Lewis Acid Mediated Selective Chalcogenalkylation of Silyl Enol Ethers with [*O*,*S*]-Acetals

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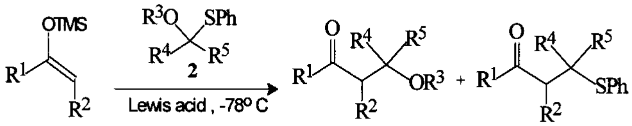
Abstract: Silyl enol ethers of ketones were selectively alkylated with [*O*,*S*]-acetals mediated by Lewis acid in a Mukaiyama type Aldol reaction. The products were β-alkoxy- and/ or β-sulfanyl carbonyl compounds depending on the catalyst employed.

Key words: Lewis acid, monothioacetal, silyl enol ether, β-chalcogeno ketone

[*O*,*S*]-acetals are compounds which are synthetically useful[1] when applied, for example, to electrooxidative carbon–carbon bond formation,[2] as precursors of free radicals in alkylation reactions,[3] to generate α-chalcogenalkyllithiums on reaction with butyllithiums,[4] and as precursors of α-sulfanyl or α-oxocarbenium ions which react with allyl and allenyltin compounds.[5] They can be hydrolysed to carbonyl compounds under mild conditions.[4] Recently we described a general and efficient methodology for the preparation of these compounds by addition of thiols to enol ethers.[6] In view of our continued interest in the organochalcogen stabilized carbocations applied to the stereoespecific formation of new carbon–carbon bonds, we undertook a systematic investigation of the reaction between [*O*,*S*] acetals and silyl enol ethers,[7] i.e. a Mukaiyama type crossed aldol reaction,[8] in order to obtain either the β-alkoxy- or the β-sulfanylalkyl ketones. A recent report by Hu on the reaction of α-acetoxy sulfides[9] prompted us to disclose our results.

Initially, a comparative study on the reaction of silyl enol ethers **1** with [*O*,*S*]-acetals **2** in dichloromethane in the presence of Lewis acids was undertaken (Scheme 1). The formation of β-alkoxy ketones **3** and β-sulfanyl ketones **4** proceeded as expected and it was observed that either product can be formed depending on the Lewis acid employed. $SnCl_4$ leads preferentially to β-alkoxy carbonyl compounds whereas β-sulfanyl carbonyl compounds are preferentially produced by the use of $TiCl_4$. This result can be rationalized in terms of a preferential complexation of the Lewis acid towards either chalcogen atom in the mixed acetals,[5, 10] based on the difference in the hardness (softness) of these atoms.

The alkylation reaction was carried out by adding a slight excess of Lewis acid to equimolar amounts of the silyl enol ether and the [*O*,*S*]-acetal dissolved in dichloromethane at low temperature under argon. After stirring for 1.5 h at low temperature, the reaction was worked up in the usual way and the β-chalcogeno carbonyl compounds were purified by column chromatography. The products and yields from the reaction of various acetals with three silyl enol ethers are reported in Table 1.



1 3 4

Product **3 or 4**	R^1	R^2	R^3	R^4	R^5
a	CH_2CH_3	CH_3	CH_3	CH_3	CH_3
b	CH_2CH_3	CH_3	CH_2CH_3	CH_3	H
c	CH_2CH_3	CH_3	CH_3	H	H
d	$-(CH_2)_3-$		CH_3	CH_3	CH_3
e	$-(CH_2)_3-$		CH_2CH_3	CH_3	H
f	$-(CH_2)_3-$		CH_3	H	H
g	$-(CH_2)_4-$		CH_3	CH_3	CH_3
h	$-(CH_2)_4-$		CH_2CH_3	CH_3	H
i	$-(CH_2)_4-$		CH_3	H	H

Scheme 1

Substitution of the $SnCl_4$ or $TiCl_4$ by other Lewis acids such as $AlCl_3$, $BF_3{\cdot}Et_2O$, $ZnBr_2$ and $ZnCl_2$ leads to the formation of a complex mixture of products containing only a small amount of the expected β-chalcageno ketones without selectivity.

We observed that the reaction of silyl enol ether of ketones with higher substituted [*O*,*S*]-acetals **2a–b** give β-chalcogeno ketones in good yields and that the reaction of the same silyl enol ethers with unsubstituted [*O*,*S*]-acetal **2c**, gives poor yields of the desired products. The good yields obtained in the reaction with secondary and tertiary alkylating agents can be attributed to the additional stabilization of the intermediate cation exerted by the methyl groups.

