XXII INTERNATIONAL SYMPOSIUM „ADVANCES IN THE CHEMISTRY OF HETEROORGANIC COMPOUNDS”

Centre of Molecular
and Macromolecular Studies
Polish Academy of Sciences

Section
of Heteroorganic Chemistry
Polish Chemical Society

ŁÓDŹ
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ORGANIZED BY

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Synthesis of Coumarin-4-ylethyl Phosphonic Acid Derivatives

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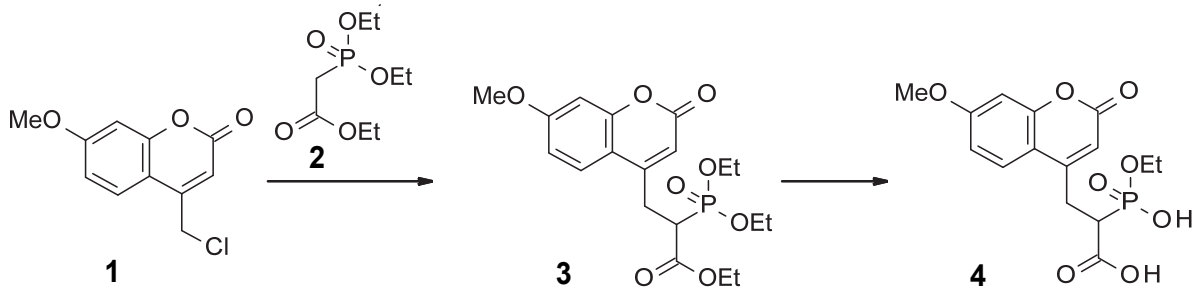
Naturally occurring coumarin umbelliferone (7-hydroxycoumarin) and its *O*-methyl ether (herniaryn, 7-methoxycoumarin) exhibit different types of biological activity. Modifications of coumarins made it possible to obtain biologically active molecules, which is important in the drug design.[1, 2] In order to expand the diversity of bearing phosphonic acid moiety coumarins, the possibility for the synthesis of homologues previously obtained 4-phosphonomethylcoumarins with antiviral activity [3] was studied.



Scheme 1. Synthesis of coumarin-4-ylethyl phosphonic acid derivatives.

We investigated the reaction of 7-methoxy-4-chloromethylcoumarin (**1**) and ethyl (diethoxyphosphoryl) acetate (**2**) in various solvents (1,4-dioxane, dimethyl ether ethylene glycol, dimethylformamide, 1-methylpyrrolidone, 1,3-dimethyltetrahydropyrimidin-2-one) in the presence of various bases (potassium *tert*-butoxide, sodium hydride, lithium or sodium hexamethyldisilazide), which led us to the synthesis of ethyl 2-(diethoxyphosphoryl)-3-(7-methoxy-2-oxo-2*H*-chromen-4-yl) propanoate (**3**). It was found that the ratio of 4-chloromethylcoumarin / ethyl (diethoxyphosphoryl) acetate / sodium hydride 1: 2: 2 using dimethylformamide as the solvent was optimal. The reaction proceeds at a temperature of 25-35ºC for 7-14 days.

Alkaline hydrolysis of ester **3** with lithium hydroxide excess affords new 2-(ethoxyphosphoryl)-3-(7-methoxy-2-oxo-2*H*-chromen-4-yl) propionic acid (**4**).

The structure and purity of compounds **3** and **4** were confirmed by spectroscopic studies: ^{1}H NMR, ^{13}C and ^{31}P and LCMS.

References

[1] S. C. Demmer *at al.*, *Chem. Rev.*, **2011**, *111*, 7981.
[2] F. Borges *at al.*, *Cur. Med. Chem.*, **2005**, *12*, 887.
[3] K. M. Kondratyuk *at al.*, *Chem. Nat. Compd.*, **2019**, *55*, 632.