S-Methyl diethylthiophosphinate in mono- and di(dechloromethylthioylation) of substituted benzylidene chlorides

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The main route of a new reaction of (dichloromethyl)arenes with *S*-methyl diethylthiophosphinate is the attack of the thiol sulfur atom (P—SMe) on the methylene carbon atom. A new method for synthesizing dimethyl dithioacetals of arenecarbaldehydes without using highly toxic methanethiol was developed. The suggested approach involves di(dechloromethylthioylation) of the dichloromethyl group of (dichloromethyl)arenes with *S*-methyl diethylthiophosphinate at a reagent ratio of 1 : 2.

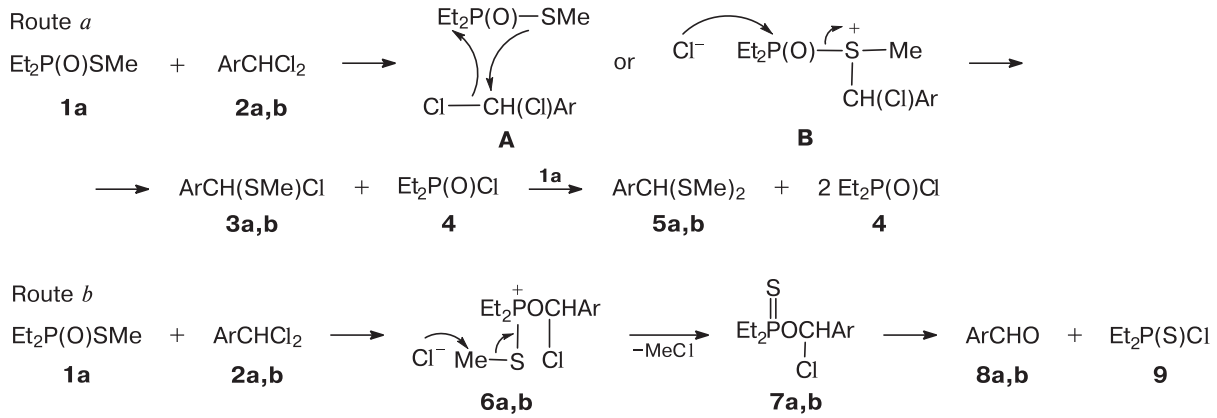
Key words: *S*-methyl diethylthiophosphinate, substituted benzylidene chlorides, mono- and di(dechloromethylthioylation), thiol sulfur atom, dimethyl dithioacetals of arenecarbaldehydes, methanethiol.

Earlier, the reactions of the ambident (P=O,P—O)-nucleophiles, namely, the full methyl esters of phosphorus(IV) acids, with (dichloromethyl)arenes to give aromatic aldehydes and the anhydrides of the corresponding P^{IV} acids have been described.[1,2] However, no data on the reactions of these *gem*-dichlorides with ambident (P=O,P—S)-nucleophiles, including *S*-methyl diethylthiophosphinate, were published.

The aim of the present work is the prediction and experimental confirmation of the main route of a new reaction of *S*-methyl diethylthiophosphinate (**1a**) with (dichloromethyl)arenes **2** and elaboration of the synthetic method towards dimethyl dithioacetals of arenecarbaldehydes avoiding the use of highly toxic gaseous methanethiol with strong unpleasant odor.

We found a new reaction taking place between *S*-methyl diethylthiophosphinate (**1a**) and (dichloromethyl)arenes **2a**,**b**. Theoretically, this reaction can proceed following two routes. We believe that dechloromethylthioylation to give compounds **3a**,**b** (Scheme 1, route *a*) can be accomplished by two following pathways: without charge separation as a concerted electron transfer involving four-membered transition state **A** and with charge separation *via* intermediate sulfonium cation **B**. Subsequent substitution of the chlorine atom of compounds **3a,b** with the methylthio group should result in dithioacetals **5a,b** and

Scheme 1



2, 3, 5—8: Ar = 4-$MeOC_6H_4$ (**a**), 3,5-Bu^t_2-4-HOC_6H_2 (**b**)

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diethylphosphinoyl chloride (**4**). An alternative route (Scheme 1, route *b*) is an attack of the phosphoryl oxygen atom on the methine carbon atom of *gem*-dichloride **2**. In this case, the initially formed quasi-phosphonium salt **6** losses methyl chloride to give the dechlorodiethylthiophosphinyloxylation product **7**. This compound, in analogy with its oxygen-containing counterpart ArCH(Cl)-$OP(O)Et_2$, should be unstable and decompose to arenecarbaldehyde **8** and diethylphosphinoyl chloride **9**.

