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Alkylation reactions of phosphachroman-2,4-diones and 4-hydroxy phosphacoumarins

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Abstract

Phosphachroman-2,4-dione and 4-alkoxyphosphacoumarin derivatives, phosphonic analogues of chromones and coumarins with potential biological activities, were synthesized in good yields through sequential base-catalyzed intramolecular cyclization of *O*-alkyl-*O*′-(2′-methoxycarbonyl phenyl)-(substituted) benzyl phosphonates and alkylation. The synthesis sets the stage for an examination of the biological activities.

Keywords: Phosphachroman-2,4-dione; Phosphacoumarin; Intramolecular cyclization; Alkylation

1. Introduction

Chromones and coumarins, two kinds of important natural products with various biological activities, have attracted great interest in the area of pharmacology [1]. Many chromones and coumarins were synthesized leading to molecules with more potent medicinal

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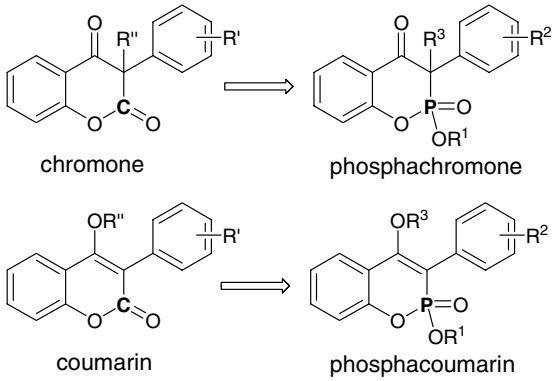


Fig. 1. The structure of chromones, coumarins, and their analogs phosphachromones, phosphacoumarins.

and biological activities [2]. The development of phosphorus chemistry has led to organophosphorus compounds that have applications in the area of pharmacy [3], agriculture [4], and synthetic chemistry [5]. Phosphonic acids and their derivatives often exhibit similar biological activity to the natural carboxylic acids and their derivatives [6] because the former are similar to the tetrahedral intermediates of the latter. Hence, introduction of the phosphorus atom into coumarins and chromanones to form phosphachromones and phosphacoumarins (Fig. 1) may result in the development of new molecules with biological activities. Chen and Rodios's groups [7] have synthesized phosphacoumarins by a condensation reaction of salicylaldehyde with triethylphosphonoacetate in low yields (not more than 21%), and the major products were phosphonocoumarins. Mironov et al. [8] have also reported the preparation of 4-aryl phosphacoumarin using benzene-1,2-diol and substituted phenyl acetylene as the starting materials.

In our previous work [9], a convenient and efficient approach to 4-O-acylated, phosphorylated and sulfonylated phosphacoumarins has been developed through reactions of phosphachroman-2,4-diones and 4-hydroxy phosphacoumarins with acetic anhydride, diethoxylphosphoryl chloride, *p*-toluenesulfonyl chloride, and methylsulfonyl chloride. In order to enrich the library of phosphacoumarins, we attempted reactions of phosphachroman-2,4-diones and 4-hydroxy phosphacoumarins with alkyl halides, and a mixture of O-alkylation and C-alkylation products was obtained in different ratios. To the best of our knowledge, the C-alkylation products, phosphachromones have not been reported so far.

2. Materials and methods

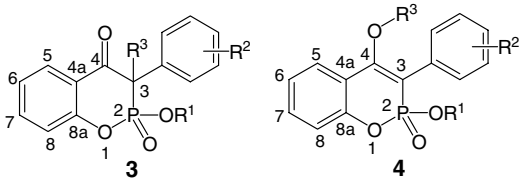
^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 300 spectrometer using tetramethylsilane as the internal standard. High resolution mass spectra were recorded on a Bruker APEX-II Fourier transform ion cyclotron resonance (FT-ICR) MS instrument equipped with 4.7 T super-conduction magnet and an analytical electrospray source.

