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Electrochemical phosphorylation of coumarins catalyzed by transition metal complexes (Ni—Mn, Co—Mn)*

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A possibility of electrochemical phosphorylation of coumarins (coumarin, 6-methylcoumarin, 7-methylcoumarin) with diethyl phosphite was shown. The approach is based on the oxidation of a mixture of the aromatic compound and diethyl phosphite (1 : 1) under mild conditions (room temperature, atmospheric pressure) in the presence of a bimetallic catalytic systems: Mn^{II}bipy/Ni^{II}bipy and Mn^{II}bipy/Co^{II}bipy (bipy is the 2,2´-bipyridine). This method allows one to obtain diethyl arylphosphonates in high yields (up to 70%) and 100% conversion of the phosphite.

Key words: phosphorylation, oxidation, electrosynthesis, catalyst, coumarin, CH-functionalization.

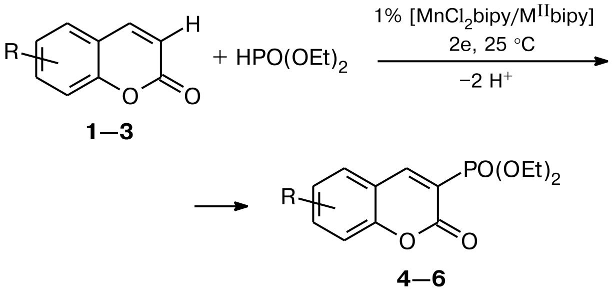
Coumarins, the structural framework of which is encountered in a number of natural compounds and is also a fragment of compounds possessing pharmacological activity[1—5] or belonging to fluorescent and laser dyes,[6—9] attract noticeable attention of researchers in the last years. Thus, it was shown that some 3-phosphorylated coumarins exhibit cytotoxicity against human leukemia cells *in vitro* and *in vivo*,[4,5] as well as a high alkylating activity.[10]

Earlier, 3-phosphonated coumarins were commonly obtained by the Arbuzov[11—14] or Knoevenagel[15—17] reaction. These methods, as a rule, give side products, are frequently based on multi-step sequential reactions, do not correspond to the atom-economy principles and, therefore, have low efficiency. Until recently, only limited publications[18—20] described phosphonation of coumarins by the radical reaction using excessive amount of $Mn(OAc)_3$ (3 equiv.) and an aliphatic acid as a solvent[18] or noble metal (silver[20] or palladium[19]) salts. The approaches described in the works[18—20] have a number of other disadvantages: high temperature, long-time synthesis, low yield of the final product, and low conversion.

The formation of the C—P bond by direct phosphorylation of a C—H bond in aromatic substrates remains one of the most important approaches, since it meets generally accepted principles of "green chemistry", namely, the atom-economy, small amount of waste and small number of steps in the process. In this connection, catalytic reactions, including electrochemical,[21—26] of direct phosphorylation of aromatic compounds become especially attractive.

Based on the data obtained in the studies of oxidative metal-induced phosphorylation of benzene,[27] we have suggested that phosphorylation of coumarin can be effected at room temperature in one step. The pairs $MnCl_2$bipy/$Ni(BF_4)_2$bipy and $MnCl_2$bipy/$CoCl_2$bipy (bipy is the 2,2´-bipyridine) have been chosen as catalytic systems for electrochemical phosphorylation of coumarins **1—3**. The process is distinguished by the equimolar ratio coumarin : dialkyl phosphite and room temperature (Scheme 1, Table. 1).

Scheme 1



M = Ni, Co
R = H (**1**, **4**), 6-Me (**2**, **5**), 7-Me (**3**, **6**)
bipy = 2,2´-bipyridine

The phosphorylation does not occur without the catalyst. It is important to note that a 100% conversion of diethyl phosphite is reached in these syntheses (completely consumed after passing 2 F of electricity). In contrast to the reaction conditions of phosphorylation of coumarins

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Table 1. Electrochemical phosphorylation of coumarins **1—3** with diethyl phosphite in the presence of different catalysts*

Entry	Substrate	Catalytic system	Product	Product yield (%)
1	**1**	$[MnCl_2bipy/Ni(BF_4)_2bipy]$	**4**	30
2	**1**	$[MnCl_2bipy/CoCl_2bipy]$	**4**	55
3	**2**	$[MnCl_2bipy/Ni(BF_4)_2bipy]$	**5**	31
4	**2**	$[MnCl_2bipy/CoCl_2bipy]$	**5**	61
5	**3**	$[MnCl_2bipy/Ni(BF_4)_2bipy]$	**6**	37
6	**3**	$[MnCl_2bipy/CoCl_2bipy]$	**6**	70

