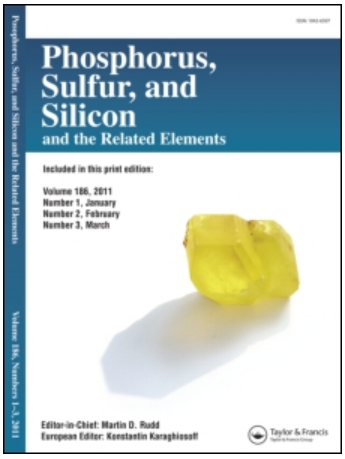

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Triphenylphosphine-Mediated Reaction Between Dimethyl Acetylenedicarboxylate and NH-Acids Derived from Diaminobenzenes

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Triphenylphosphine-Mediated Reaction Between Dimethyl Acetylenedicarboxylate and NH-Acids Derived from Diaminobenzenes

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Protonation of the 1:1 adduct produced in the reaction between triphenylphosphine and dimethyl acetylenedicarboxylate with ethyl 2-[(2-{[2-(ethyloxy)-2-oxoacetyl]amino}phenyl}amino]-2-oxoethanoate leads to a vinylphosphonium salt, which undergoes an intermolecular Wittig reaction to produce dimethyl 4-(acetyloxy)-1-(2-{[2-(ethyloxy)-2-oxoacetyl]amino}phenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate. Using ethyl 2-[(3-{[2-(ethyloxy)-2-oxoacetyl]amino}phenyl)amino]-2-oxoethanoate or ethyl 2-[(4-[2-(ethyloxy)-2-oxoacetyl]amino}phenyl)amino]-2-oxoethanoate as an NH acid produces dimethyl 4-(acetyloxy)-1-(3-{3-(ethyloxy)-4,5-bis[(methyloxy)carbonyl]-2-oxo-2,5-dihydro-1H-pyrrol-1-yl}phenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate or dimethyl 4-(ethyloxy)-1-(4-{3-(ethyloxy)-4,5-bis[(methyloxy)carbonyl]-2-oxo-2,5-dihydro-1H-pyrrol-1-yl}-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate.

Keywords Acetylenic ester; intramolecular Wittig rection; pyrrole derivatives; triphenylphosphine

INTRODUCTION

Simple nitrogen-containing heterocycles receive considerable attention in the literature as a consequence of their exciting biological properties and their role as pharmacophores of historical importance.[1] Of these heterocycles, the synthesis, reactions, and biological activities of pyrrole-containing molecules stand as an area of research in heteroaromatic chemistry, and this structural motif appears in a large number

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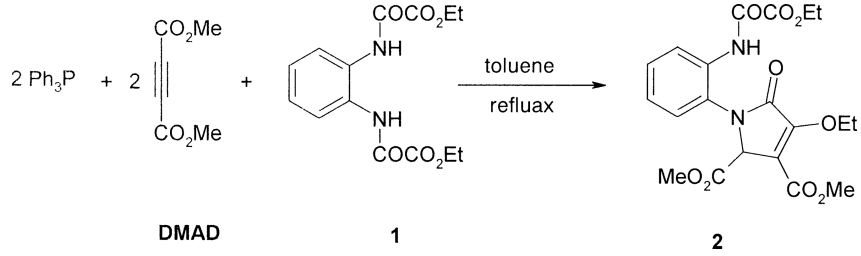
of pharmaceutical agents and natural products.[2] Accordingly, many strategies have been developed for the preparation of pyrroles.[2,3] Five-membered ring lactams have been used in routes to various alkaloids[4] and are suitable precursors for γ-amino acids such as statine and its analogues.[5] There are many examples of pyrroline-containing natural products with interesting pharmacological activates. Typical examples are the platelet aggregation inhibitor PI-091 and the antitumor alkaloide Jatropham.[6,7] As part of our current studies on the development of new routes to heterocyclic systems,[8] we now report that the reaction of dimethyl acetylenedicarboxylate (DMAD) with ethyl 2-[2-{[2-(ethyloxy)-2-oxoacety)]amino}phenyl}amino]-2-oxoethanoate (**1**) in the presence of triphenylphosphine leads to dimethyl 4-(acetyloxy)-1-(2-{[2-(ethyloxy)-2-oxoacetyl]amino}-phenyl)-5-oxo-2,5-dihydro-1 *H*-pyrrole-2,3-dicarboxylate (**2**) in a 72% yield (Scheme 1). Attempts to construct another 5-oxo-2,5-dihydro-1 *H*-pyrrole moiety by reacting **2** with DMAD and triphenylphosphine were unsuccessful.



