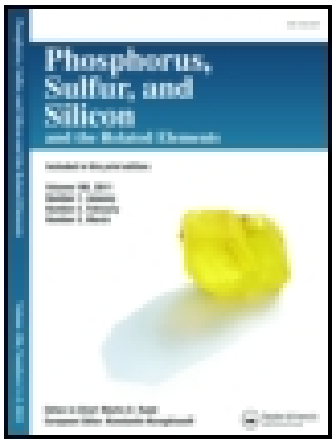

Phosphorus, Sulfur, and Silicon and the Related Elements

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Triphenylphosphine-Catalyzed Simple Synthesis of Dimethyl 1-Aryl-4-ethoxy-5-oxo-4,5-dihydro-1 H -pyrrole-2,3-dicarboxylates

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TRIPHENYLPHOSPHINE-CATALYZED SIMPLE SYNTHESIS OF DIMETHYL 1-ARYL-4-ETHOXY-5-OXO-4,5-DIHYDRO-1*H*-PYRROLE-2,3-DICARBOXYLATES

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*Ethyl 2-arylamino-2-oxo-acetates undergo a complex reaction with dimethyl acetylenedicarboxylate in the presence of triphenylphosphine to produce dimethyl 1-aryl-4-ethoxy-5-oxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates in good yields. Dynamic NMR study of dimethyl 1-(2-methylphenyl)-4-ethoxy-5-oxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate shows a fairly high energy barrier ($\Delta G^{\neq} = 53.2$ kJmol^{-1}) for rotation around the N-aryl single bond, which leads to an observable atropisomerism.*

Keywords: Acetylenic ester; NH-acid; restricted rotation; stereochemistry; triphenylphosphine

INTRODUCTION

It is perhaps unnecessary to emphasize the importance of the pyrrole nucleus in organic chemistry, especially in natural products such as chlorophyll, hemoglobin, bile pigments and mold metabolites. *N*-Substituted 2-pyrrolines are an important class of heterocyclic compounds that exhibit biological activity[1] and serve as useful synthetic intermediates.[2,3] Despite their wide applicability, available routes for the synthesis of 2-pyrrolin-5-ones are limited.[4–6] As part of our current studies on the development of new routes to heterocyclic and carbocyclic systems,[7–10] we now report a simple one-pot synthesis of highly functionalized 2-pyrrolin-5-ones **2**. Thus, reaction of ethyl 2-arylamino-2-oxo-acetates **1** with dimethyl acetylenedicarboxylate (DMAD) in the

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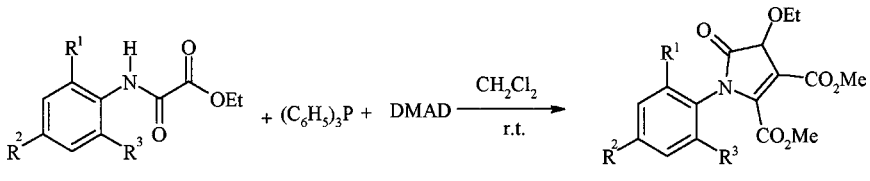


