Electrochemical oxidative phosphorylation of azoles in the presence of silver catalysts

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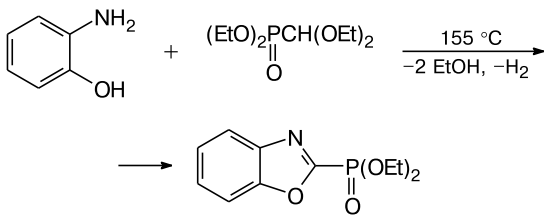
A new method for the phosphorylation of benzo-1,3-azoles (benzoxazole, benzothiazole, and 3-methylindole) with diethyl phosphite by electrocatalytic oxidation was proposed. The process occurs under electrochemical mild conditions (room temperature, normal pressure) in the presence of silver salts or silver oxide. This method allows one to obtain 2-phosphorylated products of benzo-1,3-azoles in good yield (up to 75%).

Key words: CH-functionalization, phosphorylation, oxidation, electrosynthesis, catalyst, benzo-1,3-azoles.

Benzo-1,3-azoles and their derivatives have unique biological properties. For example, benzoxazoles exhibit anticancer activity[1,2] and are new non-nucleoside inhibitors of topoisomerase I.[3] They can be considered as structural bioisomers of natural nucleotides such as adenine and guanine, which allow their easy reactions with polymers in living systems.[4] Products for plant protection (for example, insectoacaricide Zolon with contact-intestinal action (*S*-2,3-dihydro-(6-chloro-2-oxybenzoxazol-3-ylmethyl)-*O*,*O*-diethyl dithiophosphate)),[5] herbicides,[6] antidiabetics, and neuroleptics[7] were prepared on the basis of the benzoxazole derivatives. It has recently been found[8] that 3-phosphoindoles are good inhibitors of AIDS-1. Search for new low-waste routes of production of phosphorus-containing derivatives of heterocycles, including azoles, by direct phosphorylation of C—H bonds is an urgent trend.

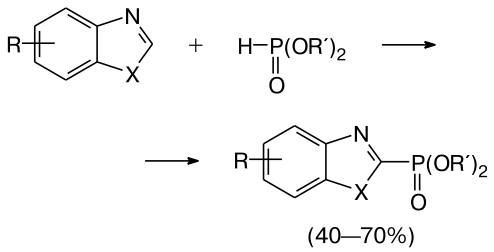
The phosphorylated derivatives of benzoxazoles have first been synthesized as early as in the 1960s by A. I. Razumov by heating *ortho*-aminophenol and diethyldiethoxymethyl phosphonate with distillation of ethanol[9,10] (Scheme 1).

Scheme 1



In the recent decade, serious efforts were focused on the reactions of direct functionalization of the C(sp^2)—H bonds of azoles to form the 2-substituted derivatives. They were successfully arylated, alkylated, carboxylated, carbonylated, and aminated.[11] The method of direct catalytic oxidative phosphorylation of aromatic azoles in the absence of bases and acids involving palladium salts as a catalyst and excess $K_2S_2O_8$ as an oxidant (Scheme 2) has recently[12] been described. The reaction at 100 °C occurs slowly, and the yields of the C(2)-phosphorylated azole derivatives are 40—70%.

Scheme 2



Reagents: $Pd(OAc)_2$ (5 mol.%), ligand (30 mol.%), $K_2S_2O_8$ (excess).

The cross-coupling of 1*H*-indole and diethyl phosphites to form the C(sp^2)—P bond (Scheme 3) was described in 2012.[13] Phosphorylated 1*H*-indoles (16 compounds) were obtained in 18—71% yields and regioselectivity >15 : 1.

Later, urans, thiophenes, thioazoles, pyrroles, and pyridines were phosphorylated in the presence of catalytic

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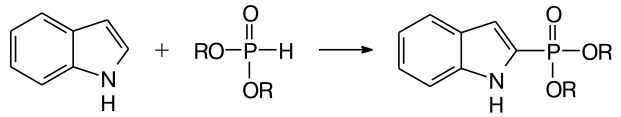
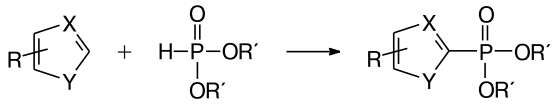
Scheme 3



(2 equiv.)

