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Synthesis of Chromonyl-Containing α -Aminophosphonates

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Synthesis of Chromonyl-Containing α -Aminophosphonates

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Urumqi Xinjiang, P. R. China

*A series of novel chromonyl-containing α -aminophosphonates were synthesized by a one-pot reaction from 3-formylchromones, substituted aromatic amines, and dialkylphosphites. Synthesized compounds were characterized by elemental analysis, and ^1H NMR and IR spectroscopy. Single crystal x-ray diffraction data of compound **6e** was obtained, and analysis indicates that the crystal belongs to triclinic system with space group $P\bar{1}$, $a = 9.4200(4) \text{ \AA}$, $b = 10.5970(6) \text{ \AA}$, $c = 12.3506(5) \text{ \AA}$, $\alpha = 84.178(2)^\circ$, $\beta = 73.5830(10)^\circ$, $\gamma = 68.2720(10)^\circ$. $V = 1098.59(9) \text{ \AA}^3$, $Z = 2$, $\mu = 0.163 \text{ mm}^{-1}$, $F(000) = 456$, $R[F^2 > 2\sigma(F^2)] = 0.0835$, $\omega R(F^2) = 0.2328$.*

Keywords α -Aminophosphate; chromone; crystal structure; synthesis

INTRODUCTION

α -Aminophosphoric acids and α -aminophosphates are phosphorus-substituted analogs of α -amino carboxylic acids. Their utilities as enzyme inhibitors, antitumor, antibiotics, antihypertensive, pharmacological agents, and many other applications have attracted chemists' interests since 1959.^{1–4} Among the literature methods, the Kabachnik–Fields reaction is one of the most convenient approaches to the synthesis of α -aminophosphonates. It is a one-pot, three-component reaction of carbonyl compound, amines, and dialkylphosphites. The reaction usually needs a Lewis acid catalyst such as indium (III) chloride, rare earth elements triflates, and scandium tris (dodecyl sulfate). Recently, SmI_2 , LiClO_4 , metal triflates $[\text{M}(\text{OTf})_n]$, $\text{M} = \text{Li}, \text{Mg}, \text{Al}, \text{Cu}, \text{Ce}$], $\text{TaCl}_5\text{-SiO}_2$, montmorillonite clay, Al_2O_3 , $\text{CF}_3\text{CO}_2\text{H}$, scandium (tris-dodecyl sulfate), $\text{BF}_3\cdot\text{H}_2\text{O}$, and tetra-*tert*butyl-substituted

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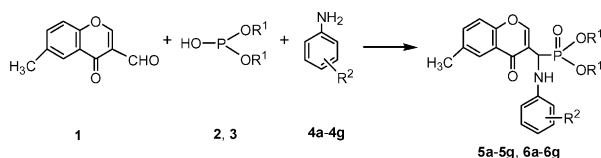
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phthalocyanines Pht-1-Pht-3 have also been reported as catalysts. A broad range of catalysts has been employed for the Kabachnik–Fields reaction. However, many of these catalysts are expensive. The catalyst-free synthesis of α -aminophosphonates is rather limited.⁵

Chromones and their derivatives are a group of naturally occurring compounds that are ubiquitous in nature, especially in fruits, vegetables, nuts, seeds, flowers, and tree bark. Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the diet of humans.^{6,7} Chromones not only have been extracted from natural products, but also synthesized by chemical methods.⁸ In studies to improve the bioactivity of chromones, chemists have found that chromone-linked heterocyclic frameworks have a broad biological activity, especially at the C-3 position, with strong propensities to act as antitumor, antibacterial, antiviral, antimicrobial, and antiphlogistic agents.⁹ Several flavonoid and chromone derivatives have also been found with inhibitory activity against the AR enzyme.¹⁰

In this article, the catalyst-free synthesis and physical characterization of new α -aminophosphonates containing chromonyl group are described. Based on previous work,¹¹ compounds **5a–5g** and **6a–6g** were synthesized, and a single-crystal structure of compound **6e** was obtained. All new compounds were analyzed by elemental analysis, and ¹H NMR and IR spectroscopy. The route of synthesis is shown in Scheme 1.



