Selective Synthesis of *cis*-α,β-Unsaturated Sulfoxides and Sulfides by the Horner–Wittig Reaction with Bis(2,2,2-trifluoroethyl)phosphono Sulfoxides and Aromatic Aldehydes

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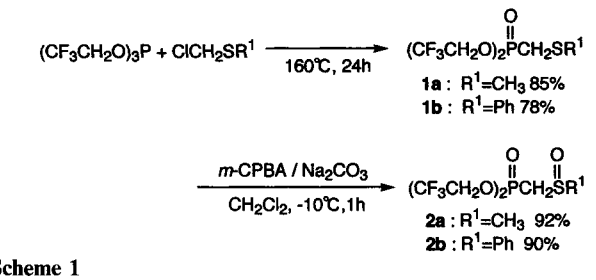
cis-α,β-Unsaturated sulfoxides were predominantly formed in the Horner–Wittig reaction with bis(2,2,2-trifluoroethyl)phosphono sulfoxides and aromatic aldehydes, while the reaction of the corresponding sulfides showed *trans*- or lower *cis*-selectivity. The reduction of *cis*-α,β-unsaturated sulfoxides with tributylphosphine in carbon tetrachloride gave *cis*-vinyl sulfides with retention of stereochemistry.

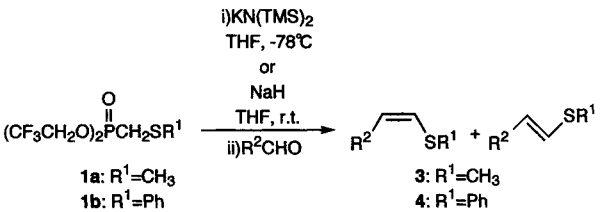
Vinyl sulfides and sulfoxides are useful synthetic intermediates; the former can couple with Grignard reagents[1] in the presence of a nickel–phosphine complex retaining the original geometry and is frequently applied to the synthesis of insect pheromones,[1] with the latter being used as Michael acceptors[2] or dienophiles.[3] In spite of the increasing importance of geometrically controlled unsaturated sulfides and sulfoxides, only a few synthetic methods[3,4] of their *cis*-isomers are known. Although vinyl sulfides and sulfoxides are conveniently prepared[5] by the Horner–Wittig reaction, the geometrical selectivity is generally low or thermodynamically favored *trans*-isomers are preferentially formed. Still et al. reported the selective synthesis of *cis*-unsaturated esters using bis(2,2,2-trifluoroethyl)phosphono esters,[6] which seemed to be applicable to the selective synthesis of unsaturated compounds with sulfur groups. In this paper we describe a new preparation of the modified Horner–Wittig reagents containing sulfur groups, *cis*-selective synthesis of α,β-unsaturated sulfoxides, and their conversion to *cis*-unsaturated sulfides.

Bis(2,2,2-trifluoroethyl)phosphono sulfides **1a** and **1b** were prepared by the Arbuzov reaction of tris(2,2,2-trifluoroethyl) phosphite with chloromethyl methyl sulfide or chloromethyl phenyl sulfide in good yields. The oxidation of phosphono sulfides **1a** and **1b** with *m*-chloroperbenzoic acid (*m*-CPBA) readily gave phosphono sulfoxides **2a** and **2b** in excellent yields (Scheme 1).

The olefination was carried out using **1** and various aromatic aldehydes in the presence of sodium hydride[7] or potassium bis(trimethylsilyl)amide [$KN(TMS)_2$][6] in tetrahydrofuran (Scheme 2). The results are shown in Table

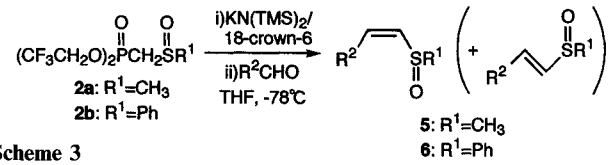


Scheme 1



Scheme 2

1. The reaction of **1a** with benzaldehyde or *p*-tolualdehyde in the presence of NaH gave almost the same ratio of the isomers as reported by Mikolajczyk et al. using diethyl methylthiomethylphosphonate.[5] When **1a** reacted with *p*-nitrobenzaldehyde, only *trans*-vinyl sulfide **3c** was formed. However, the introduction of an electronegative fluorinated group on the phosphorus atom was found to affect *cis*-selectivity in the reaction of **1b** and benzaldehyde in the presence of $KN(TMS)_2$, and predominantly gave *cis*-vinyl sulfide **4**. However, the selectivity was not yet synthetically useful.



