New Method for Isomerization of (*Z*)-Stilbenes into the (*E*)-Isomers Catalyzed by Diaryl Disulfide

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A new method for isomerization of (*Z*)-stilbenes into the (*E*)-isomers, catalyzed by diaryl disulfide, has been developed. Diphenyl disulfide is the most versatile catalyst, smoothly effecting the isomerization of stilbene, methoxystilbenes, and hydroxystilbenes. For dimethoxystilbenes, whose isomerization by diphenyl disulfide is slow, 4,4′-dinitrodiphenyl disulfide or 2,2′-dipyridyl disulfide greatly accelearted the isomerization. Diphenyl disulfide is ineffective for the isomerization of stilbenes bearing electron-attracting substituent(s). The isomerization of these stilbenes was greatly accelerated by catalysts bearing an electron-donating substituent, such as 4,4′-dimethoxydiphenyl disulfide.

Keywords stilbene; (*Z*)–(*E*) isomerization; electron donating substituent; electron attracting substituent; diaryl disulfide; diphenyl disulfide; 4,4′-dimethoxydiphenyl disulfide; 4,4′-dinitrodiphenyl disulfide; 2,2′-dipyridyl disulfide

Symmetrical (*E*)-stilbenes are readily preparable in high yield by reductive coupling of arylaldehydes.[1] However, this method is not applicable to unsymmetrical stilbenes. On the other hand, unsymmetrical stilbenes are readily prepared by Wittig reaction of an arylaldehyde with an arylmethylenephosphorane, usually as a mixture of (*E*)- and (*Z*)-isomers with predominance of the latter. To obtain pure (*E*)-stilbenes from this mixture, a number of methods for isomerization of (*Z*) to (*E*)-stilbenes have been proposed.[2] Among them, iodine-catalyzed isomerization[3] and photoisomerization[2] with or without diphenyl disulfide are the most popular. However, these methods are sometimes accompanied with side reactions or do not go to completion, thus requiring repeated chromatography (*e.g.*, on a silver nitrate-impregnated silica gel column) or repeated fractional crystallizations for isolation of the pure (*E*)-isomers.[2a] For example, the photoisomerization method sometimes yields phenanthrene derivatives by cyclization of (*Z*)-stilbenes.[2b] We also observed that treatment of (*Z*)-3,5-dihydroxystilbene with a catalytic amount of iodine in benzene gave the undesired (*E*)-3,5-dihydroxy-4-iodostilbene together with (*E*)-3,5-dihydroxystilbene. (*Z*)-3,5-Dimethoxystilbene gave a similar result.

Recently, Miyata *et al.*[4] reported that (*Z*)-2-alkenoic esters, when heated with a catalytic amount of diphenyl disulfide in tetrahydrofuran (THF), were converted into the (*E*)-isomers in good yields. This method was applied for the isomerization of (*Z*)-stilbenes into the (*E*)-isomers.

When a mixture of (*E*)/(*Z*)-isomers of methoxy- or hydroxystilbenes was heated with a catalytic amount of diphenyl disulfide in THF, the corresponding (*E*)-isomers were produced exclusively. The progress of the reaction was monitored by gas chromatography (GC), where (*Z*)-isomers exhibited smaller retention time than the corresponding (*E*)-isomers. The produced (*E*)-isomers were readily separated from the catalyst by column chromatography on silica gel and they were characterized by examination of the ^{1}H-nuclear magnetic resonance (NMR) spectra: the coupling constant between the two olefinic protons was 16—17 Hz for unsymmetrical (*E*)-isomers, while that of (*Z*)-isomers was 12 Hz. Thus, all (*E*)/(*Z*)-methoxy- and hydroxy-stilbenes were converted to the (*E*)-isomers in excellent yields without side reactions (Table I).

Although the conversion is usually completed within a few hours, a longer reaction time is needed for stilbenes bearing two methoxy groups on one benzene ring at positions 2, 3 (run 5) and 2, 5 (run 7), In these cases, use of larger amount of the catalyst and addition of azobisisobutyronitrile (AIBN) accelerated the reaction (run 8). Conversion of a hydroxystilbene proceeded faster than that of methoxystilbenes (run 16).

The solvent effect in this isomerization reaction is as follows: the isomerization proceeds more rapidly in THF than in the other solvents, indicating that THF is the most suitable solvent for this conversion reaction (Table II).

