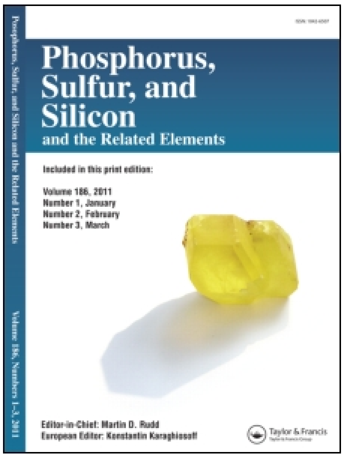

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SYNTHESIS OF DISTYRYL SULPHIDES, SULPHOXIDES AND SULPHONES BY HORNER-WITTIG REACTION IN TWO-PHASE SYSTEM

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SYNTHESIS OF DISTYRYL SULPHIDES, SULPHOXIDES AND SULPHONES BY HORNER-WITTIG REACTION IN TWO-PHASE SYSTEM[1]

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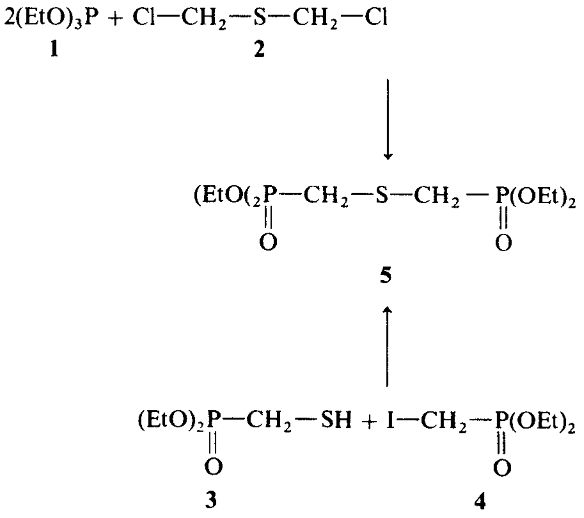
A convenient method is described for the formation of distyryl sulphides, sulphoxides and sulphones. Thus, Horner-Wittig reaction in two-phase system of the corresponding phosphonates with aromatic aldehydes affords the desired α, β unsaturated sulphur compounds. The geometry of compounds so formed was assigned with the aid of NMR spectroscopic methods.

INTRODUCTION

Recently, unsaturated sulphur compounds have found a wide application in organic synthesis.[2,3] To date, numerous examples have been provided which demonstrate the utility of these reagents in the synthesis of carbonyl systems,[2] olefines[4] as well as some natural products.[5,6] The best synthetic approach to unsaturated organosulphur compounds is based on the Horner–Wittig reaction of the corresponding phosphonates bearing sulphur containing substituents.[7–10] It is interesting to point out that in the course of our study directed in the area of the Horner–Wittig reaction we found the two-phase system very convenient for the synthesis of unsaturated sulphur compounds.[11,12] In an extension of this work we wish to report the preparation of bis-diethylphosphorylmethyl sulphide (**5**), sulphoxide (**6**) and sulphone (**7**) as well as their use in the synthesis of the corresponding distyryl sulphur derivatives. It should be noted, that there is no general method for the synthesis of these compounds. The previously described methods involve elimination of suitably substituted sulphides and sulphones,[13] addition of sulphur dichloride to acetylenes[14] and the Witting reaction of the corresponding phosnium salt.[15]

RESULTS

The phosphonate (**5**) was synthesized in 79% yield from triethyl phosphite (**1**) and bis-chloromethyl sulphide in thermal Arbuzov reaction and alternatively in 80% yield from diethylphosphorylmethane thiol (**3**)[10] and diethyliodomethyl phosphonate (**4**) in ethanol in the presence of sodium ethoxide.



$$\underset{\mathbf{1}}{2(EtO)_3P} + \underset{\mathbf{2}}{Cl{-}CH_2{-}S{-}CH_2{-}Cl}$$

