Cyclization of allenyl phosphonates to 3-chloro-4-(diethylphosphono)-2,5-dihydrofurans induced by $CuCl_2$

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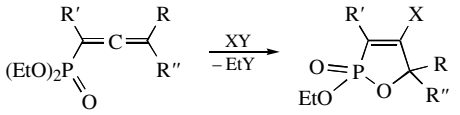
3-Chloro-4-(diethylphosphono)-2,5-dihydrofurans **5a–f** were synthesised by the reaction of 1-(hydroxymethyl)allenyl phosphonates with $CuCl_2$.

Phosphorylated alkadienes are frequently used as building blocks in organic synthesis.[1] These compounds react with halogens,[2] proton acids,[3] sulfenyl chlorides,[4(a)] selenyl chlorides,[4(b)–(e)] potassium dichloroiodate ($KICl_2$)[5] and *N*,*N*-diethylbenzeneselenylamide (in the presence of Py/SO_3)[6] with the formation of 1,2-oxaphosphol-3-enes **2** due to the participation of the phosphoryl oxygen atom as an internal nucleophile at the final step of addition (Scheme 1).



1 **2**

Scheme 1

In continuation of earlier works in the synthesis of 1,2- and 1,3-alkadienes and in connection with our interest in developing new synthetic strategies for the construction of heterocyclic phosphonates,[7] we report here an unusual halogenation of 1-(hydroxymethyl)allenyl phosphonates **1** by copper(II) halides to new chlorinated 2,5-dihydrofuryl phosphonates.

The application of copper(II) halides to the transformation of organic compounds is documented. They were used for the halogenation of aromatic molecules,[8] compounds with double and triple bonds,[9] ketones,[10,11] esters,[12] enolates, phosphorus ilydes,[13] 2-sulfonyl and phosphinoxy anions.[14] The lactonization of allenic carboxylic acids by the action of $CuCl_2$ and $CuBr_2$ was published.[15]

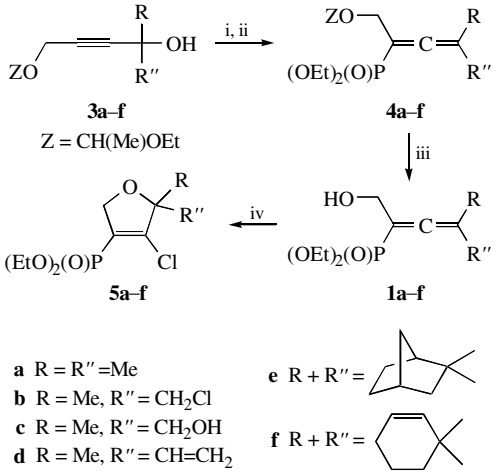
In addition to the previously reported preparation of 4-unsubstituted 2,5-dihydrofuryl phosphonates through cyclization of allenes **1** by $AgNO_3$,[3(c)] we carried out the halogenation of 1-(hydroxymethyl)allenyl phosphonates **1a–f** with $CuCl_2$.

Allenes **1a–f** were prepared[7(c)] starting from propargyl alcohols **3a–f**. Halogenation was carried out by adding two equivalents of copper(II) chloride hydrate to a solution of allenyl phosphonate **1a–f** in acetonitrile at room temperature. The progress of reaction was controlled by TLC. When the conversion was complete (12–24 h), the products were separated from CuCl and isolated as yellowish oils by column chromatography on silica gel (Scheme 2).

The following mechanism can be proposed for this reaction (Scheme 3): the coordination of $CuCl_2$ with 2,3-π-bonds causes a distortion and polarization of allenic system and increases the contribution of resonance structure **8** with a σ-coordinated Cu atom. The intermolecular nucleophilic attack of the hydroxyl group allows us to 'catch' this structure, and resulting intermediate **9** rapidly transforms to **5** by the oxidative coupling of ligands.

The structures of **5a–f** were clearly assigned by ^1H, ^{13}C and ^{31}P NMR spectroscopy.† The NMR spectra of **5a–f** were in good agreement with published data for 2,5-dihydrofuryl phosphonates.[7(c),7(f)]

