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A new approach to synthesis of the dimethyl dithioacetals of the arenecarbaldehydes

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ABSTRACT

A reaction of S-methyldiethylphosphinate with the (dichloromethyl)arenes was first studied to develop a new approach to the synthesis of the dimethyl dithioacetals of the arenecarbaldehydes without use of methyl mercaptan. The most probable route of this reaction was predicted proceeding from electron structure of S-alkyl esters of P(IV) acids: the values of the IP n_s are considerably lower (9.03-9.30 eV), than the values of the IP $p\pi$,o (9.81-10.54 eV). Therefore MeS group has higher electron donating properties than P=O group. Thiol sulfur (SMe) first attacks the methine carbon atom of the (dichloromethyl)arene. One or two chlorine atoms are substituted depending on the ratio of the initial reagents, 1:1 or 2:1, resulting in the formation of chlorothioether and dimethyl dithioacetal. Thus a new approach to the synthesis of the dimethyl dithioacetals of the arenecarbaldehydes based on mono- and di(dechloromethylthioylation) of the dichloromethylarenes with S-methyl diethyl phosphinate was developed.

KEYWORDS: S-methyl diethylthiophosphinate, dichloromethylarenes, thiol sulfur atom, mono- and di(dechloromethylthioylation), arenecarbaldehydes dimethyl dithioacetals, methyl mercaptan.

INTRODUCTION

Dithioacetals of aldehydes are broadly used in organic synthesis [1a, b]. Transformation of an aldehyde carbonyl into its dithioacetal function is known to provide it with stability in nucleophilic substitution, oxidation and reduction reactions (a dithioacetal protection). Dithioacetals can be convenient precursors for generating respective reagents in the presence of basic compounds such as butyllithium.

An initial approach to synthesis of dimethyl dithioacetals of arenecarbaldehydes $ArCH(SMe)_2$ **1** was to use a direct reaction of aromatic aldehydes ArCHO with methyl mercaptan MeSH **2** [2a-c]. As methanethiol is a highly toxic gaseous compound with an unpleasant odor, attempts were made to find substitutes for it. Dimethyl disulfide MeSSMe **3** [2d] was one of candidates for substitution. The reaction was performed in the presence of trimethylsilyl chloride Me_3SiCl **4** and involved formation of (methylthio)trimethylsilane $MeSSiMe_3$ **5** [2d] as an intermediate compound. As an affordable method was known for synthesis of the compound **5** [2e], it was used for synthesis of dithioacetals **1** [2f, g]. The reaction of methyl di(methylthio)aluminum $MeAl(SMe)_2$ **6** with benzaldehyde resulted in the formation of the mixture of products with dithioacetal $PhCH(SMe)_2$ **1a** among its main components [2h]. Tri(methylthio) borane $(MeS)_3B$ **7** and aryldi(methylthio)borane $ArB(SMe)_2B$ **8** can easily transform aromatic aldehydes into the compounds **1** [2i]. Synthesis of the compounds **4-8**, however, requires methanethiol or its mercaptides [2e, h-m]. Therefore, in the methods described above [2d-i], methanethiol is also used, but not directly. Among methods not

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involving methyl mercaptan **2**, electroreduction of S-methyl arenethiocarboxilates ArC(S)SMe **9** is worth mentioning [2n]. This reaction produces a mixture of substances containing acetals $PhCH(SMe)_2$ and $4\text{-}MeOC_6H_4CH(SMe)_2$ with the yield of 44 and 33% respectively. It should be noted that synthesis of thioesters **9** involves toxic carbon disulfide and Mg-organic compounds [2o, p].

Thus, the motivation for this research was the development of a "non-mercaptan" method for synthesis of dithioacetals **1**.

MATERIALS AND METHODS

Dichlroromethylarenes and O-methyl diethylthiophosphinate were prepared according to the literature description [3a-b, 3c]. A purification of the solvents was carried out according to [3d]. S-methyl diethylthiophosphinate was synthesized using the Pistchimuca reaction [4] by heating the mixture of O-methyl diethylthiophosphinate with methyl iodide at 50 °C.

