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Synthesis of 4-halophosphaisocoumarins via halocyclization of 2-(1-alkynyl)phenylphosphonates

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Abstract—A series of 4-halophosphaisocoumarins were prepared with high regioselectivity in good to excellent yields under mild conditions by the reaction of 2-(1-alkynyl)phenylphosphonic acid diesters with I_2 in $CHCl_3$ or ICl in CH_2Cl_2, or by the reaction of 2-(1-alkynyl)phenylphosphonic acid monoesters with NBS or NCS in DMF. Whether the alkynylphosphonates could cyclize or not was affected by the substituents, reaction solvents and electrophiles. A rationale for this reaction is discussed.

1. Introduction

4-Chloroisocoumarins **1** are effective irreversible inhibitors of serine proteases[1] and potent inhibitors of amyloid peptide production.[2] Since there is a remarkable similarity in bioactivities between the carbon species and their phosphorus counterparts,[3] one would anticipate that phosphorus 4-chloroisocoumarin analogs **2–4** might have potential bioactivities similar to those of the 4-chloroisocoumarins reported herein (Fig. 1).

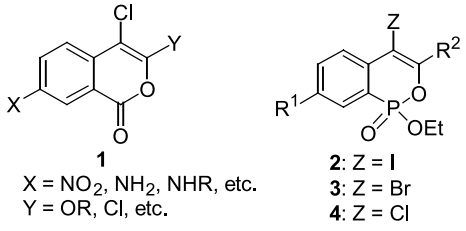

Figure 1. 4-Chloroisocoumarins and 4-haolophosphaisocoumarins.

In a recent communication, we described the synthesis of 4-iodophosphaisocoumarins **2** via iodocyclization of 2-(1-alkynyl)phenylphosphonic acid diesters with I_2 or ICl.[4] However, the bromo- and chlorophosphaisocoumarins **3** and **4** remain unknown compounds as yet. On the other hand, during the course of preparing **2**, we found that this iodocyclization reaction showed very high 6-*endo*-dig[5] regioselectivity and the yields of **2** were dependent on the substituents of the substrates and the strength of the electrophiles. We think it is necessary to further study the cyclization of phosphonates to C–C triple bond with other electrophiles and synthesize more type of phosphaisocoumarins for future bioassays. Herein, we wish to present a detailed study on the halocyclization of 2-(1-alkynyl)-phenylphosphonates with I_2, ICl, NBS and NCS, respectively, and discuss the plausible mechanisms in this paper.

2. Results and discussion

We first examined the reaction of 2-(phenylethynyl) phenylphosphonate **5a** with 2.0 equiv of iodine in several different organic solvents at room temperature. It was obvious that the reaction was highly dependent on the type of solvent used (Table 1, entries 1–5). In CH_3CN and DMF, the diiodide **6a** was the major product (entries 1, 2); in benzene, a ketone byproduct **7a** was isolated (entry 3) (Fig. 2). Fortunately, when the reaction was run in $CHCl_3$ or CH_2Cl_2, the desired product **2a** was produced in good yield (entries 4, 5).

To explore the scope of this reaction, other 2-(1-alkynyl) phenylphosphonic acid diesters **5** with a variety of substituents were allowed to react with I_2 in $CHCl_3$ or with ICl in CH_2Cl_2 and the results are summarized in Table 1. I_2 was efficient in most cases and a series of 4-iodophosphaisocoumarins were obtained in good to excellent yields. However, **5c** with an H group on the

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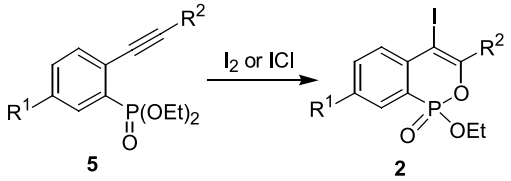
Table 1. Synthesis of phosphaisocoumarins via iodocyclization of **5**[a]