Application of the above method for the isomerization of nitrostilbenes, however, did not give a satisfactory result. The reaction of nitrostilbenes with diphenyl disulfide was

TABLE I. (*Z*) to (*E*) Conversion of Stilbenes with Diphenyl Disulfide

Run	Stilbene	(*E*)/(*Z*) Ratio[a]	$(PhS)_2$ mol eq	Time (h)	(*E*)/(*Z*) Ratio[a]	(*E*)-Isomer Isolated yield (%)
1	Stilbene	0/100	0.2	4	—	99
2	2-Methoxy	5/95	0.1	9	94/6	81
3	3-Methoxy	25/75	0.2	4	95/5	87
4	4-Methoxy	35/65	0.1	6	—	91
5	2,3-Dimethoxy	10/90	0.2	18	99/1	96
6	2,4-Dimethoxy	22/78	0.2	8	100/0	96
7	2,5-Dimethoxy	12/88	0.2	22	100/0	92
8	2,5-Dimethoxy	12/88	1.0[b]	8	100/0	—
9	3,4-Dimethoxy	35/65	0.1	5	—	83
10	3,5-Dimethoxy	40/60	0.2	4	100/0	96
11	2,4′-Dimethoxy	8/92	0.1	4	—	99
12	3,4′-Dimethoxy	25/75	0.1	2	—	95
13	4,4′-Dimethoxy	35/65	0.1	2	—	98
14	3,4′,5-Trimethoxy	48/52	0.2	1	—	98
15	2,3′,4,5′-Tetramethoxy	75/25	0.2	6	—	94
16	3,5-Dihydroxy	0/100	0.2	0.5	100/0	99
17	4-Methoxycarbonyl	46/54	1.0[b]	10	100/0	—

a) Determined by GC analysis. *b*) One mol eq of AIBN was added.

TABLE II. Solvent Effect in (*Z*)–(*E*) Isomerization of 3-Methoxystilbene with Diphenyl Disulfide[a]

(*Z*)/(*Z*) Ratio[b]	Solvent	Product (*E*)/(*Z*) Ratio[b]
42:58	THF	99:1
42:58	Toluene	69:31
42:58	$CHCl_3$	42:58
42:58	AcOEt	83:17
42:58	MeOH	84:16
42:58	CH_3CN	42:58

a) Reaction with 0.2 mol eq of $(PhS)_2$ under reflux for 3 h. *b*) Determined by GC analysis.

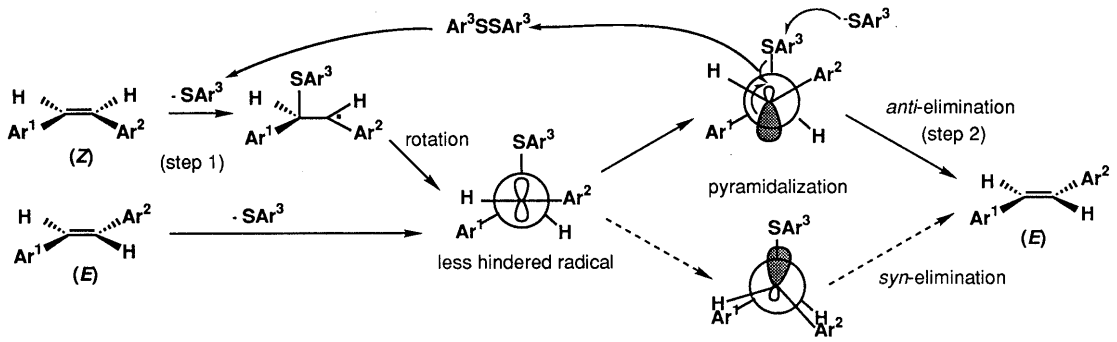

Chart 1. Proposed Mechanism for (*Z*) to (*E*) Isomerization of Stilbenes with Diaryl Disulfide

TABLE III. (*Z*) to (*E*) Conversion of Nitro-, Methoxycarbonyl-, and Dimethoxystilbenes

Run	Stilbene	(*E*)/(*Z*) Ratio[a]	Isomerization			Product	
			Catalyst[b]	Mol eq	Time (h)	(*E*)/(*Z*) Ratio[a]	(*E*)-Isomer Isolated yield (%)
1	2-Nitro	0/100	A	1.0	10	10/90	—
2	2-Nitro	0/100	B	1.0	10	40/60	—
3	2-Nitro	0/100	I_2[c]	0.2	24	100/0	93
4	3-Nitro	0/100	A	2.0	10	57/43	—
5	3-Nitro	0/100	B	0.2	6	100/0	90
6	3-Nitro	0/100	I_2[c]	0.2	3	100/0	98
7	4-Methoxycarbonyl	46/54	A	0.2	4	50/50	—
8	4-Methoxycarbonyl	46/54	B	0.2	10	97/3	85
9	4-Methoxycarbonyl	46/54	I_2[c]	0.2	3	100/0	96
10	2,3-Dimethoxy	10/90	C	0.2	6	100/0	89
11	2,3-Dimethoxy	10/90	D	0.2	6	100/0	91
12	2,5-Dimethoxy	12/88	D	0.2	9	100/0	85

a) Determined by GC analysis. *b*) A, diphenyl disulfide; B, 4,4′-dimethoxydiphenyl disulfide; C, 4,4′-dinitrodiphenyl disulfide; D, 2,2′-dipyridyl disulfide. All with a small amount of AIBN. *c*) Reflux in benzene.