Reagents and conditions: AgOAc (3 equiv.), $ClCH_2CH_2Cl$, 90 °C.

Scheme 4

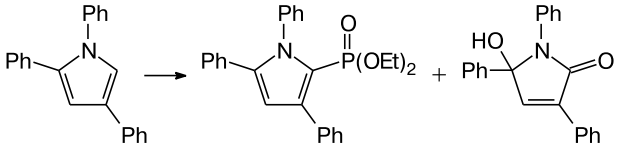


X = C, N, H; Y = O, S, NMe; R′ = Me, Et

Reagents and conditions: $AgNO_3$ (0.2 equiv.), $K_2S_2O_8$ (3 equiv.), CH_2Cl_2, H_2O, 20 °C.

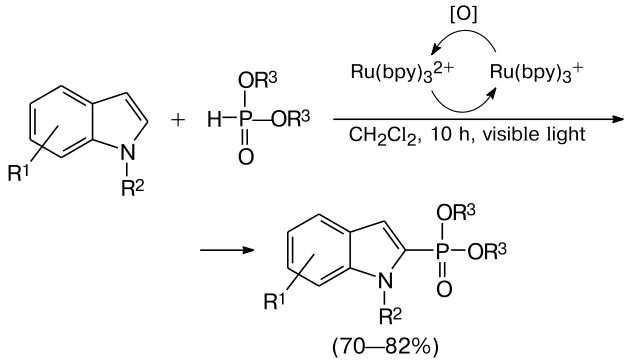
amounts of $AgNO_3$ using $K_2S_2O_8$ as an oxidant (Scheme 4).[14] Dehydrocondensation between substituted pyrroles and dialkyl phosphites occurs under similar conditions (Scheme 5).[15]

Scheme 5



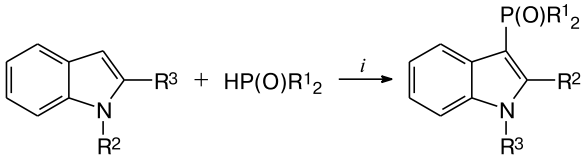
Reagents: $HP(O)(OEt_2)$ (3 equiv.), oxidant.

Scheme 6

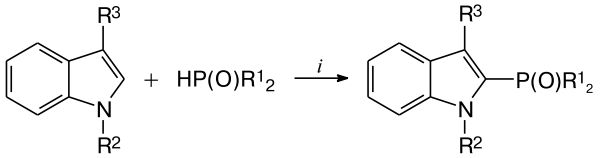


R^1 = H, 5-CN; R^2 = Me, Bu, Bn; R^3 = Me, Et, Pr^i

Scheme 7



R^2 = H, Me; R^3 = COOMe, Me, COOEt



R^2 = H, Me; R^3 = CHO, CN, Ph, COOMe

Reagents and conditions: *i.* $AgCO_3$ (10 mol.%), $Mg(NO_3)_2$ (1.5 equiv.), MeCN, 80 °C, 24 h.

The regioselective cross-coupling of *N*-substituted indoles with dialkyl phosphites is considered in the work[16] published in 2016 (Scheme 6). The reaction was carried out in the presence of the $Ru(bpy)_3(PF_6)_2$ photoredox catalyst and oxygen as an oxidant. An intermediate phosphorus radical cation is formed under the visible light irradiation and then adds to the substrate to give 2-indolyl phosphonates in 70—82% yields.[16]

