A Facile Conversion of (*Z*)-2-Alkenoic Esters into the (*E*)-Isomers with Diphenyl Disulfide

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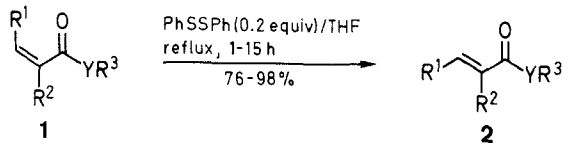
Diphenyl disulfide is shown to be an efficient catalyst for the isomerization of (*Z*)-2-alkenoic esters to (*E*)-2-alkenoic esters in boiling tetrahydrofuran.

Nonconjugated olefins, when heated with diphenyl disulfide, undergo geometrical isomerization[1-3] due to the generation of phenylsulfanyl radicals (PhS•) from diphenyl disulfide which react with olefins to produce a mixture of geometric isomers whose composition represents their thermodynamic equilibrium,[4] with only 2–3% of positional isomers. However, no systematic investigation of the geometric inversion of conjugated olefins with diphenyl disulfide has been reported though highly useful application is expected.

We have now investigated the direct isomerization of 2-alkenoic esters and amides using diphenyl disulfide as catalyst and found that the (*Z*)-2-alkenoic esters and amides can be stereoselectively converted into the (*E*)-isomers by a convenient procedure.



1 2

1, 2	R^1	R^2	R^3	Y
a	Me	Me	Me	O
b	*i*-Pr	Me	Et	O
c	Ph	H	Me	O
d	Ph	Me	Me	O
e	Me	NHAc	Me	O
f	Me	$-(CH_2)_3-$		O
g	Me	$-(CH_2)_3-$		NMe
h	Me	Me	Et	NEt

Table 1. Isomerization of (*Z*)-2-Alkenoic Acid Derivatives **1** with Diphenyl Disulfide (0.2 equiv) in THF

Substrate	Reaction Time (h)	Product	Yield (%)	Solvent for MCC	Ratio[a] **2/1**
1a	1.5	**2a**	81	CH_2Cl_2	98 : 2
1b	9	**2b**	95	hexane/Et_2O (10 : 1)	93 : 7
1c	7	**2c**	93	CH_2Cl_2	>99 : < 1[c]
1d	15	**2d**	88	CH_2Cl_2	49 : 51
1d[b]	12	**2d**	90	CH_2Cl_2	90 : 10
1e	1.5	**2e**	98	EtOAc/CH_2Cl_2 (1 : 1)	98 : 2
1f	4	**2f**	76	CH_2Cl_2	96 : 4
1g	1	**2g**	95	EtOAc	96 : 4
1h[b]	5	**2h**	87	CH_2Cl_2/Et_2O (1 : 1)	32 : 68

[a] Determined by ^{1}H-NMR analysis using a Varian XL-200 (200 MHz) instrument.
[b] Reaction in refluxing benzene in the presence of diphenyl disulfide and AIBN.
[c] No isomer detected.

Heating the (*Z*)-2-alkenoic esters **1a–c** in refluxing tetrahydrofuran in the presence of 0.2 equivalent of diphenyl disulfide followed by chromatography (to remove the catalyst) readily gave the (*E*)-2-alkenoic esters **2a–c** in almost 100% isomeric purity and in high yields. This convenient olefin inversion with diphenyl disulfide was successfully applied not only to the chemically unstable dehydroamino acid ester **1e** but also to lactone **1f** [(*Z*)-2-ethylidene-5-pentanolide] and lactam **1g** [(*Z*)-2-ethylidene-*N*-methyl-5-pentanelactam] to afford the corresponding (*E*)-isomers **2e, g** in almost quantitative yields. Isomerization of methyl (*Z*)-2-methyl-3-phenylpropenoate **(1d)** proceeded smoothly in the presence of a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) in addition to diphenyl disulfide to afford the (*E*)-isomer **2d** while in the absence of AIBN a 1 : 1 mixture of (*Z*)-**1d** and (*E*)-**2d** was obtained. *N,N*-Diethylangelamide **(1h)** gave a 7 : 3 *Z*/*E* mixture even after prolonged reaction in the presence of AIBN. Under the reaction conditions both in the presence and absence of AIBN, methyl tiglate **(2a)** and dimethyl maleate did not give any detectable amount of the corresponding geometrical isomers.

