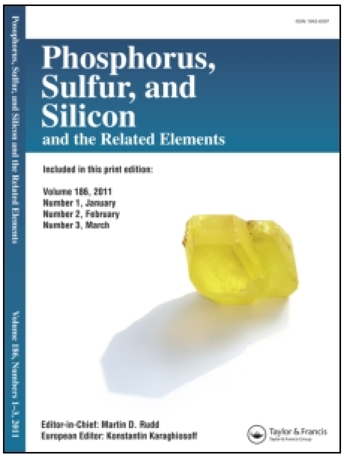

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF PROTECTED α-KETOESTER DERIVATIVES USING SILYL KETENE ACETALS OF ALKYL DIALKOXYACETATES

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To cite this Article Malhiac, Catherine , Tekin, Jacques , Ramiandrasoa, Guy , Leveque, Hubert and Combret, Jean-Claude(1995) 'SYNTHESIS OF PROTECTED α-KETOESTER DERIVATIVES USING SILYL KETENE ACETALS OF ALKYL DIALKOXYACETATES', Phosphorus, Sulfur, and Silicon and the Related Elements, 102: 1, 127 — 132

To link to this Article: DOI: 10.1080/10426509508042550

URL: http://dx.doi.org/10.1080/10426509508042550

Phosphorus, Sulfur, and Silicon, 1995, Vol. 102, pp. 127–132
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SYNTHESIS OF PROTECTED α-KETOESTER DERIVATIVES USING SILYL KETENE ACETALS OF ALKYL DIALKOXYACETATES

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(Received November 28, 1994; in final form January 10, 1995)

Two readily accessible $(RO)_2\,C{=}C(OSiMe_3)(OR)$ react smoothly with oxygenated electrophiles (aldehydes, ketals, orthoesters) leading, with good yields, to the corresponding β-functionalized α,α dialkoxyesters.

Key words: 1,2,2 trialkoxy-1-trimethylsilyloxyethylene, silyl ketene acetals, aldol-type reactions, protected α-ketoester derivatives, nucleophilic synthon C2.

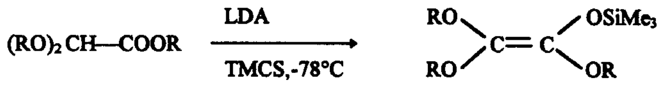
INTRODUCTION

α-Ketoesters and derivatives of pyruvic acid, besides their important role in various biological processes,[1] are very useful compounds in organic synthesis.[2]

We present in this work a facile synthesis of the silyl ketene acetals **2**, from corresponding alkyl dialkoxyacetates **1**, and various examples of their reactivity. The protected forms of β-functionalized esters **4**, **6**, **8** thus obtained are valuable intermediates for the selective synthesis of dihydroxy and hydroxyamino esters (acids).

RESULTS AND DISCUSSION

The silyl ketene acetals **2** are prepared from the derivatives of glyoxylic esters **1** using a method close to that described by AINSWORTH[3] with addition of chlorotrimethylsilane (TMCS) to the base at −78°C before introduction of the ester. The conjugated anion of **1** is thus trapped in situ and yield mainly **2**, avoiding the Claisen reaction that predominates in the condition of the preceding reference.



1a R= CH_3
b R= C_2H_5

2a-b

Two 1,2,2 trialkoxy-1-trimethylsilyloxyethylenes **2** are obtained with good yields and their main characteristics are collected in Table I.

TABLE I

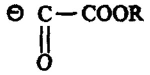
Physical properties of the compounds **2a** and **2b**

	R	Yield *	bp °C/ mmHg	^{1}H NMR	MS m / e
2a	CH_3	75%	80/15	0.20(9H,s) ; 3.50(3H,s) 3.52(3H,s) ; 3.55(3H,s)	206 73(100)
2b	C_2H_5	70%	100/16	0.16(9H,s) ; 1.20(9H,m) 3.75(4H,m) ; 4.20(2H,m)	248 73(100)

* Yield after distillation

As indicated, these silyl ketene acetals are easily isolated, purified by distillation and may be stored under inert gas at low temperature (−15°C) for a few weeks.