Scheme 3

Table 1. *cis*/*trans* Ratio in the Horner–Wittig Reaction of Phosphono Sulfides **1a,b** with Aromatic Aldehydes

Product	Phosphonate	R^2	Conditions	Yield (%)[a]	*cis*/*trans* Ratio[b]
3a	**1a** ($R^1=CH_3$)	Ph	NaH/r.t./8 h	60	1.0/5.0
			$KN(TMS)_2$/18-crown-6/−78 °C/8 h	53	1.0/3.8
3b		*p*-$CH_3C_6H_4$	NaH/r.t./8 h	90	1.0/6.0
3c		*p*-$NO_2C_6H_4$	NaH/r.t./8 h	50	*trans*-isomer
4	**1b** (R^1=Ph)	Ph	$KN(TMS)_2$/18-crown-6/−78 °C/5 h	64	2.7/1.0
			$KN(TMS)_2$/−78 °C/4 h	62	4.5/1.0

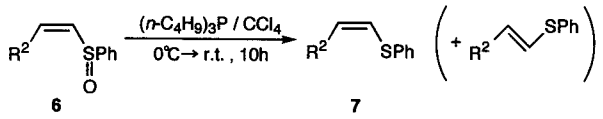
[a] Isolated yields by column chromatography.
[b] These ratios were determined by ^1H NMR.

In contrast, the olefination of phosphono sulfoxides **2a** and **2b** with aromatic aldehydes in the presence of $KN(TMS)_2$ and 18-crown-6[6] in THF (Scheme 3) showed higher *cis*-selectivity and pure *cis*-isomers **5** and **6** were readily isolated from the mixture by column chromatography. Absence of 18-crown-6 reduced the *cis*-selectivity. The results are shown in Table 2. Of these entries, some reactions gave only *cis*-isomers **5d, e, 6a, b** and **d**. The *cis*-selectivity is apparently independent of the electronic nature of substituents of the aromatic aldehydes. The successful formation of **6b** as only a *cis*-isomer is synthetically interesting because *E*, *Z*-conjugated dienes can be readily synthesized in this manner after transformations of the functional groups. The reaction of **2b** with saturated aliphatic aldehydes such as *n*-octanal showed no selectivity, and *cis*- and *trans*-isomers were formed in almost equal amounts. As observed in the reaction of Still's bis(2,2,2-trifluoroethyl)phosphono esters,[6] the *cis*-selectivity of **2b** with the saturated or unsaturated aliphatic aldehydes was also found to be low. Geometrical selectivity would depend upon electronic and steric effects but the details are unknown. This problem is under investigation in our laboratory. It is noteworthy that shift reagents such as $Eu(dpm)_3$ or $Eu(fod)_3$ are very effective at determining the geometries of unsaturated sulfoxides in ^1H NMR spectra; namely, the olefinic β-protons are much lower in field than the α-protons, which enables the determination of *cis* (J = ca. 10 Hz)/*trans* (J = ca. 15 Hz) ratios.

Table 2. *cis*/*trans* Ratio in the Horner–Wittig Reaction of Phosphono Sulfoxides **2a, b** with Aldehydes

Product	Phosphonate	R^2	Yield (%)[a]	*cis*/*trans* Ratio[b]
5a	**2a** (R^1 = CH_3)	Ph	61	17/1
		Ph	67	7.0/1[c]
5b		*p*-$CH_3C_6H_4$	77	10/1
		p-$CH_3C_6H_4$	64	8.0/1[c]
5c		*p*-$NO_2C_6H_4$	79	1.8/1
5d		*p*-ClC_6H_4	75	*cis*-isomer
5e		*p*-$CH_3OC_6H_4$	69	*cis*-isomer
5f		*p*-$(CH_3)_2NC_6H_4$	36	4.7/1
6a	**2b** (R^1 = Ph)	Ph	81	*cis*-isomer
		Ph	61	2.8/1[c]
6b		(*E*)-PhCH=CH	88	*cis*-isomer
6c		(*E*)-CH_3CH=CH	71	2.8/1
6d		*p*-ClC_6H_4	74	*cis*-isomer
6e		n-C_7H_{15}	75	1.0/1

[a] Isolated yields by column chromatography.
[b] These ratios were determined by ^1H NMR adding shift reagents (see text).
[c] In the absence of 18-crown-6.



