J. prakt. Chem. 339 (1997) 176–178

Journal für praktische Chemie
Chemiker-Zeitung

Wittig-Horner Synthesis of Vinyl Sulfoxides from Aryl Alkyl or Diaryl Ketones under Sonication

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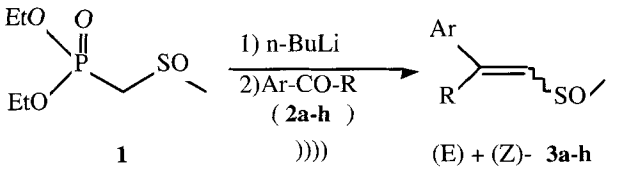
Received February 21st, 1996 respectively June 12th, 1996

The synthesis of vinyl sulfoxides through a Wittig-Horner condensation between lithium salts of α-phosphoryl sulfoxides and carbonyl compounds at low temperature (–78°C) is a well established process [1–4]. Using the lithium derivative of methyl (diethylphosphoryl) methyl sulfoxide **1**, it was found that raising the temperature above –50 °C leads to its partial decomposition [1]. Furthermore, although this procedure was largely applied to various aldehydes, few aliphatic, cyclic or aromatic ketones were used until now. On the other hand, attempts to perform the reactions at room temperature in a two-phase system catalysed or not by quaternary ammonium salts or crown ethers was limited to aromatic aldehydes, enolizable ones or ketones remaining unreactive [5, 6]. More recently, a synthesis of vinyl sulfoxides using sulfinyl phosphonates in the presence of potassium carbonate was performed under ultrasonic irradiation from two aromatic aldehydes [7]. However, no indication was given concerning yields optimization of the sonicated reactions comparatively to that of the thermal ones.

In this paper, we wish to report that the Wittig–Horner reaction of sulfinyl phosphonate **1** and ketones **2** affording vinyl sulfoxides **3** as (*E*)/(*Z*) mixtures, may be carried out at room temperature with *n*-butyllithium under ultrasonic irradiation.



1 (E) + (Z)- **3a-h**

	Ar	R		Ar	R
2a, 3a	*p*-NO_2-C_6H_4	CH_3	**2e, 3e**	*p*-CH_3-C_6H_4	CH_3
2b, 3b	*p*-F-C_6H_4	CH_3	**2f, 3f**	*p*-CH_3O-C_6H_4	CH_3
2c, 3c	*p*-Cl-C_6H_4	CH_3	**2g, 3g**	C_6H_5	CF_3
2d, 3d	*p*-Br-C_6H_4	CH_3	**2h, 3h**	*p*-NO_2-C_6H_4	C_6H_5

Results and Discussion

The best yields in vinyl sulfoxides **3** were obtained by the use of 1.2 equivalents of 1.6 M *n*-butyllithium in hexane. Ketones **2** were added under sonication to the soluble lithium salt of **1** in four equal portions over two hours. Ultrasonic irradiation was performed with a 20 kHz probe (9.5 mm diameter, 50 W electrical power input).

The overall yields of all the sonochemical reactions are largely higher than those carried out under the same conditions except sonication. Thus, with ketones **2a** and **2e–2h** the yields of the silent reactions are in the range of 15–20%. Attempts to prepare compounds **3b–d** under thermal conditions (at room temperature) from fluoro (**2b**), chloro (**2c**) or bromoacetophenone (**2d**) failed.

In contrast to the thermal Wittig–Horner synthesis of vinyl sulfoxides from enolizable ketones [2, 3] no β–γ-isomerization

Table 1 Yield and (*E*)/(*Z*) ratio of vinyl sulfoxides **3a–h**

Compound	Yield %[a]	(*E*)/(*Z*) of **3**
3a	50	30/70
3b	80	40/60
3c	77	30/70
3d	70	40/60
3e	40	30/70
3f	60	30/70
3g	65	70/30 [b]
3h	55	40/60

[a] Calculated from the isolated pure products **3**.
[b] The presence of the trifluoromethyl group changes the priority for the (*E*) and (*Z*) nomenclature.

into allyl sulfoxydes was observed in the present case even in the presence of an excess of *n*-butyllithium.