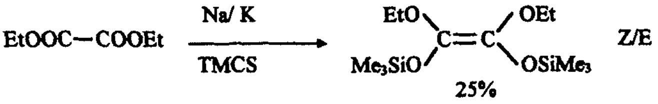
These reagents are valuable synthetic equivalents of the nucleophilic synthon C2 **2′** owing to the known reactivity of silyl ketene acetals. Other equivalents of the synthon C2 have already been described, such as the anions of protected forms (acetals,[4] thioacetals[5]) of glyoxylic esters of silyl derivatives from oxalic ester.[6]



$\ominus\,\underset{\displaystyle \overset{\|}{O}}{C}-COOR$ **2'**

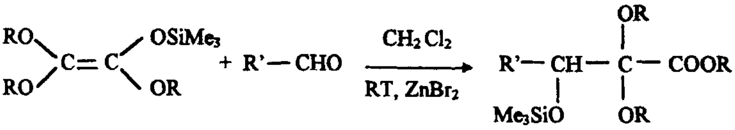
The instability of the anionic reagents and important side reactions may explain their limited use in the field of alkylation and some aldol-type reactions.

The silyl derivative described more recently by Reetz and coll. is rather stable and reactive but unfortunately difficult to obtain as outlined in the following scheme.[6]



As expected, compounds **2** react smoothly with various oxygenated electrophilic reagents using a stoichiometric amount of zinc bromide (ketones, however, do not lead to satisfactory results in these conditions owing to lack of reactivity).

Thus, β silyloxy α,α dialkoxyesters **4** are isolated in good yields from different aldehydes. β silyloxy α,α dialkoxyesters **4** are easily isolated, purified and characterised (Table II) as are the corresponding free hydroxyesters (after treatment with acidic water).



2 **3** **4 a-i**

The synthesis and properties of these protected forms of β-hydroxy α-ketoesters have been studied in our laboratory.[7] In the same way, protected esters such as "alkoxyacetals" **6** or "bis acetals" **8** esters are formed from ketals **5** and orthoesters **7**. A few examples (not yet optimised) of these reactions are summarised in Table

TABLE II

Physical properties of the compounds **4**

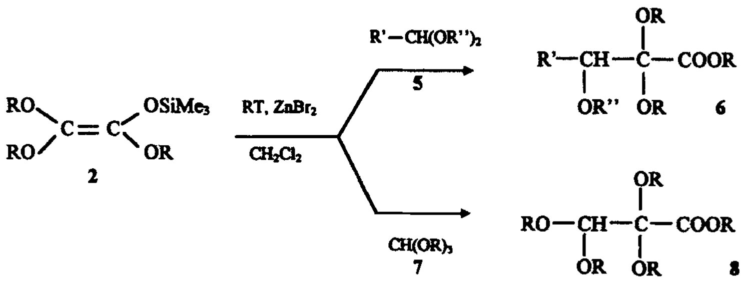
	R	R'	Time	Yield	bp °C / x mmHg
4 a	CH_3	CH_3	2h	70%	70 / 2
4 b	CH_3	iC_3H_7	2h	80%	78 / 2
4 c	CH_3	ϕ	3h	75%	130 / 2
4 d	CH_3	CH_3-CH=CH	6h	80%	90 / 2
4 e	CH_3	ϕ-CH=CH	6h	80%	140 / 2
4 f	C_2H_5	iC_3H_7	2h	70%	82 / 2
4 g	C_2H_5	ϕ	2h	71%	135 / 2
4 h	C_2H_5	CH_3-CH=CH	6h	82%	110 / 2

TABLE III

Physical properties of the compounds **6** and **8**

	R	R'	R"	Time	Yield	bp °C/x mmHg
6a	CH_3	CH_3	C_2H_5	12h	70%	85 / 2
6b	CH_3	ϕ	CH_3	18h	75%	130 / 2
6c	C_2H_5	CH_3	C_2H_5	12h	70%	85/2
6d	C_2H_5	ϕ	C_2H_5	18h	65%	135 / 2
8a	CH_3	—	—	18h	70%	80/2
8b	C_2H_5	—	—	18h	70%	95/2

III. The reaction of **2** with aminoderivatives of carbonyl compounds is currently being studied and further work on selective synthetic use of these protected esters is under way.



