Tetrahedron Letters No. 23, pp 2179 - 2182. 0040-4039/79/0601-2179$02.00/0

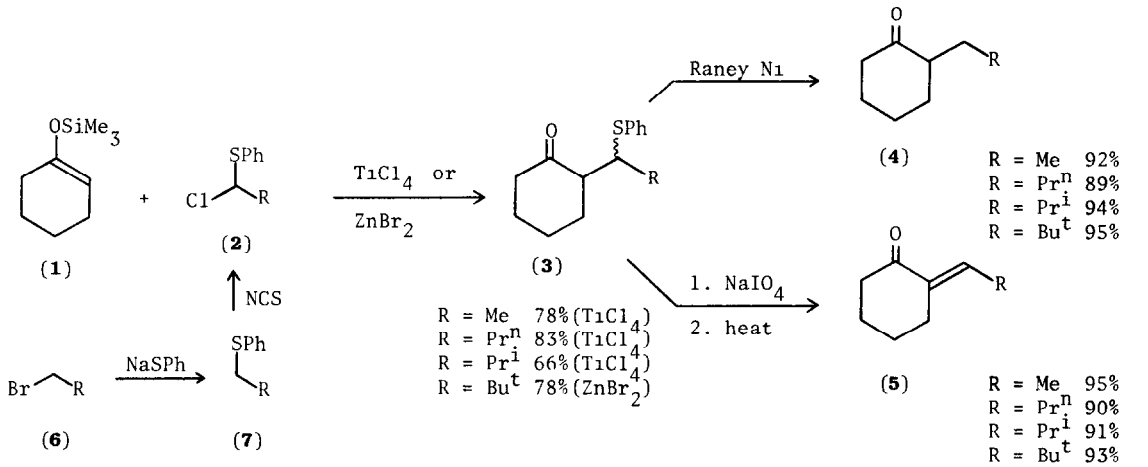
α-ALKYLATION AND α-ALKYLIDENATION OF CARBONYL COMPOUNDS: LEWIS ACID-PROMOTED PHENYLTHIOALKYLATION OF *O*-SILYLATED ENOLATES[1]

Ian Paterson* and Ian Fleming

(University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England)

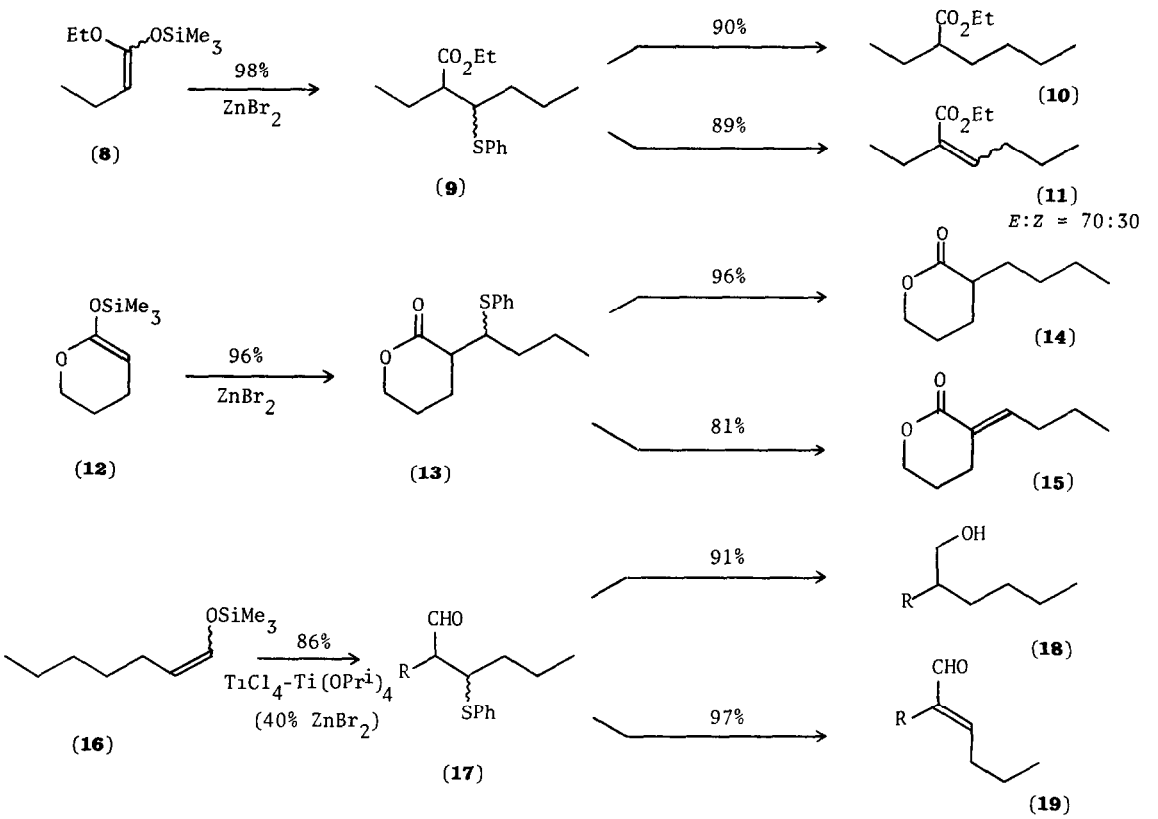
Summary: The *O*-silylated enolates of ketones, aldehydes, esters, and lactones can be phenylthioalkylated in the presence of Lewis acids; reductive or oxidative sulphur-removal gives the regiospecifically α-alkylated or alkylidenated carbonyl compounds.