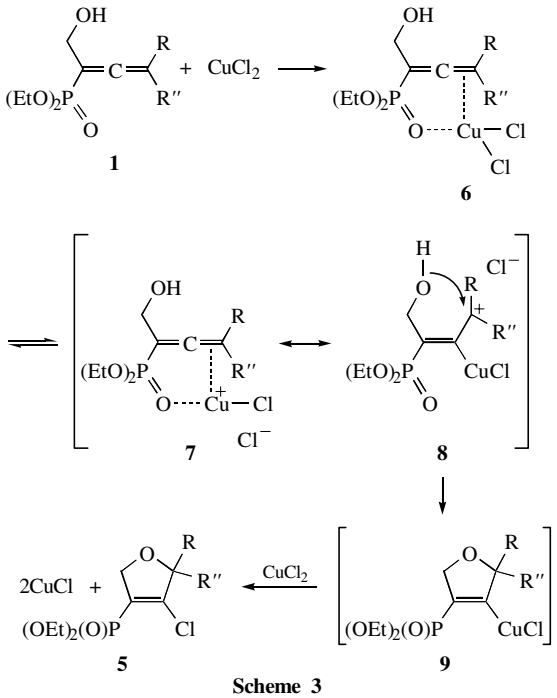
Thus, we developed an easy and convenient synthesis of 3-chloro-4-(diethyphosphono)-2,5-dihydrofurans **5a–f**, which are building blocks for the synthesis of biologically and pharmaceutically interesting molecules.



3a–f **4a–f** **5a–f** **1a–f**

a R = R″ = Me
b R = Me, R″ = CH_2Cl
c R = Me, R″ = CH_2OH
d R = Me, R″ = $CH{=}CH_2$
e R + R″ =
f R + R″ =

Scheme 2 *Reagents and conditions*: i, $(EtO)_2PCl$, Et_3N, Et_2O, –20 °C; ii, room temperature, 24 h; iii, *p*-$TolSO_3H$, MeOH, room temperature, 1 h; iv, 2$CuCl_2$, MeCN, room temperature, 24 h.



1 **6** **7** **8** **5** **9**

Scheme 3

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† *3-Chloro-4-(diethylphosphono)-2,2-dimethyl-2,5-dihydrofuran* **5a**. *Typical procedure*: a solution of **1a** (0.12 g, 0.52 mmol) in 3 ml of anhydrous MeCN was introduced into a 30 ml round-bottom flask containing 5 ml of anhydrous MeCN and $CuCl_2·H_2O$ (0.178 g, 1.04 mmol). The resulting brown solution was kept at room temperature for 24 h. Reactions were monitored by TLC on silica gel and ^{1}H NMR spectroscopy. MeCN was removed in a vacuum, and the black residue was extracted several times with warm methylene chloride. The solvent was evaporated, and the crude product was chromatographed on a silica gel column with light petroleum–ethyl acetate (2:1 to 1:3) as an eluent to give **5a** (0.106 g, 76%). R_f 0.68 ($CHCl_3$–MeOH, 10:0.3). ^{1}H NMR ($CDCl_3$) δ: 1.34 (dt, 6H, 2Me, J 1.0 and 7.2 Hz), 1.40 (s, 6H, 2Me), 4.17 (dq, 4H, $2CH_2OP$, J 8.0 and 7.2 Hz), 4.80 (dd, 2H, OCH_2, J 1.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 16.07 (d, Me, $J_{C–P}$ 6.8 Hz), 16.13 (d, Me, $J_{C–P}$ 6.4 Hz), 25.13 (d, Me, $J_{C–P}$ 1.5 Hz), 62.22 (d, $POCH_2$, $J_{C–P}$ 5.7 Hz), 73.28 (d, $COCH_2$, $J_{C–P}$ 16.3 Hz), 89.51 (d, $OCMe_2$, $J_{C–P}$ 14.8 Hz), 121.33 (d, PC=, $J_{C–P}$ 200.0 Hz), 147.22 (d, ClC=, $J_{C–P}$ 3.1 Hz). ^{31}P NMR ($CDCl_3$) δ: 9.80. IR (film, ν/cm^{-1}): 1243 (P=O), 1619 (C=C). Found (%): C, 44.82; H, 6.71; P, 11.65. Calc. for $C_{10}H_{18}ClPO_4$ (%): C, 44.70; H, 6.75; P, 11.53.

