Synthesis of Dithioic Acid Esters by a Mitsunobu-Type Reaction of Alkanedithioic Acids and Alcohols

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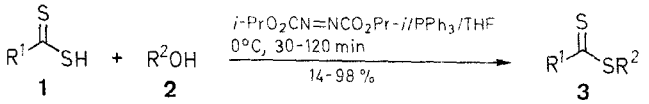
Alcohols react with dithioic acids in the presence of the complex of diisopropyl azodicarboxylate and triphenylphosphine to give various dithioic acid esters, via a Mitsunobu-type reaction.

Synthetic studies[1,2] carried out with dithioic acid esters, $R^1CS_2R^2$, have employed various R^1 group as the main carbon chain. In contrast, relatively few variations of the SR^2 group nature have been reported.[3-5] Thiocarbonyl compounds have recently gained interest for regiocontrolled Michael addition reaction,[6-8] aldol reaction[9,10] and Claisen rearrangement.[11-13] In order to achieve stereocontrol for these reactions, we required a convenient preparation of dithioic acid esters with the R^2 part coming from the large range of available alcohols, including homochiral compounds.

Previously reported dithioic acid esters preparation methods[2,14-16] mostly use alkyl halides or thiols as a source for the R^2 substituent. To our knowledge no method using dithioic acids **1** and alcohols **2** is available. We now report that alcohols can be used via a Mitsunobu-type reaction.[17-21]

The adduct of diisopropyl azodicarboxylate with triphenylphosphine is preformed in tetrahydrofuran and treated with a mixture of dithioic acid **1** and alcohol **2** during 30–120 min at 0 °C. After work-up dithioic acid esters **3** are isolated (Table 1).



1 + **2** → **3**

Table 1. Synthesis of Dithioic Acid Esters **3**

Reactants				Time (min)	Dithioate	
Dithioic acid **1**	R^1	Alcohol **2**			**3**	Yield[a] (%)
a	Et	**a**	1-pentanol	120	**aa**	95
a	Et	**b**	1-dodecanol	90	**ab**	88
a	Et	**c**	benzyl	30	**ac**	82
a	Et	**d**	furfuryl	120	**ad**	94
a	Et	**e**	allyl	30	**ae**	61
a	Et	**f**	crotyl	30	**af**	98
a	Et	**g**	*N*,*N*-dimethyl-ethanolamine	120	**ag**	29
a	Et	**h**	(1*S*, 2*S*, 5*S*)-(−)-myrtanol	120	**ah**	71
a	Et	**i**	(*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol	120	**ai**	75
a	Et	**j**	cyclopentanol	90	**aj**	62
a	Et	**k**	cyclohexanol	90	**ak**	14
a	Et	**l**	β-cholesterol	30	**al**[b]	33
b	CH_3	**c**	benzyl	30	**bc**	48
b	CH_3	**l**	β-cholesterol	30	**bl**[b]	29
c	*i*-Bu	**c**	benzyl	30	**cc**	92
c	*i*-Bu	**f**	crotyl	30	**cf**	93

[a] Satisfactory microanalyses obtained: C ±0.40, H ±0.47, S ±0.43.
[b] Conversion of the configuration.

A variety of dithioic acids can be used: **1a–c**. Excellent yields of **3** were obtained with primary alcohols **2a–i**. Lower yields were observed with secondary alcohols **2j–l** and some failures have been met (menthol, borneols). Crotyl alcohol **2f** selectively afford products **3af** and **3cf** with allylic chain configuration retention. 3β-Cholesterol is converted to isomerically pure dithioates **3al** and **3bl**, most probably of 3 α-configuration as a result of complete configuration inversion.[19-21] Thus the present method offers an easy and novel entry to alkanedithioic acid esters **3**, including the homochiral derivatives **3ah**, **3ai**, **3al**, and **3bl**.

