Stereoselective Synthesis of 2-Alkenoic Esters from Carbonyl Compounds and the Dilithio Derivative of Ethyl Mercaptoacetate

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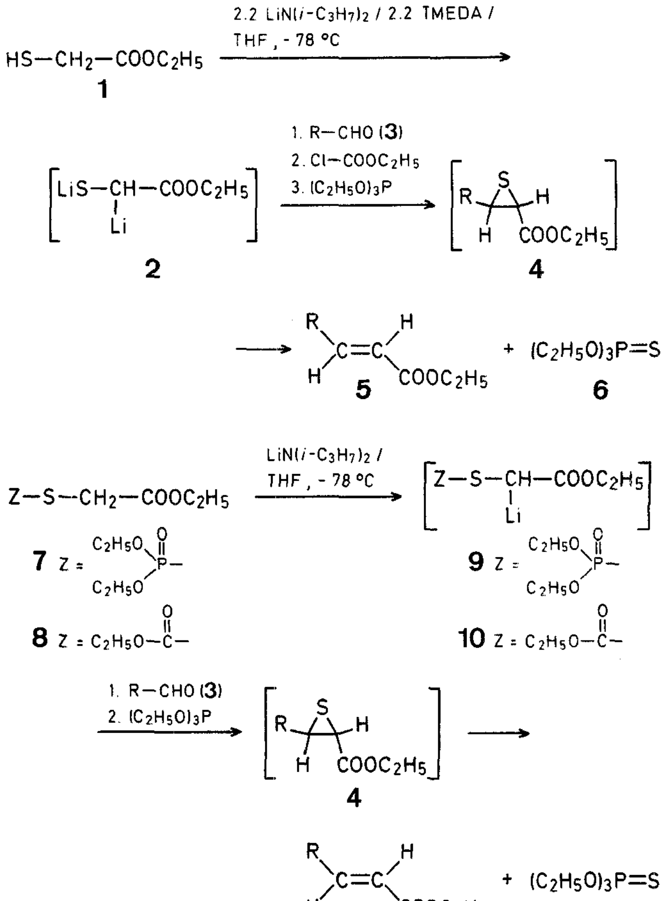
A number of methods have been reported for the synthesis of 2-alkenoic esters (α,β-unsaturated esters) employing phosphorus- and silicon-stabilized carbanions. 2-Alkenoic esters are useful intermediates in organic synthesis and constitute biologically active natural products[1]. However, there have been only a few methods for the stereoselective synthesis of these esters from carbonyl compounds using sulfur-stabilized carbanions[2]. Recently, a route to 2-alkenoic esters from carbonyl compounds and the dilithium enolate of ethyl mercaptoacetate was reported. Unfortunately, the yields were unsatisfactory[3].

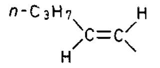
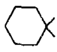
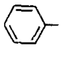
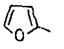
We have found that, when trivalent phosphorus compounds such as triethyl phosphite or hexamethylphosphorous triamide are used as desulfurization agent, the reaction of the dianion (**2**) derived from ethyl mercaptoacetate (**1**) with a variety of aldehydes (**3**) gives (*E*)-2-alkenoic esters (**5**) in high yield with higher than 85% stereoselectivity.

The monolithio derivatives **9** and **10** formed from *O,O*-diethyl *S*-ethoxycarbonylmethyl phosphorothioate[4] (**7**) and *O*-ethyl *S*-ethoxycarbonylmethyl thiocarbonate[5] (**8**) also react with aldehydes to give 2-alkenoic esters (**5**).



It is worthy of note that the reaction of dilithio derivative **2** with hexanal in the absence of a phosphorus(III) compound

Table 1. 2-Alkenoic Esters (**5**) prepared

Ester component	R	Product	Yield[a]	(*E*/*Z*)-Ratio[b]	b.p. [°C]/torr	Molecular formula[c] or b.p. [°C]/torr reported
1	n-C_5H_{11}	**5a**	72	85/15	64-65°/2	$C_{10}H_{18}O_2$ (170.3)
7	n-C_5H_{11}	**5a**	90	93/7		
1		**5b**	72	95/5	39-41°/1	$C_{10}H_{16}O_2$ (168.2)
8	n-C_6H_{13}	**5c**	80	97/3	72-73°/2	50°/1[3]
1	n-C_6H_{13}	**5c**	90	91/9		
1	n-C_7H_{15}	**5d**	78	88/12	87-88°/2	$C_{12}H_{22}O_2$ (198.3)
1	n-C_7H_{15}	**5d**	86[d]	74/26[d]		
7	n-C_7H_{15}	**5d**	85	88/12		
1	n-C_9H_{19}	**5e**	68	89/11	93-94°/2	$C_{14}H_{24}O_2$ (226.4)
7		**5f**	89	100/0	57-58°/2	$C_{11}H_{18}O_2$ (182.3)
1		**5g**	84	100/0	99-100°/2	86°/0.7[3]
1		**5h**	86	92/8	83-84°/2	$C_9H_{10}O_3$ (166.2)

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[a] Yield of isolated product.

[b] Determined by G.L.C. analysis (20% Silicon DC 550 on Celite 545; 0.15 cm × 120 cm) and ¹H-N.M.R. spectrometry.

[c] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.31; H, ±0.43.

[d] Hexamethylphosphorous triamide, $P[N(CH_3)_2]_3$, was used as desulfurization reagent.