R¹ **5a–5g**: CH₃; **6a–6g**: C₂H₅

R² **5a, 6a**: H; **5b, 6b**: 2-CH₃; **5c, 6c**: 4-CH₃; **5d, 6d**: 4-Cl; **5e, 6e**: 4-OCH₃; **5f, 6f**: 2-NO₂; **6g**,

6g: 4-NO₂

SCHEME 1

RESULTS AND DISCUSSION

In the process of the synthesis of these all new compounds, we found that the reaction could take more time when there is an electron-withdrawing group (for instance NO₂) on the benzene-ring, but is faster with electron-contributing groups, for example OCH₃. The data of

TABLE I Physical Data and Elemental Analysis of Compounds

Compd.	mp (°C)	Yield (%)	Formula	Analysis found (calcd.)%		
				C	H	N
5a	169–170	59.4	C ₁₉ H ₂₀ NO ₅ P	60.98(61.11)	5.42(5.40)	3.74(3.75)
5b	152–154	42.4	C ₂₀ H ₂₂ NO ₅ P	61.87(62.00)	5.71(5.73)	3.63(3.62)
5c	151–153	57.1	C ₂₀ H ₂₂ NO ₅ P	61.82(62.00)	5.71(5.73)	3.61(3.62)
5d	168–169	65.7	C ₁₉ H ₁₉ ClNO ₅ P	55.89(56.01)	4.68(4.70)	3.42(3.44)
5e	148–150	59.4	C ₂₀ H ₂₂ NO ₆ P	59.66(59.54)	5.52(5.50)	3.45(3.47)
5f	165.5–167	52.2	C ₁₉ H ₁₉ N ₂ O ₇ P	54.64(54.53)	4.57(4.58)	6.68(6.70)
5g	177–180	16.0	C ₁₉ H ₁₉ N ₂ O ₇ P	54.42(54.53)	4.60(4.58)	6.68(6.70)
6a	165–166	51.7	C ₂₁ H ₂₄ NO ₅ P	62.94(62.82)	6.01(6.03)	3.50(3.49)
6b	164–166	51.9	C ₂₂ H ₂₆ NO ₅ P	63.71(63.59)	6.33(6.31)	3.38(3.37)
6c	181.5–182.5	57.1	C ₂₂ H ₂₆ NO ₅ P	63.46(63.59)	6.29(6.31)	3.36(3.37)
6d	199–201	53.4	C ₂₁ H ₂₃ ClNO ₅ P	58.03(57.92)	5.31(5.33)	3.23(3.22)
6e	185–186	69.5	C ₂₂ H ₂₆ NO ₆ P	61.35(61.23)	6.06(6.08)	3.26(3.25)
6f	134–135	18.3	C ₂₁ H ₂₃ N ₂ O ₇ P	56.60(56.49)	5.22(5.20)	6.26(6.28)
6g	176–177.5	47.5	C ₂₁ H ₂₃ N ₂ O ₇ P	56.38(56.49)	5.18(5.20)	6.30(6.28)

physical properties and elemental analysis of all new compounds are listed in Table I.

In the IR spectra, all new compounds exhibited medium-strong bands at 3400~3100 cm⁻¹, assigned to their NH stretches. The strong band that appeared at about 1650 cm⁻¹ was assigned to the carbonyl group of all new compounds.

In the ¹H NMR spectra, the signal of methyl group protons that connects with chromone appeared at about δ 2.3, and the proton in chromone at C-2 position appeared at about δ 8.0. The signal of NH appeared as a broad peak, at about δ 4.5. Because of coupling with the phosphorus atom, the proton of P(O)CH exhibited a doublet at about δ 5.2 and their coupling constants (²J_{HP}) are around 24.0 Hz. The data of the ¹H NMR and IR spectra of the new compounds are listed in Table II.

