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Preparation of halo enol phostones by reaction of acetylenic phosphonate monoesters with (bis-collidine)halo hexafluorophosphate

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ABSTRACT

Reaction of non-conjugated acetylenic phosphonate monoesters with (bis-collidine) bromo and iodo hexafluorophosphates was found to lead to the formation of halo enol phostones. Depending on the size of the heterocyclic compounds formed (6–8-membered compounds), *endo* or a mixture of *endo* and *exo* cyclization products were obtained.

We recently reported a study concerning the formation of phostones by reaction of ethylenic phosphonate monoesters with (bis-collidine)halo hexafluorophosphates.[1] We want now to report our results concerning the reaction of acetylenic phosphonate monoesters.[2] No results have been reported concerning the possibility to prepare halo enol phostones by electrophilic cyclizations, except the preparation of 4-halo phosphaisocoumarins by reaction of 2-(1-alkynyl)phenylphosphonates with halo reagents such as I_2, ICl, NBS and NCS.[3] The reaction of acetylenic carboxylic acids with halo reagents has been intensively studied, and led to the formation of halo enol lactones.[4] Interesting biological activities have been reported for these derivatives.[5] The phosphorus equivalents of these compounds should also present useful biological properties.

The phosphonate monoesters **3a,b** and **6a–d** have been prepared in satisfactory yields as reported in Scheme 1, using standard procedure from the corresponding alcohols. These latter were either commercially available or prepared by alkylation of true acetylenic alcohols.[6]

The halo cyclizations were then carried out in dichloromethane in the presence of (bis-collidine)bromo or -iodo hexafluorophosphates as indicated in Scheme 2.[7]

Our results are reported in Table 1.[8] With the phosphonate monoester **3a**, no product was isolated. This result can be explained by the instability of the resulting 4-membered phostone. However, a similar result was observed with the phosphonate **3b**, for which a 5-*endo* cyclization was expected, so the hypothesis of the instability under these reaction conditions of propargylic phosphonates can also be advanced. Interestingly, phosphonate **6a** led to the formation of phostones **7** and **8** in good yields. The iodo and the bromo reagents yielded exclusively the 6-*endo* cyclization products. With phosphonate **6b**, for which the carbon chain was increased of one atom compared to compound **6a**, the *exo* cyclization products **9** and **11** became the major products of the reaction. This was also the case for the iodo product **18** in the case of phosphonate **6d**. However, starting from phosphonates **6c** and **6d**, the reaction of the bromo reagent furnished only the phostones **13** and **16** corresponding to the 8-*endo* cyclizations. With the iodo reagent, a mixture of *endo* and *exo* cyclization products was obtained. We previously reported the biggest trend of the bromo reagent, compared to the iodo reagent, to lead to *endo* cyclization products.[9] The fact that the yields were higher with the phosphonate monoester **6d** than the phosphonate monoester **6c**, seemed to be due to the higher electronic donating effect of the butyl group compared to the methyl group, which probably favoured the electrophilic addition of the halonium onto the triple bond.

The structural determination of phostones **7–18** was difficult, due to the fact that their carbon–carbon double bond was tetrasubstituted. This problem was solved mainly using HMBC and HSQC NMR experiments. A correlation between the hydrogen fixed at the methylene β to the carbon–carbon double bond and the closest vinyl carbon on this double bond was observed and allowed to