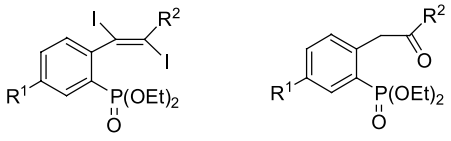


5 **2**

Entry	R^1	R^2	Solvent	Product(s)	Yield (%)[b]
1	H	C_6H_5	CH_3CN	**6a**	85
2	H	C_6H_5	DMF	**6a**	65
3	H	C_6H_5	PhH	**2a**+**7a**	35+15
4	H	C_6H_5	CH_2Cl_2	**2a**	80
5	H	C_6H_5	$CHCl_3$	**2a**	83
6	H	*n*-C_4H_9	$CHCl_3$	**2b**	70
7	H	H	$CHCl_3$	**2c**+**6c**	4+65
8[b]	H	H	CH_2Cl_2	**2c**	35
9	Cl	4-EtC_6H_4	$CHCl_3$	**2d**+**7d**	64+30
10[c]	Cl	4-EtC_6H_4	$CHCl_3$	**2d**	78
11	Cl	C_6H_5	$CHCl_3$	**2e**+**7e**	67+25
12[c]	Cl	C_6H_5	$CHCl_3$	**2e**	80
13	Cl	*n*-C_4H_9	$CHCl_3$	**2f**	64
14	Cl	Cyclopropyl	$CHCl_3$	**2g**	76
15	Cl	CH_2OCH_3	$CHCl_3$	**2h**	46
16	Cl	$SiMe_3$	$CHCl_3$	**2i**	0
17[b]	Cl	$SiMe_3$	CH_2Cl_2	**2i**	82
18	CH_3O	C_6H_5	$CHCl_3$	**2j**	93

[a] All reactions were conducted at room temperature with 2.0 equiv of I_2 in solvent for 12 h and the solvent was used as received unless otherwise specified.
[b] The reaction was carried out at room temperature with 1.2 equiv of ICl in CH_2Cl_2 under N_2 for 10 h.
[c] In this reaction, the solvent $CHCl_3$ was distilled from calcium hydride.

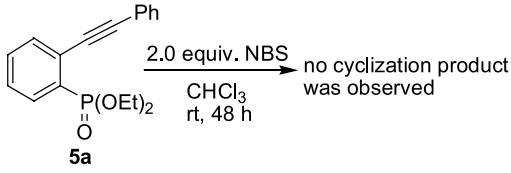
acetylenic moiety (R^2=H) gave the diiodide as the major product (entry 7). A bulky $SiMe_3$ group (entry 16) totally halted the reaction and the starting material **5i** was completely recovered under these conditions. Use of the strong electrophile ICl instead of I_2 afforded the desired products **2c** and **2i** in moderate yields for **5c** and **5i** (entries 8 and 17). It is also worth mentioning that for the reactions of **5d** and **5e** (entries 9 and 11), the corresponding α-ketone byproducts **7d** and **7e** resulting from water attacking onto the iodonium intermediates were also isolated (entries 9 and 11);[4] the α-ketone byproducts could be reduced substantially when the above reactions were carried out in anhydrous $CHCl_3$ (entries 10 and 12) (Fig. 2).



6 **7**

Figure 2. The structures of **6** and **7**.

We next studied the bromocyclization reaction of **5a**. Under the similar conditions used for the iodocyclization of **5a**, the reaction of **5a** with 2.0 equiv of NBS in $CHCl_3$ at room temperature for 48 h did not lead to any cyclization products but rather to an unidentified product (Scheme 1). This result was not surprising. Iodocyclization of unsaturated compounds is one of the most important procedures to construct various heterocycles containing N, O, S atoms.[6] However, there are far fewer reports about bromocyclization reactions[7] and especially chlorocyclization reactions,[7a,b] probably because of the stability of the corresponding halonium intermediates decreasing in the order of I>Br>Cl.[8] It has been reported that iodocyclization of alkenylphosphonic acid diesters could proceed smoothly, while under the similar conditions, bromocyclization of the same substrates only led to dibromides.[9] Although Shibuya and co-workers at last synthesized phostones by bromocyclization of alkenylphosphonic acid monoesters, they did not extend it to the chlorocyclization reactions.[10] The weak nucleophilicity of phosphonyl group and the lower reactivity of alkynes towards electrophilic reagents than that of alkenes might add more challenge to our proposed halocyclization reactions.



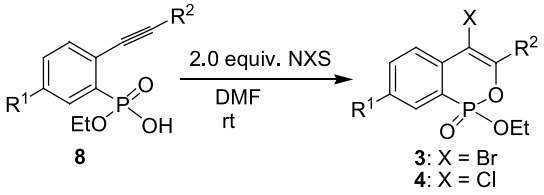
5a

Scheme 1. The reaction of **5a** with NBS in $CHCl_3$.

