Tetrahedron Letters, Vol.32, No.44, pp 6329-6332, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

# Synthesis of E Functionalized Prenyl Orthothioesters

**Guy Solladié*, Valérie Berl**

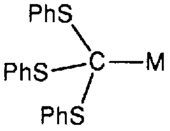
Ecole Européenne des Hautes Etudes des Industries Chimiques, 67008 Strasbourg, France.

**Abstract** : A stereospecific route to (E)-3-[tris (phenylthio)-methyl]-2-methyl propenal **5** and to (E) 3-(4-methylthio 1,3-dithiane-2-yl)-2-methyl propenal 7 is described.

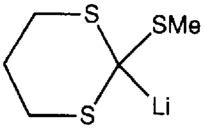
Bifunctional prenyl derivatives are important building blocks in terpene synthesis. The E or Z stereochemistry of these compounds is indeed the more crucial problem. We report in this paper the synthesis of the E isomer of 3-[tris (phenylthio)-methyl]-2-methyl propenal **5** and 3-(4-methylthio 1,3-dithiane-2-yl)-2-methyl propenal 7.

There has been considerable debate in the literature concerning the factors influencing the regioselectivity of nucleophilic addition to aldehydes and ketones[1]. It was shown that 1-2 addition is particularly favoured for α, ß-unsaturated aldehydes (due to carbonyl-metal interaction). However co-solvents such as HMPA and DMPU, reducing complexation of the metal ion to the carbonyl group, favour 1,4-addition as well as steric hindrance in the substrate and nucleophile in THF solution does.

Conjugate addition of tris (phenylthio) methyl lithium **1a** to α, ß-unsaturated ketones is also a well documented reaction. γ-ketoorthothioesters are usually obtained in high yields from cyclohexen-2-one and various α, ß-unsaturated ketones, except for hindered ß, ß-disubstituted enones[2]. It was also reported that reaction of **1a** with unsaturated aldehydes gives products resulting from 1,2-addition[3].