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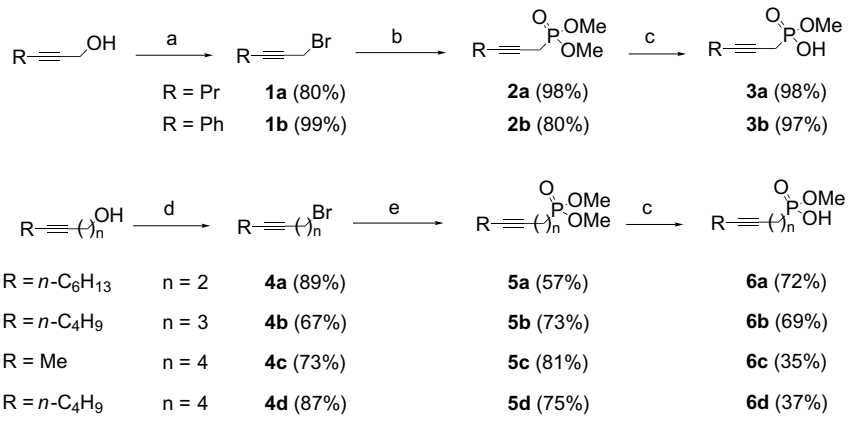
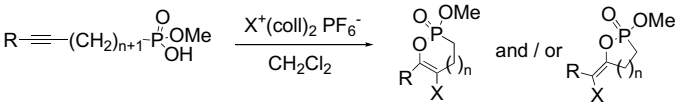


Scheme 1. Preparation of phosphonate monoesters **3a**,**b** and **6a–d**. Reagents and conditions: (a) PBr_3, pyridine; (b) $(MeO)_3P$; (c) (i) NaI, butan-2-one; (ii) 1 N HCl; (d) (i) MsCl, Et_3N, Et_2O; (ii) LiBr, acetone; (e) $HP(O)(OMe)_2$, NaH, THF.

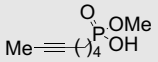
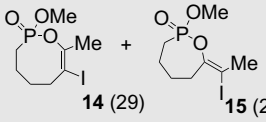
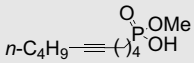
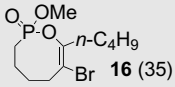
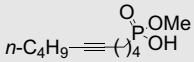
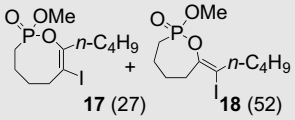


Scheme 2. Halocyclization of phosphonate monoesters **3a**,**b** and **6a–d**.

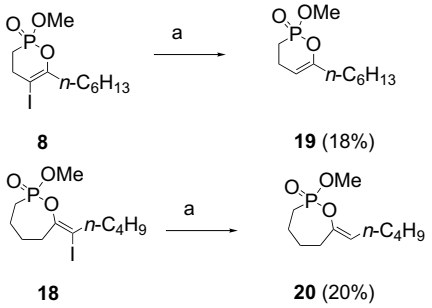
Table 1
Reaction of phosphonates with (bis-collidine)halo hexafluorophosphates

Entry	Phosphonate	Halo reagent[a]	Photone (Y, %)	δ(P)	δ(C_{sp^2}—X)	δ(C_{sp^2}—O)
a	Pr—≡—P(O)(OMe)OH **3a**	BXH	Degradation	—	—	—
b	Ph—≡—P(O)(OMe)OH **3b**	BXH	Degradation	—	—	—
c	*n*-C_6H_{13}—≡—(CH$_2$)$_2$—P(O)(OMe)OH **6a**	BBH	**7** (69)	20.5	100.7	149.9
d	*n*-C_6H_{13}—≡—(CH$_2$)$_2$—P(O)(OMe)OH **6a**	BIH	**8** (91)	21.5	98.9	155.7
e	*n*-C_4H_9—≡—(CH$_2$)$_3$—P(O)(OMe)OH **6b**	BBH	**9** (20) + **10** (12)	26.5 21.8	64.8 110.0	147.6 149.8
f	*n*-C_4H_9—≡—(CH$_2$)$_3$—P(O)(OMe)OH **6b**	BIH	**11** (75) + **12** (13)	25.6 24.9	91.5 83.6	147.1 150 .0
g	Me—≡—(CH$_2$)$_4$—P(O)(OMe)OH **6c**	BBH	**13** (14)	31.7	113.8	144.2

Table 1 (*continued*)

Entry	Phosphonate	Halo reagent[a]	Phostone (Y, %)	δ(P)	$\delta(C_{sp^2}-X)$	$\delta(C_{sp^2}-O)$
h	 **6c**	BIH	 **14** (29) + **15** (27)	30.5 30.6	83.2 89.2	144.2 144.2
g	 **6d**	BBH	 **16** (35)	31.7	113.6	147.5
h	 **6d**	BIH	 **17** (27) + **18** (52)	30.5 30.3	89.0 92.7	149.6 146.1

[a] BBH: (bis-collidine)bromo hexafluorophosphate. BIH: (bis-collidine)iodo hexafluorophosphate.



