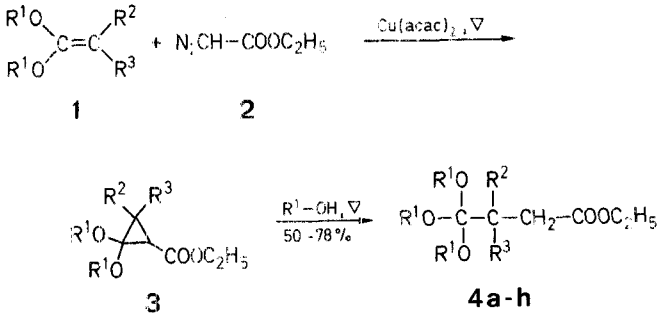
Reactions of Ketenes; XIX[1]. A General Method for the Synthesis of 4,4,4-Trialkoxybutanoic Esters

M. L. GRAZIANO*, M. R. IESCE

Dipartimento di Chimica Organica e Biologica dell'Università, via Mezzocannone 16, I-80134 Napoli, Italy

Only a limited number of 4,4,4-trialkoxybutanoic esters have been synthesized[2,3], and none has alkyl or aryl substituents. On the other hand, the stability of orthoesters under alkaline conditions together with their easier hydrolysis than that of the ordinary esters under acidic conditions makes the orthoester function a useful protecting group[4]. Therefore, it was desirable to develop a general procedure for the synthesis of bifunctional compounds with both alkoxycarbonyl and trialkoxymethyl groups.

Recently we reported that, in the presence of bis-[acetoacetonato]copper(II) [$Cu(acac)_2$], ketene dialkyl acetals **1** react with ethyl diazoacetate (**2**) to give the cyclopropanes **3** as the major products, which generally can be handled only in strictly anhydrous conditions since they easily undergo hydrolysis to ethyl 3-alkoxycarbonylpropanoates[1]. In order to obtain 4,4,4-trialkoxybutanoic esters **4**, we have now carried out the alcoholysis of the cyclopropanes **3**, prepared by a modification of the procedure previously described[1].



4	R^1	R^2	R^3
a	CH_3	H	H
b	C_2H_5	H	H
c	CH_3	CH_3	H
d	C_2H_5	CH_3	H
e	CH_3	C_2H_5	H
f	CH_3		H
g	CH_3	CH_3	CH_3
h	CH_3	$-(CH_2)_4-$	

As shown in the Table, the conversion of ketene dialkyl acetals **1** into esters **4** via cyclopropanes **3** has a wide range of applicability. Furthermore, the new synthetic method can be accomplished without isolation of the cyclopropane precursors, some of which are too unstable to be isolated by distillation (as previously reported, the cyclopropanes **3** having at least one hydrogen atom at position 3 isomerise on heating to ethyl 4,4-dialkoxybut-3-enoates[1]) or by chromatographic methods (with the exception of **3g**, cyclopropanes **3** undergo hydrolysis to ethyl 3-alkoxycarbonylpropanoates on contact with the absorbent[1]).

Table. Ethyl 4,4,4-Trialkoxybutanoates **4a–h** prepared

Product	Alcoholysis Time[a]	Yield[b] [%]	b.p. [°C]/torr	Molecular Formula[c] or Lit. b.p. [°C]/torr	I.R. (CCl_4)[d] ν[cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[e] δ[ppm]
4a	60 min	73	66–67°/1.5	$C_9H_{18}O_5$ (206.2)	1733	1.25 (t, J = 7 Hz, 3H, CH_2CH_3); 2.10–2.50 (m, 4H, $-CH_2-CH_2-$); 3.29 (s, 9H, $3OCH_3$); 4.15 (q, J = 7 Hz, 2H, OCH_2)
4b	60 min	70	93–95°/1.5	127–128°/18[3]	1735	1.18 (t, J = 7 Hz, 9H, $3OCH_2CH_3$); 1.25 (t, J = 7 Hz, 3H, $COOCH_2CH_3$); 2.10–2.50 (m, 4H, $-CH_2-CH_2-$); 3.54 (q, J = 7 Hz, 6H, $3OCH_2$); 4.15 (q, J = 7 Hz, 2H, $COOCH_2$)
4c	60 min	72	76–77°/2.5	$C_{10}H_{20}O_5$ (220.2)	1730	0.98 (d, J = 7 Hz, 3H, $CHCH_3$); 1.25 (t, J = 7 Hz, 3H, $COOCH_2CH_3$); 1.70–2.90 (m, 3H, $-CH-CH_2-$)[f]; 3.31 (s, 9H, $3OCH_3$); 4.14 (q, J = 7 Hz, 2H, $COOCH_2$)
4d	90 min	76	69–71°/0.5	$C_{13}H_{26}O_5$ (262.3)	1731	0.98 (d, J = 7 Hz, 3H, $CHCH_3$); 1.18 (t, J = 7 Hz, 9H, $3OCH_2CH_3$); 1.25 (t, J = 7 Hz, 3H, $COOCH_2CH_3$); 1.70–2.90 (m, 3H, $-CH-CH_2-$); 3.58 (q, J = 7 Hz, 6H, $3OCH_2$); 4.15 (q, J = 7 Hz, 2H, $COOCH_2$)
4e	60 min	78	68–70°/1.0	$C_{11}H_{22}O_5$ (234.3)	1730	0.91 (t, J = 7 Hz, 3H, CH_2CH_3); 1.25 (t, J = 7 Hz, 3H, $COOCH_2CH_3$); 0.95–1.35 (m, 2H, CH_2CH_3); 1.80–2.90 (m, 3H, $-CH-CH_2-$); 3.33 (s, 9H, $3OCH_3$); 4.12 (q, J = 7 Hz, 2H, $COOCH_2$)
4f	360 min	67	108–110°/0.4	$C_{15}H_{22}O_5$ (282.3)	1728	1.12 (t, J = 7 Hz, 3H, $COOCH_2CH_3$); 2.50–3.80 (m, 3H, $-CH-CH_2-$); 3.29 (s, 9H, $3OCH_3$); 4.05 (q, J = 7 Hz, 2H, $COOCH_2$); 7.30 (s, $5H_{arom}$)
4g	480 min	66	71–72°/0.5	$C_{10}H_{22}O_5$ (222.3)	1727	1.08 (s, 6H, $2CH_3$); 1.25 (t, J = 7 Hz, 3H, CH_2CH_3); 2.32 (s, 2H, CH_2); 3.36 (s, 9H, $3OCH_3$); 4.15 (q, J = 7 Hz, 2H, $COOCH_2$)
4h	480 min	50	90–91°/1.0	$C_{13}H_{26}O_5$ (262.3)	1725	1.25 (t, J = 7 Hz, 3H, $COOCH_2CH_3$); 1.40–2.00 [m, 8H, $-(CH_2)_4-$]; 2.31 (s, 2H, CH_2); 3.37 (s, 9H, $3OCH_3$); 4.14 (q, J = 7 Hz, 2H, $COOCH_2$)

