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Synthesis of 4,5-dialkyl 5-acetyl-3-oxo-3-(triphenylphosphoranylidene)-tetrahydrofuran-4,5-dicarboxylates

Issa Yavari,*[a,b] Bita Mohtat[a] and Hasan Zare[a]

[a] *Department of Chemistry, Science and Research Campus, Islamic Azad University, Ponak, Tehran, Iran*
[b] *Department of Chemistry, Tarbiat Modarres University, 14115-175, Tehran, Iran.*
Fax: +98 21 8800 6544; e-mail: yavarisa@modares.ac.ir

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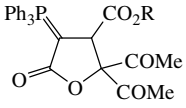
Alkyl 2-chloroacetoacetates undergo a complex reaction with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine to produce a nearly 1:1 mixture of the *cis*/*trans* isomers of dialkyl 5-acetyl-2-oxo-3-(triphenylphosphoranylidene)tetrahydrofuran-4,5-dicarboxylates in excellent yields.

The synthesis of organophosphorus compounds is of considerable interest.[1–5] As a result, a large number of methods have appeared describing novel syntheses of organophosphorus compounds.[3–8] The successful attack of nucleophilic trivalent phosphorus on a carbon atom is facilitated when the latter is conjugated with a carbonyl group. The reaction between trivalent phosphorus nucleophiles and α,β-unsaturated carbonyl compounds in the presence of a proton source has been studied using alcohols or phenols as reaction adjuncts.[9]



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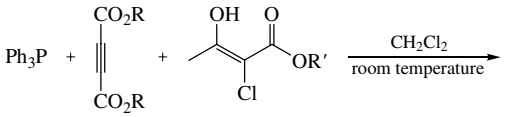
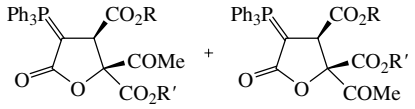
Previously,[10] we described a convenient method for the preparation of alkyl 5,5-diacetyl-2-oxo-3-(triphenylphosphoranylidene)-tetrahydrofuran-4-dicarboxylates **1** by a three-component reaction of 3-chloropentane-2,4-dione, dialkyl acetylenedicarboxylates **2** and triphenylphosphine (Ph_3P). Here, we extend this methodology using alkyl 2-chloroacetoacetates **3** (Scheme 1). Compound **3** is commercially available; it is apparently completely enolised in a liquid phase, as indicated by ^1H and ^{13}C NMR spectroscopy.



2a R = Me **3a** R′ = Me
2b R = Et **3b** R′ = Et
2c R = Pr^i
2d R = Bu^t



trans-**4** *cis*-**4**

4	R	R′	Yield of **4** (%)	*cis*:*trans*
a	Me	Me	86	45:41
b	Et	Me	85	47:38
c	Pr^i	Me	92	50:42
d	Bu^t	Me	88	48:40
e	Me	Et	93	52:41
f	Et	Et	90	48:42
g	Pr^i	Et	84	46:38
h	Bu^t	Et	85	52:33

Scheme 1

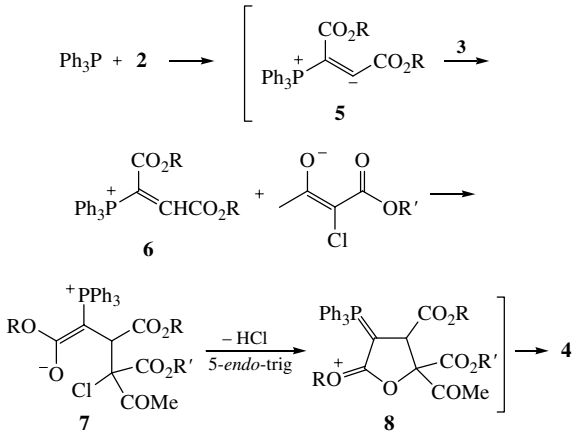
The reaction of **2** with **3** in the presence of Ph_3P at room temperature in CH_2Cl_2 was complete within a few hours. The ^1H and ^{13}C NMR spectra of the crude reaction mixtures clearly indicated the formation of **4** as a nearly 1:1 mixture of the *cis* and *trans* geometrical isomers (Scheme 1).