Assignment of configuration (*E*) or (*Z*) to the respective isomers of vinyl sulfoxides **3** was made by ^{1}H NMR spectroscopy at 300 MHz. The geometrical isomers are differentiated by the chemical shifts of the methyl groups and the vinylic protons and the allylic coupling constants of the latter. Thus, for **3a–3f** and **3h** the signals of the methylsulfinyl group and of the vinylic protons are shifted to a higher field in the (*Z*)-isomers (respectively 2.54–2.77 and 6.37–6.93 ppm) as compared to the (*E*)-isomers (2.62–2.78 and 6.49–6.97 ppm). The chemical shifts of the vinylic methyl groups in vinyl sulfoxides **3a–3f** are shielded in the (*Z*)-isomers (2.16–2.30 ppm) comparatively to those of the (*E*)-ones (2.30–2.40 ppm). Concerning the vinylic protons of **3a–3f**, the allylic coupling constants ^4J(H–CH_3) are higher in the (*Z*)-isomers (1.3–1.4 Hz) than in (*E*)-ones (1 Hz). The chemical shifts data are in good agreement with those of literature [1, 3], and similar values for allylic couplings have also been reported for (*E*) and (*Z*) vinylic protons [3]. For compound **3g**, the presence of the trifluoromethyl group has changed the priority for (*E*) and (*Z*) nomenclature. So, we assigned a (*Z*) configuration to the stereoisomer in which the methylsulfinyl group and the vinylic proton are the most deshielded ones. These assignments agree with the additive increments method [8] used for other vinyl sulfoxides [9]. They are also supported by ^{1}H NOE experiments performed on pure (*E*)-**3d** and (*Z*)-**3d**. Indeed, irradiation of the vinylic proton or the vinylic methyl group in the (E)-isomer gives a response to the aromatic protons only, while irradiation of the vinylic methyl group in the (*Z*)-isomer gives a response to both the vinylic and the aromatic protons. The (*Z*)-**3** vinyl sulfoxides were obtained as the major stereoisomers in the mixtures of (*Z*)/(*E*) geometrical isomers. This observed stereochemistry can be rationalized on the basis of the degree of reversibility and stability of the intermediates usually proposed for the mechanism of the Wittig–Horner reaction [1]. This result is in good agreement with the previous observations concerning ketones as substrates [1, 3].

The ratio of the isomeric vinyl sulfoxides seems to be independent from the conditions of ultrasonic irradiation. Indeed, no (*Z*) to (*E*) isomerization was observed in the absence of any added reagent after sonication in the dark of a THF solution of pure (*E*)-**3a** or (*Z*)-**3a** for 2 hours.

This work describes an efficient synthesis of vinyl sulfoxides from aryl alkyl or diaryl ketones under ultrasonic irradiation and confirms the sensitivity of homogeneous Wittig–Horner reaction to ultrasound. In contrast with previous methods, our procedure keeps its efficiency at room temperature.

Dr. D. Peters would like to thank the Claude Bernard University for a position as a guest researcher. This work was effected under the auspices of the COST organization (Programme Chemistry D6) as a collaboration with Prof. R. Miethchen (University of Rostock, Germany) whom we thank for useful discussions.

Experimental

Anhydrous THF was distilled under nitrogen from sodium/benzophenone ketyl. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel F-254 aluminium sheets. Matrex 60 A (35–70 μm) silica gel was used for column chromatography. Separation of the *(E)* and *(Z)*-isomers was made by circular preparative thin layer chromatography (Harrison Research Chromatotron 8924) with Merck silica gel containing gypsum. Sonication of the solutions was carried out in a thermostated reactor (internal dimensions: 35 mm diameter and 80 mm depth) with a Labsonic U generator (20 kHz, probe 9.5 mm diameter, 50 W electrical power input). Melting points were determined in open capillary tubes with a Büchi 510 apparatus. Infrared spectra (IR) were recorded on a Perkin-Elmer 1310 spectrophotometer. The ^{1}H NMR spectra were performed at 300 MHz in $CDCl_3$ on a Bruker AM 300 spectrometer. Chemical shifts δ are reported in ppm downfield relative to tetramethylsilane. Coupling constants J in Hz.

