Hz), 4.28 (t, 1 H, J = 9.0 Hz), 6.24 (d, 1 H, J = 4.9 Hz); IR (CCl_4) 2990, 2950, 2905, 1740, 1715, 1370, 1360, 1230, 1170, 1125, 1005, 945, 895 cm^{-1}].

Acknowledgment. High-field ^1H NMR measurements were made by Mr. E. G. Brown and Mr. C. B. Green. Acknowledgment is made to the Commitee on Research of the University of California, Davis and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

Registry No. (±)-**1e**, 95976-00-4; (±)-**1z**, 95976-01-5; (±)-**2e**, 95865-60-4; (±)-**2z**, 95865-61-5; (±)-**3a**, 95976-02-6; (±)-**3a** (acid), 95976-09-3; (±)-**3b**, 95976-03-7; (±)-**3b** (acid), 95976-14-0; (±)-**4a**, 95976-04-8; (±)-**4b**, 95976-05-9; (±)-**5a**, 95865-62-6; (±)-**5a** (diol), 95865-70-6; (±)-**5b**, 95865-63-7; (±)-**5b** (diol), 95865-75-1; (±)-**6a**, 95865-64-8; (±)-**6a** (diol), 95976-10-6; (±)-**6b**, 95865-65-9; (±)-**6b** (diol), 95976-11-7; (±)-**7a**, 95865-66-0; (±)-**7a** (diol), 95976-12-8; (±)-**7b**, 95865-67-1; (±)-**7b** (diol), 95976-13-9; **8**, 27098-03-9; (±)-**9a**, 95865-68-2; (±)-**9b**, 95976-06-0; (±)-**10a**, 95865-69-3; (±)-**10a** (TBDMS ether), 95865-72-8; (±)-**10b**, 51552-44-4; (±)-**10b** (TBDMS ether), 95865-73-9; (±)-**11a**, 95976-07-1; (±)-**11b**, 95976-08-2; (*E*)-$CH_3CH{=}CHCH_2OH$, 7204-29-7; (*Z*)-$CH_3CH{=}CHCH_2OH$, 7204-36-6; CH_3CHO, 75-07-0; $(CH_3)_2CHCHO$, 78-84-2; 2-(1-hydroxyethyl)-3-methylpent-4-enal, 95865-74-0; methyl 2-allylacetoacetate, 95865-71-7.

A Study of the Reaction of 2-Haloacyl Halides with Trialkyl Phosphites. Synthesis of (2-Substituted acyl)phosphonates[1]

David R. Brittelli

Central Research & Development Department, Experimental Station, E. I. du Pont de Nemours & Company, Wilmington, Delaware 19898

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Reactions of triethyl and trimethyl phosphites with chloroacetyl chloride (1), which give phosphinylethenyl phosphates, formally 2:1 adducts, have been reinvestigated. From observed characteristics of the reactions, it has been deduced that a 2:1 adduct precursor forms before dealkylation occurs and that by hindering formation of the precursor, either by using a sterically bulky trialkyl phosphite or a dialkyl trimethylsilyl phosphite, (chloroacetyl)phosphonates may be obtained directly from 1. The effect of the nature of the 2-leaving group in 2-substituted acetyl chlorides on the formation of the phosphinylethenyl phosphate and/or the (2-substituted acetyl)phosphonate is also reported.

The reaction of phosphorus III nucleophiles bearing at least one alkoxy group with organic electrophiles is one of the oldest and best-known preparative methods in organophosphorus chemistry (the Michaelis–Arbuzov reaction).[2] Acyl halides function normally in this reaction, leading to acylphosphonates. In the case of chloroacetyl chloride, it has long been known that the reaction leads to a 2:1 product **3** (Scheme I), even when conducted with 1:1 stoichiometry.[3]

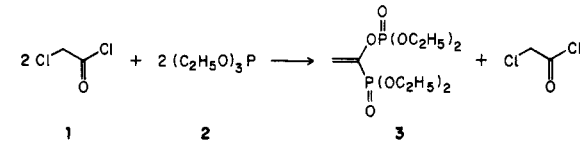
This has been interpreted to mean that the reactants initially react in the Michaelis–Arbuzov manner to give the (chloroacetyl)phosphonate **4**, with a subsequent Perkow[2] reaction of **4** forming **3** (Scheme II).[4,5] This scheme requires that k_2 be much faster that k_1, or only **4** would be formed with this stoichiometry.

