Tetrahedron Letters,Vol.23,No.33,pp 3419-3420,1982 0040-4039/82/333419-02$03.00/0
Printed in Great Britain

THE ESTER ENOLATE CLAISEN REARRANGEMENT OF ALLYL α-HYDROXYACETATES AND α-PHENYLTHIOACETATES[1] .

By David J. Ager*

Department of Organic Chemistry, Robert Robinson Laboratories,
P.O. Box 147, Liverpool, L69 3BX

and Richard C. Cookson

Department of Chemistry, The University, Southampton SO9 5NH

Summary: The ester enolates of allyl α-hydroxyacetates and α-phenylthioacetates undergo a Claisen rearrangement to give α-substituted-γ,δ-unsaturated acids.

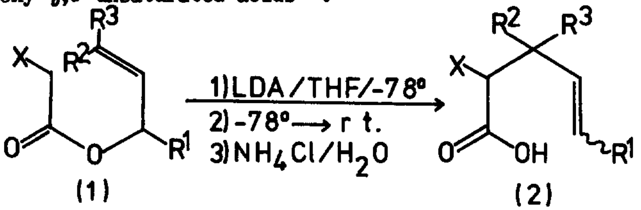
In our studies towards the synthesis of macrolide and ionophoric antibiotics, a synthesis of α-hydroxy and α-phenylthioγδ-unsaturated acids was required. For this we turned to the Claisen ester enolate rearrangement which although discovered by Arnold *et al*[2] in the late 1940's, it has not become synthetically useful until recently, with work led by Ireland[3-9] Ireland has used the reaction to synthesise dihydrojasmone[3], prostaglandin analogues[4], furanoid and pyranoid glycals[5], tirandamycic acid[6] and nonactin acid[9]. The use of the reaction has been increased by the predictable stereochemical outcome of the Claisen rearrangement[10]; in the case of allyl esters, the stereochemical outcome is decided by the generation of the E- or Z- enolate[4-8].

Lythgoe has shown that allyl esters of α-phenylthioacetic acid undergo the Claisen rearrangement when the trimethylsilyl enol ethers are heated to 50-60°C[11]. This was confirmed for allyl α-phenylthioacetate $(1;R^1=R^2=R^3=H,X=PhS)$; the rearranged product $(2;\ R^1=R^2=R^3=H,X=PhS)$ was isolated in 82% yield. Ireland had found that the use of the trimethylsilyl enol ether was advantageous for acetate esters but in substituted cases the lithium enolate rearranged rapidly at room temperature or slightly above[3]. This was indeed the case for the allyl α-phenylthioacetates; when the solution of a lithium enolate of $(1;X=PhS)$ was allowed to warm up from -78°C to room temperature, the product isolated, after aqueous work-up, was the acid $(2;\ X=PhS)$ in high yield (see Table and Scheme) thus alleviating the necessity of the silyl enol ethers.

Encouraged by these results, we turned to other α-substituted acetates. The first group to be investigated was trimethylsiloxy, but to date, however, no success has been achieved with the Claisen rearrangement of the allyl ester $(1;R^1=R^2=R^3=H,X=Me_3SiO)$. The failure of the reaction may be because of the labile silyl group as Whitesell and Helbling[12] have used the methyl ethers $(3;\ X=MeO)$ and Bartlett[13] amides with success. Other silyl ethers will be investigated but the use of a hydroxyl protecting group is not necessary as the parent esters (1; X=OH) rearrange.

The allyl α-hydroxyacetates (1; X=OH) when treated with two equivalents of LDA in THF at -78°C and then allowed to warm to room temperature over 10h gave, after aqueous work-up, the α-hydroxy-γ,δ-unsaturated acids (2; X=OH) in high yield (see Table).

As the allyl α-hydroxyacetates are easily prepared from glycollic acid, the reaction provides a useful method for preparing α-hydroxy-γ,δ-unsaturated acids[14].



Scheme

Claisen rearrangements of allyl α-substituted acetate enolates.

R^1=	R^2=	R^3=	Yield of (2) (%)	
			X = PhS	X =OH
H	H	H	88 (82^a)	79
H	Ph	H	86	81
H	Me	Me	88 (80%^{a,10})	-^{b}
Me	H	H	79	75
Me	Me	Me	71	71
Ph	H	H	89	79

[a] The yield obtained when the trimethylsilyl enol ether was heated at 60°C for 1h.

[b] Denotes that this reaction has not been carried out.

References.

1. Part of this work was carried out at the Department of Chemistry, The University, Southampton, SO9 5NH. An S.R.C. postdoctoral fellowship (to D.J.A.) for this part of the work is acknowledged.
2. R.T. Arnold and S. Searles, J.Am.Chem.Soc., 1949, 71, 1150.
   R.T. Arnold, W.E. Parham and R.M. Dodson, J.Am.Chem.Soc., 1949, 71, 2439.
3. R.E. Ireland and R.H. Mueller, J.Am.Chem.Soc., 1972, 94, 5897.
4. R.E. Ireland, R.H. Mueller and A.K. Willard, J.Org.Chem., 1976,41,986
5. R.E. Ireland, S. Thaisrwongs, N. Vanier and C.S. Wilcox, J.Org.Chem., 1980, 45, 48
6. R.E. Ireland, P.G.M. Wuts and B. Ernst, J.Am.Chem.Soc., 1981, 103, 3205.
7. R.E. Ireland, R.H. Mueller and A.K.Willard, J.Am.Chem.Soc., 1976, 98, 2868
8. R.E. Ireland and C.S. Wilcox, Tetrahedron Lett., 1977, 2839.
9. R.E. Ireland and J.-P. Vevert, J.Org.Chem., 1980, 45, 4259
10. G.B. Bennett, Synthesis, 1977, 589 and references cited therein.
11. B. Lythgoe, J.R. Milner and J. Tideswell, Tetrahedron Lett., 1975 2593
12. J.K. Whitesell and A.M. Helbling, J.Org.Chem., 1980, 45, 4135
13. P. A. Bartlett and J.F. Barstow, Tetrahedron Lett., 1982, 23, 623
14. The reaction is being investigated with other α-substituents and also with metals other lithium as the counterion; we are also looking at the stereochemical control of the reaction.

(Received in UK 1 June 1982)