The regiospecific alkylation of lithium enolates is often restricted to reactive alkyl halides such as methyl iodide and allylic or benzylic halides.[2] Alternative methods using enolate equivalents[3] are generally restricted to aldehydes and ketones and, along with quaternary ammonium enolates,[4] are best suited for alkylation at the less-substituted side of unsymmetrical ketones. We now report that simple primary alkyl groups, *including neopentyl*, may be easily introduced by Lewis acid-promoted phenylthioalkylation of *O*-silylated enolates[7] using α-chloroalkyl phenyl sulphides (**2**), followed by Raney nickel desulphurisation (e.g. **1** → **3** → **4**);[5,6] this is an extension of our earlier work on phenylthiomethylation (**1** → **3** → **4**, R = H).[8] As in the earlier work, the sulphur may also be removed oxidatively using sodium metaperiodate (e.g. **3** → **5**), to give, effectively, the *E*-product (**5**) of a directed aldol condensation.[9]



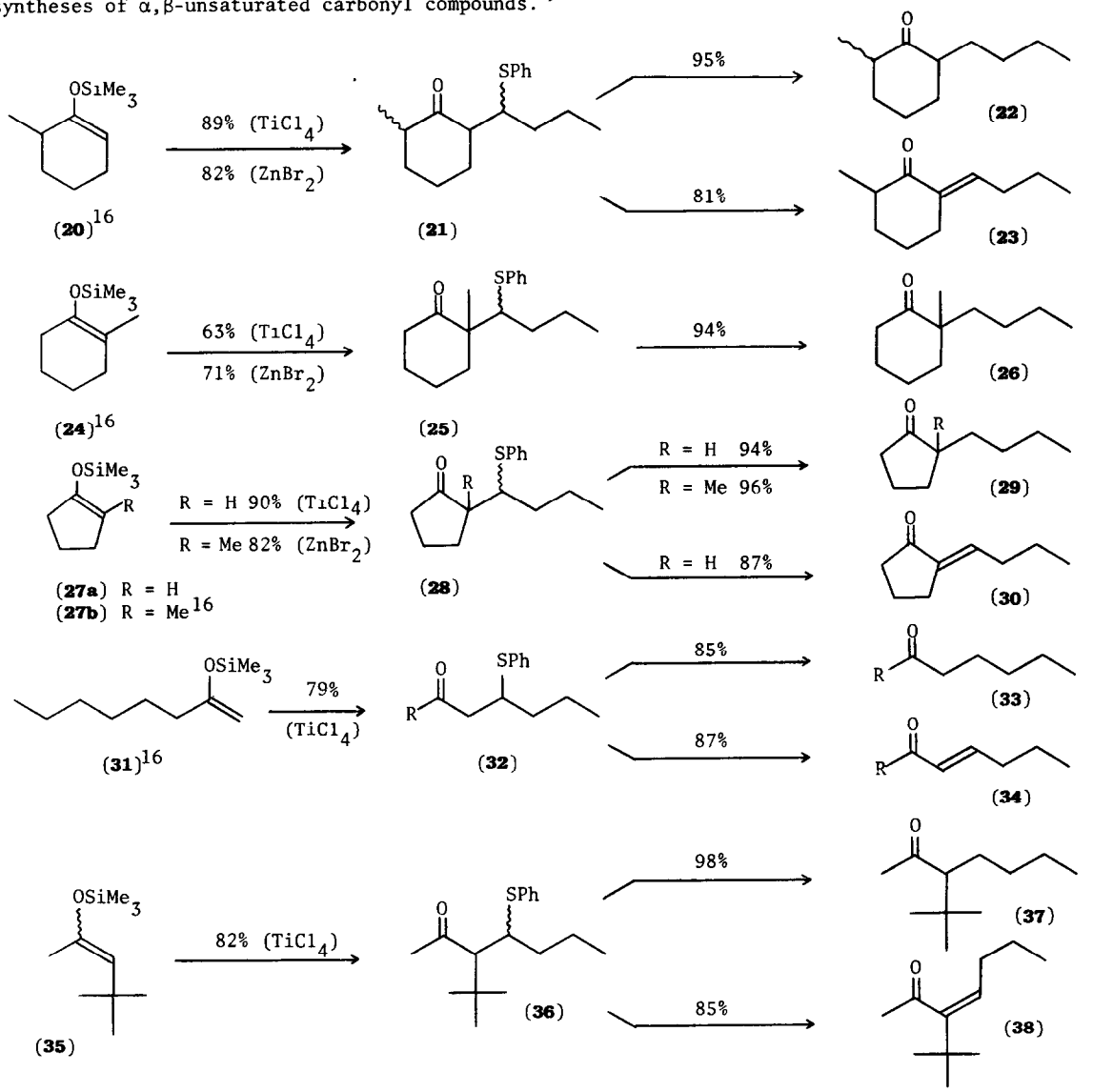
The α-chloroalkyl phenyl sulphides (**2**), which serve as both alkyl halide and aldehyde equivalents, were prepared in two steps (**6** → **7** → **2**) from the corresponding alkyl bromide, generally in better than 90% yield: the halide (**6**) was converted to the alkyl phenyl sulphide (**7**)(NaSPh, EtOH, 20°), which was then chlorinated (*N*-chlorosuccinimide, CCl_4, 20°, 6 h), and the product (**2**) used directly[10] after filtration and evaporation of the solvent.

