Efficient synthesis of highly functionalised 5-oxo-4,5-dihydro-1*H*-pyrroles and 5-oxo-2,5-dihydro-1*H*-pyrroles derivatives

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Methyl 2-(2-benzoylphenylamino)-2-oxoacetate and dimethyl 2,2′-(4,4′-methylenebis(4,1- phenylene)bis(azanediyl)) bis(2-oxoacetate) undergo a smooth reaction with triphenylphosphine and dialkyl acetylenedicarboxylates to produce corresponding highly functionalised 5-oxo-4,5-dihydro-1*H*-pyrroles and 5-oxo-2,5-dihydro-1*H*-pyrroles derivatives.

Keywords: NH-acid, dialkyl acetylenedicarboxylates, triphenylphosphine, 5-oxo-4,5-dihydropyrrole, 5-oxo-2,5-dihydropyrrole

N-Substituted pyrrolines derivatives are important starting materials for the preparation of a variety of biologically active compounds due to their ability to react as acceptors in conjugate addition reactions of organocuprates, enolates and nitrogen nucleophiles, beyond suffering hydroxylation, epoxidation, cyclopropanation and cycloaddition reactions.[1–6] Five-membered ring lactams have successfully been used in routes to various alkaloids and are suitable precursors for unusual γ-amino acids such as statine and its analogues.[7–17]

Despite their wide applicability, available routes for the synthesis of *N*-substituted pyrrolines derivatives are limited. As part of our current studies on the development of new routes to heterocyclic and carbocyclic systems, we now report a facile one-pot synthesis of highly functionalised 5-oxo-4,5-dihydro-1*H*-pyrroles and 5-oxo-2,5-dihydro-1*H*-pyrroles derivatives. Thus, reactions of compounds **3** and **7** with dialkyl acetylenedicarboxylate in the presence of triphenylphosphine lead to the corresponding synthetic compounds **4a**, **4b**, **8a**, **8b** and **9** in fairly good yields (Schemes 1 and 3).

Compound **4** is readily prepared via an intramolecular Wittig reaction. Thus, triphenylphosphine and dialkyl acetylenedicarboxylates (**2**) in the presence of a strong NH-acid, such as methyl 2-(2-benzoylphenylamino)-2-oxoacetate undergo a smooth reaction at ambient temperature to produce a phosphorus ylide. This, in turn, experiences an intramolecular Wittig reaction under the reaction conditions employed to produce dialkyl 1-(2-benzoylphenyl)-4-methoxy-5-oxo-4,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (**4**) (Scheme 1). No other products could be detected by NMR spectroscopy.

The structures of compounds **4a** and **4b** were deduced from their elemental analyses and their high-field ^{1}H and ^{13}C NMR and IR spectral data. The mass spectra of these compounds displayed molecular ion peaks at *m/z* = 411 and 439. Although we have not yet established the mechanism of the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates in the presence of methyl 2-(2-benzoylphenylamino)-2-oxoacetate in an experimental manner, but a possible explanation of reactions is proposed in Scheme 2.

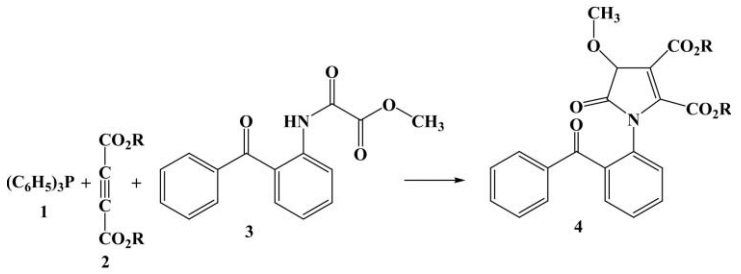
On the basis of the well-established chemistry of trivalent phosphorus nucleophiles, it is reasonable to assume that the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by the NH-acid leads to compound **4**. Then, the positively charged ion might be attacked by the conjugate base of the NH-acid to form phosphorane (**5**), which is converted to pyrrole derivative (**6**). Compound **6** apparently isomerises under the reaction conditions to produce the 5-oxo-4,5-dihydropyrrole ring system (**4**) (Scheme 2).

^{1}H NMR spectroscopy was used to distinguish structure **4** from the primary adduct, the 5-oxo-2,5-dihydropyrrole derivative (**6**). Thus, each of the products exhibited a methine hydrogen resonance at about δ = 5.16 and 5.12 ppm. The chemical shift of the methine hydrogen in 6 is expected to appear at about δ = 5.3–5.5 ppm.[18,19]

We have also used dimethyl 2,2′-(4,4′-methylenebis(4,1-phenylene)bis(azanediyl))bis(2-oxoacetate) (**7**) in this reaction (Scheme 3).