* **Reaction conditions:** the ratio of coumarin : diethyl phosphite = = 1 : 1, catalyst (0.01 equiv.), 20 °C, Q = 2 F per 1 mole of diethyl phosphite, galvanostatic regime, MeCN; an anode potential of 0.7 V relative to Ag/AgCl.

according to the method described in the work[19] (10% Pd^{II}bipy, oxidant $K_2S_2O_8$ (3 equiv.)), under conditions found by us the phosphonate is formed in the presence of a bimetallic catalytic system Mn^{II}bipy/Ni^{II}bipy or Mn^{II}bipy/Co^{II}bipy without use of any additional reagents, with the yields of 3-phosphonated products **4—6** being higher: in the work[19] under the optimum conditions the highest yield was 48%. As a rule, coumarins with electron-donating groups **2** and **3** give better yields of the corresponding phosphorylation products than unsubstituted coumarin **1**. It is interesting that 7-methylcoumarin **3** (see Table 1, entry *6*) turned out to be the most suitable substrate for phosphorylation at position 3. Apparently, this is due to the +I-effect of the methyl group in combination with the +M-effect of the heteroatom. In the case when a methyl group is at position 6 (coumarin **2**), the yields of the CH-substitution product are lower. The reaction of unsubstituted coumarin **1** with diethyl phosphite proceeds also less selective as compared to 7-methylcoumarin **3**. The use of monometallic systems sharply decreases efficiency of the target reaction and leads to an unseparable suspension.

It should be noted that all the 3-phosphonylated coumarins obtained in the present work are described in the literature, however, strange disagreements are observed in their physicochemical characteristics and some spectral data. Thus, for example, in the work[20] published in 2015, diethyl(2-oxo-2*H*-chromen-3-yl)phosphonate (**4**) was described as a viscous liquid, though it is a white powder with m.p. 65—66 °C (our data, agreeing with the data in the work[18]), whereas in the ^{13}C NMR spectrum of this compound, the signal at δ 117.9 (d) was by mistake reported to have the spin-spin coupling constant of J_{P-C} = = 23.2 Hz, whereas according to our data, which agree with the data in the work,[18] it is J = 196—197 Hz. Note that in the work,[18] the data on the ^{31}P NMR spectra are absent, which is very important for the monitoring the reaction progress, which is carried out in acetic acid upon heating, *i.e.*, under the conditions causing decomposition of diethyl phosphite (see, for example, Refs 28 and 29). The ^{31}P NMR spectrum of compound **3** is reported in the work.[12] Therefore, in the Experimental section we report all physicochemical data for all the isolated products.

In the preceding study,[27] we found specific features of electrocatalytic phosphorylation of aromatic compounds taking benzene as an example. This study included detail analysis of electrochemical properties of catalyst complexes in the absence and in the presence of diethyl phosphite and arene by cyclic voltamperometry. It should be noted that the earlier published studies do not have data confirming the mechanism of phosphorylation in the presence of complexes or metal salts (Pd, Ag, Mn). A radical mechanism is commonly assumed, however, the additives of TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxyl), as a rule, have no influence on the product yield, whereas organic oxidants capable of generating radicals in the system, for example, *tert*-butylhydroperoxide, inhibit the reaction.[19] This indicated that the reaction can follow not only the radical mechanism.

Earlier, it was shown[27] that the first step of electrochemically induced phosphorylation is the formation of metal phosphonates, which undergo oxidation more easily than the starting catalyst complexes. Diethyl phosphite does not undergo oxidation under the studied conditions. The preparative electrolysis proceeds exactly at potentials corresponding to the oxidation of phosphonate complexes. Since nickel and cobalt phosphonate complexes oxidize earlier (about 0.5 V) than the manganese complexes (1.0 V)[27] the phosphorylation process is triggered by this reaction involving cations of Ni or Co. The cations of manganese coordinates at the carbonyl group of coumarin and participates in the generation of phosphonyl radicals, directing the substitution reaction at position 3 of coumarin under the oxidation conditions. The details of the mechanism of this complex reaction require further studies.