THF is distilled from sodium/benzophenone prior to use. Medium pressure chromatography was carried out with a Jobin-Yvon Chromatospac Prep 10 apparatus. ^{1}H-NMR spectra were obtained using a Varian EM 360 or a Jeol JNM-EX 200 MHz spectrometer. ^{13}C-NMR spectra were recorded on a Bruker WP 80 spectrometer. UV spectra were measured on a Beckman Acta M6 spectrometer. Observed rotations were recorded at the Na-D line at 20 °C using a Roussel-Jouan polarimeter.

Table 2. Data of Dithioic Acid Esters **3**

Product	Molecular Formula or Ref.	^{1}H-NMR (CCl_4/TMS) δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ	UV (cyclohexane) λ_{max} (nm) (log ε)	$[\alpha]_D^{20}$ $CHCl_3$ (c)
3aa	$C_9H_{18}S_2$ (190.3)	1.40 (m, 14H); 2.93 (q, 2H, J = 8); 3.08 (q, 2H, J = 7.4)	13.9; 15.4; 22.5; 27.4; 28.8; 31.3; 36.4; 45.3; 240.2	305 (3.78) 456 (1.27)	
3ab	$C_{15}H_{30}S_2$ (274.5)	1.30 (m, 26H); 2.95 (q, 2H, J = 8); 3.10 (q, 2H, J = 7)	14.1; 15.4; 22.7; 27.0; 27.4; 29.2; 29.3; 29.5; 29.6; 31.9; 36.4; 45.3; 240.1	305 (4.09) 456 (1.30)	
3ac	[22]	1.32 (t, 3H, J = 7.5); 2.95 (q, 2H, J = 8); 4.38 (s, 2H); 7.35 (s, 5H$_{arom}$)	15.4; 41.3; 45.0; 127.7; 128.7; 129.1; 240.2		
3ad	$C_8H_{10}S_2O$ (186.3)	1.35 (t, 3H, J = 7); 2.96 (q, 2H, J = 7); 4.45 (s, 2H); 6.18 (m, 2H$_{arom}$); 7.22 (m, 1H$_{arom}$)	15.2; 33.4; 44.8; 108.7; 110.6; 142.3; 148.7; 238.2		
3ae	[23,24]	1.32 (t, 3H, J = 7); 2.90 (q, 2H, J = 7); 3.76 (d, 2H, J = 7); 5.70 (m, 3H)	15.4; 39.2; 45.0; 119.1; 131.0; 239.2		
3af[a]	[24,25]	1.32 (t, 3H, J = 7); 1.68 (d, 3H, J = 5); 2.93 (q, 2H, J = 7); 3.72 (d, 2H, J = 7); 5.54 (m, 2H)	15.4; 17.7; 38.9; 45.2; 123.5; 130.8; 240.1		
3ag	$C_7H_{15}S_2N$ (177.3)	1.35 (t, 3H, J = 7); 2.20 (s, 6H); 2.50 (t, 2H, J = 7); 2.95 (q, 2H, J = 7); 3.30 (t, 2H, J = 7)	15.4; 34.6; 45.3; 56.7; 240.9		
3ah	$C_{13}H_{22}S_2$ (242.4)	1.08 (m, 16H); 2.84 (q, 2H, J = 7); 3.15 (d, 2H, J = 7)	15.4; 22.1; 23.2; 26.2; 28.0; 33.4; 38.7; 39.6; 41.3; 43.5; 45.3; 46.0; 240.1	305 (4.09) 456 (1.30)	−16.9 (35.5)
3ai	$C_9H_{16}S_2O_2$ (220.3)	1.32 (m, 9H); 2.97 (q, 2H, J = 7); 3.33 (d, 2H, J = 6); 3.35 (d, 2H, J = 6); 4.10 (m, 1H)	15.3; 25.5; 26.9; 39.2; 45.2; 68.5; 73.5; 109.6; 239.5	305 (4.06) 448 (1.30)	−7.7 (59.7)
3aj	$C_8H_{14}S_2$ (174.3)	1.32 (t, 3H, J = 7); 1.68 (m, 8H); 2.90 (q, 2H, J = 7); 4.00 (m, 1H)	15.5; 25.2; 32.0; 45.2; 49.0; 241.3	305 (4.06) 456 (1.41)	
3ak	$C_9H_{16}S_2$ (188.3)	1.32 (t, 3H, J = 7); 1.50 (m, 10H); 2.90 (q, 2H, J = 7); 3.8 (m, 1H)	15.3; 25.7; 25.9; 30.4; 31.5; 45.3; 48.5; 239.1		
3al[b]	$C_{30}H_{50}S_2$ (474.8)	1.42 (m, 46H); 2.88 (q, 2H, J = 7); 4.18 (m, 1H); 5.12 (m, 1H)	11.9; 15.4; 18.7; 19.1; 20.8; 22.5; 22.8; 23.9; 24.3; 26.2; 26.9; 27.9; 28.2; 31.8; 35.8; 36.2; 36.6; 37.2; 39.5; 39.8; 42.3; 45.5; 49.3; 50.2; 56.3; 56.8; 122.5; 139.1; 239.4	307 (4.1) 456 (1.91)	+39 (34)
3bc	$C_9H_{10}S_2$ (182.3)	2.72 (s, 3H); 4.30 (s, 2H); 7.15 (s, 5H$_{arom}$)	38.7; 42.0; 127.6; 128.2; 128.6; 129.1; 135.3; 231.8	303 (4.12) 458 (1.46)	
3bl[c]	$C_{29}H_{48}S_2$ (460.8)	1.28 (m, 4H); 2.70 (s, 3H); 4.2 (m, 1H); 5.30 (m, 1H)	11.9; 18.8; 19.1; 20.8; 22.6; 23.9; 24.3; 26.2; 28.0; 28.2; 31.8; 35.8; 36.2; 36.7; 37.3; 39.6; 39.8; 42.4; 50.3; 56.8; 122.6; 139.1; 231.9		+36.3 (34.3)
3cc	$C_{12}H_{16}S_2$ (224.9)	0.98 (d, 6H, J = 6); 2.32 (m, 1H); 2.82 (d, 2H, J = 7); 4.40 (s, 2H); 7.22 (s, 5H$_{arom}$)	22.2; 30.9; 41.6; 61.0; 127.8; 128.9; 129.3; 135.7; 237.4		
3cf[d]	$C_9H_{16}S_2$ (188.3)	0.92 (d, 6H, J = 7); 1.70 (d, 3H, J = 6); 2.32 (m, 1H); 2.82 (d, 2H, J = 7); 3.80 (d, 2H, J = 7); 5.58 (m, 2H)	17.7; 22.0; 30.6; 39.0; 61.0; 123.5; 130.8; 237.6		