DMAD 1 2

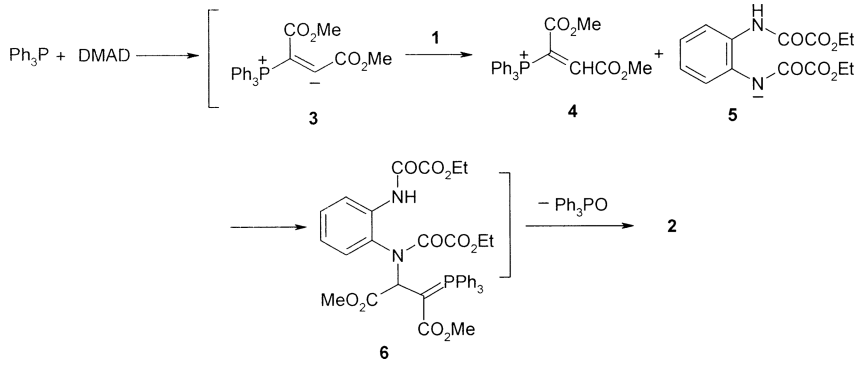
SCHEME 1

RESULTS AND DISCUSSION

The reaction of DMAD with **1** in the presence of triphenylphosphine proceeded spontaneously room temperature in CH_2Cl_2 and was finished within 24 h. ^1H and ^{13}C NMR spectra of the crude products clearly indicated the formation of **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.[8–10] Thus, the 2,5-dihydropyrrole derivative **2** may be regarded as the product of an intramolecular Wittig reaction.[10] Such an addition-cyclization product apparently results from an initial addition of triphenylphosphine to DMAD and the subsequent protonation of the 1:1 adduct **3** by **1** (Scheme 2). Then the positively charged ion **4** is attacked by the nitrogen atom of the conjugated

base of the NH-acid to form the phosphorane **6**, which is converted to the 2,5-dihydropyrrole derivative **2**.