8 **19** (18%)

18 **20** (20%)

Scheme 3. Reagents: (a) PPh_3, Et_3N, HCO_2H, $Pd(OAc)_2$.

determine the nature *endo* or *exo* of these compounds. We have reported in Table 1 the chemical shift of these characteristic carbons and that of the phosphorus atom.

We decided to test also the dehalogenation of these compounds in view of their potential synthetic applications. Different methods are reported in the literature in the case of vinyl halides.[10] Under the rather harsh conditions necessary to remove vinyl halides these phostones appeared somewhat unstable. Messy products were usually obtained. However, formic acid in the presence of triphenylphosphine and palladium acetate as catalyst[11] gave encouraging results in the case of iodo derivatives.[12] We report in Scheme 3 examples of our results. Work is in progress to improve these results.

In conclusion, we reported for the first time the formation of halo enol phostones by electrophilic cyclizations of acetylenic phosphonate monoesters. These cyclizations allow the formation of 6–8-membered compounds, either by *endo* or *exo* cyclizations. Compared to the results observed in the case of acetylenic carboxylic acids,[4] our results show that with phosphonates, *endo* cyclizations are usually favoured over *exo* cyclizations.[13] This is particularly true for the cyclization of phosphonate **6a**, since no 5-*exo* cyclization was observed, whilst pent-4-ynoic acid derivatives led to lactones by *exo* cyclizations.[4,14] The fact that (bis-collidine)halo reagents were used allowed the formation of 8-membered compounds. These compounds could probably not obtained using halo reagents such as halogens, NXS or ICl.[9]