The reaction of dialkyl acetylenedicarboxylates with dimethyl 2,2′-(4,4′-methylenebis(4,1-phenylene)bis(azanediyl)) bis(2-oxoacetate) in the presence of triphenylphosphine proceeded spontaneously at ambient temperature in chloroform and was completed within a few hours. ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of **8a**, **8b** and **9** (Scheme 3).

On the basis of the chemistry of trivalent phosphorus nucleophiles it is reasonable to assume that compound **8** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by dimethyl



4	R
a	-CH_3
b	-CH_2CH_3

Scheme 1

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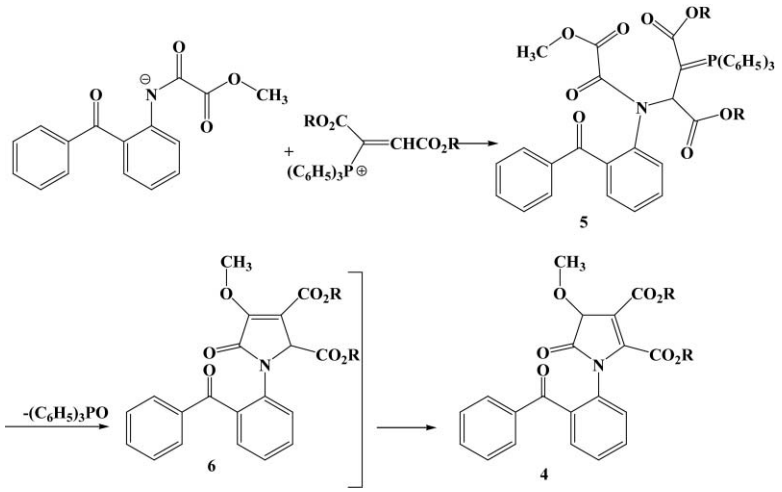
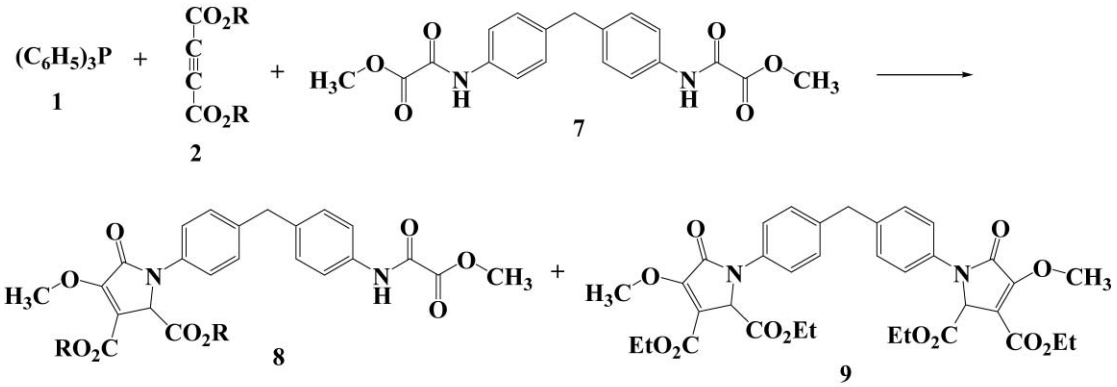


Scheme 2



8	R
a	$-CH_3$
b	$-CH_2CH_3$

Scheme 3

2,2′-(4,4′-methylenebis(4,1-phenylene)bis(azanediyl))bis(2-oxoacetate). Then, the positively charged ion is attacked by the conjugate base of the NH-acid to form phosphorane **10**, which is converted to pyrrole derivative **8**.

^{1}H NMR spectroscopy was used to distinguish structure **8** from the 5-oxo-4,5-dihydropyrrole derivative. Thus, each of the products exhibited a methine hydrogen resonance at about δ = 5.34, 5.32 and 5.33 ppm. The chemical shift of the methine hydrogen in **8** and **9** are expected to appear at about δ = 5.1–5.2 ppm.[20,21]

In addition, the reaction of diethyl acetylenedicarboxylate with **7** in the presence of triphenylphosphine in ratios of 1:1:1 and 2:1:2 produced the compounds **8b** and **9**. In this connection, when we used dimethyl acetylenedicarboxylate in place of diethyl acetylenedicarboxylate only compound **8a** was obtained.

