Chloropropiolaldehyde dimethyl acetal: preparative scalable synthesis and unusual three-component reaction with trimethyl phosphite and chloroform*

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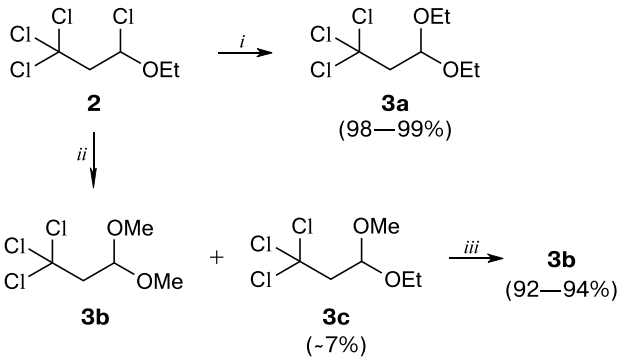
Haloacetylenes have been known for a long time, but in the last three decades, the chemistry of these compounds has developed intensively. Nowadays, they became multipurpose versatile reagents in organic synthesis.[1] The poorly studied chloropropiolaldehyde acetals[2—4] are stable haloacetylenes containing a masked aldehyde group at the C≡C bond. This opens up wide possibilities for their further functionalization (chloropropynal itself is extremely unstable and can only be stored in dilute solutions at low temperatures[4]).

Chloropropiolaldehyde diethyl acetal (**1a**) was first synthesized in 1955 by a four-step procedure[2] from available 1,1,1,3-tetrachloro-3-ethoxypropane (**2**), which in turn was obtained in high yield by the radical addition of CCl_4 to available ethyl vinyl ether.[5] The main disadvantage of this method is the strong contamination of the target product **1a** with 3,3-dichloroacrolein diethyl acetal, the fraction of which may exceed 35% and which is very difficult to separate from **1a** by rectification. An alternative approach to compound **1a** is the low-temperature chlorination of the lithiated propynal diethyl acetal[3]. However we found that method to be poorly reproducible and explosive, especially when scaling up. Chloropropiolaldehyde dimethyl acetal **1b** has not been described so far.

The aim of this work was to develop a simple and easily scalable procedure to obtain chloropropiolaldehyde diethyl and dimethyl acetals **1a,b**.

For this, we paid attention to patent data[6] where chloride **2** reacted exothermically with ethanol to afford 3,3,3-trichloropropionaldehyde diethyl acetal **3a**. By simplifying this procedure, we could synthesize acetal **3a** in almost quantitative yield, and according to ^{1}H and ^{13}C NMR data, the product was pure even without its final distillation *in vacuo* (Scheme 1). It was also found that compound **2** reacted with excess methanol exothermically already at 20 °C. The evolved HCl caused transacetalization of the initially formed mixed methyl ethyl acetal **3c** to yield 3,3,3,3-trichloropropionaldehyde dimethyl acetal **3b**, which contained ~7% of mixed acetal **3c** (^{1}H NMR). Repeated treatment of the mixture with methanolic HCl (to prepare such a solution rapidly, it was convenient to add a calculated amount of acetyl chloride to cold methanol) completed the transacetalization and provided product **3b** in 92—94% yield.

Scheme 1



Reagents and conditions: *i*. EtOH. 20 °C, 6 h; *ii*. MeOH. 20 °C, 4 h; *iii*. MeOH, HCl, 20 °C, 6 h.

A series of bases were tested in the conversion of trichlorides **3a,b** to the corresponding chloropropiolaldehyde acetals **1a,b**. A two-phase system containing 40% aqueous NaOH—CH_2Cl_2 in the presence of benzyltriethylammonium chloride as a phase transfer catalyst was found to be optimal. Our pro-

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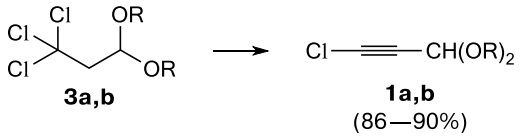
cedure is very preparatively simple, requires relatively small amounts of benzyltriethylammonium chloride, allows the complete removal of the 3,3-dichloroacrolein acetal admixtures, and provides pure target products **1a,b** in high yields (Scheme 2).

