Indian Journal of Chemistry
Vol. 48B, September 2009, pp. 1333-1336

Note

An efficient synthesis of α-(alkylidene)-5, 5-dimethyl-δ-lactones

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Received 15 September 2008; accepted (revised) 28 May 2009

2-(-Alkylidene substituted)-5,5-dimethyl-δ-lactones have been synthesized in two steps. The stable phosphorane carboethoxymethyledene (α-prenyl)-triphenylphosphorane is condensed with different carbonyl compounds to afford α,β-unsaturated esters which are cyclised using PPA to give title compounds.

Keywords: Phosphorane, δ-lactones, acid mediated cyclisation, domino, Wittig reaction

2-(Alkylidene substituted)-lactones are a target for developing synthetic methodologies[1] due to the presence of this unit in natural products[2] and the biological activities[3-8] associated with these molecules. These activities are mainly attributed to the presence of unsaturation which acts as (Michael acceptor) alkylating agent.

Although there are various methods available for the synthesis of γ-substituted α-(alkylidene substituted)-γ-butyrolactones[1a-h], for the corresponding δ-lactones there are only a few reports[1i,j]. So, there is a need to develop a general approach for the synthesis of such compounds which should be useful in providing libraries for biological testing. In continuation of the interest[9] in phosphorus chemistry, herein is reported a convenient and general route towards α-(alkylidene)-5,5-dimethyl-δ-lactones. Thus, stable phosphorane **1** prepared[10] by prenylation of carboethoxymethylene-triphenylphosphorane was condensed with benzaldehyde **2a** to get unsaturated ester **3a** in 92% yield. The downfield shift of the olefinic proton suggested *E* geometry for the double bond.

The ester was then cyclised to the benzylidene (*E*) lactone **4a** using conc. H_2SO_4 in 57% yield. The yield of cyclisation reaction was improved to 96% with PPA. No isomerisation of the *E* lactone to *Z* lactone was observed during acid mediated cyclisation. The Wittig reaction worked well for electron withdrawing group on benzene ring **2b** and **2c**, and also for electron donating group **2d** and **2e**. For extending the protocol for aliphatic system, the domino oxidation-Wittig reaction approach[9] was used to get ester **3f** which was then successfully cyclised to lactone **4f** (**Scheme I**). Attempted reaction on ketone (benzophenone and ethyl methyl ketone) failed to provide the corresponding unsaturated compound.

In conclusion, a convenient and efficient method has been developed using Wittig reaction for the synthesis of **4a-f** lactones.

Experimental Section

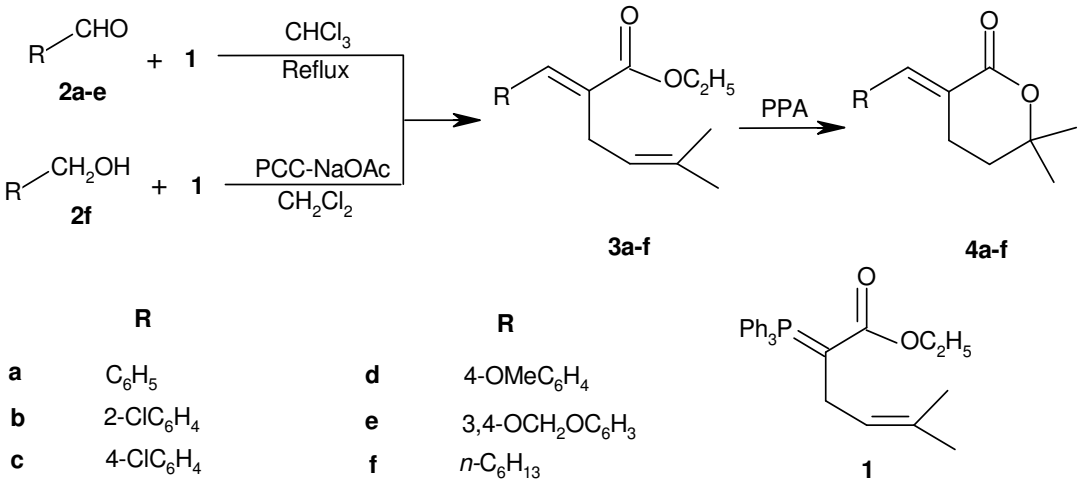
IR spectra were recorded on Shimadzu FT-IR spectrophotometer (KBr pellet). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Bruker instrument. The multiplicities of carbon signals were obtained from Distortionless Enhancement by Polarization Transfer (DEPT) experiments. Chemical shift (ppm) are relative to the internal standard Me_4Si (0 ppm). Thin layer chromatography was performed on silica gel G (13% $CaSO_4$ as binder)

