2648 Russian Chemical Bulletin, International Edition, Vol. 54, No. 11, pp. 2648—2651, November, 2005

# Novel C-phosphorylated heterodienes based on pentachloroethyl isocyanate*

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A preparative method for the synthesis of novel *N*-phosphorylcarbonyl- and *N*-alkoxycarbonyltrichloroacetimidoylphosphonates from accessible pentachloroethyl isocyanate was developed. Factors that determine the C/N-selectivity of the phosphorylation of trichloroacetimidoyl chlorides were revealed: phenyl substituents at the P atom and an electron-withdrawing *N*-alkoxycarbonyl group in imidoyl chloride favored N-phosphorylation, while reactions with silyl phosphite gave exclusively C-phosphorylation products.

**Key words:** imidoyl chlorides, imidoylphosphonates, isocyanates, oxaza dienes, vinyl amides.

*N*-Acyl imidoylphosphonates belong to a novel type of electron-deficient C-phosphorylated heterodienes. These compounds are highly reactive and can undergo various chemical transformations since they have several electrophilic sites. In particular, the presence of the >P(O)C=N fragment, which is readily prone to reductive functionalization, opens up a route to various derivatives of biologically important aminophosphonic acids.

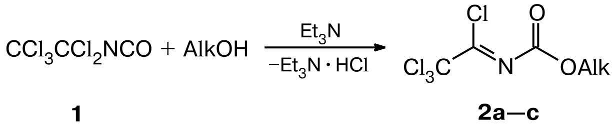
Only a few examples of trichloroacetimidoylphosphonates have been documented.[1,2] Reactions of imidoyl chlorides with phosphites represent a general route to imidoylphosphonates.[3] However, this approach is not always suitable for the synthesis of trichloroacetimidoylphosphonates because of a competition between the imidoyl Cl atom and the trichloromethyl group, as well as secondary phosphorylation of reactive imidoylphosphonates.[1,3,4] In addition, the effect of the substituents at the N atom on the reaction pathway has been studied inadequately.

In the present work, we investigated the possibility of obtaining *N*-carbonyltrichloroacetimidoylphosphonates from pentachloroethyl isocyanate (**1**). This bifunctional electrophile is attractive because of its accessibility and the possibility of employing different strategies in the synthesis of the target products: (1) reactions of compound **1** with nucleophiles XH at the isocyanate group followed by phosphorylation and (2) phosphorylation at the C atom of the $CCl_2$ group of isocyanate **1** followed by functionalization of the heterocumulene fragment.

## Results and Discussion

Controlled selective alcoholysis of isocyanate **1** gave both known (**2a,b**)[5,6] and new (**2c**) imidoyl chlorides with different electronic and steric parameters of substituents at the carbonyl C atom (Scheme 1).

**Scheme 1**



Alk = Me (**a**), Bu$^t$ (**b**), $CH_2CF_3$ (**c**)

Reactions of imidoyl chlorides **2** with phosphorus(III) acid esters were found to yield imidoylphosphonates **3** and isomeric *N*-phosphoryl-*N*-trichlorovinylcarbamates **4** (*i.e.*, the Arbuzov and aza-Perkow reactions are competitive here). The selectivity of the process depends on both the type of the alkoxy substituent in imidoyl chloride and the nature of the phosphorus reagent (Scheme 2; Table 1).

For instance, the reactions of imidoyl chlorides **2** with $(EtO)_2POSiMe_3$ gave exclusively imidoylphosphonates **3**, while the reactions with ethyl diphenylphosphinite yielded N-phosphorylation product **4**. The reactions with triethyl phosphite followed both pathways and the ratio of the C- and N-phosphorylation products (**3** : **4**) was virtually independent of the steric properties of the substituent at the carbonyl group (Alk = Me or Bu$^t$) and increased with an increase in the electron-withdrawing properties of the alkoxy group ($CF_3CH_2O$ > MeO, Bu$^t$O).