EXPERIMENTAL

^1H NMR spectra were recorded on a BRUCKER AC 200 spectrometer in $CDCl_3$ as solvent. All RMN spectra were measured with $SiMe_4$ as internal standard.

Mass spectra were recorded on a GC/MS HEWLETT-PACKARD HP 5890/MCD HF 5970 at 70 eV.

General procedure for addition of **2** *to aldehydes* **3**, *ketals* **5** *and orthoformiate* **7**. All reactions are carried out under inert gas atmosphere. To a mixture of oxygenated electrophile (10^{-2} mole/10 cm^3 CH$_2$Cl$_2$) and zinc bromide (10^{-2} mole/C = 2 M/l) is added a solution of **2** (10^{-2} mole/10 cm^3 CH$_2$Cl$_2$). The mixture is stirred continuously for the time indicated in Table II or III. Solvents are evaporated, 20 cm^3 of water is added to the residue. The aqueous layer is extracted with diethylether. The organic extracts are combined, dried with MgSO$_4$, then evaporated in vacuo.

The crude product may be purified by distillation.

Hydrolysis of **4**: *β-hydroxy-α,α-dialkoxyesters* **4'**. The residue is treated with acidic water (10% HCl solution) for during 30 minutes. After neutralisation (NaOH 10%), the β hydroxy-α,α-dialkoxy ester is extracted with diethylether. The organic extracts are combined, dried with MgSO$_4$ and evaporated in vacuo.

β-silyloxy-α,α-dialkoxyesters **4**

Methyl 2,2-dimethoxy-3-trimethylsilyloxybutanoate **4a**

M = 250 g/mol bp = 70°C/2 mmHg
^{1}H NMR 0.12 (9H, s); 1.19 (3H, d J = 6.7 Hz); 3.30 (3H, s); 3.39 (3H, s); 3.83 (3H, s); 4.12 (d, 1H J = 6.7 Hz)
m/e 219; 206; 203; 191; 133; 117; 89; 73 (100); 59

Methyl 2,2-dimethoxy-3-trimethylsilyloxy-4-methylpentanoate **4b**

M = 278 g/mole bp = 78°C/2 mmHg
^{1}H NMR 0.12 (9H, s); 0.77 (3H, d J = 2.7 Hz); 0.87 (3H, d J = 2.7 Hz); 1.27 (1H, m); 3.23 (3H, s); 3.28 (3H, s); 3.63 (3H, s); 3.75 (d, 1H J = 6.4 Hz)
m/e 235; 219; 191; 206; 145; 133; 73 (100); 59; 43

Methyl 2,2-dimethoxy-3-trimethylsilyloxy-3-phenylpropanoate **4c**

M = 312 g/mole bp = 130°C/2 mmHg
^{1}H NMR 0.10 (9H, s); 3.12 (3H, s); 3.46 (3H, s); 3.76 (3H, s); 3.75 (d, 1H J = 6.4 Hz); 5.10 (1H, s); 7.34 (5H, m)
m/e 281; 253; 206; 179 (100); 133; 89; 73; 59

Methyl 2,2-dimethoxy-3-trimethylsilyloxyhex-4-enoate **4d**

M = 312 g/mole bp = 90°C/2 mmHg
^{1}H NMR 0.10 (9H, s); 1.75 (3H, d J = 6.3 Hz); 4.40 (1H, d J = 6.25 Hz); 3.34 (3H, s); 3.40 (3H, s); 3.82 (3H, s); 5.57 (1H, d-d J = 14.6 Hz J = 6.30 Hz); 5.83 (1H, m)
m/e 261; 245; 229; 217; 206; 191; 143; 133 (100); 113; 89; 73; 59; 45

