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New phosphacoumarins containing aldehyde group: synthesis and properties

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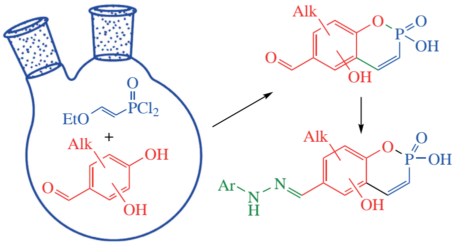
New phosphacoumarins containing an aldehyde group at the periphery were obtained in a 'one-pot' reaction of 2-ethoxyvinylphosphonic dichloride with 2,4-dihydroxybenzaldehyde derivatives. The further reaction of these compounds with 2,4-dinitrophenylhydrazine afforded new hydrazones which exist only as *E*-isomers.



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Coumarins and their derivatives attract attention due to their high biological activity and wide possibilities of use in medical practice. Unlike coumarins, their phosphorus-containing analogues have been less studied. At the same time, phosphacoumarins are known to inhibit cholesterol esterase[1] and tyrosine protein phosphatase SHP-1.[2] This is of interest from the viewpoint of creating antidiabetic drugs, their antibacterial activity[3] and cytotoxicity against cancer cell lines.[4,5] These data on biological activity make phosphacoumarins and their derivatives attractive for the creation of new types of effective drugs for the therapy of human diseases. Currently, several approaches to the construction of the phosphacoumarin structure are known. Some of the most common ones are gold complex-catalyzed intramolecular cyclization of *O*-aryl alkynylphosphonates,[6,7] the reaction of alkynylphosphonates with (2-hydroxyaryl)boronic acids,[8–10] and the reaction of 2-alkenylphenols with phosphorus(III/V) chlorides.[11] The synthesis of phosphacoumarins through the reaction of 3-aryl-1-(2-hydroxyaryl)propane-1,3-diones with diethyl phosphite[12] or phosphorus(V) oxychloride,[13] as well as the reaction between trihalobenzodioxaphospholes and alkynes[14–16] are documented. We would like to note our approach to such compounds based on the reaction of substituted phenols with 2-ethoxyvinylphosphonic dichloride. Phosphacoumarins[17–20] thus obtained are strong Brønsted acids. Organophosphorus acids are actively used in organocatalysis, including asymmetric synthesis (the Akiyama–Terada catalysts).[21–26] There is little information about the production of phosphacoumarins with an aldehyde group on the periphery. The synthesis of such phosphacoumarins should open up new opportunities for their targeted modification and creation of new substances with high and diverse biological activity. They can also be used as organocatalysts. Therefore, research in this area is an important and urgent task for organic and organophosphorus chemistry.

The synthesis of phosphacoumarins containing an aldehyde group was herein carried out through a 'one-pot' reaction between the corresponding derivatives of dihydroxybenzaldehyde and 2-ethoxyvinylphosphonic dichloride **1** (Scheme 1) in dry benzene in the presence of triethylamine. The resulting *O*-phosphorylated phenol when boiled for 15 h in the presence of trifluoroacetic acid undergoes the intramolecular Friedel–Crafts-type alkylation with the formation of new phosphacoumarins **2**, **3a**,**b** in yields of 72–75%. These compounds are white powders well soluble in DMSO. Importantly, the initial phosphorylation occurred exclusively at 4-positioned hydroxy group for all 2,4-dihydroxybezaldehydes while the final cyclization should involve free =CH position. As a result, 3-methylated 2,4-dihydroxybezaldehyde was converted into 7-hydroxy phosphacoumarin **2** while 5-alkylated analogues were transformed into 5-hydroxy ones **3a**,**b**.

The reaction completion was monitored by $^{31}P\{^1H\}$ NMR. Structure of the obtained compounds **2**, **3a**,**b** was proven using ^{31}P, ^1H, ^{13}C NMR and IR spectroscopy as well as mass spectrometry and elemental analysis. Their ^{31}P NMR spectra contained a singlet in the ~4 ppm region, which is typical for compounds with a four-coordinated phosphorus atom in phosphacoumarins. The olefinic protons are presented as doublet of doublets, the proton of the aldehyde group as a singlet. The characteristic signals for compound **2** in the ^1H NMR spectrum are as follows: 6.26 (1H, dd, $^2J_{HP}$ 20.0, $^3J_{HH}$ 12.7 Hz, P–C*H*=), 7.41 (1H, dd, $^3J_{HP}$ 42.7, $^3J_{HH}$ 12.7 Hz, P–CH=C*H*), 9.97 (1H, s, –CHO).

