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ADDITIONS OF ORGANOMETALLICS TO ENETHIOLIZABLE β-OXODITHIOESTERS - POTENTIAL SYNTHETIC USES.

Serge Masson and André Thuillier

Laboratoire des Composés Thioorganiques, ISMRA, Université, 14000, CAEN, France.

Summary Enethiolizable β-oxodithioesters allowing the successive formation of carbon-carbon bonds at the carbonyl and at the thiocarbonyl sites, are precursors of α-unsaturated dithioesters and can be used as a^3d^1 or a^3a^1 synthons.

It has been shown [1,2]that aliphatic Grignard reagents react stereoselectively with non-enethiolizable β-oxodithioesters to give, via a thiophilic addition, 2,2-bis (alkylthio)-cyclopropanols. This communication presents our first results related to the reactions of organometallics with enethiolizable β-oxodithioesters, which demonstrate that these readily available bifunctional compounds [3] are precursors for the synthesis of α-ethylenic dithioesters and can be used as a^3d^1 or a^3 a^1 synthons [4].

When β-oxodithioesters (1, 2), which exist mainly in their enolic form, were treated with at least two equivalents [5] of the organometallics and under the experimental conditions mentioned in table I, β-hydroxydithioesters (3 to 7), resulting from an exclusive addition to the carbonyl group, were obtained in good yield The chemoselectivity of these reactions and the fact that no or little (less than 15 %) retro-Claisen reaction occurs contrast with the results reported for the addition of Grignard reagents to β-ketoesters [6].

When there was no substituant on C_2 (R^1= H), dehydration of the β-hydroxydithioesters (table II) could be performed by use of p.toluenesulfonic acid (p.TsOH) but when R^1 = CH_3 , the main reaction was the cleavage of 7 into acetone and methyl propanedithioate. Dehydration of 7 via its mesylate [7] was satisfying and this procedure appeared to be convenient in both cases. New α-unsaturated dithioesters such as 9, 10 and 11 [8] (10 is monoterpenic and has the cis-trans geranic acid structure) were prepared starting from β-oxodithioesters and this method complements the few known procedures [9]

It is known that saturated and unsaturated (allylic, benzylic, propargylic) Grignard reagents can give respectively thiophilic and carbophilic additions to dithioesters[10] [11]. The chemoselective addition of organometallics to the carbonyl group and the use of the dithioester function as acyl anion (via thiophilic addition) or acyl cation equivalent (via carbophilic addition) make possible the use of β-oxodithioesters as the two synthetic equivalents shown below

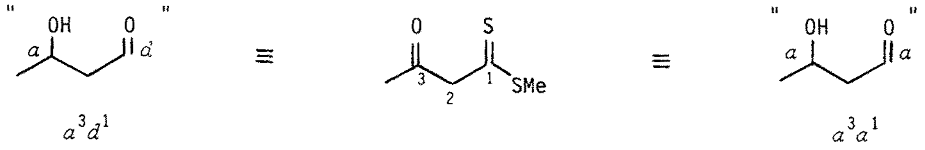
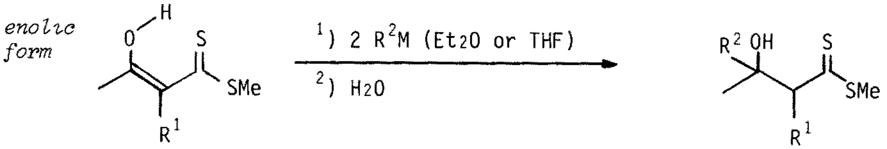


Table I Addition of organometallics to the carbonyl group of β-oxodithioesters



β-oxo dithioester	R^1	R^2	M (solvent)	β-hydroxy dithioester (a)	% Yield (b)
1	H	Methyl	MgI (Et2O)	3	85
	H	Methyl	MgBr (THF)		90
	H	Methyl	Li (Et2O)		77
1	H	n-Butyl	Li (Et2O, hexane)	4	95
1	H	Crotyl	MgBr (THF)	5 (c)	88
1	H	4-methyl--3-pentenyl	MgBr (THF)	6	80
2	CH_3	Methyl	MgBr (Et2O)	7	92