*2.1. General procedure for the preparation of **3** and **4***

Anhydrous K_2CO_3 (1 mmol) was added to mixture of **1** and **2** (0.5 mmol) in 5 mL of anhydrous acetonitrile, and the mixture was stirred for 20 min. Methyl iodide, benzyl bromide or allyl bromide (0.6 mmol) in 2 mL of acetonitrile was then added dropwise

within 10 min. The mixture was stirred at room temperature for another 1 h, 10 mL of dichloromethane was added to the resulting solution, and filtered. The solid was washed with dichloromethane (2× 5 mL), and the filtrate was combined. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (3:1–2:1) as eluent to give **3** and **4**.

2.2. The numbers of the core structure



2.3. 2-Ethoxy-3-methyl-3-(4-methylphenyl)-phosphachroman-2,4-dione (*3ag*) and 2-ethoxy-3-(4-methylphenyl)-4-methoxy-phosphacoumarin (*4ag*)

Yellowish solid; total yield: 84%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 14.46 (**4ag**), 25.35 (**3ag**) the ratio of **3ag** to **4ag** is 1.3:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (tt, $^{3}J_{H-H} = 6.6$ Hz, 3H, OCH_2CH_3), 1.98 (qs, 3-CH_3 of **3ag**), 2.36 (qs, of 3-PhCH_3, 3H), 3.49 (ds, 4-CH_3O of **4ag**), 4.03 (m, 3H, OCH_2CH_3 of **3ag** and **4ag**), 7.15–8.11 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 (d, $^{3}J_{P-C} = 4.5$ Hz, $POCH_2CH_3$), 20.1 (m, 3-PhCH_3 and 3-CH_3 of **3ag**), 55.5 (d, $^{1}J_{C-P} = 121.5$ Hz, C-3 of **3ag**), 60.8 (m, OCH_3 of **4ag**) 64.4 (td, $^{2}J_{P-C} = 7.5$ Hz, $POCH_2CH_3$), 106.1 (d, $^{1}J_{C-P} = 175.0$ Hz, C-3 of **4ag**), 118.0–137.9 (Ar-C), 149.8 (d, $^{2}J_{P-C} = 5.0$ Hz, *C*-8a), 152.5 (*C*-8a of **3ag**) 158.5 (*C*-4 of **4ag**), 193.2 (*C*-4 of **3ag**); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 331.1099. Found: 331.1095.

2.4. 3-Methoxy-2-methyl-3-phenyl-phosphachroman-2,4-dione (*3bg*) and 2,4-dimethoxy-3-phenyl-phosphacoumarin (*4bg*)

Yellowish solid; total yield: 84%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 15.49 (**4bg**), 26.27 (**3bg**), the ratio of **3bg** to **4bg** is 4:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (d, $^{3}J_{H-P} = 17.5$ Hz, 2.4H, 3-CH_3 of **3bg**), 3.53–3.68 (m, 4-OCH_3 and $POCH_3$, 3.6H), 7.20–8.13 (m, Ar-H, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5 (dd, $^{2}J_{P-C} = 4.5$ Hz, 3-$CH_3$of **3bg**), 54.4 (4-OCH_3 of **4ag** and $POCH_3$), 57.0 (d, $^{1}J_{P-C} = 121.0$ Hz, C-3 of **3bg**), 119.9–136.7 (Ar-C), 152.5 (*C*-8a), 160.0 (*C*-4 of **4bg**), 192.9 (*C*-4 of **3bg**); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 303.0786. Found: 303.0780.

2.5. 2-Ethoxy-3-methyl-3-(4-chlorophenyl)-phosphachroman-2,4-dione (*3dg*) and 2-ethoxy-3-(4-chlorophenyl)-4-methoxy-phosphacoumarin (*4dg*)

Yellowish solid; total yield: 81%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 14.10 (**4dg**, trace), 24.39 (**3dg**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, $^{3}J_{H-P} = 7.1$ Hz, 3H, OCH_2CH_3),

1.96 (d, 3H, 3-CH_3), 4.06 (m, 2H, OCH_2CH$_3$), 7.20–8.14 (m, Ar-H, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (d, $^2J_{P-C} = 5.1$ Hz, POCH$_2$CH_3), 19.3 (d, $^2J_{P-C} = 5.0$ Hz, 3-CH$_3$), 55.2 (d, $^1J_{P-C} = 121.3$ Hz, C-3), 64.4 (d, $^2J_{P-C} = 7.9$ Hz, POCH_2CH$_3$), 119.8–136.7 (Ar-C), 152.8 (d, $^2J_{P-C} = 4.3$ Hz, *C*-8a), 192.5 (*C*-4); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 350.0475. Found: 350.0472.