(*E*) Ethyl -2-benzylidene-5-methyl-4-ene-hexanoates, 3a-e

A solution of aldehyde (1 mmole) **2a-e** in chloroform (10 mL) was refluxed with phosphorane[10] **1** (1 mmole) for 3 hr. The solvent was removed under reduced pressure to give a residue that was purified by column chromatography (silica gel, hexanes-EtOAc, 9:1) to give pure **3a-e** as a viscous liquid. The spectral data of the compounds **3a-e** is given below.

3a: Thick viscous liquid, yield 92%. b.p. 134-39°C/0.06 mm Hg (Bath temp.). IR (KBr): 1709 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, *J*=6.9 Hz), 1.67 (s, 3H), 1.75 (s, 3H), 3.24 (d, 2H, *J*=6.3 Hz), 4.20 (q, 2H, *J*=6.9 Hz), 5.18 (m, 1H), 7.38 (m, 5H), 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.29 (CH_3), 17.95 (CH_3), 25.74 (CH_3), 26.84 (CH_2), 60.77 (OCH_2), 121.68 (CH), 128.26 (CH), 128.36 (2×CH), 129.35 (2×CH), 132.62 (CH), 132.93 (C), 135.81 (C), 138.74 (CH), 168.34 (C=O); GC-MS: *m/z* 244 (M^+).

3b: Thick viscous liquid, yield 93%. b.p. 180-85°C/0.07 mm Hg (Bath temp.). IR (KBr): 1713 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, *J*=7.2 Hz),



Scheme I

1.54 (s, 3H), 1.64 (s, 3H), 3.03 (d, 2H, *J*=6.6 Hz), 4.23 (q, 2H, *J*=7.2 Hz), 5.07 (m, 1H), 7.23 (m, 3H), 7.36 (m, 1H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.24 (CH_3), 17.79 (CH_3), 25.70 (CH_3), 27.04 (CH_2), 60.88 (OCH_2), 121.32 (CH), 126.44 (CH), 129.35 (CH), 129.45 (CH), 130.33 (CH), 132.87 (C), 134.02 (C), 134.35 (C), 134.51 (C), 135.79 (CH), 167.73 (C=O); GC-MS: *m/z* 278 (M^+).

3c: Thick viscous liquid, yield 90%. b.p. 205-10°C/0.11 mm Hg (Bath temp.). IR (KBr): 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, *J*=7.2 Hz), 1.62 (s, 3H), 1.72 (s, 3H), 3.18 (d, 2H, *J*=6.6 Hz), 4.23 (q, 2H, *J*=7.2 Hz), 5.12 (t, 1H, *J*=7.2 Hz), 7.34 (m, 4H), 7.61 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.26 (CH_3), 17.97 (CH_3), 25.70 (CH_3), 26.81 (CH_2), 60.87 (OCH_2), 121.33 (CH), 128.60 (2×CH), 130.41 (C), 130.64 (2×CH), 133.20 (C), 134.21 (C), 136.87 (C), 137.35 (CH), 168.03 (C=O); GC-MS: *m/z* 278 (M^+).

3d: Thick viscous liquid, yield 88%. b.p. 188-95°C/0.07 mm Hg (Bath temp.). IR (KBr): 1711 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3H, *J*=7.2 Hz), 1.64 (s, 3H), 1.68 (s, 3H), 3.19 (d, 2H, *J*=6.3 Hz), 3.78 (s, 3H), 4.21 (q, 2H, *J*=7.2 Hz), 5.1 (m, 1H), 6.84 (d, 2H, *J*=8.7 Hz), 7.31 (d, 2H, *J*=8.7 Hz), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.31 (CH_3), 18.01 (CH_3), 25.73 (CH_3), 26.80 (CH_2), 55.26 (OCH_3), 60.65 (OCH_2), 113.86 (2×CH), 121.84 (CH), 130.41 (C), 128.30 (C), 130.51 (C), 131.16 (2×CH), 132.90 (C), 138.50 (CH), 159.73 (C), 168.58 (C=O); GC-MS: *m/z* 274 (M^+).