1,2	R^1	R^2	R^3	% Yield of **2**
a	Me	H	H	85
b	Me	H	Me	90
c	Cl	Cl	H	90

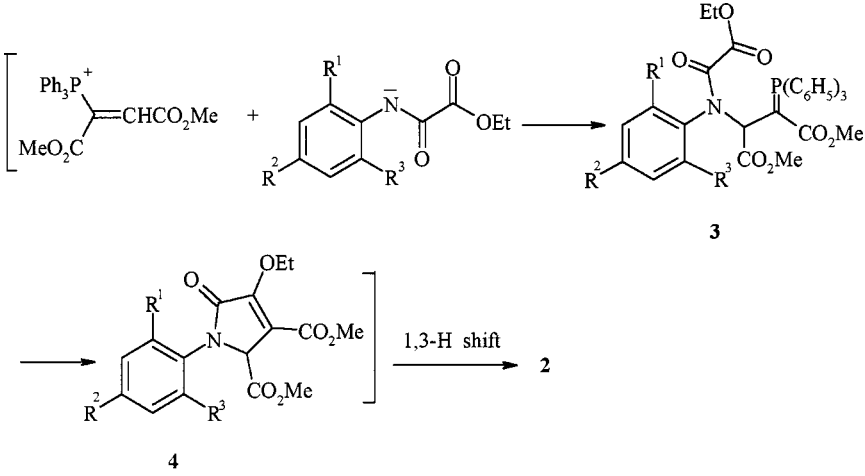
SCHEME 1

presence of triphenylphosphine leads to the corresponding dimethyl 1-aryl-4-ethoxy-5-oxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates **2a–c** in good yields (see Scheme 1).

RESULTS AND DISCUSSION

The reaction of ethyl 2-arylamino-2-oxo-acetates (**1**) with DMAD in the presence of triphenylphosphine proceeded spontaneously at room temperature in dichloromethane and was finished within 24 h. ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of dimethyl 1-aryl-4-ethoxy-5-oxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates (**2**). 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 4,5-dihydropyrrole derivative **2** may be regarded as the product of an intramolecular Wittig reaction. Such addition-cyclization products apparently result from an initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by ethyl 2-aryl-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 **4**. Compound **4** apparently isomerizes under the reaction conditions employed to produce the 4,5-dihydropyrrole isomer **2** (see Scheme 2).



SCHEME 2

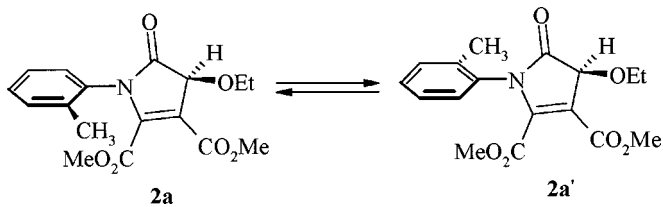
The structures of compounds **2a–c** were deduced from their elemental analyses and their IR, ^{1}H, and ^{13}C NMR spectra. The mass spectra of these compounds are fairly similar, as expected, and confirm their molecular weights. Initial fragmentations involve loss from or complete loss of the side chains and scission of the heterocyclic ring system. ^{13}C NMR spectroscopy was used to distinguish structure **2** from the primary product, 2,5-dihydropyrrole derivative **4**. Thus, the ^{13}C NMR spectrum of each of the isolated products exhibited a methine carbon resonance at about $\delta = 69$. The chemical shift for the methine carbon in **4** is expected to appear at about $\delta = 52$–56.[13,14]

The ^{1}H NMR spectrum of **2a** exhibited four single sharp lines, readily recognized as arising from methyl ($\delta = 3.65$ and 3.84 ppm) and methine ($\delta = 5.15$ ppm) protons, along with characteristic multiplets for the ethoxy and phenyl groups. The ^{13}C NMR spectrum of **2a** showed seventeen distinct resonances in agreement with the 4,5-dihydropyrrole structure. The ^{1}H and ^{13}C NMR spectra of **2b** and **2c** are similar to those of **2a**, except for the ester moieties, which exhibited characteristic resonances with appropriate chemical shift.

The most noteworthy feature of the ^{1}H NMR spectrum of **2a** in $CDCl_3$ at room temperature (25°C) is the methoxy region which exhibits a slightly broad and a sharp single at $\delta = 3.65$ and 3.84 ppm respectively. At 50°C, both singlets are sharp. Decreasing the temperature results in splitting of the signal at $\delta = 3.65$ ppm ($T_c = -18 \pm 1$°C), and at −50°C, two sharp singlets ($\delta = 3.62$ and 3.68 ppm) in nearly 1:1 ratio, together with a slightly broad singlet ($\delta = 3.82$ ppm) are observed.