2.6. 2-Ethoxy-3-methyl-3-(4-cyanophenyl)-phosphachroman-2,4-dione (**3eg**) and 2-ethoxy-3-(4-cyanophenyl)-4-methoxy-phosphacoumarin (**4eg**)

Yellowish solid; total yield: 86%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 13.03 (**4eg**), 23.22 (**3eg**), the ratio of **3eg** to **4eg** is 12:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, $^3J_{H-H} = 6.9$ Hz, 3H, OCH$_2$CH_3), 1.97 (ds, 2.8H, 3-CH_3 of **3eg**), 3.53 (s, 0.2H, 4-CH_3O of **4eg**), 4.05 (m, 2H, OCH_2CH$_3$ of **3eg** and **4eg**), 7.23–8.11 (m, 8H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 (d, $^3J_{P-C} = 5.0$ Hz, POCH$_2$CH_3), 19.4 (d, $^2J_{P-C} = 5.0$ Hz, 3-CH_3 of **3eg**), 56.0 (d, $^1J_{P-C} = 120.5$ Hz, C-3 of **3eg**), 64.7 (d, $^2J_{P-C} = 7.2$ Hz, POCH_2CH$_3$), 112.0 (*C*N), 118.5–138.8 (Ar-C), 152.8 (*C*-8a of **3eg**), 192.1 (*C*-4 of **3eg**); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 342.0895. Found: 342.0896.

2.7. 3-Benzyl-2-ethoxy-3-(4-methylphenyl)-phosphachroman-2,4-dione (**3ah**)

Yellowish solid; mp 90–92 °C; yield: 72%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 23.74; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, $^3J_{H-H} = 6.8$ Hz, 3H, OCH$_2$CH_3), 2.35 (s, 3H, PhCH_3), 3.67–3.94 (m, 4H, OCH_2CH$_3$, PhCH_2), 6.99–8.00 (m, 13H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9 (d, $^3J_{P-C} = 5.4$ Hz, POCH$_2$CH_3), 21.0 (Ph*C*H$_3$), 40.1 (Ph*C*H$_2$), 61.3 (d, $^1J_{P-C} = 120.1$ Hz, C-3), 64.4 (d, $^2J_{P-C} = 7.9$ Hz, O*C*H$_2$CH$_3$), 119.4–136.1 (Ar-*C*), 152.5 (*C*-8a), 192.1 (*C*-4); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 407.1412. Found: 407.1415.

2.8. 4-Benzoxy-2-ethoxy-3-(4-methxylphenyl)-phosphacoumarin (**4ah**)

Yellowish solid; mp 83–85 °C; yield: 12%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 14.04, 14.18, 14.69; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04, 1.46, 1.26 (tt, $^3J_{H-H} = 7.2$ Hz, 3H, OCH$_2$CH_3), 2.32, 2.39, 2.45 (ts, 3H, PhCH_3), 4.01–4.07 (m, 2H, OCH_2CH$_3$), 4.51–4.57 (m, 2H, PhCH_2O), 7.28–7.78 (m, 13H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9 (d, $^3J_{P-C} = 5.8$ Hz, POCH$_2$CH_3), 19.9, 20.5, 21.3 (ts, Ph*C*H$_3$), 63.8 (d, $^2J_{P-C} = 6.5$ Hz, PO*C*H$_2$CH$_3$), 75.1 (Ph*C*H$_2$O), 107.5 (d, $^1J_{P-C} = 112.8$ Hz, C-3), 118.5–138.3 (Ar-*C*), 149.8 (d, $^2J_{P-C} = 5.1$ Hz, *C*-8a), 157.8 (d, $^2J_{P-C} = 20.0$ Hz, *C*-4); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 407.1412. Found: 407.1417.