Some of the β-chalcogeno ketones **3** and **4** are not very stable compounds and were identified by infrared and ^1H

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NMR spectroscopy immediately after the isolation and purification (Table 2).[11]

In conclusion, [*O*,*S*]-acetals **2** have proved to be synthetically useful precursors of α-sulfanyl or α-oxycarbenium ions, which can be generated selectively by the appropriate choice of the Lewis acid.

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AC 80 or Bruker AC 200 spectrometer; chemical shifts are reported in ppm using $CDCl_3$ as solvent and TMS as internal standard. IR spectra were obtained on a Perkin-Elmer 599-B and Bomem MB-Series spectrophotometer, microanalyses were performed on Heraeus Vario EL and Perkin Elmer CHN 2400. Bps were uncorrected, determined on a Büchi GKR-50 apparatus. Mps were determined on Reichert Thermovar apparatus. Analytical TLC was performed on 0.25 mm precoated silica gel plates. Flash chromatography was carried out with 230–400 mesh silica gel (E. Merck).

Mukaiyama type Aldol Reaction of Silyl Enol Ethers with [*O*,*S*]-Acetals; General Procedure:

To a mixture of [*O*,*S*]-acetals (1.0 mmol) and the silyl enol ether (2.0 mmol) in CH_2Cl_2 (2 mL) at the temperature indicated in Table 1 was added dropwise $TiCl_4$ (2.0 mmol). The mixture was stirred for 1.5 h at the same temperature and then allowed to reach r.t. A sat. $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the organic layer was worked up in the usual way. The residue was chromatographed on silica gel using hexane/EtOAc (9:1) as eluent. Yields and physical data are shown in Tables 1 and 2.

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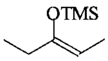
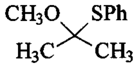
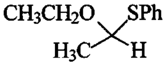
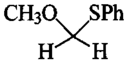
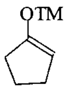
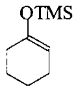
Table 1 β-Chalcogeno Ketones **3** and **4** Prepared According to Scheme 1

Silyl Enol Ethers **1**	[*O*, *S*] acetals **2**	Lewis Acid	Products [yields (%)]			
	 **2a**	$SnCl_4$	**3a**	(62)	**4a**	(2)
		$TiCl_4$	**3a**	(4)	**4a**	(86)
	 **2b**	$SnCl_4$	**3b**	(73)	**4b**	(9)
		$TiCl_4^a$	**3b**	(3)	**4b**	(70)
	 **2c**	$TiCl_4$	**3c**	–	**4c**	(35)
	**2a**	$SnCl_4$	**3d**	(71)	**4d**	(3)
		$TiCl_4$	**3d**	(12)	**4d**	(68)
	2b	$SnCl_4$	**3e**	(70)	**4e**	(13)
		$TiCl_4^a$	**3e**	(3)	**4e**	(58)
	2c	$TiCl_4$	**3f**	–	**4f**	(30)
	**2a**	$SnCl_4$	**3g**	(60)	**4g**	(3)
		$TiCl_4$	**3g**	(4)	**4g**	(65)
	2b	$SnCl_4$	**3h**	(80)	**4h**	(2)
		$TiCl_4^a$	**3h**	(4)	**4h**	(82)
	2c	$TiCl_4$	**3i**	–	**4i**	(27)

[a] The reaction was performed at –23°C

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Table 2 Characteristic Spectroscopic Data of Products **3** and **4**