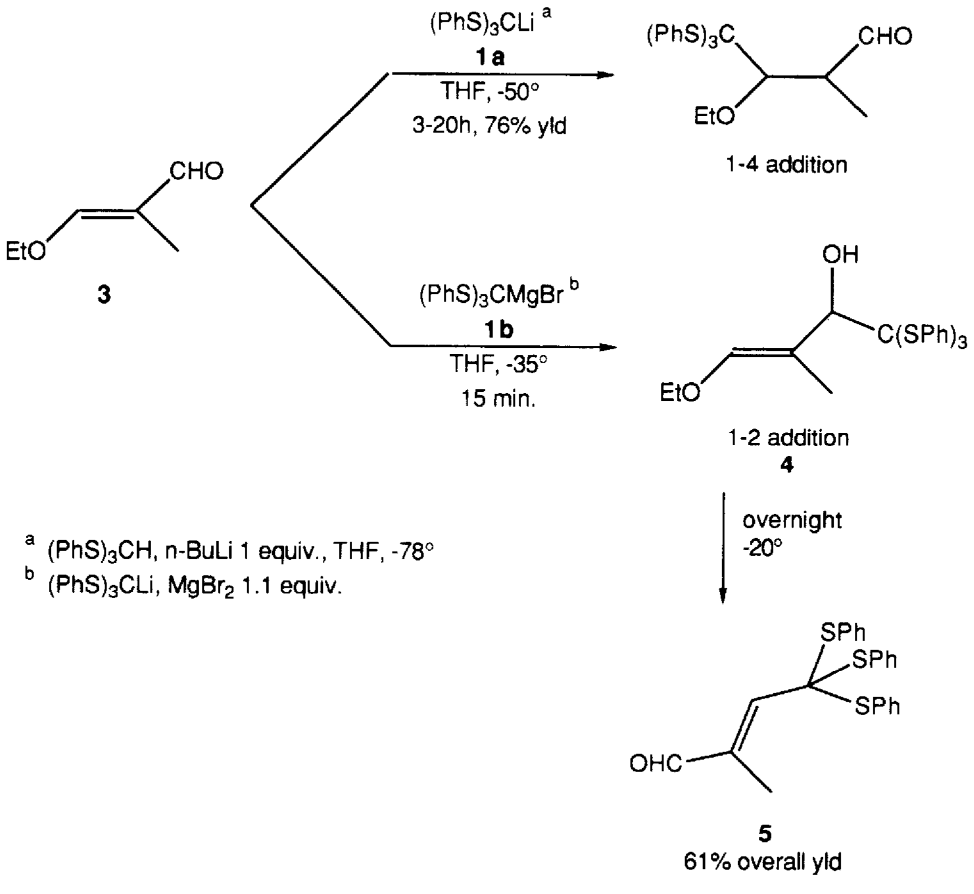
**1a** : M=Li
**1b** : M=MgBr



**2a**

During our investigations towards the synthesis of functionalized prenylorthothioesters we found a strong directive effect of the counter ion and of the sulfur substituents on the regioselectivity of orthothioformate anions addition to α, ß-unsaturated aldehyde **3**.

As shown on scheme 1, addition of the lithiated species **1a** to ethoxymethacrolein **3**, gave only the 1-4 adduct, a result which is not consistent with literature[3]. However, lithium exchange with magnesium afforded only the 1,2 adduct. This directive effect can be explained by a strong chelation between magnesium and the carbonyl oxygen.



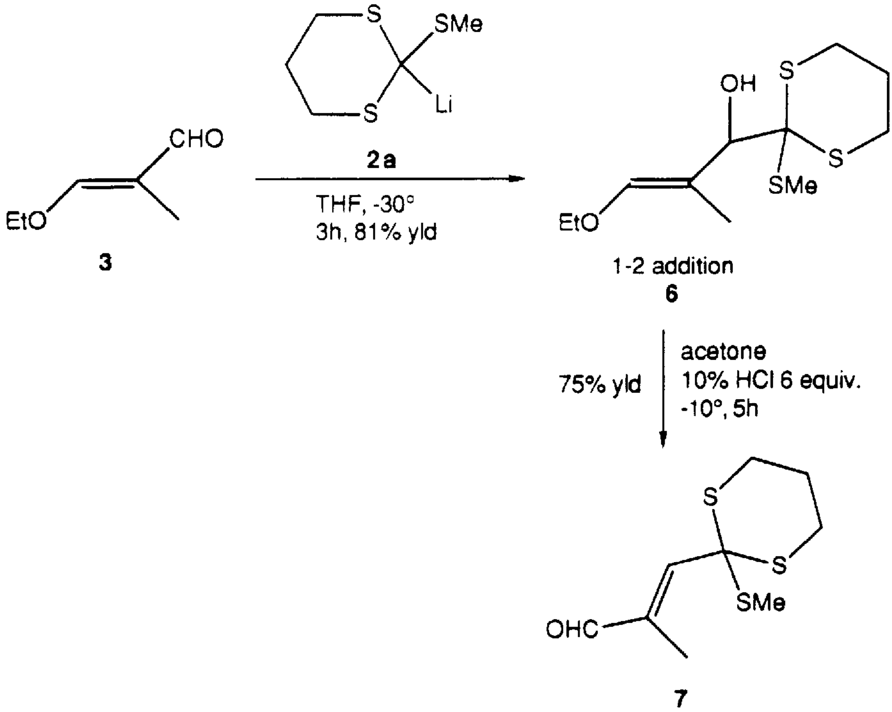
[a] $(PhS)_3CH$, n-BuLi 1 equiv., THF, -78°
[b] $(PhS)_3CLi$, $MgBr_2$ 1.1 equiv.

Scheme 1

The crude product **4**, which can be isolated and fully characterized, gave, on standing overnight at -20°, the orthothioester **5**[4] in 61 % yield.

A few additional results on the counter ion effect showed that in the magnesium case a longer reaction time did not change the result. However by changing the solvent from pure THF to a THF/hexane mixture (1/1.8), we observed, as expected from literature results in similar cases[5], competition between 1-2 (39 %) and 1-4 additions (61 %).

Finally the counter ion effect was shown to be dependent on the α,ß-unsaturated aldehyde structure. By replacing in compound **3** the ethoxy substituent by a methyl group (E, buten-2-al), a 1 to 1 mixture of 1,2 and 1,4 adducts was obtained in both cases (**1a** and **1b**). The ethoxy group in compound **3** has also a strong effect on the regioselectivity of the reaction.