Thus, the isomerization of (*Z*)-2-alkenoic esters and amides to the (*E*)-isomers is readily and efficiently achieved in the presence of diphenyl disulfide, without the formation of detectable amounts of positional isomers which are often formed as side products in the photochemical[5] and in the conventional acid- or base-catalyzed isomerization of the 2-alkenoic esters. The present procedure provides a convenient access to geometrically pure (*E*)-2-alkenoic esters since the corresponding *Z*/*E* mixtures are readily available. However, the method appears to be limited to sterically unstable (*Z*)-2-alkenoic esters and (*Z*)-α-ethylidene-lactones and -lactams since attempts to extend the reaction to methyl tiglate **(2a)** with the stable *E*-configuration and to dimethyl maleate with two electron-withdrawing groups were unsuccessful.

Melting points were determined with a Kofler-type hot-stage apparatus. Mass spectra were recorded with Hitachi M-80 spectrometers. IR spectra were measured with a Hitachi 270–30 spectrometer. ^{1}H-NMR spectra were recorded with a Varian XL-200 (200 MHz) instrument.

Medium-pressure column chromatography (MCC) was performed with a 530-4-10V (Yamazen) apparatus using Lobar Grösse B (310–25, Lichroprep Si60, Merck).

Ester **1a** was purchased from Tokyo Kasei Kogyo Co. Ltd., Japan. Esters **1b**,[6] **1c**,[7,8] and **1e**,[9,10] lactone **1f**,[11] and lactam **1g**[12] were prepared according to reported procedures.

Methyl (*Z*)-2-Methyl-3-phenylpropenoate (1d):[13]
This ester is prepared by the stereospecific addition–elimination reaction[14] of thiophenol with methyl (*E*)-2-methyl-3-phenylpropenoate [(*E*)-α-methylcinnamate, **2d**].

Table 2. Physical and Spectral Data of Compounds **1a–h** and **2a–h**

Compound	mp (°C) or bp (°C)/Torr	Lit. mp (°C) or bp (°C)/Torr or Molecular Formula	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
1a	50/100	128/764[17]	1.89 (split s, 3H), 1.97 (split d, 3H, J = 7), 3.73 (s, 3H), 6.06 (split q, 1H, J = 7)
1b	112/110	oil[6]	0.98 (d, 6H, J = 7), 1.32 (t, 3H, J = 7), 1.89 (d, 3H, J = 1.5), 3.22 (d hept, 1H, J = 10, 7), 4.23 (q, 2H, J = 7), 5.17 (br dq, 1H, J = 10, 1.5)
1c	107/2	oil[7]	3.74 (s, 3H), 5.98 (d, 1H, J = 12.5), 7.00 (d, 1H, J = 12.5), 7.38 (m, 3H), 7.64 (m, 2H)
1d	oil	oil[13]	2.10 (d, 3H, J = 1.5), 3.66 (s, 3H), 6.74 (br s, 1H), 7.20–7.66 (m, 5H)
1e	oil	oil[10]	2.11 (d, 3H, J = 7.5), 2.12 (s, 3H), 3.88 (s, 3H), 7.21 (q, 1H, J = 7.5), 7.48 (br s, 1H)
1f	97/2	oil[11]	1.92 (m, 2H), 2.10 (dt, 3H, J = 7, 1.5), 2.58 (m, 2H), 4.38 (t, 2H, J = 6), 6.18 (qt, 1H, J = 7, 2)
1g	82/2	oil[12]	1.88 (m, 2H), 2.13 (br d, 3H, J = 7), 2.42 (m, 2H), 2.96 (s, 3H), 3.32 (t, 2H, J = 6), 5.86 (br q, 1H, J = 7)
1h	60/2	$C_9H_{17}NO$[a] (155.2)	1.14 (t, 3H, J = 7), 1.18 (t, 3H, J = 7), 1.61 (dq, 3H, J = 7, 1.5), 1.88 (quint, 3H, J = 1.5), 3.39 (q, 2H, J = 7), 3.46 (q, 2H, J = 7), 5.44 (qq, 1H, J = 7, 1.5)
2a	138/760	139/760[17]	1.82 (split d, 3H, J = 7), 1.86 (split s, 3H), 3.74 (s, 3H), 6.90 (split q, J = 7)
2b	120/100	oil[6]	1.02 (d, 6H, J = 7), 1.32 (t, 3H, J = 7), 1.86 (d, 3H, J = 1.5), 2.66 (d hept, 1H, J = 10, 7), 4.24 (q, 2H, J = 7), 6.62 (br dq, 1H, J = 10, 1.5)
2c	33–34	36[7]	3.84 (s, 3H), 6.50 (d, 1H, J = 16.5), 7.42 (m, 3H), 7.56 (m, 2H), 7.66 (d, 1H, J = 16.5)
2d	35–36	37–38[13]	2.12 (d, 3H, J = 1.5), 3.82 (s, 3H), 7.42 (m, 5H), 7.72 (br q, 1H, J = 1.5)
2e	40–41	oil[10]	1.80 (br d, 3H, J = 7.5), 2.14 (s, 3H), 3.78 (s, 3H), 6.85 (br q, 1H, J = 7.5), 7.20 (br s, 1H)
2f	107/2	oil[11]	1.78 (dt, 3H, J = 7, 1.5), 1.94 (m, 2H), 2.53 (br t, 2H, J = 6.5), 4.32 (t, 2H, J = 6.5), 7.14 (br qt, 1H, J = 7, 2.5)
2g	91/2	oil[12]	1.74 (br dt, 3H, J = 7, 1), 1.86 (m, 2H), 2.47 (br t, 2H, J = 6), 3.01 (s, 3H), 3.36 (t, 2H, J = 6), 6.94 (br qt, 1H, J = 7, 2)
2h	92/5	$C_9H_{17}NO$[b] (155.2)	1.13 (t, 6H, J = 7), 1.68 (dq, 3H, J = 7, 1.5), 1.85 (quint, 3H, J = 1.5), 3.37 (q, 4H, J = 7), 5.98 (qq, 1H, J = 7, 1.5)