A single crystal of compound **6e** was gained by slow evaporation of solvent in its diluted toluene solution. X-ray single crystal diffraction analysis indicates that the crystal belongs to triclinic system with space group *P*-1, *a* = 9.4200(4) Å, *b* = 10.5970(6) Å, *c* = 12.3506(5) Å, α = 84.178(2)°, β = 73.5830(10)°, γ = 68.2720(10)°. *V* = 1098.59(9) Å³, *Z* = 2, μ = 0.163 mm⁻¹, *F*(000) = 456, *R*[*F*² > 2 σ (*F*²)] = 0.0835, $\omega R(F^2)$ = 0.2328. The benzene ring [C(12), C(13), C(14), C(15), C(17), C(18)] and the conjunction nitrogen N(1) atom are fairly planar, and the deviation from the least squares plane through the ring atom is 0.0188 Å. The plane equation is 1.5323 (0.0124) \times -6.2256 (0.0126) *y* + 8.8682

TABLE II ^1H NMR and IR Data of Compounds

Compd.	^1H NMR (CDCl_3) δ	IR ν cm^{-1}
5a	8.10–6.55 (m, 8H, ArH), 8.04 (s, 1H, OCH), 5.40 (d, $^2J = 23.8$ Hz, 1H, NCH), 4.71 (br, 1H, NH), 4.01 (d, $^3J = 10.4$ Hz, 3H, POCH_3), 3.76 (d, $^3J = 10.4$ Hz, 3H, POCH_3), 2.42 (s, 3H, CH_3)	3334 (NH), 1682 (C=O), 1339 (P=O), 1060 (P–O–C)
5b	8.20–6.77 (m, 7H, ArH), 8.10 (s, 1H, OCH), 5.36 (d, $^2J = 22.6$ Hz, 1H, NCH), 4.40 (br, 1H, NH), 3.98 (d, $^3J = 10.8$ Hz, 3H, POCH_3), 3.86 (d, $^3J = 10.8$ Hz, 3H, POCH_3), 2.35 (s, 3H, CH_3), 2.24 (s, 3H, CH_3)	3350 (NH), 1680 (C=O), 1342 (P=O), 1066 (P–O–C)
5c	7.96–6.70 (m, 7H, ArH), 8.06 (s, 1H, OCH), 5.29 (d, $^2J = 23.0$ Hz, 1H, NCH), 4.73 (br, 1H, NH), 3.91 (d, $^3J = 10.8$ Hz, 3H, POCH_3), 3.61 (d, $^3J = 10.8$ Hz, 3H, POCH_3), 2.52 (s, 3H, CH_3), 2.35 (s, 3H, CH_3)	3451 (NH), 1684 (C=O), 1339 (P=O), 1084 (P–O–C)
5d	8.10–6.70 (m, 7H, ArH), 8.03 (s, 1H, OCH), 5.30 (d, $^2J = 24.0$ Hz, 1H, NCH), 4.70 (br, 1H, NH), 3.92 (d, $^3J = 10.8$ Hz, 3H, POCH_3), 3.68 (d, $^3J = 10.8$ Hz, 3H, POCH_3), 2.42 (s, 3H, CH_3)	3300 (NH), 1643 (C=O), 1324 (P=O), 1033 (P–O–C)
5e	8.01–6.70 (m, 7H, ArH), 8.03 (s, 1H, OCH), 5.31 (d, $^2J = 22.6$ Hz, 1H, NCH), 4.35 (br, 1H, NH), 3.92 (d, 3H, OCH_3), 3.73 (d, $^3J = 10.6$ Hz, 3H, POCH_3), 3.68 (d, $^3J = 10.6$ Hz, 3H, POCH_3), 2.43 (s, 3H, CH_3)	3100 (NH), 1674 (C=O), 1277 (P=O), 1014 (P–O–C)
5f	7.83–6.69 (m, 7H, ArH), 8.14 (s, 1H, OCH), 5.34 (d, $^2J = 23.8$ Hz, 1H, NCH), 4.68 (br, 1H, NH), 3.64 (d, $^3J = 11.0$ Hz, 3H, POCH_3), 3.39 (d, $^3J = 11.0$ Hz, 3H, POCH_3), 2.42 (s, 3H, CH_3)	3270 (NH), 1698 (C=O), 1337 (P=O), 1035 (P–O–C)
5g	7.84–6.80 (m, 7H, ArH), 8.14 (s, 1H, OCH), 5.32 (d, $^2J = 23.8$ Hz, 1H, NCH), 4.68 (br, 1H, NH), 3.91 (d, $^3J = 11.0$ Hz, 3H, POCH_3), 3.58 (d, $^3J = 11.0$ Hz, 3H, POCH_3), 2.42 (s, 3H, CH_3)	3342 (NH), 1652 (C=O), 1311 (P=O), 1059 (P–O–C)
6a	8.10–6.74 (m, 8H, ArH), 8.04 (d, $^4J = 1.2$ Hz, 1H, OCH), 5.35 (d, $^2J = 23.6$ Hz, 1H, NCH), 4.70 (br, 1H, NH), 4.26 (m, 2H, POCH_2), 4.09 (m, 2H, POCH_2), 2.50 (s, 3H, CH_3), 1.32 (t, $^3J = 7.2$ Hz, 3H, CH_3), 1.22 (t, $^3J = 7.2$ Hz, 3H, CH_3)	3492 (NH), 1686 (C=O), 1270 (P=O), 1020 (P–O–C)
6b	8.14–6.76 (m, 7H, ArH), 8.01 (d, $^4J = 1.2$ Hz, 1H, OCH), 5.34 (d, $^2J = 23.4$ Hz, 1H, NCH), 4.72 (br, 1H, NH), 4.01 (m, 2H, POCH_2), 3.97 (m, 2H, POCH_2), 2.52 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 1.23 (t, $^3J = 7.1$ Hz, 3H, CH_3), 1.11 (t, $^3J = 7.1$ Hz, 3H, CH_3)	3332 (NH), 1682 (C=O), 1354 (P=O), 1004 (P–O–C)
6c	7.98–6.67 (m, 7H, ArH), 8.03 (d, $^4J = 1.6$ Hz, 1H, OCH), 5.43 (d, $^2J = 24.0$ Hz, 1H, NCH), 4.52 (br, 1H, NH), 4.11 (m, 2H, POCH_2), 4.05 (m, 2H, POCH_2), 2.49 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 1.20 (t, $^3J = 7.4$ Hz, 3H, CH_3), 1.14 (t, $^3J = 7.4$ Hz, 3H, CH_3)	3421 (NH), 1681 (C=O), 1331 (P=O), 1048 (P–O–C)
6d	7.70–6.37 (m, 7H, ArH), 8.20 (d, $^4J = 1.2$ Hz, 1H, OCH), 5.21 (d, $^2J = 23.2$ Hz, 1H, NCH), 4.56 (br, 1H, NH), 3.97 (m, 2H, POCH_2), 3.67 (m, 2H, POCH_2), 2.40 (s, 3H, CH_3), 1.28 (t, $^3J = 7.1$ Hz, 3H, CH_3), 1.12 (t, $^3J = 7.1$ Hz, 3H, CH_3)	3418 (NH), 1641 (C=O), 1339 (P=O), 1011 (P–O–C)

