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

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Chemistry of Ethanediyl S, S-Acetals. VII. A Stereoselective Synthesis of Allylic Alcohols with cis-Configurated Double Bond

Romualdo Caputo [a] , Carla Ferreri [a] , Luigi Longobardo [a] , Domenico Mastroianni [a] , Giovanni Palumbo [a] & Silvana Pedatella [a]

[a] Dipartimento di Chimica Organica e Biologica , Università di Napoli , “Federico II” Via Mezzocannone, 16 I-80134, Napoli, (Italy)

To cite this article: Romualdo Caputo , Carla Ferreri , Luigi Longobardo , Domenico Mastroianni , Giovanni Palumbo & Silvana Pedatella (1994) Chemistry of Ethanediyl S, S-Acetals. VII. A Stereoselective Synthesis of Allylic Alcohols with cis-Configurated Double Bond, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:9, 1223-1229, DOI: 10.1080/00397919408011721

To link to this article: http://dx.doi.org/10.1080/00397919408011721

SYNTHETIC COMMUNICATIONS, 24(9), 1223-1229 (1994)

CHEMISTRY OF ETHANEDIYL *S,S*-ACETALS 7¶

A STEREOSELECTIVE SYNTHESIS OF ALLYLIC ALCOHOLS WITH *CIS*-CONFIGURATED DOUBLE BOND

Romualdo Caputo, Carla Ferreri, Luigi Longobardo, Domenico Mastroianni,
Giovanni Palumbo*, and Silvana Pedatella

Dipartimento di Chimica Organica e Biologica, Università di Napoli "Federico II"
Via Mezzocannone, 16 I-80134 Napoli (Italy)

ABSTRACT: A new high yielding coupling reaction of C-2 monosubstituted 5,6-dihydro-1,4-dithiins with aldehydes is reported. In this way allylic alcohols having the cis-substituted double bond tied up by a sulfur-containing ring can be readily prepared. Subsequent stereoselective sulfur removal then affords allylic alcohols with cis-configurated double bond.

Pursuing our interest in the chemistry[1-3] of 5,6-dihydro-1,4-dithiins, we wish to report in this paper a promising synthetic route to achieve allylic alcohols having *cis*-substituted double bond, stereoselectively from carbonyl compounds. In fact, we recently reported[1,2] that 5,6-dihydro-1,4-dithiins are readily obtained from carbonyl compounds *via* ring expansion occurring in their corresponding

---

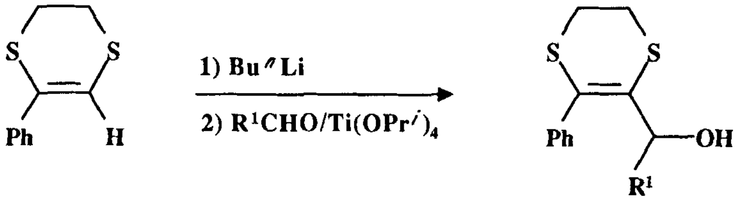
¶ Part 6 in the same series: Ref. 8.

*To whom correspondence should be addressed.

ethanediyl *S,S*-acetal (1,3-dithiolane) derivatives, by simple treatment with halogens in anhydrous chlorinated solvents. 5,6-Dihydro-1,4-dithiins coming from 1,3-dithiolanes of enolizable aldehydes and of methylketones possess a vinylic hydrogen atom that, as is in the case of enolthioethers[4], can be selectively extracted by a strong base leading to a sulfur-stabilized carbanionic species. The reactions of the latter with electrophiles[3] then lead to coupling products characterized by the presence of a *cis*-substituted double bond tied up by the sulfur-containing dihydro-dithiin ring which is known to be susceptible of selective removal[3,5] or replacement by alkyl groups[6].

At the time we started investigating such a strategy, the only coupling reactions we could perform involved alkyl and acyl halides as electrophilic substrates[3], whereas aldehydes, which would have been more interesting from a synthetic point of view, turned out to be only sparingly reactive hence leading to unsatisfactory results. This was in agreement with the reported[4] modest reactivity toward aldehydes of the analogous carbanionic species obtained from vinyl sulfides by Bu^{n}Li.

We have now found that couplings of lithiated 5,6-dihydro-1,4-dithiins with aldehydes can be performed with excellent yields in the presence of titanium (IV) isopropoxide as catalyst.



1 2a-c

Some experiments we have carried out on the model reaction of lithiated 2-phenyl-

Table 1 - Catalyst Effect on the Coupling of Lithiated Dihydrodithiin 1 with Benzaldehyde.