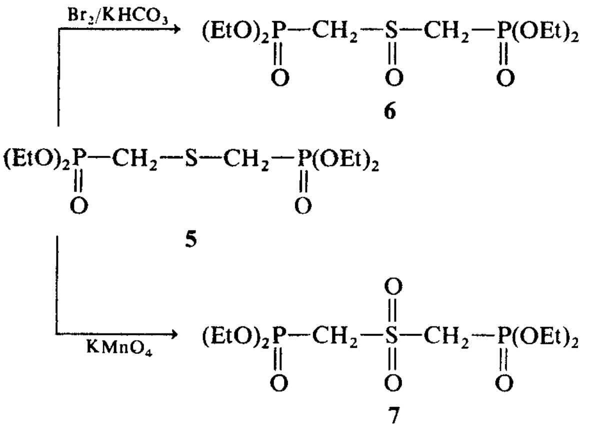
$$\downarrow$$

$$\underset{\mathbf{5}}{(EtO(_2\underset{O}{\underset{\|}{P}}{-}CH_2{-}S{-}CH_2{-}\underset{O}{\underset{\|}{P}}(OEt)_2}$$

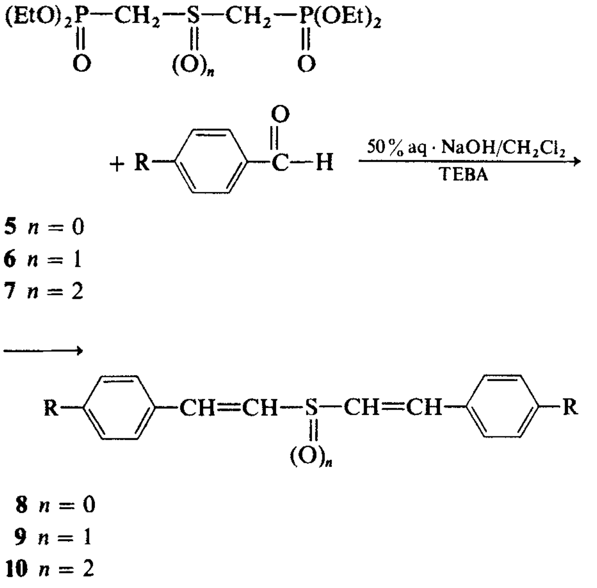
$$\uparrow$$

$$\underset{\mathbf{3}}{(EtO)_2\underset{O}{\underset{\|}{P}}{-}CH_2{-}SH} + \underset{\mathbf{4}}{I{-}CH_2{-}\underset{O}{\underset{\|}{P}}(OEt)_2}$$

The corresponding sulphoxide (**6**) and sulphone (**7**) have been prepared by oxidation of sulphide (**5**) by means of bromine in presence of aqueous potassium hydrogen carbonate[16] and potassium permanganate,[13] respectively.


$$(EtO)_2P(O)-CH_2-S-CH_2-P(O)(OEt)_2 \ (\mathbf{5}) \xrightarrow{Br_2/KHCO_3} (EtO)_2P(O)-CH_2-S(O)-CH_2-P(O)(OEt)_2 \ (\mathbf{6})$$
$$(EtO)_2P(O)-CH_2-S-CH_2-P(O)(OEt)_2 \ (\mathbf{5}) \xrightarrow{KMnO_4} (EtO)_2P(O)-CH_2-S(O)_2-CH_2-P(O)(OEt)_2 \ (\mathbf{7})$$

We found out that the Horner–Wittig reaction of phosphonates (**5**–**7**) with aromatic aldehydes carried out in aqueous two-phase system is particularly convenient for the synthesis of distyryl sulphides (**8**), sulphoxides (**9**) and sulphones (**10**).


$$(EtO)_2P(O)-CH_2-S(O)_n-CH_2-P(O)(OEt)_2 + R-C_6H_4-CHO \xrightarrow[\text{TEBA}]{50\%\,aq\cdot NaOH/CH_2Cl_2} R-C_6H_4-CH{=}CH-S(O)_n-CH{=}CH-C_6H_4-R$$

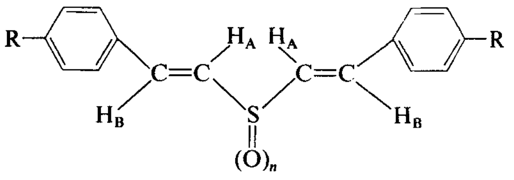
5 $n = 0$
6 $n = 1$
7 $n = 2$

8 $n = 0$
9 $n = 1$
10 $n = 2$

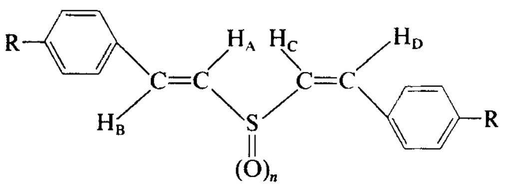
The results obtained are summarized in Table 1.