We then investigated the reaction of 2-(phenylethynyl) phenylphosphonic acid monoester **8a** with NBS. When using $CHCl_3$ as the solvent, the reaction of **8a** with 2.0 equiv of NBS at room temperature for 24 h afforded only a trace amount of the cyclization product **3a**. However, we were pleased to see that when using DMF as the solvent, the reaction of **8a** with NBS gave **3a** as the single product in 74% isolated yield (Table 2, entry 1). We thought that the solvents had a large effect on the reaction largely because the solvent DMF could act as a Lewis base to enhance the nucleophilicity of the phosphonyl oxygen.[11]

To explore the scope of this bromocyclization reaction, a series of 2-(1-alkynyl)phenylphosphonic monoesters **8** were

Table 2. Synthesis of phosphaisocoumarins via bromo- and chlorocyclization of **8**[a]

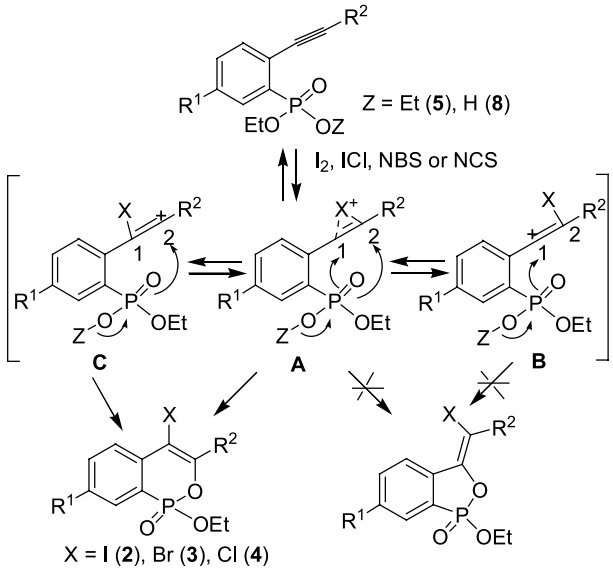


Entry	R^1	R^2	NXS	Product	Yield (%)[b]
1	H	C_6H_5	NBS	**3a**	74
2	Cl	C_6H_5	NBS	**3b**	84
3	Cl	4-EtC_6H_4	NBS	**3c**	85
4	Cl	Cyclopropyl	NBS	**3d**	73
5	Cl	*n*-C_4H_9	NBS	**3e**	85
6	Cl	CH_2OCH_3	NBS	**3f**	Trace
7	CH_3O	C_6H_5	NBS	**3g**	51
8	H	C_6H_5	NCS	**4a**	73
9	Cl	C_6H_5	NCS	**4b**	66
10	Cl	4-EtC_6H_4	NCS	**4c**	69
11	Cl	Cyclopropyl	NCS	**4d**	73
12	Cl	*n*-C_4H_9	NCS	**4e**	Trace
13	Cl	CH_2OCH_3	NCS	**4f**	Trace
14	CH_3O	C_6H_5	NCS	**4g**	Trace

[a] All reactions were conducted at room temperature with 2.0 equiv of NBS or NCS in DMF for 24 h.
[b] Isolated yield.

allowed to react with NBS or NCS in DMF at room temperature and the results are summarized in Table 2. Apparently, the substituents and electrophiles have large effects on the reaction. The substrates **8a–d** with aryl and cyclopropyl groups on the acetylenic moiety could react with both NBS and NCS to give the desired products in good to excellent yields (entries 1–4, 8–11). The substrate **8f** with an electron-withdrawing methoxymethyl group did not participate in either bromo- or chlorocyclization reaction (entries 6 and 13). The reaction of **8e** having a *n*-butyl group on the acetylenic moiety with NBS produced the desired product **3e** in 85% yield (entry 5), but most of the starting material **8e** was recovered even after extended exposure to NCS under the same conditions (entry 12). Moreover, the reaction of **8g** bearing an electron-donating methoxy group on the benzene with NBS gave the product **3g** only in 51% yield (entry 7), and the chlorocyclization of **8g** did not proceed at all under our conditions (entry 14). It is also worth mentioning that no 5-*exo*-dig[5] cyclization products were detected in each case. The bromo- and chlorocyclization products are assigned as **3** and **4** based on comparison of their IR, ^{1}H NMR, ^{31}P NMR spectrum with those of **2**.[4]