Catalyst	(% mol)	Coupling Yield (%)
None		62
$TiCl_4$	(100)	no reaction
$TiCl_4$	(20)	50
$Ti(OPr^i)_4$	(100)	52
$Ti(OPr^i)_4$	(20)	90

5,6-dihydro-1,4-dithiin **1** with benzaldehyde, in order to devise the experimental conditions are worthy of note and are reported in Table 1.

$Ti(OPr^i)_4$ should act as a Lewis acid enhancing the electrophilic character of the formyl carbon. $TiCl_4$ is likely too much acid[7] thus interfering with the lithiated dithiin and leading to extremely poor results (see Table 1), even worse than for the coupling in the absence of any catalysts. A nearly analogous situation probably occurs when equimolar amounts of $Ti(OPr^i)_4$ are utilized. In our experience the best results, considering both yields and coupling rates, are achieved when a 20% molar amount (in respect with the aldehyde) of $Ti(OPr^i)_4$ is utilized. This may mean that the latter acts as a true catalyst, probably forming a five membered cyclic intermediate with the aldehyde[9], and is released just after the coupling occured.

Under our conditions, 2-phenyl-5,6-dihydro-1,4-dithiin **1**, that we used as the model compound for devising the coupling procedure, is treated at -78° C with Bu^nLi for a few minutes. The proper aldehyde and $Ti(OPr^i)_4$ are added and the resulting clear solution is kept at low temperature for 15 minutes, then left to reach the room temperature (see experimental), and eventually worked up.

The results we have obtained, using **1** as a model 5,6-dihydro-1,4-dithiin, are reported in Table 2. The compound **2b** was desulfurized by Raney nickel under the conditions reported in the experimental part. This represents an example of how the sulfur atoms in compounds **2a-e** can be stereoselectively replaced by hydrogens with complete retention of the double bond configuration and negligible overreduction[5] to obtain allylic alcohols with *cis*-configuration at the double bond. Work is in progress to consider the feasibility of having asymmetric induction during the formation of the allylic chiral center, by using chiral 5,6-dihydro-1,4-dithiins, and the results will be reported in due time.

All reagents were obtained commercially. Anhydrous tetrahydrofuran (THF, reagent grade, Carlo Erba) was distilled from $LiAlH_4$. Silica gel (70-230 mesh) was purchased from Carlo Erba. ^1H NMR spectra were recorded on a Bruker WH (270 MHz) instrument in $CDCl_3$ solutions.

Coupling reaction of 2-phenyl-5,6-dihydro-1,4-dithiin (1) with benzaldehyde. Typical procedure. To a solution of pure title compound (0.30 g; 1.56 mmol) in anhydrous THF (5 cm^3), at -78° C under dry argon (or nitrogen) atmosphere, a 1.6 M solution of Bu^nLi in *n*-hexane (1.16 cm^3; 1.9 mmol) is added dropwise *via* cannula over 10 min under magnetic stirring. After 15 min a solution of freshly distilled benzaldehyde (0.20 g; 1.9 mmol) and $Ti(OPr^i)_4$ in the same solvent is also added *via* cannula. The temperature is kept at -78° C for 15 min and then let to raise to room temperature. After 30 min the reaction mixture is treated carefully with 10% aq NH_4Cl (15 cm^3) and extracted with Et_2O (3 x 100 cm^3). The combined organic layers are washed with H_2O until neutral, dried (Na_2SO_4) and

Table 2 - Products of Dihydrodithiin 1 with Aldehydes R^1CHO and $Ti(OPr^i)_4$ (20%mol)

