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REGIOSPECIFIC α-METHYLENATION AND α-METHYLATION OF KETONES: TITANIUM TETRACHLORIDE PROMOTED PHENYLTHIOMETHYLATION OF SILYL ENOL ETHERS[1]

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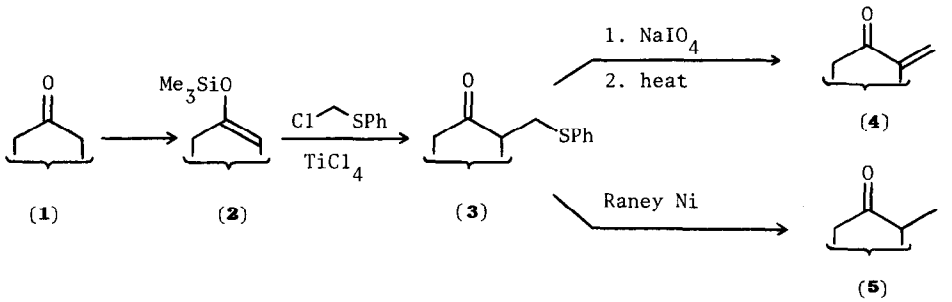
An α-methyleneketone group is a key feature of various sesquiterpenes and antibiotics,[2] as well as being important in synthesis for its Michael-acceptor[3] and dienophile properties.[4] Existing synthetic methods for α-methylenation of ketones have, in general, been based on alkylation by formaldehyde[3] or Mannich reagents[5,6] followed in one or two steps by β-elimination. These methods suffer from the disadvantages that: they are not regiospecific with unsymmetrical ketones, unless a kinetically generated specific enolate is available; the β-hydroxy and β-aminoketones are sensitive intermediates; and the necessary elimination conditions sometimes cause the destruction of the enone products. Consequently a regiospecific method, which permits the construction of the α-methylene unit in a stable, masked form, and which allows unmasking under controlled conditions should be useful.

Reich and Renga[7] have reported that the alkylation of ketone enolates with bromomethyl benzyl sulphide can give α-benzylthiomethylketones, and heating the corresponding sulphoxide then gives the α-methyleneketone. However, this approach has not been shown to be regiospecific and yields are only moderate. We now report that silyl enol ethers,[8] prepared in high yield and regioisomeric purity from ketones,[9] can be regiospecifically alkylated on treatment with chloromethyl

