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O-SILYLATED ENOLATES IN ORGANIC SYNTHESIS: SULPHUR-MEDIATED ALKYLATION OF ESTERS WITH ALKENES.

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Summary: *O*-Silylated ester enolates can be alkylated, under $ZnBr_2$-catalysis, by the PhSCl-adducts of mono- and di-substituted alkenes to give γ-phenylthioesters, from which sulphur can be removed both reductively and oxidatively. This alkene carbosulphenylation reaction is stereospecific (*anti*) with variable Markovnikov regioselectivity.

Addition of metal enolates to electron-defficient alkenes, the Michael reaction, is a well-established method for the α-alkylation of carbonyl compounds. Simple alkenes, in contrast, are not directly useful in enolate chemistry and need first to be suitably activated to nucleophilic attack.[1] We now report that the desired transformations (e.g. **1** → **2** or **1** → **3** + **4**) can be easily accomplished by using the adducts (**6**) of alkenes with phenylsulphenyl chloride[2] as alkylating agents, under mild $ZnBr_2$-catalysis, for *O*-silylated enolates.[3,4] This is then followed by either (a) simple reductive desulphurisation (**7** → **2**), or (b) sulphoxide formation and cycloelimination (**7** → **3** + **4**).[3]

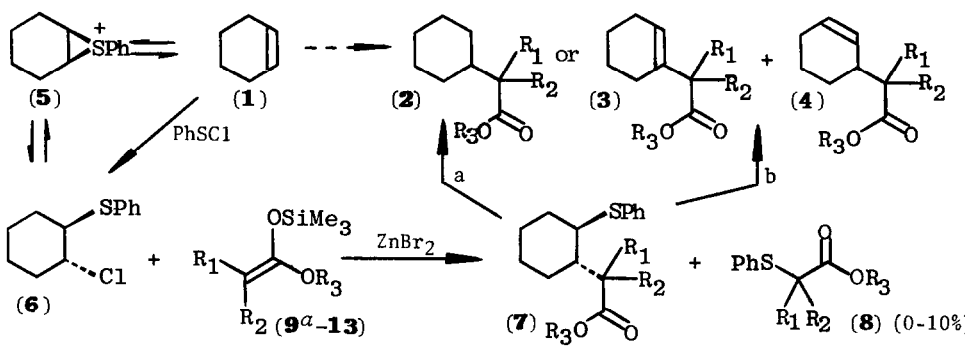


TABLE: Reaction of *O*-silylated enolates with **6** (1 equiv., CH_2Cl_2, 20°C, 16h), catalysed by dry $ZnBr_2$,[8] followed by (a) reductive desulphurisation (Raney Ni; Me_2CO, 20°C, 3h) or (b) sulphur oxidation ($NaIO_4$; aq. MeOH, 20°C, 16h) and sulphoxide thermal cycloelimination (Cl_2CCCl_2, 120°C, 1-3h).

O-Silylated Enolate	R_1	R_2	R_3	Yield[b] of **7** (%)	Yield of **2**(%)	Yield of **3** + **4**(%)	Ratio[c] of **3** : **4**
9[a]	H	H	Me	77	95	88	50 : 50
10	Me	Me	Me	70	96	93	50 : 50
11	H	Me	Et	76[d]	92	95	43 : 57
12	H	Et	Et	76[d]	86	95	42 : 58
13	H	Ph	Me	80[d]	91	91	25 : 75

a the *t*-butyldimethylsilyl enolate (i.e. Bu^tMe_2Si for Me_3Si in **9**)[4] was used for the acetate reactions. *b* yields refer to isolated products throughout. *c* determined by ^{1}H-NMR. *d* mixture of two diastereomers, both *trans*.