Crude products were purified by column chromatography on silica gel.

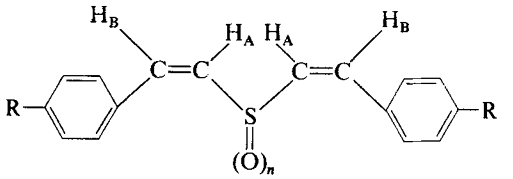
Sulphides (**8**), sulphoxides (**9**) and sulphones (**10**) obtained can exist as E-E, E-Z and Z-Z geometrical isomers as shown below.



E-E



E-Z

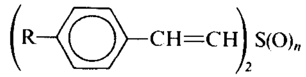


Z-Z

The isomeric compositions of (**8**–**10**) were determined from the ^1H NMR spectra and in the case of sulphides (**6**) from GLC, additionally. For assignment of E and Z configurations to the respective isomers of (**8**–**10**) the well established geometrical dependence of vicinal proton coupling constant as well as additive increments method were applied.[17–19] The letter method permitted also to assign the chemical shifts to H_A, H_B, H_C, and H_D protons in all unsaturated sulphur compounds (**8**–**10**). The ^1H NMR spectra of compounds (**8**–**10**) reveal AB systems for trans and cis vinyl protons with $^3J_{H,H}$ of ca. 15.6 Hz and 10.2 Hz, respectively. The observed and calculated vinyl proton resonance positions corresponding to proposed configurations are shown in Table 2. Although, in the case of sulphide (**8a**) there are substantial differences between the calculated and observed chemical shifts values, the configurational assignments seems to be justified by our previous experience.[18,19] It is interesting to note that the Horner–Wittig reaction was fully stereoselective only in the case of sulphone (**7**), affording the pure E-E isomers of (**10**). In the case of sulphide (**5**) and sulphoxide (**6**) the mixtures of geometrical

TABLE I

Preparation of distyryl sulphides (**8**) (n = 0), sulphoxides (**9**) (n = 1) and sulphones (**10**) (n = 2)



Product	R	Reaction conditions (temp./time)	Yield[a] (%)	M.p. (°C)	Isomer ratio (E-E/E-Z)	Molecular formula	Elemental analysis C Calcd. found	 H Calcd. found	 Cl, Br Calcd. found	 S Calcd. found
8a[15]	H	reflux/6h	74	96[c]	51:49	$C_{16}H_{14}S$ (238.4)	80.62 80.45	5.93 6.02	—	13.45 13.63
8b	Cl	reflux/5h	72	96–108	41:59	$C_{16}H_{12}SCl_2$ (307.2)	62.55 62.16	3.94 4.15	23.08 22.73	10.44 10.21
8c	OCH_3	reflux/16h	59	96–126	30:70	$C_{18}H_{18}O_2S$ (298.2)	72.49 72.34	6.04 6.28	—	10.75 10.82
9a	H	r.t./16h	60	66[b]	95:5	$C_{16}H_{14}OS$ (254.4)	75.55 75.16	5.55 5.67	—	12.61 12.66
9b	Cl	r.t./15h	62	188[b]	92:8	$C_{16}H_{12}O_2SCl_2$ (323.2)	59.45 59.47	3.74 4.03	21.93 21.89	9.92 9.74
9c	Br	r.t./15h	58	194[b]	87:13	$C_{16}H_{12}Br_2OS$ (412.2)	46.63 47.40	2.93 3.29	38.77 38.68	7.78 7.79
9d	OCH_3	r.t./8h	68	108[b]	97:3	$C_{18}H_{18}O_3S$ (314.4)	68.76 68.66	5.77 5.93	—	10.20 10.38
10a[15]	H	r.t./8h	79	156	100:0	$C_{16}H_{14}O_2S$ (270.2)	71.12 71.30	5.18 5.35	—	11.87 11.84
10b	Cl	r.t./3h	84	224	100:0	$C_{16}H_{12}O_2SCl$ (339.3)	56.64 56.37	3.57 3.52	20.90 21.21	9.45 9.44
10c	Br	r.t./5h	94	238	100:0	$C_{16}H_{12}Br_2O_2S$ (428.3)	44.88 44.57	2.83 3.02	37.33 37.04	7.48 7.73
10d	OCH_3	r.t./8h	64	163	100:0	$C_{18}H_{18}O_4S$ (330.4)	65.43 65.49	5.49 5.57	—	9.70 9.70

