Pergamon

Tetrahedron Vol. 50, No. 24, pp. 7265-7268, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)E0346-U

Diastereoselective Desulfurization of 5,6-Dihydro-1,4-dithiins. Synthesis of Muscalure from *Musca domestica* L.

Romualdo Caputo, Giovanni Palumbo,* Silvana Pedatella

Dipartimento di Chimica Organica e Biologica dell'Università
Via Mezzocannone, 16 I-80134 Napoli (Italy)

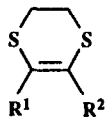
Abstract: A procedure is reported for the chemo- and stereo-selective sulfur removal from 5,6-dihydro-1,4-dithiins which completes the pathway to synthesize *cis* configurated olefins from carbonyl compounds. A four step synthesis of (Z)-9-tricosene (muscalure) with the dithiin moiety serving as the penultimate olefin precursor is also reported as an example of the proposed synthetic strategy.

The 5,6-dihydro-1,4-dithiin moiety has been shown[1] to be a useful synthetic intermediate to mimic *cis* configurated double bonds, in the preparation of simple alkenes and other unsaturated compounds as well. Indeed, 5,6-dihydro-1,4-dithiins can be easily obtained from the readily available ethanediyl *S,S*-acetal (1,3-dithiolane) derivatives of carbonyl compounds, by smooth treatment with bromine or *N*-bromosuccinimide in anhydrous acetonitrile at room temperature.[2]

However, the actual synthetic utilization of such intermediates was somewhat limited by the subsequent desulfurization step, since the common desulfurization conditions[3-6] are often plagued by poor stereoselectivity as well as by overreduction of the double bond formed, thus leading to undesired by-products. Therefore, we began a comprehensive investigation on the diastereoselective sulfur removal from 5,6-dihydro-1,4-dithiins and now wish to report in this paper some of the more significant results we have obtained. Based on the current literature, the reducing systems we have tested [utilizing 2,3-diphenyl-5,6-dihydro-1,4-dithiin (**1a**) as a model compound] are Raney nickel W2,[4] $NiCl_2/NaBH_4$ (nickel boride),[5] and $Ti(OPr^i)_4/LiAlH_4$ complex,[7] under various experimental conditions.

The principal results of this investigation are reported in Table 1: from our point of view, practically all the experiments were quite unsatisfactory, if stereoselectivity of sulfur removal, overreduction, and overall yield of the desulfurization process are considered. Suitable conditions to conjugate all these features were therefore investigated and eventually the desulfurization of the starting 5,6-dihydro-1,4-dithiin **1a** was devised by using Raney nickel W2 in glacial acetic acid for a few minutes at room temperature: as a matter of fact, under these conditions, **1a** is stereoselectively converted into *cis*-stilbene in satisfactory yield and without traces (GC/MS, ^1H NMR) of its *trans* isomer and/or 1,2-diphenylethane (overreduction product), only accompanied by some unreacted starting material.

Such conditions seem to be rather general, as is shown by the experiments reported in Table 2, and



1

2

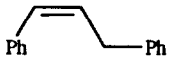
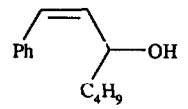
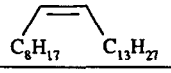
a) $R^1 = R^2 = Ph$; b) $R^1 = Ph$, $R^2 = CH_2Ph$; c) $R^1 = Ph$, $R^2 = CH(OH)C_4H_9$; d) $R^1 = C_8H_{17}$, $R^2 = C_{13}H_{27}$

Table 1 - Desulfurizations of 2,3-Diphenyl-5,6-dihydro-1,4-dithiin (1a) under Various Conditions

Reducing system[a]		Solvent	Temp. (°C)	Time (min)	Products[b]			
Ra-Ni W2	(1.2 g)	dioxane	20	30	30	30	30	10
"	"	diox./acetone[c,4]	20	30	20	10	40	30
$NiCl_2$:$NaBH_4$	(21:18)	EtOH	65	60	40	-	-	60
$Ti(OPr^i)_4$:$LiAlH_4$	(8:2)	THF	70	150	-	20	75	5
"	"	THF	20	150	-	30	10	60
"	"	THF	0	150	-	-	-	100
"	(8:4)	THF	20	150	-	30	60	10
"	(8:16)	THF	20	90	-	50	50	-
" [+ quinoline (0.15)]	"	THF	20	15	-	100	-	-

[a] The reported amounts of reducing agents are expressed in number of mmol (excepting Ra-Ni, g) referred to 1.0 mmol of starting product. [b] Molar ratios of *cis* : *trans* : overreduction product : recovered starting product. [c] Ratio 1:1.