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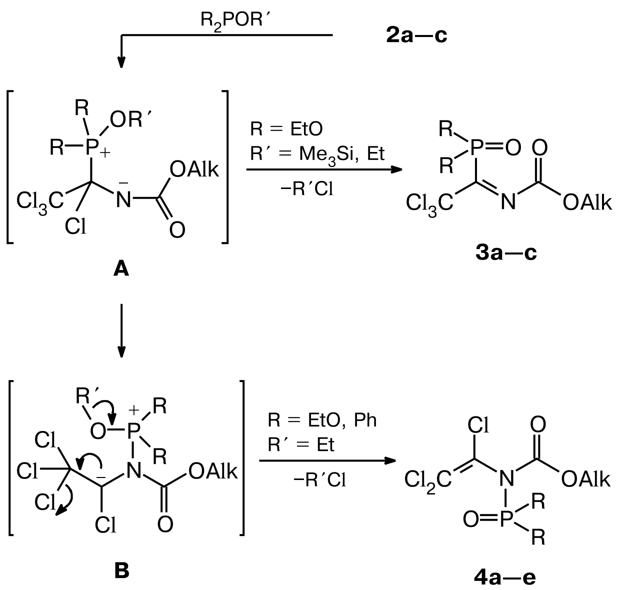
* Dedicated to the Corresponding Member of the Russian Academy of Sciences T. A. Mastryukova.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2563—2566, November, 2005.

**Scheme 2**



| Compound | R | Alk | Compound | R | Alk |
|---|---|---|---|---|---|
| **3a, 4a** | EtO | Me | **4d** | Ph | $Bu^t$ |
| **3b, 4b** | EtO | $Bu^t$ | **4e** | Ph | $CH_2CF_3$ |
| **3c, 4c** | EtO | $CH_2CF_3$ | | | |

In all cases, the first act is most likely a nucleophilic attack of the P atom on the most electrophilic imine C atom, which gives rise to bipolar intermediate **A**. Its stabilization and subsequent transformations are determined by the nature of the substituents at the P atom and the carbonyl group. The trimethylsilyl group ($R' = Me_3Si$) is highly mobile, which favors rapid desilylation of intermediate **A** (apparently, *via* O→N migration of the $Me_3Si$ group) leading to imidoylphosphonate **3**. The stabilization of the phosphonium center in intermediate **A** by phenyl radicals[7,8] and the high migrating ability of the $Ph_2P(O)$ group[9] are responsible for C—N transfer of the phosphorus group in reactions with $Ph_2POEt$ and for the exclusive formation of N-phosphorylation products **4**. Triethyl phosphite is intermediate between these reagents and the reaction pathway is determined by the substituents at the carbonyl group. The selectivity of the process did not change with an increase in the bulkiness of the substituent ($Bu^t$ > Me) since the decisive factor here is a reduction in the steric strains at the quaternary C atom upon the rearrangement **A**→**B**. At the same time, the stabilization of the anionic center in intermediate **A** by a stronger electron-withdrawing alkyl substituent ($CF_3CH_2O$ > $Bu^tO$) favors phosphorotropic migration and the occurrence of the aza-Perkow reaction.

**Table 1.** Ratio of the C- and N-phosphorylation products (**3** : **4**) in the reactions of imidoyl chlorides **2** with $P^{III}$ acid esters

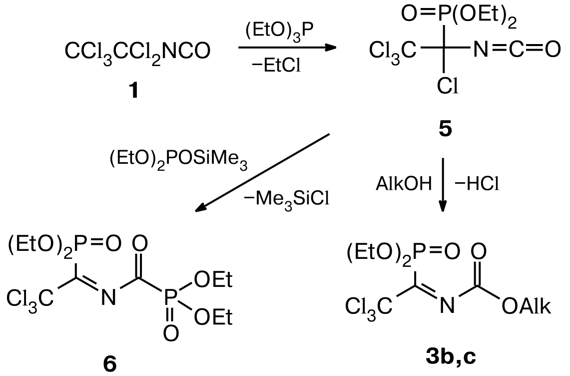
| Alk | $(EtO)_3P$ | $Ph_2POEt$ | $(EtO)_2POSiMe_3$ |
|---|---|---|---|
| Me | 33 : 67 | — | — |
| $Bu^t$ | 33 : 67 | 0 : 100 | 100 : 0 |
| $CF_3CH_2$ | 0 : 100 | 0 : 100 | 100 : 0 |

Thus, variation in substituents in imidoyl chloride and a phosphorus reagent makes it possible to control the selectivity of the process and synthesize both imidoylphosphonates **3** and *N*-trichlorovinyl amides **4**.