(Continued on next page)

TABLE II ^1H NMR and IR Data of Compounds (Continued)

Compd.	^1H NMR (CDCl_3) δ	IR ν cm^{-1}
6e	7.92–6.40 (m, 7H, ArH), 8.14 (d, $^4J = 1.6$ Hz, 1H, OCH), 5.18 (d, $^2J = 22.8$ Hz, 1H, NCH), 4.65 (br, 1H, NH), 3.97 (m, 2H, POCH_2), 3.73 (m, 2H, OCH_3), 3.67 (m, 3H, POCH_2), 2.53 (s, 3H, CH_3), 1.26 (t, $^3J = 7.5$ Hz, 3H, CH_3), 1.14 (t, $^3J = 7.5$ Hz, 3H, CH_3)	3491 (NH), 1689 (C=O), 1390 (P=O), 1005 (P–O–C)
6f	8.08–6.47 (m, 7H, ArH), 8.11 (d, $^4J = 1.4$ Hz, 1H, OCH), 5.30 (d, $^2J = 23.0$ Hz, 1H, NCH), 4.65 (br, 1H, NH), 4.11 (m, 2H, POCH_2), 3.78 (m, 2H, POCH_2), 2.36 (s, 3H, CH_3), 1.20 (t, $^3J = 7.3$ Hz, 3H, CH_3), 1.12 (t, $^3J =$ 7.3 Hz, 3H, CH_3)	3497 (NH), 1698 (C=O), 1396 (P=O), 1034 (P–O–C)
6g	8.12–6.60 (m, 7H, ArH), 8.12 (d, $^4J = 1.4$ Hz, 1H, OCH), 5.36 (d, $^2J = 23.0$ Hz, 1H, NCH), 4.58 (s, 1H, NH), 4.10 (m, 2H, POCH_2), 3.88 (m, 2H, POCH_2), 2.34 (s, 3H, CH_3), 1.36 (t, $^3J = 7.2$ Hz, 3H, CH_3), 1.18 (t, $^3J = 7.2$ Hz, 3H, CH_3)	3481 (NH), 1686 (C=O), 1297 (P=O), 1020 (P–O–C)

