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A Synthesis of 3-Alkenylcycloalkenones

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In a recent study of the synthesis of LTB_3 leucotrienes[1] it had been necessary to condense dimethyl (lithiomethyl)phosphonate with dimethyl glutarate (**1b**) in order to prepare the 1:1 reaction product. Although this reaction proved feasible, it tended to furnish undesired side products whose origin could be attributed to a 2:1 condensation. The reaction now has been revisited in order to gain more insight into the latter observations.

$MeO_2C(CH_2)_nCO_2Me$

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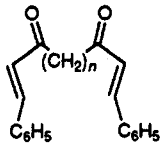
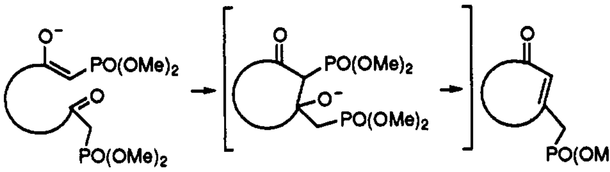


2

a, *n* = 2; **b**, *n* = 3; **c**, *n* = 4

When dimethyl glutarate (**1b**) was exposed to 4 equiv of dimethyl (lithiomethyl)phosphonate, cyclohexenone **4** could be isolated in 77% yield. Apparently the bis-ketophosphonate intermediate had undergone intramolecular aldol condensation, followed by phosphate elimination (eq 1). Condensation of dimethyl succinate (**1a**) with the lithiated phosphonic ester afforded cyclopentenone **3** in 51% yield. When, in an attempt to prepare the cycloheptenone equivalent of ketones **3** and **4**, dimethyl adipate (**1c**) was involved in the condensation, only intractable materials were formed.



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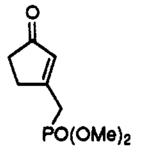

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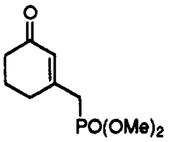
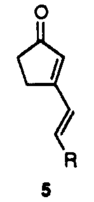


4

Since cycloalkenones **3** and **4** are vinylogues of the ketophosphonates normally employed for Horner–Emmons reactions with aldehydes and ketones, they were expected to perform similarly in such condensations. Indeed, for example, interaction of phosphonate **4** with *n*-butyllithium and then with acetaldehyde produced dienone **6b**[2] in 84% yield. However, it could be shown that all condensations from the diester to the ultimate dienone could be performed in a "one-pot" operation. Thus a combination of dimethyl (lithiomethyl)phosphonate, dimethyl glutarate (**1b**), and benzaldehyde provided dienone **6a**[2,3] in 71% yield. The same combination, except for dimethyl succinate (**1a**) replacing the glutaric ester, led to dienedione **2a** (13%) and dienone **5a** (46%). Finally, the combination in the case of the utilization of dimethyl adipate (**1c**) produced dienedione **2c** in 70% yield. It thus became clear that the intramolecular aldol condensation of the intermediate bis-ketophosphonates from the succinic and adipic esters is much slower than that of the glutarate-derived bis-ketophosphonate.



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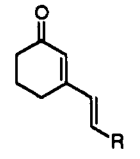

6

a, R = C_6H_5; **b**, R = CH_3

In conclusion, it is worth noting that the above chemistry constitutes a short, efficient, new synthesis of 3-alkenyl-2-cyclohexenones (and, to a lesser extent, of cyclopentenone equivalents).

Experimental Section

General. Melting points are uncorrected. Ultraviolet and infrared spectra were recorded on methanol solutions and on neat liquids (of liquid compounds) or KBr pellets (of solid compounds), respectively. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were observed at 300 and 50.3 MHz, respectively. All reactions were executed under nitrogen and all crude product solutions dried over Na_2SO_4.

3-((Dimethoxyphosphonyl)methyl)-2-cyclohexenone (4). A 2.5 M hexane solution of *n*-butyllithium (10 mL, 25 mmol) was added dropwise to a stirring solution of 3.10 g (25 mmol) of dimethyl methylphosphonate in 50 mL of dry THF at −78 °C under nitrogen, and the stirring was continued at this temperature for 0.5 h. Freshly distilled dimethyl glutarate (960 mg, 6 mmol) was added and the mixture stirred at −78 °C for 0.5 h. The latter was allowed to warm to −30 °C and the stirring was continued for 2 h. Glacial acetic (720 mg, 12 mmol) was added, the mixture permitted to reach room temperature, and stirring continued for 2 h. Upon the addition of 780 mg (13 mmol) more of acetic acid, the mixture was evaporated. The residue was treated with 100 mL of CH_2Cl_2 and 50 mL of 5% ammonium hydroxide. The separated organic phase was washed with brine and water, dried, and evaporated. Distillation of the pale yellow, residual oil (1.5 g) afforded 1.00 g (77%) of colorless, liquid ketone **4**: bp 182 °C (1 Torr); UV λ_{max} 234 nm (log ϵ 4.051); IR C=O 1668 (s), C=C 1625 (s), P=O 1253 (s), POR 1042 (s) cm^{-1}; ^1H NMR δ 1.83 (quint, 2, J = 6 Hz, C-5 Hs), 2.17 (t, 2, J = 6 Hz, C-4 Hs), 2.2–2.4 (m, 2, C-6 Hs), 2.61 (d, 2, J = 24 Hz, PCH_2), 3.58 (d, 6, J = 11 Hz, Me), 5.77 (d, 1, J = 5 Hz, H-2); ^{13}C NMR δ 22.1 (C-5), 29.9 (C-4; d, J = 2 Hz), 34.6 (CH_2P; d, J = 135 Hz), 36.5 (C-6), 52.5 (Me; d, J = 7 Hz), 128.9 (C-2; d, J = 11 Hz), 155.2 (C-3; J = 11 Hz), 198.4 (C=O); exact mass *m/e* 218.0704 (calcd for $C_9H_{15}O_4P$ 218.0708).