The targeted synthesis of trichloroacetimidoylphosphonates can be effected by employing a strategy of initial phosphorylation of isocyanate **1** followed by modification of the heterocumulene fragment. Earlier,[10] it has been reported that pentachloroethyl isocyanate reacts with triethyl phosphite to give a mixture of products inseparable by distillation. We found conditions for the selective reaction of isocyanate **1** with triethyl phosphite giving C-phosphorylated tetrachloro isocyanate **5** in high yield. In turn, despite the presence of several reactive sites, isocyanate **5** selectively reacted with alcohols to form *N*-alkoxycarbonyl imidoylphosphonates **3**.

Modification of the isocyanate group in phosphonate **5** by other types of nucleophiles opens up new synthetic prospects. In particular, we found that the reaction of compound **5** with diethyl trimethylsilyl phosphite also proceeds selectively to give the first representative (**6**) of novel 1,3-heterodienes in high yield (Scheme 3). Note that triethyl phosphite under analogous conditions did not react with isocyanate **5**. Compound **6** contains the fragments of two known classes of compounds, namely, α-oxo phosphonates and α-imidoylphosphonates and can serve as a useful precursor in the synthesis of potential metal protease inhibitors.[11]

**Scheme 3**



Imidoylphosphonates **3** and **6** are oils or low-melting crystalline compounds, which are stable in a moisture-free atmosphere. Their structures were confirmed by spectroscopic and analytical methods. The position and multiplicity of the imine C atom with a characteristic coupling constant in the $^{13}$C NMR spectrum ($\delta_C$ 158.9—163.0, $^1J_{C,P}$ = 159—165 Hz) is structurally most indicative. The $^{31}$P NMR spectrum of compound **6** shows signals for two nonequivalent P atoms ($\delta_P$ = –2.3 and 0.8) of equal intensities. The presence of the fragment P—C=N—C(O)—P unambiguously follows from the $^{13}$C NMR spectrum containing doublets of doublets for the imine and carbonyl C atoms with a coupling constant characteristic of directly connected C and P atoms ($\delta_C$ 159.5, $^1J_{C,P}$ = 159 Hz, $^3J_{C,P}$ = 6.3 Hz (C=N); $\delta_C$ 173.4, $^1J_{C,P}$ = 225 Hz, $^3J_{C,P}$ = 8 Hz (C=O)).

## Experimental

$^1$H, $^{19}$F, $^{31}$P, and $^{13}$C NMR spectra were recorded on a Varian VXR-300 spectrometer (299.95, 282.20, 121.42, and 75.429 MHz, respectively). Chemical shifts are referenced to $Me_4Si$ ($^1$H, $^{13}$C) and $CFCl_3$ ($^{19}$F) as the internal standards and to 85% $H_3PO_4$ ($^{31}$P) as the external standard. IR spectra were recorded on a UR-20 instrument with KBr pellets or a solution of $CCl_4$.

The physicochemical constants of *N*-(methoxycarbonyl)trichloroacetimidoyl chloride (**2a**),[5] diethyl *N*-(methoxycarbonyl)trichloroacetimidoylphosphonate **3a** (see Ref. 1), and methyl *N*-diethoxyphosphoryl-*N*-trichlorovinylcarbamate **4a** (see Ref. 1) were in agreement with the literature data.

Solvents were thoroughly purified and dehydrated according to standard methods. Triethyl phosphite, diethyl trimethylsilyl phosphite, and ethyl diphenylphosphinite (Sigma-Aldrich) were used freshly distilled over sodium.

**Synthesis of imidoyl chlorides 2 (general procedure).** Triethylamine (1.01 g, 10 mmol) was added to a stirred ice-cold mixture of isocyanate **1** (2.43 g, 10 mmol) (see Ref. 12) and an appropriate alcohol (10 mmol) in diethyl ether (15 mL). After 1 h, the precipitate was filtered off, the solvent was removed, and the residue was distilled.

