Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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To cite this article: Romualdo Caputo , Carla Ferreri , Patrizia Isita , Luigi Longobardo , Domenico Mastroianni & Giovanni Palumbo (1992) Chemistry of Ethanediyl S,S-Acetals - 4. Promising Way to Cis-Substituted Olefins, Stereoselectively from Carbonyl Compounds, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:9, 1345-1350, DOI: 10.1080/00397919208019317

To link to this article: http://dx.doi.org/10.1080/00397919208019317

SYNTHETIC COMMUNICATIONS, 22(9), 1345-1350 (1992)

CHEMISTRY OF ETHANEDIYL S,S-ACETALS - 4.[§] A PROMISING WAY TO CIS-SUBSTITUTED OLEFINS, STEREOSELECTIVELY FROM CARBONYL COMPOUNDS

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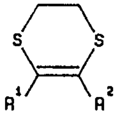
Abstract: Aldehydes and methyl ketones readily afford 5,6-dihydro-1,4-dithiins that can be converted by *n*-butyllithium into their corresponding sulfur stabilized carbanions. Coupling of the latter with alkyl halides leads to species having a *cis*-configurated, disubstituted double bond tied up by the sulfur-containing ring which is known to be susceptible of selective removal.

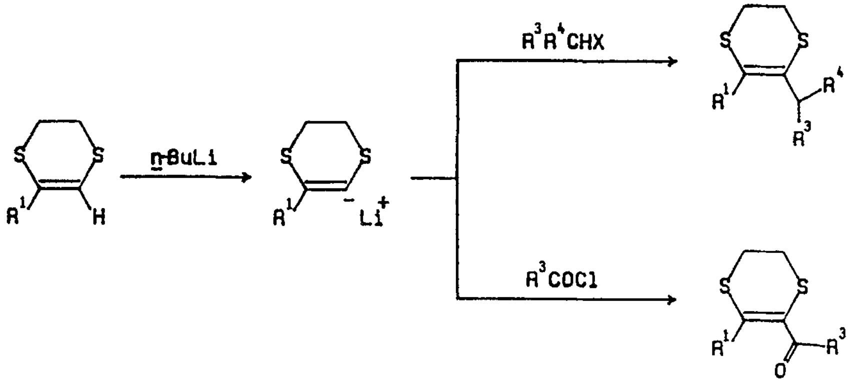
We have recently reported[1,2] a new reaction leading to 5,6-dihydro-1,4-dithiins (1) from carbonyl compounds, *via* a ring expansion that occurs in their corresponding ethanediyl S,S-acetal (1,3-



[§] Part 3 in the same series: Caputo, R., Ferreri, C., Palumbo, G. Russo, F., Tetrahedron, 1991, 47, 4187.

dithiolane) derivates, by treatment with halogens in anhydrous chlorinated solvents.

1,3-Dithiolanes of enolizable aldehydes and methyl ketones, when treated under such conditions, afford 5,6-dihydro-1,4-dithiins having a vinylic hydrogen that, as is in the case of enolthioethers,[3] can be selectively extracted by a strong base leading to a sulfur-stabilized carbanionic species. The reactions of the latter with electrophiles may then afford various coupling products that are characterized by the presence of a *cis*-substituted double bond tied up by the sulfur-containing dihydrodithiin ring. Provided that the sulfur atoms can be stereoselectively removed[4] or replaced by alkyl groups,[5] this approach represents an appealing route to the stereoselective synthesis of molecules having *cis*-substituted double bonds.



Therefore, we considered interesting to test the coupling reactions of monosubstituted 5,6-dihydro-1,4-dithiins towards alkyl and acyl halides respectively, as is shown above. 2-Phenyl-5,6-dihydro-1,4-dithiin was utilized as a model compound to devise suitable coupling conditions. It is initially lithiated by *n*-butyllithium in anhydrous tetrahydrofuran at -78 °C and then let to react with the

Table – Coupling Reactions of Dihydrodithiin 1 (R^1= Ph, R^2= H) with R^3R^4CHX and R^3COCl Electrophiles.

