

Synthesis of *N*-Phosphorylated Dimethylsulfoximides

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N-Phosphorylated-*S,S*-dimethylsulfoximides were prepared in good yields from the reaction between *N*-unsubstituted-*S,S*-dimethylsulfoximide and dialkyl (diaryl) phosphites, phosphorochloridates or phosphorochloridothionates. The same products could be obtained from trialkyl phosphites using *N*-bromo-*S,S*-dimethylsulfoximide and from the reaction between *N*-silylated dimethylsulfoximide and dialkyl phosphorochloridate. The new compounds obtained were characterized by their IR and ¹H NMR data.

The widespread interest in the chemistry of sulfoximides in recent years is evidently due to the versatility of their application in stereochemical studies^{1–4} and as reagent in organic synthesis.⁵ Also their biological activity is of interest⁶ and for some *N*-sulfonylated sulfoximides slight antimalarial effects have been found.⁷

N-Substituted sulfoximides have been synthesized by nucleophilic substitution of *N*-unsubstituted sulfoximides with alkyl halides, acid halides, acid anhydrides and sulfonyl halides.^{8,9} No reports on phosphorylated or thiophosphorylated sulfoximides are found in the literature, although such compounds seem interesting for stereochemical studies regarding both the S and the P atoms. Also the biological effect of this new structure may

be of interest.

This paper describes the syntheses of simple model compounds containing the >P(O)N=S(O)< and the >P(S)N=S(O)< groupings.

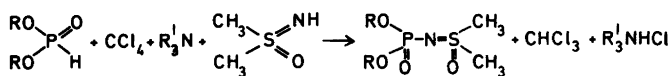
We have found that *N*-unsubstituted sulfoximide can be *N*-phosphorylated with satisfactory results by the modified Atherton-Todd procedure.^{10,11} This involves the application of dialkyl phosphite-tetrachloromethane system, in the presence of tertiary amine, as a source of dialkyl phosphorochloridate as the reactive phosphorylating agent, (method 1, Scheme 1).

This slightly exothermic reaction proceeds in CHCl₃ solution under mild conditions giving good yields and often analytically pure crude products.

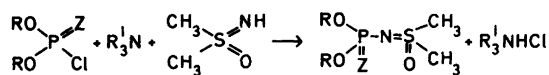
Nucleophilic substitution of preformed phosphorochloridates or phosphorochloridothionates with *S,S*-dimethylsulfoximide offers an alternative route to *N*-phosphorylated dimethylsulfoximides, (method 2, Scheme 2).

Methods 1 and 2 are versatile and can be used complementarily depending on the availability of the respective phosphites or phosphorochloridates.

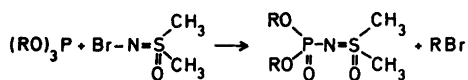
N-Phosphorylated sulfoximides are also accessible from trialkyl phosphites by reaction with *N*-bromo-*S,S*-dimethylsulfoximide in an Arbusov-type rearrangement, (method 3, Scheme 3).



Scheme 1. (Compound,R): 1,Me; 2,Et; 3,Pr; 4,Prⁱ; 5,Bu; 7,Bzl.



Scheme 2. (Compound,R,Z): 2,Et,O; 5,Bu,O; 6,(Me)₂C(CH₂)₂,O; 8,Ph,O; 9,Et,S; 10,Pr,S; 11,Bu,S.



Scheme 3. (Compound,R): 2,Et.

This reaction may be carried out without isolation of *N*-bromo-*S,S*-dimethylsulfoximide, which is prepared by direct bromination of dimethylsulfoximide.¹² Filtering off the sulfoximidium bromide from the bromination mixture gave a solution of *N*-bromo-*S,S*-dimethylsulfoximide, adequate for reaction with the trialkyl phosphite.

It is well known that *N*-silylation of amidic nitrogen enhances its reactivity towards electrophilic reagents. Thus presilylated dimethylsulfoximide¹³ can be readily converted into *N*-phosphorylated-*S,S*-dimethylsulfoximide by reaction with dialkyl phosphorochloridate in CH_2Cl_2 solution, (method 4, Scheme 4).