The structure of the phosphacoumarins was confirmed by X-ray analysis of the representative compound **2** (Figure 1).†

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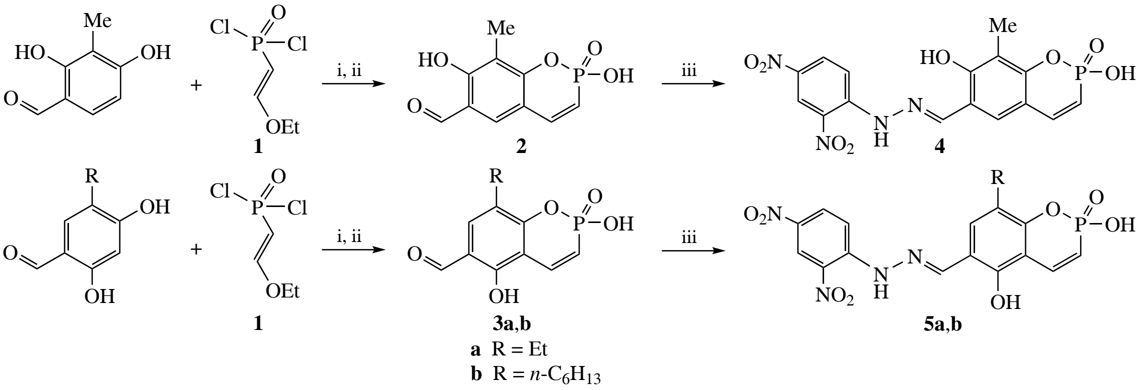
† *Crystallographic data for* **2**. $C_{10}H_9O_5P$ (M = 240.14), colorless plate crystal, triclinic, $P\bar{1}$, a = 4.7873(10), b = 6.8584(15) and c = 14.831(3) Å, α = 90.842(6)°, β = 98.581(6)°, γ = 92.956(6)°, V = 480.73(18) Å^3,



Scheme 1 *Reagents and conditions*: i, Et$_3$N, C$_6$H$_6$, room temperature, 5 h; ii, CF$_3$CO$_2$H, reflux, 15 h; iii, 2,4-(O$_2$N)$_2$C$_6$H$_3$NHNH$_2$, EtOH, reflux, 5 h.

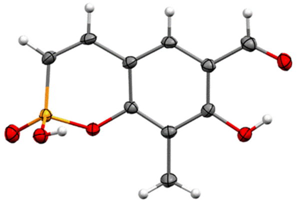


Figure 1 ORTEP view of the molecule in the crystal of **2**. Displacement ellipsoids are drawn at the 50% probability level.

The crystal structure of **2** was solved in the triclinic space group $P\bar{1}$, the asymmetric part of the unit cell is represented by a single molecule ($Z' = 1$). In the crystal of **2**, a dimer is formed by the O–H···O=C interactions.

Next, we studied the chemical properties of the obtained phosphacoumarins. The presence of an aldehyde group in the molecule predetermined the choice of reagents. Convenient reagents for aldehyde groups are arbitrary hydrazines. It was necessary to find out the influence of a strong acid group in the molecule on the synthetic result. As a result of optimization of experimental conditions, it was found that the most suitable solvent for the reaction was ethanol. The condensation of phosphacoumarins **2**, **3a**,**b** with 2,4-dinitrophenylhydrazine was carried out in ethanol upon boiling the reaction mixture for 5 h (see Scheme 1), which afforded hydrazones **4**, **5a**,**b** in 85–88% yields. These compounds are orange powders that are highly soluble in DMSO and insoluble in ethanol, from which they precipitate.

The structure and composition of hydrazones **4**, **5a**,**b** was proven using ^{31}P, ^{1}H, ^{13}C NMR, IR spectroscopy, ESI-TOF mass spectrometry, and elemental analysis. In addition, 1D/2D correlation NMR experiments were used. Only the *E*-isomers were observed in the spectra, the assignment was made by analogy with our previous wark.[27] According to published data, the chemical shift of the α-carbon of the hydrazone group in the *Z*-isomer is lower than that for the *E*-isomer, namely, ~140 ppm and ~150 ppm, respectively. In our case, the chemical shift of *C*H=N–NHAr atom is 149.8 ppm, which corresponds to the *E*-isomer. Moreover, a definitive criterion is the direct spin–spin coupling constant $^{1}J_{\mathrm{CH}}$ in the fragment *CH*=N–. For the *Z*-isomer, this value is ~180 Hz, while for the *E*-isomer it is ~15 Hz less. For the studied compound **2**, the $^{1}J_{\mathrm{CH}}$ was 165.6 Hz, which agrees with the literature data for the *E*-isomer.

To conclude, a 'one-pot' reaction between 2-ethoxyvinylphosphonic dichloride and 2,4-dihydroxybenzaldehydes afforded new phosphocoumarins bearing aldehyde group at the periphery. Their reaction with 2,4-dinitrophenylhydrazine gave the corresponding new hydrazones which exist as *E*-isomers. Based on the new phosphacoumarins obtained, a large library of compounds with various practically useful properties, including effective organocatalysts, can be purposefully synthesized.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7862.