^1H and ^{13}C NMR spectra were recorded on Tesla BS-567A (working frequencies of 100 MHz) and AVANCE 400 WB (working frequencies of 400.13 and 100.61 MHz) instruments in $CDCl_3$. The chemical shifts are shown in respect to $SiMe_4$ using the signals of residual protons and carbon nuclei of deuterated solvent. ^{31}P NMR spectra were run on AVANCE 400 WB and Bruker MSL-400 (working frequencies of 162.0 MHz) relative to 85% H_3PO_4 as an internal standard.

4-Methoxybenzenecarbaldehyde dimethyl dithioacetal (1a)

A. A mixture of 4-methoxybenzylidene chloride **2a** (3.82 g, 20 mmol) and of S-methyl diethylthiophosphinate **10a** (7.61 g, 50 mmol) was heated at 100 ºC for 4 h. The action mixture was treated with 20 ml of diethyl ether, washed with H_2O (2x20 ml), dried over Na_2SO_4. Solvent was evaporated under reduced pressure and residue was distilled *in vacuo* to obtain 2.10 g (49%) of compound **1a**, b. p. 169-170 ºC (12 mmHg) [34%, 129-132ºC (0.2 mmHg] [2n]. Found: C 55.80; H 6.73; S 29.47. $C_{10}H_{14}OS_2$. Requires: C 56.03; H 6.58; S 29.92. ^1H NMR (400 MHz, CCl_4 + $CDCl_3$) δ: 7.24, 6.76 (both d, 4H, C_6H_4, J = 8.6 Hz), 4.70 (s, 1H, CH), 3.75 (s, 3H, OMe), 2.03 (s, 6H, SMe).

B. A mixture of dichloride **2a** (3.82 g, 20 mmol) and thiophosphinate **10a** (3.04 g, 20 mmol) was heated at 100 ºC for 4 h. In ^1H NMR spectrum of reaction mixture, resonance signals were observed at δ: 6.04 (s, ClCHS), 2.32 (s, CHSMe), corresponding to the α-chlorothioether **12a**. Extra thiophosphinate **10a** (4.57 g, 30 mmol) was added and mixture was heated at 100 ºC for 3 h. By working up of the reaction mixture as in A, 2.23 g (52%) of the product **1a** was obtained.

4-Hydroxy-3,5-di-tert-butylbenzaldehyde dimethyl dithioacetal 1b

Similar to compound **1a**, 0.53 g (43%) of substance **1b** in the form of colorless crystals was obtained from dichloride **2b** (1.00 g, 3.5 mmol) and thiophosphinate **10a** (1.58 g (10.5 mmol), m. p. 69-70 ºC. Found: C 64.89; H 9.15; S 20.13. $C_{17}H_{28}OS_2$. Requires: C 65.33; H 9.03; S 20.52. ^1H NMR (400 MHz, CCl_4 + acetone-d_6) δ, ppm: 7.32 (s, 2H, C_6H_2), 5.56 (s, 1H, OH), 4.89 (s, 1H, CH), 2.24 (s, 6H, SMe), 1.59 (s, 18H, CMe_3).

(4-Hydroxy-3,5-di-tert-buthylphenyl)(methylthio) methanedimethoxyphosphonate 24a

A mixture of dichloride **2b (**1.45 g, 5 mmol) and S-methyl diethylthiophosphinate **10a** (1.14 g, 7.5 mmol) was heated at 80 ºC for 1 h. After spontaneously reaching room temperature trimethyl phosphite **23a** (1.55 g, 12.5 mmol) was added dropwise. Warming up and methyl chloride evolution were observed. The reaction mixture was allowed to stand overnight, dissolved in 10 ml of diethyl ether, washed with H_2O (2x10 ml) and dried over Na_2SO_4. Solvent was removed *in vacuo* and residue was worked up with hexane (10 ml) to obtain 0.86 g (46%) of compound **24a**, m. p. 130-131 ºC. Found: C 57.47; H 8.63; P 8.19; S 8.31. $C_{18}H_{31}O_4PS$. Requires: C 57.73; H 8.34; P 8.27; S 8.56. ^1H NMR (400 MHz, acetone-d_6) δ: 7.40 (d, 2H, C_6H_2, J = 1.8 Hz), 6.19 (s, 1H, OH), 4.16 (d, 1H, CH, J = 19.3 Hz), 3.80 and 3.57 (both d, 6H, OCH_2, J = 10.5 Hz), 2.16 (d, 3H, SMe, J = 1.0 Hz), 1.49 (s, 18H, CMe_3). ^{31}P NMR (162 MHz, CCl_4) δ: 25.4. IR (KBr) sm^{-1}: 3138 (OH), 1224 (P=O), 1179 (P-O-C), 752, 634, 622 (C-S-C).