Scheme 4

For the synthesis of *cis*-α,β-unsaturated sulfides, the conversions of *cis*-α,β-unsaturated sulfoxides were carried out under various conditions (Scheme 4). The results are shown in Table 3. Although there have been several reports[8] on the reduction of sulfoxides to sulfides, only a few examples of α,β-unsaturated sulfoxides are known, and the reduction of *cis*-α,β-unsaturated sulfoxides has not been investigated to our knowledge. After some efforts, the adduct of tributylphosphine and carbon tetrachloride, prepared at 0 °C, was found to be most effective at converting to the unsaturated sulfides **7** without isomerization.

Thus, we have demonstrated a highly *cis*-selective synthesis of aromatic α,β-unsaturated sulfoxides by the Horner–Wittig reaction with bis(2,2,2-trifluoroethyl)phosphono sulfoxides and the transformation to *cis*-unsaturated sulfides by mild reduction of these sulfoxides. This study also suggests that highly polarized electron-withdrawing groups,[9] such as esters or sulfoxides, are necessary for high *cis*-selectivity in the modified Horner–Wittig reaction with fluorinated phosphoryl groups.

All solvents were dried by standard methods. ^1H NMR spectra were obtained on JEOL PMX60 using TMS as an internal standard in $CDCl_3$. HRMS spectra were determined on HITACHI M-80B mass spectrometer.

Bis(2,2,2-trifluoroethyl)phosphonomethyl Methyl Sulfide (1a); Typical Procedure:

A mixture of tris(2,2,2-trifluoroethyl) phosphite (7.16 g, 21.83 mmol) and chloromethyl methyl sulfide (2.11 g, 21.83 mmol) was heated at 160 °C for 24 h. Vacuum distillation gave **1a**; yield: 5.68 g (85%); bp 74 °C/1 mmHg.

^1H NMR: δ = 2.30 (s, 3H), 3.40 (d, 2H, J_{PH} = 17 Hz), 4.07–4.77 (m, 4H).

Table 3. *cis*/*trans* Ratio of Unsaturated Sulfides **7** by the Reduction of **6**

Product	R^2	Condition	Yield (%)[a]	*cis*/*trans* Ratio[b]
7a	Ph	Ph_3P/CCl_4/reflux/10 h	81	9.5/1
		(n-$C_4H_9)_3P/CCl_4$/r.t./10 h	94	*cis*-isomer
		(morpholino)$_3P/CCl_4$/r.t./28 h	43	*cis*-isomer
		$(CF_3CH_2O)_2O/(CH_3)_2S/CH_2Cl_2$/−10 °C/5 min	100	1/7.7
7b	(*E*)-PhCH=CH	Ph_3P/CCl_4/reflux/10 h	73	2.5/1[c]
		(n-$C_4H_9)_3P/CCl_4$/r.t./10 h	60	*cis*-isomer[c]
7c	*p*-ClC_6H_4	(n-$C_4H_9)_3P/CCl_4$/r.t./10 h	69	*cis*-isomer

[a] Isolated yields by column chromatography.
[b] These ratios were determined by ^1H NMR.
[c] Determined after conversion to the sulfoxide.

HRMS: *m/z* calc. for $C_6H_9F_6O_3SP$: 305.9913, found 305.9896.

Bis(2,2,2-trifluoroethyl)phosphonomethyl Phenyl Sulfide **(1b):**

Phosphono sulfide **1b** was obtained by the same procedure; yield (78%) bp 150°C/1 mmHg (Kugelrohr).

^{1}H NMR: $\delta = 3.27$ (d, 2H, $J_{PH} = 13$ Hz), 4.00–4.73 (m, 4H), 7.03–7.63 (m, 5H).

HRMS: *m/z* calc. for $C_{11}H_{11}F_6O_3SP$: 368.0070, found 368.0067.

Bis(2,2,2-trifluoroethyl)phosphonomethyl Methyl Sulfoxide (2a); Typical Procedure:

A solution of *m*-CPBA (2.40 g, 13.91 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a solution of **1a** (3.87 g, 12.65 mmol) in CH_2Cl_2 (80 mL) in the presence of Na_2CO_3 (1.47 g, 13.91 mmol) at −10°C and stirred at the same temperature for 1 h. After removal of solvent, the residue was neutralized with a sat. aq Na_2CO_2 and extracted with chloroform (3 × 50 mL). The organic layer was dried (Na_2SO_4). The solvent was removed under reduced pressure to give **2a**; yield: 3.75 g (92%).