Phosphonic ester **1** is prepared from the corresponding sulfide [10] by oxidation with $NaIO_4$ [11]. All the reaction were carried out under argon after previous deoxygenation of the phosphonic ester **1** and ketone **2** solutions for 45 min.

General procedure for the synthesis of vinyl sulfoxydes (3a–h).

To a solution of the phosphonic ester **1** (0.985g, 4.6 mmol) in 30 mL of anhydrous THF a solution of *n*-butyllithium 1.6 M in hexane (3.31 mL, 5.52 mmol) was added dropwise with a syringe at room temperature. After a sonication time of 30 min, a solution of the appropriate ketone **2** (4.6 mmol) in THF (2 mL) was added in four equivalent fractions over a period of two hours. Sonication was continued for 30 min. The evolution of the reaction was followed by TLC using AcOEt/MeOH 90/10 as eluent. The final reaction mixture was then poured into 100 mL of a sat. aq. solution of NH_4Cl and extracted by 3×30 mL of CH_2Cl_2. The organic layer was successively washed with sat. aq. solution of $NaHCO_3$ and NaCl and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography (EtOAc/MeOH 90/10 as eluent). The *(Z)* and *(E)*-isomers were separated from the resulting mixture by preparative circular thin layer chromatography using 2 mm plates of silica gel and a mixture of EtOAc/MeOH 95/5 as eluent.

1-(Methylsulfinyl)-2-(p-nitrophenyl)-propene (**3a**)

(Z)-**3a**: *m.p.* 105 °C. – IR: 1595, 1520, 1340, 1010. – ^{1}H NMR: 8.28 (dd, 2H, J = 8.6 and 5,3'-H and 5'-H); 7.45 (dd, 2H, J = 8.6 and 5, 2'-H and 6'-H); 6.52 (q, 1H with allylic coupling, J = 1.3, H vinyl); 2.65 (s, 3H, CH_3SO); 2.29 (d, 3H with allylic coupling, J = 1.3, CH_3). – $C_{10}H_{11}NO_3S \cdot 0.3\,H_2O$ (225.26), Calcd.: C 52.02 H 4.76 N 6.06 S 13.87; Found: C 51.96 H 4.76 N 5.93 S 13.88.

(E)-**3a**: (not isolated from the *(E)*+*(Z)* mixture). – ^{1}H NMR: 8.28 (dd, 2H, J = 8.8 and 5, 3'-H and 5'-H); 7.62 (dd, 2H, J = 8.8 and 5, 2'-H and 6'-H); 6.65 (q, 1H with allylic coupling, J = 1, H vinyl); 2.72 (s, 3H, CH_3SO); 2.4 (d, 3H with allylic coupling, J = 1, CH_3).

1-(Methylsulfinyl)-2-(p-fluorophenyl)-propene (**3b**)

(Z)-**3b**: liquid. – IR: 1600, 1300, 1080. – ^{1}H NMR: 7.25 (dd, 2H, J = 8.6 and 2, 3'-H and 5'-H); 7.05 (dd, 2H, J = 8.6 and 2, 2'-H and 6'-H); 6.38 (q, 1H with allylic coupling, J = 1, H vinyl); 2.62 (s, 3H, CH_3SO); 2.23 (d 3H with allylic coupling, J = 1, CH_3). –

$C_{10}H_{11}FOS \cdot 0.4\,H_2O$ (198.26), Calcd.: C 58.45 H 5.78 F 9.24 S 15.60, Found: C 58.77 H 5.90 F 9.21 S 15.55.
(E)-**3b**: liquid. – IR: 1600, 1300, 1080. – ^{1}H NMR: 7.45 (dd, 2H, J = 8.6 and 2, 3'-H and 5'-H); 7.05 (dd, 2H, J = 8.6 and 2, 2'-H and 6'-H); 6.52 (q, 1H with allylic coupling, J = 1, H vinyl); 2.69 (s, 3H, CH_3SO); 2.36 (d, 3H with allylic coupling, J = 1, CH_3).