(4-Hydroxy-3,5-di-tert-buthylphenyl) (methylthio)methanediethoxyphosphonate 24b

Similar to compound **24a**, 1.29 g (64%) of substance **24b** was obtained as a colorless powder from

dichloride **2b** (1.45 g, 5 mmol), thiophosphinate **10a (**1.14 g (7.5 mmol) and triethylphosphite **23b** (2.08 g, 12.5 mmol), m. p. 101-104ºC. Found: C 59.37; H 8.76; P 7.52; S 7.85. $C_{20}H_{35}O_4PS$. Requires: C 59.62; H 8.62; P 7.71; S 7.96. ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.38 (d, 2H, C_6H_2, J = 1.8 Hz), 6.21 (s, 1H, OH), 4.36-3.88 (m, 1H, CH; 4H, OCH_2), 2.18 (d, 3H, SMe, J = 1.0 Hz), 1.50 (s, 18H, CMe_3), 1.31 and 1.15 (both t, 6H, Me, J = 7.0 Hz). ^{31}P NMR (162 MHz, CCl_4) δ: 23.1.

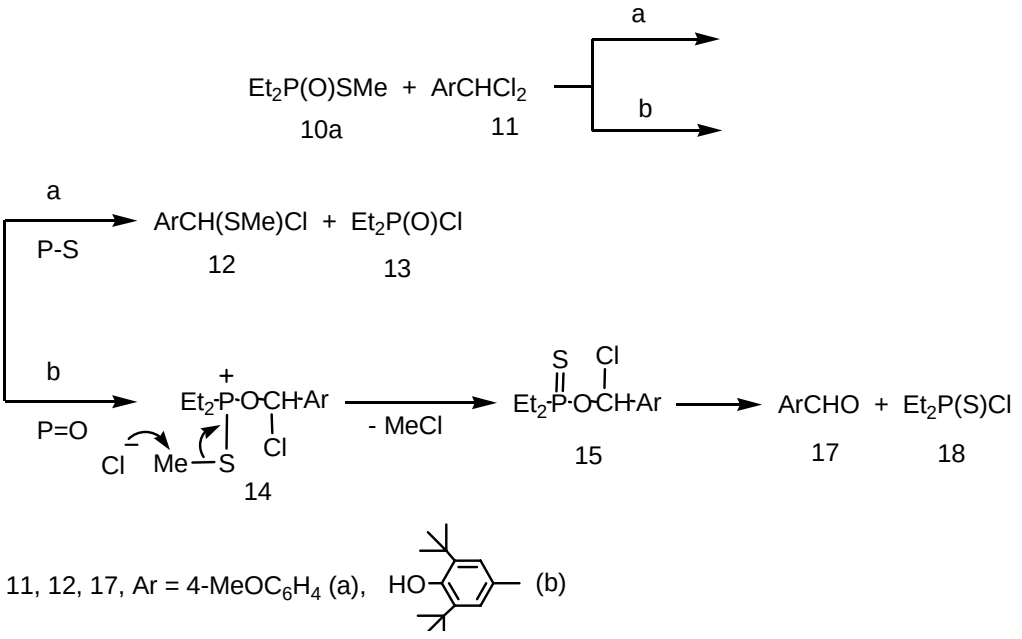
RESULTS AND DISCUSSION

To develop a new approach to synthesis of dithioacetals **1** without the use of methyl mercaptan **2**, we studied the reactions of S-methyl diethylthiophosphinate **10a** with (dichloromethyl) arenes **11**, which have not been described in scientific literature before. Theoretically, there can be two possible routes of this reaction (Scheme 1). The primary attack of the methine carbon atom of the compound **11** by the thiol sulfur atom (P-S) and substitution of one of chlorine atoms by the methylthio-group (dechloromethylthioylation) resulting in the formation of α-chlorothioether **12** and diethylphosphinoyl chloride **13** (route a). To predict the most probable reaction route, we paid attention at the electron structure of S-alkyl esters of P(IV) acids $R^1R^2P(O)SR$ **10**. Table 1 below represents ionization potentials (IP) of upper two or three molecular orbitals of these compounds [5].

This table demonstrates that for all type of compounds **10**, the values of the IPn_S are considerably lower (9.03-9.30 eV), than the values of the $IPp_{\pi,o}$ (9.81-10.54 eV). We can predict from these values that the most probable route of the reaction (Scheme 1) is the route a. It should be noted that we selected the compound **10a** for this study because it contains only two electron donating centers (SMe and P=O) as opposed to compounds **10c-e**.

Being the group with the strongest electron donating properties, thiol sulfur (MeS) attacks first the methine carbon atom of the compound **11**. One of chlorine atoms is substituted by a methylthio-group (dechloromethylthioylation) (Scheme 1, route a) resulting in the formation of α-chlorothioether **12** and diethylphosphinoyl chloride **13**.