This three-component reaction[11] produces a nearly 1:1 mixture of the *cis*/*trans* isomers of hitherto unknown 3-(triphenylphosphoranylidene)butyrolactones **4a**–**h** in 84–93% yields.† Compounds **4a**–**h** are stable oils, whose structure is fully supported by elemental analyses and IR, ^1H and ^{13}C NMR and mass spectral data.‡ The *cis*/*trans* isomers of **4** were separated by preparative TLC.

A possible mechanism for the formation of products *cis*-**4** and *trans*-**4** is proposed in Scheme 2. The reaction starts from the addition of Ph_3P to the electron-deficient acetylenic ester to form 1,3-dipolar intermediate **5**,[12] which is subsequently protonated by CH acid **3**. Then, an attack by the enolate anion forms stabilised ylide **7**, which is then converted to butyro-

† The ^1H, ^{13}C and ^{31}P NMR spectra were measured at 300, 75 and 120 MHz, respectively, on a Bruker 300-AVANCE FT-NMR instrument with $CDCl_3$ as a solvent. Elemental analyses for C and H were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded with a Hewlett-Packard MSD 5973 mass spectrometer at an ionization potential of 70 eV.

Typical procedure for the preparation of 4,5-dimethyl 5-acetyl-3-oxo-3-(triphenylphosphoranylidene)tetrahydrofuran-4,5-dicarboxylate **4a**: 0.28 g of **2a** (2 mmol) in 2 ml CH_2Cl_2 was added dropwise for 10 min to a stirred solution of 0.30 g of **3a** (2 mmol) and 0.52 g of Ph_3P (2 mmol) in 5 ml CH_2Cl_2. The reaction mixture was then allowed to warm up to room temperature and stand 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 chloroform–*n*-hexane–EtOAc (1:1:2) as an eluent. Zones were detected by quenching of indicator fluorescence upon exposure to 366 nm UV light. The product was obtained by the extraction of silica gel with CH_2Cl_2 to produce *trans*-**4a** and *cis*-**4a**.



Scheme 2

lactone derivatives **4**, presumably, by HCl elimination and ring closure.[13]

The ^{1}H NMR spectrum of *trans*-**4a** exhibited three single sharp resonances readily recognisable as arising from the methyl (δ 2.49 ppm) and methoxy (δ 3.22 and 3.78 ppm) protons, along with a doublet ($^3J_{PH}$ 1.8 Hz) at δ 4.15 for the methine proton. A fairly complex multiplet was observed for the aromatic protons at δ 7.50–7.65 ppm. The ^{13}C NMR spectrum of *trans*-**4a** displayed 14 distinct resonances in agreement with the lactone structure. The assignment of the *trans* geometry to this compound is based on the ^{13}C chemical shift of the carbonyl group, which is about 5 ppm downfield compared to that of the *cis*-isomer. The carbonyl group of the latter is shielded as a result of the *gauche*-gama effect[14] of the CO_2R group. The ^{31}P NMR chemical shift (δ 16.24 ppm) of compound **4a** is similar to those reported for other stabilised phosphorus ylides.[1] The ^{1}H and ^{13}C NMR spectra of the *cis*/*trans* isomers of **4b–h** are similar to those of *trans*-**4a** and *cis*-**4a**, except for the ester groups, which exhibited characteristic resonances with appropriate chemical shifts.

Functionalised butyrolactones **4a–h** may be considered as potentially useful synthetic intermediates because they possess carbon atoms with different oxidation states. The procedure described here may be an acceptable method for the preparation of butyrolactones with variable functionalities.