In order to choose the most probable route of this reaction, we analyzed the electronic structure of *S*-alkyl esters of phosphorus(IV) acids $R^1R^2P(O)SR$ **1a—e**. Table 1 summarizes the vertical ionization potential (IP) of the highest occupied molecular orbitals of compounds **1a—e**.[3,4]

Table 1 indicates that the IP values of the n_S molecular orbitals of compounds **1a—e** are much lower (9.03—9.30 eV) than the IP values of the $p_{\pi,0}$ molecular orbitals (9.81—10.54 eV), consequently, the electron donating ability of the Me—S group is much higher than that of the P=O group. These data allowed us to conclude that the most probable pathway of this reaction is the route *a* (see Scheme 1).

Compound **1a** was selected for further studies since it contains, in contrast to compounds **1c**,**d**, only two electron donating centers, the S—Me and P=O groups. The reactions of (dichloromethyl)arenes **2a,b** and *S*-methyl diethylthiophosphinate (**1a**) were carried out at a ratio **1a** : **2** = = 1 : 1 at 80—100 °C. The experiments completely confirmed that this reaction proceeds by the route *a*. According to ^1H and ^{31}P NMR spectroscopy, the mixture obtained by the reaction of 4-methoxybenzylidene dichloride (**2a**) and ester **1a** under the above conditions contains mainly compounds **4** (δ_P 75.0) and **3a** (δ_H 6.04 (s, ClC<u>H</u>SMe), 2.32 (s, SMe)). These data are indicative of the initial attack of the thiol sulfur atom of compound **1a** on the methine carbon atom of *gem*-dichloride **2**.

Apparently, no attack of the phosphoryl oxygen atom of ester **1a** on the methine carbon atom of dichloride **2** occurs since the ^1H and ^{31}P NMR spectra of the reaction mixtures contain no signals at δ_H 10.0 (ArC<u>H</u>O, compound **8**) and δ_P 108.8 ($Et_2P(S)Cl$, compound **9**).

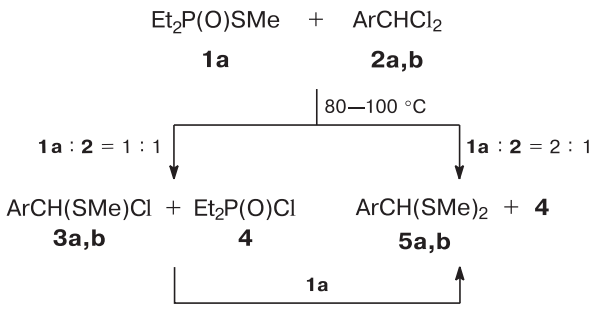
Table 1. Vertical ionization potentials of the n_S, $p_{\pi,0}$, and n_0 molecular orbitals of *S*-alkyl esters of phosphorus(IV) acids **1a—e**

Compound	n_S	$p_{\pi,0}$	n_0
		eV	
$MeSP(O)Et_2$ (**1a**)	9.17*	9.87*	—
$EtSP(O)Et_2$ (**1b**)	9.03	9.81	—
$MeSP(O)(OEt)_2$ (**1c**)	9.12	10.48	11.23
$EtSP(O)(OEt)_2$ (**1d**)	9.26	10.54	10.95
EtSP(O)(OMe)Me (**1e**)	9.30	10.12	10.70

* Calculated from additivity of IP of the n_S and $p_{\pi,0}$ orbitals of compounds **1b** and **1c**,**d**.

When the reaction between compounds **1a** and **2** was carried out at a molar ratio **1a** : **2** = 2.5 : 1 or the reaction mixture obtained at a molar ratio **1a** : **2** = 1 : 1 was treated with an additional 1 equiv. of phosphinate **1a** and then heated for 1.5—3 h, compounds **2** undergo di(dechloromethyl)thioylation to give dithioacetals **5a,b**. Compounds **5a**,**b** were isolated pure by vacuum distillation (Scheme 2).