(0.0112) $z = 3.8664$ (0.0097). Atoms in chromone ring [C(1), C(2), C(3), C(4), C(5), C(7), C(8), C(9), C(10), O(2)] are also quite planar, and the deviation from the least squares plane through the ring atom is 0.0136 Å. The plane equation is -7.2607 (0.0042) $x - 0.5413$ (0.0100) $y + 4.2302$ (0.0070) $z = 2.4239$ (0.0068). The dihedral angle between the plane of chromone group and the plane of the benzene is $83.84(0.08)^\circ$, and the torsion angle of C(10)–C(11)–N(1)–C(12) is $74.5(4)^\circ$. The structure of the phosphorus atom in compound **6e** is distorted tetrahedron. Two kinds of hydrogen bond exist in the crystal lattice. Intramolecular H-bond exists in this structure and the structure is stabilized by the hydrogen bond between the hydrogen attached to the amine nitrogen (N1) and the phosphite oxygen (O5). The N1–H1...O5 distance is $3.158(4)$ Å and the N1–H1...O5 angle is 104.2° . The data of the crystal of the compound are listed in Table III, Table IV, and Table V. The molecular structure of the title compound **6e** is shown in Figure 1. The packing diagram of the unit cell of compound **6e** is shown in Figure 2. Complete crystallographic data for the structural analysis of compound **6e** have been deposited with the Cambridge Crystallographic Data Centre, CCDC numbers 684911.

EXPERIMENTAL

General Method

Melting points were taken on a Yanaco MP-S3 micromelting point apparatus. The IR spectra were recorded in KBr pellets on a Bruker

TABLE III Crystal Data and Structure Refinement for 6e

Empirical formula	C ₂₂ H ₂₆ NO ₆ P	Limiting indices	-12 < = h < = 12, -13 < = k < = 13, -13 < = l < = 16
Formula weight	431.41	Reflections collected/unique	10899/4995 [R(int) = 0.0186]
Temperature	153(2) K	Completeness to theta = 27.48	99.1%
Wavelength	0.71073 Å	Max. and min. transmission	0.9483 and 0.9058
Crystal system, space group	triclinic, <i>P</i> -1	Refinement method	Full-matrix least-squares on <i>F</i> ²
Unit cell dimensions	<i>a</i> = 9.4200(4) Å, <i>b</i> = 10.5970(6) Å, <i>c</i> = 12.3506(5) Å α = 84.178(2)°, β = 73.5830(10)°, γ = 68.2720(10)°	Data/restraints/ parameters	4995/0/272
Volume	1098.59(9) Å ³	Goodness-of-fit on <i>F</i> ²	1.117
Z, Calculated density	2, 1.304 Mg/m ³	Final R indices [I > 2sigma(I)]	R1 = 0.0835, ω R2 = 0.2328
Absorption coefficient	0.163 mm ⁻¹	R indices (all data)	R1 = 0.1061, ω R2 = 0.2635
F(000)	456	Absolute structure parameter	0(10)
Crystal size	0.62 × 0.58 × 0.33 mm	Extinction coefficient	0.014(5)
Theta range for data collection	3.31 to 27.48 deg.	Largest diff. peak and hole	1.710 and -1.601 e. Å ⁻³