^{1}H NMR: $\delta = 2.87$ (s, 3H), 3.40 (d, 2H, $J_{PH} = 17$ Hz), 4.07–4.77 (m, 4H).

HRMS: *m/z* calc. for $C_6H_9F_6O_4SP$: 321.9863, found 321.9864.

Bis(2,2,2-trifluoroethyl)phosphonomethyl Phenyl Sulfoxide **(2b)**:

Phosphono sulfoxide **2b** was obtained by the same procedure; yield (90%).

^{1}H NMR: $\delta = 3.45$ (d, 2H, $J_{PH} = 16$ Hz), 4.03–4.77 (m, 4H), 7.23–7.83 (m, 5H).

HRMS: *m/z* calc. for $C_{11}H_{11}F_6O_4SP$: 384.0019, found 384.0010.

β-Methylthiostyrene (3a); Typical Procedure:

A solution of **1a** (0.80 g, 2.61 mmol) and benzaldehyde (0.28 g, 2.61 mmol) in THF (10 mL) was added dropwise to a suspension of NaH (60% in oil, 0.13 g, 3.13 mmol) in THF (20 mL) at r.t. and the mixture was stirred at the same temperature for 8 h under N_2. After removal of the solvent, sat. aq NH_4Cl was added to the residue and the product was extracted with Et_2O (3 × 30 mL). The extract was washed with brine (30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using benzene as an eluant to give **3a**; yield: 0.23 g (60%).

^{1}H NMR: for *cis*; $\delta = 2.30$ (s, 3H), 6.08 and 6.35 (AB system, 2H, $J_{HH} = 11.0$ Hz), 7.17 (s, 5H), for *trans*; $\delta = 2.30$ (s, 3H), 6.17 and 6.67 (AB system, 2H, $J_{HH} = 15.8$ Hz), 7.17 (s, 5H).

2-(4-Methylphenyl)-1-methylthioethylene **(3b)**:

^{1}H NMR: for *cis*; $\delta = 2.30$ (s, 6H), 5.95 and 6.32 (AB system, 2H, $J_{HH} = 10.0$ Hz), 7.03 (s, 4H), for *trans*; $\delta = 2.30$ (s, 6H), 6.17 and 6.67 (AB system, 2H, $J_{HH} = 14.0$ Hz), 7.03 (s, 4H).

trans-1-Methylthio-2-(4-nitrophenyl)ethylene **(3c)**:

^{1}H NMR: $\delta = 2.33$ (s, 3H), 6.27 and 7.07 (AB system, 2H, $J_{HH} = 15.8$ Hz), 7.40 and 8.17 (AB system, 4H, $J_{HH} = 8.4$ Hz).

2-Phenyl-1-(phenylthio)ethylene (4):

A solution of $KN(TMS)_2$ (0.5 mol/L toluene solution, 4 mL, 2 mmol) was added dropwise to a solution of **1b** (0.77 g, 2 mmol) in the presence of 18-crown-6 (2.64 g, 10 mmol) in THF (40 mL) at −78°C and the mixture was stirred at the same temperature for 1 h under N_2. A solution of benzaldehyde (0.21 g, 2 mmol) in THF (2 mL) was then added and the mixture was stirred at the same temperature for 5 h. After removal of the solvent, sat. aq NH_4Cl was added to the residue and the product was extracted with Et_2O (3 × 20 mL). The extract was washed with brine (20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using benzene as an eluant to give **4** as a *cis/trans* mixture (*cis/trans* = 2.7/1; yield: 0.27 g (64%).

^{1}H NMR: for *cis*; $\delta = 6.40$ and 6.58 (AB system, 2H, $J_{HH} = 11.0$ Hz), 7.00–7.66 (m, 4H), for *trans*; $\delta = 6.63$ and 6.92 (AB system, 2H, $J_{HH} = 14.0$ Hz), 7.00–7.66 (m, 4H).

The same procedure without the addition of 18-crown-6 gave **4** as a *cis/trans* mixture (*cis/trans* = 4.5/1) in a 62% yield.