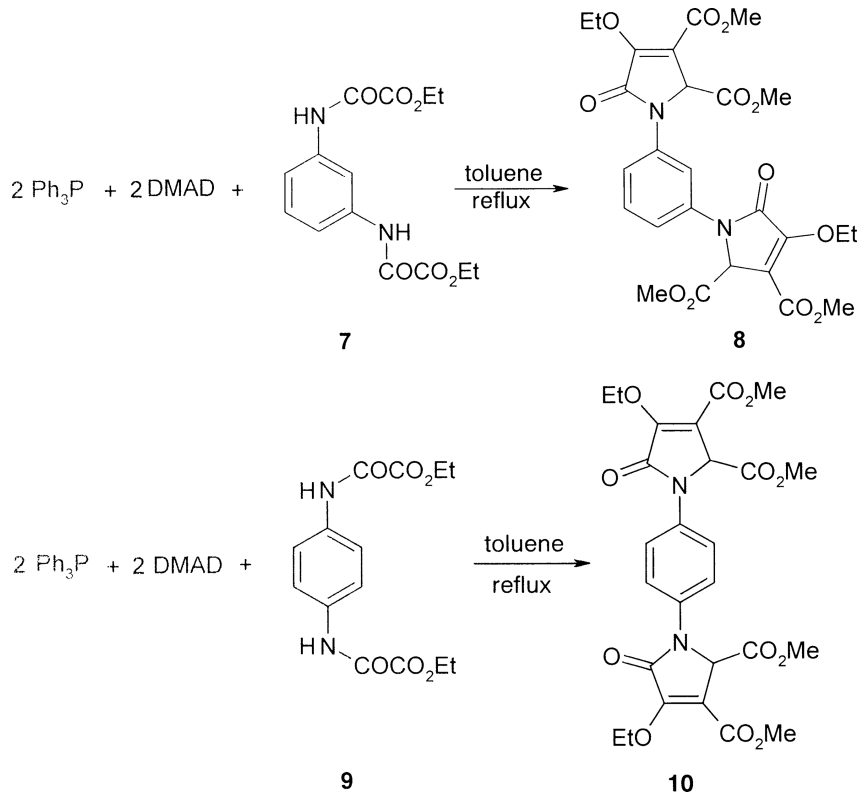
SCHEME 2

The structure of **2** was deduced from its elemental analyses and its IR, ^{1}H, and ^{13}C NMR spectra. The mass spectrum of this compound confirms its molecular weight. Initial fragmentation involves the loss from or the complete loss of the side chains and the scission of the heterocyclic ring system.

The ^{1}H NMR spectrum of **2** exhibits three sharp lines for methoxy ($\delta = 3.61$ and 3.84 ppm) and methine ($\delta = 5.31$ ppm) protons. The aryl moiety shows characteristic signals in the appropriate region of the spectrum. The ^{13}C NMR spectrum of **2** shows 18 sharp signals in agreement with the proposed structure.

When the reaction between DMAD and triphenylphosphine was carried out in the presence of ethyl 2-[(3-{[2-(ethyloxy)-2-oxoacetyl]-amino}phenyl)amino]-2-oxoethanoate (**7**) or ethyl 2-[(4-{[2-(ethyloxy)-2-oxoacetyl]amino}phenyl)amino]-2-oxoethanoate (**9**) as an NH-acid, the corresponding dimethyl 4-(acetyloxy)-1-(3-3-(ethyloxy)-4,5-bis[(methyloxy)carbonyl]-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl}phenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (**8**) or dimethyl 4-(ethyloxy)-1-(4-{3-(ethyloxy)-4,5-bis[(methyloxy) carbonyl]-2-oxo-2,5- dihydro-l*H* pyrrol-l-yl}-5-oxo-2,5-dihydro-l*H*-pyrrole-2,3-dicarboxylate (**10**) was obtained in good yield (see Scheme 3).

The ^{1} H and ^{13}C NMR spectra of **8** and **10** are similar to those of **2**. The proposed structures for these compounds were confirmed by their elemental analyses and IR spectra. The mass spectra of these isomeric structures are fairly similar and confirm their molecular weights.



SCHEME 3

In conclusion, the presented reaction gives a simple one-pot entry into the synthesis of polyfunctionalized 5-oxo-2,5-dihydro-1*H*-pyrrole derivatives of potential synthetic interest.

EXPERIMENTAL

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. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Bruker Avance DPX-300 MHz NMR instrument with $CDCl_3$ as a solvent. Chemical shifts (δ) are reported relative to TMS as the internal standard. The reagents and solvents used in this work were obtained from Fluka and used without further purification.

Preparation of 1,7, and 9 Examplified on Ethyl 2-[(2-{[2-(Ethyloxy)-2-oxoacetyl]amino}phenyl}amino]-2-oxoethanoate (1): Typical Procedure

To a stirred solution of 1,2-diaminobenzene (1.08 g, 10 mmol) in dry diethyl ether (30 mL) was added, dropwise, a solution of ethyl oxalyl chloride (3.0 g, 22 mmol) in 10 mL of dry diethyl ether at 10°C over 10 min. The reaction mixture was allowed to stand at r.t. for 24 h. The solvent was removed under reduced pressure and the viscous residue was crystallized from ethanol to produce **1** as pale yellow crystals; m.p. 162–165°C; yield: 2.7 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 3305 (N—H), 1720 and 1728 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta_H = 1.44$ (6 H, t, $^3J_{HH} = 7.2$ Hz, 2 CH_3), 4.43 (4 H, q, $^3J_{HH} = 7.2$ Hz, 2 OCH_2), 7.34–7.76 (4 H, m, C_6H_4), 9.32 (2 H, s, 2 NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$,): $\delta_C = 14.3$ (2 CH_3), 64.2 (2 OCH_2), 125.3 (2 CH), 127.8 (2 CH), 129.2 (2 C), 155.4 (2 C=O), 160.6 (2 C=O) ppm.