In addition to the reactions on the *O*-silylated enolate (**1**) of cyclohexanone, we have also carried out the n-butylation and n-butylidenation sequences on the *O*-silylated enolates of a range of carbonyl compounds using α-chloro-n-butyl phenyl sulphide (**2**, R = Pr^n) as the electrophile, as summarised in diagrams **8** to **38**. The phenylthioalkylation reaction was successful with the *O*-silylated enolates of an ester (**8**), a lactone (**12**), an aldehyde (**16**), and a range of symmetrical (**1** and **27a**) and unsymmetrical (**20**, **24**, **27b**, **31**, and **34**) ketones.



Titanium tetrachloride and zinc bromide are the most effective Lewis acids; but which is better depends upon the substrate. With the ester- and lactone-derived *O*-silylated enolates (**8** and **12**), $ZnBr_2$ was clearly the best Lewis acid (CH_2Cl_2, 20°, 15 min), as we had previously found for phenylthiomethylation.[8] For the aldehyde-derived *O*-silylated enolate (**16**), a 1:1 mixture of $TiCl_4$ and $Ti(OPr^i)_4$ was best (CH_2Cl_2, -78°, 1 h), zinc bromide giving a lower yield. For the *O*-silylated enolates of ketones (**1**, **20**, **24**, **27**, **31**, and **35**) both $ZnBr_2$ (CH_2Cl_2, 20°, 1 h) and $TiCl_4$ (CH_2Cl_2, -23°, 1.5 h) were successful. $ZnBr_2$ has the advantages of mildness, catalytic use, and ease of operation, but $TiCl_4$ may occasionally be superior in being more apt to give regiospecific alkylation.[6] Both Lewis acids were successful, however, in promoting regiospecific[11] phenylthiobutylation of the two isomeric *O*-silylated enolates of 2-methylcyclohexanone (**20** → **21** and **24** → **25**). In contrast, the corresponding lithium enolates are not easily n-butylated without competing equilibration.[12]

Our method is particularly effective for alkylation at the more-substituted side of unsymmetrical ketones (**24**, **27b**, and **35**), complementing the alternative methods;[3,4] it also works in the regiospecific alkylation of hindered enolates,[13] such as those having an adjacent quaternary carbon as in **35**. Finally, the ease, efficiency, and high stereoselectivity[14] of the oxidative removal of sulphur makes the reactions described here attractive alternatives to existing syntheses of α,β-unsaturated carbonyl compounds.[9,15]



