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NOVEL STRUCTURAL ANALOGS OF GLYPHOSATE BASED ON AZOLES. 1. SYNTHESIS OF 1H-IMIDAZOLES CONTAINING CARBOXYL AND PHOSPHORYL GROUPS IN THE RING

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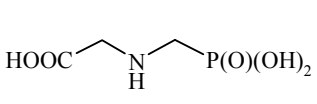
A general method has been developed for the synthesis of 1H-imidazoles containing a phosphoryl group in positions 2 or 4(5) based on lithium intermediates. The possibility of further functionalization of the ring using electrophiles has also been demonstrated.

Keywords: imidazole, lithium intermediates, electrophiles, hydrolysis, protecting groups, phosphorylation.

Glyphosate (N-phosphonomethylglycine **1** [1]) is the active component of the very efficient, ecologically clear herbicide Roundup® with a broad spectrum of activity. The commercial success of glyphosate has stimulated a vigorous search for similar phosphonates with improved biological properties [2]. Cyclic structural analogs of N-phosphonomethylglycine, e.g. 5-phosphonoproline **2** [3] and 3-hydroxy-1,2,4-triazol-5-ylphosphonic acid **3** [4] have also been prepared.



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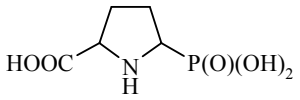

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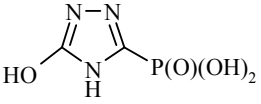

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Until now, compounds in this series with biological activity comparable to that of glyphosate have not been discovered. Continuing our search in this direction we have turned to developing novel spatial structures for this herbicide based on imidazole. The synthesis of the structural mimetics of glyphosate **4** and **5**, as chosen on the basis of molecular modelling, is the goal of our study.

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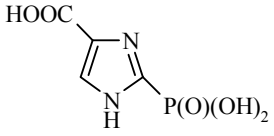
There are several examples of the electrophilic introduction of phosphorus-containing substituents into an imidazole ring in the literature. Thus imidazol-2-ylphosphinic acids were prepared by the phosphorylation of N-substituted imidazoles by P(III) [5] and P(V) [6, 7] acid chlorides. Reaction of 1,2-disubstituted imidazoles with P(III) halo derivatives in pyridine gave a series of 5-phosphorylated imidazoles with substituent at positions 1 and 2 in the heterocycle [8]. Phosphorylation of imidazole in position 4(5) has also been reported in a publication [9] for the Pd-catalyzed reaction of 4(5)-bromoimidazoles with diethylphosphite and in a patent [10] which describes the reaction of the corresponding lithio imidazole derivatives with diethylchlorophosphate.



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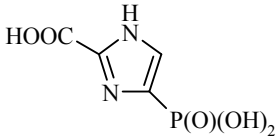

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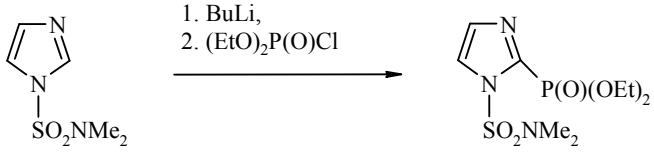
There are several methods reported in the literature for the construction of imidazol-4(5)-ylphosphonates, *viz.* heterocyclization of functionalized enamines [11], the base-catalyzed cycloaddition of diethyl isocyanomethylphosphonate to imidoylchlorides [12], and the condensation of secondary amines with diethyl (2,2-dichloro-1-isocyanoethenyl)phosphonate [13]. Finally, a method has been reported for the synthesis of diethyl 2-(ethoxycarbonyl)imidazol-4(5)-ylphosphonate through the thermal rearrangement of a functionalized O-vinyl-oxime [14].

For preparing 2- and 4(5)-phosphorylated 1H-imidazoles we have turned to the widespread used for functionalization of this heterocycle method of the metallation of N-substituted imidazoles and subsequent reaction of the carbanions obtained with the appropriate electrophiles [15]. The generation of the carbanions was brought about using BuLi. As electrophiles for the introduction of a phosphoryl group we used the P(V) and P(III) compounds $(Et_2O)_2P(O)Cl$ and $(Et_2N)_2PCl$. For protection of the nitrogen atom of the imidazole ring, two alkyl type groups were used, *viz.* benzyl and [2-(trimethylsilyl)ethoxy]methyl (SEM) and the electron- acceptor dimethylsulfamoyl group SO_2NMe_2.

This investigation began with a study of the C-2 phosphorylation of imidazoles having the three types of protecting groups noted above with the $(Et_2O)_2P(O)Cl$ as electrophile and this allowed the introduction of a fragment with a tetracoordinated phosphorus atom into the imidazole ring.