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‡ *trans*-**4a**: yellow oil, yield 0.42 g (41%). IR (neat, ν_{max}/cm^{-1}): 1738, 1733 and 1692 (C=O). ^{1}H NMR, δ: 2.49 (s, 3H, Me), 3.22 (s, 3H, OMe), 3.78 (s, 3H, OMe), 4.15 (d, 1H, CH, $^3J_{PH}$ 1.8 Hz), 7.50–7.65 (m, 15H, 3Ph). ^{13}C NMR, δ: 28.3 (Me), 36.5 (d, P=C, J_{PC} 138.6 Hz), 51.9 (OMe), 53.5 (d, CH, $^2J_{PC}$ 13.3 Hz), 53.8 (OMe), 89.4 (d, C–O, $^3J_{PC}$ 12.0 Hz), 124.6 (d, C_{ipso}, $^1J_{PC}$ 92.5 Hz), 129.6 (d, C_{meta}, $^3J_{PC}$ 12.4 Hz), 133.3 (d, C_{para}, $^4J_{PC}$ 2.8 Hz), 134.0 (d, C_{ortho}, $^2J_{PC}$ 10.6 Hz), 168.9 (C=O), 172.0 (d, C=O, $^3J_{PC}$ 20.1 Hz), 174.2 (C=O), 206.7 (C=O). ^{31}P NMR, δ: 16.24. MS, *m*/*z* (%): 504 (M$^+$, 4), 461 (75), 445 (81), 262 (61), 242 (95), 199 (100), 59 (21), 43 (70). Found (%): C, 66.61; H, 5.07. Calc. for $C_{28}H_{25}O_7P$ (504.5) (%): C, 66.66; H, 5.00.

cis-**4a**: yellow oil, yield 0.45 g (45%). IR (neat, ν_{max}/cm^{-1}): 1739, 1732 and 1693 (C=O), 1438, 1299, 1155, 1108. ^{1}H NMR, δ: 2.40 (s, 3H, Me), 3.25 (s, 3H, OMe), 3.27 (s, 3H, OMe), 4.17 (d, 1H, CH, $^3J_{PH}$ 1.1 Hz), 7.47–7.64 (m, 15H, 3Ph). ^{13}C NMR, δ: 26.3 (Me), 36.1 (d, P=C, $^1J_{PC}$ 137.5 Hz), 52.0 (OMe), 52.1 (d, CH, $^2J_{PC}$ 9.3 Hz), 54.2 (OMe), 89.7 (d, C–O, $^3J_{PC}$ 12.3 Hz), 124.6 (d, C_{ipso}, $^1J_{PC}$ 92.8 Hz), 129.5 (d, C_{meta}, $^3J_{PC}$ 12.6 Hz), 133.3 (d, C_{para}, $^4J_{PC}$ 2.8 Hz), 134.0 (d, C_{ortho}, $^2J_{PC}$ 10.3 Hz), 167.5 (C=O), 171.2 (d, C=O, $^3J_{PC}$ 19.6 Hz), 174.0 (C=O), 202.9 (C=O).

trans-**4b**: yellow oil, yield 0.38 g (38%). IR (neat, ν_{max}/cm^{-1}): 1748, 1726 and 1694 (C=O). ^{1}H NMR, δ: 0.90 (t, 3H, Me, $^3J_{HH}$ 7.1 Hz), 2.49 (s, 3H, Me), 3.77 (s, 3H, OMe), 3.8 (2H, ABX_3 system, OCH_2), 4.12 (d, 1H, CH, $^3J_{PH}$ 2.2 Hz), 7.40–7.63 (m, 15H, 3Ph). ^{13}C NMR, δ: 14.1 (Me), 28.4 (Me), 36.6 (d, P=C, $^1J_{PC}$ 138.7 Hz), 53.6 (d, CH, $^2J_{PC}$ 13.5 Hz), 53.8 (OMe), 61.2 (OCH_2), 89.5 (d, C–O, $^3J_{PC}$ 11.5 Hz), 124.6 (d, C_{ipso}, $^1J_{PC}$ 92.5 Hz), 129.5 (d, C_{meta}, $^3J_{PC}$ 12.7 Hz), 133.3 (d, C_{para}, $^4J_{PC}$ 2.7 Hz), 134.0 (d, C_{ortho}, $^2J_{PC}$ 10.4 Hz), 169.0 (C=O), 172.0 (d, C=O, $^3J_{PC}$ 20.0 Hz), 173.6 (C=O), 206.5 (C=O). ^{31}P NMR, δ: 16.27. MS, *m*/*z* (%): 518 (M$^+$, 3), 465 (83), 445 (71), 262 (80), 256 (92), 213 (100), 73 (42), 43 (52). Found (%): C, 67.31; H, 5.17. Calc. for $C_{29}H_{27}O_7P$ (518.5) (%): C, 67.18; H, 5.25.