We rationalized our results by plausible mechanisms shown in Scheme 2. Electrophilic addition of I_2, ICl, NBS or NCS to the C–C triple bond might form the corresponding intermediates **A**, **B** or **C**; their stabilities and the nucleophilicity of the phosphonyl oxygen play crucial roles in determining whether the alkynylphosphonates will cyclize or not. Intramolecular nucleophilic attack by the phosphonyl oxygen onto the position 2 of **A** or **C** would give the desired products **2**, **3** or **4**. Alternatively, the phosphonyl oxygen might also attack onto the position 1 of **A** or **B** to give the five-membered-ring products. However, all the examined substrates showed high regioselectivity for six-membered-ring products, indicating that the 5-*exo*-dig process was very disadvantageous for 2-(1-alkynyl)phenylphosphonates. The above regioselectivity might be caused by the following factors: (1) the longer bond lengths of C–P and P–O would make the phosphonyl oxygen much closer to the farther position of the triple bonds; (2) the tetrahedral phosphonates might further increase the ring strain and lower the stabililty of the corresponding five-membered-ring products. Thus, the substrates (e.g., **8e** and **8g**), bearing groups that can better stabilize the benzylic cations **B** other than intermediates **C**, did not proceed the chlorocyclization reactions smoothly (Table 2, entries 12, 14). By way of contrast, the substituents have fewer effects on the iodo- and bromocyclization than on the chlorocyclization, probably because iodonium ions compete more effectively with open carbocations than bromonium ions, chloronium ions compete less effectively,[8] and it is difficult for open carbocations **B** to form the desired cyclization products.



Scheme 2. Plausible mechanisms of the halocyclization of 2-(1-alkynyl) phenylphosphonates.

3. Conclusions

In conclusion, a series of 4-iodophosphaisocoumarins were prepared with high regioselectivity in good yields via iodocyclization of 2-(1-alkynyl)phenylphosphonic acid diesters with I_2 in $CHCl_3$ or ICl in CH_2Cl_2, and 4-bromo- and 4-chlorophosphaisocoumarins were synthesized by the reaction of 2-(1-alkynyl)phenylphosphonic acid monoesters with NBS and NCS in DMF. These halocyclization reactions have been much affected by the substituents of the substrates, reaction solvents and electrophiles, which could be rationalized by the proposed mechanisms in this paper.

4. Experimental

4.1. General

NMR spectra were all recorded on a Varian Mercury 300 spectrometer using $CDCl_3$ as the solvent. The ^1H NMR spectra used $CDCl_3$ (with TMS) as the internal reference at 7.27 ppm. ^{31}P NMR spectra used the 85% H_3PO_4 as the external reference. MS spectra were determined using a HP5989A mass spectrometer. IR spectra were measured on a Y-Zoom Cursor instrument. Starting materials **5** and **8** were prepared as described previously.[11]

4.2. General procedure for the halocyclization of 5 by I_2

A mixture of **5** (0.50 mmol) and I_2 (1.00 mmol) was dissolved in $CHCl_3$ (5.0 mL). After stirring at room temperature for 12 h, the reaction mixture was then diluted with EtOAc and washed with 5% aqueous $Na_2S_2O_3$. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel using hexane/EtOAc as eluent to give the corresponding product **2**.

4.3. General procedure for the halocyclization of 5 by ICl

To the substrate **5** (0.10 mmol) was added ICl (0.12 mmol) in CH_2Cl_2 (1.2 mL), and the resulting mixture was stirred in the dark under nitrogen at room temperature for 10 h. The reaction mixture was then diluted with EtOAc and washed with 5% aqueous $Na_2S_2O_3$. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel using hexane/EtOAc as eluent to give the product **2**.

For the characterization data of compounds **2** in Table 1, see the Supporting information of Ref. 4.

