Therefore, many strategies have been developed for the preparation of pyrroles [4–9]. In recent years, oximes have proved to be very useful building blocks for the one-pot synthesis of a variety of important functionalized pyrroles [10, 11]. As part of our current studies on the development of new routes to heterocyclic systems [12-14], in this letter we describe an efficient and facile synthesis of dialkyl 1-alkoxypyrrole-dicarboxylates **5** from one-pot three-component reaction of α-oximinoketones, dialkylacetylendicarboxylate in the presence of trialkylphosphite using intramolecular Wittig mechanism (Scheme**1**).

Results and discussion

The essential structures of compounds **5a–f** were deduced from their elemental analyses and their ^{1}H and ^{13}C NMR spectra as well as from the IR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values.

The ^{1}H NMR spectrum of **5a** displayed four single sharp lines arising from one methyl group (2.05, CH_3-pyrrole ring) and three methoxy (δ = 3.84, δ = 3.96, and δ = 4.19 for NOMe) protons, along with characteristic signals for the phenyl group. The ^{13}C NMR spectrum of **5a** appeared signals for methyl (δ 12.3 CH_3-pyrrole ring); and three methoxy at δ 52.2,

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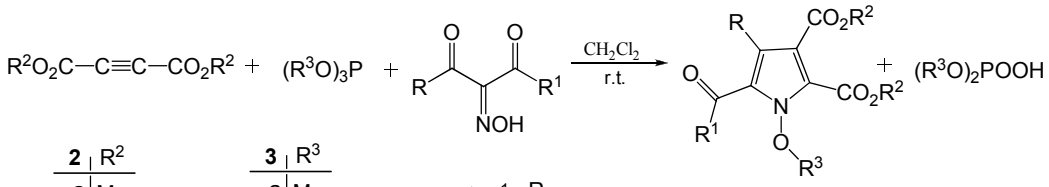
53.3, and 69.8 ppm, along with four signals at δ 113.7, 123.6, 126.7, and 128.3 pyrrole ring Cs. The chemical shifts of the ester carbonyl groups at 160.5 and 164.4 proved the unsymmetrical structure of **5a**. The signal for ketone carbonyl group appeared at δ 186.7 ppm. The mass spectrum of **5a** displayed the molecular ion peak at *m/z* = 331. The ^{1}H and ^{13}C NMR spectra of **5b-5f** were similar to those of **5a**, except for the side chains, which exhibited characteristic signals with appropriate chemical shifts (see Experimental).