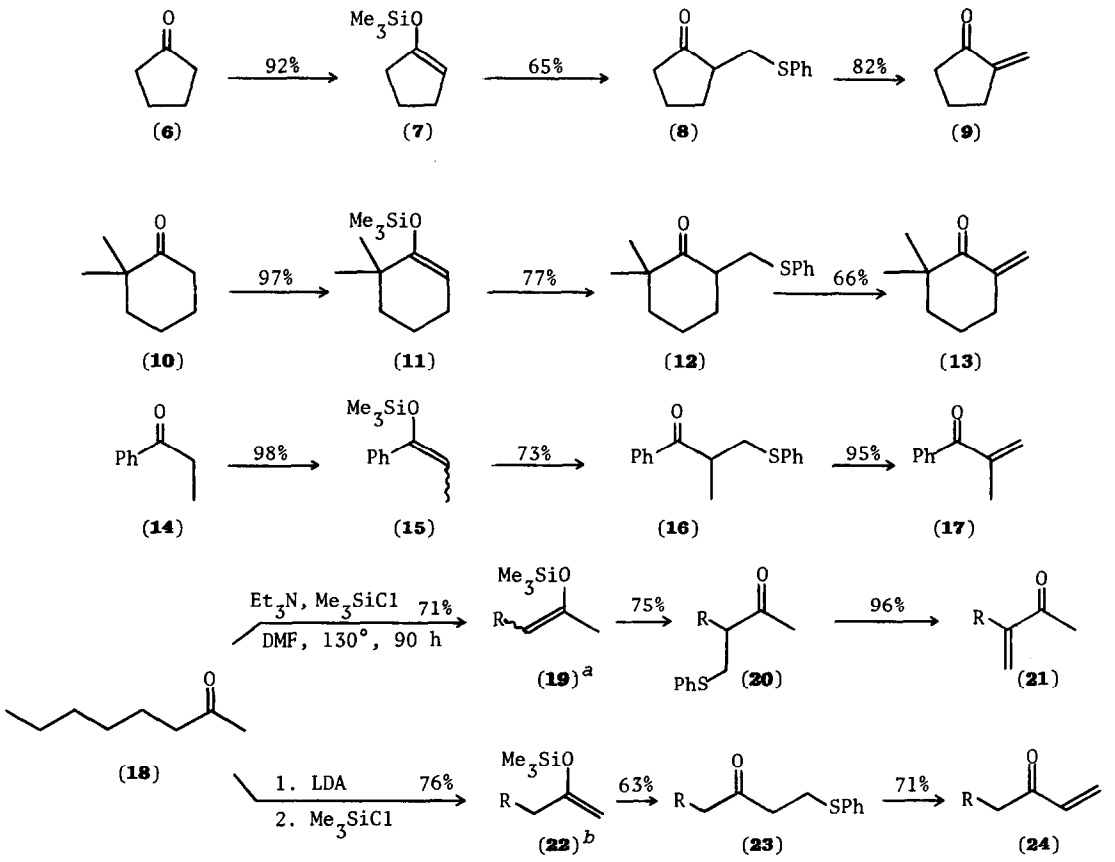


(1) (2) (3) (4) (5)

phenyl sulphide[10] ($PhSCH_2Cl$), in the presence of Lewis acid, to give α-phenylthiomethylketones (**1**→**3**). Oxidative sulphur removal[7,11] then provides the α-methyleneketones (**3**→**4**). Alternatively, sulphur can be removed reductively by Raney nickel hydrogenolysis[12] to make available a new method for the regiospecific α-methylation of ketones (**3**→**5**).

Titanium tetrachloride[13] was found to be the most effective Lewis acid for the alkylation of silyl enol ethers[14] with chloromethyl phenyl sulphide; the milder zinc bromide[15] could also be used catalytically, but gave lower yields. The results for a range of silyl enol ethers

using this α-methylenation sequence are summarised in diagrams **6** to **24**. Typically, a solution of titanium tetrachloride (5.5 mmol) in dry CH_2Cl_2 (5 ml) was added at -23° by syringe to a stirred solution of silyl enol ether (5 mmol) and chloromethyl phenyl sulphide (7 mmol) in CH_2Cl_2 (5 ml) under nitrogen. After 1 h, the resulting deep red solution was poured into saturated sodium bicarbonate solution (25 ml) and extracted repeatedly with ether. The organic phase was dried and evaporated *in vacuo* to give, after chromatography on silica gel, the α-phenylthiomethylketone.



(**6**) (**7**) (**8**) (**9**)

(**10**) (**11**) (**12**) (**13**)

(**14**) (**15**) (**16**) (**17**)

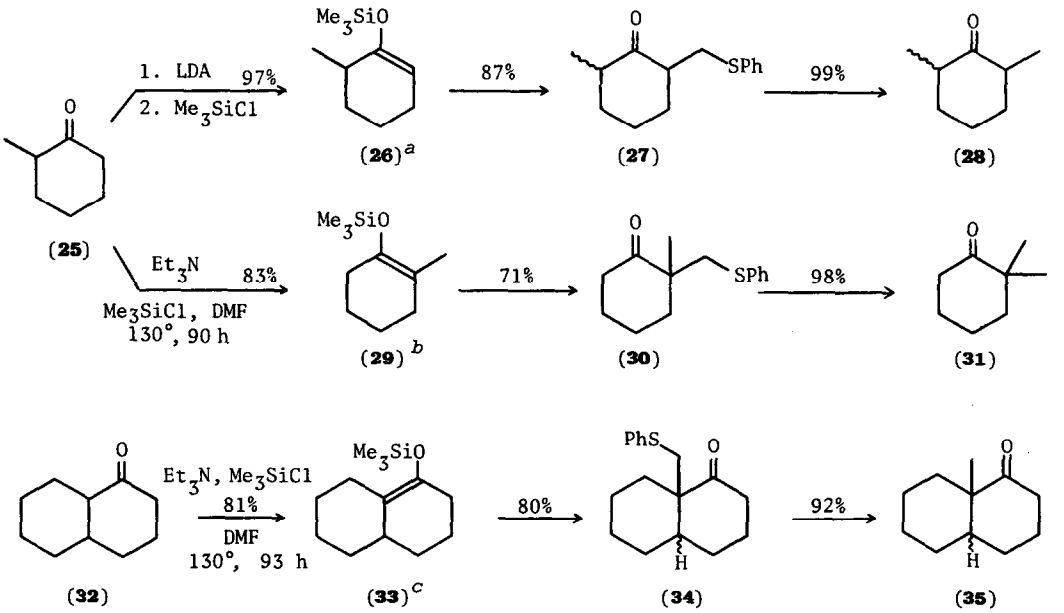
(**18**) (**19**)[a] (**20**) (**21**)

(**22**)[b] (**23**) (**24**)

([a]**19**:**22** in the proportion 92:8; [b]**22**:**19** in the proportion 85:15.)