3-((Dimethoxyphosphonyl)methyl)-2-cyclopentenone (3). The above procedure was followed exactly, except for 880 mg (6 mmol) of dimethyl succinate being used, the reaction mixture having been refluxed for 4 h just prior to the second addition of acetic acid, and the final distillation having been replaced by chromatotron-aided purification (elution with 20:5:1 hexane/CH_2Cl_2/MeOH). It led to a 51% yield of colorless, liquid ketone **3**: UV λ_{max} 229 nm (log ϵ 4.063); IR C=O 1705 (s), C=C 1615 (s), P=O 1249 (s), POR 1029 (s) cm^{-1}; ^1H NMR δ 2.42 (t, 2, J = 4

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Hz, H-4), 2.73 (t, 2, $J = 4$ Hz, H-5), 3.00 (d, 2, $J = 23$ Hz, PCH$_2$), 3.76 (d, 6, $J = 11$ Hz, Me), 6.09 (s, 1, H-2); ^{13}C NMR δ 30.4 (C-P; d, $J = 137$ Hz), 32.1 (C-4; d, $J = 3$ Hz), 35.2 (C-5) 52.7 (Me; d, $J = 7$ Hz), 132.0 (C-2; d, $J = 10$ Hz), 170.4 (C-3; d, $J = 10$ Hz), 208.6 (C=O); exact mass *m/e* 204.0545 (calcd for $C_8H_{13}O_4P$ 204.0552).

3-Propenyl-2-cyclohexenone (6b).[2] A 2.5 M hexane solution of *n*-butyllithium (0.8 mL, 2 mmol) was added to a stirring solution of 440 mg (2 mmol) of phosphonate 4 in 20 mL of dry THF at −78 °C. The stirring was continued for 0.5 h and the mixture allowed to warm to room temperature. Acetaldehyde (176 mg, 4 mmol) was added and the stirring continued for 2 h. Ether was added and the solution washed with water, dried, and evaporated. Purification on a chromatotron (elution with hexane) gave 230 mg (84%) of colorless, liquid dienone **6b**:[2] UV λ_{max} 237 nm (log ϵ 4.196), 276 (4.28); IR C=O 1668 (s), C=C 1588 (m) cm^{-1}.

3-(β-Styryl)-2-cyclohexenone (6a).[2,3] The above procedure for the preparation of ketone 4 was followed exactly, except for the addition of 636 mg (6 mmol) of benzaldehyde instead of the second addition of acetic acid. Stirring of the reaction mixture was continued at room temperature for 4 h, whereupon 100 mL of ether was added and the mixture washed with water, dried, and evaporated. Crystallization of the residue from 9:1 hexane/Et$_2$O yielded 840 ng (71%) of dienone **6a**:[2,3] mp 68 °C; UV λ_{max} 235 nm (log ϵ 4.084), 322 (4.572); IR C=O 1649 (s), C=C 1615 (s), 1582 (s) cm^{-1}.

1,8-Diphenyl-1(*E*),7(*E*)-octadiene-3,6-dione (2a) and 3-(β-Styryl)-2-cyclopentenone (5a). The above procedure was followed exactly, except for the reaction mixture having been refluxed for 4 h prior to the second addition of acetic acid and then treated with 1.06 g (10 mmol) of benzaldehyde. The reaction mixture was stirred at room temperature for 4 h and ether added. The mixture was washed with water, dried, and evaporated. Chromatotron-aided separation of the residue (elution with 4:2:1 hexane/cyclohexane/EtOAc) afforded at first 230 mg (13%) pale yellow, crystalline dienedione **2a**: mp 121 °C (hexane); UV λ_{max} 220 nm (log ϵ 4.386), 292 (4.713); IR C=O 1691 (s), C=C 1612 (s) cm^{-1}.

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.79; H, 6.34. Found: C, 82.73; H, 6.25.

Second, there was obtained 510 mg (46%) of pale yellow, crystalline dienone **5a**: mp 103 °C (hexane–EtOH); UV λ_{max} 232 nm (log ϵ 3.986), 249 (3.992), 318 (4.667); IR C=O 1669 (s), C=C 1622 (s), 1582 (s) cm^{-1}.

Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.62; H, 6.62.

1,10-Diphenyl-1(*E*),9(*E*)-decadiene-3,8-dione (2c). The above procedure for the preparation of ketone 4 was followed exactly, except for the addition of 1.04 g (6 mmol) of dimethyl adipate and of 1.27 g (12 mmol) benzaldehyde instead of the second addition of acetic acid. (Refluxing of the reaction mixture prior to the addition of benzaldehyde, a method fostering ring closure, caused no change in the reaction outcome.) Stirring the mixture for 4 h at room temperature and subsequent reaction workup as above led to a material whose crystallization from ethanol gave 1.31 g (70%) of pale yellow, crystalline dienedione **2c**: mp 119 °C; UV λ_{max} 220 nm (log ϵ 4.424), 287 (4.732); IR C=O 1658 (s), C=C 1628 (s) cm^{-1}.

Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.98; H, 6.97. Found: C, 82.59; H, 6.94.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of 3 and 4 and ^{1}H and ^{13}C NMR spectral data of **2a**, **2c**, **5a**, **6a**, and **6b** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.