Although an extensive line-shape analysis in relation to the dynamic ^{1}H NMR effect observed for **2a** was not undertaken, the variable temperature spectra allowed to calculate the free energy barrier (if not the enthalpy or entropy of activation) for the dynamic NMR process in **2a**. From coalescence of the methyl proton resonances and using the expression, $k = \pi \Delta \upsilon / \sqrt{2}$, we calculate that the first-order rate constant (k) for the dynamic NMR effect in **2a** is 67 s^{-1} at 255 K. Application of the absolute rate theory with a transmission coefficient of **1** gives a free-energy of activation ($\Delta G^{\neq}$) of 53.2 × 2 kJmol^{-1}, where all known sources of errors are estimated and included.[15] The experimental data available are not suitable for obtaining meaningful values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, even though the errors in $\Delta G^{\neq}$ are not large.[16]

The dynamic NMR effect observed for **2a** can be attributed to restricted rotation around the aryl-nitrogen single bond as a result of the steric effect of the methyl group (see Scheme 3), which exhibits a sharp singlet at room temperature, and two singlets ($\delta = 2.205$ and 2.223 ppm) in 1:1 ratio at −60°C ($T_c = 245$ K). For compound **2b**, with two methyl groups, rotation around the aryl-nitrogen bond is slow at ambient temperature and two sharp singlets ($\delta = 2.02$ and 2.12 ppm) are observed for the CH_3-aryl groups, together with two sharp singlets ($\delta = 3.56$ and 3.74 ppm) for the methoxy protons. These signals exhibit little broadening at 50°C, the highest temperature investigated. The ^{1}H NMR spectrum of **2c** shows two sharp singlets ($\delta = 3.58$ and 3.74 ppm) for the methoxy groups. The high-field signal exhibits little broadening at −60°C, the lowest temperature investigated. Thus, rotation around the aryl-nitrogen bond in **3c** is fast on the NMR timescale at −60°C, as a result of smaller steric interaction of the chlorine atom compared to that of the methyl group in **2a**.



SCHEME 3

In summary, the reaction of ethyl 2-arylamino-2-oxo-acetates with dimethyl acetylenedicarboxylate in the presence of triphenylphosphine provide a simple one-pot entry into the synthesis of polyfunctionalized 5-oxo-4,5-dihydro-1*H*-pyrrole derivatives of potential synthetic interest. Dynamic NMR effects are observed in the ^{1}H NMR spectra of **2a** and are attributed to restricted rotation around the aryl-nitrogen bond.

EXPERIMENTAL

Melting points were measured on Buchi B-540 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with Bruker DRX-500 AVANCE instrument with $CDCl_3$ as solvent at 500.1 and 125.8 MHz, respectively. The mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Ethyl oxalyl chloride, triphenylphosphine, dimethyl acetylenedicarboxylate, and aniline derivatives were obtained from Fluka (Buchs Switzerland) and used without further purification.

Preparation of Ethyl Arylamino-2-oxo-acetates (1)

General Procedure

To a magnetically stirred solution of the aniline derivative (2 mmol) and 0.20 g of triethylamine (2 mmol) in 20 mL of CH_2Cl_2 was added, dropwise, a solution of 0.27 g of ethyl oxalyl chloride (2 mmol) in 10 mL of CH_2Cl_2. After 24 h stirring at reflux, the mixture was washed three times with the same volume of 6 M HCl solution. The organic phase was dried over $MgSO_4$ and evaporated. The product was recrystalized from ethanol.