Ethyl 2-[(3-{[2-(Ethyloxy)-2-Oxoacetyl]amino}phenyl)amino]-2-oxoethanoate (7)

Pale yellow crystals; m.p. 121–123°C; yield: 2.8 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 3301 (N—H), 1718 and 1723 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta_H = 1.38$ (6 H, t, $^3J_{HH} = 7$ Hz, 2 CH_3), 4.38 (4 H, q, $^3J_{HH} = 7$ Hz, 2 OCH_2) 7.34–7.53 (3 H, m, 3 H of C_6H_4), 8.03 (1 H, t, $^4J_{HH} = 2$ Hz, H of C_6H_4), 9.09 (2 H, s, 2 NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta_C = 14.3$ (2 CH_3), 64.2 (2 OCH_2), 111.6 (2 CH), 117.2 (CH), 130.4 (CH), 137.5 (2 C), 154.5 (2 C=O), 161.1 (2 C=O) ppm.

Ethyl 2-[(4-{[2-(Ethyloxy)-2-oxoacetyl]amino}phenyl)amino]-2-oxoethanoate (9)

Pale yellow crystals; m.p. 203–205°C; yield: 2.9 g (93%).

IR (KBr) (ν_{max}/cm^{-1}): 3304 (N—H), 1714 and 1725 (C=O). ^{1}H NMR (300 MHz, $CHCl_3$): $\delta_H = 1.45$ (6 H, t, $^3J_{HH} = 7.2$ Hz, 2 CH_3), 4.45 (4 H, q, $^3J_{HH} = 7.2$ Hz, 2 OCH_2), 7.69 (4 H, s, C_6H_4), 8.91 (2 H, s, 2 NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$.): $\delta_C = 14.3$ (2 CH_3), 64.2 (2 OCH_2), 120.9 (4 CH), 134.0 (2 C), 154.1 (2 C=O), 161.3 (2 C=O) ppm.

Preparation of 2, 8, and 10 Examplified on Dimethyl 4-(Acetyloxy)-1-(2-{[2-ethyloxy)-2-oxoacetyl]amino}phenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate(2): Typical Procedure

To a stirred solution of **1** (0.6 g, 2 mmol) and triphenylphosphine (0.52 g, 2 mmol), in 10 mL of toluene was added, dropwise, a solution of DMAD (0.28 g, 2 mmol) in 5 mL of toluene at 20°C over 10 min. The reaction

mixture was refluxed for 8 h. The solvent was removed under reduced pressure and the viscous residue was purified by preparative TLC on silica gel (Merck silica gel DC-Fertigplatten 60/Kieselgur F_{254}) 20×20 cm plates using $CHCl_3$ and EtOAc (10:1) as an eluent. Zones were detected by the quenching of indicator fluorescence upon exposure to 366 nm of UV light. The product was obtained by the extraction of the silica gel with CH_2Cl_2 to produce a yellow powder; m.p. 120–123°C; yield: 0.6 g (72%). IR (KBr) (ν_{max}/cm^{-1}): 1644 and 1717 (C=O). ^1H NMR (300 MHz, $CHCl_3$): $\delta_H = 1.43$ (3 H, t, $^3J_{HH} = 7.1$ Hz, CH_3), 1.49 (3 H, t, $^3J_{HH} = 7.1$ Hz, CH_3), 3.61 (3 H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.42 (2 H, q, $^3J_{HH} = 7.1$ Hz, OCH_2), 4.86 (2 H, q, $^3J_{HH} = 7.1$ Hz, OCH_2), 5.31 (1 H, s, CH), 7.29–7.43 (3 H, m, 3 H of C_6H_4), 8.20 (1 H, d, $^3J_{HH} = 8.0$ Hz, H of C_6H_4), 9.42 (1H, s, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta_C = 14.3$ (CH_3), 16.1 (CH_3), 52.5 (OCH_3) 53.8 (OCH_3), 62.8 (OCH_2), 63.9 (CH), 69.2 (OCH_2), 113.9 (O–C=*C*), 124.9 (CH), 126.8 (CH), 126.9 (CH 127.4 (CH), 130.1 (C), 133.6 (C) 153.7 (O–C=C), 154.8 (C=O), 160.7 (C=O), 162.3 (C=O), 164.3 (C=O), 168.45 (C=O) ppm. MS (El, 70 eV): m/z (%) = 436 ($M^+ + 1$, 7), 326 (100), 298 (74), 230 (58), 57 (47), 41 (38). Anal. calcd. of $C_{20}H_{22}N_2O_9$ (436.4): C, 55.04; H, 5.54; N, 6.42. Found: C, 55.26; H, 5.71; N, 6.46%.