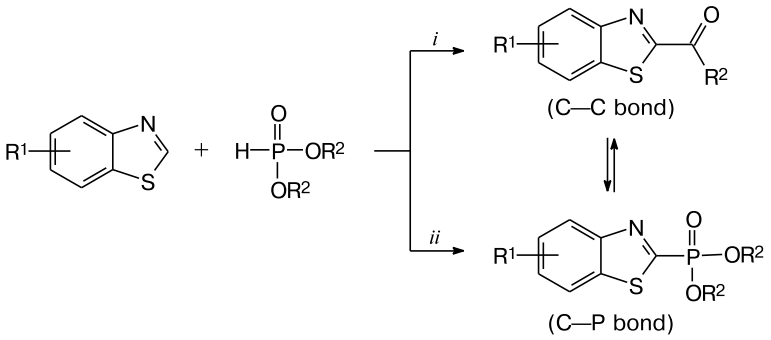
The Ag-catalyzed phosphorylation of indoles substituted at positions 2 and 3 in the presence of 1.5 equiv. $Mg(NO_3)_2$ as an oxidant was conducted later. The yield of the 3-phosphorylated derivatives from 2-substituted indoles is higher than that of the 2-phosphorylated compounds from 3-substituted indoles (Scheme 7).[17]

In 2014, chinese scientists have found[18] that various products can be obtained by the reactions of benzothiazoles and *H*-phosphonates under mild conditions depending on the nature of the oxidant (peroxide): derivatives of benzothiazoles, 2-acylbenzothiazoles, and dialkylbenzothiazol-2-yl phosphonates (Scheme 8).

The method of $C(sp^2)$—P bond formation was described[19] in 2016 *via* the cross-coupling of the benzothiazole derivatives with phosphorus-containing organic compounds in the presence of threefold excess $Mn(OAc)_3$ under the ball-milling conditions (Scheme 9).

As a rule, a drawback of the above described reactions is the necessity to use a large excess oxidant. The development of more ecologically safe and simple catalytic methods is especially urgent. Therefore, electrochemical methods corresponding to criteria of green chemistry seem to be attractive, since they are characterized by mild conditions of the process (low temperature, normal pressure), the possibility of recovering the active form of the catalyst at the electrode, as well as ecological safety and

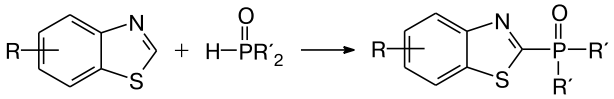
Scheme 8



R^1 = H, Me, OMe, Cl, Br, NO_2

Reagents and conditions: *i*. TBHP, MeCN, 80 °C, 24 h; *ii*. DTBP, MeCN, 80 °C, 30 h.

Scheme 9



Reagents and conditions: $Mn(OAc)_3 \cdot 2\ H_2O$ (3 equiv.), ball-milling, 1.5 h, in air.

low-waste character. New electrochemical reactions of $C(sp^2)$—H bond phosphorylation were proposed in the recent years.[20—27]

The purpose of this work is the development of a new method for the phosphorylation of the benzo-1,3-azole derivatives with dialkyl phosphites under the conditions of electrochemical oxidation in the presence of the silver salts.

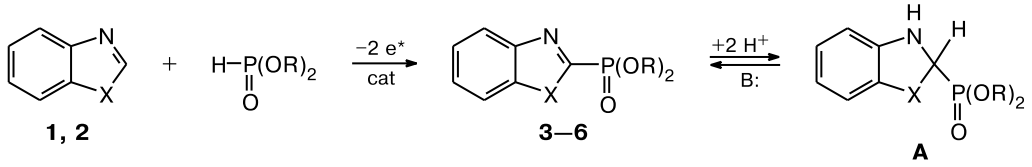
Results and Discussion

The joint electrolysis of a mixture of benzoxazole (**1**) (or benzothiazole (**2**)) and dialkyl phosphites under the oxidation conditions in the presence of catalytic amounts of the silver salts at room temperature affords 2-phosphorylated benzothia(oxa)zoles, dialkylbenzothia(oxa)-zol-2-yl phosphonates **3**—**6** (Scheme 10).

Electrolysis was carried out in a cell with divided cathodic and anodic spaces. The silver salts (nitrate, acetate, and carbonate) and silver oxide were tested as catalysts. The electrolysis progress was monitored by ^{31}P NMR spectroscopy. The results of the electrolyses are presented in Table 1.