[a] bp 101–107°C/12 mbar.
[b] mp 107–109°C.
[c] mp 92–98°C.
[d] bp 110–116°C/12 mbar.

Dithioic acids **1a–c** were prepared by reaction of Grignard reagents with carbon disulfide and acid treatment.[22]

Alkyl Alkanedithioic Acid Esters 3; General Procedure:
In a nitrogen filled round-bottomed flask with magnetic stirrer, PPh_3 (1.36 g, 5.2 mmol) is dissolved in THF (20 mL) and cooled at 0°C. Diisopropyl azodicarboxylate (1.05 g, 5.2 mmol) is added. The mixture is stirred for 30 min. A milky precipitate is formed. A solution of dithioic acids (**1**; 6 mmol, 2 equiv; caution: obnoxious) and alcohol (**2**; 4 mmol, 1 equiv) in THF (5 mL) is added dropwise. The reaction mixture that becomes dark brown is stirred at 0°C for 30–120 min (Table 1). It is concentrated with a rotary evaporator. Cyclohexane (5 mL) is added. The heterogeneous mixture is filtered over a Celite pad. The residue is filtered over silica gel and then chromatographed at medium pressure on a silica gel column (10 × 4 cm; 5–40 microns) using cyclohexane as eluent. The dithioate **3** (Table 2) is isolated as a yellow oil.

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