In conclusion, the electrochemical synthesis of diethyl phenylphosphonate proceeds under mild conditions (room temperature, atmospheric pressure, equimolar ratio of reagents) and allows one to obtain product in high yield (up to 70%) and 100% conversion in the presence of the bimetallic catalytic system Mn^{II}bipy/Ni^{II}bipy or Mn^{II}bipy/Co^{II}bipy without use of any additional oxidants.

Experimental

The NMR spectra were recorded on a Bruker AVANCE-400 multinuclear spectrometer (400.1 (^1H), 100.6 (^{13}C), and 162.0 (^{31}P) MHz) in $CDCl_3$. Chemical shifts were recorded relative to the signals of the deuterated solvent (in the case of ^1H and ^{13}C NMR) or phosphoric acid (in the case of ^{31}P NMR).

Mass spectrometric studies (electrospray ionization) of the samples was carried out on a Bruker Daltonik GmbH AmazonX (Germany). Nitrogen was used as a nebulizer gas in the source with a temperature of 220 °C. The source voltage was 4.5 kV. Solutions of the samples were diluted with acetonitrile to a concentration of ~10^{-3} mg mL^{-1}. The samples were injected using an autosampler of an Agilent 1260 Infinity liquid chromatograph (Agilent Technologies, USA).

Coumarin **1** (99%), 6-methylcoumarin (**2**) (99%), 7-methylcoumarin (**3**) (98%) (Sigma Aldrich) were used without additional purification.

Acetonitrile served as a basic solvent in the syntheses (extra pure grade, Acros organics), which was distilled thrice before experiments: the first distillation was carried out using potassium permanganate, the second distillation was carried out over phosphorus pentoxide, the third distillation was carried out over calcium hydride under argon.

Diethyl phosphite was obtained according to the described procedure.[30] The purified solvents were stored under an inert atmosphere in the Schlenk systems.

Salt Et_4NBF_4 was obtained by mixing 30—35% aqueous solution of tetraethylammonium hydroxide Et_4NOH and HBF_4 until the medium became neutral. A white crystalline precipitate was formed in the course of the reaction, which was collected by filtration and dried. The resulted powdered salt was recrystallized from ethanol and dried for 2—3 days in a vacuum drying oven at 55 °C.

Preparative electrosyntheses were carried out using a B5-49 source of direct current in a 40-mL three-electrode cell. The working electrode potential was detected using a V7-27 DC voltmeter relative to the reference electrode Ag/AgCl (C = = 0.01 mol L^{-1}) in acetonitrile. The surface of the working platinum (Pt) U-shaped electrode was 48.00 cm^2. A ceramic plate with the pore diameter of 900 nm was used as a diaphragm. During preparative synthesis, the electrolyte was continuously stirred with a magnetic stirrer. The electrolysis was carried out under constant flow of an inert gas, which passed the system for purification from oxygen and other gaseous impurities.

Synthesis of metal complexes (general procedure). A solution of the corresponding ligand ($1.83 \cdot 10^{-2}$ mol) in EtOH (30—50 mL) was slowly added to a solution of metal salt MX_2 (M = Co, Ni) ($1.83 \cdot 10^{-2}$ mol) in EtOH (100 mL) with stirring. The reaction mixture was stirred for 3—24 h at a constant temperature (25 °C) until a crystalline precipitate was formed, which was collected by filtration under argon and washed with ice-cold ethanol. The resulting complex was dried in a vacuum drying oven for 2—3 days at a temperature of 25—55 °C. Physicochemical characteristics of the obtained complexes corresponded to the literature data: $CoCl_2$bipy[31] and $Ni(BF_4)_2$bipy.[32]

Electrocatalytic phosphorylation of coumarins (general procedure). Diethyl phosphite ($1.2 \cdot 10^{-3}$ mol), coumarin **1**—**3** ($1.2 \cdot 10^{-3}$ mol), and metal complex MX_2L (M = Co, Ni) ($1.2 \cdot 10^{-5}$ mol) in MeCN (40 mL) were placed in an electrochemical cell. Electrolysis was carried out in an electrochemical cell with separated anode and cathode compartments at a temperature of 23 °C under dry argon at a working electrode potential of 0.7 V in the galvanostatic regime. The amount of passed electricity was 2 F per 1 mole of phosphite. After the electrolysis was completed, the reaction mixture was washed with a saturated solution of ammonium chloride (3×50 mL) and extracted with chloroform (3×70 mL). After separation, the organic layer was dried with magnesium sulfate, the solvent was evaporated. The residue was purified by column chromatography on silica gel (eluent ethyl acetate—hexane). Physicochemical characteristics of the products corresponded to the data given in the work,[18] except for the ^{31}P NMR spectra and IR spectra, which were not reported. The product yields are given in Table 1.