Low yields of phosphorylated benzothia(oxa)zoles were observed (see Table 1, entries *1*—*4*) when $AgNO_3$ was used as the catalyst. An increase in the quantity of electricity exerted no effect on the conversion of the initial dialkyl phosphite, the signal of which is always detected in the spectrum of the reaction mixture, and on the yield of the final product. Under these conditions, diisopropyl phosphite turned out to be less reactive than diethyl phosphite. The catalytic activity of silver acetate AgOAc turned out to be higher than that of $AgNO_3$. After passing 1 F electricity through the reaction mixture diethyl phosphite : benzoxazole (**1**) : silver acetate = 1 : 1 : 0.1, the ^{31}P NMR spectrum of the reaction mixture always contains the signals of the initial diethylphosphorous acid at δ 8.90 (J = 688.3 Hz), the reaction product, phosphonate **3**, at δ −0.33, and the protonated form of the reaction product **A** at δ 2.81 (J = 566.29 Hz). Only after passing 3 F electricity through the reaction mixture, the signal of the initial acid disappears, and only signals of two reaction

Scheme 10



* The amount of passed electricity was 1.5 times higher than the theoretical value.

X = O (**1**), S (**2**)
R = Et, X = O (**3**), S (**4**); R = Pr^i, X = O (**5**), X = S (**6**)

Table 1. Results of the electrochemical phosphorylation of benzoxazole (**1**) and benzothiazole (**2**) with diethyl phosphite in MeCN

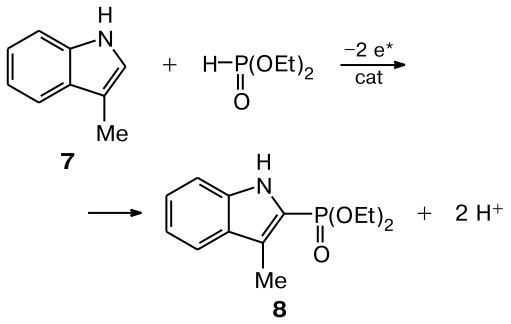
Entry	Azole	Catalyst	Base	Potential of anode/V	Product	Yield of product (%)	
						Substance	Current
1	**1**	$AgNO_3$	—	2.14	**3**	41	26
2	**1**	$AgNO_3$*	—	1.75	**5**	30	19
3	**2**	$AgNO_3$	—	1.73	**4**	42	26.5
4	**2**	$AgNO_3$*	—	1.70	**6**	45	26.5
5	**1**	AgOAc	Treatment with Bu^tOK after electrolysis	2.22	**3**	61	39
6	**1**	AgOAc	K_2CO_3	2.08	**3**	63	40.5
7	**1**	AgOAc	Na_3PO_4	2.16	**3**	75	48
8	**1**	AgOAc	NaH_2PO_3	2.22	**3**	63	40.5
9	**2**	AgOAc	Na_3PO_4	2.17	**4**	51	32.5
10	**2**	AgOAc	NaH_2PO_3	2.12	**4**	54	34.5
11	**1**	Ag_2CO_3	—	2.00	**3**	8	5
12	**1**	Ag_2O	—	1.28	**3**	34	22.5

* Phosphorylation with diisopropyl phosphite.