[a] Yield of analytically pure products.
[b] Melting point refers to the pure E-E isomer obtained after crystallization from ethanol.
[c] Melting point of the E-Z isomer.

TABLE II

Assignments of proton resonance position in AB system and structural assignments to geometrical isomers in sulphides (**8**), sulphoxides (**9**) and sulphones (**10**)

Product	Observed chemical shifts H_A	H_B	H_C	H_D	Calculated chemical shifts H_A	H_B	H_C	H_D
8a (E-E)	6.60	6.73	—	—	6.34	6.72	—	—
8a (E-Z)	6.60	6.73	6.39	6.51	6.34	6.72	6.29	6.50
8b (E-E)[a]	6.59	6.76	—	—	6.64	6.76	—	—
8b (E-Z)[a]	6.60	6.78	6.46	6.46	6.46	6.76	6.45	6.54
8c (E-E)[a]	6.58	6.70	—	—	6.51	6.68	—	—
8c (E-Z)[a]	6.58	6.70	—[b]	—[b]	6.51	6.68	6.30	6.46
9a (E-E)	6.89	7.27	—	—	6.88	7.30	—	—
9a (E-Z)	6.89	7.27	6.40	—[b]	6.88	7.30	6.45	7.04
9b (E-E)	6.87	7.27	—	—	6.92	7.33	—	—
9b (E-Z)	6.87	7.27	6.49	—[b]	6.92	7.33	6.51	7.07
9c (E-E)	6.90	7.27	—	—	6.92	7.33	—	—
9c (E-Z)	6.90	7.27	6.44	—[b]	6.92	7.33	6.51	7.07
9d (E-E)	6.68	7.18	—	—	6.79	7.25	—	—
9d (E-Z)	6.68	7.18	6.36	—[b]	6.79	7.25	6.36	6.99
10a (E-E)	6.94	7.61	—	—	7.16	7.79	—	—
10b (E-E)[a]	6.83	7.60	—	—	6.98	7.64	—	—
10c (E-E)[a]	6.83	7.57	—	—	6.98	7.64	—	—
10d (E-E)[a]	6.72	7.57	—	—	6.85	7.56	—	—

[a] Calculations based on the parent compounds method[21].

[b] Chemical shifts were not established.

E-E and E-Z isomers were formed. By fractional crystallisation from ethanol we were able to isolate isomerically pure samples of the E-E isomers of sulphoxides (**9**). We have also been successful in purifying of the E-Z isomer of sulphide (**8a**).

EXPERIMENTAL

^1H NMR spectra were recorded at 60 MHz with a R 12 B Perkin-Elmer spectrometer. ^{31}P and ^{13}C NMR spectra were obtained on a Jeol JNM-C-60H1 spectrometer with external H_3PO_4 and internal Me_4Si as the standards, respectively. Column chromatography was done on Merck silica gel 100 (70–230 mesh) using methylene chloride as the eluent.

PREPARATION OF BIS-DIETHYLPHORYLMETHYL SULPHIDE (5)

Method A

The mixture of triethyl phosphite (**1**) (13.28 g, 0.08 mol) and bis-chloromethyl sulphide (**2**) (4.44 g, 0.034 mol) was heated at 140–155° for 35 hours. Product was isolated by fractional distillation; yield: 8.98 g (79%);