Table 2 - Desulfurizations of Miscellaneous 2,3-Disubstituted 5,6-Dihydro-1,4-dithiins (1a-d) by Raney Nickel in Glacial Acetic Acid[a]

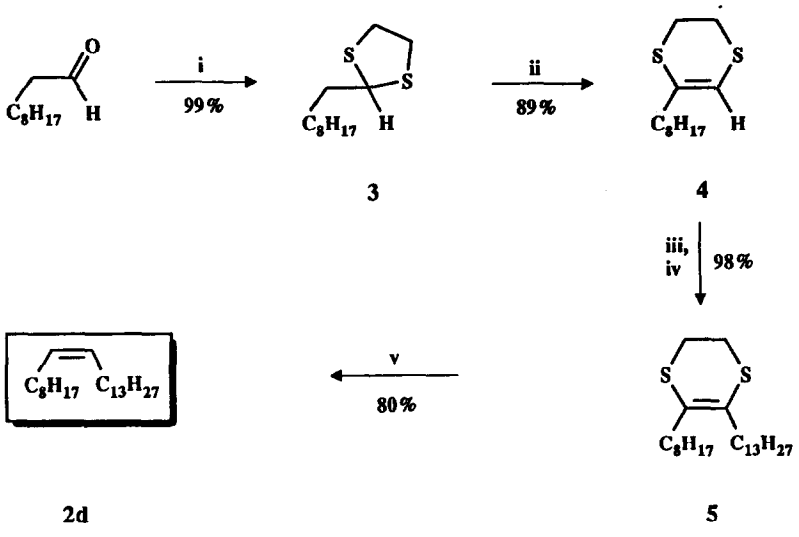
	Olefin	Time (min)	Yield (%)	^1H NMR ($CDCl_3$) δ; *J*(Hz)
2a		10	85	6.60 (*s*, 2H, CH=CH)
2b		20	79	3.71 (*d*, 2H, *J* = 8.0, =C-CH_2); 5.87 (*dt*, 1H, J_{cis} = 12.0,[b] *J* = 8.0, =CH-C); 6.59 (*d*, 1H, J_{cis} = 12.0, Ph-CH=)
2c		8	75	4.57 (*m*, 1H, CHOH); 5.66 (*dd*, 1H, J_{cis} = 11.6,[b] *J* = 9.5, =CH-CHOH); 6.55 (*d*, 1H, J_{cis} = 11.6,[b] PhCH=)
2d		10	80	2.0 (*m*, 4H, CH_2-C=); 5.40 (*t*, 2H, J_{cis} = 6.0, CH=CH)

[a] Raney nickel is used in a ratio of 6 g (wet) per 1.0 mmol of starting product. [b] The *J* value = 16 Hz for the E diastereomer (*cfr.* ref. 13).

represent to the best of our knowledge the first example of a reliable stereoselective desulfurization procedure. Beside, they complete and make effective the 5,6-dihydro-1,4-dithiin chemistry in mimicking *cis* configurated double bonds.

It is also noteworthy that the desulfurization can be stereoselectively oriented toward the formation of the *trans* configurated double bond, when $Ti(OPr^i)_4$/$LiAlH_4$ and quinoline[3] are used, as is reported in Table 1.

To demonstrate the utility of the dithiin approach for producing *cis* configurated double bonds, we have prepared the sex pheromone muscalure,[9] (Z)-9-tricosene (**2d**), from the common house fly *Musca domestica* L. by a quick synthesis in which the 5,6-dihydro-1,4-dithiin moiety serves as the penultimate olefin precursor (Scheme 1). Treatment of decanal ethanediyl *S,S*-acetal (**3**) by NBS in anhydrous chloroform afforded 2-octyl-5,6-dihydro-1,4-dithiin (**4**). The latter was then treated with Bu^nLi, at -78° C in THF, and the resulting sulfur-stabilized carbanionic species coupled[1] with 1-iodotridecane to afford the muscalure-parent 5,6-dihydro-1,4-dithiin **5**. The stereoselective desulfurization of **5**, under the above reported conditions, eventually gave the desired pheromone **2d**, in 80% yield from the parent dithiin **5** and 69% overall yield from the starting decanal.



i = $HSCH_2CH_2SH$, AcOH, TosOH, r. t., 60 min; ii = NBS, dry $CHCl_3$, r. t., 30 min; iii = Bu^nLi, dry THF, under Ar,-78° C, 15 min; iv = $ICH_2(CH_2)_{11}CH_3$, dry THF, under Ar, 0° C, 20 min; v = conditions reported in Table 2.