TABLE IV Selected Bond Lengths (Å) for the Compound 6e

P(1)-O(5)	1.429(4)	O(3)-C(16)	1.335(5)	C(8)-C(9)	1.463(4)
P(1)-O(6)	1.530(4)	O(4)-C(19)	1.464(4)	C(9)-C(10)	1.457(4)
P(1)-O(4)	1.541(3)	O(6)-C(21)	1.160(8)	C(10)-C(11)	1.517(4)
P(1)-C(11)	1.812(3)	C(1)-C(10)	1.345(4)	C(12)-C(18)	1.392(4)
N(1)-C(12)	1.407(4)	C(2)-C(3)	1.382(5)	C(12)-C(13)	1.386(5)
N(1)-C(11)	1.454(4)	C(2)-C(8)	1.388(4)	C(13)-C(14)	1.391(5)
O(1)-C(9)	1.233(4)	C(3)-C(4)	1.378(5)	C(14)-C(15)	1.381(5)
C(1)-C(10)	1.345(4)	C(4)-C(5)	1.399(5)	C(15)-C(17)	1.381(5)
O(2)-C(1)	1.342(4)	C(5)-C(6)	1.513(5)	C(17)-C(18)	1.394(4)
O(2)-C(2)	1.377(4)	C(5)-C(7)	1.385(5)	C(19)-C(20)	1.442(7)
O(3)-C(15)	1.388(4)	C(7)-C(8)	1.405(4)	C(21)-C(22)	1.418(9)

TABLE V Selected Bond Angles (°) for the Compound **6e**

O(5)-P(1)-O(6)	111.8(4)	O(2)-C(2)-C(3)	116.5(3)	C(9)-C(10)-C(11)	119.5(3)
O(5)-P(1)-O(4)	117.4(2)	C(3)-C(2)-C(8)	122.2(3)	N(1)-C(11)-C(10)	115.4(2)
O(6)-P(1)-O(4)	102.6(3)	C(4)-C(3)-C(2)	118.4(3)	C(10)-C(11)-P(1)	113.6(2)
O(5)-P(1)-C(11)	115.39(17)	C(3)-C(4)-C(5)	122.1(3)	C(18)-C(12)-N(1)	118.8(3)
O(6)-P(1)-C(11)	106.7(2)	C(7)-C(5)-C(4)	118.0(3)	C(13)-C(12)-N(1)	122.9(3)
O(4)-P(1)-C(11)	101.62(14)	C(7)-C(5)-C(6)	121.0(3)	C(17)-C(15)-O(3)	124.6(3)
C(12)-N(1)-C(11)	119.1(3)	C(5)-C(7)-C(8)	121.5(3)	C(14)-C(15)-O(3)	115.2(3)
C(16)-O(3)-C(15)	120.5(3)	C(1)-C(10)-C(9)	119.7(3)	C(15)-C(17)-C(18)	119.1(3)
C(19)-O(4)-P(1)	122.2(3)	C(2)-C(8)-C(7)	117.8(3)	C(12)-C(18)-C(17)	121.6(3)
C(21)-O(6)-P(1)	156.2(7)	C(2)-C(8)-C(9)	120.6(3)	C(20)-C(19)-O(4)	110.1(4)
O(2)-C(1)-C(10)	125.5(3)	N(1)-C(11)-P(1)	107.3(2)	O(6)-C(21)-C(22)	133.6(8)

FT-IR Equinox apparatus. The ^1H NMR spectra were recorded on a Varian INOVA-400 (using TMS as internal standard, CDCl_3 as solvent). Elemental analyses were performed on a Thermo Flash EA-1112 elemental analyzer. X-ray single-crystal diffraction data for compound

