Thiosulfonic S-Esters; 6. Fluoride-Mediated α-Phenylsulfenylation of Cyclic Ketones and Esters via their Trimethylsilyl Enol Ethers[1]

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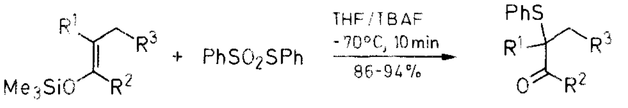
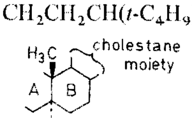
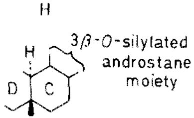
Ketones and carboxylic acid esters are conveniently converted to their α-sulfenylated derivatives. This new procedure is likely to represent the first reliable one for regiospecific monosulfenylation of carbonyl compounds. It is based on the reaction of their trimethylsilyl enol ether derivatives with tetrabutylammonium fluoride in the presence of thiosulfonic *S*-esters, in anhydrous tetrahydrofuran, under mild conditions, at −70 °C for a few minutes.

β-Ketosulfides are well recognized in synthetic organic chemistry as versatile precursors of a large number of interesting organic compounds.[2] The main methods for their preparation are based on the reaction of regiospecifically generated enolate anions with various species containing an electrophilic sulfur atom.[2,3] With all these specific enolates, some problems remain unresolved: side reaction leading to bissulfenylation[4] and loss of regiospecificity, the latter being attributable to the generally low reactivity[3] of lithium enolates toward the electrophilic sulfur moiety. Now, we wish to report a new general procedure for sulfenylation of carbonyl compounds that improves significantly the present status, making the regiospecific monosulfenylation much more feasible.

Based on our experience in the chemistry of thiosulfonic *S*-esters, and in view of the reported[5] activation of enolate anions by substitution of the countercation from lithium to quaternary ammonium, we examined the reaction of regiospecifically generated trimethylsilyl enol ethers with tetrabutylammonium fluoride (TBAF), in the presence of *S*-phenyl benzenethiosulfonate.[6] Under these conditions, the rather hard[7] quaternary ammonium enolate anion, which is expected[5,8] to result from the reaction of fluoride anion with the silyl enol ether, could rapidly attack the sulfenyl sulfur of the thiosulfonic *S*-ester, with loss of the sulfinate anion moiety.



1 **2**

1, 2	R^1	R^2	R^3
a	H	$CH_2CH_2CH_2$	
b	H	$CH(CH_3)CH_2CH_2$	
c	CH_3	$CH_2CH_2CH_2$	
d	H	$CH_2CH_2CH(t\text{-}C_4H_9)$	
e	H		
f	H		
g	H	OEt	$n\text{-}C_7H_{15}$

Using specific silyl enol ethers of various ketones **1a–1f** and of ethyl decanoate (**1g**), the reaction turned out to be of general application, leading in all cases (Table) to the desired products in satisfactory yields. In fact, the regiochemistry of sulfenylation, in such a procedure, is assured by the use of silyl enol ethers[9] (which can be generated with the desired regiochemistry, isolated, and purified before the reaction, if considered necessary), as well as by the mild experimental conditions (– 70 °C for a few minutes) that do not allow equilibration *in situ* of any intermediate enolate anions.

Sulfenylation via silyl dienol ethers of α,β-unsaturated ketones had already been attempted, although this procedure is far from being regarded as a general one, if one considers that silyl enol ethers as such turn out to be rather unreactive and, in the absence of fluoride activation, can interact only with strong electrophiles like the sluggish sulfenyl chlorides.[9] Taking into account regiospecificity of substitution and yields of monosulfenylated products, our method leads to better results when sulfenylation occurs at the less highly substituted position.[10] Finally, it is noteworthy that the stereochemistry of the products is consistent with that already observed [3] in other sulfenylation reactions, and silylated alcoholic hydroxy groups present in the substrate molecule remain unchanged under the reaction conditions.

The combination of high yields, the mild conditions, the ease of performance and work-up, demonstrates that this regiospecific monosulfenylation procedure should find rather broad application in synthesis.

