A one-pot synthesis of functionalised 3-pyrolin-2-ones by a four-component reaction between triphenylphosphine, primary amines, dimethyl acetylenedicarboxylate and ethyl chlorooxoacetate

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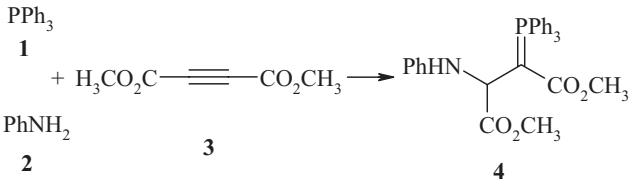
Reaction between triphenylphosphine, dimethy acetylenedicarboxylate and amines produces phosphorus ylids which undergo a smooth reaction with ethyl chlorooxoacetate and triethylamine to produce dimethyl *N*-aryl-(or alkyl)-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrole-2,3-dicarboxylates in high yields.

Keywords: primary amines, dimethyl acetylenedicarboxylate, ethyl chlorooxoacetate, 3-pyrolin-2-ones, multi component reactions

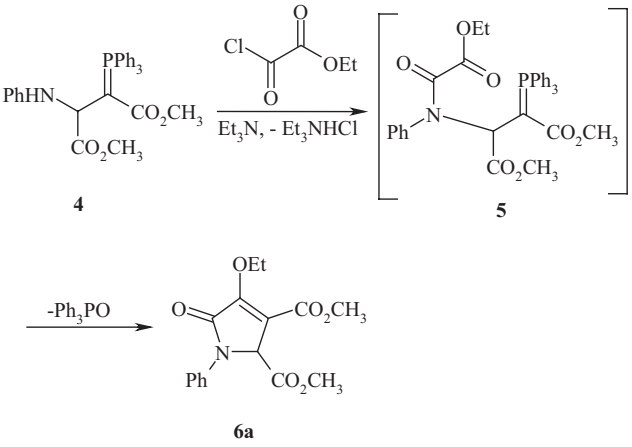
N-Substituted 3-pyrrolines are important compounds which exhibit neuritogenic activity[1] and serve as useful synthetic intermediates.[2] Despite their wide applicability, available routes for the synthesis of 3-pyrolin-2-ones are limited.[3,4]

Reaction between triphenylphosphine, dimethyl acetylenedicarboxylate (DMAD) and primary amines was previously reported to produce β-amino phosphoranes **4** (Scheme 1).[5] Following our previous work on the reaction between phosphorus nucleophiles and acetylenic esters in the presence of organic acids,[6-10] we decided to investigate the reaction of these phosphorus ylids with ethyl chlorooxoacetate and triethylamine. Ylid **4** was expected to react with ethyl chlorooxoacetate to produce oxamate **5** which may then undergo intramolecular Wittig reaction to produce dimethyl *N*-phenyl-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrole-2,3-dicarboxylate **6a** (Scheme 2). Thus, ylid **4** was prepared by the reaction between triphenylphosphine, DMAD and aniline by the previously reported procedure.[5] When phosphorane **4** was stirred with an equimolar amount of ethyl chlorooxoacetate and triethylamine in dichloromethane, a smooth reaction took place. After completion of the reaction (monitored by TLC) *N*-phenyl-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrole-2,3-dicarboxylate **6a** was obtained in nearly quantitative yield. Being successful in this reaction, we decided to investigate the one-pot synthesis of 3-pyrolin-2-one **6a** (Scheme 3). Thus, equimolar amounts of triphenylphosphine, aniline and DMAD were mixed in dichloromethane as solvent. After stirring for 1 min, triethylamine and ethyl chlorooxoacetate were added and the progress of the reaction was monitored by TLC. After 24 hours the TLC of the mixture of the reaction showed only the presence of product **6a** and triphenylphosphine oxide. Silica-gel chromatography afforded the product *N*-phenyl-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrole-2,3-dicarboxylate **6a** in 98% yield. To investigate the scope of the reaction, different aryl and alkyl amines were reacted with triphenylphosphine, DMAD and ethyl chlorooxoacetate. As showed in Scheme 3, different amines may be used to produce the corresponding 3-pyrrolin-2-ones in good yields. Most of the compounds reported here are known compounds, which were previously reported to be prepared by the reaction between triphenylphosphine, DMAD and *N*-substituted oxamates.[11] Compounds **6a** and **6c–i** were compared with the corresponding compounds prepared by the reported procedure.[11] Compound **6b** was new and its structure was deduced by elemental and spectral analysis.