Experimental 1 or 2 was added slowly in a solution (~1N) of 2,5 to 3 equiv of organometallic at -15 to -10°C. The mixture was allowed to warm to 0°C (~2 hrs) then hydrolyzed in a cold dilute solution of HCl and extracted with petroleum ether. With MeLi and BuLi the reactions were carried out respectively at -20 and -60°C

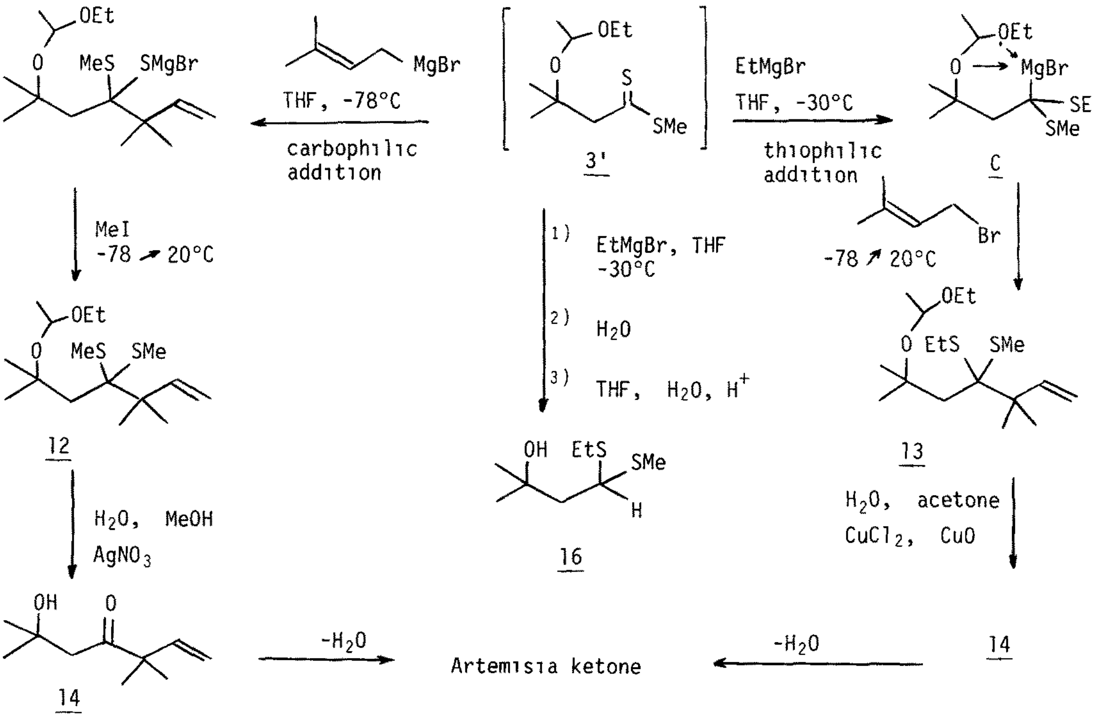
a) Structures were deduced from NMR, IR and mass spectra.
b) Yields of crude β-hydroxydithioesters (partial degradation occurs during distillation or chromatography through silica gel) 7 is solid, m.p.= 42°C
c) in 5 , R^2= $CH_2=CH-CH(Me)-$ (inversion of the allylic chain)

Table II Preparation of α, β-ethylenic dithioesters.

β-hydroxy dithioester	R^1	R^2	Procedure	ethylenic dithioester	% Yield (a)
3	H	Me	(A)	8	63
			(B)	8	85
5	H	$CH_2=CH-CH(Me)-$	(A)	9	55
6	H	$(Me)_2C=CH-(CH_2)_2-$	(B)	10	53
7	Me	Me	(B)	11 (b)	65

(A) The β-hydroxydithioester was treated with p TSOH (0,5 equiv) in refluxing benzene (60 cm^3 for 10^{-2} mole) in a Dean Stark apparatus for 1 5 hr.
(B) 1 3 10^{-2} mole of $MeSO_2Cl$ was added to the solution of 10^{-2} mole of β-hydroxydithioester in 20 cm^3 of CH_2Cl_2 and 2,5 10^{-2} mole of $N(Et)_3$ cooled to -10°C. The mixture was then allowed to warm to room temperature (3 and 6) or kept at 60°C for 2 hrs (7).
(a) Yield after purification by passing through a column of silica gel (eluant petroleum ether).
(b) 25 % of the β-unsaturated dithioester were formed. This was readily converted into its conjugated isomer by a trace of DBU in refluxing THF.

