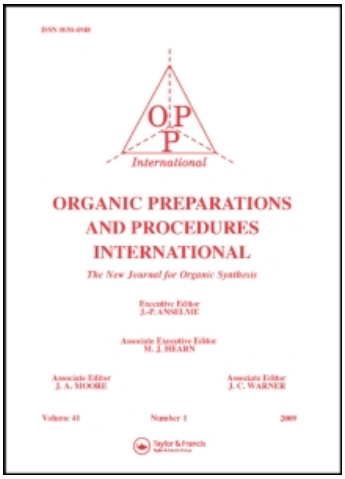

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A SYNTHESIS OF (E)-ω-CARBOXY-2-ALKENOIC ESTERS

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A SYNTHESIS OF (*E*)-ω-CARBOXY-2-ALKENOIC ESTERS

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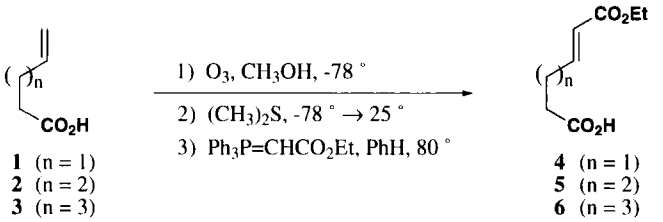
Substrates bearing differentiated functionality hold great value in organic synthesis. In the course of our studies, we needed access to 10-gram quantities of (*E*)-5-(ethoxycarbonyl)-4-pentenoic acid (**4**), (*E*)-6-(ethoxycarbonyl)-5-hexenoic acid (**5**) and (*E*)-7-(ethoxycarbonyl)-6-heptenoic acid (**6**). These compounds are known and have proven useful in a number of synthetic applications.[1-3] For example, **4** and **5** have been explored as annulating agents[1b,1c,2] while **6** has been employed in the synthesis of a leukotriene analogue.[3] In prior reports, these compounds were prepared by multistep

procedures (2-4 steps) with overall yields ranging from 18-75%. We report here a high-yield, one-flask procedure for the preparation of **4-6**.

The synthesis starts with ω-alkenoic acids (**1-3**), available commercially or by malonic ester synthesis.[4] Treatment of these acids with ozone at –78° in dichloromethane or methanol (see below) was followed by reduction of the ozonide with dimethyl sulfide and olefination using (ethoxycarbonylmethylene)triphenylphosphorane[5] in benzene. Workup by extraction with base followed by acidification then gave **4-6** in 86-96% yield. The isolated product contains 5-7% of the *Z* double bond isomer but is otherwise pure by NMR analysis.



1 (n = 1)
2 (n = 2)
3 (n = 3)

4 (n = 1)
5 (n = 2)
6 (n = 3)

It was generally found that dichloromethane was the best solvent for the reaction. Methanol could also be used but problems were sometimes encountered with acetal formation; the acetal failed to react with the Wittig reagent resulting in lower yields. Methanol-dichloromethane mixtures increased acetal formation due to traces of acid present in dichloromethane. Only in the case of **1** did methanol give a superior result.[6] Ozonolysis of **1** in dichloromethane produced a gelatinous residue on the inside of the flask that trapped some of the starting acid resulting in a *ca.* 5% contamination of the final product. This residue was not observed when the reaction was run in methanol. Treatment of **2** and **3** with ozone in dichloromethane gave cloudy mixtures but did not deposit significant quantities of insoluble material on the walls of the flask.

In conclusion, we have developed a simple and efficient route to (*E*)-ω-carboxy-2-alkenoic esters. The procedure requires only an intermediate change of solvent and produces material that can be used directly without purification. The reaction has been run routinely on scales that produce 8-10 grams of the final product, but larger runs are possible.

EXPERIMENTAL SECTION

Commercial reagents and solvents were used as received. The 6 M HCl, saturated Na_2CO_3 and saturated NaCl used in various procedures refer to aqueous solutions. Temperatures of –78° were obtained through the use of a dry ice-acetone bath. Reactions were monitored by TLC using UV light or I_2 for visualization. PTLC was carried out on 20-cm x 20-cm silica gel GF plates (Analtech no. 2015). IR spectra were run as thin films on NaCl disks and were referenced to polystyrene. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$. High resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

The 4-pentenoic acid used was commercial; 5-hexenoic acid and 6-heptenoic acid were prepared by alkylation of diethyl malonate with 4-bromo-1-butene and 5-bromo-1-pentene, respectively, followed by hydrolysis and decarboxylation.[4] (Ethoxycarbonylmethylene)triphenylphosphorane was prepared

according to the literature procedure.[5]

***Caution**: Though we have never experienced any problems with the ozonolysis procedures described below, caution is advised in working with the ozonolysis mixtures prior to treatment with the ylide.*