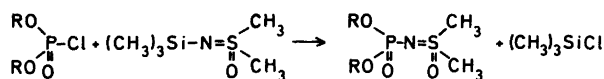
The prepared *N*-phosphorylated dimethylsulfoximides are stable oily pale yellow liquids which can be purified by high vacuum distillation; or colourless solids which can be recrystallized from butanone. All compounds gave satisfactory microanalytical data and their IR and ¹H NMR spectral data (given in the experimental part) were in accordance with the proposed structure.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer model 225 grating spectrograph, ¹H NMR spectra on a JEOL JNM-MH-60/II instrument. Elemental analyses were carried out by the Microanalysis Department of Chemical Laboratory II, University of Copenhagen, The H. C. Ørsted Institute. Melting points (uncorrected) were determined on a Büchi melting point apparatus. Refractive indexes were determined on Zeiss' Abbe refractometer.

Starting materials. Dialkyl phosphites, trialkyl phosphites, dialkyl phosphorochloridates and phosphorochloridothionates were prepared by conventional methods or were commercial reagents, distilled prior to use.

Dimethylsulfoximide was prepared by action of hydrazoic acid on dimethyl sulfoxide.¹³



Scheme 4. (Compound,R): 2,Et; 5,Bu.

N-(Trimethylsilyl)-*S,S*-dimethylsulfoximide.¹³ A solution of trimethylchlorosilan (0.1 mol) in dry benzene (15 ml) was added slowly into a refluxing solution of dimethylsulfoximide (0.1 mol) and triethylamine (0.1 mol) in dry benzene (100 ml). The reaction mixture was gently refluxed for a further 2 h, cooled and the precipitated triethylamine hydrochloride filtered off and washed with benzene. The filtrate was evaporated and the residue distilled *in vacuo* affording *N*-(trimethylsilyl)-*S,S*-dimethylsulfoximide as a colourless liquid. Yield 82%, b.p. 45–46 °C/0.15 mmHg, n_D^{23} 1.4632. The compound crystallized on refrigeration, m.p. 34 °C.

N-Bromo-*S,S*-dimethylsulfoximide¹² was prepared by bromination of dimethylsulfoximide in tetrahydrofuran solution. The solution was used for further experiments (see below).

Method 1. Reaction of dialkyl phosphites with tetrachloromethane and dimethylsulfoximide. Dialkyl phosphite (0.1 mol) was added dropwise into a stirred mixture of dimethylsulfoximide (0.1 mol), triethylamine (0.1 mol) and CCl_4 (20 ml) dissolved in chloroform (50 ml). The temperature rose slowly from 20 to 70 °C. The reaction mixture was stirred at room temperature for 4 h, and evaporated to dryness (40 °C bath). Benzene (25 ml), was added and evaporated again to remove the traces of CHCl_3 . Dry benzene (100 ml) was added to the residue and the precipitate of triethylamine hydrochloride was filtered off and washed with benzene (50 ml). From the combined filtrate and washings the solvent was evaporated. The crude *N*-(dialkoxyphosphinyl)-*S,S*-dimethylsulfoximides were oily, pale yellow liquids or colourless solids. They were purified by means of high vacuum distillation or recrystallization, respectively.

Method 2. Reaction of phosphorochloridates and phosphorochloridothionates with dimethylsulfoximide. A solution of dialkyl phosphorochloridate (or phosphorochloridothionate) (0.1 mol) in chloroform (15 ml) was added dropwise into a stirred solution of sulfoximide (0.1 mol) and triethylamine (0.1 mol) in chloroform (60 ml). A slightly exothermic reaction took place. After the addition the reaction mixture was refluxed (64 °C) for 15 min and then stirred for 2 h at room temperature. The reaction mixture was worked up analogous to method 1.

*Method 3. Reaction of trialkyl phosphites with N-bromo-*S,S*-dimethylsulfoximide.* A solution of bromine (0.1 mol) in dry benzene (50 ml) was added dropwise to a solution of *S,S*-dimethylsulfoximide

(0.2 mol) in a mixture of tetrahydrofuran (50 ml) and benzene (100 ml) at room temperature. No exothermic effect was observed. The bromine colour disappeared instantaneously, precipitate was formed, and the solution became yellow. The reaction mixture was stirred for 0.5 h at room temperature, and the yellowish precipitate of *S,S*-dimethylsulfoximidium bromide was filtered off and washed thoroughly with dry benzene. The combined filtrates were concentrated to the total volume of 50 ml (30 °C bath).

