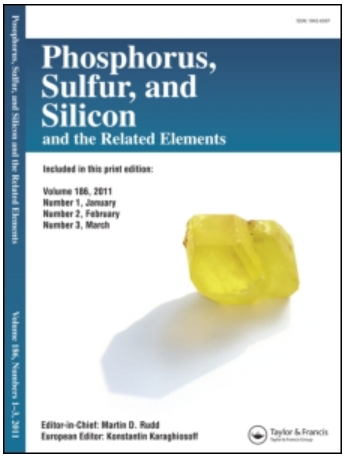

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Synthesis of Dimethyl 1-Aryl-4-ethoxy-5-oxo-2,5- dihydro-1*H*-pyrrole-2,3-dicarboxylates Mediated by Triphenylphosphine

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*Ethyl 2-arylamino-2-oxo-acetates undergo a complex reaction with dimethyl acetylendicarboxylate in the presence of triphenylphosphine to produce dimethyl 1-aryl-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylates in good yields. Dynamic NMR study of dimethyl 1-(2-methyl-6-nitrophenyl)-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate shows a fairly high energy barrier ($\Delta G^{\#} = 95 \pm 2$ kJ mol^{-1}) for rotation around the N-aryl single bond, which leads to an observable atropisomerism.*

Keywords Acetylenic esters; atropisomers; hindered rotation; intramolecular *Wittig* reaction; triphenylphosphine

INTRODUCTION

Five-membered-ring lactams have successfully been used in routes to various alkaloids[1,2] and are suitable precursors for unusual γ-amino acids.[3,4] There are also many examples of pyrroline-containing natural products with interesting pharmacological activities. Typical examples are the antitumor alkaloide Jatropham.[5] As part of our current studies on the development of new routes to heterocyclic and carbocyclic systems[6–10] we now report a simple one-pot synthesis of dimethyl l-aryl-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates **2** in good yields (Scheme 1).

RESULTS AND DISCUSSION

The reaction of ethyl 2-arylamino-2-oxo-acetates **1** with dimethyl acetylendicarboxylate in the presence of triphenylphosphine proceeded

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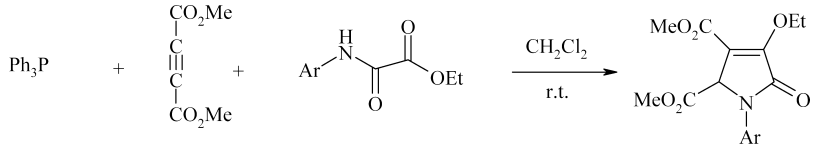


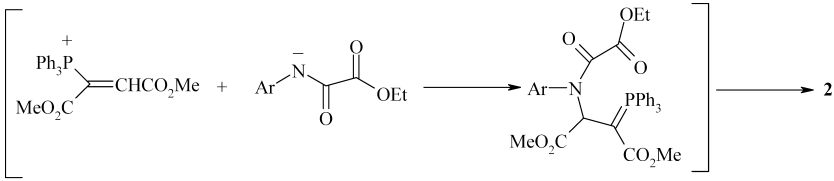
1 2

1, 2	Ar	%Yield of 2
a	2,6-diisoprpylphenyl	85
b	2-methyl-6-nitrophenyl	87
c	8-quinolinyl	88

SCHEME 1 Synthesis of 2 form dimethyl acetylenedicarboxylate and 1 mediated by triphenylphosphine.

spontaneously at room temperature in CH_2Cl_2 and was finished within 24 h. ^1H and ^{13}C NMR spectra of the crude product clearly indicated the formation of dimethyl l-aryl-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates **2a–2c**. Any product other than **2** could not be detected by NMR spectroscopy.

Reactions are known in which an unsaturated heterocyclic compound is produced from a phosphorane connected with a carbonyl group by a chain containing a heteroatom.[7–12] Thus, the 2,5-dihydropyrrole derivative **2** may be regarded as the product of an intramolecular Wittig reaction. Such addition-cyclization product apparently results from an initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by ethyl 2-arylamino-2-oxo-acetate. Then, the positively-charged ion is attacked by the nitrogen atom of the conjugate base of the NH-acid to form the phosphorane **3**, which is converted to the 2,5-dihydropyrrole derivative **2** (Scheme 2).



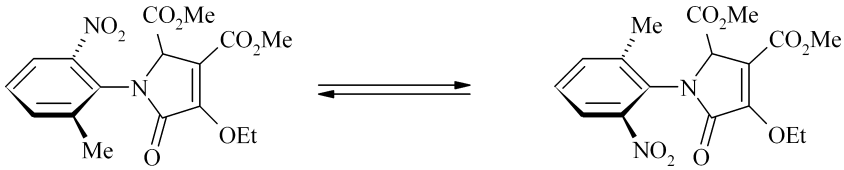
3

SCHEME 2 A plausible mechanism for formation of z.

The structures of **2a–2c** were deduced from their elemental analyses and their IR, ^1H, and ^{13}C NMR spectra. The mass spectra of these compounds are fairly similar, as expected, and confirm their molecular weights. Initial fragmentation involves loss from or complete loss of the side chains and scission of the heterocyclic ring system.