Methyl 2,2-dimethoxy-3-trimethylsilyloxy-5-phenylpent-4-enoate **4e**

M = 338 g/mole bp = 140°C/2 mmHg
^{1}H NMR 0.10 (9H, s); 3.35 (3H, s); 3.40 (3H, s); 3.76 (3H, s); 4.59 (1H, d J = 6 Hz); 6.32 (1H, d-d J = 16 Hz J = 6 Hz); 6.55 (1H, d J = 16 Hz); 7.23 (5H, m)
m/e 307; 291; 279; 249; 206 (100); 175; 133; 115; 89; 73; 59

Ethyl 2,2-diethoxy-3-trimethylsilyloxy-4-methylpentanoate **4f**

M = 320 g/mole bp = 82°C/2 mmHg
^{1}H NMR 0.10 (9H, s); 0.83 (3H, d J = 3.9 Hz); 0.86 (3H, d J = 3.9 Hz); 1.20 (9H, m); 3.56 (4H, m); 3.78 (1H, d J = 3.9 Hz); 4.20 (2H, q J = 3.8 Hz)
m/e 275; 247; 219; 185; 175; 145; 119; 103; 91; 73 (100); 45

Ethyl 2,2-diethoxy-3-trimethylsilyloxy-3-phenylpropanoate **4g**

M = 354 g/mole bp = 135°C/2 mmHg
^{1}H NMR 0.10 (9H, s); 1.26 (9H, m); 3.72 (4H, m); 4.20 (2H, J = 6.25 Hz); 5.09 (1H, s); 7.30–7.47 (5H, m)
m/e 309; 295; 281; 237; 264; 209; 191; 179; 175; 163; 147; 119; 106; 91; 73; 46; 29 (100)

Ethyl 2,2-diethoxy-3-trimethylsilyloxyhex-4-enoate **4h**

M = 318 g/mole bp = 110°C/2 mmHg
^{1}H NMR 0.10 (9H, s); 1.25 (9H, m); 1.75 (3H, d J = 6.3 Hz); 3.72 (4H, q J = 6.7 Hz); 4.23 (2H, q 6.4 Hz); 4.85 (1H, d J = 4 Hz); 5.66 (1H, m); 5.83 (1H, m)
m/e 273; 245; 219; 201; 175 (100); 147; 143; 119; 91; 73; 29

β-hydroxy-α,α-dialkoxy esters **4'**

4'a 4'b 4'c 4'f 4'g have already been described (7).

Methyl 3-hydroxy-2,2-dimethoxyhex-4-enoate **4'd**

M = 204 g/mole bp = 82°C/2 mmHg
^{1}H NMR 1.70 (3H, d J = 65.33 Hz); 3.27 (3H, s); 3.33 (3H, s); 3.73 (3H, s); 4.30 (1H, d J = 4 Hz) 5.33 (1H, d-d J = 14.7 Hz J = 4 Hz); 5.63 (1H, m)
m/e 173; 145; 133 (100); 85; 59

Methyl 3-hydroxy-2,2-dimethoxy-5-phenylpent-4-enoate **4'e**

M = 266 g/mole bp = 115°C/0.5 mmHg
^{1}H NMR 3.37 (3H, s); 3.43 (3H, s); 3.67 (3H, s); 4.50 (1H, d J = 4.5 Hz); 6.13 (1H, d-d J = 16 Hz J = 4.5 Hz); 6.63 (1H, d J = 15.8 Hz) 7.17 (5H, m)
m/e 133 (100); 89; 59; 43

Ethyl 3-hydroxy-2,2-diethoxyhex-4-enoate **4'h**

M = 246 g/mole bp = 87°C/0.8 mmHg
^{1}H NMR 1.25 (9H, m); 1.70 (3H, d J = 5.3 Hz); 3.72 (4H, q J = 6.7 Hz); 4.20 (2H, q 6.7 Hz); 4.85 (1H, d J = 4 Hz); 5.66 (1H, m); 5.83 (1H, m)
m/e 201; 175; 147; 119; 91; 71; 47; 29 (100)

β-alkoxy-α,α-dialkoxyesters **6**

Methyl 2,2-dimethoxy-3-ethoxylbutanoate **6a**

M = 206 g/mole bp = 82°C/2 mmHg
^{1}H NMR 1.2 (3H, d J = 6.7 Hz); 1.15 (3H, t J = 6.7 Hz); 3.30 (6H, s); 3.40 (2H, q J = 6.7 Hz); 4.77 (3H, s); 4.75 (1H, q J = 6.7 Hz)
m/e 147; 133; 119; 101; 87; 73; 59; 45 (100); 28