Triethyl phosphite (0.1 mol) diluted with benzene (15 ml) was added dropwise to this solution of *N*-bromo-*S,S*-dimethylsulfoximide. The temperature of the reaction was kept at 40 °C. After addition the reaction mixture was refluxed for 10 min and then stirred for 2 h at room temperature. Solvent was evaporated and the crude *N*-(diethoxyphosphinyl)-*S,S*-dimethylsulfoximide was distilled *in vacuo*.

Method 4. Reaction of dialkyl phosphorochloridates with *N*-(trimethylsilyl)-*S,S*-dimethylsulfoximide. A solution of dialkyl phosphorochloridate (0.1 mol) in dichloromethane (20 ml) was added dropwise at room temperature into a stirred solution of *N*-(trimethylsilyl)-*S,S*-dimethylsulfoximide (0.1 mol) in dichloromethane (70 ml). Slight exothermic effect was observed. The reaction mixture was then refluxed for 2 h, evaporated and the residue was distilled *in vacuo* affording *N*-(dialkoxyphosphinyl)-*S,S*-dimethylsulfoximide.

N-(Dimethoxyphosphinyl)-*S,S*-dimethylsulfoximide 1 was prepared by method 1 in 34% yield, b.p. 118 °C/0.005 mmHg, n_D^{22} 1.4805. Anal. $C_4H_{12}NO_4PS$: C, H, N, S. 1H NMR ($CDCl_3$): δ 3.33 (6 H, d, J_{HP} 1.2 Hz), 3.74 (6 H, d, J_{HP} 11.8 Hz). IR ($CHCl_3$, cm^{-1}): 3000 (s), 1250 (s), 1160 (s), 1030 (s), 820 (s).

N-(Diethoxyphosphinyl)-*S,S*-dimethylsulfoximide 2 was prepared by the methods 1, 2, 3, 4 in yields of 81%, 77%, 40% and 60%, respectively. B.p. 123 °C/0.001 mmHg, n_D^{20} 1.4670. Anal. $C_6H_{16}NO_4PS$: C, H, N, S. 1H NMR ($CDCl_3$): δ 1.33 (6 H, dt, J_{HH} 7.1 Hz and J_{HP} 0.9 Hz), 3.32 (6 H, d, J_{HP} 1.0 Hz), 4.11 (4 H, dq, J_{HH} 7.1 Hz and J_{HP} 7.1 Hz). IR ($CHCl_3$, cm^{-1}): 2980 (s), 1250 (s), 1160 (s), 1030 (s), 950 (s), 810 (s).

N-(Dipropoxyphosphinyl)-*S,S*-dimethylsulfoximide 3 was prepared by method 1 in 83% yield, b.p. 127 °C/0.005 mmHg, n_D^{22} 1.4632. Anal. $C_8H_{20}NO_4PS$: C, H, N, S. 1H NMR ($CDCl_3$): δ 0.78–1.13 (6 H, m), 1.38–2.05 (4 H, m), 3.30 (6 H, d, J_{HP} 1.0 Hz), 3.98 (4 H, q). IR ($CHCl_3$, cm^{-1}): 2960 (s), 1250 (s), 1160 (s), 1020 (s), 850 (s).

N-(Diisopropoxyphosphinyl)-*S,S*-dimethylsulfoximide 4 was prepared by method 1 in 79% yield, b.p. 115 °C/0.001 mmHg, m.p. 66–68 °C. Anal. $C_8H_{20}NO_4PS$: C, H, N, S. 1H NMR ($CDCl_3$): δ 1.30 (6 H, s), 1.40 (6 H, s), 3.30 (6 H, s), 4.32–4.94

(2 H, m). IR (CCl_4 , cm^{-1}): 2990 (s), 1250 (s), 1170 (s).