$Z' = 1$, $d_{\mathrm{calc}} = 1.659$ g cm^{-3}, μ(Mo Kα) = 0.288 mm^{-1}. $F(000) = 248$, reflections collected = 11938, unique = 2094, $R_{\mathrm{int}} = 0.0651$, full-matrix least-squares on F^2, parameters = 154, restraints = 2. Final indices $R_1 = 0.0678$, $wR_2 = 0.1620$ for 1937 reflections with $I > 2\sigma(I)$, goodness-of-fit on $F^2 = 1.255$, largest difference in peak and hole (0.838 and –0.376 e Å^{-3}), data completeness 0.999. X-ray diffraction (XRD) data were collected on a Bruker D8 QUEST three-circle diffractometer with a PHOTON III area detector and an IμS DIAMOND microfocus X-ray tube at 150(2) K: λ(Mo Kα) = 0.71073 Å, ω/φ scanning mode with a step of 0.5°. Data collection and indexing, determination, and refinement of unit cell parameters were carried out using the APEX3 software package. Numerical absorption correction based on the crystal shape, additional spherical absorption correction, and systematic error correction were performed using the SADABS-2016/2 software.[28] The structure was solved by the intrinsic phasing method using the SHELXT-2018/2 program[29] and refined by full-matrix least-squares on F^2 using the SHELXL-2018/3 program.[29] Non-hydrogen atoms were refined anisotropically. Positions of H(O) hydrogen atoms were determined from difference electron density maps and refined isotropically. The positions of hydrogen atoms of methyl group were inserted using the rotation of the group with idealized bond angles. The remaining hydrogen atoms were refined using a riding model. Most calculations were performed using the WinGX-2021.3 software package.[30]

CCDC 2440419 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

References

1 B. Li, B. Zhou, H. Lu, L. Ma and A.-Y. Peng, *Eur. J. Med. Chem.*, 2010, **45**, 1955; https://doi.org/10.1016/j.ejmech.2010.01.038.

2 X. Li, D. Zhang, H. Pang, F. Shen, H. Fu, Y. Jiang and Y. Zhao, *Org. Lett.*, 2005, **7**, 4919; https://doi.org/10.1021/ol051871m.

3 M. Hariri, F. Darvish, K.-P. Mengue Me Ndong, R. Babouri, G. Mwande-Maguene, A. R. Burilov, P. Licznar-Fajardo, J.-L. Pirat, T. Ayad and D. Virieux, *GSC Biol. Pharm. Sci.*, 2021, **16**, 283; https://doi.org/10.30574/gscbps.2021.16.2.0252.

4 V. V. Sennikova, A. V. Zalaltdinova, Y. M. Sadykova, A. R. Khamatgalimov, A. S. Gazizov, A. D. Voloshina, A. P. Lyubina, S. K. Amerhanova, J. K. Voronina, E. A. Chugunova, N. O. Appazov, A. R. Burilov and M. A. Pudovik, *Int. J. Mol. Sci.*, 2022, **23**, 14348; https://doi.org/10.3390/ijms232214348.

5 E. Budzisz, E. Brzezinska, U. Krajewska and M. Rozalski, *Eur. J. Med. Chem.*, 2003, **38**, 597; https://doi.org/10.1016/S0223-5234(03)00086-2.

6 C.-E. Kim, T. Ryu, S. Kim, K. Lee, C.-H. Lee and P. H. Lee, *Adv. Synth. Catal.*, 2013, **355**, 2873; https://doi.org/10.1002/adsc.201300545.

7 C.-E. Kim, J.-Y. Son, S. Shin, B. Seo and P. H. Lee, *Org. Lett.*, 2015, **17**, 908; https://doi.org/10.1021/acs.orglett.5b00020.

8 J. Corpas, P. Mauleón, R. Gómez Arrayás and J. C. Carretero, *Org. Lett.*, 2020, **22**, 6473; https://doi.org/10.1021/acs.orglett.0c02281.

9 S. H. Ji, S. Kim, G. Nam, D.-H. Lee and S.-J. Han, *Org. Lett.*, 2022, **24**, 8295; https://doi.org/10.1021/acs.orglett.2c03231.

10 D. Ma, S. Hu, S. Chen, J. Pan, S. Tu, Y. Yin, Y. Gao and Y. Zhao, *Org. Lett.*, 2020, **22**, 8156; https://doi.org/10.1021/acs.orglett.0c03151.

11 D. A. Tatarinov, E. A. Mikulenkova, I. A. Litvinov, K. R. Khayarov and V. F. Mironov, *Org. Biomol. Chem.*, 2024, **22**, 1629; https://doi.org/10.1039/D3OB01718D.