Scheme 2

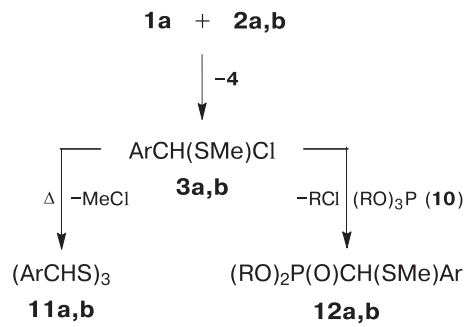


2, **3**, **5:** Ar = 4-$MeOC_6H_4$ (**a**), 3,5-Bu^t_2-4-HOC_6H_2 (**b**)

Conventionally, compound **5** is synthesized from methanethiol and its different mercaptides.[5—7] Only one example[8] of the synthesis of compound **5** by electroreduction of alkyl dithiocarboxylates is known. Note that alkyl dithiocarboxylates used in the synthesis were prepared[9] using toxic CS_2 and oranomagnesium compounds.

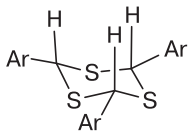
Intermediate α-chlorothioesters **3a**,**b** were not isolated pure; their structures were confirmed by several transformations: by the reactions with an additional 1 equiv. of compound **1a** (see Scheme 2) and trialkyl phosphites **10** (Scheme 3), and by thermal decomposition to arenethiocarbaldehydes, which are stable only in trimeric forms **11a**,**b** (see Scheme 3). The reactions of compounds **3a**,**b** with trialkyl phosphites **10** were performed as three component reactions between compounds **1a**, **2**, and **10**. This reactions result in new *P*,*S*-containing organic compounds **12a**,**b**.

Scheme 3



11: Ar = 4-$MeOC_6H_4$ (**a**), 3,5-Bu^t_2-4-HO-C_6H_2 (**b**)
12: Ar = 3,5-Bu^t_2-4-HO-C_6H_2, R = Me (**a**), Et (**b**)

α-, β-, and γ-Forms of trimers of arenethiocarbaldehydes were described earlier.[10] α- and β-Forms are different stereoisomers of individual trimers and γ-form is a eutectic mixture of α- and β-forms. Melting point of α-form is much lower than that of β-form. High melting points and ^{1}H NMR spectral data of the synthesized trimers **11a**,**b** (one singlet signal for three axial CH protons[10]) indicate that they exist in the β-form. According to Campaigne and co-workers,[10] the trithiane ring of β-form of arenethiocarbaldehyde trimers adopts the chair conformation with the axially positioned three methine hydrogen atoms and the equatorially positioned aryl groups. Thus, β-form of trimers of arenecarbaldehydes **11a**,**b** is (*e*,*e*,*e*)-*cis*,*cis*-2,4,6-triaryl-1,3,5-trithiane.



11a,b

In summary, in the present work we described a new reaction between *S*-methyl diethylthiophosphinate and (dichloromethyl)arenes. The analysis of the electronic structure of *S*-alkyl esters of phosphorus(IV) acids predicted and the experimental studies confirmed that this reaction proceeds as either mono- or di(dechloromethylthioylation) of the dichloromethyl group to give α-chlorothioester and dithioacetal of arenecarbaldehyde, respectively. The developed approach towards dimethyl dithioacetals of arenecarbaldehydes excludes the use of highly toxic gaseous methanethiol with an unpleasant odor.

Experimental

^{1}H NMR spectra were run on Tesla BS-567A and Bruker MSL-400 instruments (the working frequencies of 100 and 400 MHz). The ^{1}H NMR chemical shifts are given in the δ scale relative to the residual proton signals of the deuterated solvents (DMSO-d_6, acetone-d_6, $CDCl_3$). ^{31}P NMR spectra were recorded on a Bruker MSL-400 spectrometer (the working frequency of 162 MHz) using 85% H_3PO_4 as an external standard. IR spectra were recorded on a Perkin-Elmer Spectrum 65 FT-IR spectrometer within the range of 400—4000 cm^{-1}; the samples were prepared as the Nujol mulls. The reaction course was monitored by ^{1}H and ^{31}P NMR spectroscopy.