Experimental

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. TLC and NMR indicated that there is no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-300 Avance spectrometer at 300.13 and 75.467 MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionisation potential of 20 eV. Flash chromatography columns were prepared from Merck silica gel powder.

General procedure for preparation of methyl 2-(2-benzoylphenylamino)-2-oxoacetate (**3**) To a magnetically stirred solution of the 2-aminobenzophenone (2 mmol, 0.39 g) and 0.20 g of triethylamine (2 mmol) in 20 mL of $CHCl_3$ was added, dropwise, a solution of 0.24 g of methyl chloroglyoxylate (2 mmol) in 10 mL of $CHCl_3$. 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 recrystalised from ethanol.

Methyl 2-(2-benzoylphenylamino)-2-oxoacetate (**3**): White powder, 0.485 g, m.p. 126 °C, yield 91%. IR (KBr)(ν_{max}, cm^{-1}): 3234.68 (N–H), 3075.06, 2954.72, 1728.93, 1712.02, 1633.27, 1577.97, 1445.75, 1295.81, 1264.77, 1200.89, 1170.03, 981.07, 939.92, 770.21, 710.53, 697.95. ^{1}H NMR ($CDCl_3$) δ_H: 4.00 (3H, s, OCH_3), 7.22 (1H, t, $^3J_{HH}$ = 7.6 Hz, arom), 7.50 (2H, t, $^3J_{HH}$ = 7.6 Hz, arom), 7.75 (2H, d, $^3J_{HH}$ = 7.8 Hz, arom), 7.60–7.68 (3H, m, arom), 8.70–8.73 (1H, m, arom), 12.24 (N–H). ^{13}C NMR ($CDCl_3$) δ_C: 53.98 (1C, OCH_3), 121.52, 123.64, 128.34, 130.02, 132.68, 133.65, 134.26 (9C of = CH), 124.25, 138.23, 138.57 (3C), 154.63, 160.83, 199.05 (3C=O). Anal. Calcd for $C_{16}H_{13}NO_4$ (283.28): C, 67.84; H, 4.63; N, 4.94. Found: C, 67.61; H, 4.56; N, 4.90%.

*General procedure for preparation of dimethyl 2,2′-(4,4′-methylenebis(4,1-phenylene)bis(azanediyl))bis(2-oxoacetate) (***7***)*

To a magnetically stirred solution of the 4,4′-methylenedianiline (2 mmol, 0.40 g) and 0.40 g of triethylamine (4 mmol) in 20 mL of $CHCl_3$ was added, dropwise, a solution of 0.49 g of methyl chloroglyoxylate (4 mmol) in 10 mL of $CHCl_3$. 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 recrystallised from ethanol.

Dimethyl 2,2′-(4,4′-methylenebis(4,1-phenylene)bis(azanediyl))bis (2-oxoacetate) (**7**): White powder, 0.62 g, m.p. 140 °C, yield 84%. IR (KBr)(ν_{max}, cm^{-1}): 3338.46 (N–H), 3041.31, 2951.46, 2925.86, 1754.79, 1731.67, 1715.67, 1686.17, 1523.58, 1413.90, 1297.85, 1267.11, 1162.64, 984.21, 764.11, 703.65. ^{1}H NMR ($CDCl_3$) δ_H: 3.97 (6H, s, $2OCH_3$), 3.97 (2H, s, CH_2), 7.19 (4H, d, $^3J_{HH}$ = 8.4 Hz, arom), 7.57 (4H, $^3J_{HH}$ = 8.4, arom), 8.82 (2 N-H). ^{13}C NMR ($CDCl_3$) δ_C: 38.74 (1C of CH_2), 54.02 (2C of CH_3), 120.07 and 129.63 (8C of =CH), 134.46 and 138.26 (4C), 153.48 and 161.49 (4C=O). Anal. Calcd for $C_{19}H_{18}N_2O_6$ (370.36): C, 61.62; H, 4.90, 7.56. Found: C, 61.55; H, 4.81; N, 7.49%.

General procedure for preparation of **4a, 4b, 8a, 8b** *and* **9**

To a magnetically stirred solution of N–H acid (1 mmol) and triphenylphosphine (1 mmol) in 20 mL of $CHCl_3$ was added a solution of dialkyl acetylenedicarboxylate (1 mmol) in 3mL of $CHCl_3$ at −5 °C over 10 min. The reaction mixure was then allowed to warm to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography using petroleum ether:ethyl acetate (10:2) as eluent. The solvent was removed under reduced pressure to afford the products.