4.4. Characterization data for compounds 6a, 6c, 7d, and 7e listed in Table 1

4.4.1. Diethyl 2-((*E*)1,2-diiodo-2-phenylvinyl)phenylphosphonate (6a). Red oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.20–8.23 (m, 2H), 7.50–7.88 (m, 7H), 3.97–4.11 (m, 4H), 1.28 (t, $J=6.9$ Hz, 6H); MS (EI), *m/z* (%): 441 [$(M-I)^+$, 5], 412 (2), 385 (2), 241 (82), 213 (28), 185 (100), 167 (22), 105 (19), 77 (25); IR (film, cm^{-1}): ν 3062, 2924, 1596, 1450, 1209, 1146, 1099, 1019, 934.

4.4.2. Diethyl 2-((*E*)1,2-diiodovinyl)phenylphosphonate (6c). Red oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.83–7.93 (m, 1H), 7.33–7.53 (m, 2H), 7.11–7.23 (m, 2H), 4.00–4.19 (m, 4H), 1.25–1.34 (m, 6H); MS (EI), *m/z* (%): 365 [$(M-I)^+$, 86], 336 (30), 309 (100), 291 (10), 182 (46), 165 (23), 153 (43), 136 (26), 118 (21); IR (film, cm^{-1}): ν 3058, 2980, 1592, 1466, 1391, 1243, 1140, 1081, 1049, 1024, 970.

4.4.3. {5-Chloro-2-[2-(4-ethyl-phenyl)-2-oxo-ethyl]-phenyl}-phosphonic acid diethyl ester (7d). Pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90–7.98 (m, 3H), 7.19–7.50 (m, 4H), 4.66 (s, 2H), 3.96–4.11 (m, 4H), 2.72 (q, $J=7.5$ Hz, 2H), 1.20–1.27 (m, 9H); MS (EI), *m/z* (%): 394 (M^+, 1), 291 (2), 254 (6), 178 (6), 150 (49), 133 (100), 105 (92), 77 (39); IR (film, cm^{-1}): ν 2969, 1686, 1606, 1478, 1384, 1250, 1221, 1182, 1106, 1019, 971. Anal. Calcd for $C_{20}H_{24}ClO_4P$: C, 60.82; H, 6.14. Found: C, 61.03; H, 6.18.

4.4.4. [5-Chloro-2-(2-oxo-2-phenyl-ethyl)-phenyl]-phosphonic acid diethyl ester (7e). Pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–8.06 (m, 7H), 7.24–7.29 (m, 1H), 4.73 (s, 2H), 4.03–4.17 (m, 4H), 1.25 (dt, $J_1=7.2$ Hz, $J_2=2.4$ Hz, 6H); MS (EI), *m/z* (%): 366 (M^+, 6), 261 (1), 228 (2), 187 (4), 165 (2), 105 (100), 77 (28); IR (film, cm^{-1}): ν 2982, 1691, 1598, 1478, 1384, 1330, 1250, 1217, 1150, 1019, 969; HRMS (EI): calcd for $C_{18}H_{20}ClO_4P$ (M^+): 366.07877. Found: 366.07821.

4.5. General procedures for the preparation of 3 and 4

A mixture of **8** (0.50 mmol), NBS (1.00 mmol) or NCS (1.00 mmol) was dissolved in DMF (5.0 mL). After stirring at room temperature for 24 h, the reaction mixture was then diluted with EtOAc and washed with 5% aqueous $Na_2S_2O_3$. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel using hexane–EtOAc (5/1–2/1) as eluent to give the corresponding product **3** or **4**. The isolated yield and the physical data for **3** and **4** are as follows:

4.5.1. 1-Ethoxy-3-phenyl-4-bromobenzo[*c*][1,2]oxaphosphinine 1-oxide (3a). White solid, mp 109–110 °C. Yield: 74%. ^1H NMR (300 MHz, $CDCl_3$): δ 7.92–8.01 (m, 2H), 7.71–7.88 (m, 3H), 7.45–7.56 (m, 4H), 4.25–4.31 (m, 2H), 1.36 (t, $J=6.9$ Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.94; MS (EI), *m/z* (%): 364 (M^+, 97), 336 (100), 279 (9), 257 (12), 239 (38), 229 (1), 165 (19), 105 (54), 77 (43); IR (KBr, cm^{-1}): ν 2992, 1608, 1446, 1268, 1234, 1070, 1019, 970. Anal. Calcd for $C_{16}H_{14}BrO_3P$: C, 52.62; H, 3.87. Found: C, 52.55; H, 3.88.