In the case of **2a**, the methyl groups of isopropyl moieties are diastereotopic due to the existing chiral center. Thus, the ^{1}H NMR spectrum of **2a** exhibits four doublets at 1.12, 1.13, 1.17, and 1.30 ppm for the isopropyl groups as a result of the presence of a stereogenic center in **2a**.

The ^{1}H NMR and ^{13}C NMR spectra of **2b** clearly show that this compound exhibits atropisomerism and shows two rotational isomers in about 70:30 ratio at room temperature. Thus, for compound **2b**, with methyl and nitro groups, rotation around the aryl-nitrogen bond is slow at ambient temperature (Scheme 3).



SCHEME 3 Rotation around the N-aryl bond in 2 leads to two rotational isomers.

The ^{1}H NMR spectrum of **2b** in 1,2-dichlorobenzene at ambient temperature display four single resonances due to C-Me ($\delta = 2.32$ and 2.35 ppm) and methine ($\delta = 4.96$ and 5.12 ppm) protons. At about 120°C the resonances arising from the methine protons are appreciably broadened when compared with the corresponding signals at room temperature. These resonances coalesced near 180°C. From the coalescence of the methine proton resonances using the expression $k = \pi \Delta\nu\sqrt{2}$ we calculated the first order rate constant (k) for the *N*-aryl bond rotation in **2b** to be 60 s^{-1} at 180°C. Application of the absolute rate theory with a transmission coefficient of 1 gives a free energy of activation ($\Delta G^{\#}$) of 95 ± 2 kJ mol^{-1}, where all known sources of errors were estimated and included.[13] The experimental data available were not suitable for obtaining meaningful values of $\Delta H^{\#}$ and $\Delta S^{\#}$, even though the errors in $\Delta G^{\#}$ were not large.[14] The $\Delta G^{\#}$ value measured for **2c** is slightly less than twice of the value (53 kJ mol^{-1}) obtained for derivatives lacking the nitro group.[15] The dynamic NMR effect for **2b** can be attributed to restricted rotation around the aryl-nitrogen single bond[15,16] as a result of the steric effect of the methyl and nitro groups at the ortho positions (Scheme 3).

The ^{1}H NMR spectrum of **2c** shows two sharp singlets ($\delta = 3.52$ and 3.82 ppm) for the methoxy groups together with a sharp signal ($\delta = 6.11$ ppm) for the methine proton. No dynamic NMR effect was observed in the ^{1}H NMR spectrum of **2c**, when a $CDCl_3$ solution of this compound

was cooled to −70°C. Thus rotation around the aryl-nitrogen bond in **2c** is fast on the NMR timescale at −70°C, as a result of smaller steric interaction of the lone pair compared to that of a hydrogen atom in α-substituted naphthalene derivatives.[16]

The presented reaction provides a simple one-pot entry into the synthesis of polyfunctionalized 5-oxo-2,5-dihydro-1*H*-pyrrole derivatives of potential synthetic interest. Dynamic NMR effects are observed in the ^{1}H NMR spectra of **2b** and are attributed to restricted rotation around the aryl-nitrogen bond.

EXPERIMENTAL

Dimethyl acetylenedicarboxylate, ethyl oxalyl chloride, and arylamines were obtained from Fluka (Buchs, Switzerland) and were used without further purification. 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. These results agreed favorably with the calculated values. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-500 AVANCE instrument with CDCl3 as solvent at 500.1 and 125.7 MHz. Dynamic ^{1}H NMR spectra were measured on a JEOL-90 MHz NMR instrument. IR spectra were measured on a Shimadzu IR-460 spectrometer.

Preparation of Dimethyl 1-(2,6-Diisopropylphenyl)-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (2a)

General Procedure

To a stirred solution of ethyl 2-(2,6-diisopropylphenyl)-2-oxo-acetate (0.55 g, 2 mmol) and dimethyl acetylendicarboxylate (0.28 g, 2 mmol) in CH_2Cl_2 (10 mL) was added drop wise to a mixture of triphenylphosphine (0.52 g, 2 mmol) in CH_2Cl_2 (4 mL) at 0°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 column chromatography, using *n*-hexane:EtOAc, 3:1, as eluent, to yield **2a** as colorless oil (0.69 g, yield 85%).

IR (KBr) (ν_{max}, cm^{-1}): 1740 and 1708 (C=O).

^{1}H NMR (500.1 MHz, $CDCl_3$) δ 1.12, 1.13, 1.17, and 1.30 (12 H, 4 d, $^3J_{HH}$ 7 Hz, 2 CH*Me*$_2$), 1.44 (3 H, t, $^3J_{HH}$ 7 Hz, CH_3), 2.45 and 2.86 (2 H, m, 4 H, 2 C*H*Me$_2$), 3.63 and 3.80 (6 H, 2 s, 2 OMe), 4.83 (2 H, m, CH_2), 4.86 (1 H, s, CH), 7.16–7.28 (3 H, m, Ar) ppm.