An alternative process is the attack of the methine carbon atom of the compound **11** by phosphoryl oxygen (route b). The initially formed quazi-phosphonium salt **14** turns into the product of dechlorodiethylthiophosphinyloxylation **15** after removal of methyl chloride. Compound **15**, as well as its oxygen analogue $ArCH(Cl)OP(O)Et_2$



Scheme 1. Routes a and b of the reaction between compounds **10a** and **11**.

Table 1. Vertical ionization potentials n_S, $p_{\pi,o}$ and n_o of orbitals of some S-alkyl esters of P(IV) acids.

№	Compound	IPn_S, eV	$IPp_{\pi,o}$, eV	IPn_o, eV
10a	$MeSP(O)Et_2$	9.17*	9.87*	—
10b	$EtSP(O)Et_2$	9.03	9.81	—
10c	$MeSP(O)(OEt)_2$	9.12	10.48	11.23
10d	$EtSP(O)(OEt)_2$	9.26	10.54	10.95
10e	EtSP(O)(OMe)Me	9.30	10.12	10.70

*additive values obtained from IPn_S- and $p_{\pi,o}$- orbitals of compounds **10b** and **10c-d**.

16 [6] are likely unstable compounds decomposing to arenecarbaldehyde **17** and diethylphosphinethioyl chloride **18**. According to Table 1, however, the $IPp_{\pi,o}$ (9.81 eV) is considerably higher than the IPn_S (9.03 eV). Therefore, P=O has lower electron donating properties than MeS, resulting in low probability of the route b. It is worth mentioning that nucleophilic attack of the dibromomethyl group in 1,4-bis(dibromomethyl)benzene 4-$Br_2CHC_6H_4CHBr_2$ **19** by the phosphoryl oxygen P=O is realized if the former interacts with trimethyl phosphate $(MeO)_3$ P=O **20** with the $IP_{P\pi,o}$ = 10.81 and the IPn_o = 11.40 eV [5b, c]. Even if the compound **20** is introduced in excessive amounts, the reaction is finished with the formation of aldehyde 4-$Br_2CHC_6H_4CHO$ **21**, while the compound 4-$Br_2CHC_6H_4CH(OMe)_2$ **22** is not detected in the reaction mixture [7a, b], thus, debromomethoxylation does not occur.

Substitution of the chlorine atom in the compound **12** by a methylthio- group or di-, (dechloromethylthioylation) of the compound **10a** is supposed to lead us to the target product **1**. Thus, the new approach to synthesis of dimethyl dithioacetals of arenecarbaldehydes is the selection of the new methylthio-group source, that is the compound **10a**, instead of methyl mercaptan and its derivatives **4-8** [2d-i], and introduction of this compound into the reaction with (dichloromethyl) arenes **11**.