2.9. 3-Benzyl-2-ethoxy-3-phenyl-phosphachroman-2,4-dione (**3ch**)

Yellowish solid; mp 105–108 °C; yield: 51%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 23.57; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, $^3J_{H-H} = 6.9$ Hz, 3H, OCH$_2$CH_3), 3.87–3.95 (m, 4H, OCH_2CH$_3$, PhCH_2), 6.95–8.00 (m, 14H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (OCH$_2$CH_3), 40.1 (3-Ph*C*H$_2$), 61.7 (d, $^1J_{P-C} = 119.0$ Hz, C-3), 64.5 (d, $^2J_{P-C} = 7.5$ Hz, PO*C*H$_2$CH$_3$), 118.0–136.3 (Ar-*C*), 152.6 (*C*-8a), 192.1 (*C*-4); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 317.0943. Found: 317.0942.

2.10. 4-Benzoxy-2-ethoxy-3-phenyl-phosphacoumarin (**4ch**)

Yellowish solid; mp 112–114 °C; yield: 31%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 13.92; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, $^{3}J_{H-H} = 7.2$ Hz, 3H, OCH_2CH_3), 4.07 (m, 2H, $POCH_2CH_3$), 4.62 (s, 2H, $PhCH_2O$), 7.16–7.44 (m, 14H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2 (d, $^{3}J_{P-C} = 6.5$ Hz, $POCH_2CH_3$), 63.9 (d, $^{2}J_{P-C} = 6.2$ Hz, $POCH_2CH_3$), 75.4 ($PhCH_2O$), 109.5 (C-3), 123.8–131.6 (Ar-*C*), 150.0 (d, $^{2}J_{P-C} = 5.0$ Hz, *C*-8a), 158.9 (d, $^{2}J_{P-C} = 18.6$ Hz, *C*-4); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 317.0943. Found: 317.0940.

2.11. 3-Benzyl-2-ethoxy-3-(4-chlorophenyl)-phosphachroman-2,4-dione (**3dh**) and 4-benzoxy-2-ethoxy-3-(4-chlorophenyl)-phosphacoumarin (**4dh**)

Yellowish solid; total yield: 83%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 13.52 (**4dh**), 22.92 (**3dh**), the ratio of **3dh** to **4dh** is 13.2:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, $^{3}J_{H-H} = 7.2$ Hz, 3H, OCH_2CH_3), 3.80 (d, $^{3}J_{P-H} = 23.0$ Hz, 1.9H, $PhCH_2$of **3dh**), 4.65 (s, $PhCH_2O$, 0.2H), 7.04–8.00 (m, Ar-H, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9 (d, $^{2}J_{P-C} = 5.8$ Hz, OCH_2CH_3), 39.9 ($PhCH_2$ of **3dh**), 61.1 (d, $^{1}J_{P-C} = 119.0$ Hz, C-3 of **3dh**), 64.5 (d, $^{2}J_{P-C} = 7.9$ Hz, OCH_2CH_3), 119.1–136.4 (Ar-C), 152.2 (d, $^{2}J_{P-C} = 4.3$ Hz, *C*-8a), 191.5 (*C*-4 of **3dh**); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 427.0866. Found: 427.0862.

2.12. 3-Allyl-2-ethoxy-3-(4-chlorophenyl)-phosphachroman-2,4-dione (**3di**) and 4-alloxy-2-ethoxy-3-(4-chlorophenyl)-phosphacoumarin (**4di**)