Ethyl 2-(2-Methylanilino)-2-oxo-acetate (1a)

White powder, 0.34 g, m.p. 35–36°C, yield 85%. IR (KBr) (υ_{max}/cm^{-1}): 1731 and 1706 (C=O), 3255 (N–H). Analyses: Calcd for $C_{11}H_{13}NO_3$ (208.1): C, 63.75; H, 6.32; N, 6.75%. Found: C, 63.5; H, 6.4; N, 6.7%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (3 H, t, $^3J_{HH} = 7.2$ Hz, CH_3); 2.25 (3 H, s, CH_3); 4.34 (2 H, q, $^3J_{HH} = 7.2$ Hz, CH_2); 7.04–7.19 (3 H, m, Ar); 7.93 (1 H, d, $^3J_{HH} = 7.4$ Hz, CH_{ortho}); 8.83 (H, s, NH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.98 and 17.44 (2 CH_3); 63.63 (OCH_2); 121.83 (C-6); 125.88 (C-4); 126.92 and 128.67 (C-3,5); 130.60 (C-2); 134.42 (C-1); 153.99 and 161.10 (2 C=O).

Ethyl 2-(2,6-Dimethylanilino)-2-oxo-acetate (1b)

White powder, 0.40 g, m.p. 75–76°C, yield 90%. IR (KBr) (υ_{max}/cm^{-1}): 1724 and 1674 (C=O); 1523 (N–H). Analyses: Calcd for $C_{12}H_{15}NO_3$ (221.2): C, 65.14; H, 6.83; N 6.33%. Found: C, 65.3; H, 6.9; N, 6.3%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (3 H, t, $^3J_{HH} = 7.1$ Hz, CH_3); 2.22 (6 H, s, CH_3); 4.38 (2 H, q, $^3J_{HH} = 7.1$ Hz, CH_2); 7.06–7.14

(3 H, m, Ar); 8.47 (1 H, s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.01 and 18.43 (2 CH_3); 63.56 (CH_2); 127.93 (C-4); 128.36 (C-3,5); 132.27 (C-2,6); 135.04 (C-1); 154.68 and 160.94 (C=O).

Ethyl 2-(2,4-Dichloroanilino)-2-oxo-acetate (1c)

White powder, 0.48 g, m.p. 117–118°C, yield 90%. IR (KBr) (υ_{max}/cm^{-1}): 1723 (C=O); 1521 (N–H). Analyses: Calcd for $C_{10}H_9NO_3Cl_2$ (262.1): C, 45.82; H, 3.46; N, 5.34%. Found: C, 46.0; H, 3.5; N, 5.4% ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.25 (3 H, t, $^3J_{HH} = 7.2$ Hz, CH_3); 4.25 (2 H, q, $^3J_{HH} = 7.2$ Hz, CH_2); 7.03–7.24 (2 H, m, Ar); 8.21 (1 H, d, $^3J_{HH} = 8.8$ Hz, H_{ortho}); 9.23 (1 H, s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$); δ 14.07 (CH_3); 64.02 (CH_2); 121.81(C-6); 124.03 (C-2); 128.14 (C-5); 129.02 (C-3); 130.43 (C-4); 132.17 (C-1); 153.83 and 160.30 (C=O).

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

General Procedure

To a magnetically stirred solution of **1** (2 mmol) and 0.78 g of triphenylphosphine (3 mmol) in 20 mL of CH_2Cl_2 was added a solution of 0.31 g of dimethyl acetylenedicarboxylate (2.2 mmol) in 3 mL of CH_2Cl_2 at 0°C. After 24 h the solvent was removed under reduced pressure and the viscous residue was purified by column chromatography (silica gel, 70-230 mesh, CH_2Cl_2 eluent). The solvent was removed and the product was obtained as white crystals, 0.46 g, m.p. 78–79°C, yield 70%. IR (KBr) (υ_{max}/cm^{-1}): 1749, 1708, and 1636 (C=O). MS, *m/z* (%): M$^+$, 333 (12), 274 (19), 91 (62), 118 (100). Analyses: Calcd for $C_{17}H_{19}NO_6$ (333.3): C, 61.26; H, 5.74; N, 4.20%. Found: C, 61.3; H, 5.8; N, 4.2%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (3 H, t, $^3J_{HH} = 7.0$ Hz, CH_3); 2.24 (3 H, s, CH_3); 3.65 and 3.84 (2 OCH_3); 4.88 (2 H, q, $^3J_{HH} = 7.0$ Hz, CH_2); 5.15 (1 H, s, CH); 7.10–7.31 (4 H, m, Ar). ^{13}C NMR (20.1 MHz, $CDCl_3$): δ 15.68 and 17.83 (2 CH_3); 51.92 and 52.74 (2 OCH_3); 62.52 (CH_2); 68.62 (CH); 112.79 (C); 126.91 (C-6); 127.26 (C-4); 128.90 and 131.35 (C-3,5); 134.36 (C-2); 136.56 (C-1); 154.34 (C); 162.18, 163.60 and 168.19 (C=O).