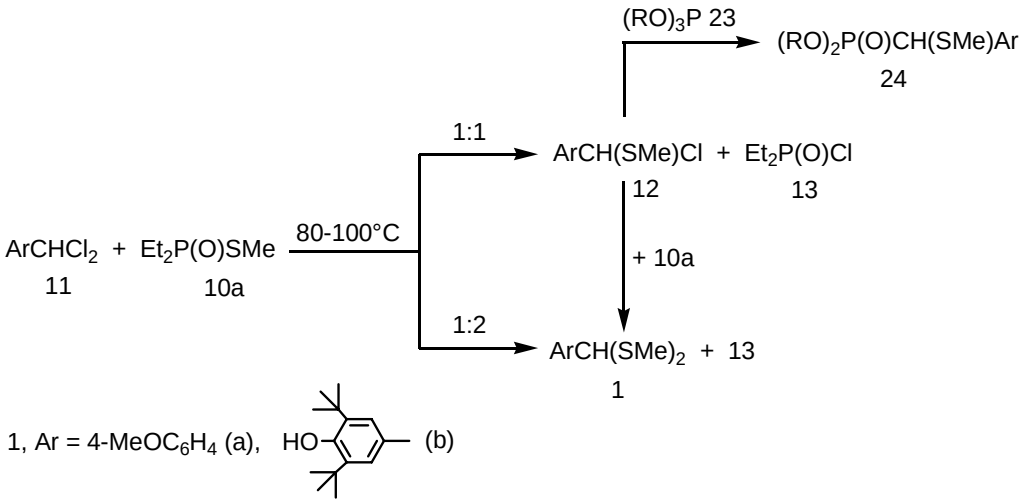
The experiments we performed have completely confirmed the prediction about possible realization of the reaction route a. The reaction of (dichloromethyl) arenes **11** with S-methyl diethylthiophosphinate **10a** at the 1:1 ratio was carried out at 80-100 °C. According to the NMR ^1H and ^{31}P spectra data, the resulting reaction mixture after interaction of 4-methoxybenzylidene chloride **11a** with the ester **10a** contained mostly the compounds **13** (δ_P 75.0 ppm) and **12a** (δ_H, ppm: 6.04 s ClC<u>H</u>SMe, 2.32 s SMe). It indicates a primary attack of the methine carbon atom in *gem*-dichloride **11a** by the thiol sulfur atom.

Obviously, the attack of the methine carbon atom in dichloride **11** by phosphoryl oxygen does not occur, as the NMR ^1H and ^{31}P spectra of the reaction mixture do not contain resonance signals at δ_H 10.0 ppm (Ar<u>CH</u>O **17**) and δ_P 108.8 ppm ($Et_2P(S)Cl$ **18**).

The reaction between the compounds **10a** and **11** at the ratio of 1:2.5 or addition of another phosphinate **10a** equivalent to the reaction mixture with the 1:1 initial ratio of components and further heating for 1.5-3 hours will result in the formation of dithioacetals **1**, which have been separated from the reaction mixture as individual substances (Scheme 2).

Thus, we have confirmed the feasibility of this new approach to synthesis of the dimethyl dithioacetals of the arenecarbaldehydes without use of methyl mercaptan.

α-Chlorothioethers **12** were not separated as individual substances. Their structure, however, was confirmed by several transformations: their introduction into reaction with another equivalent of the compound **10a** (Scheme 2) and trialkyl phosphites (Scheme 2). In the reaction with phosphites **23**, new P- and S-containing organic compounds **24** were synthesized.



Scheme 2. Experimental confirmation of realization of a new approach to synthesis of dimethyl dithioacetals **1**.

CONCLUSION

To summarize, a new approach to synthesis of the dimethyl dithioacetals of the arenecarbaldehydes was developed. The synthesis process does not involve methyl mercaptan and is based on mono- and di(dechloromethylthioylation) of the (dichloromethyl)arenes with S-methyl diethyl thiophosphinate.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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