Tetrahedron Letters,Vol.24,No.32,pp 3391-3394,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

EXTENDED ENOLATE IONS FROM γ-PHENYLTHIO-CROTONATE ESTERS

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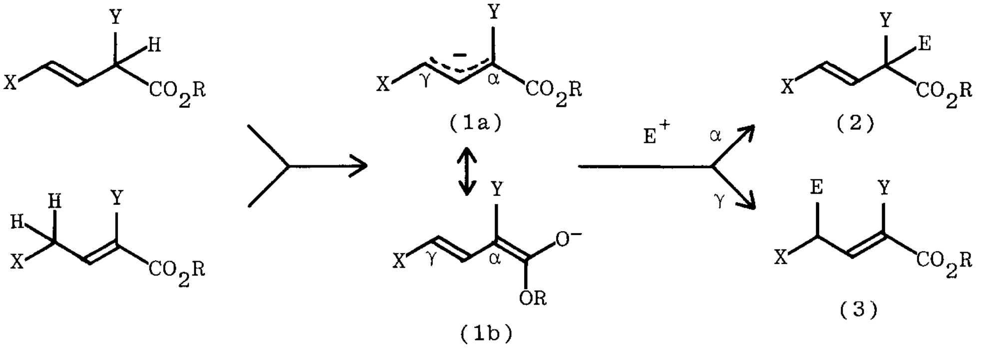
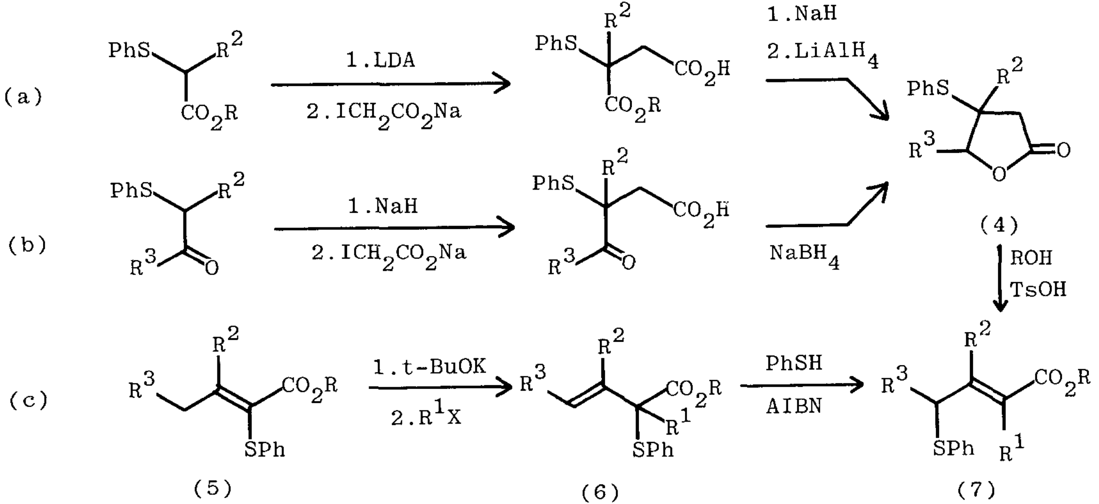
Summary: Substituted γ-phenylthio-crotonate esters (7) can be made by [1,2] and [1,3] PhS shifts: they form extended enolate anions which react with electrophiles at the carbon atom α to the carbonyl group and γ to sulphur.



Extended enolate ions from the esters (1, X,Y = H, alkyl) react with electrophiles mostly at the α atom.[1] This is a kinetically controlled process as the γ-product (3) is more conjugated than the α-product (2). Anions from allyl sulphides are less predictable but generally react with alkyl halides at the atom α to sulphur.[2] It appears that both CO_2R and RS increase the coefficient of the HOMO at their point of attachment to the allyl anion.[3] When both groups are at the same end of an allyl anion (1, X = H,alkyl; Y = RS), exclusive α-alkylation is the rule,[4] e.g. (5) - (6), as each group reinforces the α-directing effect of the other. We now report on the reactions of anions (1, Y = H, alkyl; X = SPh) in which the directing effects of the two groups conflict.