Dimethyl 1-(2-benzoylphenyl)-4-methoxy-5-oxo-4,5-dihydro-1H-pyrrole-2,3-dicarboxylate (**4a**): Viscous oil, 0.30g, yield 73%. IR (KBr)(ν_{max}, cm^{-1}): 2957.92, 1750.11, 1720.27, 1666.35, 1647.84, 1596.22, 1447.16, 1359.99, 1292.04, 1233.04, 1157.40, 761.02, 714.72, 700.83. ^{1}H NMR ($CDCl_3$) δ_H: 3.696, 3.78 and 4.24 (9H, s, $3OCH_3$), 5.16 (1H, s, CH of methine), 7.30 (1H, d, $^3J_{HH}$ = 7.8 Hz, arom), 7.42–7.62 (6H, m, arom), 7.79 (2H, d, $^3J_{HH}$ = 7.8Hz, arom). ^{13}C NMR ($CDCl_3$) δ_C: 52.04, 52.94, 60.21 (3C of OCH_3), 63.29 (1C, of methine), 128.17, 128.35, 128.78, 130.19, 130.87, 131.90, 133.28 (9C of =CH), 112.20, 134.37, 136.78, 137.12, 154.29 (5C), 161.95, 164.42, 168.14, 195.47 (4C=O). MS: *m/z* (%); 411 (M^+, 18), 230 (62), 182 (43), 166 (100), 135 (65), 80 (76). Anal. Calcd for $C_{22}H_{19}NO_7$ (409.12): C, 64.54; H, 4.68; N, 3.42. Found: C, 64.21; H, 4.31; N, 3.19%.

Diethyl 1-(2-benzoylphenyl)-4-methoxy-5-oxo-4,5-dihydro-1H-pyrrole-2,3-dicarboxylate (**4b**): Viscous oil, 0.31 g, yield 71%. IR (KBr) (ν_{max}, cm^{-1}): 2982.87, 1724.88 (br), 1663.75, 1597.43, 1449.03, 1369.82, 1274.72, 1206.91, 1026.17, 927.94, 765.88, 700.18. ^{1}H NMR ($CDCl_3$) δ_H: 1.15 (3H, t, $^3J_{HH}$ =7.2 Hz, CH_3), 1.28 (3H, t, $^3J_{HH}$ = 7.2Hz, CH_3), 4.08–4.25 (7H, m, $2OCH_2$ and OCH_3), 5.12 (1H, s, CH of methine), 7.32 (1H, d, $^3J_{HH}$ = 7.8 Hz, arom), 7.42–7.60 (6H, m, arom), 7.79 (2H, d, $^3J_{HH}$ = 7.2 Hz, arom). ^{13}C NMR ($CDCl_3$) δ_C: 13.94, 14.07 (2C of CH_3), 60.36 (1C of OCH_3), 61.00 and 62.01 (2C of OCH_2), 63.76 (1C, of methine), 128.09, 128.33, 128.92, 130.15, 130.53, 131.79, 133.24 (9CH of =CH), 112.40, 134.45, 136.82, 137.08, 154.29 (5C), 161.34, 164.50, 167.60 and 195.47 (4C=O). MS: *m/z* (%); 439 (M^+, 15), 256 (54), 182 (38), 166 (100), 135 (72), 80 (84). Anal. Calcd for $C_{24}H_{23}NO_7$ (437.15): C, 65.90; H 5.30; N 3.20. Found: C, 65.76; H, 5.15; N, 2.99%.

Dimethyl 4-methoxy-1-{4-[4-(2-methoxy-2-oxoacetamido)benzyl] phenyl}-5-oxo-4,5-dihydro-1H-pyrrole-2,3-dicarboxylate (**8a**): Viscous oil, 0.45 g, yield 91%. IR (KBr)(ν_{max}, cm^{-1}): 3386.51, 3053.68, 2952.50, 1749.44, 1761.68, 1647.94, 1513.12, 1437.13, 1394.61, 1287.34, 1235.23, 1195.35, 1118.93, 721.69, 695.31. ^{1}H NMR ($CDCl_3$) δ_H: 3.65, 3.83, 4.39 (9H, s, $3OCH_3$), 3.96 (5H, br, CH_2 and OCH_3 of oxalate), 5.34 (1H, s, CH of methine), 7.16–7.21 (1H, m, arom), 7.43–7.49 (3H, m, arom), 7.52–7.58 (2H, m, arom), 7.64–7.71 (2H, m, arom), 8.90(NH). ^{13}C NMR ($CDCl_3$) δ_C: 52.14, 53.13, 53.99, 60.34 (4C of OCH_3), 61.00 (1C of methine), 120.11, 122.02, 128.41, 128.57, 129.69, 131.84, 131.91, 132.02, 132.15 (8C of =CH), 111.18, 133.21, 134.53, 137.96, 139.19, 153.57 (6C), 154.70, 161.46, 162.04, 163.46, 168.13 (C=O). MS: *m/z* (%); 498 (M^+, 7), 231 (100), 167 (30),104 (21), 87 (18). Anal. Calcd for $C_{25}H_{24}N_2O_9$ (496.15): C, 60.48; H, 4.87; N, 5.64. Found: C, 60.38; H, 4.71; N, 5.58%.