Scheme 2

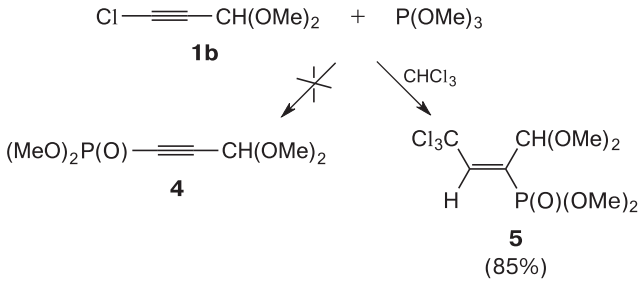


R = Et (**a**), Me (**b**)

Reagents and conditions: 40% NaOH—CH_2Cl_2, Et_3NBnCl, 36 °C, 5 h.

The reaction of haloacetylenes with trialkyl phosphites (the Arbuzov—Michaelis reaction) usually proceeds as a substitution of the halogen atom at the C≡C bond by a phosphoryl moiety and is one of the synthetic approaches to phosphoryl acetylenes.[7,8] Chloro acetals **1a,b** were also expected to react with trimethyl phosphite in a similar way to afford the corresponding phosphorylpropiolaldehyde acetals. Studying the reaction of acetal **1b** with trimethylphosphite in boiling chloroform, we observed the release of gaseous CH_3Cl and expected to isolate (dimethoxyphosphoryl)propiolaldehyde dimethyl acetal **4**. Instead, a new unusual transformation was found affording dimethyl (*E*)-(4,4,4-trichloro-1,1-dimethoxybut-2-en-2-yl)phosphonate (**5**) as a single stereoisomer (Scheme 3).

Scheme 3

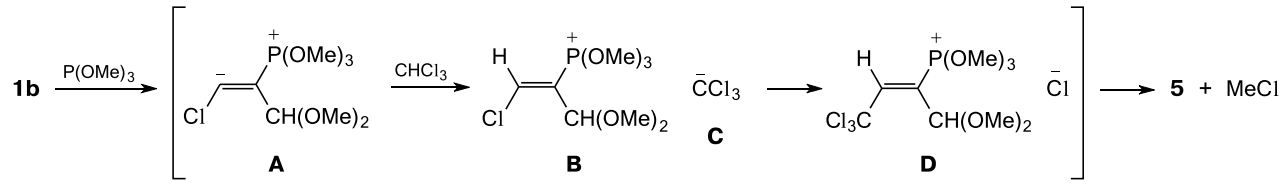


The product obtained in two parallel runs had a significantly higher boiling point than that expected for compound **4**. Also, its yield in each of the experiments was significantly higher than the quantitative yield based on compound **4**, indicating a different reaction route. To determine the structure of the novel compound **5**, the following spectral parameters proved to be important: the IR spectrum of **5** lacks the C≡C absorption band in the region 2100—2300 cm^{-1}, but absorption bands at 1629 cm^{-1} (C=C) and 1256 cm^{-1} (P=O) are present. ^{13}C NMR spectrum contains no signals for the C≡C bond, however, it shows the signals for the C=C bond at δ 147.0 and 129.8, where the latter signal has a large coupling constant $^1J_{C,P}$ = 181.0 Hz. The ^1H NMR spectrum features the signal for the proton at the C=C bond at δ 7.14 and $^3J_{H,P}$ = 42.80 Hz. Moreover, the ^{13}C NMR spectrum shows the "acetal" signal of $\underline{C}H(OMe)_2$ near δ 101.0 with $^2J_{C,P}$ = 15.6 Hz, and also a characteristic CCl_3 signal at δ 90.5 with $^3J_{C,P}$ = 8.2 Hz. Comparing the values of these two $J_{C,P}$ with those described in the literature (*cf.* Refs 9, 10) suggests that the acetal and phosphoryl groups are bonded to the same carbon atom of the C=C bond, while the CCl_3 substituent and hydrogen atom are bonded to another one. The value of $^3J_{C,P}$ = 8.2 Hz for the CCl_3 signal unambiguously indicates *trans* configuration of this group relative to the phosphoryl moiety (see Refs 11, 12); in the case of *cis* configuration of vicinal phosphoryl and carbon substituents, the value of $J_{C,P}$ never exceeds 4.0 Hz, whereas in the case of *trans* configuration, the coupling constant always exceeds 6.5 Hz). In the proton-coupled ^{13}C NMR spectrum, the signal for the C=C carbon atom at δ 147.0 changes from a singlet to a doublet with $J_{C,H}$ = 170.0 Hz, while the signal for the second carbon atom of the C=C–P-moiety near δ 129.8 remains unchanged. This also provides convincing evidence that the hydrogen atom and the phosphoryl group are located on different carbon atoms of the C=C bond. In addition, the proton-coupled ^{13}C NMR spectrum makes the signals for the $\underline{C}H(OMe)_2$ and CCl_3 moieties easily distinguishable. The composition of compound **5** was also confirmed by elemental analysis data.