TBAF was a commercial (Aldrich Chemical Co.) 1 M solution in THF. *S*-Phenyl benzenethiosulfonate[6] was purchased from Fluka AG (Switzerland). Anhydrous THF (reagent grade, Carlo Erba) was distilled from $LiAlH_4$. Silica gel (70–230 mesh) was purchased from Carlo Erba.

Table. α-Phenylsulfenylation of Carbonyl Compounds via Silyl Enol Ethers

Silyl Enol Ether	Product	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c] or Lit. Data	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, *J* (Hz)
1a	2-Phenylthiocyclohexanone **(2a)**	94	oil	–[e]	3.82 (t, 1H, *J* = 5); 7.30 (m, 5H)
1b	2-Methyl-6-phenylthiocyclohexanone **(2b)**[f]	92	oil	–[e]	0.99 (d, 2.10H, *J* = 6); 1.10 (d, 0.90H, *J* = 6); 3.82 (m, 0.70H); 3.95 (dd, 0.30H, *J* = 11); 7.32 (m, 5H)
1c	2-Methyl-2-phenylthiocyclohexanone **(2c)**	86	oil	–[e]	1.22 (s, 3H); 3.36 (ddd, 1H, *J* = 14); 7.28 (m, 5H)
1d	4-*tert*-Butyl-2-phenylthiocyclohexanone **(2d)**[g]	92	oil	–[e]	3.10 (ddd, 1H, *J* = 14); 3.79 (m, 0.78H); 3.94 (dd, 0.22H, *J* = 12); 7.32 (m, 5H)
1e	2α-Phenylthio-5α-cholestan-3-one **(2e)**[h]	94	164–166 (*n*-hexane)	$C_{33}H_{50}OS$ (494.8)	4.00 (dd, 1H, *J* = 13); 7.32 (m, 5H)
1f	3β-*O*-Silyl-16β-phenylthio-5α-androstan-17-one **(2f)**	74	128–130 (*n*-hexane)	$C_{29}H_{42}O_2SiS$ (482.7)	3.54 (t, 1H, *J* = 8); 7.30 (m, 5H)
	16-α-Epimer of **2f** characterized as its 3-hydroxy derivative	19	120–122 (*n*-hexane)	$C_{29}H_{34}O_2S$ (398.6)	3.94 (dd, 1H, *J* = 6)
1g	Ethyl 2-Phenylthiodecanoate **(2g)**	90	oil	–[e]	1.0 (t, 3H, *J* = 7); 3.7 (t, 1H, *J* = 6); 4.2 (t, 2H, *J* = 7); 7.2 (m, 5H)

[a] Yield of isolated product(s). Purity ≥94%, by HPLC and ^{1}H-NMR data.

[b] Uncorrected, measured with a Kofler apparatus.

[c] Microanalyses obtained: C ±0.59, H ±0.52.

[d] Obtained on a Varian XL 200 spectrometer. Solvent for **1g**: CCl_4. Only relevant signals are given.

[e] These compounds are reported in Ref. 3. The physical state of the compounds is not reported.

[f] *cis*/*trans* = 30 : 70.

[g] *cis*/*trans* = 22 : 78.

[h] No traces of 2β-epimer (cf. also Ref. 11).

2-Methyl-6-phenylthiocyclohexanone (2b); Typical Procedure:

To a magnetically stirred solution of the silyl enol ether **1b** (184 mg, 1.0 mmol) and *S*-phenyl benzenethiosulfonate (300 mg, 1.2 mmol) in anhydrous THF (4–5 mL), cooled in acetone/CO_2 bath and under dry N_2 atmosphere, TBAF (1.0 mL) is added in one portion, and the clear solution becomes cloudy in 5–10 min. The mixture is then diluted with Et_2O (20 mL) and washed with H_2O (3 × 10 mL). Evaporation of the dried (Na_2SO_4) organic layer *in vacuo* affords an oily residue, which is chromatographed on silica gel (*n*-hexane) to give **2b**; yield: 202 mg (92%); *cis*/*trans* ratio = 30:70 (Table).

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