The anion (1, X = MeS, Y = H, R = Me) has been used by Kende[5] in reactions with alkyl halides and Michael acceptors at the α-atom. This compound was made from the available methyl γ-bromocrotonate ester. We have made substituted γ-PhS crotonate esters (7) by three routes. In routes (a) and (b) (scheme 1) lactones[6] (4) rearrange[7] in the presence of an alcohol by a [1,2] PhS shift. In route (c), the products of α-alkylation of (5) rearrange by a [1,3] PhS shift[8] after radical (PhS·) initiation. Table 1 shows that good yields of (7) in a range of substitution patterns are available by these routes.

Scheme 1: Synthesis of γ-Phenylthio-crotonate Esters (7)



Anions from (5) were difficult to make[4] because of the low kinetic acidity of the γ-proton and the high reactivity of (5) as a Michael acceptor. The γ-PhS group in (7) enhances the acidity of the γ-proton and the absence of an α-PhS group reduces Michael reactivity so that anions from (7) are relatively easy to make (t-BuOK, THF, -78°C). Quenching the extended enolates (8) with a proton ($NaHCO_3$) gives good yields of the β,γ-unsaturated esters (9). This is presumably kinetic protonation at the α-position, but there is some evidence to

Table 1

Synthesis of γ-Phenylthio-Crotonate Esters (7) (Scheme 1)

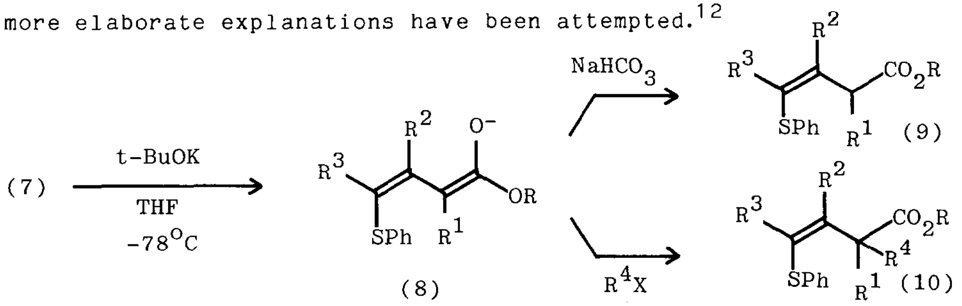
Starting Material					Product (7)		
Compound[a]	R^1	R^2	R^3	R	Compound	Yield	Stereo
(4a)	H	H	H	Et	(7a)	74	E
(6b)	$PhCH_2$	H	H	Et	(7b)	94	85:15 E:Z
(4c)	H	Me	H	Me	(7c)	66	mixture
(4d)	H	H	Me	Me	(7d)	64	E
				Et	(7e)	88	E
				n-Bu	(7f)	85	E
(4e)	H	Et	H	Me	(7g)	84	4:3
(6f)	Me	Me	H	Me	(7h)	96	4:3 E:Z
(4g)	H	Me	Me	Me	(7i)	81	4:1 E:Z
				n-Bu	(7j)	75	4:1 E:Z
E-(6h)	Et	H	Et	Me	(7k)	92	82:18 E:Z[b]
(4i)	H	H	Ph	Me	(7l)	87	3:2

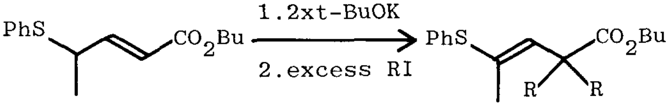
a. For (4), see ref. 6: for (6), see ref 4.

b. Trisubstituted alkenes separated by h.p.l.c. and geometry assigned by n.m.r.

suggest that PhS may be at least as good as a carbonyl group at conjugating with a double bond.[9]