We doubted this mechanistic picture, in particular finding it hard to accept the notion that **4** would be more reactive than acid chloride **1** toward phosphite **2**.

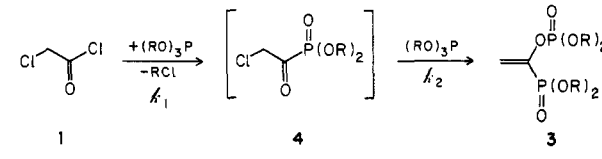
We have reinvestigated this reaction and have reached an understanding of the mechanism and structure-reactivity relationships which have allowed us to develop syntheses of compounds of type **4**.

Initially, the reaction of **1** with **2** in a 1:1 molar ratio was investigated at low temperature to see if the reaction could be halted at the supposed first step and **4** isolated. Even with addition of **2** to **1** at −78 °C and subsequent warmup, the 2:1 product **3** and none of **4** is produced. The reaction of trimethyl phosphite (**5**) and **1** at 10 °C evolved no chloromethane (bp −24 °C), suggesting for the first time that some type of 2:1 adduct forms even before the dialkylation in the putative first Michaelis–Arbuzov process

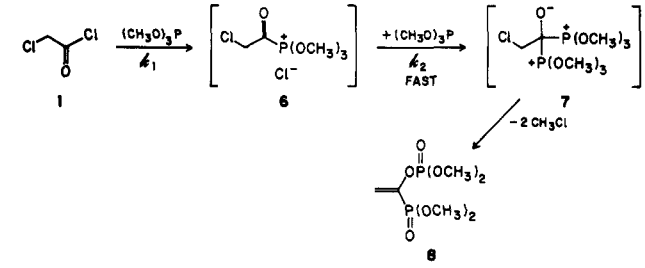
Scheme I



Scheme II



Scheme III



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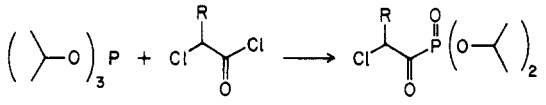
takes place. More informatively, when this particular reaction is conducted in pentane (in which both starting materials are soluble) at 10 °C, a pentane-insoluble liquid separates. The pentane supernate may be removed to recover half the starting chloroacetyl chloride. Subsequent warmup leads to vigorous chloromethane evolution starting at ~17 °C and to formation of a nearly quantitative yield of the 2:1 product **8**. This clearly shows that all the trimethyl phosphite is tied up with half the acid chloride in an initial adduct and is consistent with the following mechanism for this reaction (Scheme III).

Phosphite **5** reacts with **1** to give as the initial adduct the acylpseudophosphonium salt **6**, which reacts more rapidly than **1** with a second phosphite to yield a 2:1 adduct such as **7** or a related C-to-O rearranged intermediate (the pentane-insoluble substance). Subsequent warming affords dealkylation to give the final product **8**. It seems reasonable that acyl pseudophosphonium salt **6** would be more reactive toward phosphite addition than the acid chloride **1**, as is required by fact. This proposed mechanism is consistent with the observed features of the reaction and indicates that (chloroacetyl)phosphonates like **4** are not intermediates in the formation of the isolated 2:1 adducts **3** and **8**. A corollary to this mechanistic hypothesis is that one may obtain **4** by preventing formation of the initial 2:1 adduct of type **6**. We have found two ways to accomplish this goal.

In the first of these, use of the branched, hindered triisopropyl phosphite retards formation of a 2:1 adduct, leading smoothly to **9a,b** as distillable pure products.

