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A Rearrangement of O,O-Silylketene Acetals Leading to γ-Thiomethylation of Butenoic Acid Derivatives

Libuse Jaroskova, Manuel Bourgaux, Isabelle Wenkin and Leon Ghosez*

Laboratoire de Chimie organique de Synthèse, Université catholique de Louvain, Place Louis Pasteur 1, B-1348 Louvain-la-Neuve, Belgium.

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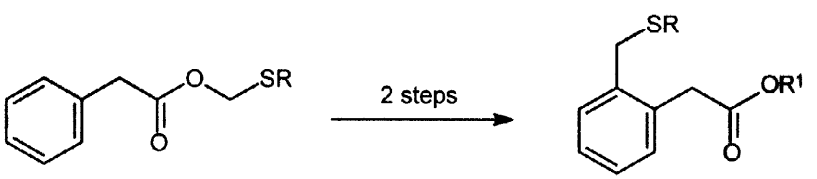
Abstract : Methylthiomethyl esters of α,β-unsaturated acids **2** were converted into the corresponding ketene acetals **3** by O-silylation. Ketene acetals rearranged in refluxing toluene to give, after methanolysis, the corresponding γ-methylthiomethyl substituted methyl esters **4**. In the case of phenylthiomethylesters the products of α-substitution were observed. © 1998 Published by Elsevier Science Ltd. All rights reserved.

We recently reported an unusual rearrangement of O,O-silylketene acetals derived from methylthiomethyl- and phenylthiomethyl-arylacetic esters to the corresponding ortho-substituted arylacetic silylesters or acids[1] (Scheme 1).



Scheme 1

The proposed mechanism for this smooth isomerisation reaction consists of two successive shifts of CH_2SR group. The first step leads to the formation of an intermediate sulfonium ylide that undergoes a fast [2,3] shift to yield the ortho-substituted aryl acetic acid derivatives. Now we describe an extension of these findings to α,β-unsaturated acid derivatives which leads to γ-substituted-α,β-unsaturated acids (Scheme 2).

* e-mail : ghosez@chor.ucl.ac.be fax : + 32-10.47.41.68

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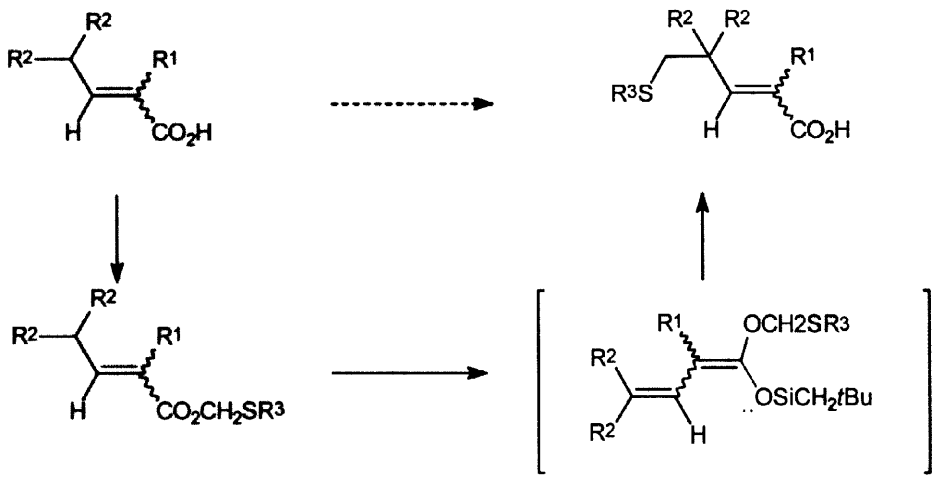
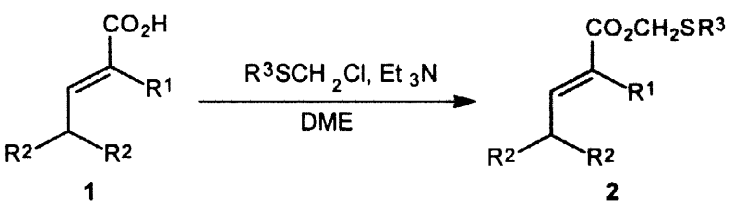


Scheme 2

Esters **2a-f** were readily prepared by treatment of the corresponding acids **1a-f** with excess (1.5-2 equiv.) of methylthiomethyl or phenylthiomethyl chloride in the presence of triethylamine (1.5 - 2 equiv.) (Scheme 3).

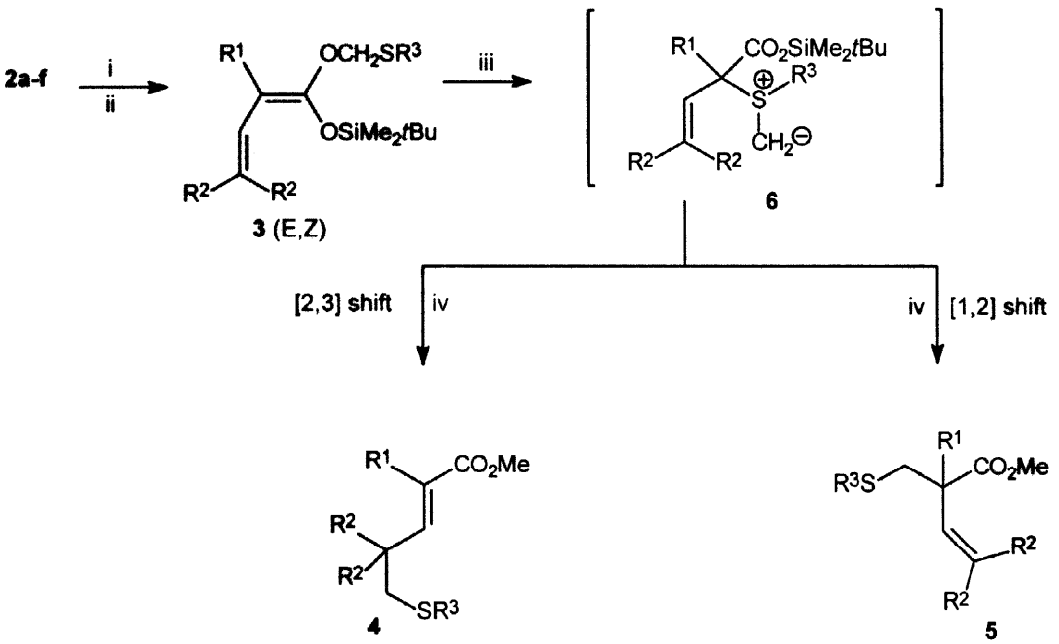
Ester	R^1	R^2	R^3	Yield (%)
2a	H	H	CH_3	70
2b	CH_3	H	CH_3	65
2c	H	CH_3	CH_3	62
2d	H	H	Ph	62
2e	CH_3	H	Ph	65
2f	H	CH_3	Ph	74