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7. *General procedure for the halo cyclizations*: To a dichloromethane solution (5 mL) of (bis-collidine)halo hexafluorophosphate (0.36 mmol, 1.3 equiv) was added in the dark, in 2 h, a dichloromethane solution (3 mL) of monoester phosphonate (0.3 mmol). After 1 h at room temperature, the solvent was removed under vacuum and the residue was purified by liquid chromatography over silica gel (EtOAc).
8. Compound **7**: ^{1}H NMR δ 3.75 (d, *J* 11.0, 3H), 2.85–2.72 (m, 2H), 2.41–2.27 (m, 2H), 2.08–1.94 (m, 2H), 1.49 (quintuplet, *J* 7.2, 2H), 1.33–1.18 (m, 6H), 0.84 (t, *J* 6.5, 3H). ^{13}C NMR δ 149.9 (d, *J* 7.5, C_{sp^2}–O), 100.7 (d, *J* 15.7, C–Br), 51.9 (d, *J* 7.0, OMe), 33.9 (d, *J* 4.5, CH_2), 31.3 (d, *J* 6.8, CH_2), 28.3 (CH_2), 25.9 (CH_2), 21.6 (d, *J* 138.8, CH_2), 13.9 (CH_3). IR ν (cm^{-1}) 2979.5 (C–H), 1467.2 (P–O–C), 1382.3, 1097.9, 907.3. HRMS calcd for $C_{11}H_{20}O_3BrNaP$ [M+Na$^+$] 333.0231, found 333.0229. Compound **8**: ^{1}H NMR δ 3.82 (t, *J* 11.1, 3H), 3.06–2.80 (m, 2H), 2.53–2.44 (m, 2H), 2.19–1.90 (m, 2H), 1.55 (quintuplet, *J* 8.0, 2H), 1.38–1.23 (m, 6H), 0.9 (t, *J* 7.5, 3H). ^{13}C NMR δ 155.7 (d, *J* 8.9, C_{sp^2}–O), 98.9 (d, *J* 21.0, C–I), 52.2 (d, *J* 7.0, OMe), 37.8 (d, *J* 4.4, CH_2), 35.6 (d, *J* 9.0, CH_2), 31.5 (CH_2), 28.4 (CH_2), 26.4 (CH_2), 22.5 (CH_2), 21.2 (d, *J* 127.7, CH_2), 14.0 (CH_3). IR ν (cm^{-1}) 2985.0 (C–H), 1470.2 (P–O–C), 1382.2, 1096.6, 907.3. HRMS calcd for $C_{11}H_{20}O_3INaP$ [M+Na$^+$] 381.0092, found 381.0097. Compound **9**: ^{1}H NMR δ 3.76 (d, *J* 11.0, 3H), 2.78–2.67 (m, 1H), 2.56–2.37 (m, 3H), 2.13–1.88 (m, 4H), 1.61–1.41 (m, 2H), 1.41–1.22 (m, 2H), 0.88 (t, *J* 7.0, 3H). ^{13}C NMR δ 147.6 (d, *J* 8.4, C_{sp^2}–O), 64.8 (d, *J* 5.0, C–Br), 52.0 (d, *J* 7.0, OMe), 37.5 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 25.9 (d, *J* 134.0, CH_2), 22.0 (CH_2), 20.8 (d, *J* 7.0, CH_2), 13.7 (CH_3). Compound **10**: ^{1}H NMR δ 3.85 (d, *J* 11.0, 3H), 2.78–2.67 (m, 1H), 2.56–2.37 (m, 3H), 2.13–1.88 (m, 4H), 1.61–1.41 (m, 2H), 1.41–1.22 (m, 2H), 0.90 (t, *J* 7.0, 3H). ^{13}C NMR δ 149.8 (d, *J* 8.3, C_{sp^2}–O), 110.6 (d, *J* 5.7, C–Br), 52.3 (d, *J* 7.0, OMe), 47.0 (CH_2), 33.8 (CH_2), 27.6 (CH_2), 21.7 (CH_2), 21.1 (d, *J* 8.9, CH_2), 17.5 (d, *J* 130.0, CH_2), 13.8 (CH_3). Compound **11**: ^{1}H NMR δ 373 (d, *J* 10.8, 3H), 2.98–2.87 (m, 1H), 2.64–2.49 (m, 1H), 2.49–2.42 (m, 1H), 2.42–2.28 (m, 1H), 2.07–1.70 (m, 4H), 1.52–1.37 (m, 2H), 1.37–1.23 (m, 2H), 0.87 (t, *J* 7.2, 3H). ^{13}C NMR δ 147.1 (d, *J* 9.0, C_{sp^2}–O), 91.5 (d, *J* 5.2, C–I), 35.7 (CH_2), 32.0 (d, *J* 6.4, CH_2), 32.0 (d, *J* 6.4, CH_2), 31.3 (CH_2), 21.8 (d, *J* 128.6, CH_2), 21.5 (CH_2), 20.0 (d, *J* 8.4 CH_2), 13.8 (CH_3). IR ν (cm^{-1}) 2958.8, 1650.7, 1468.4, 1216.8, 1166.4, 907.3. HRMS calcd for $C_{10}H_{18}O_3INaP$ [M+Na$^+$] 366.9936, found 366.9937. Compound **12**: ^{1}H NMR δ 3.80 (d, *J* 11.2, 3H), 2.89 (t,