R^3, R^4	X	Yield (%)[a]	m.p. (°C) (solvent)	Molecular Formula or Lit. Data[b]	^1H NMR[c] δ, *J* (Hz)
Methyl, H	Cl	25	oily	$C_{12}H_{14}S_2$ (222.4)	1.0 (*t*, 3H, *J* = 6.5, $-CH_3$), 2.2 (*q*, 2H, *J* = 6.5, $-CH_2$), 3.2 (*s*, 4H, $-CH_2CH_2-$), 7.3 (*s*, 5H, $-C_6H_5$)
Methyl, H	Br	70	"	"	
Methyl, H	I	88	"	"	
H, H	I	95	oily	oily[6]	1.8 (*s*, 3H, $-CH_3$), 3.2 (*s*, 4H, $-CH_2CH_2-$), 7.3 (*s*, 5H, $-C_6H_5$)
n-Butyl, H	Br	65	oily	$C_{15}H_{20}S_2$ (264.4)	0.9 (*t*, 3H, $-CH_3$), 1.4 (*m*, 6H, $-CH_2CH_2CH_2-$), 2.3 (*t*, 2H, *J* = 7.0, allyl Hs), 3.0 (*s*, 4H, $-CH_2CH_2-$), 7.5 (*s*, 5H, $-C_6H_5$)
Methyl, Methyl	I	24	oily	$C_{13}H_{16}S_2$ (239.4)	1.3 (*d*, 6H, *J* = 7.0, 2 $-CH_3$), 2.4 (*m*, 1H, $-CH-$), 7.3 (*s*, 5H, $-C_6H_5$)
Phenyl, H	Br	97	95–96 (*n*-hexane)	96–97[7]	3.2 (*s*, 4H, $-CH_2CH_2-$), 3.5 (*s*, 2H, $-CH_2-$) 7.3 (*m*, 10H, two $-C_6H_5$)
Cl-ethyl, H	Br	60	oily	$C_{13}H_{15}ClS_2$ (270.8)	1.5 (*m*, 2H, $-CH_2-$), 2.4 (*t*, 2H, *J* = 6.0, allyl Hs), 3.4 (*t*, 2H, *J* = 7.0, $-CH_2Cl$), 3.0 (*s*, 4H, $-CH_2CH_2-$), 7.5 (*s*, 5H, $-C_6H_5$)
Cl-ethyl, H	I	75	"	"	
Phenyl		70	108–109 (*n*-hexane)	$C_{17}H_{14}OS_2$ (298.4)	3.4 (*s*, 4H, $-CH_2CH_2-$), 7.4 (*m*, 10H, two $-C_6H_5$)
t-Butyl		75	88–89 (*n*-hexane)	$C_{15}H_{18}OS_2$ (278.4)	3.4 (*s*, 4H, $-CH_2CH_2-$), 7.3 (*m*, 5H, $-C_6H_5$), 1.1 (*s*, 9H, *t*-butyl)

[a] Yield of pure isolated product (purity ≥ 96%, by HPLC and ^1H-NMR data). [b] Microanalyses obtained C ± 0.35, H ± 0.25. Mass spectra obtained on a Kratos MS 80 spectrometer. [c] Obtained on a Varian EM 360A spectrometer using $CDCl_3$ solutions and TMS as internal standard.

proper electrophile. The temperature is quite critical in order to avoid abstraction of a proton from the methylene groups alpha to the sulfur atoms and therefrom cleavage of the sulfur-containing ring.

The reaction with alkyl halides (see Table) follows the usual reactivity order for nucleophilic substitution and this can be exploited to effect double substitutions using dihalides like 1-chloro-3-bromopropane and 1-chloro-3-iodopropane or longer-chain α , ω mixed dihalides, in order to prepare isolated diene systems having both cis-configurated double bonds.

Acyl halides also play a role of good electrophilic substrates that, under the same conditions, lead in satisfactory yields to α ,β -unsaturated ketones with protected double bond (see Table); unfortunately, the presence of α hydrogen atoms leads acyl chlorides to self-condensation prior to coupling.

Sulfonyl chlorides undergo halogen exchange affording a vinyl chlorodithiin and lithium sulfinate.

Attempts to carry out the same reaction using aldehydes as electrophiles were not completely satisfactory: the couplings, in the absence of catalysts, are affected by too low reaction rates and synthetically useless yields. The use of titanium catalysts, considering some of our preliminary experiments, seems to open the way to the preparation of cis-substituted allylic alcohols with the same strategy, and these results will be published in due course.

Experimental Section

All reagents were obtained commercially and were used without further purification. Anhydrous tetrahydrofuran (THF) was obtained according to a literature[8] procedure.

Coupling reaction of 1 with methyl iodide. Typical procedure. To a solution of pure 5,6-dihydro-1,4-dithiin **1** (1.5 g; 7.7 mmol) in anhydrous THF (20 mL), at -78° C under dry argon atmosphere, a M solution of *n*-BuLi in *n*-hexane (8.5 mL) is added dropwise over 10 min under magnetic stirring. Then dry CH_3I (1.1 g; 7.7 mmol) in anhydrous THF is added slowly. The temperature is kept at -78° C for 15 min and then let raise to room temperature. After 30 min the reaction mixture is treated carefully with 10% aq NH_4Cl (65 ml) and extracted with Et_2O (3 x 100 ml). The combined organic layers are washed with H_2O until neutral, dried (Na_2SO_4) and evaporated *in vacuo*. Chromatography (silica-gel; *n*-hexane) of the crude residue finally affords pure 2-phenyl-3-methyl-5,6-dihydro-1,4-dithiin (1.5 g; 7.3 mmol; yield 95%).

Under the same conditions, all the coupling reactions with alkyl and acyl halides reported in the table were also performed.

Acknowledgement: Financial support from Ministero della Ricerca Scientifica e Tecnologica to R.C. is gratefully acknowledged.

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(Received in UK 16 December, 1991)