***N*-(*tert*-Butoxycarbonyl)trichloroacetimidoyl chloride (2b).** The yield was 1.85 g (66%), b.p. 61—63 °C (0.07 Torr) (*cf.* Ref. 6: 67 °C (0.05 Torr)). Found (%): C, 29.87; H, 3.37; Cl, 50.68. $C_7H_9Cl_4NO_2$. Calculated (%): C, 29.92; H, 3.23; Cl, 50.47. IR ($CCl_4$), ν/cm$^{-1}$: 1690 (C=N); 1750 (C=O). $^1$H NMR ($CDCl_3$), δ: 1.59 (s, 9 H, Bu$^t$). $^{13}$C NMR ($CDCl_3$), δ: 27.9 ($CH_3$); 85.7 (C—O); 94.2 ($CCl_3$); 145.4 (C=N); 154.8 (C=O).

***N*-(2,2,2-Trifluoroethoxycarbonyl)trichloroacetimidoyl chloride (2c).** The yield was 1.75 g (57%), b.p. 82—83 °C (15 Torr). Found (%): C, 19.51; H, 0.79; Cl, 46.39. $C_5H_2Cl_4F_3NO_2$. Calculated (%): C, 19.57; H, 0.66; Cl, 46.21. IR ($CCl_4$), ν/cm$^{-1}$: 1700 (C=N); 1790 (C=O). $^1$H NMR ($CDCl_3$), δ: 4.70 (q, 2 H, $CH_2$, $^3J_{H,F}$ = 8 Hz). $^{13}$C NMR ($CDCl_3$), δ: 62.8 (q, $CH_2O$, $^2J_{C,F}$ = 37 Hz); 93.8 (s, $CCl_3$); 122.3 (q, $CF_3$, $^1J_{C,F}$ = 279 Hz); 149.3 (s, C=N); 155.1 (s, C=O). $^{19}$F NMR ($CDCl_3$), δ: –74.2 (t, $^3J_{F,H}$ = 8 Hz).

***N*-Alkoxycarbonyltrichloroacetimidoylphosphonates 3 (general procedure).** ***A.*** Diethyl trimethylsilyl phosphite (2.10 g, 10 mmol) was added at –10 °C to a solution of imidoyl chloride **2** (10 mmol) in diethyl ether (15 mL). After 2 h, the solvent was removed *in vacuo* and the residue was washed with light petroleum.

***B.*** Triethylamine (0.16 g, 1.58 mmol) was added at 0 °C to a stirred solution of isocyanate **5** (0.5 g, 1.46 mmol) and an appropriate alcohol (1.46 mmol) in diethyl ether (10 mL). After 2 h, triethylammonium chloride was filtered off, the solvent was removed, and the residue was washed with light petroleum.

**Diethyl *N*-(*tert*-butoxycarbonyl)trichloroacetimidoylphosphonate (3b).** The yield was 3.1 g (80%) (method *A*) and 0.52 g (93%) (*B*). Found (%): C, 34.42; H, 4.86; P, 8.13. $C_{11}H_{19}Cl_3NO_5P$. Calculated (%): C, 34.53; H, 5.01; P, 8.10. IR ($CCl_4$), ν/cm$^{-1}$: 1060 (POC); 1250 (P=O); 1695, 1750 (C=N, C=O). $^1$H NMR ($CDCl_3$), δ: 1.38 (m, 6 H, $CH_3$, $^3J_{H,H}$ = 7 Hz); 1.59 (s, 9 H, Bu$^t$); 4.43—4.53 (m, 4 H, $CH_2O$). $^{13}$C NMR ($CDCl_3$), δ: 16.1 (d, $^3J_{C,P}$ = 7 Hz, $\underline{C}H_3CH_2$); 28.0 (s, $(\underline{C}H_3)_3C$); 64.4 (d, $OCH_2$, $^2J_{C,P}$ = 6.5 Hz); 84.8 (s, $(\underline{C}H_3)_3\underline{C}$); 94.9 (d, $CCl_3$, $^2J_{C,P}$ = 51 Hz); 156.9 (d, C=O, $^3J_{C,P}$ = 13 Hz); 158.9 (d, C=N, $^1J_{C,P}$ = 165 Hz). $^{31}$P NMR ($CDCl_3$), δ: –2.0.