Sec-alkylation using β-chlorosulphide (**6**)[2] was successful with a wide range of ester-derived[5] *O*-silylated enolates (**9**-**13** in Table). *Trans*-products (**7**)[6], J_{vic} = 11-12 Hz, were obtained in each case (i.e. retention of configuration in **6**). This new alkene carbosulphenylation reaction[7] presumably involves initial Lewis acid-catalysed equilibration of the β-chlorosulphide (**6**) to the episulphonium ion (**5**), followed by nucleophilic trapping[7] to give **7**. Sulphenylation, however, can be a competing pathway, leading to the isolation of varying amounts of the simple α-phenylthioesters (**8**) as side-products. For mono- and di-substituted alkenes **8** was usually a minor product (0-10%), but for tri- and tetra-substituted cases sulphenylation occurred almost exclusively.

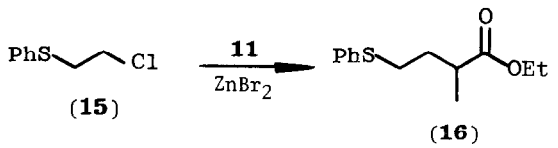
Raney nickel desulphurisation of **7** cleanly gave the saturated esters (**2**), while sulphur oxidation followed by sulphoxide thermal cycloelimination gave mixtures of the β,γ- and γ,δ-unsaturated esters (**3** and **4**, respectively).

We next examined the stereo- and regio-chemistry[6] of the alkylation of representative *O*-silylated ester enolates (mainly **9** and **10**) with a range of PhSCl-adducts of alkenes, as summarised in diagrams (**15**) to (**27**). In each case, the addition of PhSCl (CH_2Cl_2, -78 → 20°C)[2] was essentially quantitative, and the alkene adduct(s)[2] formed could be used directly in a 'one pot' reaction with the appropriate *O*-silylated enolate and $ZnBr_2$[8] (CH_2Cl_2 20°C, 1-16h).

Ethylene itself gave the least reactive β-chlorosulphide (**15**) examined, which gave a low yield of γ-phenylthioester (**16**), even under forcing conditions. Cyclopentene carbosulphenylation proceeded smoothly and, in the case of **17** for R_1=R_2=Me, sulphoxide thermolysis gave a mixture of the alkylated cyclopentenes (**18** and **19**), where the trisubstituted isomer (**18**) predominated. Notably, *cis*- and *trans*-but-2-ene reacted stereospecifically[6] to give the diastereomeric esters (**20** and **21**, respectively), where overall *anti* addition is inferred from the *trans*-adducts obtained from cycloalkenes. In addition, oxidative sulphur removal from **20** and **21** (R=H or Me) gave mixtures of mono- and tri-substituted alkenes (**22** + **23**, or **22** + **24**, respectively).

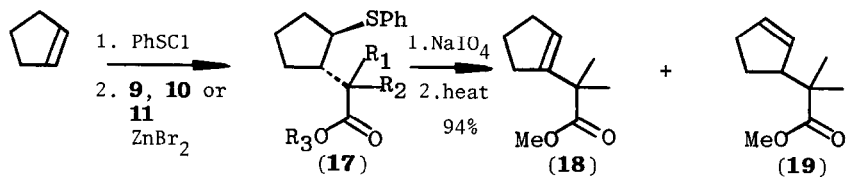
The ratio[6] of secondary (Markovnikov) to primary alkylation using terminal alkenes was found to be variable. Styrene gave exclusively the α-*sec*-benzyl esters (**25**, R_1=Ph, R_2=H, R_3=H or Me), while propene and hex-1-ene gave mixtures (highest selectivity 6:1) of **25** and **26**. The more substituted *O*-silylated enolate (**10**) generally gave higher regioselectivity than **9** towards *sec*-alkylation. *Iso*-butene gave only *tert*-alkylated products (**25**, R_1=R_2=Me) in reaction of its PhSCl adducts[2] with both **9** and **10**. Attempts to use more highly substituted alkenes, e.g. 2-methylbut-2-ene and 2,3-dimethylbut-2-ene, failed to give useful amounts of alkylated products; the α-phenylthioesters (**8**) were now obtained in high yield.