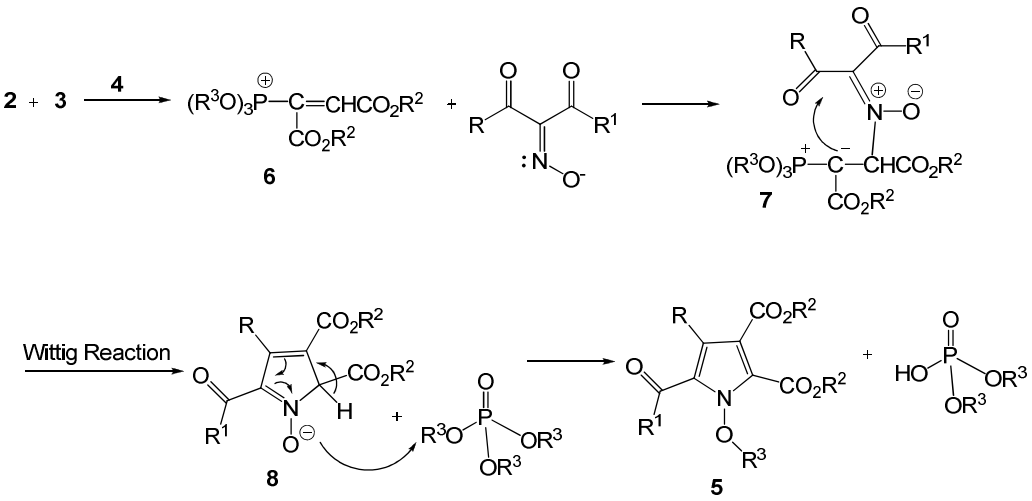
2	R^2
a	Me
b	Et

3	R^3
a	Me
b	Et

4	R^1	R
a	Me	Ph
b	Ph	Ph
c	Me	OEt

5	R	R^1	R^2	R^3	Yield%
a	Me	Ph	Me	Me	85
b	Me	Ph	Me	Et	82
c	Me	Ph	Et	Me	79
d	Ph	Ph	Me	Et	81
e	Me	OEt	Me	Et	88
f	Me	OEt	Me	Me	82

Scheme 1. Synthesis of tetrasubstituted N-alkoxypyrrole **5** via the intramolecular Wittig reaction



Scheme 2. Proposed mechanism for the formation of compounds **5**

Although the mechanistic details of the reaction are not known, a plausible mechanism for the formation of N-alkoxyprrroles **5** is shown in Scheme **2**. The reaction proceeds by addition of the trialkylposphite **3** to the activated acetylene **2** to produce the zwitterionic intermediate which is protonated by the OH oxime **4**. Then, the positively charged ion 6 is attacked by the nitrogen atom of the anion of the oxime to generate ylide **7**. Intramolecular Wittig reaction of **7** leads to intermediate **8**, which undergoes a nucleophilic reaction with trialkylphosphate to produce N-alkoxy pyrrole dicarboxylates **5** in 79- 88% yields (Scheme **2**).

In conclusion, the reaction of α-oximinoketones with electron-deficient acetylenic esters in the presence of trialkylphosphites provides a simple one-pot entry into the synthesis of new tetrasubstituted N-alkoxypyrroles of potential synthetic interest. The present procedure carries the advantage that not only is the reaction performed under convenient conditions, but also the substances can be mixed without any activation or modification.

Experimental

1, 3-Diketooximes **4a-c** were generated from nitrosation of β-diketones by $NaNO_2$ under acid conditions [15]. Sodium nitrite, 1, 3-diketones, trialkylphosphites and dialkyl acetylene dicarboxylates were obtained from fluka and were used without

further purification. m.p.: Electrothermal-9100 apparatus; IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H and ^{13}C NMR spectra: *Bruker DRX-300 AVANCE* instrument; in $CDCl_3$ at 300 and 75 MHz, respectively; δ in ppm, J in Hz; EI-MS (70 eV): *Finnigan-MAT-8430* mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a *Heraeus CHN-O-Rapid* analyzer. The results agreed favorably with the calculated values.

General procedure for the preparation of compounds ***5:***

To a stirred solution of the dialkyl acetylendicarboxylate **2** (1 mmol) and 1, 3-diketooxime **4** (1 mmol) in CH_2Cl_2 (5 mL), a solution of trialkylphosphite **3** (1.2 mmol, in excess) in CH_2Cl_2 (1 mL) was added dropwise at 5 ˚C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 12 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel (Merck silica gel 60, 230–400 mesh) column chromatography using AcOEt/n-Hexane (1:3) as eluent to afford pure product **5**.

Spectroscopic data for compounds 5a-f:

*Dimethyl 5-benzoyl-1-methoxy-4-methyl-1H-pyrrole-2, 3-dicarboxylate (**5a**):*

White powder, m.p. 73-75 ºC, yield: 0.28 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1720, 1632, 1623, 1542, 1420, 1245, 1201. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05 (3 H, s, Me), 3.84 (3 H, s, OMe), 3.96 (3 H, s, OMe), 4.19 (3 H, s, NOMe), 7.48 (2 H, t, ^3J = 7.9, 2 CH), 7.61 (1 H, t, ^3J = 7.9, CH), 7.80 (2 H, d, ^3J = 7.9, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3 (Me), 52.2 (OMe), 53.3 (OMe), 69.8 (NOMe), 113.7 (C), 123.6 (C), 126.7 (C), 128.3 (C), 129.0 (2 CH), 130.0 (2 CH), 133.8 (CH), 138.5 (C), 160.5 (C=O), 164.4 (C=O), 186.7 (C=O). EI-MS (*m/z*, %): 331 (M+, 40), 300 (75), 269 (45), 254 (39), 238 (28), 226 (36), 105 (100), 77 (18). Anal. Calcd for $C_{17}H_{17}NO_6$ (331.32): C, 66.63; H, 5.17; N, 4.23. Found: C, 66.11; H, 4.89; N, 5.09.

