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REACTIVITY OF A NOVEL AMBIDENT DIANION FORMED BY DOUBLE DEPROTONATION OF β-THIOSUBSTITUTED DITHIOPROPANOATES : A LITHIO-ACRYLATE EQUIVALENT.

Pierre BESLIN*and Alain DLUBALA.

Laboratoire de Chimie des Composés Thioorganiques, ISMRa, Université de Caen
14032 CAEN CEDEX, FRANCE.

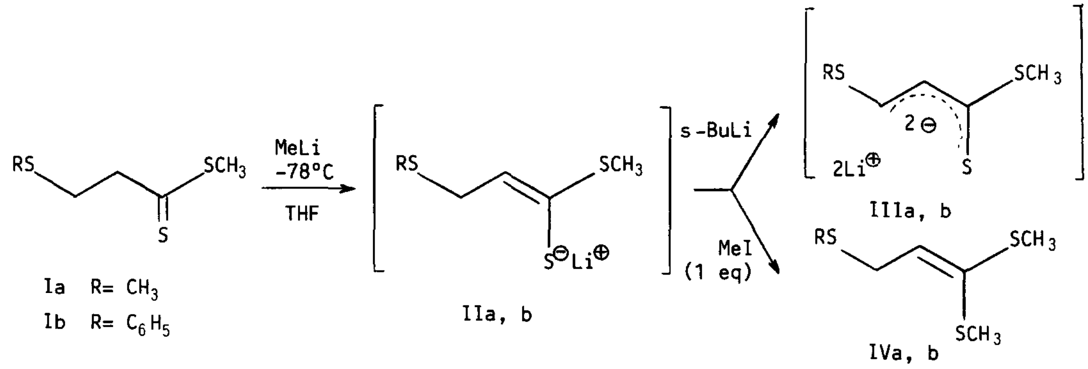
Summary : A novel lithium allyl dianion has been generated by double deprotonation of β-alkyl (aryl) thio-dithioester. Reactions of this dianion with alkyl iodide, trimethylsilyl chloride and epoxyde occur at the γ-site. The regiochemistry of its addition to carbonyl compounds depends on the carbonyl compounds, e.g., for aldehydes and ketones, α -and γ-regioselectivity respectively, were observed. The reactivity with cyclopentenone was also examined.

The problem of the regiochemistry encountered in the reaction of allyl anion has been solved by the use of sulfur-stabilized anion [1]. The reaction of mono alkylthio-allyl anion with electrophiles occurs generally with α-regioselectivity [1]. This selectivity is sensitive to the presence and the nature of additional substituent [2] : α and γ-reactions of gem-dialkylthio-allyl anion with respectively alkyl halides and carbonyl compounds were reported [3]. Unusual γ-exclusive alkylations in addition to the more expected γ-additions to carbonyl compounds were recently observed in the case of a triphenylthio-allyl anion [4]. The doubly metalated derivative of 2-propene thiol exhibits a similar behaviour [5]

We now wish to report the novel allylic dianionsIII generated from β-thio-substituted dithioesters and our first results on their regioselective alkylation and addition to carbonyl compounds.

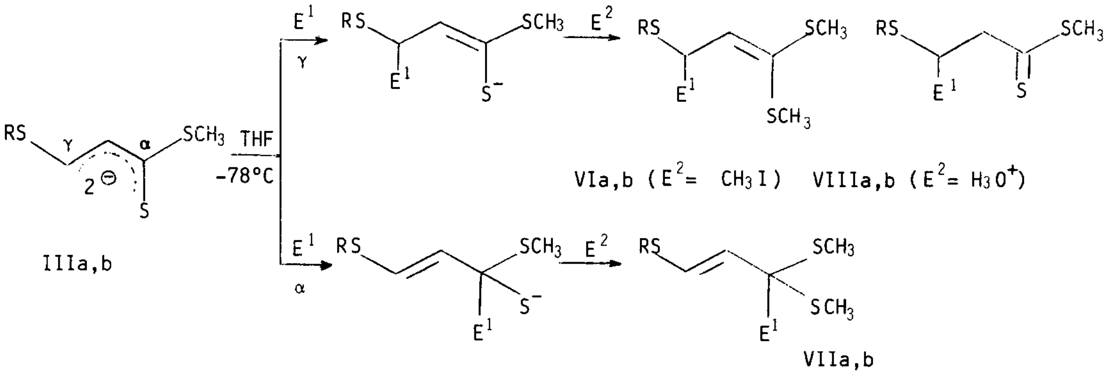
For this purpose two new dithioesters, methyl 3-methylthio dithiopropanoate I a and methyl 3-phenylthio dithiopropanoate Ib, were prepared from the corresponding nitriles [6] by a Pinner reaction [7]. Deprotonation of these two dithioesters by methyllithium [8a] in THF at -78°C affords the stable cis monoanion [8b] IIa, b as indicated by their almost quantitative transformation to the ketene acetals IVa, b (scheme I). A second deprotonation by s-BuLi in presence or absence of TMEDA was achieved at -78°C for Ib and at -50°C for Ia, giving the deep red coloured dianions IIIa, b (see scheme I).