In a typical alkylation reaction, a solution (1*M* in CH_2Cl_2) of PhSCl[9] (2.0 ml, 2 mmol) was added dropwise to a stirred solution of alkene (2.1 mmol) in dry CH_2Cl_2 (2 ml) at -78°C under Ar. Alternatively, gaseous alkenes could be bubbled into the PhSCl[9] solution at -78°C until the red colour disappeared. The colourless solution of β-chlorosulphide[2] produced was warmed to room temperature, and the *O*-silylated enolate[3,4] (2 mmol) was added, which was followed directly by a catalytic amount of dry $ZnBr_2$[8] (*ca.* 20 mg). After 1-16h, the reaction was evaporated *in vacuo* and the residue flash chromatographed on SiO_2 to give the α-alkylated ester directly. Reductive and oxidative sulphur removal were carried out as described previously,[3] except that Cl_2CCCl_2 was now used as solvent for the cycloeliminations.



(15) (16)

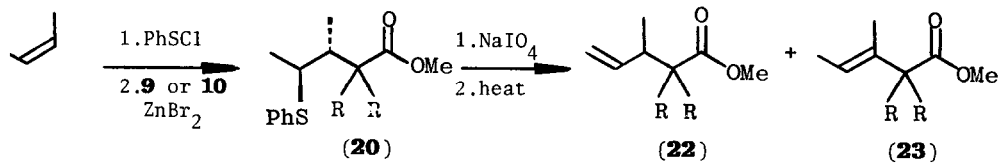
23% (CH_2Cl_2, reflux, 16h)
28% (CH_2ClCH_2Cl, reflux 16h)



(17) (18) (19)

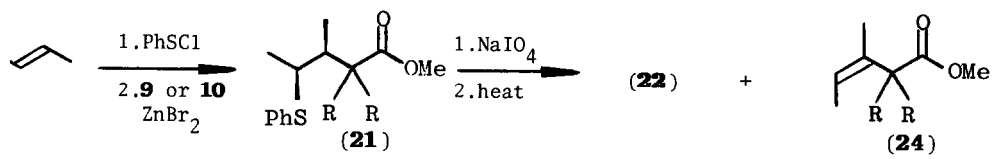
72:28

R_1	R_2	R_3	
H	H	Me	80%
Me	Me	Me	60%
H	Me	Et	68%



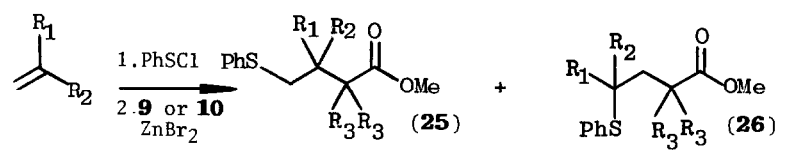
(20) (22) (23)

R = H 68% R = H 91% 70 : 30
R = Me 62% R = Me 92% 57 : 43



(21) (24)

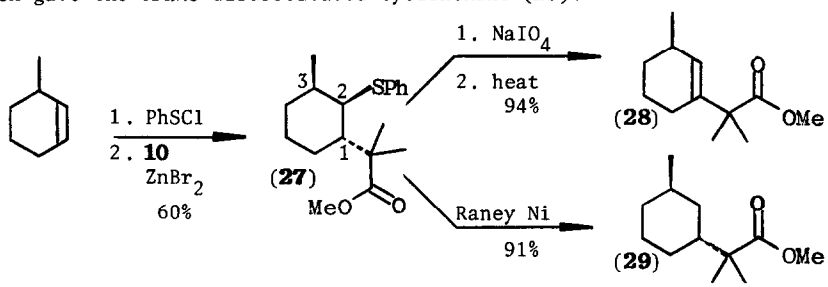
R = H 68% R = H 90% 80 : 20
R = Me 68% R = Me 94% >95 : <5



(25) (26)

R_1	R_2	R_3	Ratio of 6 **25** : **26**	Yield of **25** + **26** (%)
Ph	H	H	100 : 0	86
Ph	H	Me	100 : 0	95
Me	H	H	60 : 40	57
Me	H	Me	80 : 20	52
Bu^n	H	H	42 : 58	48
Bu^n	H	Me	86 : 14	58
Me	Me	H	100 : 0	61
Me	Me	Me	100 : 0	71