Dimethyl 1-(2,6-Dimethylphenyl)-4-ethoxy-5-oxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (2b)

White powder, 0.66 g, m.p. 78–79°C, yield 95%. IR (KBr) (υ_{max}/cm^{-1}): 1751, 1714, and 1694 (C=O). MS, *m/z* (%): M$^+$, 347 (16.7), 348 (100), 288 (67); 105 (18.7), 228 (35). Analyses: Calcd for $C_{18}H_{21}NO_6$ (347.3): C, 62.24; H, 6.09; N, 4.03%. Found: C, 62.3; H, 6.6; N, 3.9%. ^{1}H NMR

(500 MHz, $CDCl_3$): δ 1.34 (3 H, t, $^3J_{HH} = 7.0$ Hz, CH_3); 2.02 and 2.12 (2 CH_3); 3.56 and 3.74 (2 OCH_3); 4.71 (2 H, q, $^3J_{HH} = 7.0$ Hz, CH_2); 5.12 (1 H, s, CH); 7.14–7.25 (3 H, m, Ar). ^{13}C NMR (128.5 MHz, $CDCl_3$): δ 15.67, 17.78 and 18.04 (3 CH_3); 51.99 and 52.76 (2 OCH_3); 61.35 (CH_2); 68.73 (CH); 112.53 (C); 128.92 (C-4); 132.97 (C-3,5); 135.74 (C-1); 137.59 (C-2,6); 154.39 (C); 162.27, 163.81 and 167.96 (C=O).

Dimethyl 1-(2,4-Dichlorophenyl)-4-ethoxy-5-oxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (2c)

White powder, 0.48 g, m.p. 85–86°C, yield 70%. IR (KBr) (υ_{max}/cm^{-1}): 1755, 1722, and 1689 (C=O). MS, *m/z* (%): M^+, 388 (38), 400 (25), 268 (100), 145 (14.6), 59 (65). Analyses Calcd for $C_{16}H_{15}NO_6Cl_2$ (388.2): C, 49.50; H, 3.89; N, 3.60%. Found: C, 49.6; H, 3.9; N, 3.6%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (3 H, t, $^3J_{HH} = 7.0$ Hz, CH_3); 3.58 and 3.74 (2 OCH_3); 4.74 (2 H, q, $^3J_{HH} = 7.0$ Hz, CH_2); 5.18 (1 H, s, CH); 7.12 (1 H, d, $^3J_{HH} = 8.5$ Hz, H_{ortho}); 7.23–7.26 (1 H, d, d, $^3J_{HH} = 8.5$ Hz, $^4J_{HH} = 2.3$ Hz, H_{meta}); 7.44 (1 H, d, $^4J_{HH} = 2.3$ Hz, H_{meta}). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 15.47 (CH_3); 51.89 and 52.82 (2 OCH_3); 61.40 (CH_2); 68.60 (CH); 112.89 (C); 130.35 (C-6); 130.99 and 131.58 (C-3,5); 133.24 (C-2); 133.56 (C-4); 135.45 (C-1); 153.76 (C); 161.92, 163.99 and 167.58 (C=O).

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