Scheme I



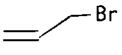
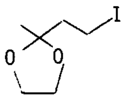
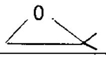
Reaction of IIIa, b with excess methyl iodide yields γ-methylated ketene acetals VIa, b which a priori may result from either γ-methylation, followed by S-methylation or the reverse. However if the S-methylation takes place first, it is known [3a] that methyl iodide would react at the α-site of the ensuing ketene dithioketal, and we have shown by independent deprotonation of IVa, followed by addition of methyl iodide that this gave the ratio α/γ 85/15.

Scheme II



Numerous other alkyl iodides, trimethylsilylchloride, and an epoxyde, were reacted with dianions IIIa, b. A unique γ-regioisomer was uniformely formed confirming the γ-regioselective nucleophilic substitution observed with methyl iodide (see table I). The γ-substituted ketenedithioacetals VI or β-alkylthio dithioesters VIII (obtained with $E^2 = H_2O$) may be hydrolysed respectively to β-alkylthio-thioesters [9] and β-alkylthio esters.

Table I

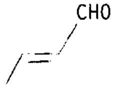
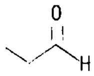
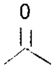
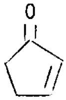
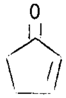
Entry	Dithioester	E^1	E^2	VI or VIII	VII	Yield* (%)
1	Ia	CH_3I	CH_3I	100	0	65
2	Ib			100	0	60
3	Ia	 Br	CH_3I	100	0	42
4	Ib			100	0	41
5	Ib	C_2H_5I	H_2O	100	0	60
6	Ia		H_2O	100	0	66
7	Ib			100	0	40
8	Ib	$(CH_3)_3SiCl$	H_2O	100	0	45
9	Ia		CH_3I	100	0	21

* Yield of MPLC purified product, not optimized.

Reactions of dianions IIIa, b with carbonyl compounds were also examined (see table II).The regioselectivities of the aldehyde addition are controlled by the nature of R in dianions III. Thus α-selectivity was found when R= C_6H_5 , but no selectivity was observed when R= CH_3 (see entries 10-14). Additions of III to saturated ketones provide preferentially γ-adducts, independently of the nature of R in III (see entries 15-18). With unsaturated carbonyl compounds, the question of 1-2 and 1-4 addition now complicates the problem of α -and γ -addition. With cyclopentenone the 1,2-selectivity (ratio γ-1,2/ γ-1,4/ α-1,2= 70/20/10) is reversed when the dianion is treated with 5 equivalents of HMPA ; a γ-exclusive, and γ-1,4 preferential selectivity (ratio γ-1,2/ γ-1,4= 17/83) is observed(see entries 19-20).

A synthetic use of these α-adducts may be their conversion into unsaturated 3-furanones. For the formation of γ-adducts, the dianion may be considered to be a β-lithio-acrylate equivalent [4,11] as has been illustrated by the transformation of similar γ -adducts into ± eldanolide [4] . 1,4-addition adducts are versatile intermediates in prostaglandin synthetic strategy [12] .

Table II

Entry	Dithioester	E^1	E^2	VI**	VII (E isomer)	Yield* (%)
10	Ia		CH_3I	50	50	73
11	Ib			25	75	75
12	Ia		CH_3I	51	49	87
13	Ib			25	75	70
14	Ib		CH_3I	35	65	45
15	Ia		CH_3I	87	13	44
16	Ib			83	17	58
17	Ia		CH_3I	90	10	52
18	Ib			94	6	55
19	Ib		CH_3I	70 (1, 2) 20 (1, 4)	10 (1, 2)	59
20	Ib HMPA		CH_3I	83 (1,4) 17 (1, 2)	0	22

* Yield not optimized. ** mixture of two diastereoisomers.

The observed difference in the regioselectivities of the ambident dianion III may be interpreted in terms of a lack of coincidence for the largest coefficient of the HOMO[13] on the γ-site and the highest electron π charge density[13] on the α-site. Nucleophilic substitutions occur under orbital control and carbonyl addition under charge control or a combination of the two. By modifying the nature of the thiosubstituents it may be possible to shift the highest electron π charge density to the γ-site in order to reinforce the γ-regioselectivity.

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