4-Methoxybenzaldehyde dimethyl dithioacetal (5a). ***A***. A mixture of 4-methoxybenzylidene dichloride (**2a**) (3.82 g, 20 mmol) and *S*-methyl diethylthiophosphinate (**1a**) (7.61 g, 50 mmol) was heated at 100 °C for 4 h. The reaction mixture was treated with diethyl ether (20 mL), washed with water (2×20 mL), and dried with anhydrous sodium sulfate. Removal of the solvent *in vacuo* and subsequent vacuum distillation of the residue afforded 2.10 g (49%) of compound **5a**, b.p. 169—170 °C (12 Torr) (*cf.* Ref. 8: b.p. 129—132 °C (0.2 Torr)). ^{1}H NMR ($CDCl_3$), δ: 2.03 (s, 6 H, SCH_3); 3.75 (s, 3 H, OCH_3); 4.70 (s, 1 H, CH); 6.76, 7.24 (both d, 2 H each, C_6H_4, $^3J_{H,H}$ = 8.6 Hz). Found (%): C, 55.88; H, 6.73; S, 29.47. $C_{10}H_{14}OS_2$. Calculated (%): C, 56.03; H, 6.58; S, 29.92.

B. A mixture of dichloride **2a** (3.82 g, 20 mmol) and *S*-methyl diethylthiophosphinate (**1a**) (3.04 g, 20 mmol) was heated at 100 °C for 4 h. ^{1}H NMR spectrum of the reaction mixture showed the resonances of compound **3a** at δ_H 6.04 (s, ClCH—S) and δ_H 2.32 (s, CHS<u>Me</u>). To the reaction mixture, compound **1a** (4.57 g, 30 mmol) was added and the mixture was heated at 100 °C for 3 h. The mixture was worked up as described in method ***A*** to afford 2.23 g (52%) of compound **5a**.

3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde dimethyl dithioacetal (5b) was synthesized as described for compound **5a** following method ***A*** from dichloride **2b** (1.00 g, 3.5 mmol) and thiophospinate **1a** (1.58 g, 10.5 mmol). Yield 0.53 g (43%), colorless crystals, m.p. 69—70 °C. ^{1}H NMR (acetone-d_6), δ: 1.59 (s, 18 H, $C(CH_3)_3$); 2.24 (s, 6 H, SCH_3); 4.89 (s, 1 H, CH); 5.56 (s, 1 H, OH); 7.32 (s, 2 H, C_6H_2). Found (%): C, 64.89; H, 9.15; S, 20.13. $C_{17}H_{28}OS_2$. Calculated (%): C, 65.33; H, 9.03; S, 20.52.

Dimethyl [(3,5-di-*tert*-butyl-4-hydroxyphenyl)(methylthio)-methyl]phosphonate (12a). A mixture of 3,5-di-*tert*-butyl-4-hydroxybenzylidene dichloride (**2b**) (1.45 g, 5 mmol) and *S*-methyl diethylthiophosphinate (**1a**) (1.14 g, 7.5 mmol) was heated at 80 °C for 1 h. The mixture was cooled to room temperature and treated dropwise with trimethyl phosphite **10a** (1.55 g, 12.5 mmol) under stirring. The warming up of the reaction mixture and evaluation of methyl chloride were observed. After 16 h, the reaction mixture was diluted with diethyl ether (10 mL) and washed with water (2×10 mL). The organic layer was separated, dried with anhydrous $NaSO_4$, and the drying agent was filtered off. The solvent was removed *in vacuo* and the residue was treated with anhydrous hexane (10 mL) to afford 0.86 g (46% for two steps) of compound **12a**, colorless crystals, m.p. 130—131 °C (heptane). ^{1}H NMR (acetone-d_6), δ: 1.49 (s, 18 H, $(CH_3)_3$); 2.16 (d, 3 H, SCH_3, $^4J_{P,H}$ = 1.0 Hz); 3.57, 3.80 (both d, 3 H each, OCH_2, $^3J_{P,H}$ = 10.5 Hz); 4.16 (d, 1 H, CH, $^2J_{P,H}$ = = 19.3 Hz); 6.19 (s, 1 H, OH); 7.40 (d, 2 H, C_6H_2, $^4J_{H,H}$ = 1.8 Hz). ^{31}P NMR (acetone-d_6), δ: 25.4. IR, ν/cm^{-1}: 622, 634, 752 (C—S—C); 1179 (P—O—C); 1224 (P=O); 3138 (br., OH). Found (%): C, 57.47; H, 8.63; P, 8.05, 8.19; S, 8.16, 8.31. $C_{18}H_{31}O_4PS$. Calculated (%): C, 57.73; H, 8.34; P, 8.27; S, 8.56.