cis-**4b**: yellow oil, yield 0.48 g (47%). IR (neat, ν_{max}/cm^{-1}): 1729 and 1691 (C=O). ^{1}H NMR, δ: 0.92 (t, 3H, Me, $^3J_{HH}$ 7.1 Hz), 2.40 (s, 3H, Me), 3.70 (s, 3H, OMe), 3.73 (2H, ABX_3 system, OCH_2), 4.14 (d, 1H, CH, $^3J_{PH}$ 1.4 Hz), 7.45–7.64 (m, 15H, 3Ph). ^{13}C NMR, δ: 14.2 (Me), 26.2 (Me), 36.1 (d, P=C, $^1J_{PC}$ 137.7 Hz), 52.1 (d, CH, $^2J_{PC}$ 13.0 Hz), 53.3 (OMe), 61.2 (OCH_2), 89.8 (d, C–O, $^3J_{PC}$ 12.2 Hz), 124.6 (d, C_{ipso}, $^1J_{PC}$ 92.8 Hz), 129.5 (d, C_{meta}, $^3J_{PC}$ 12.6 Hz), 133.2 (d, C_{para}, $^4J_{PC}$ 2.8 Hz), 134.0 (d, C_{ortho}, $^2J_{PC}$ 10.5 Hz), 167.4 (C=O), 171.2 (d, C=O, $^3J_{PC}$ 19.8 Hz), 173.4 (C=O), 202.9 (C=O).

trans-**4c**: yellow oil, yield 0.48 g (42%). IR (neat, ν_{max}/cm^{-1}): 1748, 1722 and 1694 (C=O), 1438, 1302, 1200, 1108. ^{1}H NMR, δ: 0.82 (d, 3H, Me, $^3J_{HH}$ 6.2 Hz), 1.03 (d, 3H, Me, $^3J_{HH}$ 6.2 Hz), 2.50 (s, 3H, Me), 3.78 (s, 3H, OMe), 4.07 (d, 1H, CH, $^3J_{PH}$ 1.3 Hz), 4.63 (sept, 1H, OCH, $^3J_{HH}$ 6.2 Hz), 7.47–7.69 (m, 15H, 3Ph). ^{13}C NMR, δ: 21.6 (Me), 22.0 (Me), 28.6 (Me), 36.5 (d, P=C, $^1J_{PC}$ 139.4 Hz), 53.7 (d, CH, $^2J_{PC}$ 13.4 Hz), 53.8 (OMe), 69.1 (OCH), 89.8 (d, C–O, $^3J_{PC}$ 11.5 Hz), 124.6 (d, C_{ipso}, $^1J_{PC}$ 92.5 Hz), 129.5 (d, C_{meta}, $^3J_{PC}$ 12.6 Hz), 133.3 (d, C_{para}, $^4J_{PC}$ 2.8 Hz), 134.1 (d, C_{ortho}, $^2J_{PC}$ 10.3 Hz), 169.1 (C=O), 172.1 (d, C=O, $^3J_{PC}$ 19.6 Hz), 173.0 (C=O), 206.2 (C=O). ^{31}P NMR, δ: 16.23. MS, *m*/*z* (%): 533 (M$^+$, 10), 490 (71), 446 (52), 271 (82), 262 (91), 87 (94), 43 (100). Found (%): C, 67.51; H, 5.62. Calc. for $C_{30}H_{29}O_7P$ (533.5) (%): C, 67.54; H, 5.67.