J 6.0, 2H), 2.55 (t, *J* 7.0, 2H), 2.29–1.99 (m, 2H), 1.99–1.76 (m, 2H), 1.60–1.49 (m, 2H), 1.42–1.30 (m, 2H), 0.93 (t, *J* 7.2, 3H). ^{13}C NMR δ 150.0 (d, *J* 7.8, C_{sp^2}–O), 83.6 (d, *J* 7.0, C–I), 52.1 (d, *J* 7.0, OMe), 41.1 (d, *J* 2.2, CH_2), 37.1 (CH_2), 28.1 (CH_2), 25.6 (d, *J* 133.0, CH_2), 22.1 (CH_2), 20.9 (d, *J* 7.3, CH_2), 13.8 (CH_3). IR ν (cm^{-1}) 2958.8, 1650.7, 1468.4, 1216.8, 1166.4, 907.3. HRMS calcd for $C_{10}H_{18}O_3INaP$ [M+Na$^+$] 366.9936, found 366.9941. Compound **13**: ^{1}H NMR δ 3.82 (d, *J* 11.1, 3H), 2.88–2.77 (m, 1H), 2.62–2.52 (m, 1H), 2.17 (br s, 3H), 2.12–1.96 (m, 1H), 1.94–1.73 (m, 4H), 1.71–1.55 (m, 1H). ^{13}C NMR δ 144.2 (d, *J* 9.1, C_{sp^2}–O), 113.8 (d, *J* 7.0, C–Br), 52.1 (d, *J* 6.7, OMe), 32.9 (CH_2), 25.6 (CH_2), 23.5 (d, *J* 133.0, CH_2), 20.1 (CH_2), 17.9 (d, *J* 6.0, CH_2). HRMS calcd for [M+Na$^+$] $C_8H_{14}O_3BrNaP$ 290.9762, found 290.9762. Compound **14**: ^{1}H NMR δ 3.79 (d, *J* 11.0, 3H), 2.86–2.75 (m, 2H), 2.45 (dt, *J* 2.0/1.0, 3H), 2.07–1.43 (m, 6H). ^{13}C NMR δ 146.4 (d, *J* 5.9, C_{sp^2}–O), 83.2 (d, *J* 9.6, C–I), 52.1 (d, *J* 6.7, OMe), 35.8 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 24.8 (d, *J* 129.8, CH_2), 21.5 (d, *J* 5.5, CH_2). IR ν (cm^{-1}) 1653.1, 1469.8, 1247.2, 1041.9. HRMS calcd for [M+Na$^+$] $C_8H_{14}O_3INaP$ 338.9623, found 338.9620. Compound **15**: ^{1}H NMR δ 3.78 (d, *J* 11.0, 3H), 2.96–2.86 (m, 2H), 2.25 (dt, *J* 2.2/0.5, 3H), 2.07–1.43 (m, 6H). ^{13}C NMR δ 146.2 (d, *J* 6.2, C_{sp^2}–O), 89.2 (d, *J* 7.5, C–I), 52.2 (d, *J* 7.3, OMe), 36.1 (CH_2), 25.7 (CH_2), 23.5 (CH_2), 23.5 (d, *J* 133.7, CH_2), 17.5 (d, *J* 6.3, CH_2). IR ν (cm^{-1}) 1653.1, 1469.8, 1247.2, 1041.9. HRMS calcd for [M+Na$^+$] $C_8H_{14}O_3INaP$ 338.9623, found 338.9621. Compound **16**: ^{1}H NMR δ 3.76 (d, *J* 10.7, 3H), 2.85–2.69 (m, 1H), 2.58–2.44 (m, 3H), 2.09–1.65 (m, 6H), 1.65–1.40 (m, 2H), 1.40–1.22 (m, 2H), 0.88 (t, *J* 7.0, 3H). ^{13}C NMR δ 147.5 (d, *J* 8.9, C_{sp^2}–O), 113.6 (d, *J* 7.0, C–Br), 52.0 (d, *J* 7.0, OMe), 32.9 (CH_2), 32.7 (CH_2), 27.9 (CH_2), 25.3 (d, *J* 2.0, CH_2), 23.3 (d, *J* 134.0, CH_2), 21.9 (CH_2), 17.7 (d, *J* 6.0, CH_2), 13.7 (CH_2). HRMS calcd for [M+Na$^+$] $C_{11}H_{20}O_3BrNaP$ 333.0231, found 333.0227. Compound **17**: ^{1}H NMR δ 3.77 (d, *J* 11, 3H), 2.98–2.68 (m, 2H), 2.66–2.43 (m, 2H), 2.11–1.61 (m, 6H), 1.61–1.17 (m, 4H), 0.90 (t, *J* 7.0, 3H). ^{13}C NMR δ 149.5 (d, *J* 8.8, C_{sp^2}–O), 89.0 (d, *J* 8.0, C–I), 52.1 (d, *J* 7.0, OMe), 36.2 (CH_2), 36.1 (CH_2), 28.3 (CH_2), 25.6 (CH_2), 23.5 (d, *J* 134.0, CH_2), 21.9 (CH_2), 17.4 (d, *J* 5.5, CH_2), 13.9 (CH_3). IR ν (cm^{-1}) 1470.6, 1382.2, 1096.2, 907.3. HRMS calcd for [M+Na$^+$] $C_{11}H_{20}O_3INaP$ 381.0092, found 381.0095. Compound **18**: ^{1}H NMR δ 3.78 (d, *J* 11.0, 3H), 2.98–2.68 (m, 2H), 2.66–2.43 (m, 2H), 2.11–1.61 (m, 6H), 1.61–1.17 (m, 4H), 0.88 (t, *J* 7.0, 3H). ^{13}C NMR δ 146.1 (d, *J* 6.0, C_{sp^2}–O), 92.7 (d, *J* 10.0, C–O), 52.1 (d, *J* 7.0, OMe), 36.6 (CH_2), 36.0 (CH_2), 31.2 (CH_2), 26.5 (CH_2), 25.1 (d, *J* 134.0, CH_2), 21.5 (CH_2), 17.4 (d, *J* 6.0, CH_2), 13.8 (CH_3). IR ν (cm^{-1}) 1470.6, 1382.2, 1096.2, 907.3. HRMS calcd for [M+Na$^+$] $C_{11}H_{20}O_3INaP$ 381.0092, found 381.0096.