Diethyl [(3,5-di-*tert*-butyl-4-hydoxyphenyl)(methylthio)-methyl]phosphonate (12b) was synthesized as described for compound **12a** from dichloride **2b** (1.45 g, 5.0 mmol), thiophosphinate **1a** (1.14 g, 7.5 mmol), and triethyl phosphite **10b** (2.08 g, 12.5 mmol). Yield 1.29 g (64%), colorless crystals, m.p. 101—104 °C. ^{1}H NMR (acetone-d_6), δ: 1.15, 1.31 (both t, 3 H each, CH_3, $^3J_{H,H}$ = 7.0 Hz); 1.50 (s, 18 H, $C(CH_3)_3$); 2.18 (d, 3 H, SCH_3, $^4J_{P,H}$ = 1.0 Hz); 3.88—4.36 (m, 5 H, CH and 2 OCH_2); 6.21 (s, 1 H, OH); 7.38 (d, 2 H, C_6H_2, $^4J_{H,H}$ = 1.8 Hz). ^{31}P NMR (acetone-d_6), δ: 23.1. Found (%): C, 59.37; H, 8.76; P, 7.46, 7.52; S, 7.85, 8.01. $C_{20}H_{35}O_4PS$. Calculated (%): C, 59.62; H, 8.69; P, 7.71; S, 7.96.

(*e*,*e*,*e*)-*cis*,*cis*-2,4,6-Tris(4-methoxyphenyl)-1,3,5-trithiane (11a). A mixture 4-methoxybenzylidene dichloride (**2a**) (3.82 g, 20 mmol) and *S*-methyl diethylthiophosphinate (**1a**) (3.04 g, 20 mmol) was heated at 100 °C for 2 h and at 140 °C for 4 h. The reaction mixture was treated with anhydrous CCl_4 (10 mL), the crystalline product was collected by filtration, and washed

successively with anhydrous CCl_4 (2×5 mL) and acetone to obtain 2.28 g (75%) of compound **11a**, m.p. 181—182 °C (ethyl acetate—acetic acid, 1 : 4) (*cf.* Ref. 11: m.p. 183 °C). ^{1}H NMR (DMSO-d_6), δ: 3.74 (s, 9 H, OCH_3); 5.70 (s, 1 H, CH); 6.96, 7.39 (both d, 6 H each, C_6H_4, $^3J_{H,H}$ = 8.5 Hz). Concentration of the filtrate *in vacuo* and subsequent vacuum distillation of the residue afforded 1.21 g (43%) of diethylphosphinoyl chloride, b.p. 99—101 °C (11 Torr) (*cf.* Ref. 7: b.p. 102—104 °C (15 Torr)). ^{31}P NMR (DMSO-d_6), δ: 75.0. Found (%): C, 62.94; H, 5.37; S, 20.86. $C_{24}H_{24}O_3S_3$. Calculated (%): C, 63.13; H, 5.30; S, 21.07.

(*e*,*e*,*e*)-*cis*,*cis*-2,4,6-Tris(3,5-di-*tert*-butylphenyl-4-hydroxy)-1,3,5-tritiane (11b) was synthesized as described for compound **11a** from dichloride **2b** (2.89 g, 10 mmol) and thiophosphinate **1a** (1.52 g, 10 mmol). Yield 1.30 g (52%), yellowish powder, m.p. 278—279 °C (decomp.). IR (Nujol), ν/cm^{-1}: 620, 700, 722 (S—C—S); 3641 (narrow, OH). Found (%): C, 71.59, 71.66; H, 9.12, 9.21; S, 12.99, 13.13. $C_{45}H_{66}O_3S_3$. Calculated (%): C, 71.95; H, 8.85; S, 12.80. Work up of the filtrate afforded 0.42 g (30%) of diethylphosphinoyl chloride (**4**), b.p. 98—100 °C (10 Torr) (*cf.* Ref. 11: b.p. 102—104 °C (15 Torr)). ^{31}P NMR (DMSO-d_6), δ: 75.0.

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