[a] At solution reflux.
[b] Yield of pure isolated product; based on the ethyl diazoacetate (**2**) used.
[c] Satisfactory microanalises obtained: C ±0.24, H ±0.09, microanalyses by Mikroanalytisches Laboratorium E. Thommen, CH-4126 Bettingen, Switzerland.
[d] Perkin-Elmer 399 spectrophotometer.
[e] Varian EM-360 A spectrometer.
[f] In the ^{1}H-N.M.R. spectrum recorded on Bruker WH270 spectrometer in the range of δ = 1.5–2.8 ppm, the multiplet is simplified into three groups of signals at δ = 2.12 (dd, 1H, J = 15.4 Hz, 9.2 Hz); 2.51 (m, 1H, on decoupling methyl protons at δ = 0.98 resolved into dd, J = 4.1 Hz, 9.2 Hz); 2.63 ppm (dd, 1H, J = 4.1 Hz, 15.4 Hz).

Ethyl 4,4,4-Trialkoxybutanoates 4; General Procedure:
A solution of ethyl diazoacetate (**2**; 10 mmol) in dry benzene (4 ml) is added dropwise to a stirred suspension of $Cu(acac)_2$ (4.6×10^{-2} mmol) in ketene acetal **1** (25 mmol) and dry benzene (2.5 ml) heated at 85°C (oil bath). The catalyst dissolves readily after addition of a few drops of the diazoester solution. When the addition is complete (60 min), the mixture is heated at 85°C for a further 20 min. Then dry methanol (10 ml) [dry ethanol (10 ml) in the preparation of **4b** and **4d**] is added and the resulting solution is refluxed for the time given in the Table, until complete disappearance of cyclopropanes **3** as monitored by ^{1}H-N.M.R. spectrometry. The solvents are removed under reduced pressure and the residue is distilled in vacuo to give, first, the orthoester derived from alcohol addition to unreacted ketene acetal **1** and then pure **4**.

Ethyl 2,2-Dimethoxycyclopropane-1-carboxylates 3e, 3f, and 3h:
The previously unreported cyclopropanes **3e** and **3h** can be isolated, after completion of the reaction between ketene acetals **1e**[5] and **1h**[6] and ethyl diazoacetate (**2**), by removal of benzene and distillation in vacuo.

3e; yield: 75%; b.p. 70–71°C/4 torr.

$C_{10}H_{18}O_4$ (202.2) calc. C 59.38 H 8.97
found 59.28 8.95

I.R. (CCl_4): ν = 1723 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 0.9–2.15 (m, 4H, CH—CH—CH_2); 1.00 (t, J = 7 Hz, 3H, CH_2CH_3); 1.25 (t, J = 7 Hz, 3H, OCH_2CH_3); 3.39 (s, 3H, OCH_3); 3.42 (s, 3H, OCH_3); 4.15 ppm (q, J = 7 Hz, 2H, OCH_2).

3h; yield 48%; b.p. 74–75°C/1.5 torr.

$C_{12}H_{20}O_4$ (228.3) calc. C 63.13 H 8.83
found 63.07 8.81

I.R. (CCl_4): ν = 1725 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.23 (t, J = 7 Hz, 3H, CH_3); 1.55–2.15 [m, 9H, $-(CH_2)_4-$ + CH]; 3.36 (s, 6H, $2OCH_3$); 4.15 ppm (q, J = 7 Hz, 2H, OCH_2).

The known **3f** obtained in a purity of ~80% (^{1}H-N.M.R.) by a different route[7] was prepared as described above. Distillation

yielded a fraction (b.p. 150–160°C/0.2 torr) consisting (^{1}H-N.M.R.) of ~ 60% of the cyclopropane **3f**[8]; yield of **3f**: ~ 35% (^{1}H-N.M.R.).

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[1] For Part XVIII, see: Graziano, M.L., Scarpati, R. *J. Chem. Soc. Perkin Trans. 1* **1985**, 289.
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[8] Detailed results on the reaction will be published soon; Graziano, M.L., Iesce, M.R., Scarpati, R., in preparation.