Scheme 1 - Stereoselective Synthesis of Muscalure *via* 5,6-Dihydro-1,4-dithiin Chemistry

EXPERIMENTAL

Raney nickel W2 (water slurry) was purchased from Fluka. ^1H NMR spectra were recorded on a Bruker WH 270 instrument. GC/MS analyses were performed on a Hewlett-Packard 5980 GS / 5971 MS instrument.

Desulfurization of 1a. Typical procedure. A solution of **1a** (0.10 g; 0.37 mmol) in glacial acetic acid (10 cm^3) is added in one portion to a stirred suspension of Ra-Ni W2 (2 g, wet) in the same solvent (10 cm^3) at room temperature and under dry argon (or nitrogen) stream. The resulting suspension is stirred for 10 min (GC/MS monitoring). Then the solid is filtered off and washed with glacial acetic acid (3 x 5 cm^3). The filtrate is neutralized with saturated aq Na_2CO_3 and extracted with Et_2O (3 x 100 cm^3). The combined organic layers are washed with water until neutral, dried (Na_2SO_4), and evaporated *in vacuo* to afford a crude residue that, after chromatography (silica gel; 8:2 light pet.:Et_2O), gives the pure oily *cis*-stilbene[10] (**2a**, Table 2) ($0.57x10^{-1}$ g; 85% yield).

Under the same conditions the olefins **2b**, **2c** and **2d** were prepared from their parent 5,6-dihydro-1,4-dithiins. Desulfurization times, yields, and significant ^1H NMR signals are summarized in Table 2.

Cross-over desulfurization of 1a. Typical procedure. To a solution of $Ti(OPr^i)_4$ (0.88 cm^3; 2.96 mmol) in anhydrous THF (5 cm^3), at room temperature and under dry argon (or nitrogen) stream, a suspension of $LiAlH_4$ (0.22 g; 5.92 mmol) in the same solvent (5 cm^3) is added dropwise. After 1 h stirring, a solution of **1a** (0.10 g; 0.37 mmol) and quinoline ($6.5x10^{-3}$ cm^3; $5.5x10^{-2}$ mmol) in anhydrous THF is then added dropwise to the suspension. After 25 min (GC/MS monitoring) the reaction mixture is treated with brine and 1 M aq HCl (10 cm^3) and extracted with Et_2O (3 x 100 cm^3). The combined organic layers are washed with water until neutral, dried (Na_2SO_4), and evaporated *in vacuo*. Chromatography (silica gel; 9:1 light pet.:Et_2O) of the crude residue finally affords the pure *trans*-stilbene[10] ($0.72x10^{-1}$ g; 100% yield).

2-Nonyl-1,3-dithiolane (3). To a magnetically stirred solution of freshly distilled decanal (10 g; 64 mmol) in glacial acetic acid (20 cm^3) *p*-toluenesulfonic acid (1.2 g; 6.4 mmol) and ethanedithiol (5.4 cm^3; 64 mmol) are added in sequence, both in one portion, at room temperature, the stirring being continued for 1 h. The reaction

is then quenched by adding 10% aq Na_2CO_3 (40 cm^3) and the resulting mixture is extracted with Et_2O (3 x 100 cm^3). Evaporation *in vacuo* of the combined ethereal extracts, after their washing with water until neutral and drying (Na_2SO_4), affords an amber oil the distillation of which at reduced pressure (3.0 mbar; 10 cm Vigreux column, ϕ 1.5 cm) yields the pure title compound **3** (14.7 g; 99% yield) as a colourless liquid bp 100° C; ^1H NMR: δ 3.18 (*s*, 4H, S-CH_2-CH_2-S); 4.40 (*t*, 1H, *J*=6 Hz, CH).