Yellowish solid; total yield: 80%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 13.12 (**4di**), 23.13 (**3di**), the ratio of **3di** to **4di** is 2.1:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (m, $^{3}J_{H-H} =$ 7.2 Hz, 3H, OCH_2CH_3 of **3di** and **4di**), 2.97, 3.58 (m, about 1.3H, 3-$CH_2CH{=}CH_2$ of **3di**), 4.03 (m, about 2.6H, $POCH_2CH_3$ and 4-$OCH_2CH{=}CH_2$ of **4di**), 5.00 (dm, 0.66H, 3-$CH_2CH{=}CH_2$ of **3di**), 5.10 (dm, 0.33H, 4-$OCH_2CH{=}CH_2$ of **4di**), 5.56 (m, 0.66H, 3-$CH_2CH{=}CH_2$ of **3di**), 5.80 (m, 0.33H, 4-$OCH_2CH{=}CH_2$ of **4di**), 7.21–8.10 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 (dd, $^{2}J_{P-C} = 5.1$ Hz, $POCH_2CH_3$), 35.9 (3-$CH_2CH{=}CH_2$ of **3di**), 59.6 (d, $^{1}J_{P-C} = 120.5$ Hz, C-3 of **3di**), 64.6 (dd, $^{2}J_{P-C} =$ 7.9 Hz, $POCH_2CH_3$), 74.2 (4-$OCH_2CH{=}CH_2$ of **4di**), 109.8 (d, $^{1}J_{P-C} = 172.8$ Hz, C-3 of **4di**), 120.2–136.7 (Ar-C), 149.9 (d, $^{2}J_{P-C} = 5.7$ Hz, *C*-8a of **4di**), 152.6 (d, $^{2}J_{P-C} =$ 5.0 Hz, *C*-8a of **3di**), 159.1 (d, $^{2}J_{P-C} = 18.7$ Hz, *C*-4 of **4di**), 190.7 (*C*-4 of **3di**); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 377.0709. Found: 377.0701.

2.13. 3-Benzyl-2-ethoxy-3-(4-cyanophenyl)-phosphachroman-2,4-dione (**3eh**) and 4-benzoxy-2-ethoxy-3-(4-cyanophenyl)-phosphacoumarin (**4eh**)

Yellowish solid; total yield: 82%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 12.73 (**4eh**), 21.87 (**3eh**), the ratio of **3eh** to **4eh** is 2.1:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (dt, $^{3}J_{H-H} =$ 7.2 Hz, 3H, OCH_2CH_3), 3.85 (m, 3.4H, OCH_2CH_3 and $PhCH_2$of **3eh**), 4.62 (q, 0.6H, $PhCH_2O$), 6.92–7.74 (m, Ar-H, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (dd, $^{2}J_{P-C} =$ 5.0 Hz, $POCH_2CH_3$), 39.9 ($PhCH_2$ of **3eh**), 61.4 (d, $^{1}J_{P-C} = 119.0$ Hz, C-3 of **3eh**), 64.7 (d, $^{2}J_{P-C} = 7.8$ Hz, $POCH_2CH_3$), 111.9 (CN), 124.9–136.9 (Ar-C), 150.2 (*C*-8a of **4eh**), 152.3 (d, $^{2}J_{P-C} = 5.0$ Hz, *C*-8a pf **3eh**), 160.2 (d, $^{2}J_{P-C} = 17.2$ Hz, C-4 of **4eh**), 191.1 (*C*-4 of **3eh**); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 418.1208. Found: 418.1204.

2.14. 3-(2-Bromophenyl-2-ethoxy-3-methyl-phosphachroman-2,4-dione (**3fg**) and 3-(2-bromophenyl-2-ethoxy-4-methoxy-phosphacoumarin (**4fg**)

Yellowish solid; total yield: 90%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 12.95 (**4fg**), 22.76 (**3fg**), the ratio of **3fg** to **4fg** is 1:49; 1H NMR (300 MHz, $CDCl_3$) δ 1.09 (dt, $^3J_{H-H}$ = 7.3Hz, 3H, OCH_2CH_3), 1.99 (ds, 0.3H, 3-CH_3 of **3fg**), 3.51 (s, 0.2.7H, 4-CH_3O of **4fg**), 3.95 (m, 2H, OCH_2CH_3 of **3fg** and **4fg**), 7.11–8.14 (m, 8H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 (dd, $^3J_{P-C}$ = 5.6 Hz, $POCH_2CH_3$), 22.7 (3-CH_3 of **3fg**), 60.4 (d, $^3J_{P-C}$ = 15.8 Hz, CH_3O of **4fg**), 64.0 (d, $^2J_{P-C}$ = 7.2 Hz, $POCH_2CH_3$), 105.0 (dd, C-3 of **4fg**), 118.7–132.8 (Ar-C), 149.9 (*C*-8a of **4fg**), 159.3 (*C*-4 of **4fg**), 191.2 (*C*-4 of **3fg**); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 395.0048. Found: 395.0042.