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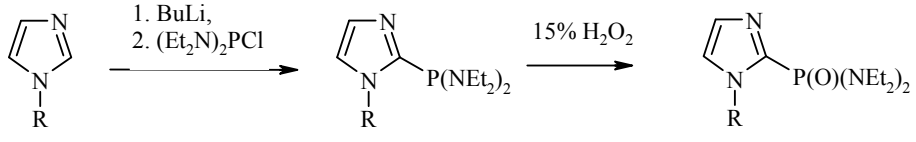
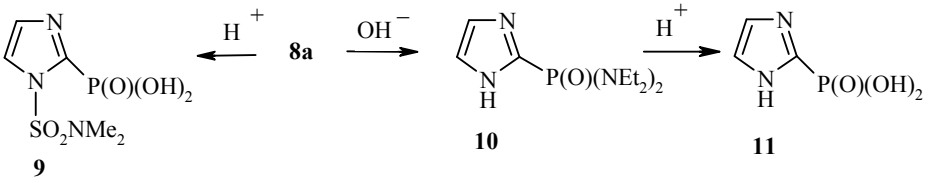
All three examples gave a complex reaction mixture from which only the imidazole **6** could be isolated in a yield of ~ 8%. The use of bis(diethylamino)chlorophosphite in place of the chlorophosphate and subsequent oxidation of the P(III) derivatives **7a-c** gave the 2-phosphorylated imidazoles **8a-c**.



7a–c **8a–c**

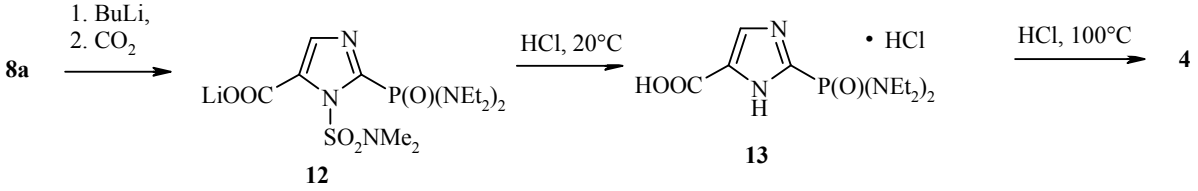
a R = SO_2NMe_2 (85%), **b** R = CH_2Ph (33%), **c** R = SEM (38%)

The imidazole **8a** formed in high yield can be hydrolyzed by hydrochloric acid to give the N-substituted imidazolylphosphonic acid **9**. Saponification of compound **8a** removed the N-protection to give the known phosphonamide **10** [7] which was converted to the imidazol-2-ylphosophonic acid **11** with acid.



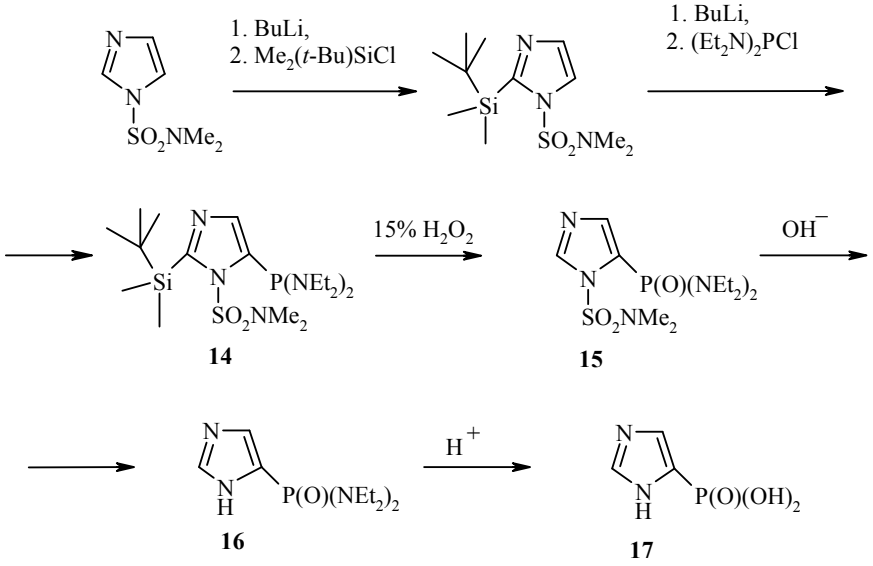
Treatment of compound **8a** with BuLi generates a carbanion at position 5 of the heterocycle [15] which gives the imidazole **12** in 92% yield upon carboxylation.

The N-sulfamoyl protection in compound **12** can be readily removed by the action of dilute HCl at 20ºC to give the hydrochloride **13** which yields the target imidazole **4** upon refluxing with HCl. It should be noted that compound **4** is formed in 62% yield since partial decarboxylation to the phosphonic acid **11** occurs in the course of the hydrolysis.

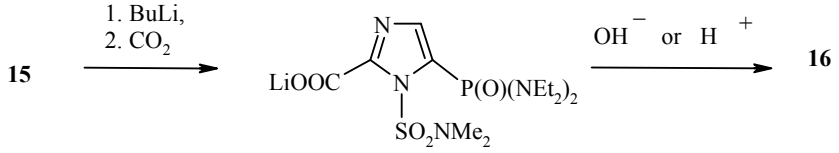


Phosphorylation at position 5 of the N-substituted imidazole ring using lithium reagents is only possible in those cases where the 2 position is protected. We have used the readily available and readily removed $Me_2(t\text{-Bu})Si$ group (TBDMS) [16] which is stable to lithiation and migration and used the electron-acceptor sulfamoyl group (based on the positive results we obtained for the synthesis of imidazole **4**) as protection for the heterocyclic N atom.

