Tetrahedron Letters,Vol.24,No.3,pp 323-326,1983 0040-4039/82/030323-04$03.00/0
Printed in Great Britain

# A REGIOSPECIFIC SYNTHESIS OF γ-KETO ESTERS: THE ALKYLATION OF O-SILYLATED ENOLATES WITH METHYL α-CHLORO-α-PHENYLTHIOACETATE

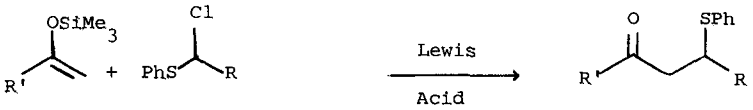
Thomas V. Lee* and Jonathan O. Okonkwo

(Department of Chemistry, Brunel University, Uxbridge UB8 3PH, England)

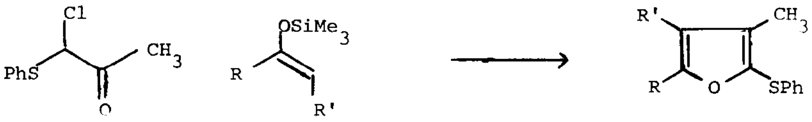
*Summary: Methyl α-chloro-α-phenylthio acetate (2) regiospecifically alkylates O-silylated enolates to form γ-keto esters.*

As part of a synthetic programme the need arose to perform a non-basic, regiospecific introduction of a carbomethoxy methyl group α to a carbonyl group. Under basic conditions one would normally react a lithium enolate anion with methyl bromoacetate and so we decided to investigate an equivalent to this process using O-silyl enolates[1].

The alkylation of O-silylated enolates with stabilised carbocations, under Lewis acid catalysis is now well established. One of the most versatile methods is the use of phenyl thioalkylation, as developed by Paterson and Fleming, with a variety of substituted phenylthio alkyl chlorides having now been reacted with O-silylated enolates, in a regiospecific manner[2].



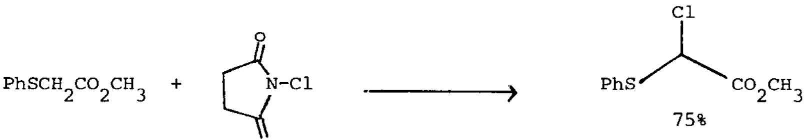
One example included a report of the reaction of α-chloro-α-phenylthioacetone (1) and O-silylated enolates, resulting in the formation of a furan[3]. To date, this paper contains the only reported use of phenylthioalkylating agents containing a carbonyl function.



(1)

We now report the reaction of methyl α-chloro-α-phenylthioacetate (2) with O-silylated enolates for the regiospecific introduction of a carbomethoxy methyl group α to a carbonyl group.

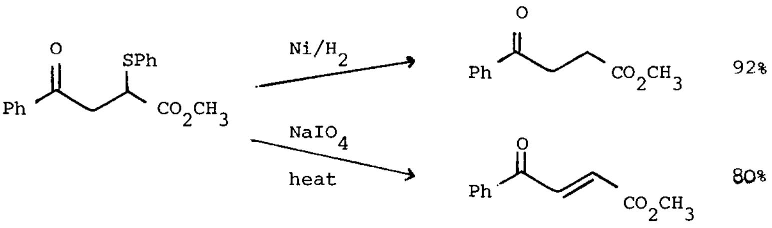
The required ester (2) is readily prepared as reported by Campbell[4] or by reacting methyl phenylthioacetate with N-chlorosuccinimide.



(2)

As shown the ester reacts with a variety of O-silylated enolates to form γ-keto esters in a regiospecific manner, shown by enol ether (3). Reaction with the O-silylated enolate (4) occurs exclusively at the γ-position to form an enone[9], so extending its use to the preparation of vinylogous γ-keto esters.

The phenylthio group of the γ-keto esters can either be removed by Raney nickel reduction or oxidized to a sulphoxide and heated to eliminate phenylsulphenic acid, providing

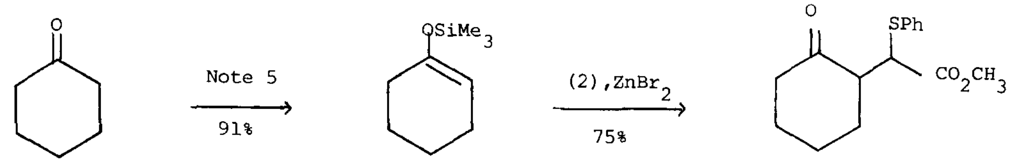


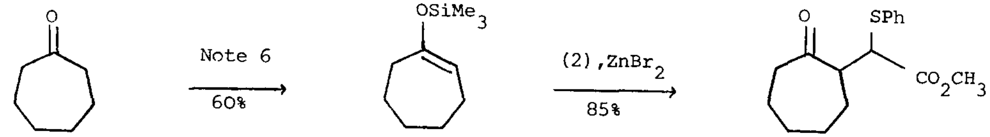
(5)

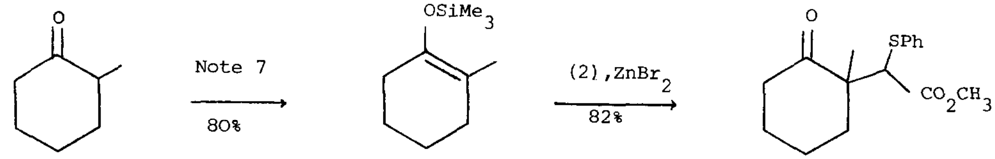
the unsaturated γ-keto ester (5).