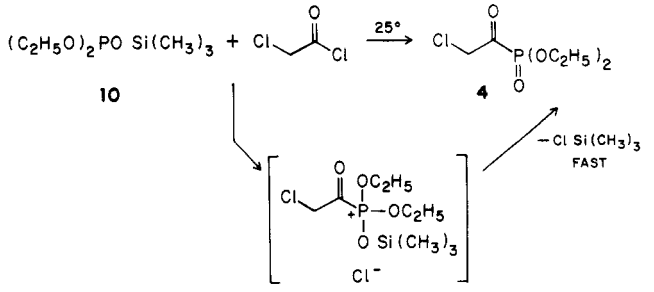


9a, R = H
9b, R = CH_3

It is interesting in this connection that **2** reacts with 2-bromopropionyl chloride to give a ~1:1 mixture of phosphinylvinyl phosphate and (2-bromopropionyl)-phosphonate, indicating that steric congestion in the acyl halide can also influence the course of this reaction in the desired way.

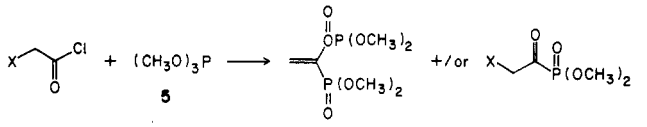
More interesting from the mechanistic standpoint is use of a phosphite with a rapidly removable substituent, namely, the silyl phosphite **10**.[6]

In this reaction, the initial adduct of type **6** (**11**) apparently loses chlorotrimethylsilane rapidly to give **4**.



With **4** in hand, we were in a position to show that **4** is not an intermediate in the formation of **3**. Treatment of **4** with **2** at temperatures up to 30 °C (i.e., at least 12 °C higher than conditions under which **3** forms from **1** and **2**) results in no reaction. At higher temperatures, **4** is converted into **3**. Thus the observed temperature characteristics of the reaction of **1** with **2** are critical to the unraveling of the mechanistic picture.

Table I. Substituent Effects in Reactions of 2-Substituted Acetyl Chlorides with Trimethyl Phosphite



Nucleofuge, X	σm	σp	Approx. pKa	% Products	
Br-	0.29	0.39	-9	100 (**8**)	0
Cl-	0.23	0.37	-7	100 (**8**)	0
C_6H_5O-	-0.03	0.25	10.1	100 (**8**)	0
CH_3O-	-0.27	0.12	~16	0	100 (**12**)

The formation of the novel 2:1 intermediate adducts is interesting and clearly depends on the electronic effect of the 2-substituent. This is shown by the following study of the reactions of **5** with acetyl chlorides 2-substituted with varying nucleofugic groups in a search to identify the limits of this reaction (Table I). Physicochemical[7,8] parameters (σ constants and pK_a's of the corresponding conjugate acids) have been used to rank leaving-group abilities.

Only with a leaving group as poor as methoxide does the formation of an acylphosphonate (**12**) proceed straightforwardly.

Conclusions

The reaction of lower alkyl phosphites with chloroacetyl chloride proceeds via formation of an unusual 2:1 adduct, not through a Michaelis–Arbuzov reaction/Perkow reaction sequence. And, (2-chloroacetyl)phosphonates are not intermediates in these reactions. By avoiding the formation of such adducts, either by steric control or by reactivity modification of the phosphites, such (2-chloroalkanoyl)phosphonates may be obtained in good yields and high purity.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 263B spectrophotometer. Proton NMR spectra were obtained on a Varian EM-390 or IBM NR80 spectrometer and were recorded in deuteriochloroform solutions. Chemical shifts are reported in parts per million from tetramethylsilane as an internal standard. Acyl halides were freshly distilled prior to use and handled under an atmosphere of dry nitrogen or argon. The acyl phosphonate products were noted to be moisture sensitive and were treated similarly.

Diethyl trimethylsilyl phosphite (**10**) was prepared by the method of M. Sekine, K. Okimoto, K. Yamada, and T. Hata, *J. Org. Chem.* **1981**, *46*, 3199.