3e: Thick viscous liquid, yield 84%. b.p. 175-80°C/0.06 mm Hg (Bath temp.). IR (KBr): 1705 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.33 (t, 3H, *J*=7.2 Hz), 1.70 (s, 3H), 1.75 (s, 3H), 3.23 (br.d, 2H, *J*=6.0 Hz), 4.27 (q, 2H, *J*=7.2 Hz), 5.15 (m, 1H), 6.00 (s, 2H), 6.81-6.92 (m, 3H), 7.60 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.29 (CH_3), 17.98 (CH_3), 25.71 (CH_3), 26.84 (CH_2), 60.72 (OCH_2), 101.24 (CH_2), 108.31 (CH), 109.4 (CH), 121.67 (CH), 124.34 (CH), 129.77 (C), 131.01 (C), 132.97 (C), 147.72 (2×C), 168.43 (C=O); GC-MS: *m/z* 288 (M^+).

(*E*) Ethyl -2-(3-methylbut-2-enyl)non-2-enoate, 3f

To a magnetically stirred suspension of PCC (1.5 mmole) and NaOAc (1.5 mmole) in anhyd. CH_2Cl_2 (10 mL), alcohol **2f** (1 mmole) in anhyd. CH_2Cl_2 (5 mL) was added followed by phosphorane[10] **1** (1 mmole) in one portion. After 3 hr, Et_2O (5 mL) was added and the supernatant solution was decanted from the black granular solid. The combined organic layers were filtered through a short pad of celite. The residue obtained after evaporation of the solvent was further purified by column chromatography (silica gel, hexanes) to afford pure **3f** as a thick viscous liquid. The spectral data of the compound **3f** is given below.

3f: Thick viscous liquid, yield 95%. b.p. 178-85°C/0.07 mm Hg (Bath temp.).

IR (KBr): 1715 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 0.91 (skewd t, 3H, *J*=6.9 Hz), 1.28-1.71 (m, 17H), 2.21 (m, 2H), 3.02 (d, 2H, *J*=6.6 Hz), 4.20 (q, 2H, *J*=7.2 Hz), 5.03 (m, 1H), 6.76 (t, 1H, *J*=7.5 Hz); ^{13}C NMR ($CDCl_3$): δ 14.01 (2×CH_3), 14.23 (CH_3), 22.53 (CH_2), 23.98 (CH_3), 28.59 (CH_2), 28.71 (CH_2), 28.78 (CH_2), 28.97 (CH_2), 31.62 (CH_2), 60.35 (OCH_2), 121.95 (CH), 131.58 (C), 131.79 (C), 142.63 (CH), 168.05 (C=O); GC-MS: *m/z* 252 (M^+).

(*E*) α-Benzylidene-δ-dimethyl-δ-lactones, 4a-e and (*E*) α-heptylidene-δ-dimethyl-δ-lactone, 4f

Compound **3a-f** (1 mmole) were added to the stirred solution of polyphosphoric acid (2 mL). The reaction mixture was warmed on water bath for 5 min. Chilled water (15 mL) was added to the reaction mixture and it was subsequently extracted with diethyl ether (3×10 mL). The organic layer was washed twice with saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. The solvent was removed under vaccum pump and the residue was purified by column chromatography (silica gel, hexanes-EtOAc, 9:1) to give pure **4a-f**. The spectral data of the compounds **4a-f** is given below.

4a: Thick colourless viscous liquid, yield 96%. b.p. 140-45°C/0.09 mm Hg (Bath temp.). IR (KBr): 1703 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.46 (s, 6H), 1.90 (t, 2H, *J*=6.9 Hz), 2.92 (dt, 2H, *J*=6.9 and 2.1 Hz), 7.38-7.51 (m, 5H), 7.96 (br.s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.69 (CH_2), 27.80 (2×CH_3), 33.16 (CH_2), 80.19 (C), 124.42 (C), 128.55 (2×CH), 129.14 (CH), 130.33 (2×CH), 135.13 (C), 141.51 (CH), 167.10 (C=O); HRMS: *m/z* Found 239.1049. Calcd for $C_{14}H_{16}O_2$, $[M+Na]^+$ 239.1048.