	R^1	Yield (%)	Molecular Formula	m.p.(°C) (solvent)	H NMR, δ, *J* (Hz)
2a	CH_3CH_2	88	$C_{13}H_{16}S_2O$	81.5° - 82° (*n*-hexane)	0.90 (*t*, 3H, *J*=7.20, CH_3); 1.70 (*m*, 2H, CH_2-CH_3); 3.30 (*m*, 4H, S-CH_2-CH_2-S); 4.30 (*t*, *J*=6.80, CH-OH); 7.35 (*m*, 5H, aromatic Hs).
2b	$CH_3(CH_2)_3$	90	$C_{15}H_{20}S_2O$	70.5° - 71.5° (*n*-hexane)	0.85 (*t*, 3H, *J*=7.20, CH_3); 1.48 (*m*, 4H, CH_2-CH_2-CH_3); 1.61 (*m*, 2H, CH_2-CHOH); 3.24 (*m*, 4H, S-CH_2-CH_2-S); 4.29 (*t*, 1H, *J*=7.0, CH-OH); 7.29 (*m*, 5H, aromatic Hs).
2c	$CH_3(CH_2)_6$	88	$C_{18}H_{26}S_2O$	oil	0.87 (*t*, 3H, *J*=7.25 CH_3); 1.45 (*m*, 10H, $(CH_2)_5$-CH_3); 1.68 (*m*, 2H, CH_2-CHOH); 3.25 (*m*, 4H, S-CH_2-CH_2-S); 4.32 (*t*, 1H, *J*=7.6, CH-OH); 7.25 (*m*, 5H, aromatic Hs).
2d	C_6H_5	90	$C_{17}H_{16}S_2O$	110° - 111° (*n*-hexane)	3.25 (*m*, 4H, S-CH_2-CH_2-S); 5.58 (*s*, 1H, CH-OH); 7.40 (*m*, 10H, aromatic Hs).
2e	$C_6H_5CH_2$	85	$C_{18}H_{18}S_2O$	oil	2.92 (*t*, 2H, *J*=6.2, CH_2-C_6H_5), 3.32 (*m*, 4H, S-CH_2-CH_2-S); 4.50 (*m*, 1H, CH-OH); 6.85-7.25 (*m*, 10H, aromatic Hs).

evaporated *in vacuo*. Chromatography (silica gel; 9:1 benzene:Et_2O) of the crude residue finally affords the pure **2d** (0.42 g; 1.4 mmol; 90% yield).

Under the same conditions, all the coupling reactions with aldehydes reported in Table 2 were also performed.

Desulfurization of 2b. Typical procedure. A solution of **2b** (0.20 g; 0.72 mmol) in glacial acetic acid (10 cm^3) is added in one portion to a suspension of commercial (Aldrich, water slurry) Ni(Raney) W2 (2 g, moist) in the same solvent (10 cm^3) at room temperature and under magnetic stirring. The resulting suspension is stirred for 10 min. Then the solid is filtered off and washed with glacial acetic acid (3 x 5 cm^3). The filtrate is then neutralized with saturated aq Na_2CO_3 and extracted with Et_2O. Careful distillation of the dried (Na_2SO_4) ethereal extract finally affords a crude residue that, after chromatography (silica gel; 8:2 benzene : Et_2O), gives the pure oily (*Z*)-1-phenyl-3-hydroxy-eptene (0.11 g; 0.58 mmol; 80% yield): ^1H NMR: δ 0.90 (*t*, 3H, *J*=6.60 Hz, CH_3); 4.57 (*m*, 1H, CHOH); 5.66 (*dd*, 1H, J_{cis}=11.60 Hz, *J*=9.50 Hz, =CH-CHOH); 6.55 (*d*, 1H, J_{cis}=11.60 Hz, PhCH=); 7.22-7.38 (*m*, 5H, aromatic Hs).

ACKNOWLEDGMENT: Financial support from Ministero dell'Università e della Ricerca Scientifica e Tecnologica to R.C. is gratefully acknowledged.

REFERENCES AND NOTES

1. Caputo, R., Ferreri, C., Palumbo, G., Capozzi, G., *Tetrahedron*, **1986**, *42*, 2369.
2. Caputo, R., Ferreri, C., Palumbo, G., *Synthesis*, **1991**, 223.

3. Caputo, R., Ferreri, C., Isita, P., Longobardo, L., Mastroianni, D., Palumbo, G., *Synthetic Communications*, **1992**, 22, 1345.
4. Oshima K., Shimoji K., Takahashi H., Yamamoto H., Nozaki H., *J. Am. Chem. Soc.*, **1973**, *95*, 2693
5. A comprehensive study of the conditions to remove the sulfur atoms will be reported in a forthcoming paper.
6. Tiecco, M., Testaferri, L., Tingoli, M., Chianelli, D., Wenkert, E., *Tetrahedron Letters*, **1982**, *23*, 4629.
7. Reetz, M.T., "Organotitanium Reagents in Organic Synthesis", Springer-Verlag,1985, *vol.24*.
8. Caputo, R., De Nisco, M., Palumbo, G., Adamo, C., Barone, V., *Tetrahedron*, submitted.
9. Honda, Y., Tuchihashi, G., *Chemistry Letters*, **1988**, *1937*.

(Received in the UK 05 October 1993)