Typically, for the $ZnBr_2$-phenylthioalkylation procedure, a catalytic amount (*ca.* 25 mg) of powdered anhydrous $ZnBr_2$ was added to a solution of the α-chloroalkyl phenyl sulphide (6 mmol) and the *O*-silylated enolate (5 mmol) in dry CH_2Cl_2 (10 ml) at room temperature, and the mixture shaken every 5-10 min. After 15 min (esters and lactones) or 1 h (ketones), the solvent was simply evaporated and the residue chromatographed on silica gel to give the α-phenylthioalkyl

ketone, ester, or lactone directly. $TiCl_4$ was used in the same way as described for phenylthiomethylation,[8] except in the case of aldehydes (**17**), where the reactants were treated with a preformed mixture of $TiCl_4$-$Ti(OPr^i)_4$ (1 equivalent of each) in CH_2Cl_2 (-78°, 1 h) and worked up in the usual way.[8]

Reductive sulphur removal was carried out with W-2 Raney nickel[17] (Me_2CO-EtOH 9:1, 20°, 0.5-2 h) as described previously.[8] In the case of the aldehyde (**17**), reduction to the primary alcohol (**18**) occurred under these conditions. Oxidative sulphur removal to the α,β-unsaturated carbonyl compound was carried out by treatment with sodium metaperiodate[18] followed by heating, as necessary. Typically, the α-phenylthioalkyl carbonyl compound (1 mmol) was stirred in the dark with $NaIO_4$ (1 mmol) in MeOH-H_2O (9:1, 10 ml) for 16 h. The reaction mixture was poured into water (15 ml) and extracted repeatedly with CH_2Cl_2. The organic phase was dried and evaporated *in vacuo* to give, usually, a mixture of sulphoxide and eliminated product (in the cases **3** → **5** R = Bu^t, **9** → **11**, and **36** → **38**, the sulphoxide was isolated unscathed). The crude mixture was warmed in CCl_4 (1 ml) at 60° for 1-48 h; chromatography on silica gel then gave the unsaturated carbonyl compounds.

NOTES and REFERENCES

[1] Reprints of this paper will not be available.

[2] G. Stork, *Pure Appl. Chem.*, **43**, 553 (1975).

[3] G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963); M. E. Jung, P. A. Blair, and J. A. Lowe, *Tetrahedron Letters*, 1439 (1976); E. J. Corey and D. Enders, *Chem. Ber.*, **111**, 1337 (1978).

[4] I. Kuwajima and E. Nakamura, *J. Amer. Chem. Soc.*, **97**, 3257 (1975).

[5] For the direct alkylation of *O*-silylated enolates with t-alkyl halides, see: T. H. Chan, I. Paterson, and J. Pinsonnault, *Tetrahedron Letters*, 4183 (1977) and M. T. Reetz and W. F. Maier, *Angew. Chem. Internat. Edn.*, **17**, 48 (1978).

[6] For the direct alkylation of *O*-silylated enolates with some reactive primary and secondary alkyl halides in the presence of Lewis acids, see I. Paterson, *Tetrahedron Letters*, in press.

[7] J. K. Rasmussen, *Synthesis*, 91 (1977).

[8] I. Paterson and I. Fleming, *Tetrahedron Letters*, 993 and 995 (1979).

[9] G. Wittig and H. Reiff, *Angew. Chem. Internat. Edn.*, **7**, 7 (1968).

[10] The α-chloroalkyl phenyl sulphides (**2**) may be stored for several months under N_2 at -15° without significant deterioration.

[11] In detail, the amount of regioisomer produced was proportional to the amount of the corresponding silyl enol ether present in the starting material.[16] The major regioisomeric α-phenylthioalkyl ketone was generally separated from the minor by column chromatography.

[12] I. J. Borowitz, E. W. R. Caspar, R. K. Crouch, and K. C. Yee, *J. Org. Chem.*, **37**, 3873 (1972); it can be done, however, in NH_3-THF: E. S. Binkley and C. H. Heathcock, *ibid*, **40**, 2156 (1975).

[13] R. K. Boeckman, *J. Org. Chem.*, **38**, 4450 (1973).

[14] Presumably this results from the reversibility of benzenesulphenic acid elimination. In the case of **3** → **5** for R = Bu^t, equilibration to the thermodynamically favoured *E*-isomer is slow enough that the kinetic formation of the Z-isomer and its subsequent isomerisation to the *E*-isomer can be followed by ^{1}H-NMR.

[15] E. J. Corey, D. Enders, and M. G. Bock, *Tetrahedron Letters*, 7 (1976) and references therein.

[16] **20**:**24** in the proportion 99:1; **24**:**20** 88.12; **27b**:regioisomer 93:7; **31**:regioisomer 85:15.

[17] R. Mozingo, *Org. Synth.* Coll. Vol. III, 181 (1955).

[18] B. M. Trost and T. N. Salzmann, *J. Amer. Chem. Soc.*, **95**, 6840 (1973).

(Received in UK 26 March 1979)