cis-**4c**: yellow oil, yield 0.55 g (50%). IR (neat, ν_{max}/cm^{-1}): 1739, 1726 and 1693 (C=O), 1438, 1297, 1204, 1107. ^{1}H NMR, δ: 0.85 (d, 3H, Me, $^3J_{HH}$ 6.0 Hz), 1.02 (d, 3H, Me, $^3J_{HH}$ 6.0 Hz), 2.40 (s, 3H, Me), 3.73 (s, 3H, OMe), 4.10 (d, 1H, CH, $^3J_{PH}$ 2.6 Hz), 4.62 (sept, 1H, OCH, $^3J_{HH}$ 6.0 Hz), 7.45–7.65 (m, 15H, 3Ph). ^{13}C NMR, δ: 21.8 (Me), 21.9 (Me), 26.2 (Me), 36.1 (d, P=C, $^1J_{PC}$ 138.0 Hz), 52.1 (d, CH, $^2J_{PC}$ 13.1 Hz), 53.2 (OMe), 69.0 (OCH), 90.1 (d, C–O, $^3J_{PC}$ 12.1 Hz), 124.8 (d, C_{ipso}, $^3J_{PC}$ 92.8 Hz), 129.5 (d, C_{meta}, $^3J_{PC}$ 12.7 Hz), 133.2 (d, C_{para}, $^4J_{PC}$ 2.8 Hz), 134.1 (d, C_{ortho}, $^2J_{PC}$ 10.6 Hz), 167.2 (C=O), 172.2 (d, C=O, $^3J_{PC}$ 19.7 Hz), 172.9 (C=O), 203.1 (C=O).

trans-**4d**: yellow oil, yield 0.38 g (40%). IR (neat, ν_{max}/cm^{-1}): 1739, 1724 and 1696 (C=O), 1438, 1368, 1108, 973, 720. ^{1}H NMR, δ: 1.22 (s, 9H, 3Me), 2.46 (s, 3H, Me), 3.74 (s, 3H, OMe), 3.97 (d, 1H, CH, $^3J_{PH}$ 2.6 Hz), 7.40–7.65 (m, 15H, 3Ph). ^{13}C NMR, δ: 28.0 (Me), 29.6 (3Me), 36.7 (d, PC, $^1J_{PH}$ 134.3 Hz), 54.2 (OMe), 54.5 (d, CH, $^2J_{PH}$ 13.5 Hz), 81.8 ($OCMe_3$), 90.0 (d, C–O, $^3J_{PC}$ 11.5 Hz), 124.8 (d, C_{ipso}, $^1J_{PC}$ 92.7 Hz), 129.5 (d, C_{meta}, $^3J_{PC}$ 12.5 Hz), 132.2 (d, C_{para}, $^4J_{PC}$ 2.8 Hz), 134.1 (d, C_{ortho}, $^2J_{PC}$ 16.4 Hz), 169.2 (C=O), 172.2 (d, C=O, $^3J_{PC}$ 20.2 Hz), 172.8 (C=O), 206.1 (C=O). MS, *m*/*z* (%): 546 (M$^+$, 8), 503 (70), 445 (61), 284 (42), 262 (77), 241 (100), 101 (67), 43 (86). Found (%): C, 68.21; H, 5.67. Calc. for $C_{31}H_{31}O_7P$ (546.5) (%): C, 68.12; H, 5.72.

cis-**4d**: yellow oil, yield 0.52 g (48%). IR (neat, ν_{max}/cm^{-1}): 1736, 1726 and 1692 (C=O), 1438, 1366, 1154, 998, 694. ^{1}H NMR, δ: 1.17 (s, 9H, 3Me), 2.32 (s, 3H, Me), 3.66 (s, 3H, OMe), 3.97 (d, 1H, CH, $^3J_{PH}$ 1.8 Hz), 7.39–7.58 (m, 15H, 3Ph). ^{13}C NMR, δ: 26.2 (Me), 29.6 (CMe_3), 36.6 (d, P=C, $^1J_{PC}$ 137.8 Hz), 52.8 (d, CH, $^2J_{PC}$ 13.1 Hz), 54.3 (OMe), 81.6 (CMe_3), 90.4 (d, C–O, $^3J_{PC}$ 12.3 Hz), 124.8 (d, C_{ipso}, $^1J_{PC}$ 92.7 Hz), 129.4 (d, C_{meta}, $^3J_{PC}$ 12.7 Hz), 133.2 (d, C_{para}, $^4J_{PC}$ 2.8 Hz), 134.0 (d, C_{ortho}, $^2J_{PC}$ 10.5 Hz), 167.1 (C=O), 171.3 (d, C=O, $^3J_{PC}$ 19.9 Hz), 172.7 (C=O), 203.3 (C=O).

Spectral characteristics for *trans*- and *cis*-**4e–h** are available free *via* http://www.turpion.org/suppl/mc/2281/suppl2281.pdf as Supplementary Materials.

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