**Diethyl *N*-(2,2,2-trifluoroethoxycarbonyl)trichloroacetimidoylphosphonate (3c).** The yield was 3.8 g (92%) (*A*) and 0.56 g (94%) (*B*). Found (%): C, 26.65, H, 2.99, P, 7.72. $C_9H_{12}Cl_3F_3NO_5P$. Calculated (%): C, 26.46, H, 2.96, P, 7.58. IR (thin film), ν/cm$^{-1}$: 1050 (POC); 1240 (P=O); 1680, 1770 (C=N, C=O). $^1$H NMR ($CDCl_3$), δ: 1.40 (t, 6 H, $CH_3$, $^3J_{H,H}$ = 7 Hz); 4.20—4.41 (m, 4 H, $CH_3C\underline{H_2}O$); 4.70 (q, 2 H, $CH_2CF_3$, $^3J_{H,F}$ = 8 Hz). $^{19}$F NMR ($CDCl_3$), δ: –73.6 (t, $^3J_{F,H}$ = 8 Hz). $^{31}$P NMR ($CDCl_3$), δ: –0.9.

**Reactions of imidoyl chlorides (2b,c) with triethyl phosphite or ethyl diphenylphosphinite.** Triethyl phosphite (0.116 g, 1 mmol) or ethyl diphenylphosphinite (0.23 g, 1 mmol) was added at 5 °C to a solution of imidoyl chloride **2** (1 mmol) in benzene. The course of the reaction was monitored and the ratio of the isomers was determined by $^{31}$P NMR spectroscopy. After one day, the solvent was removed and the residue was washed with light petroleum and dried *in vacuo*. Compound **3b** ($\delta_P$ –1.8 ($C_6D_6$)) was identified in the reaction mixture by comparison with a sample obtained according to Scheme 3. *N*-Vinylcarbamate **4b** ($\delta_P$ –4) was identified by comparison with data in Ref. 1.

**2,2,2-Trifluoroethyl *N*-diethoxyphosphoryl-*N*-trichlorovinylcarbamate (4c)** was obtained as a colorless oil. The yield was 0.31 g (76%). Found (%): C, 26.59; H, 2.87; P, 7.39. $C_9H_{12}Cl_3F_3NO_5P$. Calculated (%): C, 26.46; H, 2.95; P, 7.58. IR ($CCl_4$), ν/cm$^{-1}$: 1080 (POC); 1280 (P=O); 1760 (C=O). $^1$H NMR ($CDCl_3$), δ: 1.35—1.42 (m, 6 H, $CH_3$); 4.26—4.37 (m, 4 H, $CH_3C\underline{H_2}O$); 4.62 (q, 2 H, $CH_2CF_3$, $^3J_{H,F}$ = 8 Hz). $^{19}$F NMR ($CDCl_3$), δ: –74.4 (t, $^3J_{F,H}$ = 8 Hz). $^{31}$P NMR ($CDCl_3$), δ: –4.7.

***tert*-Butyl *N*-diphenylphosphinoyl-*N*-trichlorovinylcarbamate (4d).** The yield was 0.46 g (98%), m.p. 99—100 °C. Found (%): C, 51.19; H, 4.15; Cl, 23.56; P, 6.85. $C_{19}H_{19}Cl_3NO_3P$. Calculated (%): C, 51.09; H, 4.29; Cl, 23.81; P, 6.93. IR (KBr), ν/cm$^{-1}$: 1275 (P=O); 1790 (C=O). $^1$H NMR ($CDCl_3$), δ: 1.27 (s, 9 H, $CH_3$); 7.52—7.92 (m, 10 H, Ph). $^{31}$P NMR ($CDCl_3$), δ: 27.9.

