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Diastereoselective synthesis of dialkyl 4,5,5-triacetyl-3-methylcyclopent-3-ene-1,2-dicarboxylates

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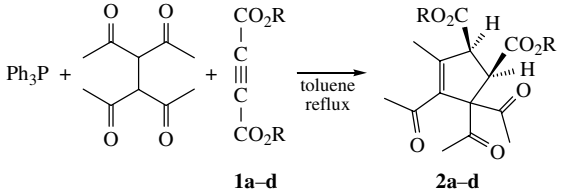
Tetraacetylethane (3,4-diacetylhexane-2,5-dione) undergoes a smooth reaction with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine to produce phosphorus ylide intermediates, which undergo a diastereoselective intramolecular Wittig reaction to produce dialkyl 4,5,5-triacetyl-3-methylcyclopent-3-ene-1,2-dicarboxylates in good yields.

Cyclopentenes are important intermediates in organic synthesis.[1] The intramolecular Wittig reaction[2] is useful for cycloalkene synthesis. The common five-, six-, and seven-membered ring cycloalkenes are produced easily by intramolecular Wittig reactions. Previously, we described the synthesis of cyclobutene derivatives using the stereoselective intramolecular Wittig reaction of a vinyltriphenylphosphonium salt.[3] As a part of our studies on heterocyclic and carbocyclic systems,[3,4] we report a convenient and facile synthesis of functionalised cyclopentenes *via* an intramolecular Wittig reaction. Thus, the reaction of tetraacetylethane with dialkyl acetylenedicarboxylates **1** in the presence of triphenylphosphine in boiling toluene led to dialkyl 4,5,5-triacetyl-3-methylcyclopent-3-ene-1,2-dicarboxylates **2** in moderate yields† (Scheme 1). Tetraacetylethane[5] is a readily available polycarbonyl system, which is apparently completely enolized in solution, as indicated by NMR spectroscopy.



Scheme 1

Structure **2** was assigned to the isolated products on the basis of their elemental analyses and IR, ^{1}H NMR, ^{13}C NMR, and mass-spectrometric data. For example, the ^{1}H NMR spectrum of **2a** displayed two doublets for vicinal methine protons at δ 3.78 and 4.20 ppm with a $^3J_{HH}$ value of 9 Hz, together with six singlets for methyl (δ 2.15, 2.21, 2.28, and 2.44 ppm) and methoxy (δ 3.68 and 3.83 ppm) protons. The ^{13}C NMR spectrum of **2a** exhibited sixteen resonances in agreement with the proposed structure. The ^{1}H and ^{13}C NMR spectra of **2b–d** are

similar to those of **2a**, except for the ester moieties. The two isopropyl groups in compound **2c** show two sets of diastereotopic methyl groups.

† Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses 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 NMR instrument with $CDCl_3$ as a solvent. Chemical shifts are reported relative to TMS as an internal standard. The reagents and solvents from Fluka were used.

Typical experimental procedure for the preparation of dimethyl 4,5,5-triacetyl-3-methylcyclopent-3-ene-1,2-dicarboxylate **2a**: a solution of dimethyl acetylenedicarboxylate (0.57 g, 4 mmol) in 5 ml of dry toluene was added dropwise to a stirred solution of tetraacetylethane (0.79 g, 4 mmol) and triphenylphosphine (1.05 g, 4 mmol) in dry toluene (20 ml) at 5 °C for 10 min. The reaction mixture was allowed to stay at room temperature for 2 h and then refluxed for 6 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}) using hexane–EtOAc (5:3) as an eluent. Zones were detected upon exposure to 366 nm UV light. The product was obtained by extraction of the silica gel with CH_2Cl_2. Yellow oil, yield 0.99 g (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.15 (d, 3H, Me, $^4J_{HH}$ 1.2 Hz), 2.21 (s, 3H, Me), 2.28 (s, 3H, Me), 2.44 (s, 3H, Me), 3.68 (s, 3H, OMe), 3.78 (d, 1H, CH, $^3J_{HH}$ 9.0 Hz), 3.83 (s, 3H, OMe), 4.21 (dq, 1H, CH, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 1.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 16.4 (Me), 27.4 (Me), 29.3 (Me), 31.3 (Me), 51.6 (CH), 52.8 (OMe), 53.2 (OMe), 58.4 (CH), 79.8 (C), 141.3 (C), 151.9 (C), 170.9 (C=O ester), 171.8 (C=O ester), 196.7 (C=O), 204.3 (C=O), 205.0 (C=O). IR (neat, ν_{max}/cm^{-1}): 3003, 2956 and 2929 (CH), 1738, 1714, 1660 and 1613 (C=O). MS (EI, 70 eV), *m/z* (%): 324 (M^+, 11), 293 (52), 281 (65), 265 (32), 264 (30), 221 (55), 180 (85), 60 (100), 43 (72). Found (%): C, 59.42; H, 6.30. Calc. for $C_{16}H_{20}O_7$ (324.3) (%): C, 59.25; H, 6.22.