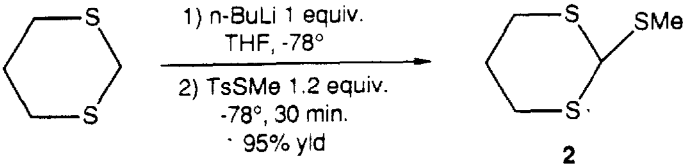
Scheme 2

In sharp contrast the lithiated orthothioformate **2a**[6] gave only 1,2 addition with the aldehyde **3** (scheme 2). A steric effect as well as a lower stabilisation of the carbanionic species could explain this difference. Compound **6**[7] was hydrolyzed and dehydrated with 10% hydrochloric acid in acetone to give E 3-(4-methylthio 1,3-dithiane-2-yl)-2-methyl propenal **7**[8] in 75% yield.

## References

1) Bulman-Page P.C., Van Niel M.B., Prodger J.C., Tetrahedron 1989, **45**, 7643.

2) Manas A.R.B., Smith R.A.J., J. Chem. Soc. Chem. Comm. 1975, 216.
3) Seebach D., Chem. Ber. 1972, **102**, 487.
4) Compound **5** : m.p. 93-4°; $^1$H NMR ($CDCl_3$, 200 MHz) : δ : 1.61 (d, 3H, J=1.5 Hz, $CH_3$), 6.37 (q, 1H, J=1.5 Hz, vinylic H), 7.61 (dd, 3H, J=2 Hz, J=8 Hz, ortho arom. H), 7.29-7.56 (m, 9H, meta arom.H), 9.13 (s, 1H, C$\underline{H}$O). Analysis : calc. for $C_{23}H_{20}OS_3$ : C, 67.61 ; H, 4.93 ; found : C, 67.83 ; H, 5.10 .The E stereochemistry was assigned by NMR from a NOE experiment : irradiation of the vinylic proton lead to a 22% NOE on the aldehydic proton signal.
5) Ostrowski P.C., Kane V.V., Tetrahedron Lett. 1977, 3549.
6) The orthothioformate **2** was readily prepared in high yield by alkylation of dithiane with S-methyl p-tolylthiosulfonate.



7) Compound **6** : m.p. 39-40°; $^1$H NMR ($CDCl_3$, 200 MHZ) : δ : 1.27 (t, 3H, J=7 Hz, $OCH_2\underline{CH_3}$), 1.84 (d, 3H, J=1 Hz, vinylic $CH_3$), 1.86 (m, 1H, $H_6$ axial), 2.09 (s, 3H, $SCH_3$), 2.10 (m, 1H, $H_6$ equat.), 2.67 (m, 2H, $H_5$ equat.), 2.98 (d, 1H, J=2.5 Hz, OH), 3.22 (m, 2H, $H_5$ axial), 3.85 (qd, 2H, J=1 Hz, J=7 Hz, $O\underline{CH_2}CH_3$), 4.06 (d, 1H, J=2.5 Hz, $H_3$), 6.21 (broad d, 1H, J=1 Hz, $H_1$). Microanalysis : calc. for $C_{11}H_{20}O_2S_3$; C, 47.11; H, 7.19; found, C, 47.37; H, 7.22.
8) Compound 7 : $^1$H NMR ($CDCl_3$, 200 MHz) : δ : 2.01 (m, 2H, $H_6$), 2.12 (s, 3H, $SCH_3$), 2.13 (d, 3H, J=1.5 Hz, vinylic $CH_3$), 2.71 (m, 2H, $H_5$ axial), 3.37 (m, 2H, $H_5$ equat.), 6.44 (q, 1H, J=1.5 Hz, $H_3$), 9.39 (s, 1H, CHO). Microanalysis : calc. for $C_9H_{14}OS_3$ : C,46.12; H,6.02; found : C, 46.22; H, 5.95. The E stereochemistry was assigned by a NOE experiment : irradiation of the vinylic hydrogen lead to a 23% NOE on the aldehydic hydrogen signal.

**Acknowledgements** : L'OREAL and CNRS are gratefully acknowledged for financial support.

(Received in France 25 June 1991)