[a] HRMS: calc: 155.1308; found: 155.1303.

[b] HRMS: calc: 155.1308; found: 155.1303.

Methyl 2-Methyl-3-phenyl-3-(phenylthio)propanoate: Thiophenol (10.1 mL, 101 mmol) is added at 0 °C to a stirred solution of BuLi (10% solution in hexane; 0.64 mL, 1 mmol) in THF (20 mL) to give a solution of a 100:1 mixture of PhSH and PhSLi. To this solution is added a solution of methyl (*E*)-α-methylcinnamate[15] (1.76 g, 10 mmol) in THF (10 mL). The mixture is stirred at r.t. for 24 h, then made alkaline by the addition of 5% aq NaOH, and extracted with CH_2Cl_2 (3 × 50 mL). The extract is dried (Na_2SO_4) and evaporated, and the residue is purified by MCC (Et_2O/hexane, 1:10) to give a diastereoisomer mixture of methyl 2-methyl-3-phenyl-3-(phenylthio)propanoate (*erythro/threo* = 81:19) as a colorless oil; yield: 2.5 g (87%).

Ester **1d**: The above *erythro/threo* mixture (2.5 g, 8.7 mmol) is dissolved in MeOH (60 mL) and a solution of $KHSO_5$ (Oxone®; 2.9 g) in H_2O (50 mL) is added dropwise with stirring at 0 °C. Stirring is continued at 0 °C for 30 min and the mixture then extracted with CH_2Cl_2 (3 × 100 mL). The extract is dried (Na_2SO_4) and evaporated to give the sulfoxide (2.45 g, 95%) which, without purification, is heated in refluxing toluene (15 mL) for 1 h. After evaporation of solvent, the residue is purified by MCC (CH_2Cl_2) to afford ester **1d** as a colorless oil; yield: 632 mg (72%). In addition, a smaller amount of the (*E*)-isomer **2d** is obtained; yield: 158 mg (18%).

(*Z*)-*N*,*N*-Diethyl-2-methyl-2-butenamide (*N*,*N*-Diethylangelamide, 1h):[16]

A solution of $SOCl_2$ (3 mL, 40 mmol) and (*Z*)-2-methyl-2-butenoic acid (angelic acid; 3 g, 30 mmol) in benzene (3 mL) is stirred at 0 °C for 2 h. The solvent is removed under reduced pressure. To a solution of the residue in benzene (30 mL) is added dropwise a solution of $HNEt_2$ (3 mL) in benzene (20 mL). The $HNEt_2 \cdot HCl$ is filtered off and the filtrate is successively washed with 10% aq NaOH (50 mL), 10% aq HCl (50 mL), and H_2O (50 mL). The benzene layer is dried (Na_2SO_4), the solvent evaporated, and the residue purified by MCC (CH_2Cl_2/Et_2O, 1:1) to afford ester **1h** as a pale yellow oil; yield: 2.3 g (49%). In addition, a smaller amount of the (*E*)-isomer **2h** is obtained as a pale yellow oil; yield: 0.58 g (12%).

Isomerization of (*Z*)-2-Alkenoic Acid Derivatives 1 to (*E*)-2-Alkenoic Acid Derivatives 2; General Procedure:

A solution of the (*Z*)-isomer **1** (1 mmol) and diphenyl disulfide (44 mg, 0.2 mmol) in dry THF (5 mL) is refluxed under N_2 for the time given in Table 1. The mixture is then cooled and the solvent is removed under reduced pressure. The residue is purified by MCC to afford the pure (*E*)-isomer **2**.

The spectral data of the (*E*)-isomers **2a–g** thus obtained were identical with those of authentic samples which are commercially available or were prepared by known procedures.

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