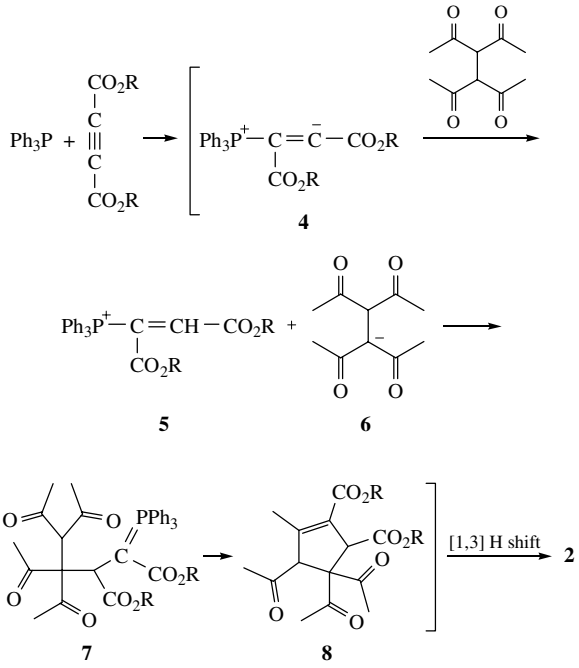
For diethyl 4,5,5-triacetyl-3-methylcyclopent-3-ene-1,2-dicarboxylate **2b**: yellow oil, yield 0.91 g (65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, 3H, OCH_2*Me*, $^3J_{HH}$ 7.2 Hz), 1.35 (t, 3H, OCH_2*Me*, $^3J_{HH}$ 7.2 Hz), 2.16 (d, 3H, Me, $^4J_{HH}$ 1.0 Hz), 2.22 (s, 3H, Me), 2.30 (s, 3H, Me), 2.44 (s, 3H, Me), 3.78 (d, 1H, CH, $^3J_{HH}$ 9.0 Hz), 4.13 (dq, 1H, CH, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 1.0 Hz), 4.16 (m, 2H, OCH_2, ABX_3 system), 4.29 (q, 2H, OCH_2, $^3J_{HH}$ 7.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.2 (Me), 14.6 (Me), 16.3 (Me), 27.5 (Me), 29.4 (Me), 31.3 (Me), 51.7 (CH), 58.6 (CH), 61.9 (OCH_2), 62.3 (OCH_2), 79.8 (C), 141.4 (C), 151.7 (C), 170.4 (C=O ester), 171.4 (C=O ester), 196.9 (C=O), 204.4 (C=O), 205.0 (C=O). IR (neat, ν_{max}/cm^{-1}): 2984 and 2932 (CH), 1733, 1715, 1660 and 1612 (C=O). MS (EI, 70 eV), *m/z* (%): 352 (M^+, 14), 309 (9), 289 (35), 288 (40), 245 (65), 180 (100), 165 (62), 137 (56), 74 (52), 73 (31), 45 (62), 43 (71). Found (%): C, 61.67; H, 6.92. Calc. for $C_{18}H_{24}O_7$ (352.4) (%): C, 61.35; H, 6.84.