1-(Methylsulfinyl)-2-(p-chlorophenyl)-propene (**3c**)

(Z)-**3c**: *m.p.* 90 °C. – IR: 1595, 1480, 1300, 1080, 1010. – ^{1}H NMR: 7.32 (2H, dd, J = 8.5, 3'-H and 5'-H); 7.18 (dd, 2H, J = 8.5, 2'-H and 6'-H); 6.37 (q, 1H with allylic coupling, J = 1.3, H vinyl); 2.63 (s, 3H, CH_3SO); 2.24 (d, 3H with allylic coupling, J = 1.3, CH_3). – $C_{10}H_{11}ClOS$ (214.71), Calcd.: C 55.94 H 5.16 Cl 16.51 S 14.93, Found: C 55.73 H 5.21 Cl 16.37 S 14.76.
(E)-**3c**: *m.p.* 72 °C. – IR: 1595, 1480, 1300, 1080, 1010; ^{1}H NMR: 7.32 (2H, dd, J = 8.5, 3'-H and 5'-H); 7.18 (dd, 2H, J = 8.5, 2'-H and 6'-H); 6.53 (q, 1H with allylic coupling, J = 1, H vinyl); 2.71 (s, 3H, CH_3SO); 2.37 (d, 3H with allylic coupling, J = 1, CH_3).

1-(Methylsulfinyl)-2-(p-bromophenyl)-propene (**3d**)

(Z)-**3d**: *m.p.* 105 °C. – IR: 1610, 1480, 1300, 1070. – ^{1}H NMR: 7.50 (dd, 2H, J = 8.4 and 2.4, 3'-H and 5'-H); 7.13 (dd, 2H, J = 8.4 and 2.4, 2'-H and 6'-H); 6.39 (q, 1H with allylic coupling, J = 1.3, H vinyl); 2.62 (s, 3H, CH_3SO); 2.22 (d, 3H with allylic coupling, J = 1.3, CH_3). – $C_{10}H_{11}BrOS$ (259.16), Calcd.: C 46.34 H 4.27 Br 30.83 S 12.37, Found: C 46.09 H 4.23 Br 30.52 S 12.22.
(E)-**3d**: *m.p.* 95 °C. – IR: 1590, 1480, 1300, 1070. – ^{1}H NMR: 7.51 (dd, 2H, J = 8.4 and 2.4, 3'-H and 5'-H); 7.30 (dd, 2H, J = 8.4 and 2.4, 2'-H and 6'-H); 6.56 (q, 1H with allylic coupling, J = 1, H vinyl); 2.7 (s, 3H, CH_3SO); 2.34 (d, 3H with allylic coupling, J = 1, CH_3).

1-(Methylsulfinyl)-2-(p-tolyl)-propene (**3e**)

(Z)-**3e**: *m.p.* 98° C. – IR: 1600, 1480, 1180, 1010. – ^{1}H NMR: 7.12 (dd, 2H, J = 8.2 and 2, 3'-H and 5'-H); 7.0 (dd, 2H, J = 8.2 and 2, 2'-H and 6'-H); 6.27 (q, 1H with allylic coupling, J = 1.4, H vinyl); 2.54 (s, 3H, CH_3SO); 2.30 (s, 3H, CH_3Ph); 2.16 (d, 3H with allylic coupling, J = 1.4, CH_3). – $C_{11}H_{14}OS$ (194.29), Calcd.: C 68.00 H 7.26 S 16.50, Found: C 67.82 H 7.31 S 16.18.
(E)-**3e**: *m.p.* 88 °C. – IR: 1600, 1480, 1180, 1010. – ^{1}H NMR: 7.32 (dd, 2H, J = 8.2 and 2, 3'-H and 5'-H); 7.14 (dd, 2H, J = 8.2 and 2, 2'-H and 6'-H); 6.49 (q, 1H with allylic coupling, J = 1, H vinyl); 2.62 (s, 3H, CH_3SO); 2.30 (overlap, 6H, CH_3 and CH_3Ph).