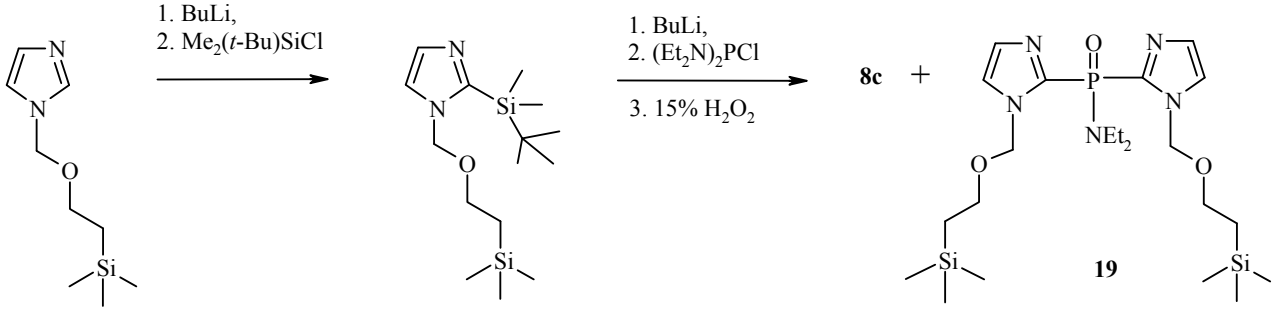
Stepwise lithiation of 1-(N,N-dimethylsulfamoyl)imidazole with successive addition of the Si- and then the P-electrophile gave compound **14**, oxidation of which in aqueous-acetone medium is accompanied by desilylation to give the phosphonamide **15** in high yield.



Saponification of compound **15** occurred with removal of the ring N-protection to give the 1H-imidazole **16**, from which refluxing in hydrochloric acid gave imidazol-4(5)-ylphosphonic acid **17**. Lithiation and subsequent carboxylation of phosphonamide **15** allowed us to prepare compound **18** as the key precursor of imidazole **5**.

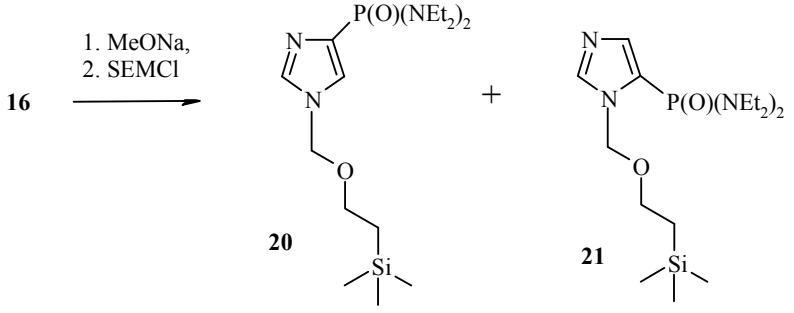


Hydrolysis of the 1,2,5-functionalized imidazole **18** in both acid and basic conditions is accompanied by decarboxylation to yield the phosphonamide **16**. This did not prove unexpected to us as the low stability of imidazol-2-ylcarboxylic acids is well known. In addition, the carboxyl group can be used as a C(2)-protecting group in the lithiation of N-substituted imidazoles at the 5 position of the ring [17]. None the less we decided to repeat the synthesis of the precursor of imidazole **5** by the scheme reported above using N–SEM protection which can be removed using F^- in anhydrous media [18]. Carrying out this synthesis gave unexpected results in that the imidazole phosphorylation occurred only at the ring position 2 despite the fact that TBDMS protection (which was stable to migration) had been used for blocking this position.



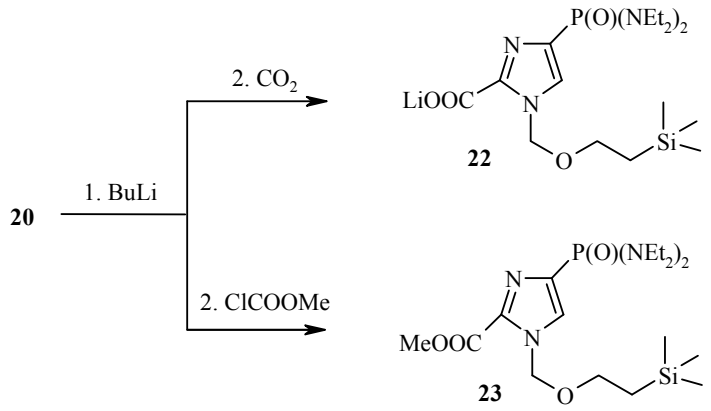
The appearance of the bis(imidazolyl)phosphonamide **19** can be explained by assuming the formation of Et_2NPCl_2 in the reaction course as the product of disproportionation of the electrophilic $(Et_2N)_2PCl$ reagent used.