products are observed in the spectrum, *i.e.*, final phosphonate **3** and its protonated form **A**, which is always present due to strong acidification of the reaction mixture during oxidation processes. The reaction mixture was treated with a base to obtain the pure product. Potassium *tert*-butylate and triethylamine were tested as bases. It turned out that only after the treatment of the reaction mixture with Bu^tOK, the protonated form of the product **A** converts completely to phosphonate **3** (entry *5*). Electrolysis in the presence of a base (K_2CO_3, Na_3PO_4, and NaH_2PO_3 were tested) made it possible to obtain the final product avoiding formation of the protonated species. Under these conditions, benzothiazole (**2**) is also phosphorylated to form 2-substituted derivative **4** (δ_P 2.19) (entries *9* and *10*). The use of silver carbonate Ag_2CO_3 in the electrochemical phosphorylation of benzo-1,3-azole (**1**) also results in the formation of 2-substituted derivative **3**, although in a low yield (entry *11*). It is most likely that the electrolysis leads to the formation of unstable carbonic acid that readily decomposes to CO_2 and H_2O, resulting in the decomposition of silver carbonate that equimolarly reacts with benzoxazole (**1**) and diethyl phosphite. Under the electrochemical conditions, excess diethyl phosphite is oxidized to tetraethyl pyrophosphate (δ_P −12). Silver oxide Ag_2O was also tested as a catalyst in the same reaction (entry *12*). After passing 3 F electricity, the spectrum of the reaction mixture contains signals of both the product and initial diethylphosphorous acid. The yield of the final 2-phosphorylated benzoxazole **3** was 34%. Thus, the highest yields (75%) were achieved when silver acetate was used as the catalyst and Na_3PO_4 served as the base (entry *7*).

3-Methylindole (**7**) was also studied as a substrate in the electrochemical phosphorylation of heterocyclic compounds, because the indole derivatives have unique biological properties. It turned out that compound **7** is phosphorylated under the chosen conditions to form phosphorylated derivative **8** in 30—50% yields (Scheme 11, Table 2). As in the case of benzo-1,3-azoles, silver acetate turned out to be the best catalyst.

Scheme 11



* The amount of passed electricity was 1.5 times higher than the theoretical value.

Thus, the convenient preparative method of electrosynthesis of 2-phosphorylated benzo-1,3-azoles was developed using the silver salts as catalysts. The electrolysis proceeds *via* one step at room temperature. Silver acetate turned out to be the best catalyst for this process of the salts studied.

Experimental

Acetonitrile was distilled over P_2O_5 and $KMnO_4$ and then over molecular sieves. Benzene was distilled over sodium metal.

Table 2. Results of the electrolytic phosphorylation of 3-methylindole with diethyl phosphite in MeCN

Entry	Catalyst	Base	Oxidation potential/V	Yield of product (%)	
				Substance	Current
1	$AgNO_3$	Na_3PO_4	1.84	41	40
2	AgOAc	Na_3PO_4	2.03	50	26.5
3	Ag_2O	Na_3PO_4	1.32	31	20

After purification, the solvents were stored under a dry argon atmosphere. Benzoxazole, benzothiazole, 3-methylindole, silver acetate, silver carbonate, silver oxide (all from Alfa Aesar), diethyl phosphite, and diisopropyl phosphite (Acros Organics) were used. All syntheses were carried out under a dry argon atmosphere. Preparative electrolyses were conducted using a B5-49 dc source in a three-electrode 30-mL cell. The potential of the working electrode was detected with a V7-27 dc voltmeter relative to the reference electrode Ag/0.01 *M* $AgNO_3$ in acetonitrile. The working surface of the platinum cylindrical cathode used as a working electrode was 20.0 cm^2. A ceramic plate with a pore size of 900 nm served as a membrane. A platinum grid served as an anode, and a saturated solution of $PyHBF_4$ in acetonitrile was used as a catholyte. During electrolysis, the electrolyte was magnetically stirred under a continuous argon flow, which was passed through the drying system. NMR spectra were recorded on a Bruker AVANCE-400 multinuclear spectrometer (400.1 (^{1}H) and 162.0 MHz (^{31}P)). Chemical shifts were detected relative to the signals of the deuterated solvent (^{1}H) and phosphoric acid (^{31}P) as internal standards. Electrospray ionization (ESI) mass spectra were obtained on an AmazonX spectrometer (Bruker Daltonik GmbH, Germany) in the positive mode with a capillary voltage of 4500 V.