The potential synthetic uses of these synthons have been demonstrated by the synthesis of 6-hydroxy-3,3,6-trimethylhept-1-en-4-one 14 through two different ways In each case, the first step was the addition of methylmagnesium iodide to 1 (prepared from CS_2 and acetone)[3] leading to the isoprenic β-hydroxydithioester 3. Protection of the hydroxyl group gave the ethoxy ethyl ether 3' which was added to a solution (~ 0.7 N, 2 equiv.) of prenyl magnesium bromide in THF at -78°C (carbophilic addition with the expected inversion of the allylic chain occurs [11])and the resulting salt was alkylated at sulfur with methyl iodide to give 12 (82 % yield). Besides, 3' was added to a solution (~1N, 2 êquiv) of ethylmagnesium bromide in THF at -30°C and the carbanion C resulting from the thiophilic addition was alkylated with prenyl bromide leading to 13 (90 % yield) These two sequences gave dithioacetals (12 and 13) which were hydrolyzed according to known procedures[13, 14] into hydroxyketone 14 [15] in 62 % and 58 % yield respectively. Dehydration of 14 (with 0.1 equiv. of p TsOH in boiling benzene for 16 hrs) gave the 3,3,6-trimethylhepta-1,5-dien-4-one (artemisia ketone)[16]



The inversion of the prenyl chain in the alkylation step of carbanion C was unexpected [17]. However, the oxygens of the ethoxy ethyl ether group can stabilize this intermediate (by chelation of the magnesium) and so modify its reactivity. Beside a direct S_N2' displacement, a pathway involving an alkylation at sulfur to give an ylide followed by a [2,3] sigmatropic rearrangement can be envisaged Such a pathway has been assumed for the alkylations in basic medium of α-alkylthio or α-alkylselenoketones by allylic halides.[18]

Quenched with water, carbanion C gave, after deprotection of the hydroxyl group, the dithioacetal of a beta-hydroxy aldehyde (16)[19] but we were not able to alkylate C with methyl iodide and again, this may be due to the stabilization of C.

The preparation of new α,β-ethylenic dithioesters from β-oxodithioesters (especially in cyclic systems) and some other synthetic applications are presently under investigation. All experimental data concerning the preparation and the description of the new compounds mentioned in this note will be published in the full paper

References and notes

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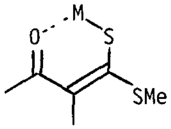
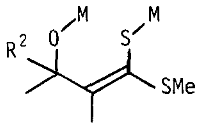
5 - The 1st equivalent which reacts with the enolic proton gives the most likely intermediate (A) and any organometallic can be used for this step. After addition of the 2nd equiv the enethiolized intermediate (B) is formed

(A)





(B)

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8 - 8 was described previously (ref 9) , ^{1}H NMR (CCl_4)δ 9 1.21 (d, J∼7 Hz, 3H), 2.08 (d, J∼1 Hz, 3H), 2 58 (s, 3H), 2 88 (m, 1H) , 4.85 to 6 06 (m, 3H), 6 53 (broad s, 1H) , 10 1.60 (s, 3H), 1 67 (∼ s, 3H), 1 87 (less abundent isomer∼ 20 %) and 2.15 (2d, J∼1 Hz, methyl on C_3), 2 57 (s, 3H), 2 to 2.8 (m, 4H), 5.07 (m, 1H), 6.22 (broad s, 1H) , 11 1 67, 1.77 and 1 90 (3 broad s, 9H), 2.59 (s, 3H).

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15 - RMN (CCl_4)δ 1 12 (s, 6H), 1.20 (s, 6H), 2 46 (s, 2H), 4 87 to 6.03 ($-CH=CH_2$)

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17 - In the absence of hydroxy group in β , allylation of such carbanion occured without inversion of the allylic chain (ref 11)

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19 - RMN (CCl_4)δ 1 20 (s, 6H), 1.26 (t, J∼7 Hz, 3H), 1 87 (d, J∼7 5 Hz, 2H). 2 08 (s, 3H), 2 60 (m∼q, J∼7 Hz, 2H), 3 93 (t, J∼7.5 Hz, 1H)

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