Diethyl 1-(Diethoxyphosphinyl)ethenyl Phosphate (3). To 8.0 mL (0.10 mol) of chloroacetyl chloride in 50 mL of ether at −78 °C was added a solution of 17.2 mL (0.10 mol) of triethyl phosphite in 25 mL of ether at −78 °C. The mixture was allowed to warm to ambient temperature. NMR of the total crude reaction mixture showed the product and unreacted chloroacetyl chloride. Kugelrohr distillation yielded 15.42 g (97.5%): bp 105–115 °C (0.1 mm); n^{20}_D 1.4405 (lit.[5] n^{20}_D 1.4405); ^1H NMR ($CDCl_3$) δ 1.37 (12, t, J = 7 Hz, CH_3), 4.22 (8, m, OCH_2), 5.65–6.15 (2, m, $=CH_2$); IR (neat) 1630 (C=C) cm^{-1}.

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Dimethyl 1-(Dimethoxyphosphinyl)ethenyl Phosphate (8). A. Stoichiometric Reaction. To 8.0 mL (0.10 mol) of 1 under nitrogen at 10 °C was added dropwise 11.8 mL (0.10 mol) of **5** at a rate such that the temperature did not exceed 15 °C. No chloromethane evolution was detected. The mixture was allowed to warm to ambient temperature. Kugelrohr distillation yielded 9.38 g (72%): bp 97–110 °C (0.1mm); n^{20}_D 1.4393 (lit.[3] n^{20}_D 1.4400); ^{1}H NMR ($CDCl_3$) δ 3.80 (6, d, J = 12 Hz, CH_3), 3.83 (6, d, J = 12 Hz, CH_3), 5.56–6.15 (2, m, $=CH_2$); IR (neat) 1630 (C=C) cm^{-1}.

B. With Two Equivalents of 1 in Pentane. To 4.7 mL (0.059 mol) of 1 in 50 mL of pentane at 0 °C was added dropwise, at 0–5 °C, a solution of 6.97 mL (0.059 mol) of **5** in 10 mL of pentane. No chloromethane evolution was observed and an insoluble layer separated. The pentane supernate was removed (pipette) and run into a solution of 5.40 mL of aniline in 100 mL of ether. Workup of the ether solution afforded 4.90 g of chlorobenzanilide. The pentane-insoluble layer was allowed to warm slowly. At 17 °C, copious gas evolution started. Isolated was 7.19 g (93.6%) of 8.

Diethyl (2-Chloroacetyl)phosphonate (4). To 2.0 mL (0.025 mol) of freshly distilled 1 was added dropwise 6.0 mL (0.026 mol) of diethyl trimethylsilyl phosphite at a rate such that the temperature did not exceed 30 °C. Trimethylchlorosilane was removed in vacuo; 5.74 g. Kugelrohr distillation yielded 2.0 g (37%); bp 110–120 °C (0.1 mm) before decomposition started. The product cannot be distilled conventionally because it decomposes: ^{1}H NMR ($CDCl_3$) δ 1.37 (6, t, J = 7 Hz, OCH_2CH_3, enol tautomer), 1.40 (6, t, J = 7 Hz, OCH_2CH_3, keto tautomer), 4.28 (4, d of g, J_{HH} = 7 Hz, J_{PH} = 7 Hz, OCH_2CH_3, both tautomers), 4.60 (2, d, J_{PH} = 6 Hz), $ClCH_2$), 6.20 (1, d, J_{PH} = 6 Hz), ClCH=), 9.9 (1, br, HOC=C).

Diisopropyl (2-Chloroacetyl)phosphonate (9a). To 8.0 mL (0.10 mol) of 1 was added dropwise 25.0 mL (0.10 mol) of triisopropyl phosphite at a rate such that the temperature stayed between 27 and 30 °C and then stirred for 1.0 h. Kugelrohr distillation yielded 9.26 g (38%), bp 80–100 °C (0.1 mm), and 4.39 g (18%), bp 105–120 °C (0.1 mm). The latter contained some 2:1 adduct. The first fraction was redistilled (Kugelrohr) to furnish 5.23 g, bp 80–100 °C (0.2 mm). The product cannot be distilled conventionally because it decomposes: ^{1}H NMR ($CDCl_3$) δ 1.41 (12, d, J = 6 Hz, CH_3), 5.12 (2, d, J_{PH} = 1.8 Hz), $ClCH_2$), 5.30 (m, 2, $OCH(CH_3)_2$); IR (neat) 3600–3100 (OH, enol tautomer), 1720 (C=O), 1260 (P=O) cm^{-1}. Anal. Calcd for $C_8H_{16}ClPO_4$: C, 39.60; H, 6.65; Cl, 14.61; P, 12.77. Found: C, 39.84; H, 6.67; Cl, 14.73; P, 12.70.