Electrolysis (general procedure). Silver salt (0.42 mmol), benzothia(oxa)zole (4.2 mmol), and dialkylphosphorous acid (4.2 mmol) in acetonitrile (30 mL) were placed in an electrochemical cell. Electrolysis was carried out in the galvanostatic mode with the simultaneous control of the working electrode potential in the cell with divided anodic and cathodic spaces with magnetic stirring and continuous argon flow. A saturated solution of $PyHBF_4$ in acetonitrile was placed in the cathodic space. Electricity (3 F, 350 mA h) was passed through the electrolyte. After complition of electrolysis, the reaction mixture was concentrated on a rotary evaporator. The residue was treated with an equimolar amount of Bu^{t}OK (this step was omitted when the electrolysis was carried out in the presence of a base), washed with an aqueous solution of ammonium chloride, and extracted with benzene (3×40 mL). After separation, the organic layer was dried for 24 h over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography on silica gel (elution with hexane—ethyl acetate).

Diethylbenzoxazol-2-yl phosphonate (**3**),[12] yellow oil. ^{1}H NMR ($CDCl_3$), δ: 7.45 (d, 1 H, J = 7.9 Hz); 7.09 (t, 1 H, J = 7.2 Hz); 7.02 (d, 1 H, J = 8.1 Hz); 6.24 (t, 1 H, J = 8.0 Hz); 4.14 (dq, 4 H, J = 7.1 Hz, J = 8.6 Hz); 1.36 (t, 6 H, J = 7.0 Hz). ^{31}P NMR ($CDCl_3$), δ: −1.14 (s). MS (ESI), *m/z*: 256.05 $[M + H]^+$.

Diethylbenzoxazol-2-yl phosphonate (**4**),[12] yellow oil. ^{1}H NMR (($CD_3)_2CO$), δ: 8.30 (d, 1 H, J = 7.5 Hz); 8.23 (d, 1 H, J = 7.7 Hz); 7.73 (t, 1 H, J = 7.1 Hz); 7.66 (t, 1 H, J = 8.1 Hz), 4.11 (dq, 4 H, J = 6.9 Hz, J = 9.2 Hz); 1.31 (t, 6 H, J = 6.9 Hz). ^{31}P NMR (($CD_3)_2CO$), δ: 4.79 (s). MS (ESI), *m/z*: 272.1 $[M + H]^+$.

Diisopropylbenzothiazol-2-yl phosphonate (**5**), yellow oil.[12] ^{1}H NMR ($CDCl_3$), δ: 7.79 (d, 1 H, J = 6.9 Hz); 7.59 (d, 1 H, J = 7.14 Hz); 7.38 (m, 2 H); 4.72 (m, 2 H); 1.36 and 1.35 (both d, 12 H, J = 6.17 and J = 6.18 Hz). ^{31}P NMR ($CDCl_3$), δ: −2.59 (s). MS (ESI), *m/z*: 284.2 $[M + H]^+$.

Diisopropylbenzoxazol-2-yl phosphonate (**6**), yellow oil.[12] ^{1}H NMR ($CDCl_3$), δ: 8.13 (d, 1 H, J = 8.18 Hz); 7.94 (d, 1 H, J = 8.00 Hz); 7.50 (t, 1 H, J = 7.10 Hz); 7.90 (t, 1 H, J = 7.19 Hz); 4.43 (m, 2 H); 1.24 and 1.23 (both d, 12 H, J = 6.17 Hz, J = 6.17 Hz). ^{31}P NMR ($CDCl_3$), δ: 1.24 (s). MS (ESI), *m/z*: 300.4 $[M + H]^+$.

Diethyl-3-methyl-1*H*-indol-2-yl phosphonate (**8**),[13,15] light yellow oil, m.p. 103 °C. ^{1}H NMR ($CDCl_3$), δ: 8.06 (br.s, 1 H); 7.71 (d, 1 H, J = 7.06 Hz); 7.54 (t, 1 H, J = 8.22 Hz); 7.03 (d, 1 H, J = 8.29 Hz); 6.91 (t, 1 H, J = 7.42 Hz); 4.74 (dq, 4 H, J = 7.1 Hz, J = 8.8 Hz); 2.30 (s, 3 H); 1.42 (t, 6 H, J = 7.0 Hz). ^{31}P NMR ($CDCl_3$), δ: 10.008 (s). MS (ESI), *m/z*: 268.2 $[M + H]^+$.

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