Product	IR (Neat) υ (cm^{-1})	^{1}H NMR (CDCl$_3$) *δ*, *J* (Hz)	^{13}C NMR (CDCl$_3$) δ
3a	2941,1716, 1101, 754	3.18 (s, 3H), 2.83 (q, 1H, *J* = 7.0), 2.48 (q, 1H, *J* = 7.0), 1.17 (s, 3H), 1.13 (s, 3H), 1.04 (d, 3H, *J* = 6.8), 0.99 (t, 3H, *J* = 7.0)	214.6, 53.7, 48.9, 37.8, 22.8, 21.0, 12.6, 7.7
4a	2972, 1710, 1436, 757	7.22-7.71 (m, 5H), 2.70 (q, 2H, *J* = 7.1), 2.43 (q, 1H, *J* = 7.1), 1.47 (s, 3H), 1.27 (s, 3H), 1.24 (d, 3H, *J* = 7.0), 0.97 (t, 3H, *J* = 7.1)	213.8, 137.4, 131.5, 128.8, 128.4, 52.6, 37.9, 27.4, 24.6, 13.4, 7.4
3b	2974, 1713, 1099, 974	3.12-3.72 (m, 3H), 2.23-2.82 (m, 3H), 1.19 (t, 3H, *J* = 7.0), 1.10 (d, 3H, *J* = 6.4), 1.08 (t, 3H, *J* = 7.2), 1.04 (d, 3H, *J* = 7.0)	212.1, 63.4, 61.2, 53.3, 35.9, 19.9, 14.7, 12.5, 7.5
4b	2973, 1712, 1438, 746	7.14-7.62 (m, 5H), 3.22-3.71 (m, 1H), 2.22-2.91 (m, 3H), 1.24 (t, 3H, *J* = 6.9), 1.07 (d, 3H, *J* = 6.7), 0.96 (d, 3H, *J* = 6.6)	213.2, 132.8, 132.2, 128.8, 127.0, 50.9, 46.3, 35.9, 20.2, 12.5, 7.5
4c	2973, 1712, 1457, 740	7.13-7.54 (m, 5H), 3.24 (d, 2H, *J* = 6.8), 2.21-2.92 (m, 3H), 1.15 (d, 3H, *J* = 6.7), 1.01 (t, 3H, *J* = 7.4)	213.2, 130.7, 129.5, 128.9, 126.5, 45.4, 36.4, 35.1, 16.7, 7.5
3d	2943, 1717, 1184, 753	3.16 (s, 3H), 1.71-2.41 (m, 7H), 1.32 (s, 3H), 1.18 (s, 3H)	217.1, 56.1, 49.1, 40.1, 25.6, 23.9, 22.0, 20.1
4d	2933, 1716, 1476, 691	7.22-7.63 (m, 5H), 1.62-2.45 (m, 7H), 1.48 (s, 3H), 1.22 (s, 3H)	217.8, 128.8, 128.3, 127.7, 127.2, 57.0, 40.3, 38.4, 29.2, 25.1, 19.2
3e	2923, 1728, 1148, 744	3.23-4.01(m, 3H), 1.85-2.32 (m, 7H), 1.24 (d, 1.5H, *J* = 6.1), 1.13 (t, 3H, *J* = 6.9), 1.05 (d, 1.5H, *J* = 6.8)	219.3, 66.7, 56.8, 53.3, 41.6, 25.5, 23.5, 19.9, 15.8
4e	2966, 1733, 1477, 740	7.13-7.54 (m, 5H), 3.51-4.01 (m, 1H), 1.66-2.53 (m, 7H), 1.38 (d, 1.5H, *J* = 6.8), 1.15 (d, 1.5H, *J* = 6.8)	217.4, 135.3, 131.5, 127.7, 127.5, 59.5, 38.1, 31.2
4f	2962, 1737, 1480, 740	7.13-7.54 (m, 5H), 3.49 (d, 1H, *J* = 3.1), 3.38 (d, 1H, *J* = 3.1), 1,65-2.82 (m, 7H)	216.2, 135.1, 130.7, 128.9, 125.0, 59.5, 38.1, 29.6, 23.3, 14.0
3g	2929, 1720, 1216, 754	3.15 (s, 3H), 1.54-2.66 (m, 9H), 1.29 (s, 3H), 1.20 (s, 3H)	207.1, 56.8, 54.5, 44.1, 35.7, 26.8, 25.9, 23.4, 21.3
4g	2934, 1709, 1442, 761	7.13-7.54 (m, 5H), 1.53-2.45 (m, 9H), 1.37 (s, 3H), 1.34 (s, 3H)	210.4, 136.9, 131.3, 128.3, 126.8, 57.5, 43.6, 41.3, 30.2, 28.5, 27.5, 25.3, 23.3
3h	2932, 1713, 1216, 756	3.23-3.91 (m, 3H), 1.62-2.42 (m, 9H), 1.36 (d, 1.5H, *J* = 5.4), 1.17 (t, 3H, *J* = 6.7), 1.16 (d, 1.5H, *J* = 6.4)	212.1, 73.1, 64.4, 55.3, 42.1, 27.9, 24.4, 18.4, 16.4, 15.2
4h	2935, 1707, 1444, 744	7.22-7.61 (m, 5H), 3.52-4.01 (m, 1H), 1.55-2.61 (m, 9H), 1.31 (d, 1.5H, *J* = 6.8), 1.24 (d, 1.5H, *J* = 6.8)	210.8, 132.2, 131.5, 128.8, 126.7, 54.0, 43.5, 41.7, 27.4, 24.8, 16.9, 13.5
4i	2934, 1707, 1438, 740	7.13-7.54 (m, 5H), 3.21-3.71 (m, 2H), 1.43-2.42 (m, 9H)	211.8, 130.4, 129.2, 128.7, 126.2, 50.1, 41.7, 33.0, 27.6, 26.7, 24.7

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(11) All compounds showed spectroscopic and analytical data consistent with the assigned structures and in accordance with the literature (cf. especially literature 7 marked with asterisk*).

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