Dimethyl 4-Etyloxy-1-{3-[3-ethyloxy-4,5-bis(methyloxycarbonyl)-2-oxo-2,5-dihydro-1H-pyrrol-1-yl]phenyl}-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (8)

Yellow powder; m.p. 111–114°C; yield: 0.66 g (60%). IR (KBr) (ν_{max}/cm^{-1}): 1651 and 1715 (C=O). ^1H NMR (300 MHz, $CHCl_3$): $\delta_H =$ 1.43 (6 H, t, $^3J_{HH} = 7.2$ Hz, 2 CH_3), 3.68 (6 H, s, 2 OCH_3), 3.82 (6 H, s, 2 OCH_3), 4.80 (4 H, q, $^3J_{HH} = 7.2$ Hz, 2 OCH_2), 5.37 (2 H, s, 2 CH), 7.42–7.47 (3 H, m, 3 H of C_6H_4), 7.90 (1 H, t,$^4J_{HH} = 2$ Hz, H of C_6H_4), ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta_C = 16.1$ (2 CH_3), 52.5 (2 OCH_3), 53.6 (2 OCH_3), 61.2 (2 CH), 69.3 (2 OCH_2), 112.2 (O–C=*C*), 114.9 (2 CH), 119.4 (CH), 130.4 (CH), 137.7(2 C), 154.5 (2 O–C=*C*), 162.0 (C=O), 164.0 (C=O), 168.4 (C=O) ppm. MS (El, 70 eV): m/z (%) = 562 ($M^+ + 1$, 7), 326 (100), 298 (74), 230 (58), 57 (47), 41 (38). Anal. calcd. for $C_{26}H_{28}N_2O_{12}$ (562.5): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.68; H, 5.01; N, 5.02%.

Dimethyl 4-Ethoxy-1-{4-[3-ethoxy-4,5-bis(methoxycarbonyl)-2-oxo-2,5-dihydro-1*H*-pyrrol-1-Yl]phenyl}-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (10)

Yellow powder; m.p. 117–120°C; yield: 0.7 g (63%). IR (KBr) (ν_{max}/cm^{-1}): 1648 and 1717 (C=O). ^1H NMR (300 MHz, $CHCl_3$): $\delta_H = 1.42$ (6 H, t,

$^3J_{HH}$ = 7.2 Hz, 2 CH_3), 3.65 (6 H, s, 2 OCH_3), 3.88 (6 H, s. 2 OCH_3), 4.81 (4 H, q, $^3J_{HH}$ = 7.2 Hz, 2 OCH_2), 5.35 (2H, s, 2 CH) 7.62 (4 H, s, C_6H_4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C = 16.0 (2 CH_3), 52.4 (2 OCH_3), 53.5 (2 O CH_3), 61.1 (2 CH), 62.2 (2 OCH_2), 112.1 (2 O–C=*C*), 122.3 (4 CH), 134.6 (2 C), 154.6 (2 O–*C*=C), 162.4 (C=O), 163.9 (C=O), 168.4 (C=O) ppm. MS (El, 70 eV): m/z (%) = 562 (M^+ + 1, 7), 326 (100). 298 (74), 230 (58), 57 (47), 41 (38). Anal. Calcd. for $C_{26}H_{28}N_2O_{12}$ (562.5): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.74; H, 5.05; N, 5.04%.

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