4b: White solid, yield 83%. m.p. 104-09°C. IR (KBr): 1691 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.41 (s, 6H), 1.80 (t, 2H, *J*=6.9 Hz), 2.66 (dt, 2H, *J*=6.9 and 2.4 Hz), 7.24 (m, 3H), 7.38 (m, 1H), 8.0 (br.s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.98 (CH_2), 27.93 (2×CH_3), 33.24 (CH_2), 80.60 (C), 126.31 (CH), 126.98 (C), 129.79 (2×CH), 129.82 (CH), 133.62 (C), 134.48 (C), 138.31 (CH), 166.12 (C=O); HRMS: *m/z* Found 251.0821. Calcd for $C_{14}H_{15}O_2Cl$, $[M+H]^+$ 251.0839.

4c: White solid, yield 79%. m.p. 103-07°C. IR (KBr): 1698 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.40 (s, 6H), 1.84 (t, 2H, *J*=6.9 Hz), 2.81 (dt, 2H, *J*=6.9 and 2.1 Hz), 7.30 (s, 4H), 7.83 (br. s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.62 (CH_2), 27.72 (2×CH_3), 33.02 (CH_2), 80.11 (C), 124.95 (C), 128.77 (2×CH), 131.43 (2×CH), 133.50 (C), 135.07 (C), 139.07 (C), 139.97 (CH), 166.62 (C=O); HRMS: *m/z* Found 273.0673. Calcd for $C_{14}H_{15}O_2Cl$, $[M+Na]^+$ 273.0658.

4d: White solid, yield 91%. m.p. 75-79°C. IR (KBr): 1695 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.39 (s, 6H), 1.84 (t, 2H, *J*=6.9 Hz), 2.83 (dt, 2H, *J*=6.9 and 2.4 Hz), 3.79 (s, 3H), 6.89 (d, 2H, *J*=9 Hz), 7.41 (d, 2H, *J*=9 Hz), 7.84 (br. s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.78 (CH_2), 27.67 (2×CH_3), 33.08 (CH_2), 55.27 (OCH_3), 79.71 (C), 113.99 (2×CH), 121.72 (C), 127.87 (C), 132.26 (2×CH), 141.16 (CH), 160.27 (C), 167.32 (C=O); HRMS: *m/z* Found 269.1146. Calcd for $C_{15}H_{18}O_3$, $[M+Na]^+$ 269.1154.

4e: White solid, yield 78%. m.p. 129-33°C. IR (KBr): 1686 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.46 (s, 6H), 1.91 (t, 2H, *J*=6.9 Hz), 2.88 (dt, 2H, *J*=6.6 and 2.1 Hz), 6.02 (s, 2H), 6.88 (d, 1H, *J*=8.4 Hz), 7.026-7.094 (m, 2H), 7.87 (br.s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.86 (CH_2), 27.76 (2×CH_3), 33.13 (CH_2), 79.85 (C), 101.5 (OCH_2O), 108.53 (CH), 109.87 (CH), 126.17 (CH), 141.29 (CH), 122.35 (C), 129.39 (C), 147.88 (C), 148.45 (C), 167.25 (C=O); HRMS: *m/z* Found 283.0945. Calcd for $C_{15}H_{16}O_4$, $[M+Na]^+$ 283.0946.

4f: Thick colourless viscous liquid, yield 81%. b.p. 210-12°C/0.07 mm Hg (Bath temp.). IR (KBr): 1722 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 0.90 (skewd t, 3H, *J*=6.6 Hz), 1.31-1.58 (m, 14H), 1.85 (t, 2H, *J*=6.9 Hz), 2.17 (q, 2H, *J*=7.2 Hz), 2.54 (br.t, 2H, *J*=6.9 Hz), 7.0 (t, 1H, *J*=7.5 Hz); ^{13}C NMR ($CDCl_3$): δ 13.98 (CH_3), 22.42 (CH_2), 24.63 (CH_2), 27.58 (CH_3), 27.71 (CH_3), 28.69 (CH_2), 29.37 (CH_2), 30.28 (CH_2), 33.80 (CH_2), 34.66 (CH_2), 80.4 (C), 126 (C), 138 (CH), 178.61 (C=O); HRMS: *m/z* Found 225.1850. Calcd for $C_{14}H_{24}O_2$, $[M+H]^+$ 225.1854.

Acknowledgement

The authors thank the UGC, New Delhi for financial assistance, NIO, Goa for spectral analysis and Department of Organic Chemistry, IISc, Bangalore for HRMS.

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