2.15. 3-Benzyl-3-(2-bromophenyl)-2-ethoxy-phosphachroman-2,4- dione (**3fh**) and 4-benzoxy-3-(2-bromophenyl-2-ethoxy-phosphacoumarin (**4fh**)

Yellowish solid; total yield: 85%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 12.85 (**4fh**), 22.31 (**3fh**), the ratio of **3fh** to **4fh** is 1:19; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.2 (dt, $^3J_{H-H}$ = 7.2 Hz, 3H, OCH_2CH_3), 3.42 (m, 0.1H, $PhCH_2$ of **3fh**), 4.06 (m, 2H, OCH_2CH_3), 4.70 (m, 1.9H, $PhCH_2O$ of **3fh**), 7.14–7.77 (m, Ar-H, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2 (dd, $^2J_{P-C}$ = 5.7;Hz, $POCH_2CH_3$), 29.8 ($PhCH_2$ of **3fh**), 64.1 (d, $^2J_{P-C}$ = 7.2 Hz, $POCH_2CH_3$), 106.6 (d, $^2J_{P-C}$ = 176.4 Hz, C-3 of **3fh**), 123.9–133.4 (Ar-C), 150.1 (d, $^2J_{P-C}$ = 15.8 Hz, *C*-8a of **4fh**), 158.9 (d, $^2J_{P-C}$ = 18.6 Hz, *C*-4 of **4fh**); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 471.0361. Found: 471.0369.

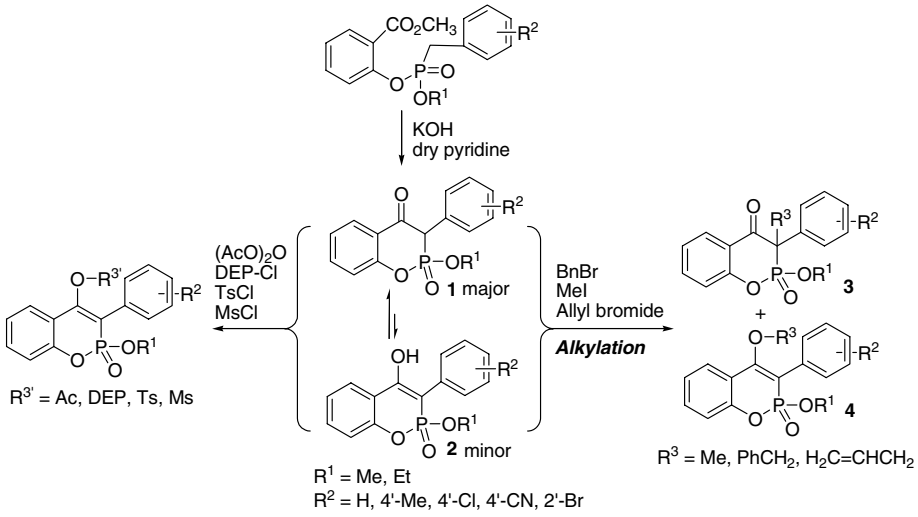
2.16. 3-Allyl-3-(2-bromophenyl)-2-ethoxy-phosphachroman-2,4-dione (**3fi**) and 4-alloxy-3-(2-bromophenyl)-2-ethoxy-phosphacoumarin (**4fi**)