Method B

To a solution of diethylphosphorylmethane thiol (**3**) 5.52 g, 0.03 mol) in ethanol (40 ml), a solution of sodium ethoxide (0.03 mol) in 40 ml of ethanol at 20° was added and after a short time a solution of diethyl iodomethanephosphonate (**4**) (8.34 g, 0.03 mol) in ethanol (20 ml) was dropped in. The reaction mixture was stirred for 3h and allowed to stand overnight. Ethanol was evaporated, the residue was dissolved in 20 ml of chloroform and washed by water, dried and evaporated to afford a crude sulphide (**5**). It was purified by distillation; yield: 8.02 g (80%); b.p. 172–176°/0.2 torr; $n_D^{23} = 1.4669$ (lit. $^{20}n_D^{20} = 1.4675$) ^{31}P *NMR* ($CHCl_3$): $\delta = 23.7$; ^1H *NMR* ($CDCl_3$): $\delta = 1.32$ (t, 12, OCH_2CH_3, $J_{HH} = 6.6$); 2.95 (d, 4, PCH_2, $J_{PH} = 12.0$); 4.12 (dq, 8, OCH_2CH_3, $J_{PH} = 6.6$); ^{13}C *NMR* ($CDCl_3$): $\delta = 14.68$ (d, OCH_2CH_3, $J_{PC} = 5.8$); 23.19 (d, PCH_2, $J_{PC} = 150.4$); 60.55 (d, OCH_2CH_3, $J_{PC} = 5.9$).

PREPARATION OF BIS-DIETHYLPHOSPHORYLMETHYL SULPHOXIDE (6)

The title compound was obtained by oxidation of sulphide (**5**) (10.02 g, 0.03 mol) by bromine/aqueous potassium hydrogen carbonate reagent in a two phase system, as described previously.[16] The crude product was purified by column chromatography (benzene: acetone 10:1); yield 8.61 g (82%); $n_D^{23} = 1.4696$.

$C_{16}H_{24}P_2SO_7$ (350.1) calcd: C, 34.31; H, 6.92; P, 17.69; S, 9.15; found: 34.28; 7.00; 17.45; 9.10; ^{31}P *NMR* ($CHCl_3$: $\delta = 17.5$; ^1H *NMR* ($CDCl_3$); $\delta = 1.30$ (t, 12, OCH_2CH_3, $J_{HH} = 6.6$); 3.58 (d, 4, PCH_2, $J_{PH} = 14.5$); 4.12 (dq, 8, OCH_2CH_3, $P_{PH} = 6.6$); ^{13}C *NMR* ($CDCl_3$): $\delta = 14.35$ (d, OCH_2CH_3, $J_{PC} = 5.9$); 47.37 (d, PCH_2, $J_{PC} = 142.6$); 69.30 (d, OCH_3, $J_{PC} = 3.9$).

PREPARATION OF BIS-DIETHYLPHOSPHORYLMETHYL SULPHONE (**7**)

Sulphone (**7**) was obtained by oxidation of sulphide (**5**) (10.02 g, 0.03 mol) by means of potassium permanganate in acetone solution at 0°. The crude product was purified by crystallization from benzene; yield 9.22 g (84%); m.p. 79° (lit.[20] m.p. 76–78°) ^{31}P *NMR* ($CHCl_3$): $\delta = 11.8$; ^{1}H *NMR* ($CDCl_3$): $\delta = 1.40$ (t, 12, OCH_2CH_3, $J_{HH} = 6.6$); 4.19 (d, 4, PCH_2, $J_{PH} = 16.2$); 4.32 (dq, 8, OCH_3, $J_{PH} = 6.6$); ^{13}C *NMR* ($CDCl_3$): $\delta = 14.55$ (d, OCH_2CH_3, $J_{PC} = 5.8$); 48.80 (d, PCH_2, $J_{PC} = 146.3$); 61.99 (d, OCH_2CH_3, $J_{PC} = 5.9$).

SULPHIDES (**8**), SULPHOXIDES (**9**) AND SULPHONES (**10**); GENERAL PROCEDURE

A solution of the phosphonate (**5**), (**6**) or (**7**) (0.01 mol) and aromatic aldehyde (0.02 mol) in 20 ml of dichloromethane was added to the heterogeneous mixture of 50% aqueous sodium hydroxide (30 ml) and dichloromethane (10 ml), containing 0.2 g triethylbenzylammonium chloride (TEBA). The reaction mixture was stirred vigorously for a few hours at room temperature or under reflux. The crude products were extracted from reaction mixtures with dichloromethane and purified by column chromatography.

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