2-Octyl-5,6-dihydro-1,4-dithiin (4). To a magnetically stirred solution of 2-nonyl-1,3-dithiolane (**3**) (1.0 g; 4.3 mmol) in anhydrous $CHCl_3$ (100 cm^3) a suspension of *N*-bromosuccinimide (1.1 g; 6.5 mmol) in the same solvent (60 cm^3) is added in one portion. After about 30 min at room temperature, the reaction mixture is treated with solid $NaHCO_3$ excess and then water. Extraction with Et_2O (3 x 100 cm^3) gives an organic layer which is washed with water until neutral, dried (Na_2SO_4), and evaporated *in vacuo* to afford a yellow oil. Chromatography of the latter (silica gel; 97:3 light pet.:Et_2O) yields the title compound **4** accompanied by about 10% starting material **3**. This mixture is treated with BF_3·Et_2O and HgO [proper amounts to hydrolize the latter, according to a reported[11] procedure] thus affording, after chromatography (silica gel; light pet.) the pure **4** as an oil (0.88 g; 89% yield); ^1H NMR: δ 2.20 (*m*, 2H, CH_2-C=); 3.15 (*m*, 4H, S-CH_2-CH_2-S); 5.85 (*s*, 1H, vinylic H).

2-Octyl-3-tridecyl-5,6-dihydro-1,4-dithiin (5). To a solution of pure **4** (0.30 g; 1.56 mmol) in anhydrous THF (5 cm^3), at -78° C under dry argon (or nitrogen) atmosphere, 1.6 M 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 freshly prepared[12] 1-iodotridecane (0.59 g; 1.9 mmol) in the same solvent (6 cm^3) is also added *via* cannula. The temperature is kept at -78° C for 15 min and then let to raise to room temperature. After 20 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 water until neutral, dried (Na_2SO_4), and evaporated *in vacuo*. Chromatography (silica gel; light pet.) of the crude residue finally affords pure **5** (0.58 g; 90% yield); ^1H NMR δ 0.87 (*t*, 6 H, *J*=6.0 Hz, CH_3); 2.20 (*t*, 4H, *J*=7.0 Hz, =CH_2-); 3.02-3.21 (*m*, 4H, S-CH_2-CH_2-S).

(Z)-9-tricosene (2d). Pure 2-octyl-3-tridecyl-5,6-dihydro-1,4-dithiin (**5**) was treated with Ra-Ni W2 in glacial acetic acid under the conditions of the typical desulfurization procedure reported above. The title compound **2d** was obtained in 80% yield. No traces of its specially prepared [$Ti(OPr^i)_4$: $LiAlH_4$: quinoline][3] *trans* isomer could be detected by GC/MS analysis. Significant ^1H NMR signals are reported in Table 2.

REFERENCES AND NOTES

1. Caputo, R.; Ferreri, C.; Longobardo, L.; Palumbo, G.; Pedatella, S. *Synth. Commun.* **1994**, *in press*.
2. Caputo, R.; Ferreri, C.; Palumbo, G. *Synthesis*, **1991**, 223.
3. Becker, S.; Fort, Y.; Caubère, P. *J. Org. Chem.*, **1990**, *55*, 6194 and literature cited therein.
4. Augustine, R.L. *Catalytic Hydrogenation*, 1965, Marcel Dekker Inc, New York, pp. 26, 132.
5. Truce, W.E.; Perry, F.M., *J. Org. Chem.*, **1965**, *30*, 1316.
6. Saigo, K.; Hashimoto, Y.; Fang, L.; Hasegawa, M. *Heterocycles*, **1989**, *29*, 2079.
7. $Ti(OPr^i)_4/LiAlH_4$ was utilized under the same conditions of the reported (ref. 6) $TiCl_4/LiAlH_4$ reducing agent. The higher acidity of $TiCl_4$ leads indeed to an effective sulfur complexation by Ti^{IV} (*cfr.* also ref. 1 and 8) and the consequent sluggishness of the reaction.
8. Ferreri, C.; Palumbo, G. ; Caputo, R. in Trost, B.M. *Comprehensive Organic Synthesis*, 1991, Pergamon Press plc, Oxford (UK), vol. 1, p 141.
9. Carlson, D.A.; Mayer, M.S.; Silhacek, D.L.; James, J.D.; Beroza, M.; Bierl, B.A. *Science*, **1971**, *174*, 76.
10. Wheeler, O.H.; Batle de Pabon, H.N., *J. Org. Chem.*, **1965**, *30*, 1473.
11. Vedejs, E.; Fuchs, P.L. *J. Org. Chem.*, **1971**, *36*, 366.
12. Raphael, R.A.; Sondheimen, F. *J. Chem. Soc.*, **1950**, 2100.
13. Laszlo, P.; Von Raguè Schleyer, P. *Bull. Soc. Chim. France*, **1964**, 87.

(*Received in UK* 21 *March* 1994; *accepted* 15 *April* 1994)