Finally, both high regio- and stereo-selectivity are sometimes possible together. Addition of PhSCl to 3-methylcyclohexene gave a complex mixture of β-chlorosulphides, which on reaction with **10** gave a single alkylation product (**27**).[6,10] Confirmation of this structure (**27**), as assigned by ^{1}H-NMR,[10] was obtained by sulphoxide thermolysis,where only alkene (**28**) was obtained. The *syn*-elimination of PhSOH from **27**[10] must occur exclusively with the axial hydrogen, H-1 (elimination to the equatorial hydrogen, H-3, would give rise to a *trans*-cyclohexene). Raney nickel desulphurisation gave the *trans*-disubstituted cyclohexane (**29**).



Acknowledgements: We thank the S.E.R.C. and the University of London Central Research fund for support.

Notes and References:

[1]For an alternative approach using Pd(II)-complexation of alkenes, see: L. S. Hegedus, R. E. Williams, M. A. McGuire, and T. Hayashi, *J. Amer. Chem. Soc., 102,* 4973 (1980).

[2]For the regio- and stereoselectivity of PhSCl addition to alkenes, see: W. H. Mueller and P. E. Butler, *ibid, 90,* 2075 (1968); P. B. Hopkins and P. L. Fuchs, *J. Org. Chem., 43,* 1208 (1978), and other references therein.

[3]This is the homologue of our earlier phenylthioalkylation reaction with α-chloroalkylphenyl sulphides (PhSCHClR): I. Paterson and I. Fleming, *Tetrahedron Letters,* 993, 995, and 2179 (1979).

[4]Y. Kita, J. Segawa, J. Haratu, H. Yasuda, and Y. Tamura, *J.C.S. Perkin I,* 1099 (1982).

[5]The less nucleophilic silyl enol ethers of ketones generally gave poor alkylation yields (typically 25-40% with **6**) using this method. For the *sec*-alkylation of ketones using thioketals, see: M. T. Reetz and A. Giannis, *Synth. Comm., 11,* 315 (1981).

[6]Isomeric purity was determined by ^{13}C- and ^{1}H-NMR (200 MHz). Isomer ratios in alkylations were measured by ^{1}H-NMR of the crude product mixtures and confirmed by weighing the HPLC-separated regioisomers.

[7]Related additions involving reaction of episulphonium ions (either isolated or generated *in situ*) with various heteroatom nucleophiles have been described; however, carbosulphenylation has so far been restricted to malonate and cyanide ions: W. A. Smit, M. Z. Krimer, and E. A. Vorob'eva, *Tetrahedron Letters,* 2451 (1975); B. M. Trost, T. Shibata, and S. J. Martin, *J. Amer. Chem. Soc., 104,* 3228 (1982).

[8]Commercial $ZnBr_2$ was dried at *ca.* 200°C/0.5 mmHg.

[9]PhSCl was prepared by chlorination of thiophenol (SO_2Cl_2, pentane, 0 → 20°C, 16h), and was stored and used as a 1*M* solution in CH_2Cl_2 under Ar. M. Fieser and L. F. Fieser, *Reagents for Organic Synthesis,* Wiley, New York, Vol. 5, p. 523 (1975).

[10]^{1}H-NMR: δ($CDCl_3$, 200 MHz) 7.08-7.45 (5H, m, Ph), 3.6 (3H, s, MeO), 3.03 (1H, dd, $J_{2,3}$ 3.9,$J_{1,2}$ 10.4,H-2_{ax}), 2.43(1H,ddd, *J* 3.8, 10.4, 10.4,H-1_{ax}), 2.07 (1H, m, H-3_{eq}), 1.78-1.95 (1H, m) 1.36-1.75 (5H, m), 1.21 (3H, s, *Me*CMe), 1.15 (3H, d, *J* 8.1, Me) and 1.12 (3H, s, MeC*Me*). ^{13}C-NMR: δ ($CDCl_3$) 179.47, 136.74, 131.35, 128.81, 126.57, 56.48, 51.90, 44.66, 41.27, 32.94, 32.94, 27.01, 26.78,20.36, 18.13, and 14.27.

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