The reaction works well for cyclic (**6** and **10**) and acyclic (**14** and **18**) ketones. Notably, alkylation of propiophenone (**14**) via its silyl enol ether gave a better yield by our method (73%) than by that using the enolate itself (60%).[7,16] Unmasking of the α-methylene function, which can potentially be stored as the sulphide through other reactions,[7] was straightforward. Sulphoxide formation with sodium metaperiodate in aqueous methanol at room temperature was essentially quantitative,[11] and elimination of benzenesulphenic acid took place in high yield in CCl_4-$CHCl_3$ at 80° for up to 48 h. The 'thermodynamic' (**19**) and 'kinetic' (**22**) silyl enol ethers of 2-octanone (**18**) reacted regiospecifically[17] with chloromethyl phenyl sulphide and $TiCl_4$ to give the products (**20** and **23**), and oxidation and elimination then gave the α-methyleneketone (**21**) and the vinyl ketone (**24**), respectively.

Removing the sulphur reductively with Raney nickel[12] changes our procedure into a regiospecific α-methylation sequence for ketones. Typically, the α-phenylthiomethyl ketone (1 mmol) was stirred vigorously with W-2 Raney nickel[18] (*ca.* 1.5 g) in acetone-ethanol (9:1, 10 ml) at room temperature for 1-2 h. The mixture was diluted with dichloromethane and the nickel cautiously removed by filtration through celite. Evaporation *in vacuo* and chromatography on silica gel gave the methyl ketone in high yield. To illustrate this other way of using these α-phenylthiomethylketones in synthesis, we phenylthiomethylated the two isomeric silyl enol ethers of 2-methylcyclohexanone (**25**). The 'kinetic' (**26**) and 'thermodynamic' (**29**) silyl enol ethers[9] reacted regiospecifically[17] with chloromethyl phenyl sulphide and $TiCl_4$ to give the products (**27** and **30**), and desulphurisation then gave the dimethylcyclohexanones (**28** and **31**, respectively) in good overall yield.



(a **26**:**29** in the proportion 99:1; b **29**:**26** in the proportion 88:12; c **33**:regioisomer in the proportion 90:10)

A general problem associated with the alkylation of kinetically generated specific enolates is loss of regiospecificity and concomitant formation of dialkylation products.[19] A key example is methylation at the bridgehead position of 1-decalone (**32**), which leads to a significant proportion (23:62)[20] of methylation on the less-substituted side of the carbonyl group. This can largely be avoided by our method. Phenylthiomethylation of **32** promoted by $TiCl_4$ regiospecifically[17] gave the bridgehead-alkylated stereoisomers (**34**), which, on treatment with Raney nickel in acetone-ethanol (20°, 2 h), gave a 4:1 mixture of *cis* and *trans* 9-methyl-1-decalone (**35**). The stereoselectivity in favour of the *cis* product is of the same order as that obtained by direct methylation of the lithium enolate corresponding to **33**,[20,21] but the proportion of bridgehead alkylation (90:10) is higher, the minor product reflecting the proportion of the regioisomeric silyl enol ether present in **33**.

Our method is therefore a useful addition to the other methods of silyl enol ether methylation, namely formation of the directed lithium[8] or benzyltrimethylammonium[19] enolate and alkylation with methyl iodide, or cyclopropanation and ring-opening with hydroxide ion.[22]

NOTES and REFERENCES

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[6]For a direct synthesis of α-methylene ketones by a Mannich route, see J. L. Gras, *Tetrahedron Letters*, 2111 and 2955 (1978).

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[14]For the alkylation of silyl enol ethers 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).

[15]See preceding paper.

[16]The only other ketone included in Reich and Renga's paper[7] was cyclooctanone, which was benzylthiomethylated in only 51% yield.

[17]In detail, the amount of regioisomer produced was proportional to the amount of the corresponding silyl enol ether present in the starting material. The major regioisomer (**20** from **19**, **23** from **22**, and **27** from **26**) was separated from the minor by column chromatography. In the case of **30**, chromatography removed only one of the diastereoisomers of **27** and the other (<*ca.* 5%) was carried through. In the case of the decalones, separation was delayed until **35**.

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