1-(Methylsulfinyl)-2-(p-methoxyphenyl)-propene (**3f**)

(Z)-**3f**: *m.p.* 62 °C. – IR: 1595, 1300, 1070. – ^{1}H NMR: 7.23 (dd, 2H, J = 8.8 and 2.1, 2'-H and 6'-H); 6.9 (dd, 2H, J = 8.8 and 2.1, 3'-H and 5'-H); 6.32 (q, 1H with allylic coupling, J = 1.3, H vinyl); 3.82 (s, 3H, CH_3O); 2.62 (s, 3H, CH_3SO); 2.22 (d, 3H with allylic coupling, J = 1.3, CH_3). – $C_{11}H_{14}O_2S$ (210.29), Calcd.: C 62.82 H 6.71 S 15.24, Found: C 62.59 H 6.69 S 15.47.
(E)-**3f**: (not isolated from the *(E)*+*(Z)* mixture). – ^{1}H NMR: 7.45 (dd, 2H, J = 8.8 and 2.1, 2'-H and 6'-H); 6.92 (dd, 2H, J = 8.8 and 2.1, 3'-H and 5'-H); 6.52 (q, 1H with allylic coupling, J = 1, H vinyl); 3.83 (s, 3H, CH_3O); 2.7 (s, 3H, CH_3SO); 2.38 (d, 3H with allylic coupling, J = 1, CH_3).

1-(Methylsulfinyl)-2-(phenyl)-2-(trifluoromethyl)-ethylene (**3g**)

(Z)-**3g**: *m.p.* 110 °C. – IR: 1600, 1300, 1050. – ^{1}H NMR: 7.4 to 7.5 (m, 3H, 3'-H, 4'-H and 5'-H); 7.31 (dd, 2H, J = 6.4, 2'-H and 6'-H); 7.13 (q, 1H with allylic coupling, ^4J(H-CF_3) = 1.2, H vinyl); 2.80 (s, 3H, CH_3SO). – $C_{10}H_9F_3OS$ (234.24), Calcd.: C 51.27 H 3.87 F 24.33 S 13.68, Found: C 51.33 H 3.87 F 23.92 S 13.52.
(E)-**3g**: *m.p.* 98 °C. – IR: 1600, 1300, 1050. – ^{1}H NMR: 7.4 to 7.5 (m, 3H, 3'-H, 4'-H and 5'-H); 7.30 (dd, 2H, J = 6.4, 2'-H and 6'-H); 6.77 (q, 1H with allylic coupling, ^4J(H–CF_3) = 0.5, H vinyl); 2.69 (s, 3H, CH_3SO).

1-(Methylsulfinyl)-2-(phenyl)-2-(p-nitrophenyl)-ethylene (**3h**)

(Z)-**3h**: *m.p.* 128 °C. – IR: 1595, 1505, 1020. – ^{1}H NMR: 8.22 (dd, 2H, J = 8.8 and 2.2, 3'-H and 5'-H); 7.4 to 7.52 (m, 5H, aromatic); 7.22 (dd, 2H, J = 8.8 and 2.2, 2'-H and 6'-H); 6.93 (s, 1H, H vinyl); 2.77 (s, 3H, CH_3SO). – $C_{15}H_{13}NO_3S \cdot 0.2\,H_2O$ (287.33), Calcd.: C 61.87 H 4.46 N 4.81 S 10.99, Found: C 61.66 H 4.74 N 4.69 S 11.08.
(E)-**3h**: *m.p.* 105 °C. – IR: 1595, 1505, 1020. – ^{1}H NMR: 8.32 (dd, 2H, J = 8.8 and 2.3, 3'-H and 5'-H); 7.4 to 7.52 (m, 5H, aromatic); 7.28 (dd, 2H, J = 8.8 and 2.3, 2'-H and 6'-H); 6.97 (s, 1H, H vinyl); 2.78 (s, 3H, CH_3SO).

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