In order to prepare the precursor of the target imidazole **5** with N–SEM protection we first alkylated the phosphonamide **16** with SEMCl to give a mixture of isomers **20** and **21** in the ratio ~ 6:1.



Compounds **20** and **21** were separated by column chromatography. The major 1,4-isomer **20** was lithiated and then reacted with CO_2 and chloroformate.

Salt **22** and ester **23** were separated and characterized. However we were unable to remove the N-protection using F^- in this case (Me_4NF, glyme or acetonitrile) while also retaining the carboxyl function at ring position 2.



Based on the experiments reported we can conclude that preparation of imidazole **5** or its NH-precursor does not appear possible using lithium reagents.

Unfortunately, initial experiments with imidazole **4** did not reveal biological activity comparable with that of glyphosate. However, we have been able to develop a general method for the synthesis of 1H-imidazoles which contain a phosphoryl group both at position 2 and at position 5 of the ring via use of lithium reagents and this allows further functionalization of the heterocycle using various electrophile.

EXPERIMENTAL

^1H and ^{31}P NMR spectra were recorded on a Varian VXR-300 instrument (300 and 121 MHz respectively) using DMSO-d_6 (compound **4**), $CDCl_3$ (compounds **6**, **8a-c**, **12**, **15**, **16**, **19-23**) and D_2O (compounds **9**, **11**, **13**, **17**, **18**) with the undeuterated solvent as internal standard. Chromatography was carried out on Fluka 40-60 μm silica gel and Aldrich Dowex WX-50 ion exchange resin. The purity of the compounds prepared was monitored by TLC on Silufol UV-254 plates. All of the operations connected with the lithiation and alkylation of the heterocycles were carried out under an argon atmosphere with solvents purified by a standard method. The hydrolysis reaction course was monitored by the ^{31}P NMR method.

Phosphorylation of N-substituted Imidazoles at Position 2 of the Heterocycle (General Method). A solution of the N-substituted imidazole (5 mmol) in anhydrous THF (30 ml) was cooled to -80ºC and a solution of BuLi (2.5 M solution, 2.2 ml, 5.5 mmol) in hexane was added dropwise, the solution was maintained at this temperature for 30 min. A solution of $(Et_2N)_2PCl$ or $(EtO)_2P(O)Cl$ (5.5 mmol) in THF (10 ml) was added dropwise maintaining the reaction mixture temperature at -80 ± 2ºC. The product was stirred at this temperature for 30 min, the temperature raised to 20ºC, and stirring was continued for 12 h. Solvent was evaporated *in vacuo* and the residue was dissolved in acetone (10 ml), cooled to 0ºC, and hydrogen peroxide (15%, 5ml) was added dropwise. The product was stirred for 5 h at 20ºC, acetone evaporated *in vacuo*, the residue diluted with water to a volume of 30 ml, and extracted with ether. The extract was dried over $MgSO_4$, ether was evaporated *in vacuo*, and the residue was purified either by crystallization of by chromatography on SiO_2.

Diethyl (1-Dimethylsulfamoyl-1H-imidazol-2-yl)phosphonate (6) was prepared chromatographically (eluent ethyl acetate) as a pale-yellow, waxy material (8%) with R_f 0.86 (ethyl acetate). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.37 (6H, t, ^3J = 7.0, $CH_2C\underline{H}_3$); 2.99 (6H, s, NCH_3); 4.28 (4H, quin, ^3J = 7.0, $^3J_{HP}$ = 7.0, $POC\underline{H}_2CH_3$); 7.18 (1H, br. s, H-4); 7.44 (1H, d, ^3J = 1.5, H-5). ^{31}P NMR spectrum, δ, ppm: 1.5 (m). Found, %: C 35.23; H 6.11. $C_9H_{18}N_3O_5PS$. Calculated, %: C 34.72; H 5.83.

(1-Dimethylsulfamoyl-1H-imidazol-2-yl)phosphonic Acid Bis(diethylamide) (8a) was prepared by freezing out from hexane as a pale-yellow, crystalline material (85%) with mp 75ºC and R_f 0.75 (ethyl acetate–methanol, 2:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.09 (12H, t, ^3J = 7.0, $CH_2C\underline{H}_3$); 3.02 (6H, s, NCH_3); 3.00-3.20 (8H, m, $PNC\underline{H}_2CH_3$); 7.13 (1H, m, H-4); 7.48 (1H, m, H-5). ^{31}P NMR spectrum, δ, ppm: 16.5 (m). Found, %: N 19.36. $C_{13}H_{28}N_5O_3PS$. Calculated, %: N 19.17.