We have proposed a cascade mechanism for this unusual three-component reaction to explain the formation of phosphonate **5** in the absence of bases or radical species in the reaction mixture (Scheme 4).

In the first step, trimethyl phosphite adds *via* the phosphorus lone pair to the C≡C bond of alkyne **1b** to give ylide **A**, the anionic center in which is effectively stabilized by a chlorine atom and a *cis*-positioned positively charged phosphonium group. The highly basic anionic center of ylide **A** promotes the

Scheme 4



deprotonation of chloroform, generating an alkenylphosphonium cation **B** and a trichloromethyl anion **C**. Cation **B** is a potent Michael acceptor, in which the C=C bond is activated by a highly electrophilic phosphonium group, which facilitates substitution of the chlorine atom by anion **C** and the formation of cation **D** and the chloride ion. The final step is actually the Arbuzov rearrangement, where the chloride ion nucleophilically attacks one of the three methyl groups of the cation **D** to afford the target product **5** and the release of CH_3Cl.

At present, we cannot identify the exact reasons for the abnormal reaction between acetal **1b**, trimethyl phosphite, and chloroform. However, there is already independent evidence of the existence of an **A**-type intermediate, which will be published soon as a follow-up of this work. We believe that functionalization of species **A** with C—H acids and various electrophiles is a new area and opens wide possibilities for stereoselective synthesis of polysubstituted alkenes.

To summarize, we have developed a simple and easily scalable synthesis of chloropropiolaldehyde diethyl and dimethyl acetals **1a,b** and discovered an unusual three-component reaction involving **1b**, trimethyl phosphite, and chloroform.

^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer (400 MHz and 100 MHz, respectively) in $CDCl_3$. IR spectra were obtained on a Bruker IFS 25 spectrometer for samples prepared in a thin film. Elemental analysis was performed in the Laboratory of Microanalysis of INEOS RAS.

3,3,3-Trichloropropionaldehyde diethyl acetal (3a). To stirred anhydrous EtOH (92.00 g, 2.0 mol), 3-ethoxy-1,1,1,3-tetrachloropropane (**2**) (45.20 g, 0.2 mol) was added, and on completion of the exothermic reaction, the resulting mixture was kept for 6 h at 20 °C. Excess EtOH was distilled off *in vacuo* on a water-jet pump, the residue was stirred for another 10 min at a pressure of 1 Torr and temperature of 20 °C to obtain product **3a** (46.63 g, 99%), which may be used without further purification. Distillation of the product gave compound **3a** (45.22 g, 96%) as a colorless liquid, b.p. 79—80 °C (7 Torr, Ref. 6: 83—84 °C (10 Torr)). ^1H NMR ($CDCl_3$), δ: 1.25 (t, 6 H, 2 $C\underline{H}_3CH_2$, J = 7.4 Hz); 3.06 (d, 2 H, CH_2—CCl_3, J = 5.3 Hz); 3.58—3.62 (m, 2 H, 2 CH—O); 3.69—3.73 (m, 2 H, 2 CH—O); 4.91 (t, 1 H, $CH(OEt)_2$, J = 4.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 15.1 (2 CH_3); 58.1 ($\underline{C}H_2$—CCl_3); 62.1 (2 CH_2O); 96.0 (CCl_3); 100.0 ($\underline{C}H(OEt)_2$).

3,3,3-Trichloropropionaldehyde dimethyl acetal (3b). To stirred anhydrous MeOH (64.00 g, 2.0 mol), tetrachloride **2** (45.20 g, 0.2 mol) was added and on completion of the exothermic reaction the resulting mixture was kept for 6 h at 20 °C. Excess MeOH was distilled off *in vacuo* on a water-jet pump. A solution of HCl (3.65 g, 0.1 mol) in MeOH (48.00 g, 1.5 mol) was added, and the resulting solution was kept for another 6 h at 20 °C. Excess MeOH was distilled off *in vacuo*, the residue was distilled to obtain product **3b** (38.60 g, 93%) as a colorless liquid, b.p. 36—37 °C (1 Torr). ^1H NMR ($CDCl_3$), δ: 3.04 (d, 2 H, CH_2—CCl_3, J = 4.4 Hz); 3.41 (s, 6 H, 2 CH_3O); 4.80 (t, 1 H, $CH(OMe)_2$, J = 4.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 53.4 (2 CH_3O); 57.3 ($\underline{C}H_2CCl_3$); 95.9 (CCl_3), 101.8 ($\underline{C}H(OMe)_2$). Found (%): C, 29.11; H, 4.50; Cl, 51.19. $C_5H_9Cl_3O_2$. Calculated (%): C, 28.92; H, 4.34; Cl, 51.33.