Yellowish solid; total yield: 90%; ^{31}P NMR (121 MHz, $CDCl_3$) δ 12.35 (**4fi**), 22.89 (**3fi**), the ratio of **3fi** to **4fi** is 1:49; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (dm, $^3J_{H-H}$ = 6.9 Hz, 3H, OCH_2CH_3 of **3fi** and **4fi**), 3.66 (d, trace), 4.16 (m, 4H, $POCH_2CH_3$ and 4-$OCH_2CH{=}CH_2$ of **4fi**), 5.17 (m, 2H, 4-$OCH_2CH{=}CH_2$ of **4fi**), 5.77 (m, 1H, 4-$OCH_2CH{=}CH_2$ of **4fi**), 7.18–7.86 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2 (dd, $^2J_{P-C}$ = 6.4 Hz, $POCH_2CH_3$), 29.7 (3-$CH_2CH{=}CH_2$ of **3fi**), 64.1 (dd, $^2J_{P-C}$ = 6.5 Hz, $POCH_2CH_3$), 73.5 (4-$OCH_2CH{=}CH_2$ of **4fi**), 106.6 (d, $^1J_{P-C}$ = 176.4 Hz, C-3 of **4fi**), 118.5–133.3 (Ar-C), 149.9 (d, $^2J_{P-C}$ = 5.7 Hz, *C*-8a of **4fi**), 158.6 (d, $^2J_{P-C}$ = 18.6 Hz, *C*-4 of **4fi**); HR-MS of $[M+H]^+$ *m*/*z* Calcd: 421.0204. Found: 421.0206.

3. Results and discussion

As shown in Scheme 1, there is an equilibrium between phosphachroman-2,4-diones (**1**) and phosphacoumarins (**2**), and the ratios of **1** to **2** in $CDCl_3$ at room temperature depend on their structures (see Table 1). The alkylation products phosphachromones (**3**) and phosphacoumarins (**4**) were obtained in good yields (77–90%) through K_2CO_3-catalyzed reaction of **1** and **2** with different alkyl halides in various ratios (see Table 2).

In the presence of base, compounds **1** and **2** produced the corresponding ambident nucleophile, which can react with electrophiles, including acetic anhydride, *p*-toluenesulfonyl chloride (Ts-Cl), methyl sulfonyl chloride (Ms-Cl), diethoxylphosphoryl chloride



Scheme 1. Reaction of phosphachroman-2,4-diones, 4-OH phosphacoumarins with acetic anhydride, *p*-toluenesulfonyl chloride (Ts-Cl), methylsulfonyl chloride (Ms-Cl), diethoxylphosphoryl chloride (DEP-Cl) and alkyl halides.

Table 1
Ratios of the intermediate products **1** and **2**

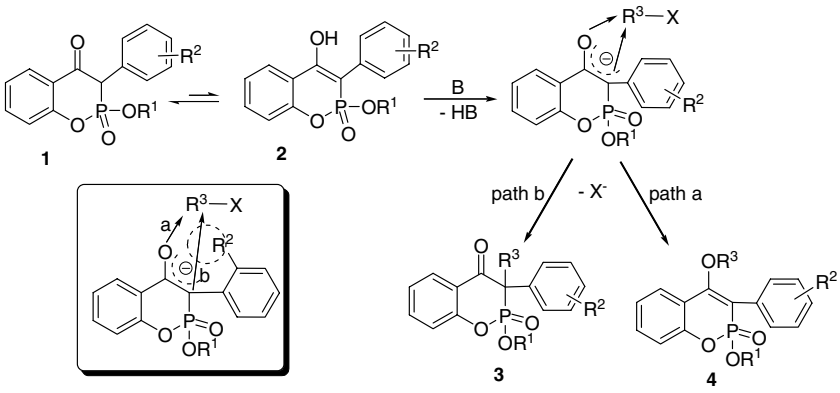
Entry	**1/2**	R^1	R^2	Ratio[a]
1	**1a/2a**	CH_2CH_3	4-CH_3	2.5:1.0
2	**1b/2b**	CH_3	H	7.3:1.0
3	**1c/2c**	CH_2CH	H	8.0:1.0
4	**1d/2d**	CH_2CH_3	4-Cl	9.3:1.0
5	**1e/2e**	CH_2CH_3	4-CN	7.7:1.0
6	**1f/2f**	CH_2CH	2-Br	5.2:1.0

[a] Ratio of **1** to **2** determined by ^{31}P NMR in $CDCl_3$.