Methyl 2,2,3-methoxy-3-phenyl-propanoate **6b**

M = 254 g/mole bp = 130°C/2 mmHg
^{1}H NMR 3.25 (3H, s); 3.32 (6H, s); 3.42 (3H, s); 3.66 (3H, s); 4.54 (1H, s); 7.35 (5H, s)
m/e 223; 195; 145; 133 (100); 121; 105; 101; 77; 59

Methyl 2,2,3-triethoxy butanoate **6c**

M = 248 g/mole bp = 85°C/2 mmHg
^{1}H NMR 1.25 (15H, m); 3.72 (6H, m); 4.27 (2H, q J = 6.67 Hz); 4.68 (1H, q J = 6.67 Hz)
m/e 203; 175; 158; 147; 129; 119; 101; 91; 73; 45 (100); 29

Ethyl 2,2,3-ethoxy-3-phenyl-propanoate **6d**

M = 296 g/mole bp = 135°C/1 mmHg
^{1}H NMR 1.22 (12H, m); 3.56 (6H, m); 4.17 (2H, q J = 5.33 Hz); 4.58 (1H, s); 7.34 (5H, m)
m/e 223; 175 (100); 163; 135; 121; 119; 106; 103; 91; 77; 47; 29

α,α,β,β-tetraalkoxyesters

Methyl 2,2,3,3-tetramethoxypropanoate **8a**

M = 208 g/mole bp = 80°C/2 mmHg
^{1}H NMR 3.46 (12H, m); 3.52 (3H, s); 3.86 (1H, s)
m/e 177; 149; 133; 103; 75 (100); 59; 47;

Ethyl 2,2,3,3-tetraethoxy propanoate **8b**

M = 278 g/mole bp = 95°C/2 mmHg
^{1}H NMR 1.24 (15H, m); 3.72 (8H, m); 4.27 (1H, q J = 6.7 Hz); 4.68 (1H, s)
m/e 233; 205; 188; 175; 147; 131; 119; 103 (100); 75; 47; 29

REFERENCES AND NOTES

1. C. Klein, G. Schulz and W. Steglich. *Lieb. Ann. Chem.*, 1623 (1983) and references cited therein.
2. For a recent example P. F. Schuda, C. Ebner and S. J. Potlock, *Synthesis*, 1055 (1987).

3. C. Ainsworth, F. Chen and Y.-N. Kuo, *J. Organometal. Chem.*, **46,** 59 (1972).
4. R. E. Damon and R. H. Schlessinger, *Tetrahedron Lett.*, **51,** 4551 (1975); F. Huet, M. Pellet and J. M. Conia, *Synthesis*, 33 (1979).
5. E. L. Eliel and A. A. Hartmann, *J. Org. Chem.*, **37,** 505 (1972); L. M. Lerner, *J. Org. Chem.*, **41,** 2228 (1975); G. S. Bates, *JCS Chem. Com.*, 161 (1979); G. S. Bates and S. Ramaswamy, *Can. J. Chem.*, **58,** 716 (1980); M. L. Lissel, *Synth Comm.*, **11,** 343 (1981); R. J. Cregge, J. L. Herrmann, J. E. Richman, R. F. Romanet and R. H. Schlessinger, *Tetrahedron Lett.*, **28,** 2595 (1973); J. L. Herrmann, J. E. Richman and R. H. Schlessinger, *Tetrahedron Lett.*, **28,** 2599 (1973).
6. M. T. Reetz, H. Heimbach and K. Schwellnus, *Tetrahedron Lett.*, **25,** 2599 (1984).
7. J. C. Combret and J. M. Patard, *C.R. Acad. Sc. Paris, C*, 281, 329 (1975); D. Gosselin, Ph.D. Thesis, Rouen, France, 1984; G. Ramiandrasoa, Ph.D. Thesis, Rouen, France, 1993.