The reaction of trialkyl phosphites and DMAD in the presence of organic NH acidic compounds lead to phosphite ylides as intermediate or final product.[6,9] Here, we also



Scheme 1



Scheme 2

report that the reaction between DMAD and *N*-aryl (or alkyl) ethyloxamate in the presence of trialkyl phosphite leads to *N*-aryl-(or alkyl)-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrole-2,3-dicarboxylates in good yields (Scheme 4). When a solution of trimethyl phosphite, DMAD and *N*-phenyl ethyloxamate in dichloromethane was stirred at room temperature for 24 hours, dimethyl *N*-phenyl-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrole-2,3-dicarboxylate **6a** was obtained as the only product in 97% yield (Scheme 1). This reaction could be carried out with other *N*-alkyl or *N*-aryl oxamates to produce dimethyl *N*-aryl-(or alkyl)-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrole-2,3-dicarboxylates in good yields. As showed in Scheme 4 this reaction could also be carried out with triethyl- or tributyl phosphite as well, but when triphenyl phosphite was used the yields were low. The advantage of the method reported here over the previously reported reaction between triphenylphosphine, DMAD and *N*-substituted ethyloxamates[11] is that here the by-product is trimethyl phosphate, which could be easily removed by washing the reaction mixture with water. In contrast, one of the most important drawbacks of the Wittig reaction is the separation of products from triphenylphosphine

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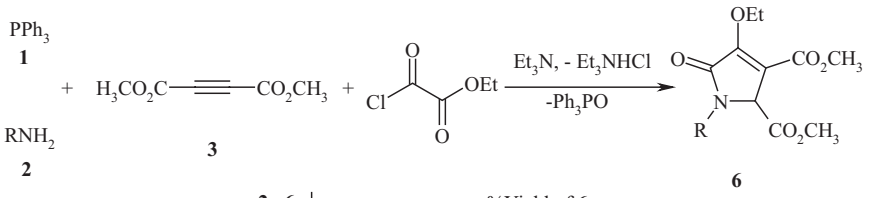


2 , 6	R	%Yield of **6**
a	C_6H_5	98
b	2-$C_2H_5C_6H_4$	95
c	4-$CH_3C_6H_4$	95
d	4-BrC_6H_4	95
e	4-$NO_2C_6H_4$	94
f	$C_6H_5CH_2$	95
g	$C_6H_5CH_2CH_2$	96
h	n-Bu	98
i	CH_3	90

Scheme 3

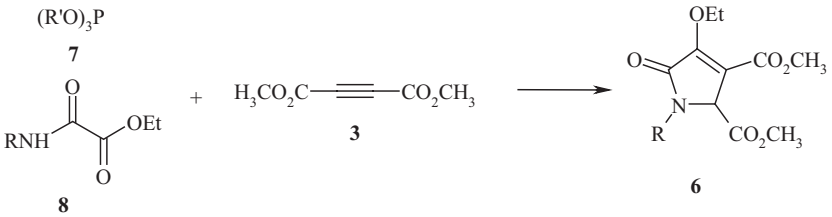
oxide. This is usually done by chromatographic methods, which are especially difficult for large-scale preparations.

It is rational to assume that compounds **6a–i** are produced from the intramolecular Wittig reaction of phosphite ylide intermediates **9** (Scheme 5).

In conclusion, we here report a four-component reaction between triphenylphosphine, DMAD, primary amines and ethyl chlorooxoacetate to produce functionalised 3-pyrolin-2-ones in high yields. The reaction between trimethyl phosphite, DMAD, and *N*-substituted ethyloxamates also leads to functionalised 3-pyrolin-2-ones in high yields The present method carries the advantage that not only is the reaction performed under neutral conditions but also that the substances can be mixed without any activation or modification.