Table 2
Yields and ratios of phosphachromones (**3**) and phosphacoumarins (**4**) from reaction of **1** and **2** with alkyl halides

Entry	**3**	**4**	R^1	R^2	R^3	Yield[a] (%)	Ratio[b]
1	**3ag**	**4ag**	CH_2CH_3	4-CH_3	CH_3	84	1.3:1
2	**3bg**	**4bg**	CH_3	H	CH_3	84	4:1
3	**3dg**	**4dg**	CH_2CH_3	4-Cl	CH_3	81	[c]
4	**3eg**	**4eg**	CH_2CH_3	4-CN	CH_3	86	11.5:1
5	**3ah**	**4ah**	CH_2CH_3	4-CH3	$PhCH_2$	79	1.3:1
6	**3ch**	**4ch**	CH_2CH_3	H	$PhCH_2$	82	1.6:1
7	**3dh**	**4dh**	CH_2CH_3	4-Cl	$PhCH_2$	83	13.2:1
8	**3di**	**4di**	CH_2CH_3	4-Cl	Allyl	80	2.1:1
9	**3eh**	**4eh**	CH_2CH_3	4-CN	$PhCH_2$	82	2.1:1
10	**3fg**	**4fg**	CH_2CH_3	2-Br	CH_3	90	1:49
11	**3fh**	**4fh**	CH_2CH_3	2-Br	$PhCH_2$	85	1:19
12	**3fi**	**4fi**	CH_2CH_3	2-Br	Allyl	90	1:49

[a] Total isolated yield.
[b] The ratio of **3** to **4**.
[c] Trace amount of **4dg**.



Scheme 2. The proposed mechanism and the steric effect of the alkylation reaction.

(DEP-Cl) and alkyl halides. Addition of acetic anhydride, Ts-Cl, Ms-Cl, DEP-Cl in the reaction system only yielded *O*-modified products, while reaction of alkyl halides with the ambident nucleophile led to 3-alkylated (**3**) and *O*-substituted products (**4**).

We tried different reaction conditions including solvents (CH_2Cl_2, acetone, and acetonitrile) and bases (K_2CO_3, TEA, and DMAP), and the experimental results showed that the ratios of **3** to **4** were not remarkably affected by these factors. By introducing different substituted group R^2 to the benzene ring at the 3-position and changing the alkyl halides, we found that the ratios of the both greatly depended on steric effect (Scheme 2). For example, when Br is ortho-position substituted group on the benzene ring, **4** are prominent products, and the ratios of the both are from 1:19 to 1:49 (entries 10–12 in Table 2). When R^3X is CH_3I, **3** are major products because methyl is a smaller group, and the ratios are from 1.3:1 to 13.2:1 (compare with entries 1, 2, 4 with 5–7 in Table 2). Interestingly, the ratios usually are high when R^3 is 4-Cl (entries 3, 9 in Table 2). In addition, the ratios were also affected by the electronic effect. For example, the ratios became larger when electron-donating group CH_3 of R^2 was replaced with electron-withdrawing group CN for same R^3. The electron-withdrawing group can improve the acidity of the 3-H of compound 1 and stabilize the negative ions at 3-position, which were favor to the nucleophilic reaction at 3-position.

In addition, **3** and **4**, such as **3ah** and **4ah**, **3fh** and **4fh**, could be isolated by silica gel column chromatography. Unfortunately, other phosphachromones (**3**) and phosphacoumarins (**4**) could not be done because of their similar polarity.

4. Conclusion

We have developed a convenient and efficient method for the synthesis of phosphachromones and phosphacoumarins via the alkylation of phosphachroman-2,4-diones and phosphacoumarins. The ratios of phosphachromones and phosphacoumarins depend on steric and electronic effects of the substituent groups. Some of phosphachromone and phosphacoumarin derivatives could be isolated by silica gel column chromatography. This can provide opportunity for the screening of molecules with biological and medicinal activity.

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