This novel preparation of γ-keto esters extends the utility of phenylthioalkylation by demonstrating the compatability of the ester group with the α-chlorosulphide function.

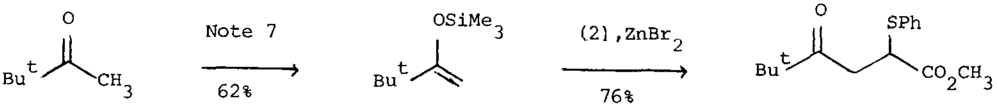
In a typical procedure the O-silylated enolate (10 mmoles) and the ester (2) (11 mmoles) were stirred, under nitrogen, at room temperature in dichloromethane, in the presence of anhydrous zinc bromide for 1-2 hours. Aqueous work up and purification by flash chromatography[10] afforded the γ-keto esters[11].

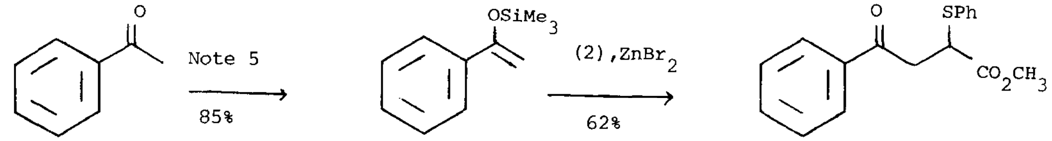

O
Note 5
91%
OSiMe3
(2),ZnBr2
75%
O
SPh
CO2CH3

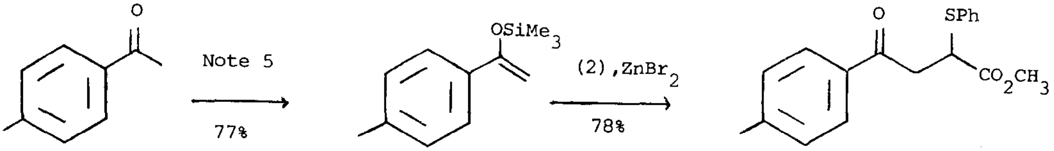

O
Note 6
60%
OSiMe3
(2),ZnBr2
85%
O
SPh
CO2CH3

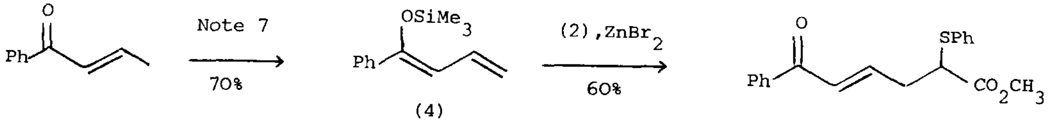

O
Note 7
80%
OSiMe3
(2),ZnBr2
82%
O
SPh
CO2CH3

(3)


O
But
CH3
Note 7
62%
OSiMe3
But
(2),ZnBr2
76%
O
SPh
But
CO2CH3


O
Note 5
85%
OSiMe3
(2),ZnBr2
62%
O
SPh
CO2CH3


O
Note 5
77%
OSiMe3
(2),ZnBr2
78%
O
SPh
CO2CH3


O
Ph
Note 7
70%
OSiMe3
Ph
(2),ZnBr2
60%
O
SPh
Ph
CO2CH3

(4)

REFERENCES AND NOTES.

1. E. Colvin, in *Silicon in Organic Synthesis.* Butterworths (1981)
2. I. Fleming, *Chimica* (1980), *34*, 265.
   I. Paterson and L.G. Price, *Tetrahedron Letters* (1981), 2829 and 2823
   I. Paterson and M.A. Khan, *Tetrahedron Letters* (1982), 2399
3. R. Tanikaga, K. Miyashita, H. Sugihara and A. Kagi, *JCS. Chem. Communs.* (1981), 1106.
4. M.M. Campbell, V.B. Jigajinni, K.A. MacLean and R.H. Wightman, *Tetrahedron Letters*, (1980), 3305.
5. These O-silylated enolates were prepared by treating the ketone with 1.1 equivalents of LDA in THF at -78°C, followed by 1.1 equivalents of $Me_3SiCl$ from -30° to room temperature, non-aqueous work-up and distillation, see reference 2.
6. This O-silylated enolate was prepared by treating the ketone in $CH_3CN$ with 1.1 equivalents of $Et_3N$, 1.1 equivalents of $Me_3SiCl$ and a catalytic amount of $ZnBr_2$, followed by non-aqueous work-up and distillation. I.Fleming, *Comprehensive Organic Chemistry*, Vol.3. P.584.
7. These O-silylated enolates were prepared: $Me_3SiCl$, $Et_3N$, DMF, reflux, with a neutral aqueous work up and distillation[8].
8. H.O. House, L.J. Czuba, M. Gall and H.D. Olmstead, *J. Org. Chem.*, (1969), *34*, 2324.
9. I. Fleming and T.V. Lee, *Tetrahedron Letters* (1981), 705.
10. W. Clark Still, M. Kahn and A. Mitra, *J. Org. Chem.*, (1978), *43*, 2923.
11. All new compounds gave satisfactory ir, nmr, and mass spectral data.

(Received in UK 15 October 1982)