(1-Benzyl-1H-imidazol-2-yl)phosphonic Acid Bis(diethylamide) (8b) was prepared chromatographically (eluent ethyl acetate–hexane, 1:1) as a colorless, viscous oil (33%) with R_f 0.19 (ethyl acetate–hexane, 1:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.94 (12H, t, ^3J = 7.0, $CH_2C\underline{H}_3$); 3.00 (8H, m, $PNC\underline{H}_2CH_3$); 5.64 (2H, s, $NC\underline{H}_2Ph$); 6.95 (1H, m, H-4); 7.15 (1H, m, H-5); 7.20 (5H, m, H arom). ^{31}P NMR spectrum, δ, ppm: 15.6 (m). Found, %: C 62.41; H 8.03. $C_{18}H_{29}N_4OP$. Calculated, %: C 62.05; H 8.39.

{1-[2-(Trimethylsilyl)ethoxymethyl]-1H-imidazol-2-yl}phosphonic Acid Bis(diethylamide) (8c) was separated chromatographically (eluent hexane–ethyl acetate, 8:5) as a colorless oil (38%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): -0.07 (9H, s, $Si(CH_3)_3$); 0.87 (2H, t, ^3J = 8.5, CH_2Si); 0.99 (12H, t, ^3J = 7.0, $CH_2C\underline{H}_3$); 3.06 (8H, m, $PNC\underline{H}_2CH_3$); 3.53 (2H, t, ^3J = 8.5, $OC\underline{H}_2CH_2$); 5.81 (2H, s, NCH_2O); 7.15 (1H, d, ^3J = 1.4, H-4); 7.25 (1H, d, ^3J = 1.4, H-5). ^{31}P NMR spectrum, δ, ppm (*J*, Hz): 16.4 (m, $^3J_{PH}$ = 14.5). Found, %: C 52.40; H 9.28. $C_{17}H_{37}N_4O_2PSi$. Calculated, %: C 52.55; H 9.60.

(1-Dimethylsulfamoyl-1H-imidazol-2-yl)phosphonic Acid (9). Compound **8a** (0.4 g, 1.1 mmol) was hydrolyzed in HCl (5 N, 15 ml) for ~ 16 h at 80ºC. The obtained solution was extracted with chloroform, the aqueous solution evaporated to dryness, and the residue was triturated with ether to give compound **9** (0.24 g, 89%) as a colorless powder with mp 284ºC. ^{1}H NMR spectrum, δ, ppm: 2.65 (6H, s, NCH_3); 7.16 (1H, m, H-4); 7.17 (1H, m, H-5). ^{31}P NMR spectrum, δ, ppm: -10.0 (m). Found, %: N 16.09. $C_5H_{10}N_3O_5PS$. Calculated, %: N 16.47.

(1H-Imidazol-2-yl)phosphonic Acid (11). A solution of KOH (2%, 25 ml) was added to a solution of imidazole **8a** in alcohol (15 ml) and refluxed for ~ 24 h. Alcohol was evaporated off and the residue was extracted with ether, the extract dried over $MgSO_4$, and the ether evaporated to give amide **10** (0.48 g) [7] which was 90% pure according to ^{1}H and ^{31}P NMR data. HCl (5 N, 20 ml) was added and the product was refluxed for ~ 12 h. The solution obtained was extracted with chloroform, the water evaporated, and the residue recrystallized to give acid **11** (0.17 g, 53%) as a colorless, hygroscopic powder with mp 169ºC (ethanol). ^{1}H NMR spectrum, δ, ppm: 7.27 (1H, s, H-4); 7.29 (1H, s, H-5). ^{31}P NMR spectrum, δ, ppm: -8.8 (s). Found, %: C 24.12; H 3.48; N 18.51. $C_3H_5N_2O_3P$. Calculated, %: C 24.34; H 3.40; N 18.93.

Lithium Salt of 2-[Bis(diethylamino)phosphoryl]-1-(N,N-dimethylsulfamoyl)-1H-imidazole-5-carboxylic Acid (12). A solution of BuLi (2.5 M, 2.3 ml, 5.75 mmol) in hexane was added dropwise to a solution of imidazole **8a** (1.89 g, 5.18 mmol) in THF (50 ml) cooled to -80ºC. It was held at this temperature for 30 min and an excess of gaseous CO_2 was passed through the reaction mixture regulating the flow such that the temperature was maintained at -80±2ºC. The product was held at this temperature for 30 min, heated to 20ºC over 3 h, and held at this temperature for 12 h. Solvent was evaporated *in vacuo* and the residue was dissolved in moist acetone, filtered, and the salt **12** (2.0 g, 92%) was precipitated using ether as a light-gray powder with mp 182ºC (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.99 (12H, t, ^3J = 7.0, $CH_2C\underline{H}_3$); 2.86 (6H, s, NCH_3); 3.00 (8H, m, $PNC\underline{H}_2CH_3$); 7.21 (1H, m, H-4). ^{31}P NMR spectrum, δ, ppm: 17.7 (m). Found, %: C 39.94; H 6.37; N 16.38. $C_{14}H_{27}LiN_5O_5PS$. Calculated, %: C 40.48; H 6.55; N 16.86.