***cis*-2-Phenyl-1-(phenylsulfinyl)ethylene (6a); Typical Procedure:**

A solution of $KN(TMS)_2$ (0.5 mol/L toluene solution, 4 mL, 2 mmol) was added dropwise to a solution of **2b** (0.77 g, 2 mmol) in the presence of 18-crown-6 (2.64 g, 10 mmol) in THF (40 mL) at −78°C and the mixture was stirred under N_2 for 1 h. A solution of benzaldehyde (0.21 g, 2 mmol) in THF (2 mL) was then added and the mixture was allowed to warm slowly to r.t. and stirred overnight. After removal of the solvent, sat. aq NH_4Cl was added to the residue and the product was extracted with Et_2O (3 × 20 mL). The extract was washed with brine (20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using hexane/EtOAc (3:1) as an eluant to give **6a**; yield: 0.37 g (81%).

^{1}H NMR: $\delta = 6.37$ and 7.07 (AB system, 2H, $J_{HH} = 11.0$ Hz), 7.22–7.80 (m, 10H).

cis-2-(4-Chlorophenyl)-1-(methylsulfinyl)ethylene **(5d)**:

^{1}H NMR: $\delta = 2.70$ (s, 3H), 6.43 and 6.97 (AB system, 2H, $J_{HH} = 11.0$ Hz), 7.33 (s, 4H).

cis-2-(4-Methoxyphenyl)-1-(methylsulfinyl)ethylene **(5e)**:

^{1}H NMR: $\delta = 3.83$ (s, 3H), 6.33 and 6.97 (AB system, 2H, $J_{HH} = 10.0$ Hz), 6.83–7.47 (m, 4H).

(1E,3Z)-1-Phenyl-4-phenylsulfinylbuta-1,3-diene **(6b)**:

^{1}H NMR: $\delta = 6.08$ (d, 1H, $J_{HH} = 11.0$ Hz), 6.40–6.90 (m, 3H), 7.07–7.80 (m, 10H).

1-Phenylsulfinylpenta-1,3-diene **(6c)**:

^{1}H NMR: $\delta = 1.86$ (d, 3H, $J_{HH} = 5.0$ Hz), 5.58–7.23 (m, 4H), 7.23–7.75 (m, 5H). The α-vinyl protons shifted to $\delta = 9.53$ (*E*) and $\delta = 10.67$ (*Z*) by the addition of $Eu(fod)_3$ (0.75 equiv) and the ratio of geometrical isomers was determined by the integration of these protons.

cis-2-(4-Chlorophenyl)-1-(phenylsulfinyl)ethylene **(6d)**:

^{1}H NMR: $\delta = 6.45$ and 7.07 (AB system, 2H, $J_{HH} = 10.4$ Hz), 7.25–7.95 (m, 9H).

1-Phenylsulfinylnon-1-ene **(6e)**:

^{1}H NMR: $\delta = 0.30$–1.05 (m, 3H), 1.05–1.80 (m, 10H), 1.80–2.87 (m, 2H), 5.90–6.93 (m, 2H), 7.03–7.80 (m, 5H). The ratio of geometrical isomers was determined by the integration of β-protons after the addition of $Eu(fod)_3$ (0.75 equiv).

***cis*-2-Phenyl-1-(phenylthio)ethylene (7a); Typical Procedure:**

CCl_4 (8 mL) was added dropwise to precooled tributylphosphine (0.78 g, 3.86 mmol) at 0°C under N_2. After 1 h a solution of **6a** (0.44 g, 1.93 mmol) in CCl_4 (3 mL) was added to the mixture at 0°C and the solution was allowed to warm to r.t. After the mixture was stirred for 10 h, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel using benzene as an eluant to give **7a**; yield: 0.38 g (94%).

^{1}H NMR: $\delta = 6.27$ and 6.47 (AB system, 2H, $J_{HH} = 10.0$ Hz), 7.03–7.57 (m, 10H).

(1E,3Z)-1-Phenyl-4-phenylthiobuta-1,3-diene **(7b)**:

^{1}H NMR: $\delta = 6.13$–6.90 (m, 3H), 7.00–7.90 (m, 11H).

cis-2-(4-Chlorophenyl)-2-(phenylthio)ethylene **(7c)**:

^{1}H NMR: $\delta = 6.41$ and 6.63 (AB system, 2H, $J_{HH} = 10.4$ Hz), 7.25–7.95 (m, 9H).

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