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12. Compound **19**: ^{1}H NMR δ 4.78–4.68 (m, 1H), 3.80 (d, *J* 10.8, 3H), 2.50–2.33 (m, 2H), 2.20–2.04 (m, 2H), 2.04–1.81 (m, 2H), 1.50 (m, 2H), 1.32–1.19 (m, 6H), 0.89 (t, *J* 6.9, 3H). ^{13}C NMR δ 152.8 (d, *J* 8.9 C_{sp^2}–O), 100.2 (d, *J* 8.5, C_{sp^2}–H), 51.7 (d, *J* 6.8, OMe), 34.6 (d, *J* 5.3, CH_2), 31.5 (CH_2), 28.5 (CH_2), 26.4 (CH_2), 22.5 (CH_2), 20.6 (d, *J* 9.0, CH_2), 18.4 (d, *J* 127.6, CH_2), 14.0 (CH_3). ^{31}P NMR δ 22.8. Compound **20**: ^{1}H NMR δ 4.70 (t, *J* 7.0, 1H), 3.82 (d, *J* 11.0, 3H), 2.54 (dd, *J* 15.0/10.0, 1H), 2.43 (dd, *J* 15.0/10.0, 1H), 2.60–2.16 (m, 2H), 2.60–1.55 (m, 6H), 1.39–1.22 (m, 4H), 0.90 (t, *J* 6.4, 3H). ^{13}C NMR δ 146.8 (d, *J* 4.6, C_{sp^2}–H), 51.9 (d, *J* 7.0, OMe), 40.0 (CH_2), 31.5 (CH_2), 28.7 (CH_2), 25.4 (d, *J* 9.0, CH_2), 24.6 (CH_2), 22.3 (CH_2), 22.0 (d, *J* 5.0, CH_2), 13.9 (CH_3). ^{31}P NMR δ 30.9.
13. Phostones **7–20** were found to be stable for several months at rt and several years at 0 °C. Phostones **19**, **20** were stable after several days at pH 8.
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