Scheme 3

Treatment of the esters **2a-f** with lithium hexamethyldisilazide in the presence of 1.3 equivalents of DMPU followed by the addition of *t*-butyldimethylsilyl triflate gave O,O-silylketene acetals **3** as mixtures of Z (major) and E (minor) isomers[2] (Scheme 4, Table 1). All ketene acetals **3** were stable at room temperature and could be analysed by NMR spectroscopy. However, after two hours in refluxing toluene, they completely rearranged to the corresponding γ- and α-substituted silyl esters which were converted into the corresponding methyl esters **4** and **5**[3]. They could be separated by column chromatography on silica gel.

O,O-silylketene acetals **3a,b** derived from methylthiomethyl esters rearranged exclusively to γ-substituted esters **4a,b** (Table 1). The γ-selectivity was still high when the γ-carbon bore two methyl groups as in **3c** but dropped in the case of phenyl substituted sulfur (compounds **3d-f**). When the phenyl group on sulfur was combined with two methyl groups on the γ-carbon as in **3f**, the selectivity was reversed in favour of the α-substituted product **5f**.



i, LiHMDS, DMPU, THF -78°C; ii, TBDMSOTf; iii, Toluene, reflux 2h; iv, MeOH, HCl.

Scheme 4

Table 1 : Thermal Rearrangement of **3**.

Acetal	R^1	R^2	R^3	Z:E ratio[a]	**4:5** ratio[a]	Yield **4**(%)	Yield **5**(%)
3a	H	H	CH_3	2.3:1	>19:1	58	-
3b	CH_3	H	CH_3	2.3:1	>19:1	70	-
3c	H	CH_3	CH_3	1.7:1	6.1:1	50	-
3d	H	H	Ph	3.2:1	7.3:1	63	-
3e	CH_3	H	Ph	3.0:1	1.7:1	35	17
3f	H	CH_3	Ph	2.8:1	0.4:1	12	30

a : determined by ^{1}H NMR of the crude product after work up

These results could be explained on the basis of the mechanism proposed earlier for the rearrangement in the aromatic series (Scheme 4)[1]. The intermediate ylide **6** could undergo a [3,2] sigmatropic rearrangement to give the γ-alkylated product **4**[4]. Alternatively a [1,2] shift would lead to the α-substituted product **5**. This [1,2] shift is analogous to the Stevens rearrangement[5-7] and could involve radical pairs or free radicals. However cross-over experiments or addition of radical scavengers did not provide any evidence for free radical species.

The above results show that γ-thiomethylation of butenoic acid derivatives could be efficiently performed using the readily available methylthiomethyl esters **2** as starting materials. The rearrangement should be synthetically useful since (for R^3 = Me) it is highly selective and yields products **4** that can be

further manipulated. We are presently examining the scope of the reaction as well as the influence of substituent on sulfur (in R^3S group) on the selectivity of the rearrangement.

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3. Selected data for **4e** : ^{1}H NMR (200MHz, $CDCl_3$) : δ 1.80 (s, 3H, CH_3), 2.49 (q, 2H, H_2-4), 3.01 (t, 2H, H_2-5), 3.73 (s, 3H, OCH_3), 6.77 (t, 1H, $J_{3,4}$ = 7.3Hz), 7.25-7.41 (m, 5H, H-arom). ^{13}C NMR (200MHz, $CDCl_3$): δ 13.12, 28.98, 33.19, 52.34, 126.90, 129.58, 131.59, 129.74, 136.41, 140.01, 188.90. Elemental analysis; calcd. for $C_{13}H_{16}O_2S$: C 66.08%; H 6.82%; S 13.54%; found : C 66.02 H 6.73, S 13.49. Data for **5e** : ^{1}H NMR (200MHz, $CDCl_3$) : δ 1.41 (s, 3H, CH_3), 3.14 and 3.38 (d, d, 2H, AB syst. J_{AB} = 12.7Hz), 3.59 (s, 3H, OCH_3), 5.17 (d, 1H, $J_{3,4A}$ = 16.9Hz), 5.18 (d, 1H, $J_{3,4B}$ = 10.7Hz), 6.02 (dd, 1H), 7.25-7.41 (m, 5H, H-arom). ^{13}C NMR (200MHz, $CDCl_3$) : δ 21.65, 44.70, 51.09, 53.11, 116.06, 127.37, 129.86, 131.24, 138.11, 141.01, 175.40. Elemental analysis; calcd. for $C_{13}H_{16}O_2S$ C : 66.08%; H 6.82%; S 13.54%; found : C 65.84, H 6.71, S 13.38.
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