For diisopropyl 4,5,5-triacetyl-3-methylcyclopent-3-ene-1,2-dicarboxylate **2c**: yellow oil, yield 1.06 g (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.18 (d, 3H, Me, $^3J_{HH}$ 6.2 Hz), 1.22 (d, 3H, Me, $^3J_{HH}$ 6.2 Hz), 1.25 (d, 3H, Me, $^3J_{HH}$ 6.2 Hz), 1.31 (d, 3H, Me, $^3J_{HH}$ 6.2 Hz), 2.13 (d, 3H, Me, $^4J_{HH}$ 1.4 Hz), 2.20 (s, 3H, Me) 2.28 (s, 3H, Me), 2.41 (s, 3H, Me), 3.72 (d, 1H, CH, $^3J_{HH}$ 9.0 Hz), 4.11 (dq, 1H, CH, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 1.4 Hz), 4.99 (sept., 1H, CH, $^3J_{HH}$ 6.2 Hz), 5.09 (sept., 1H, CH, $^3J_{HH}$ 6.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 16.2 (Me), 21.8 (Me), 22.0 (Me), 22.1 (Me), 22.2 (Me), 27.5 (Me), 29.4 (Me), 31.3 (Me), 51.8 (CH), 58.8 (CH), 69.7 (CH), 70.0 (CH), 79.7 (C), 141.4 (C), 151.5 (C), 169.8 (C=O ester), 171.0 (C=O ester), 197.1 (C=O), 204.5 (C=O), 204.9 (C=O). IR (neat, ν_{max}/cm^{-1}): 2983 and 2937 (CH), 1732, 1716, 1661 and 1612 (C=O). MS (EI, 70 eV), *m/z* (%): 380 (M^+, 16), 337 (18), 321 (29), 293 (41), 292 (54), 250 (19), 180 (75), 88 (62), 43 (100). Found (%): C, 63.42; H, 7.36. Calc. for $C_{20}H_{28}O_7$ (380.4): C, 63.14; H, 7.42.

*For di-*tert*-butyl 4,5,5-triacetyl-3-methylcyclopent-3-ene-1,2-dicarboxylate* **2d**: yellow oil, yield 1.22 g (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.38 (s, 9H, $OCMe_3$), 1.48 (s, 9H, $OCMe_3$), 2.10 (d, 3H, Me, $^4J_{HH}$ 1.0 Hz), 2.14 (s, 3H, Me), 2.21 (s, 3H, Me), 2.36 (s, 3H, Me), 3.61 (d, 1H, CH, $^3J_{HH}$ 9.0 Hz), 3.98 (dq, 1H, CH, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 1.0 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 16.2 (Me), 27.2 (Me), 28.2 (3Me), 28.4 (3Me), 29.2 (Me), 31.2 (Me), 52.2 (CH), 59.7 (CH), 79.7 (C), 82.7 (*C*Me), 82.8 (*C*Me), 141.1 (C), 151.6 (C), 169.3 (C=O ester), 170.6 (C=O ester), 197.2 (C=O), 204.6 (C=O), 204.8 (C=O). IR (neat, ν_{max}/cm^{-1}): 2980 and 2934 (CH), 1731, 1720, 1660 and 1610 (C=O). MS (EI, 70 eV), *m/z* (%): 408 (M^+, 16), 465 (43), 351 (34), 350 (24), 306 (38), 263 (42), 102 (68), 56 (100), 43 (73). Found (%): C, 64.65; H, 7.88. Calc. for $C_{22}H_{32}O_7$ (408.5) (%): C, 64.68; H, 7.90.

The stereochemical relationship of the vicinal methine protons is established by differential nuclear Overhauser measurment.[6,7] Thus, when the methine group of **2d** at δ 3.98 ppm is saturated, the intensity of the adjacent methine proton signal at δ 3.61 ppm decreases by 17%. When instead the other methine signal is saturated, a decrease of 18% is observed. The observation of a negative nOe for the methine protons in **2d** is consistent with a *cis* relationship. The coupling constant of 9 Hz is also consistent with a dihedral angle of ~0° compared with ~120° for *trans* hydrogens. The reaction is stereoselective and leads to one diastereoisomer, namely, 1*S*, 2*S* (or 1*R*, 2*R*). Our attempts to detect the second diastereomer in the reaction mixture were unsuccessful.

On the basis of the chemistry of trivalent phosphorus nucleophiles,[8–10] it is reasonable to assume that cyclopentenes **2** result from the initial addition of triphenylphosphine to the acetylenic ester with the subsequent protonation of reactive 1:1 adduct **4** by tetraacetylethane. Then, positively charged ion **5** is attacked by enolate anion **6** to form ylide **7**, which can undergo an intramolecular Wittig reaction to produce cyclopentene derivative **8**. Compound **8** apparently undergoes [1,3] hydrogen shift under the reaction conditions employed to produce **2** in fairly good yields (Scheme 2).



Scheme 2

This reaction of dialkyl acetylenedicarboxylates with tetraacetylethane in the presence of triphenylphosphine provides a simple one-pot entry into the diastereoselective synthesis of highly functionalised dialkyl 4,5,5-triacetyl-3-methylcyclopent-3-ene-1,2-dicarboxylates.

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