Diethyl 4-methoxy-1-{4-[4-(2-methoxy-2-oxoacetamido)benzyl] phenyl}-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate (**8b**): Viscous oil, 0.33 g, yield 63%.IR (KBr)(ν_{max}, cm^{-1}): 3348.36 (NH), 3055.91, 2989.93, 1701 (br), 1648.15,1512.94, 1438.22, 1190.17, 1120.36, 721.56, 696.66. ^{1}H NMR ($CDCl_3$) δ_H: 1.08 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.32 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 3.96 (5H, br, CH_2 and OCH_3 of oxoacetate), 4.39 (3H, s, OCH_3), 4.10 (2H, q, $^3J_{HH}$= 7.0 Hz, OCH_2), 4.27 (2H, q, $^3J_{HH}$= 7.0 Hz, OCH_2), 5.32 (1H, s, CH of methine), 7.15–7.21 (1H, m, arom), 7.43–7.49 (3H, m, arom), 7.52–7.58 (2H, m, arom), 7.67–7.71 (2H, m, arom), 8.89 (NH). ^{13}C NMR ($CDCl_3$) δ_C: 13.89 and 14.10 (2C, $2CH_3$), 40.82 (1C, CH_2), 53,98 and 60.49 (2C, $2OCH_3$), 61.17 and 61.32 (2C, $2OCH_2$), 62.12 (1C, CH of methine), 111.37, 133.27, 134.50, 138.07, 139.13, 153.56 (6C), 154.71, 161.46, 162.54, 163.54, 167.53 (5C=O). MS: *m/z* (%); 526 (M^+, 10), 253 (100), 167 (41), 104 (16), 87 (23). Anal. Calcd for $C_{27}H_{28}N_2O_9$ (524.18): C, 61.83; H, 5.38; N, 5.34. Found: C, 61.68; H, 5.27; N, 5.28%.

Tetraethyl 1,1′-[4,4′-methylenebis(4,1-phenylene)]bis(4-methoxy-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate) (**9**): Viscous oil, 0.163 g, yield 24%. IR (KBr)(ν_{max}, cm^{-1}):3132.01, 2982.56, 1746.00, 1720.20, 1648.17, 1514.17, 1369.66, 1208.64, 1026.86, 763.08. ^{1}H NMR ($CDCl_3$) δ_H: 1.09 (6H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH_3), 1.33 (6H, t, $^3J_{HH}$ = 7.2, $2CH_3$), 3.96 (2H, s, CH_2), 4.09 (4H, q, $^3J_{HH}$ = 7.2Hz, $2OCH_2$), 4.29 (4H, q, $^3J_{HH}$ = 7.2Hz), 4.39 (6H, s, OCH_3), 5.33 (2H of methine), 7.19 (4H, d, $^3J_{HH}$ = 8.4 Hz, arom), 7.47 (4H, d, $^3J_{HH}$ = 8.4 Hz, arom). ^{13}C NMR ($CDCl_3$) δ_C: 13.90 and 14.11 (4C of 4 CH_3), 40.80 (C of CH_2), 60.49 (2C of 2 OCH_3), 61.17 and 61.31 (4C of 4 OCH_2), 62.14 (2CH of methine), 129.66 and 122.22 (8C of =CH), 111.36, 134.46, 138.94, 154.72 (8C), 161.26, 163.55, 167.52 (6C=O). MS: *m/z* (%); 680 (M^+, 15), 424 (52), 258 (66), 168 (61), 134 (84), 92(100). Anal. Calcd for $C_{35}H_{38}N_2O_{12}$ (678.24): C, 61.94; H, 5.64; N, 4.13. Found: C, 61.89; H, 5.61; N, 3.97%.

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