**2,2,2-Trifluoroethyl *N*-diphenylphosphinoyl-*N*-trichlorovinylcarbamate (4e).** The yield was 0.36 g (77%), m.p. 96—98 °C. Found (%): C, 42.94; H, 2.61; P, 6.69. $C_{17}H_{12}Cl_3F_3NO_3P$. Calculated (%): C, 43.20; H, 2.56; P, 6.55. IR (KBr), ν/cm$^{-1}$: 1275 (P=O); 1760 (C=O). $^1$H NMR ($CDCl_3$), δ: 4.49 (q, 2 H, $CH_2CF_3$, $^3J_{H,F}$ = 8 Hz); 7.45—7.57 (m, 4 H, Ph); 7.60—7.65 (m, 2H, Ph); 7.85—8.02 (m, 4 H, Ph). $^{19}$F NMR ($CDCl_3$), δ: –74.6 (t, $^3J_{F,H}$ = 8 Hz). $^{31}$P NMR ($CDCl_3$), δ: 30.1.

**1,2,2,2-Tetrachloro-1-diethoxyphosphorylethyl isocyanate (5).** Triethyl phosphite (4.54 mL, 26.4 mmol) was added at 0 °C to a stirred solution of isocyanate **1** (6.44 g, 26.4 mmol) in diethyl ether (40 mL). The reaction mixture was stirred for 2 h. Then the solvent was removed and the residue was distilled. The yield of compound **5** was 7.3 g (80%), b.p. 101—102 °C (0.06 Torr). Found (%): Cl, 40.87; P, 9.15. $C_7H_{10}Cl_4NO_4P$. Calculated (%): Cl, 41.11; P, 8.98. IR ($CCl_4$), $\nu$/cm$^{-1}$: 1040 (POC); 1290 (P=O); 2270 (N=C=O). $^1$H NMR ($CDCl_3$), δ: 1.43 (t, 6 H, $CH_3$, $^3J_{H,H}$ = 7 Hz); 4.31—4.48 (m, 4 H, $CH_2$). $^{31}$P NMR ($CDCl_3$), δ: 9.6.

**Diethyl *N*-(diethoxyphosphorylcarbonyl)trichloroacetimidoylphosphonate (6).** Diethyl trimethylsilyl phosphite (0.51 g, 2.6 mmol) was added at −45 to −50 °C to a vigorously stirred solution of isocyanate **5** (0.9 g, 2.6 mmol) in diethyl ether (10 mL). The temperature was gradually (over 1 h) raised to ~20 °C. Then the solvent was removed and the residue was distilled. The yield of compound **6** was 0.66 g (57%), b.p. 82 °C (0.05 Torr). Found (%): C, 29.38; H, 4.57; P, 13.72. $C_{11}H_{20}Cl_3NO_7P_2$. Calculated (%): C, 29.58; H, 4.51; P, 13.87. IR (thin film), $\nu$/cm$^{-1}$: 1050 (POC); 1280 (P=O); 1700, 1740 (C=N, C=O). $^1$H NMR ($CDCl_3$), δ: 1.10—1.31 (m, 12 H, $CH_3$); 3.87—4.57 (m, 8 H, $CH_2$). $^{13}$C NMR ($CDCl_3$), δ: 16.0 (d, $\underline{C}H_3CH_2$, $^3J_{C,P}$ = 6 Hz); 16.3 (d, $\underline{C}H_3CH_2$, $^3J_{C,P}$ = 6 Hz); 64.6 (m, $CH_2$); 65.1 (m, $CH_2$); 93.7 (dd, $CCl_3$, $^2J_{C,P}$ = 46 Hz, $^4J_{C,P}$ = 5 Hz); 159.5 (dd, C=N, $^1J_{C,P}$ = 159 Hz, $^3J_{C,P}$ = 6 Hz); 176.4 (dd, C=O, $^1J_{C,P}$ = 225 Hz, $^3J_{C,P}$ = 8 Hz). $^{31}$P NMR ($CDCl_3$), δ: −2.8 (1 P), 0.1 (1 P).

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*Received September 20, 2005;*
*in revised form October 31, 2005*