very slow (Table III, runs 1 and 4) even on heating for 10 h with an increased amount of the catalyst and AIBN.

Considering the reaction mechanism (see below), it was assumed that step 1 (the addition of a phenylthio radical to the double bond) is retarded for stilbenes bearing an electron-attracting substituent(s), because the electron density on the double bond has been reduced. This consideration led to the idea that, if the electron density on the sulfur atom of the reagent is increased, step 1 may be accelerated, hence accelerating the isomerization. Thus, (*Z*)-3-nitrostilbene and (*Z*)-methoxycarbonylstilbene were heated with 4,4′-dimethoxydiphenyl disulfide in THF. As expected, isomerization proceeded more rapidly than that with diphenyl disulfide to give the corresponding (*E*)-isomers in 90% and 85% yields after 6 and 10 h reactions with 0.2 mol eq of the catalyst, respectively (Table III, runs 5 and 8).

Although the isomerization of 2-nitrostilbene was accelerated by 4,4′-dimethoxydiphenyl disulfide, the reaction was not completed with this catalyst even on prolonged heatintg (Table III, run 2). In such cases, iodine-catalyzed isomerization gave good results. The isomerization of nitro- and methoxycarbonylstilbenes with iodine in benzene proceeded rapidly to give the corresponding (*E*)-isomers in excellent yields without any side reaction (Table III, runs 3, 6, and 9).

On the other hand, the isomerization of stilbenes bearing an electron-donating substituent(s) was accelerated by a catalyst bearing an electron-attracting substituent. Therefore, isomerization of (*Z*)-2,3-dimethoxystilbene (which took 18 h with diphenyl disulfide) with a catalytic amount of 4,4′-dinitrodiphenyl disulfide in THF proceeded rapidly, giving rise to the (*E*)-isomer is 89% yield after 6 h reaction (Table III, run 10). However, the use of 4,4′-dinitrodiphenyl disulfide for isomerization of 2,3-dimethoxystilbene had a disadvantage: the relative mobility of (*E*)-2,3-dimethoxystilbene on silica gel was close to that of the reagent, hence repeated chromatography was necessary for isolation of the pure product. This disadvantage was overcome by the use of 2,2′-dipyridyl disulfide as a catalyst. The isomerization proceeded as rapidly as that with 4,4′-dinitrodiphenyl disulfide (run 11) and the catalyst was easily removed by chromatography, because it gave a very small *Rf* value. The isomerization of (*Z*)-2,5-dimethoxystilbene (it took 22 h with diphenyl disulfide) was also accelerated by 2,2′-dipyridyl disulfide (Table III, run 12). Thus, increase of the nucleophilicity of the catalyst increases the rate of isomerization of stilbenes bearing an electron-attracting substituent and increase of the electrophilicity of the catalyst increases the rate of isomerization of stilbenes bearing an electron-donating substituent.

This isomerization reaction is considered to proceed in a free radical manner. When diaryl disulfide is heated in THF (either with or without AIBN), it produces an arylthio radical which adds to the double bond of stilbene (step 1).[5] Thus, either (*E*) or (*Z*)-isomer gives the same intermediary radical species by a rotation of the C–C bond for steric reasons. Elimination of an arylthio radical from this species in either an *anti* or a *syn* manner through pyramidalization of the radical sp^2 carbon gives the (*E*)-isomer exclusively (step 2). We prefer an *anti*-elimination for this process.

The new method for isomerization of (*Z*)-stilbenes into (*E*)-isomers developed here is superior to previously known methods in the simplicity of the reaction procedure, high conversion yield, and cleanliness of the product.

Experimental

Melting points were taken on a Yanaco melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured in $CDCl_3$ solution with tetramethylsilane as an internal standard on a GSX-500 (500 MHz) spectrometer and chemical shifts are given in δ values. GC was performed with a Shimadzu GC4 CM-PF gas chromatograph using nitrogen as a carrier gas. Thin layer chromatography (TLC) was carried out with Merck Kieselgel 60 F_{254} precoated plates and spots were developed by spraying with 10% sulfuric acid and heating the plates at 100 °C until coloration took place. Wakogel C-200 (silica gel) was used for column chromatography. All organic extracts were dried over anhydrous sodium sulfate before concentration.