12 T. E. Ali, M. A. Assiri and N. M. Hassanin, *Synth. Commun.*, 2022, **52**, 1967; https://doi.org/10.1080/00397911.2022.2122843.

13 T. E. Ali, M. A. Assiri and N. M. Hassanin, *Synth. Commun.*, 2022, **52**, 2334; https://doi.org/10.1080/00397911.2022.2146514.

14 A. V. Nemtarev, V. F. Mironov, R. R. Fayzullin, I. A. Litvinov and R. Z. Musin, *Russ. J. Gen. Chem.*, 2018, **88**, 2290; https://doi.org/10.1134/S1070363218110075.

15 A. V. Nemtarev, V. F. Mironov, A. S. Aniskin, D. S. Baranov, D. B. Krivolapov, R. Z. Musin and S. F. Vasilevskii, *Russ. Chem. Bull.*, 2016, **65**, 1299; https://doi.org/10.1007/s11172-016-1452-6.

16 A. S. Aniskin, A. V. Nemtarev, D. S. Baranov, S. F. Vasilevskii and V. F. Mironov, *Russ. J. Gen. Chem.*, 2015, **85**, 2206; https://doi.org/10.1134/S1070363215090285.

17 A. V. Zalaltdinova, Y. M. Sadykova, A. S. Gazizov, A. K. Smailov, V. V. Syakaev, D. P. Gerasimova, E. A. Chugunova, N. I. Akylbekov, R. U. Zhapparbergenov, N. O. Appazov, A. R. Burilov, M. A. Pudovik, I. V. Alabugin and O. G. Sinyashin, *Int. J. Mol. Sci.*, 2024, **25**, 6327; https://doi.org/10.3390/ijms25126327.

18 Yu. M. Sadykova, N. V. Dalmatova, L. M. Sadikova, A. R. Burilov and M. A. Pudovik, *Russ. J. Gen. Chem.*, 2016, **86**, 2397; https://doi.org/10.1134/S107036321610025X.

19 Y. M. Sadykova, L. M. Sadikova, A. R. Badrtdinova, A. B. Dobrynin, A. R. Burilov and M. A. Pudovik, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2015, **190**, 2267; https://doi.org/10.1080/10426507.2015.1073283.

20 Yu. M. Sadykova, L. M. Sadikova, A. V. Zalaltdinova, Z. N. Sultanova, A. R. Burilov and M. A. Pudovik, *Russ. J. Gen. Chem.*, 2018, **88**, 1941; https://doi.org/10.1134/S1070363218090323.

21 T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744; https://doi.org/10.1021/cr068374j.

22 T. Akiyama, J. Itoh and K. Fuchibe, *Adv. Synth. Catal.*, 2006, **348**, 999; https://doi.org/10.1002/adsc.200606074.

23 J. Glöckler, S. Klützke, W. Meyer-Zaika and A. Reller, F. J. García-García, H. Strehblow, P. Keller, E. Rentschler and W. Kläui, *Angew. Chem., Int. Ed.*, 2007, **46**, 1164; https://doi.org/10.1002/anie.200603402.

24 M. Cortes-Clerget, O. Gager, M. Monteil, J.-L. Pirat, E. Migianu-Griffoni, J. Deschamp and M. Lecouvey, *Adv. Synth. Catal.*, 2016, **358**, 34; https://doi.org/10.1002/adsc.201500794.

25 N. Levi, A. M. Khenkin, B. Hailegnaw and R. Neumann, *ACS Sustainable Chem. Eng.*, 2016, **4**, 5799; https://doi.org/10.1021/acssuschemeng.6b01071.

26 A. V. Trifonov, R. K. Bagautdinova, L. K. Kibardina, M. A. Pudovik, A. P. Lyubina, A. D. Voloshina, A. S. Gazizov and A. R. Burilov, *Mendeleev Commun*., 2024, **34**, 688; https://doi.org/10.1016/j.mencom.2024.09.020.

27 V. V. Syakaev, S. N. Podyachev, B. I. Buzykin, Sh. K. Latypov, W. D. Habicher and A. I. Konovalov, *J. Mol. Struct*., 2006, **788**, 55; https://doi.org/10.1016/j.molstruc.2005.11.018.

28 L. Krause, R. Herbst-Irmer, G. M. Sheldrick and D. Stalke, *J. Appl. Crystallogr.*, 2015, **48**, 3; https://doi.org/10.1107/S1600576714022985.

29 G. M. Sheldrick, *Acta Crystallogr*., 2015, **A71**, 3; https://doi.org/10.1107/S2053273314026370.

30 J. Farrugia, *J. Appl. Crystallogr*., 2012, **45**, 849; https://doi.org/10.1107/S0021889812029111.

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