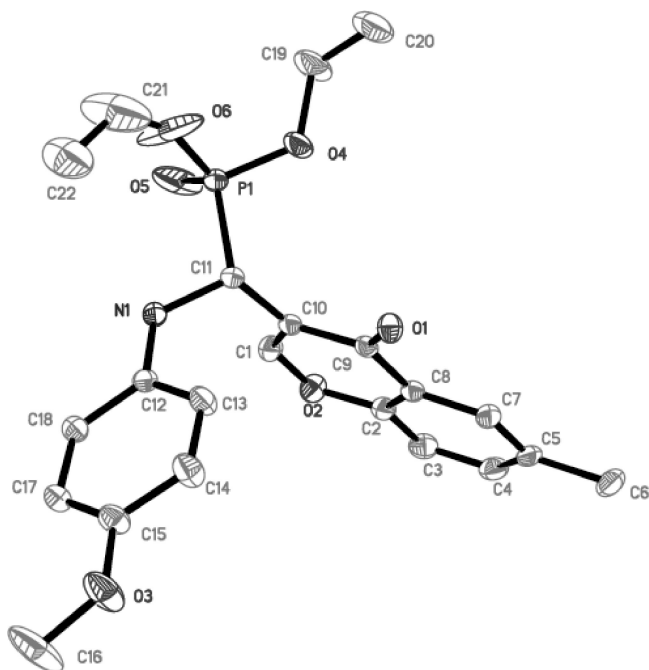


FIGURE 1 Molecular structure of compound **6e**. (Displacement ellipsoid view with 30% ellipsoids.)

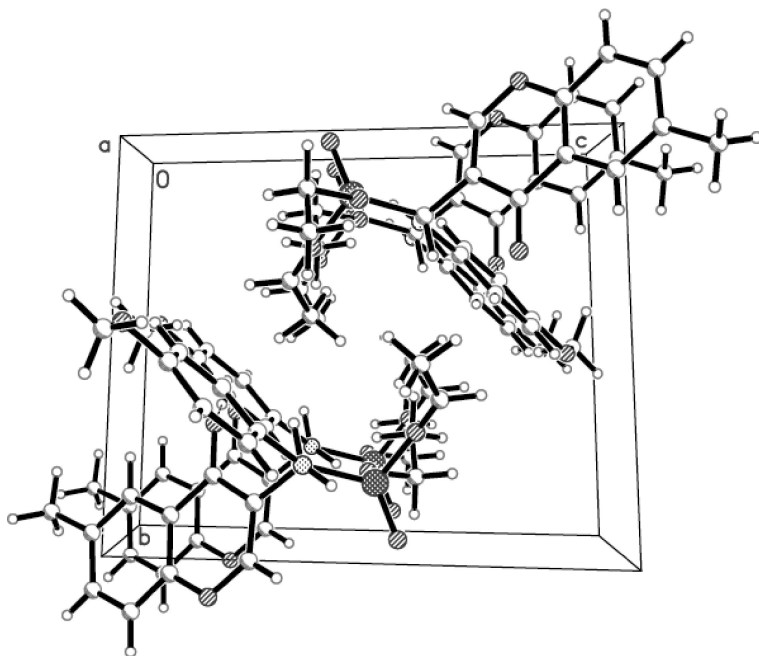


FIGURE 2 Packing diagram of the unit cell of compound **6e**. (Displacement ellipsoid view with 50% ellipsoids.)

6e were collected on a Bruker Smart 1000 CCD diffractometer at 293(2) K with Mo- $K\alpha$ radiation ($\lambda = 0.71073\text{\AA}$) by ω - ϕ scan mode. The structures was solved by direct methods using the SHELXS program of the SHELXTL package and refined by full-matrix least-squares methods with SHELXL.¹² Analytical thin-layer chromatography (TLC) was performed by GF₂₅₄ and 0.5% CMC. Detection made use of UV light; the mobile phase was petroleum ether (fraction boiling in the range of 60–90°C) and ethyl acetate (1:2). All reagents were commercial products of analytical grade and were used directly without processing except when mentioned.

Compounds 1–3

Compounds **1–3** were prepared according to reported methods.^{13,14}

Preparation of *N*-Aryl- α -amino- α -(chromon-3-yl)-*O,O'*-dialkylphosphites (**5a–5g**, **6a–6g**)

To a stirred solution of 6-methyl-3-formylchromone (1 mmol) and substituted aniline (1 mmol) in anhydrous toluene (40 mL), an equimolar

amount of dialkylphosphite was added. The mixture was refluxed for 2–5 h. The end of the reaction was detected by TLC. The reaction mixture was concentrated. The precipitate was filtered off and recrystallized from ethanol–water.

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