Materials Catalysts: Diphenyl disulfide, 4,4′-dinitrodiphenyl disulfide, 2,2′-dipyridyl disulfide are commercially available. 4,4′-Dimethoxydiphenyl disulfide was synthesized as follows. *p*-Methoxybenzenethiol (1 g) was stirred with iodine (0.2 mol eq) in benzene at room temperature for 1 h. The reaction mixture was shaken with saturated sodium thiosulfate solution and the water layer was extracted with ether. The combined organic layer was concentrated and the residue was purified by chromatography to yield 4,4′-dimethoxydiphenyl disulfide (0.8 g), as pale yellow needles, mp 48—50 °C (lit. mp 44—45 °C).[6]

(*Z*)- or (*E*)/(*Z*)-Stilbenes: These were prepared by Wittig reaction according to the conventional procedure (for example, ref. 7).

General Method for Isomerization of (*Z*)- or (*E*)/(*Z*)-Stilbene into the (*E*)-Stilbene with Diaryl Disulfide A mixture of (*Z*)- or (*E*)/(*Z*)-stilbene (each 100 mg) and diaryl disulfide (0.2 mol eq) in THF was heated under reflux with periodic monitoring of the progreess of the reaction by GC. After completion of the reaction, the solvent was evaporated off and the catalyst was separated by column chromatography to yield the (*E*)-isomer. Suitable combinations of substrate and catalyst, reaction conditions, and the yields are listed in Tables I and III. Identification of the product was made by comparisons of melting points and ^{1}H-NMR spectra with reported values. Physical data of (*E*)-methoxy- and hydroxystilbenes are given in ref. 7. The data of the other (*E*)-stilbenes are as follows.

(*E*)-3-Nitrostilbene: Pale yellow needles from hexane–ether, mp 115—116 °C (lit. 112 °C).[8]

(*E*)-4-Methoxycarbonylstilbene: Colorless leaflets from hexane–ether, mp 155—156 °C (lit. 159—160°C).[9]

Isomerization of (*Z*)-3,5-Dihydroxystilbene with Iodine in Benzene A mixture of (*Z*)-3,5-dihydroxystilbene[7] (50 mg) and iodine (0.2 mol eq) in benzene was stirred for 5 h at room temperature. The reaction mixture was shaken with saturated sodium thiosulfate solution and the water layer was extracted with ether. The combined organic extracts were concentrated and the products were separated by column chromatography to yield (*E*)-3,5-dihydroxystilbene[7] (32.2 mg, 64%, mp 156—157 °C) and (*E*)-4-iodo-3,5-dihydroxy-stilbene (10.3 mg, 13%), as dark brown needles from hexane–ether, mp 148—149 °C. ^{1}H-NMR (500 MHz): 5.32 (2H, s, OH), 6.74 (2H, s, H-2,6), 6.96, 7.08 (each 1H, d, J=16 Hz, –CH=CH–), 7.27 (1H, br t, J=8 Hz, H-4′), 7.36 (2H, t, J=8 Hz, H-3′,5′), 7.50 (2H, br d, J=8 Hz, H-2′,6′). MS *m/z* (%): 338 (M^+, 100), 210 (30). *Anal.* Calcd for $C_{14}H_{11}IO_2$: C, 49.73; H, 3.28. Found: C, 49.82; H, 3.15.

Isomerization of 2-Nitrostilbene, 3-Nitrostilbene, and 4-Methoxycarbonylstilbene with Iodine in Benzene (*Z*)-2-Nitrostilbene,[8] (*Z*)-3-nitrostilbene,[8] and (*E*)/(*Z*)-4-methoxycarbonylstilbene (each 100 mg) in benzene (10 ml) were heated with iodine (0.2 mol eq) under reflux for 24, 3, and 4 h, respectively. The reaction mixture was shaken with saturated sodium thiosulfate solution and the aqueous layer was extracted with ether. The combined organic layer was concentrated and the residue was purified by column chromatography to yield (*E*)-2-nitrostilbene (93 mg), (*E*)-3-nitrostilbene (98 mg), and (*E*)-4-methoxycarbonylstilbene (96 mg), respectively.

(*E*)-2-Nitrostilbene: Yellow plates from hexane–ether, mp 72—73 °C (lit. 70—72 °C).[8]

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