2-[Bis(diethylamino)phosphoryl]-3H-imidazole-4-carboxylic Acid Hydrochloride (13). Salt **12** (1.3 g, 3.13 mmol) was stirred in HCl (5 N, 15 ml) for 12 h at 20ºC, the solution obtained was evaporated to dryness, and the residue was triturated with acetone to give hydrochloride **13** (0.82 g, 78%) as a white powder with mp 178ºC (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.80 (12H, t, ^3J = 7.0, $CH_2C\underline{H}_3$); 2.88 (8H, dq, $^3J_{PH}$ = 11.0, ^3J = 7.0, $PNC\underline{H}_2CH_3$); 7.91 (1H, d, $^4J_{PH}$ = 2.0, H-4). ^{31}P NMR spectrum, δ, ppm: 13.2 (m). Found, %: C 42.47; H 6.54; N 16.44. $C_{12}H_{24}ClN_4O_3P$. Calculated, %: C 42.54; H 7.14; N 16.54.

2-Phosphono-1H(3H)-imidazole-4(5)-carboxylic acid (4). The hydrochloride **13** (0.52 g, 1.54 mmol) was heated at 70ºC in HCl (5 N, 10 ml) for ~ 48 h, periodically cooling the reaction mixture and filtering off the precipitated imidazole **4**. According to ^{1}H and ^{31}P NMR data the filtrate accumulated the phosphonic acid decarboxylation product **11**. Compound **4** (0.18 g, 62%) was obtained as colorless crystals with mp 291ºC (decomp.) (water). ^{1}H NMR spectrum, δ, ppm: 5.91 (1H, br. s, NH); 8.05 (1H, s, H-4). ^{31}P NMR spectrum, δ, ppm: -7.6. Found, %: C 24.84; H 3.04. $C_4H_5N_2O_5P$. Calculated, %: C 25.01; H 2.62.

Phosphorylation of the N-Substituted Imidazoles at Position 5 of the Heterocycle (General Method). BuLi (2.5 M, 4.4 ml, 11 mmol) in hexane was added dropwise to a solution of the N-substituted imidazole (10 mmol) in anhydrous THF (50 ml) held at -80ºC. This temperature was maintained for 30 min, the temperature raised to 20ºC, and stirred for 1 h. The reaction mixture was then cooled to -80ºC, a further aliquot of BuLi (11 mmol) was added dropwise, held for 30 min, and $(Et_2N)_2PCl$ (2.31 g, 11 mmol) in THF (10 ml) was added. Stirring was continued at this temperature for 1 h, the temperature was raised to 20ºC over 3 h, and the product was held for a further 12 h. Solvent was removed *in vacuo* and the residue was dissolved in acetone (20 ml), cooled to 0ºC, and hydrogen peroxide (15%, 10 ml) was added dropwise. Stirring was continued at 20ºC for 5 h, acetone was evaporated *in vacuo*, the residue was diluted with water to a volume of 50 ml, and extracted with ether. The extract was dried over $MgSO_4$, ether was evaporated *in vacuo*, and the residue was purified either by crystallization or chromatographically on SiO_2.

(1-Dimethylsulfamoyl-1H-imidazo-5-yl)phosphonic Acid Bis(diethylamide) (15) was prepared chromatographically on SiO_2 (eluent ethyl acetate) as a pale-yellow, waxy material (72%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.03 (12H, t, ^{3}J = 7.0, $CH_2C\underline{H}_3$); 2.98 (6H, s, NCH_3); 3.04 (8H, m, $PNC\underline{H}_2CH_3$); 7.22 (1H, m, H-4); 8.06 (1H, m, H-2). ^{31}P NMR spectrum, δ, ppm: 14.80 (m). Found, %: C 42.92; H 8.12. $C_{13}H_{28}N_5O_3PS$. Calculated, %: C 42.73; H 7.72.

[3H(1H)-Imidazol-4(5)-yl]phosphonic Acid Bis(diethylamide) (16). Imidazole **15** (1.6 g, 4.38 mmol) was dissolved in alcohol (15 ml), KOH solution (2%, 25 ml) was added, and refluxed for ~ 28 h. The reaction mixture was extracted with ether, the aqueous layer was evaporated to dryness, and the residue was purified by freezing out from hexane to give compound **16** (0.94 g, 83%) as pale-yellow crystals with mp 67ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.01 (12H, t, ^{3}J = 7.0, $CH_2C\underline{H}_3$); 3.06 (8H, m, $PNC\underline{H}_2CH_3$); 7.33 (1H, m, H-4(5)); 7.48 (1H, br. s, NH); 7.67 (1H, d, $^{4}J_{PH}$ = 1.5, H-2). ^{31}P NMR spectrum, δ, ppm: 15.80 (m). Found, %: C 50.91; H 8.89. $C_{11}H_{23}N_4OP$. Calculated, %: C 51.14; H 8.97.