*Dimethyl 5-benzoyl-1-ethoxy-4-methyl-1H-pyrrole-2,3-dicarboxylate (**5b**):*

White powder, m.p. 77-78 ºC, yield: 0.28 g (82%). IR (KBr) (ν_{max}/cm^{-1}): 1722, 1663, 1616, 1488, 1436, 1250, 1126. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (3 H, t, ^3J = 7.0, Me), 2.11 (3 H, s, Me), 3.85 (3 H, s, OMe), 3.96 (3 H, s, OMe), 4.43 (2 H, q, ^3J = 7.0, $NOCH_2$), 7.49 (2 H, t, ^3J = 7.4, 2 CH), 7.60 (1 H, t, ^3J = 7.4, CH), 7.79 (2 H, d, ^3J = 7.4, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2 (Me), 13.4 (Me), 52.2 (OMe), 53.2 (OMe), 78.4 ($NOCH_2$), 113.5 (C), 123.9 (C), 126.5 (C), 128.1 (C), 128.9 (2 CH), 130.0 (2 CH), 133.7 (CH), 138.6 (C), 160.6 (C=O), 164.5 (C=O), 186.8 (C=O). EI-MS (*m/z*, %): 345 (M+, 38), 314 (76), 300 (67), 283 (32), 269 (28), 240 (43), 238 (48), 105 (100), 77 (18). Anal. Calcd for $C_{18}H_{19}NO_6$ (345.35): C, 62.60; H, 5.55; N, 4.06. Found: C, 63.00; H, 5.98; N, 4.59.

*Diethyl 5-benzoyl-1-methoxy-4-methyl-1H-pyrrole-2, 3-dicarboxylate (**5c**):*

White powder, m.p. 78-79 ºC, yield: 0.27 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1735, 1682, 1656, 1490, 1440, 1265, 1150. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (3 H, t, ^3J = 7.1, Me), 1.41 (3 H, t, ^3J = 7.1, Me), 2.06 (3 H, s, Me), 4.20 (3 H, s, NOMe), 4.31 (2 H, q, ^3J = 7.1, OCH_2), 4.43 (2 H, q, ^3J = 7.1, OCH_2), 7.48 (2 H, t, ^3J = 7.7, 2 CH), 7.61 (1 H, t, ^3J = 7.7, CH), 7.81 (2 H, d, ^3J = 7.7, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3 (Me), 14.4 (Me), 14.6 (Me), 61.1 (OCH_2), 62.5 (OCH_2), 69.7 (NOMe), 113.6 (C), 123.7 (C), 127.1 (C), 128.1 (C), 129.0 (2 CH), 130.0 (2 CH), 133.7 (CH), 138.6 (C), 160.1 (C=O), 164.0 (C=O), 186.7 (C=O). EI-MS (*m/z*, %): 359 (M+, 37), 328 (68), 314 (65), 283 (26), 269 (47), 254 (40), 238 (31), 226 (28), 105 (100), 77 (21). Anal. Calcd for $C_{19}H_{21}NO_6$ (359.37): C, 63.50; H, 5.89; N, 3.90. Found: C, 63.87; H, 5.12; N, 4.23.