4.5.2. 7-Chloro-1-ethoxy-3-phenyl-4-bromobenzo[*c*][1,2]oxaphosphinine 1-oxide (3b). White solid, mp 109–110 °C. Yield: 84%. ^1H NMR (300 MHz, $CDCl_3$): δ 7.83–7.96 (m, 2H), 7.65–7.74 (m, 3H), 7.46–7.48 (m, 3H), 4.26–4.36 (m, 2H), 1.38 (t, $J=6.9$ Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 14.24; MS (EI), *m/z* (%): 400 (97), 398 (M^+, 75), 372 (100), 273 (16), 263 (10), 199 (10), 163 (14), 105 (28), 77 (25); IR (KBr, cm^{-1}): ν 2999, 1594, 1467, 1385, 1285, 1246, 1160, 1069, 1009, 973. Anal. Calcd for $C_{16}H_{13}BrClO_3P$: C, 48.09; H, 3.29. Found: C, 48.11; H, 3.18.

4.5.3. 7-Chloro-1-ethoxy-3-(4-ethylphenyl)-4-bromobenzo[*c*][1,2]oxaphosphinine 1-oxide (3c). White solid, mp 121–122 °C. Yield: 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82–7.94 (m, 2H), 7.64–7.67 (m, 3H), 7.28–7.30 (m, 2H), 4.25–4.35 (m, 2H), 2.72 (q, J=7.8 Hz, 2H), 1.37 (t, J=6.9 Hz, 3H), 1.29 (t, J=7.8 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 8.34; MS (EI), *m*/*z* (%): 426 (M^+, 78), 428 (100), 400 (69), 385 (55), 319 (12), 291 (9), 255 (11), 189 (23), 105 (14), 77 (18); IR (KBr, cm^{-1}): ν 2965, 1592, 1461, 1281, 1268, 1158, 1065, 1028, 1018, 974. Anal. Calcd for $C_{18}H_{17}BrClO_3P$: C, 50.55; H, 4.01. Found: C, 50.45; H, 3.93.

4.5.4. 7-Chloro-4-bromo-3-cyclopropyl-1-ethoxybenzo[*c*][1,2]oxaphosphinine 1-oxide (3d). White solid, mp 82–83 °C. Yield: 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.79 (m, 2H), 7.57–7.61 (m, 1H), 4.15–4.26 (m, 2H), 2.40–2.50 (m, 1H), 1.36 (t, J=6.9 Hz, 3H), 1.16–1.24 (m, 1H), 0.95–1.04 (m, 3H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.05; MS (EI), *m*/*z* (%): 362 (M^+, 30), 364 (39), 336 (38), 255 (100), 237 (24), 220 (13), 209 (23), 175 (13), 139 (10), 99 (6), 75 (4); IR (KBr, cm^{-1}): ν 2988, 1600, 1465, 1392, 1284, 1266, 1161, 1062, 1018, 970. Anal. Calcd for $C_{13}H_{13}BrClO_3P$: C, 42.95; H, 3.60. Found: C, 43.01; H, 3.59.

4.5.5. 3-Butyl-4-bromo-7-chloro-1-ethoxy-benzo[*c*][1,2]oxaphosphinine 1-oxide (3e). Pale yellow oil. Yield: 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.81 (m, 2H), 7.57–7.61 (m, 1H), 4.22–4.27 (m, 2H), 2.69–2.78 (m, 2H), 1.62–1.70 (m, 2H), 1.23–1.46 (m, 5H), 0.95 (t, J=7.2 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 12.39; MS (EI), *m*/*z* (%): 380 [$(M+2)^+$, 100], 378 (M^+, 77), 352 (26), 323 (52), 271 (90), 229 (64), 101 (6), 75 (7); IR (film, cm^{-1}): ν 2959, 1609, 1466, 1389, 1287, 1273, 1081, 1033, 971. Anal. Calcd for $C_{14}H_{17}BrClO_3P$: C, 44.30; H, 4.51. Found: C, 44.64; H, 4.47.