[3H(1H)-Imidazol-4(5)-yl]phosphonic Acid (17). Amide **16** (0.35 g, 1.36 mmol) was hydrolyzed at 60ºC in HCl (5 N, 10 ml) for ~ 12 h. The reaction mixture was extracted with chloroform, the aqueous layer was evaporated to dryness, and the residue was dissolved in NH_4OH solution (10%, 10 ml). The product was stirred for 15 min, evaporated to dryness, and the residue was triturated with acetone to give a crystalline product which was dissolved in water (5 ml). Chromatography of the obtained solution on H^+ form ion exchange resin gave the acid hydrate **17** (0.16, 80%) as a white powder with mp 127ºC. ^{1}H NMR spectrum, δ, ppm: 7.18 (1H, br. s, H-4(5)); 8.37 (1H, br. s, H-2). ^{31}P NMR spectrum, δ, ppm: -4,5 (br. s). Found, %: C 21.27; H 4.38; N 16.72. $C_3H_7N_2O_4P$. Calculated, %: C 21.69; H 4.25; N 16.87.

Lithium Salt of 5-[Bis(diethylamino)phosphoryl]-1-(dimethylsulfamoyl)-1H-imidazole-2-carboxylic Acid (18). The synthesis was carried out as for compound **12**. Amide **15** (2.25 g, 6.16 mmol) gave compound **18** (1.9 g, 74%) as a pale-yellow, hygroscopic powder with mp > 300ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.89 (12H, t, ^{3}J = 7.0, $CH_2C\underline{H}_3$); 2.79 (6H, s, NCH_3); 2.91 (8H, m, $PNC\underline{H}_2CH_3$); 7.13 (1H, d, $^{4}J_{PH}$ = 2.4, H-4). ^{31}P NMR spectrum, δ, ppm: 19.9 (m). Found, %: C 40.06; H 6.83; N 16.48. $C_{14}H_{27}LiN_5O_5PS$. Calculated, %: C 40.48; H 6.55; N 16.86.

Bis(1-[2-(trimethylsilyl)ethoxymethyl]-1H-imidazol-2-yl)phosphinic Acid Diethylamide (19). N–SEM-imidazole (2 g, 10.1 mmol) gave a reaction mixture which was chromatographed on SiO_2 using gradient elution with mixtures of hexane and ethyl acetate (5:1 going to 1:1) to yield the imidazole **8c** (0.52 g) (eluent hexane–ethyl acetate, 3: 1) and compound **19** (0.18 g, 3.5%) (eluent hexane–ethyl acetate, 1:1) as a pale-yellow, waxy

material. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): -0.06 (18H, s, $SiCH_3$); 0.83 (4H, m, CH_2Si); 1.12 (6H, t, ^3J = 7.0, $CH_2C\underline{H}_3$); 3.30 (4H, dq, $^3J_{PH}$ = 14.0, ^3J = 7.0, $PNC\underline{H}_2CH_3$); 3.48 (4H, m, $OC\underline{H}_2CH_2$); 5.72 (4H, s, NCH_2O); 7.27 (2H, d, ^3J = 1.4, H-4(5)); 7.32 (2H, d, ^3J = 1.4, H-5(4)). ^{31}P NMR spectrum, δ, ppm (*J*, Hz): 9.59 (quin, $^3J_{PH}$ = 14.0). Found, %: C 51.61; H 8.75. $C_{22}H_{44}N_5O_3PSi_2$. Calculated, %: C 51.43; H 8.63.

Alkylation of Phosphonamide 16 Using SEMCl. A solution of compound **16** (2.88 g, 11 mmol) in anhydrous THF (30 ml) was cooled to -78ºC and a solution of BuLi (2.5 M, 4.6 ml, 11.5 mmol) in hexane was added dropwise. The solution was held at the same temperature for 15 min, then a solution of SEMCl (1.92g, 15 mmol) in THF (10 ml) was added dropwise. the product was held for 15 min, the temperature raised to 20ºC, and stirred for 2 h. THF was evaporated off, HCl (1 N, 30 ml) was added to the residue at 0ºC, and the product was extracted with ethyl acetate, and dried over $MgSO_4$. Solvent was evaporated off and the residue was chromatographed with gradient elution successively with ethyl acetate and a mixture of ethyl acetate–methanol (10:1) to give the isomeric imidazoles **20** and **21**.

(1-[2-(Trimethylsilyl)ethoxymethyl]-1H-imidazol-4-yl)phosphonic Acid Bis(diethylamide) (20). Compound **20** (1.69 g, (40%) (eluent ethyl acetate–methanol 10:1) was separated as a pale-yellow oil with R_f 0.54 (ethyl–acetate, methanol, 10:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): -0.07 (9H, s, $SiCH_3$); 0.87 (2H, t, ^3J = 8.5, CH_2Si); 1.02 (12H, t, ^3J = 7.0, $CH_2C\underline{H}_3$); 3.10 (8H, m, $PNC\underline{H}_2CH_3$); 3.44 (2H, t, ^3J = 8.5, $OC\underline{H}_2CH_2$); 5.28 (2H, s, NCH_2O); 7.69 (1H, d, $^3J_{PH}$ = 2.1, H-5); 7.77 (1H, br. s, H-2). ^{31}P NMR spectrum, δ, ppm: 20.9 (m). Found, %: C 52.81; H 9.98. $C_{17}H_{37}N_4O_2PSi$. Calculated, %: C 52.54; H 9.60.