Alkyl halides also react cleanly at the position α to CO_2R and γ to PhS giving esters (10) (table 2). Dialkylation of (7, R^1 = H) can be accomplished in one step: treatment of (7f) with two equivalents of base followed by an excess of an alkyl iodide gave good yields of (11) (table 2). With no electrophile was any γ-product (3, X = PhS, Y = H, alkyl) observed. This suggests that the CO_2R group perturbs the HOMO of the allyl anion more than does the PhS group. The reverse is true of the sulphones[10] (1, X = $ArSO_2$) which react almost entirely at the γ-carbon atom. These results agree with Still and Macdonald's rule of thumb[11] for allyl anions with anion-stabilising groups, though more elaborate explanations have been attempted.[12]





(7f)

(11)

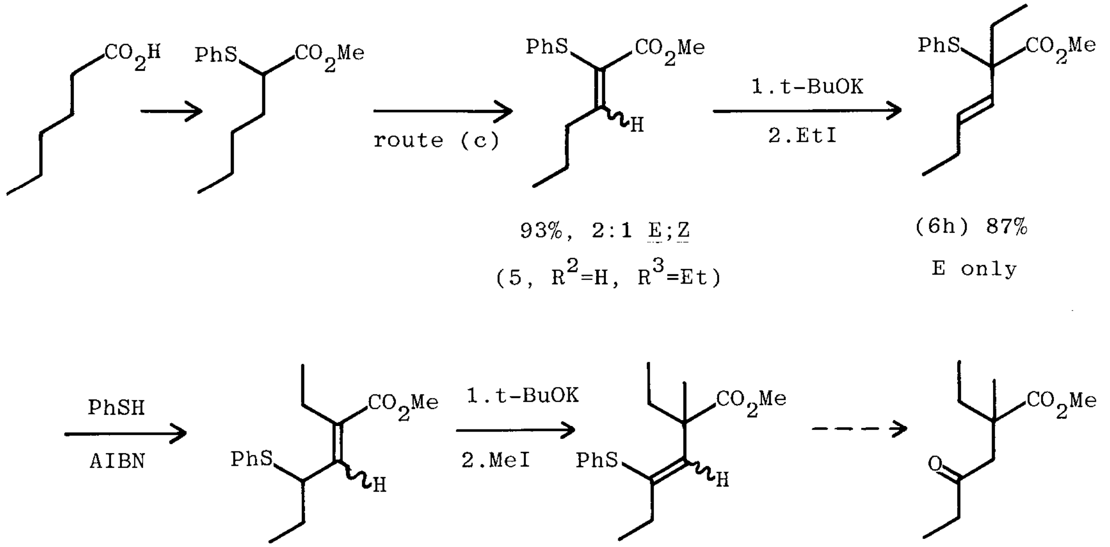
Table 2

Reaction of Extended Enolates (8) with Electrophiles

Starting Materials					Electrophile		Product		
Compound	R	R^1	R^2	R^3	R^4	Reagent	Compound	Yield	Stereo
(7a)	Et	H	H	H	H	$NaHCO_3$	(9a)	89	mixture
(7b)	Et	$PhCH_2$	H	H	Me	MeI	(10b)	91	7:1 E:Z
					Et	EtI	(10c)	89	E
(7f)	n-Bu	H	H	Me	H	$NaHCO_3$	(9b)	95	mixture
					Me	MeI	(10d)	84	mixture
(7k)	Me	Et	H	Et	Me	MeI	(10e)	88	6:1 E:Z
Dialkylations:									
(7f)	n-Bu	H	H	Me	Me	MeI	(11a)	83	mixture
					Et	EtI	(11b)	88	E
					n-Pr	n-PrI	(11c)	79	E

A complete sequence (scheme 2) shows how a simple carboxylic acid may be progressively functionalised and substituted along the carbon chain, each step being controlled by sulphur. The final product (10e) is a vinyl sulphide and thus a masked ketone. Hydrolysis by one of the methods reported[13] for this class of vinyl sulphide would give the 1,4-dicarbonyl compound (12). The stereochemistry of intermediates (5-11) is irrelevant in this application.

Scheme 2



93%, 2:1 E;Z
(5, R^2=H, R^3=Et)

(6h) 87%
E only

(7k) 92%
82:18 E:Z

(10e) 88%
6:1 E:Z

(12)

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(Received in UK 25 May 1983)