Experimental

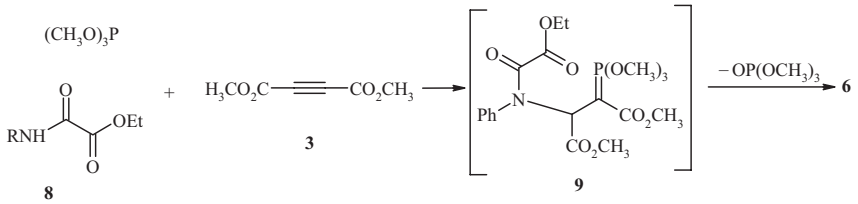
All melting points are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at 500 and 125.8 MHz, respectively. ^{1}H and ^{13}C NMR spectra were obtained on solution in $CDCl_3$ using TMS as internal standard. Column



		%Yield* of **6**			
8 , 6	R	R' = Me	R' = Et	R' = n-Bu	R' = Ph
a	C_6H_5	97	93	90	55
b	2-$C_2H_5C_6H_4$	95	90	90	49
c	4-$CH_3C_6H_4$	95	95	90	37
d	4-BrC_6H_4	97	94	95	60
e	4-$NO_2C_6H_4$	95	90	91	35
f	$C_6H_5CH_2$	95	92	89	40
g	$C_6H_5CH_2CH_2$	98	95	95	40
h	n-Bu	94	94	90	30
i	CH_3	90	93	90	35

*Isolated yield

Scheme 4



Scheme 5

chromatography was performed with Merck silica gel 60, 230–400 mesh. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Method a: To a magnetically stirred solution of triphenylphosphine (0.26 g, 1 mmol) and aniline (0.09 g, 1 mmol) in dichloromethane (10 ml) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.14 g, 1 mmol) in dichloromethane (3 ml) at room temperature over 2 min. The reaction mixture was then stirred for one minute. Triethylamine (1 mmol) and ethyl chlorooxoacetate (1.1 mmol) was added, respectively. The reaction mixture was then stirred for 24 hours. Solvent was evaporated and the residue was purified by column chromatography on silica-gel using ethyl acetate-hexane (1:4) mixture as eluent.

Method b: to a magnetically stirred solution of trimethyl phosphite (1 mmol) and *N*-phenyl ethyloxamate (1 mmol) in dichloromethane (10 ml) was added a mixture of dimethyl acetylenedicarboxylate (1 mmol) in dichloromethane (1 ml) at room temperature. The reaction mixture was then stirred for 24 h. The reaction mixture was washed with water to remove trimethyl phosphate. The organic layer was then concentrated and passed trough a silica gel pad eluting by hexane–ethyl acetate (4:1) mixture. Solvent was evaporated and the product was obtained as a white powder.

Dimethyl N-phenyl-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrole-2,3-dicarboxylate **(6a)**: White solid, m.p. 82–83°C, yield (98%). IR (KBr) (ν_{max}/cm^{-1}): 1748, 1716 and 1696 (C=O), 1644 (C=C). ^{1}H NMR (500 MH$_Z$, $CDCl_3$): δ 1.40(3H, t, $^3J_{HH}$ = 7.05 Hz, CH_3), 3.59 and 3.77 (6H, 2 s, 2 OCH_3), 4.79 (2H, q, $^3J_{HH}$ = 7.05 Hz, OCH_2), 5.34(1H, s, C–H), 7.19–7.53 (5H, m, arom.). ^{13}C NMR (125.8 MH$_Z$, $CDCl_3$): δ 16.02 (CH_3), 52.44 and 53.45 (2 OCH_3), 61.31 (OCH_2), 69.19 (CH), 112.03 (*C=C*) 122.15, 126.81, 129.64, 136.67 (C, arom), 154.77 (C=C), 162.51 and 163.97 (2 CO_2 Me), 168.58(C=O).

Dimethyl N-(2-ethylphenyl)-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrole-2,3-dicarboxylate **(6b)**: Yellow solid, m.p. 86–87°C, yield (95%). IR (KBr) (ν_{max}/cm^{-1}): 1742, 1726 and 1698 (C=O), 1654 (C=C). Anal. Calcd for $C_{18}H_{21}NO_6$ (347.36): C, 62.24; H, 6.09; N, 4.03. Found: C, 62.21; H, 6.14; N, 4.02%.,^{1}H NMR (500 MH$_Z$, $CDCl_3$): δ 1.19(3H, t, $^3J_{HH}$ = 7.52 Hz, CH_3), 1.43(3H, t, $^3J_{HH}$ = 7.05 Hz, CH_3), 2.59 (2H, m, CH_2), 3.60 and 3.78 (6H, 2 s, 2 OCH_3), 4.84 (2H, q, $^3J_{HH}$ = 7.05 Hz, OCH_2), 5.14(1H, s, C–H), 7.03–7.33 (4H, m, arom.). ^{13}C NMR (125.8 MH$_Z$, $CDCl_3$): δ 14.66 (CH_3), 16.05 (CH_3), 24.02(CH_2), 52.40 and 53.24 (2 OCH_3), 63.32 (OCH_2), 69.08 (CH), 112.62 (*C=C*), 122.14, 127.24, 129.68, 133.87, 136.21,142.61 (C, arom), 154.77 (C=C), 162.64 and 164.12 (2 CO_2 Me), 168.55(C=O). MS (*m/z*,%): 347 (M, 1).