Diethyl (2-oxo-2*H*-chromen-3-yl)phosphonate (3). A white powder. M.p. 65—66 °C. ^{31}P NMR, δ: 10.37. ^{1}H NMR, δ: 8.53 (d, 1 H, C(4)H, $^3J_{PH}$ = 17.2 Hz); 7.66—7.60 (m, 2 H, ArH); 7.37—7.33 (m, 2 H, ArH); 4.34—4.22 (m, 4 H, 2 CH_2); 1.37 (t, 6 H, 2 CH_3, J = 7.1 Hz). ^{13}C NMR, δ: 158.3 (d, J_{P-C} = 22.7 Hz); 155.3, 153.5 (d, J_{P-C} = 6.4 Hz); 134.4, 129.5, 125.1, 118.0 (d, J_{P-C} = 14.1 Hz); 117.9 (d, $^1J_{P-C}$ = 196.9 Hz); 116.9, 63.5 (d, J_{P-C} = 9.2 Hz); 16.5 (d, J_{P-C} = 10.1 Hz). MS (ESI), m/z: 282.84 $[M]^+$. IR (KBr), ν/cm^{-1}: 2983, 2920, 2875 (—CH_3, —CH_2—), 1743 (C=O), 1610, 1562 (Ar—), 1430 (P—C), 1248 (P=O), 1055 (P—O). Calculated (%): C, 55.32; H, 5.36; P, 10.97. $C_{13}H_{15}O_5P$. Found (%): C, 55.31; H, 5.33; P, 10.92.

Diethyl (6-methyl-2-oxo-2*H*-chromen-3-yl)phosphonate (4). A yellow powder. M.p. 74—76 °C. ^{31}P NMR, δ: 11.4. ^{1}H NMR, δ: 8.40 (d, 1 H, C(4)H, J = 17.1 Hz); 7.38 (d, 1 H, ArH, J = 8.5 Hz); 7.30 (s, 1 H, ArH); 7.17 (d, 1 H, ArH, J = 8.5 Hz); 4.23—4.17 (m, 4 H, 2 CH_2); 2.35 (s, 3 H, C(6)Me); 1.31 (t, 6 H, 2 CH_3, J = 7.4 Hz). ^{13}C NMR, δ: 159.0, 158.9, 153.7, 153.6, 135.6, 135.0, 129.2, 117.9, 117.8, 116.8, 63.6, 20.9, 16.6. MS (ESI), m/z: 296.44 $[M]^+$. IR (KBr), ν/cm^{-1}: 3057, 2963, 2857 (—CH_3, —CH_2—), 1719 (C=O), 1211 (P=O), 1039 (P—O). Calculated (%): C, 56.76; H, 5.78; P, 10.46. $C_{14}H_{17}O_5P$. Found (%): C, 56.64; H, 5.73; P, 10.41.

Diethyl (7-methyl-2-oxo-2*H*-chromen-3-yl)phosphonate (5). A yellow powder. M.p. 62—64 °C. ^{31}P NMR, δ: 10.9. ^{1}H NMR, δ: 8.40 (s, 1 H, C(4)H); 7.39 (d, 1 H, ArH, J = 7.5 Hz); 7.06 (d, 2 H, ArH, J = 7.4 Hz); 4.19 (m, 4 H, 2 CH_2); 2.40 (s, 3 H, C(7)Me); 1.30 (s, 6 H, 2 CH_3). ^{13}C NMR, δ: 158.9, 155.6, 153.7, 146.4, 129.3, 126.4, 117.1, 115.8, 106.6 (d, $^1J_{P-C}$ = 197.4 Hz), 63.5, 22.3, 16.6. MS (ESI), m/z: 296.47 $[M]^+$. IR (KBr), ν/cm^{-1}: 3061, 2966, 2861 (—CH_3, —CH_2—), 1721 (C=O), 1210 (P=O), 1039 (P—O). Calculated (%): C, 56.76; H, 5.78; P, 10.46. $C_{14}H_{17}O_5P$. Found (%): C, 56.67; H, 5.71; P, 10.42.

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