Representative Procedure for Ozonolysis and Wittig Reaction of ω-Alkenoic Acids in Methanol: (*E*)-5-(Ethoxycarbonyl)-4-pentenoic Acid (4).- A solution of 5.00 g (50.0 mmol) of 4-pentenoic acid in 150 mL of methanol was cooled to –78° and treated with ozone until TLC indicated complete consumption of starting material. Excess ozone was purged with a stream of dry nitrogen and 8.00 mL (6.77 g, 109 mmol) of dimethyl sulfide was added. The reaction mixture was warmed slowly to room temperature and stirred for 3 h under nitrogen. The mixture was concentrated by rotary evaporation, 25 mL of benzene was added and the mixture was again concentrated. The resulting oil was dissolved in 150 mL of benzene and 34.8 g (100 mmol) of (ethoxycarbonylmethylene)triphenylphosphorane was added; the solution became warm as the ylide dissolved. The reaction was stirred and heated at reflux under nitrogen for 12 h, then cooled to room temperature. The crude reaction mixture was extracted (3x) with saturated Na_2CO_3 and the combined washes were back extracted (1x) with ether. The carbonate solution was carefully acidified to a pH of 3 using 6 M HCl and extracted (3x) with ether. Concentration afforded 7.42 g (43.1 mmol, 86%) of **4** as a light yellow oil that was pure enough for most purposes. NMR analysis indicated that the product was a 95:5 *E*:*Z* mixture. An analytical sample was obtained by PTLC using 90:10 ether : hexane as the eluent.

IR 3722-2348, 1716, 1659 cm^{-1}; ^1H NMR δ 8.20 (br s, 1 H), 6.95 (dm, J = 15.7 Hz, 1 H), 5.87 (d, J = 15.7 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 2.54 (m, 4 H), 1.29 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 178.0, 166.4, 146.2, 122.4, 60.4, 32.1, 26.8, 14.2; HRMS *m/z*: calcd for $C_8H_{12}O_4$: 172.0735; found: 172.0733.

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 6.98. Found: C, 56.02; H, 7.00

Representative Procedure for Ozonolysis and Wittig Reaction of ω-Alkenoic Acids in Dichloromethane: (*E*)-6-(Ethoxycarbonyl)-5-hexenoic Acid (5).- A solution of 5.70 g (50.0 mmol) of 5-hexenoic acid in 150 mL of dichloromethane was cooled to –78° and treated with ozone until the solution turned a light blue color. Excess ozone was purged with a stream of dry nitrogen and 8.00 mL (6.77 g, 109 mmol) of dimethyl sulfide was added. The reaction mixture was warmed slowly to room temperature and stirred for 3 h under nitrogen, then concentrated by rotary evaporation. The resulting oil was dissolved in 150 mL of benzene, stirring was initiated, 34.8 g (100 mmol) of (ethoxycarbonylmethylene)triphenylphosphorane was added (a slight exotherm was noted), and the reaction was heated at reflux under nitrogen for 12 h. After cooling and workup as described above, the final organic extract gave 8.92 g (48.0 mmol, 96%, 93:7 *E*:*Z*) of **5** as a light yellow oil.

IR 3708-2285, 1716, 1659 cm^{-1}; ^1H NMR δ 8.09 (br s, 1 H), 6.94 (dt, J = 15.7, 6.9 Hz, 1 H), 5.85 (dt, J = 15.7, 1.5 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 2.39 (t, J = 7.4 Hz, 2 H), 2.27 (qd, J = 7.1 Hz, 1.5 Hz, 2 H), 1.83 (quintet, J = 7.4 Hz, 2 H), 1.29 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 179.0, 166.6, 147.6, 122.2, 60.3, 33.1, 31.2, 22.9, 14.2; HRMS *m/z*: calcd for $C_9H_{14}O_4$: 186.0892; found: 186.0891.

Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.53. Found: 58.17; H, 7.56

(*E*)-7-(Ethoxycarbonyl)-6-heptenoic Acid (6): 9.40 g (47 mmol, 94%, 93:7 *E*:Z); IR 3721-2318, 1716, 1659 cm^{-1}; ^1H NMR δ 8.58 (br s, 1 H), 6.95 (dt, *J* = 15.7, 6.9 Hz, 1 H), 5.83 (dt, *J* = 15.7, 1.5 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 2.38 (t, *J* = 7.3 Hz, 2 H), 2.23 (qd, *J* = 7.3, 12.5 Hz, 2 H), 1.67 (m, 2 H), 1.54 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR δ 179.4, 166.8, 148.4, 121.7, 60.2, 33.7, 31.7, 27.3, 24.1, 14.2; HRMS *m/z*: calcd for $C_{10}H_{16}O_4$: 200.1048; found: 200.1051.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00. Found: 60.24; H, 8.06

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