3-Chloro-4-(diethylphosphono)-2-chloromethyl-2-methyl-2,5-dihydrofuran **5b** was prepared from allene **1b** (0.14 g, 0.52 mmol), anhydrous MeCN (8 ml) and $CuCl_2·H_2O$ (0.178 g, 1.04 mmol). Yield 76%. R_f 0.66 ($CHCl_3$–MeOH, 10:0.3). ^{1}H NMR ($CDCl_3$) δ: 1.37 (dt, 6H, 2Me, J 1.0 and 7.2 Hz), 1.44 (s, 3H, Me), 3.67 (m, 2H, $ClCH_2$), 4.12 (dq, 4H, $2CH_2OP$, J 8.0 and 7.2 Hz), 4.84 (dd, 2H, OCH_2, J 2.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 16.06 (d, Me, $J_{C–P}$ 6.5 Hz), 22.39 (s, Me), 49.11 (s, CH_2Cl), 62.27 (d, $POCH_2$, $J_{C–P}$ 5.0 Hz), 62.52 (d, $POCH_2$, $J_{C–P}$ 5.5 Hz), 73.75 (d, $COCH_2$, $J_{C–P}$ 16.2 Hz), 91.46 [d, $OC(Me)CH_2Cl$, $J_{C–P}$ 15.1 Hz], 124.91 (d, PC=, $J_{C–P}$ 198.2 Hz), 141.56 (d, ClC=, $J_{C–P}$ 4.0 Hz). ^{31}P NMR ($CDCl_3$) δ: 7.47. IR (film, ν/cm^{-1}): 1241 (P=O), 1612 (C=C). Found (%): C, 39.57; H, 5.72; P, 10.06. Calc. for $C_{10}H_{17}Cl_2PO_4$ (%): C, 39.62; H, 5.65; P, 10.22.

3-Chloro-4-(diethylphosphono)-2-(hydroxymethyl)-2-methyl-2,5-dihydrofuran **5c** was prepared from allene **1c** (0.13 g, 0.52 mmol), anhydrous MeCN (8 ml) and $CuCl_2·H_2O$ (0.178 g, 1.04 mmol). Yield 56%. R_f 0.28 ($CHCl_3$–MeOH, 10:0.3). ^{1}H NMR ($CDCl_3$) δ: 1.31 (s, 3H, Me), 1.39 (dt, 6H, 2Me, J 1.0 and 7.8 Hz), 3.50 (br. s, 1H, OH), 3.61 (m, 2H, CH_2OH), 4.13 (dq, 4H, CH_2OP, J 8.0 and 7.8 Hz), 4.81 (dd, 2H, OCH_2, J 2.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 16.14 (d, Me, $J_{C–P}$ 6.4 Hz), 20.08 (d, Me, $J_{C–P}$ 1.4 Hz), 62.53 (d, $POCH_2$, $J_{C–P}$ 5.6 Hz), 62.58 (d, $POCH_2$, $J_{C–P}$ 5.7 Hz), 66.02 (s, $HOCH_2$), 74.97 (d, $COCH_2$, $J_{C–P}$ 16.9 Hz), 92.97 [d, $OC(Me)CH_2OH$, $J_{C–P}$ 14.5 Hz], 123.72 (d, PC=, $J_{C–P}$ 198.8 Hz), 143.51 (d, ClC=, $J_{C–P}$ 3.5 Hz). ^{31}P NMR ($CDCl_3$) δ: 9.19. IR (film, ν/cm^{-1}): 1242 (P=O), 1608 (C=C), 3674, 3602 (OH). Found (%): C, 42.30; H, 6.52; P, 10.71. Calc. for $C_{10}H_{18}ClPO_5$ (%): C, 42.19; H, 6.37; P, 10.88.

3-Chloro-4-(diethylphosphono)-2-ethenyl-2-methyl-2,5-dihydrofuran **5d** was prepared from allene **1d** (0.128 g, 0.52 mmol), anhydrous MeCN (8 ml) and $CuCl_2·H_2O$ (0.178 g, 1.04 mmol). Yield 70%. R_f 0.67 ($CHCl_3$–MeOH, 10:0.3). ^{1}H NMR ($CDCl_3$) δ: 1.34 (dt, 6H, 2Me, J 0.8 and 7.0 Hz), 1.48 (s, 3H, Me), 4.14 (dq, 4H, $2CH_2OP$, J 8.0 and 7.0 Hz), 4.80 (dd, 2H, OCH_2, J 1.9 Hz), 5.21 (dd, 1H, HHC=, J 10.6 and 1.1 Hz), 5.3 (dd, 1H, HHC=, J 17.2 and 10.6 Hz), 5.93 (dd, 1H, HC=CH_2). ^{13}C NMR ($CDCl_3$) δ: 16.17 (d, Me, $J_{C–P}$ 6.4 Hz), 23.42 (d, Me, $J_{C–P}$ 1.4 Hz), 62.33 (d, $POCH_2$, $J_{C–P}$ 5.7 Hz), 62.38 (d, $POCH_2$, $J_{C–P}$ 5.7 Hz), 73.94 (d, $COCH_2$, $J_{C–P}$ 16.4 Hz), 90.97 [d, OC(Me)CH=, $J_{C–P}$ 14.8 Hz], 115.10 (s, $=CH_2$), 122.05 (d, HC=, $J_{C–P}$ 199.4 Hz), 137.54 (d, PC=, J 1.7 Hz), 145.25 (d, ClC=, $J_{C–P}$ 3.2 Hz). ^{31}P NMR ($CDCl_3$) δ: 9.53. IR (film, ν/cm^{-1}): 1240 (P=O), 1613, 1643 (C=C). Found (%): C, 47.04; H, 6.50; P, 11.09. Calc. for $C_{11}H_{18}ClPO_4$ (%): C, 47.07; H, 6.46; P, 11.04.