Dimethyl N-(4-methylphenyl)-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrole-2,3-dicarboxylate **(6c)**: Yellow crystals, m.p. 73–75°C, yield (95%). IR (KBr) (ν_{max}/cm^{-1}): 1751 and 1721 (C=O), 1642 (C=C). ^{1}H NMR (500 MH$_Z$, $CDCl_3$): δ 1.43 (3H, t, $^3J_{HH}$ = 7.05 Hz, CH_3), 2.36 (3H, s, CH_3), 3.61 and 3.76 (6H, 2 s, 2 OCH_3), 4.83 (2H, q, $^3J_{HH}$ = 7.05 Hz, OCH_2), 5.32 (1H, s, CH), 7.06–742 (4H, m, arom.). ^{13}C NMR (125.8 MH$_Z$, $CDCl_3$): δ 15.74 (CH_3), 20.96 (CH_3), 52.14 and 53.06 (2 OCH_3), 61.32 (OCH_2), 67.86 (CH), 111.82 (*C=C*), 122.12, 129.71, 133.49, 136.48(C, arom), 154.61 (C=C), 163.23 and 164.35 (2 CO_2 Me), 169.17(C=O).

Dimethyl N-(4-bromophenyl)-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrole-2,3-dicarboxylate **(6d)**: White crystals, m.p. 81–83°C, yield (95%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1723 and 1694 (C=O), 1640 (C=C). ^{1}H NMR (500 MH$_Z$, $CDCl_3$): δ 1.52(3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.59 and 3.72 (6H, 2 s, 2 OCH_3), 4.83 (2H, q, $^3J_{HH}$ = 7 Hz, OCH_2), 5.79 (1H, s, C–H), 7.12–7.53 (4H, m, arom.). ^{13}C NMR (125.8 MH$_Z$, $CDCl_3$) δ 15.68 (CH_3), 52.39 and 53.26 (2 OCH_3), 60.67 (OCH_2), 67.69 (C–H), 111.82 (*C=C*), 119.37, 125.67, 129.63, 135.59 (C, arom), 154.43 (C=C), 162.13 and 163.55 (2 CO_2 Me), 168.99 (C=O).

Dimethyl N-(4-nitrophenyl)-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrole-2,3-dicarboxylate **(6e)**: Yellow solid, m.p. 146–147°C, yield (94%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1723 and 1705 (C=O). ^{1}H NMR (500 MH$_Z$, $CDCl_3$): δ 1.48 (3H, t, $^3J_{HH}$ = 7.05 Hz, CH_3), 3.69 and 3.73 (6H, 2 s, 2 OCH_3), 4.84 (2H, q, $^3J_{HH}$ = 7.05 Hz, OCH_2), 5.41 (1H, s, CH), 7.22–8.36 (4 CH, arom.). ^{13}C NMR (125.8 MH$_Z$, $CDCl_3$): δ 15.71 (CH_3), 52.41 and 53.61 (2 OCH_3), 61.25 (OCH_2), 69.35 (C–H), 112.47 (*C=C*), 119.88, 125.12, 142.62, 145.12 (C, arom), 153.52 (C=C), 162.34 and 163.82 (2 CO_2 Me), 167.89 (C=O).