4.5.6. 7-Methoxy-1-ethoxy-3-phenyl-4-bromobenzo[*c*][1,2]oxaphosphinine 1-oxide (3g). White solid, mp 125–126 °C. Yield: 51%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88–7.94 (m, 1H), 7.70–7.74 (m, 2H), 7.35–7.47 (m, 4H), 7.21–7.25 (m, 1H), 4.22–4.32 (m, 2H), 3.92 (s, 3H), 1.37 (t, J=7.2 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 10.37; MS (EI), *m*/*z* (%): 394 (M^+, 100), 396 (96), 366 (94), 351 (50), 269 (4), 259 (16), 195 (4), 105 (31), 77 (34); IR (KBr, cm^{-1}): ν 2985, 1598, 1486, 1280, 1261, 1154, 1030, 1020, 948. Anal. Calcd for $C_{17}H_{16}BrO_4P$: C, 51.67; H, 4.08. Found: C, 51.90; H, 4.37.

4.5.7. 1-Ethoxy-3-phenyl-4-chlorobenzo[*c*][1,2]oxaphosphinine 1-oxide (4a). White solid, mp 100–101 °C. Yield: 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76–7.91 (m, 5H), 7.46–7.60 (m, 4H), 4.21–4.33 (m, 2H), 1.35 (t, J=7.2 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 14.28; MS (EI), *m*/*z* (%): 320 (M^+, 80), 292 (100), 235 (15), 199 (9), 165 (17), 105 (49), 77 (51); IR (KBr, cm^{-1}): ν 2995, 1609, 1446, 1388, 1268, 1235, 1159, 1020, 967. Anal. Calcd for $C_{16}H_{14}ClO_3P$: C, 59.92; H, 4.40. Found: C, 59.70; H, 4.25.

4.5.8. 7-Chloro-1-ethoxy-3-phenyl-4-chlorobenzo[*c*][1,2]oxaphosphinine 1-oxide (4b). White solid, mp 138–139 °C. Yield: 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67–7.92 (m, 5H), 7.46–7.49 (m, 3H), 4.25–4.35 (m, 2H), 1.37 (t, J=6.9 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 12.19; MS (EI), *m*/*z* (%): 354 (M^+, 70), 326 (100), 269 (8), 233 (4), 199 (8), 163 (13), 105 (39), 77 (36); IR (KBr, cm^{-1}): ν 2979, 1601, 1467, 1387, 1285, 1268, 1161, 1011, 969. Anal. Calcd for $C_{16}H_{13}Cl_2O_3P$: C, 54.11; H, 3.69. Found: C, 54.12; H 3.49.

4.5.9. 7-Chloro-1-ethoxy-3-(4-ethylphenyl)-4-chlorobenzo[*c*][1,2]oxaphosphinine 1-oxide (4c). White solid, mp 105–107 °C. Yield: 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.92 (m, 2H), 7.66–7.75 (m, 3H), 7.29–7.32 (m, 2H), 4.25–4.35 (m, 2H), 2.73 (q, J=7.8 Hz, 2H), 1.36 (t, J=6.9 Hz, 3H), 1.29 (t, J=7.5 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 8.30; MS (EI), *m*/*z* (%): 382 (M^+, 100), 354 (85), 339 (82), 319 (19), 290 (11), 255 (15), 189 (14), 105 (12), 77 (18); IR (KBr, cm^{-1}): ν 2966, 1599, 1468, 1290, 1269, 1161, 1075, 1011, 972. Anal. Calcd for $C_{18}H_{17}Cl_2O_3P$: C, 56.42; H, 4.47. Found: C, 56.36; H, 4.54.

4.5.10. 4,7-Dichloro-3-cyclopropyl-1-ethoxy-benzo[*c*][1,2]oxaphosphinine 1-oxide (4d). White solid, mp 62–63 °C. Yield: 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.81 (m, 3H), 4.15–4.26 (m, 2H), 2.33–2.43 (m, 1H), 1.35 (t, J=6.9 Hz, 3H), 1.16–1.24 (m, 1H), 0.94–1.04 (m, 3H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.05; MS (EI), *m*/*z* (%): 318 (M^+, 72), 320 (47), 290 (100), 255 (94), 237 (27), 220 (15), 209 (37), 175 (21), 139 (15), 99 (9), 75 (10); IR (KBr, cm^{-1}): ν 2955, 1612, 1467, 1380, 1266, 1220, 1156, 1070, 1025, 988. Anal. Calcd for $C_{13}H_{13}Cl_2O_3P$: C, 48.93; H, 4.11. Found: C, 48.83; H 4.58.

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