Synthesis of acetals 1a,b (general procedure). To a solution of acetal **3a** (35.33 g, 0.15 mol) or acetal **3b** (31.13 g, 0.15 mol) and Et_3NBnCl (11.37 g, 0.05 mol) in CH_2Cl_2 (90 mL), 40% aqueous NaOH (130 mL) was added, and the resulting mixture was vigorously stirred on a magnetic stirrer for 5 h at 35—36 °C. The mixture was cooled, cold water (50 mL) was added, the upper organic phase was separated, the water phase was extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with cold water (3×50 mL) and dried over K_2CO_3 (when two organic phases are combined, Et_3NBnCl precipitates, it should not be filtered off). A mixture of Et_2O and CH_2Cl_2 was distilled from the flask equipped with a Vigreux column at atmospheric pressure until the temperature of the bottoms reached 70—75 °C; the residue was distilled *in vacuo* to obtain 3,3,3-trichloropropiolaldehyde diethyl acetal (**1a**) or 3,3,3-trichloropropiolaldehyde dimethyl acetal (**1b**).

Chloropropiolaldehyde diethyl acetal (1a). Colorless liquid, yield 21.94 g (90%), b.p. 51—52 °C (10 Torr;

cf. Ref. 2, 3: 49—51 °C (10 Torr)), the spectral data of the product are identical to those described in Ref. 3.

Chloropropiolaldehyde dimethyl acetal (1b). Colorless liquid, yield 17.35 g (86%), b.p. 35—36 °C (10 Torr). ^{1}H NMR ($CDCl_3$), δ: 3.36 (s, 6 H, 2 CH_3O); 5.14 (s, 1 H, $CH(OMe)_2$). ^{13}C NMR ($CDCl_3$), δ: 52.4 (2 CH_3O); 64.3 (C≡C); 64.9 (C≡C); 93.0 ($\underline{C}H(OMe)_2$). IR (thin film), ν/cm^{-1}: 2230 (C≡C). Found (%): C, 44.73; H, 5.38; Cl, 26.12. $C_5H_7ClO_2$. Calculated (%): C, 44.61; H, 5.20; Cl, 26.39.

Dimethyl (*E*)-(4,4,4-trichloro-1,1-dimethoxybut-2-en-2-yl)phosphonate (5). To a stirred solution of acetal **3b** (4.04 g, 0.03 mol) in $CHCl_3$ (12 mL), $P(OMe)_3$ (3.72 g, 0.03 mol) was added dropwise. The resulting solution was refluxed until the gas evolution stopped (~2 h). The solvent was distilled off *in vacuo*, the residue was distilled to obtain product **5** (8.35 g, 85%) as a colorless liquid, b.p. 118—119 °C (0.5 Torr). ^{1}H NMR ($CDCl_3$), δ: 3.31 (s, 6 H, $(\underline{C}H_3O)_2CH$); 3.74 (d, 6 H, $(CH_3O)_2P{=}O$, $J_{H,P}$ = 11.4 Hz); 5.03 (d, 1 H, $C\underline{H}(OMe)_2$, $J_{H,P}$ = 4.3 Hz); 7.14 (d, 1 H, H—C=C, $J_{H,P}$ = 42.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 53.0 (d, $(CH_3O)_2P{=}O$, $J_{C,P}$ = 6.1 Hz); 53.9 ($(\underline{C}H_3O)_2CH$); 90.5 (d, CH_3Cl, $J_{C,P}$ = 8.2 Hz); 101.0 (d, $\underline{C}H(OMe)_2$, $J_{C,P}$ = 15.6 Hz); 129.8 (d, P—$\underline{C}$=C, $J_{C,P}$ = 181.0 Hz); 147.5 (H—$\underline{C}$=C). ^{31}P NMR ($CDCl_3$), δ: 12.23 (P=O). IR (thin film), ν/cm^{-1}: 1256 (P=O); 1629 (C=O). Found (%): C, 29.54; H, 4.41; Cl, 32.19; P, 9.30. $C_8H_{14}Cl_3O_5P$. Calculated (%): C, 29.31; H, 4.27; Cl, 32.52; P, 9.47.

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Animal Testing and Ethics

No human or animal subjects were used in this research.

Conflict of Interest

The authors declare no competing interests.

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