Dimethyl N-benzyl-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrole-2,3-dicarboxylate **(6f)**: White crystals, m.p. 52–54°C, yield (95%). IR (KBr) (ν_{max}/cm^{-1}): 1749, 1732 and 1706 (C=O), 1640 (C=C). ^{1}H NMR (500 MH$_Z$, $CDCl_3$): δ 1.31 (3H, t, $^3J_{HH}$ = 7.05 Hz, CH_3), 3.52 and 3.57 (6H, 2 s, 2 OCH_3), 4.16 (1H, d, J_{AB} = 15 Hz, CH_2, Bn.), 4.49 (1H, s, CH), 4.64–4.71 (2H, m, OCH_2), 4.77 (1H, d, J_{AB} = 15 Hz, CH_2, Bn.), 7.15–7.92 (5H, m, arom.). ^{13}C NMR (125.8 MH$_Z$, $CDCl_3$): δ 15.64 (CH_3), 54.73 (CH_2, Bn.), 51.82 and 52.14 (2 OCH_3), 59.69 (OCH_2), 68.57 (CH), 111.37 (*C=C*), 128.11, 128.55, 128.77, 135.48 (C, arom), 154.58 (C=C), 162.13 and 164.72 (2 CO_2 Me), 168.22 (C=O).

Dimethyl N-(2-phenylethyl)-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrole-2,3-dicarboxylate **(6g)**: Pale yellow oil, yield (96%). IR (KBr) (ν_{max}/cm^{-1}): 1752, 1722 and 1698(C=O), 1625(C=C). ^{1}H NMR (500 MH$_Z$, $CDCl_3$): δ 1.38 (3H, t, $^3J_{HH}$ = 7.05 Hz, CH_3), 2.78 (1H, m, CH_2, Bn.), 2.89 (1H, m, CH_2, Bn.), 3.25 (1H, m, CHN), 3.72 and 3.74(6H, 2 s, 2 OCH_3), 3.96 (1H, m, CHN), 4.58 (1H, s, CH), 4.73 (2H, m, OCH_2), 7.14–7.30 (5H, m, arom.). ^{13}C NMR (125.8 MH$_Z$, $CDCl_3$): δ 15.28 (CH_3), 33.36 (NCH_2), 42.79 (CH_2, Bn.), 51.37 and 52.63 (2 OCH_3), 59.87(OCH_2), 67.88 (CH), 111.17(*C=C*), 126.22, 128.12, 128.16, 137.30(C, arom), 154.58 (C=C), 162.23 and 164.72 (2 CO_2 Me), 168.14 (C=O).

Dimethyl N-butyl-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrole-2,3-dicarboxylate **(6h)**: Yellow oil, yield (98%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1721 and 1698(C=O), 1635 (C=C). ^{1}H NMR (500 MH$_Z$, $CDCl_3$): δ 0.93 (3H, t, $^3J_{HH}$ = 7.05 Hz, CH_3), 1.32(2H, m, CH_2), 1.42 (3H, t, $^3J_{HH}$ = 7.05 Hz, CH_3), 1.54 (2H, m, CH_2), 3.04 (1H, m, CHN), 3.72 (1H, m, CHN), 3.54 and 3.79 (6H, 2 s, 2 OCH_3), 4.75 (1H, s, CH), 4.79 (2H, q, OCH_2). ^{13}C NMR (125.8 MH$_Z$, $CDCl_3$): δ 13.07 (CH_3), 15.13 (CH_3), 19.34 (CH_2), 29.29(CH_2), 41.09 (NCH_2), 51.49 and 52.49 (2 OCH_3), 59.86 (OCH_2), 67.92 (CH), 110.86, 154.19 (*C=C*), 162.23 and 164.53 (2 CO_2 Me), 168.89(C=O).

Dimethyl N-methyl-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrole-2,3-dicarboxylate **(6i)**: Yellow oil, yield (90%). IR (KBr) (ν_{max}/cm^{-1}): 1751, 1722 and 1695(C=O), 1642 (C=C). ^{1}H NMR (500 MH$_Z$, $CDCl_3$): δ 1.36 (3H, t, $^3J_{HH}$ = 7.05 Hz, CH_3), 2.96(3H, s, CH_3N), 3.68 and 3.78 (6H, 2 s, 2 OCH_3), 4.72 (1H, s, CH), 4.81 (2H, q, $^3J_{HH}$ = 7 Hz, OCH_2). ^{13}C NMR (125.8 MH$_Z$, $CDCl_3$): δ 15.71 (CH_3), 28.54 (NCH_3), 52.08 and 53.41(2 OCH_3), 61.79 (OCH_2), 68.52 (CH), 111.32, 154.94 (*C=C*), 163.54 and 165.21 (2 CO_2 Me), 169.31 (C=O).

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