N-(Dibutoxyphosphinyl)-*S,S*-dimethylsulfoximide 5 was prepared by method 1 and 2 in 70% yield and by method 4 in 48%. B.p. 134 °C/0.015 mmHg. Anal. $C_{10}H_{24}NO_4PS$: C, H, N, S. 1H NMR ($CDCl_3$): δ 0.73–1.90 (14 H, m), 3.29 (6 H, d, J_{HP} 1.0 Hz), 3.83–4.23 (4 H, m). IR ($CHCl_3$, cm^{-1}): 2960 (s), 1250 (s), 1160 (s), 1010 (s), 805 (s).

N-(2-Oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-yl)-*S,S*-dimethylsulfoximide 6 was prepared by method 2 in 68% yield, m.p. 126 °C from butanone. Anal. $C_7H_{16}NO_4PS$: C, H, N, S. 1H NMR ($CDCl_3$): δ 0.90 (3 H, s), 1.22 (3 H, s), 3.30 (6 H, s), 3.89–4.12 (4 H, m). IR ($CHCl_3$, cm^{-1}): 2960 (m), 1270 (s), 1170 (s), 1060 (s).

N-(Dibenzyloxyphosphinyl)-*S,S*-dimethylsulfoximide 7 was prepared by method 1 in 69% yield, m.p. 89–90 °C from butanone. Anal. $C_{16}H_{20}NO_4PS$: C, H, N, S. 1H NMR ($CDCl_3$): δ 3.15 (6 H, s), 5.00 (2 H, d), 7.33 (10 H, s). IR ($CHCl_3$, cm^{-1}): 2970 (m), 1240 (s).

N-(Diphenoxyphosphinyl)-*S,S*-dimethylsulfoximide 8 was prepared by method 2 in 60% yield, m.p. 91–92 °C from butanone–hexane. Anal. $C_{14}H_{16}NO_4PS$: C, H, N, S. 1H NMR ($CDCl_3$): δ 3.16 (6 H, s), 7.31 (10 H, s). IR ($CHCl_3$, cm^{-1}): 1595 (m), 1500 (s), 1250 (s), 1160 (s).

N-(Diethoxyphosphinothioyl)-*S,S*-dimethylsulfoximide 9 was prepared by method 2 in 50% yield, b.p. 118–119 °C/0.001 mmHg, n_D^{22} 1.5168. Anal. $C_6H_{16}NO_3PS_2$: C, H, N, S. 1H NMR ($CDCl_3$): δ 1.18–1.55 (6 H, m), 2.55–3.20 (1 H, m), 3.35 (6 H, d, J_{HP} 1.0 Hz), 3.83–4.40 (3 H, m). IR ($CHCl_3$, cm^{-1}): 3000 (s), 1260 (s), 1160 (s), 1020 (s).

N-(Dipropoxyphosphinothioyl)-*S,S*-dimethylsulfoximide 10 was prepared by method 2 in 55% yield, b.p. 122 °C/0.005 mmHg, n_D^{22} 1.5060. Anal. $C_8H_{20}NO_3PS_2$: C, H, N, S. 1H NMR ($CDCl_3$): δ 0.74–1.14 (6 H, m), 1.36–1.97 (4 H, m), 2.48–3.05 (0.6 H, m), 3.32 (6 H, d, J_{HP} 1.0 Hz), 3.76–4.22 (3.4 H, m). IR ($CHCl_3$, cm^{-1}): 2980 (s), 1260 (s), 1160 (s), 990 (s).

N-(Dibutoxyphosphinothioyl)-*S,S*-dimethylsulfoximide 11 was prepared by method 2 in 54% yield, b.p. 132 °C/0.005 mmHg, n_D^{22} 1.4998. Anal. $C_{10}H_{24}NO_3PS_2$: C, H, N, S. 1H NMR ($CDCl_3$): δ 1.72–1.87 (14 H, m), 2.58–3.12 (1.1 H, m), 3.32 (6 H, d, J_{HP} 1.0 Hz), 3.78–4.24 (2.9 H, m). IR ($CHCl_3$, cm^{-1}): 2950 (s), 1260 (s), 1160 (s), 1010 (s).

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