3-Chloro-4-(diethylphosphono)-2-(2-norbornylidene)-2,5-dihydrofuran **5e** was prepared from allene **1e** (0.149 g, 0.52 mmol), anhydrous MeCN (8 ml) and $CuCl_2·H_2O$ (0.178 g, 1.04 mmol). Yield 67%. R_f 0.68 ($CHCl_3$–MeOH, 10:0.3). ^{1}H NMR ($CDCl_3$) δ: 1.16–1.90, 2.36 (m, 10H, CH_2, CH), 1.34 (dt, 6H, 2Me, J 0.9 and 8.0 Hz), 4.14 (dq, 4H, $2CH_2OP$, J 8.0 and 8.0 Hz), 4.53 (m, 2H, OCH_2). ^{13}C NMR ($CDCl_3$) δ: 16.11 (d, Me, $J_{C–P}$ 5.5 Hz), 21.90 (s, CH_2), 27.27 (s, CH_2), 35.74 (s, CH_2), 39.19 (s, CH), 43.13 (s, CH_2), 46.69 (s, CH), 62.33 (d, $POCH_2$, $J_{C–P}$ 5.5 Hz), 62.25 (d, $POCH_2$, $J_{C–P}$ 5.5 Hz), 72.25 (d, $COCH_2$, $J_{C–P}$ 16.1 Hz), 96.64 (d, OC, $J_{C–P}$ 15.1 Hz), 125.13 (d, PC=, $J_{C–P}$ 200.7 Hz), 145.78 (d, ClC=, $J_{C–P}$ 3.0 Hz). ^{31}P NMR ($CDCl_3$) δ: 9.13. IR (film, ν/cm^{-1}): 1245 (P=O), 1605 (C=C). Found (%): C, 52.61; H, 7.06; P, 9.81. Calc. for $C_{14}H_{22}ClPO_4$ (%): C, 52.42; H, 6.91; P, 9.66.

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3-Chloro-4-(diethylphosphono)-2-(2-cyclohexenylidene)-2,5-dihydrofuran **5f** was prepared from allene **1f** (0.142 g, 0.52 mmol), anhydrous MeCN (8 ml), and $CuCl_2·H_2O$ (0.178 g, 1.04 mmol). Yield 73%. R_f 0.67 ($CHCl_3$–MeOH, 10:0.3). ^{1}H NMR ($CDCl_3$) δ: 1.33 (m, 2H, CH_2), 1.34 (dt, 6H, 2Me, J 0.9 and 8.0 Hz), 1.78 (m, 2H, CH_2), 2.10 (m, 2H, CH_2), 4.12 (dq, 4H, $2CH_2OP$, J 8.0 and 8.0 Hz), 4.81 (m, 2H, OCH_2), 5.61 (br. d, 1H, HC=CH, J 11.0 Hz), 5.97 (dt, 1H, HC=CH, J 11.0 and 2.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 16.11 (d, Me, $J_{C–P}$ 5.7 Hz), 18.30 (s, CH_2), 24.15 (s, CH_2), 31.71 (s, CH_2), 61.39 (d, $POCH_2$, $J_{C–P}$ 5.0 Hz), 72.61 (d, $COCH_2$, $J_{C–P}$ 16.5 Hz), 89.31 (d, OC, $J_{C–P}$ 14.8 Hz), 126.30 (s, HC=), 123.11 (d, PC=, $J_{C–P}$ 198.8 Hz), 130.01 (s, HC=), 146.03 (d, ClC=, $J_{C–P}$ 3.8 Hz). ^{31}P NMR ($CDCl_3$) δ: 9.14. IR (film, ν/cm^{-1}): 1241 (P=O), 1612, 1639 (C=C). Found (%): C, 50.78; H, 6.50; P, 10.20. Calc. for $C_{13}H_{20}ClPO_4$ (%): C, 50.91; H, 6.57; P, 10.10.