*Dimethyl 5-benzoyl-1-ethoxy-4-phenyl-1H-pyrrole-2,3-dicarboxylate (**5d**):*

White powder, m.p. 80-82 ºC, yield: 0.33 g (81%). IR (KBr) (ν_{max}/cm^{-1}): 1740, 1680, 1636, 1502, 1470, 1270, 1160. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (3 H, t, ^3J = 7.0, Me), 3.75 (3 H, s, OMe), 3.96 (3 H, s, OMe), 4.60 (2 H, q, ^3J = 7.0, $NOCH_2$), 7.07-7.64 (10 H, m, 10 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5 (Me), 52.7 (OMe), 53.0 (OMe), 78.6 ($NOCH_2$), 114.7 (C), 120.2 (C), 125.8 (C), 127.9 (C), 128.2 (2 CH), 128.5 (2 CH), 129.0 (CH), 130.1 (2 CH), 130.4 (2 CH), 132.1 (C), 133.6 (CH), 137.2 (C), 165.2 (C=O), 170.5 (C=O), 187.0 (C=O). EI-MS (*m/z*, %): 407 (M+, 49), 376 (71), 362 (59), 345 (27), 331 (29), 302 (38), 300 (46), 105 (100), 77 (30). Anal. Calcd for $C_{23}H_{21}NO_6$ (407.4): C, 67.80; H, 5.20; N, 3.44. Found: C, 68.22; H, 4.67; N, 3.83.

*5-Ethyl 2,3-dimethyl 1-methoxy-4-methyl-1H-pyrrole-2,3,5-tricarboxylate (**5e**):*

White powder, m.p. 58-60 ºC, yield: 0.26 g (88%). IR (KBr) (ν_{max}/cm^{-1}): 1690, 1657, 1630, 1564, 1505, 1221, 1198. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (3 H, t, ^3J = 7.1, Me), 2.47 (3 H, s, Me), 3.82 (3 H, s, OMe), 3.94

(3 H, s, OMe), 4.21 (3 H, s, NOMe), 4.38 (2 H, q, ^3J = 7.1, OCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9 (Me), 14.6 (Me), 52.1 (OMe), 53.3 (OMe), 61.2 (OCH_2), 68.9 (NOMe), 113.0 (C), 119.5 (C), 126.6 (C), 127.6 (C), 159.7 (C=O), 160.6 (C=O), 164.3 (C=O). EI-MS (*m/z*, %): 299 (M+, 48), 268 (100), 254 (82), 237 (30), 222 (40), 208 (23), 206 (36), 194 (29), 192 (56), 59 (16), Anal. Calcd for $C_{13}H_{17}NO_7$ (299.28): C, 52.17; H, 5.73; N, 4.68. Found: C, 52.62; H, 5.47; N, 4.83.

*5-Ethyl 2,3-dimethyl 1-ethoxy-4-methyl-1H-pyrrole-2,3,5-tricarboxylate (**5f**):*

White powder, m.p. 60-62 ºC, yield: 0.25 g (82%). IR (KBr) (ν_{max}/cm^{-1}): 1705, 1660, 1636, 1575, 1418, 1227, 1098. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (3 H, t, ^3J = 7.0, Me), 1.40 (3 H, t, ^3J = 7.1, Me), 2.47 (3 H, s, Me), 3.82 (3 H, s, OMe), 3.93 (3 H, s, OMe), 4.37 (2 H, q, ^3J = 7.1, OCH_2), 4.48 (2 H, q, ^3J = 7.0, $NOCH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0 (Me), 13.5 (Me), 14.7 (Me), 52.1 (OMe), 53.2 (OMe), 61.1 (OCH_2), 77.5 ($NOCH_2$), 112.9 (C), 119.5 (C), 126.6 (C), 127.5 (C), 159.7 (C=O), 160.7 (C=O), 164.4 (C=O). EI-MS (*m/z*, %): 313 (M+, 51), 282 (100), 268 (90), 237 (34), 236 (33), 222 (21), 208 (29), 192 (61), 59 (14). Anal. Calcd for $C_{14}H_{19}NO_7$ (313.30): C, 53.67; H, 6.11; N, 4.47. Found: C, 53.20; H, 5.87; N, 4.77.

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