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 15.6 ($OCH_2\mathit{CH}_3$), 24.0, 24.1, 25.2, and 25.3 (4 CH_3), 28.5 and 28.8 (2 $\mathit{C}HMe_2$), 51.9 and 52.8 (2 OCH_3), 63.5 (NCH), 68.6 ($O\mathit{CH}_2CH_3$), 112.6 (N—C=C), 123.7, 124.2, 124.3, 129.74, 146.8, and 148.5 (6 C, Ar), 154.2 (N—C=C), 162.3, 165.0, and 167.8 (3 C=O) ppm.

MS (*m*/*z*, %): 403 (M^+, 3).

Anal. Calcd for $C_{22}H_{29}NO_6$ (403.5): C, 65.49; H, 7.24; N, 3.47%. Found: C, 65.7; H, 7.4; N, 3.4%.

Dimethyl 4-Ethoxy-1-(2-methyl-6-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (2b)

Pale yellow powder, 0.66 g, yield 87%, mp 84–86°C.

IR (KBr) (ν_{max}, cm^{-1}): 1739 and 1684 (C=O).

MS (*m*/*z*, %): 370 (M^+, 5).

Anal. Calcd for $C_{19}H_{18}N_2O_6$ (370.4): C, 67.05; H, 4.90; N, 7.57%. Found: C, 67.2; H, 4.8; N, 7.7%.

2b-I, (70%), ^{1}H NMR (500.1 MHz, $CDCl_3$) δ 1.50 (3 H, q, $^3J_{HH}$ 7 Hz, CH_3), 2.32 (3 H, s, CH_3), 3.68 and 3.86 (6 H, 2 s, 2 OMe), 4.87 (2 H, m, CH_2), 4.96 (1 H, s, CH), 7.51–8.02 (3 H, m, Ar) ppm.

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 15.6 ($OCH_2\mathit{CH}_3$), 17.7 (CH_3), 52.1 and 52.9 (2 OCH_3), 61.9 (NCH), 68.9 ($O\mathit{CH}_2CH_3$), 114.0 (O—C=C), 123.9, 128.3, 129.5, 136.3, 141.7, and 146.6 (6 C, Ar), 153.5 (O—C=C), 162.0, 164.4, and 167.7 (3 C=O) ppm.

2b-II, (30%), ^{1}H NMR (500.1 MHz, $CDCl_3$) δ 1.50 (3 H, q, $^3J_{HH}$ 7 Hz, CH_3), 2.35 (3 H, s, CH_3), 3.68 and 3.91 (6 H, 2 s, 2 OMe), 4.87 (2 H, m, CH_2), 5.12 (1 H, s, CH), 7.51–8.02 (3 H, m, Ar) ppm.

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 15.6 ($OCH_2\mathit{CH}_3$), 18.4 (CH_3), 52.1 and 53.4 (2 OCH_3), 60.9 (NCH), 68.8 ($O\mathit{CH}_2CH_3$), 113.4 (N—C=C), 123.4, 127.6, 129.5, 135.9, 139.4, and 148.2 (6 C, Ar), 153.3 (N—C=C), 162.2, 164.1, and 166.4 (3 C=O) ppm.

Dimethyl 4-Ethoxy-1-(8-quinonyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (2c)

Colorless crystals, 0.65 g, yield 88%, mp 120–124°C.

IR (KBr) (ν_{max}, cm^{-1}): 1745 and 1720 (C=O).

MS (*m*/*z*, %): 378 (M^+, 7).

Anal. Calcd for $C_{17}H_{18}N2O_8$ (378.3): C, 53.97; H, 4.79; N, 7.41%. Found: C, 54.1; H, 4.7; N, 7.5%.

^{1}H NMR (500.1 MHz, $CDCl_3$) δ 1.47 (3 H, q, $^3J_{HH}$ 7 Hz, CH_3), 3.52 and 3.82 (6 H, 2 s, 2 OMe), 4.87 (2 H, q, $^3J_{HH}$ = 7 Hz, CH_2), 6.11 (1 H, s, CH), 7.43 (1H, dd, $^3J_{HH}$ = 4 Hz), 7.56 (1H, t, $^3J_{HH}$ = 8 Hz), 7.72

(1H, br d, $^3J_{HH} = 7$ Hz), 7.83 (1H, br d, $^3J_{HH} = 8$ Hz), 8.18 (1 H, br d, $^3J_{HH} = 7$ Hz), 8.88 (1 H, br d, $^3J_{HH} = 4$ Hz) ppm.

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 15.7 (OCH_2CH_3), 51.9 and 52.7 (2 OMe), 63.0 (NCH), 68.6 (OCH_2CH_3), 113.0 (O–C=C), 121.7, 126.3, and 128.7 (3 CH, Ar), 129.3 (C), 129.5 (CH), 132.3 (C), 136.5 (CH), 144.0(C), 150.5 (CH), 154.3 (O–C=C), 162.5, 165.1, and 168.6 (3 C=O) ppm.

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