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affords ethyl 2-octanoate (**5a**) in only 19% yield[3] whereas the same reaction in the presence of triethyl phosphite gives **5a** in 72% yield and the reaction of lithio derivative **9** with hexanal in the presence of triethyl phosphite gives **5a** in 90% yield.

The present methods for 2-alkenoic ester synthesis complements the Wittig and Wittig-Horner reactions and is attractive because of the mild conditions used, the high yield and stereoselectivity, and the ready availability of the starting materials.

Table 2. Spectral Data of Compounds **5**

5	I.R. (neat) $\nu_{C=C}$ [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS_{int}) δ [ppm] of (E)-Isomer
a	1640	6.82 (dt, 1H, $J=7$ Hz, 16 Hz, CH=C); 5.70 (d, 1H, $J=16$ Hz, CH=C); 4.08 (q, 2H, $J=7$ Hz, CH_2); 2.2 (m, 2H, CH_2); 1.5 (m, 9H, 3CH_2 and CH_3); 0.9 (m, 3H, CH_3)
b	1630	7.2 (m, 1H, CH=C); 6.1 (m, 2H, 2CH=C); 5.72 (d, 1H, $J=16$ Hz, CH=C); 4.13 (q, 2H, $J=7$ Hz, CH_2); 2.14 (q, 2H, $J=7$ Hz, CH_2); 1.5 (m, 2H, CH_2); 1.26 (t, 3H, $J=7$ Hz, CH_3); 0.9 (m, 3H, CH_3)
c	1645	6.84 (dt, 1H, $J=7$ Hz, 16 Hz, CH=C); 5.70 (d, 1H, $J=16$ Hz, CH=C); 4.10 (q, 2H, $J=7$ Hz, CH_2); 2.2 (m, 2H, CH_2); 1.5 (m, 11H, 4CH_2 and CH_3); 0.9 (m, 3H, CH_3)
d	1645	6.76 (dt, 1H, $J=7$ Hz, 16 Hz, CH=C); 5.72 (d, 1H, $J=16$ Hz, CH=C); 4.12 (q, 2H, $J=7$ Hz, CH_2); 2.1 (m, 2H, CH_2); 1.5 (m, 13H, 5CH_2 and CH_3); 0.9 (m, 3H, CH_3)[a]
e	1650	6.88 (dt, 1H, $J=7$ Hz, 16 Hz, CH=C); 5.74 (d, 1H, $J=16$ Hz, CH=C); 4.12 (q, 2H, $J=7$ Hz, CH_2); 2.1 (m, 2H, CH_2); 1.5 (m, 17H, 7CH_2 and CH_3); 0.9 (m, 3H, CH_3)
f	1640	6.83 (dd, 1H, $J=7$ Hz, 16 Hz, CH=C); 5.70 (d, 1H, $J=16$ Hz, CH=C); 4.13 (q, 2H, $J=7$ Hz, CH_2); 2.1 (m, 1H, CH); 1.8 (m, 4H, 2CH_2); 0.9 (m, 9H, 3CH_2 and CH_3)
g	1630	7.62 (d, 1H, $J=16$ Hz, CH=C); 7.4 (m, 5H, aromatic); 6.34 (d, 1H, $J=16$ Hz, CH=C); 4.18 (q, 2H, $J=7$ Hz, CH_2); 1.31 (t, 3H, $J=7$ Hz, CH_3)
h	1625	7.34 (d, 2H, $J=16$ Hz, 2CH=C); 6.4 (m, 2H, 2CH=C); 6.24 (d, 1H, $J=16$ Hz, CH=C); 4.17 (q, 2H, $J=7$ Hz, CH_2); 1.30 (t, $J=7$ Hz, CH_3)

[a] Spectrum of the (Z)-isomer (isolated by column chromatography on silica gel using benzene as eluent): $\delta=6.10$ (dt, 1H, $J=7$ Hz, 16 Hz, CH=C); 5.72 (d, 1H, $J=16$ Hz, CH=C); 4.10 (q, 2H, $J=7$ Hz, CH_2); 2.0 (m, 2H, CH_2); 1.4 ppm (m, 13H, 5CH_2 and CH_3).

Ethyl 2-Decenoate (5d); Typical Procedure:

A solution of ethyl mercaptoacetate (**1**; 1.403 g, 20 mmol) in tetrahydrofuran (5 ml) is added dropwise to a stirred mixture of lithium diisopropylamide (4.714 g, 44 mmol) and TMEDA (5.114 g, 44 mmol) in tetrahydrofuran (40 ml) at −78 °C. The mixture is stirred for 1 h, then a solution of octanal (2.565 g, 20 mmol) in tetrahydrofuran (5 ml) is added dropwise, and stirring at −78 °C is continued for 2 h. A solution of ethyl carbonochloridate (2.171 g, 20 mmol) in tetrahydrofuran (5 ml) is added dropwise, followed by triethyl phosphite (3.656 g, 22 mmol), and stirring is continued for 30 min at −78 °C and for 1 h at 30–35 °C. Then, saturated ammonium chloride solution (10 ml) is added and the mixture is poured into dilute hydrochloric acid (100 ml). The resultant mixture is extracted with ether (4 × 50 ml). The organic extract is washed with saturated sodium chloride solution (2 × 50 ml), dried with sodium sulfate, and concentrated under reduced pressure. The residual crude product **5d** is purified by column chromatography on silica gel using benzene as eluent to give pure **5d** as a 88 : 12 mixture of the (E)- and (Z)-isomer; yield: 3.1 g (78%).

$C_{12}H_{22}O_2$ (198.3)	calc.	C 72.73	H 11.11
	found	72.51	10.87

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