Diisopropyl (2-Chloropropionyl)phosphonate (9b). Same as the procedure for **9a** described above. Kugelrohr distillation yielded 5.65 g (43%), bp 70–75 °C (0.2 mm), and 2.90 g (22%), bp 80–84 °C (0.2 mm): ^{1}H NMR ($CDCl_3$) δ 1.38 (12, d, J = 6 Hz, CH_3), 1.67 (3, d, J = 7.5 Hz, CH_3CCl), 4.3–5.0 (3, m, ClCH and $OCH(CH_3)_2$); IR (neat) 3600–3100 (OH, enol tautomer), 1720 (C=O), 1260 (P=O) cm^{-1}. Anal. Calcd for $C_9H_{18}ClO_4P$: C, 42.12; H, 7.07. Found: C, 42.15; H, 7.27.

Dimethyl (2-Methoxyacetyl)phosphonate (12). To 6.0 mL (0.066 mol) of methoxyacetyl chloride in 75 mL of THF at −78 °C was added dropwise a solution of 9.0 mL (0.076 mol) of **5** in 30 mL of THF. The mixture was allowed to warm to ambient temperature. Distillation yielded 6.47 g (54%): bp 68–70 °C (0.55 mm); ^{1}H NMR ($CDCl_3$) δ 3.44 (3, s, CH_3OC), 3.87 (6, d, J_{PH} = 11 Hz), P(=O)OCH_3), 4.44 (2, d, J_{PH} = 1.5 Hz, OCH_2C=O); IR (neat) 1700 (C=O) cm^{-1}; HRMS (70 eV) calcd for $C_5H_{11}O_5P$ m/e 182.0344; found m/e 182.0344.

Spontaneous Hydroxylation of a Cyclization Intermediate of Allopurinol

Helmut Rosemeyer, Klaus Kaiser, and Frank Seela*

Labor für Bioorganische Chemie, Fachbereich Chemie, Universität Paderborn, D-4790 Paderborn, Federal Republic of Germany

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Phase-transfer methylation of 4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**2b**) leads to a 2:1 mixture of the N-1 and the N-2 methylated chromophores (**3**, **4**). Both were found to be converted to the corresponding methylated allopurinol derivatives (**5**, **6**) by nucleophilic displacement of the 4-methoxy groups in dilute aqueous sodium hydroxide. Alkylation of **2b** with ethyl 3-bromopropionate using the phase-transfer technique yielded—after deesterification—1-(2-carboxyethyl)-4-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**7b**) regioselectively. Via this intermediate the N-1-functionalized allopurinol **8** and its 4-amino analogue **7c** could be obtained by acidic cleavage of the 4-methoxy group of **7b** or a nucleophilic displacement reaction by either dilute aqueous sodium hydroxide or concentrated aqueous ammonia. Reaction of the acid **8** with water-soluble carbodiimide results in an intramolecular cyclization, and subsequent water addition produces the tricyclic intermediate **11**. This compound undergoes spontaneous ring opening of the pyrimidine system to give its acyclic oxo tautomer **12**. In dilute alkaline medium, deformylation occurs to give pyrazolo[1,5-*a*]pyrimidine **13**. The reaction sequence is discussed as a nonenzymatic model reaction for the hydroxylation of hypoxanthine and allopurinol by xanthine oxidase.

Allopurinol[1,2] (1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one, 1) has been found to act as a progressive inhibitor of xanthine oxidase with alloxanthine—a 6-oxo derivative of **1**—as the actual inhibitor.[3] This has led to a clinical application in the treatment of gout and related metabolic disorders.[4] The value of allopurinol as well as of its 4-amino analogue is augmented by their effects on pyrimidine and purine biosynthesis.[5,6]

In the course of our investigations on modified nucleosides[7] and polymer-linked nucleoside antimetabolites,[8] our

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