(1-[2-(Trimethylsilyl)ethoxymethyl]-1H-imidazol-5-yl)phosphonic Acid Bis(diethylamide) (21). Compound **21** (0.29 g, 7%) (eluent ethyl acetate) was separated as a light-yellow oil with R_f 0.73 (ethyl acetate–methanol, 10:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): -0.04 (9H, s, $SiCH_3$); 0.88 (2H, t, ^3J = 8.5, CH_2Si); 1.02 (12H, t, ^3J = 7.0, $CH_2C\underline{H}_3$); 3.04 (8H, m, $PNC\underline{H}_2CH_3$); 3.55 (2H, t, ^3J = 8.5, $OC\underline{H}_2CH_2$); 5.62 (2H, s, NCH_2O); 7.26 (1H, br. s, H-4); 7.83 (1H, br. s, H-2). ^{31}P NMR spectrum, δ, ppm: 17.73 (m). Found, %: C 52.93; H 9.78. $C_{17}H_{37}N_4O_2PSi$. Calculated, %: C 52.54; H 9.60.

Lithium Salt of 1-[2-(Trimethylsilyl)ethoxymethyl]-4-[bis(diethylamino)phosphoryl]-1H-imidazole-2-carboxylic Acid (22). Prepared by the method for synthesis of compound **12**. Compound **20** (0.27 g, 0.69 mmol) was carboxylated and the residue after evaporation of THF was extracted with refluxing hexane and frozen out of hexane solution to give the imidazole **22** (0.12 g, 40%) as colorless crystals with mp 198ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): -0.06 (9H, s, $SiCH_3$); 0.87 (2H, t, ^3J = 8.5, CH_2Si); 0.97 (12H, t, ^3J = 7.0, $CH_2C\underline{H}_3$); 3.07 (8H, m, $PNC\underline{H}_2CH_3$); 3.57 (2H, t, ^3J = 8.5, $OC\underline{H}_2CH_2$); 5.72 (2H, s, NCH_2O); 7.67 (1H, d, $^3J_{PH}$ = 2.0, H-5). ^{31}P NMR spectrum, δ, ppm: 25.1 (m). Found, %: C 48.82; H 8.34; N 13.08. $C_{18}H_{36}LiN_4O_4PSi$. Calculated, %: C 49.30; H 8.28; N 12.78.

Methyl (1-[2-(Trimethylsilyl)ethoxymethyl]-4-[bis(diethylamino)phosphoryl]-1H-imidazole-2-carboxylate (23). Compound **20** (1.29 g, 3.3 mmol) was lithiated using the method for compound **12**. ClCOOMe (0.35 g, 3.65 mmol) was added dropwise to the solution at -78ºC, the reaction mixture was stirred at this temperature for 30 min, and then for 12 h at 20ºC. THF was evaporated off and the residue at 0ºC was treated with HCl (1 N, 30 ml), extracted with ethyl acetate, the solution dried over $MgSO_4$, the solvent was evaporated, and residue was chromatographed using ethyl acetate as eluent to give compound **23** (0.42 g, 29%) as a viscous, colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): -0.08 (9H, s, $SiCH_3$); 0.89 (2H, t, ^3J = 8.5, CH_2Si); 1.03 (12H, t, ^3J = 7.0, $CH_2C\underline{H}_3$); 3.10 (8H, m, $PNC\underline{H}_2CH_3$); 3.52 (2H, t, ^3J = 8.5, $OC\underline{H}_2CH_2$); 3.92 (3H, s, OCH_3); 5.72 (2H, s, NCH_2O); 7.85 (1H, br. s, H-5). ^{31}P NMR spectrum, δ, ppm: 21.5 (m). Found, %: C 50.86; H 8.12; N 13.10. $C_{19}H_{39}N_4O_4PSi$. Calculated, %: C 51.10; H 8.80; N 12.55.

REFERENCES

1. J. E. Franz, Ger. Pat. 2327680 (1973); *Chem. Abstr.*, **80**, 70958 (1974).
2. L. Maier, *Heteroatom Chem.*, **11**, 454 (2000).

3. P. J. Diehl and L. Maier, *Phosphorus, Sulfur, Relat. Elem.*, **18**, 482 (1983).
4. D. K. Anderson, D. L. Deuwer, and J. A. Sikorski, *J. Heterocycl. Chem.*, **32**, 893 (1995).
5. A. A. Tolmachev, A. A. Yurchenko, A. V. Rozhenko, and M. G. Semenova, *Zh. Obshch. Khim.*, **63**, 1911 (1993).
6. I. V. Komarov, M. Yu. Kornilov, A. V. Turov, M. V. Gorichko, V. O. Popov, A. A. Tolmachev, and A. J. Kirby, *Tetrahedron*, **51**, 12417 (1995).
7. I. V. Komarov, A. V. Strizhak, M. Yu. Kornilov, A. N. Kostyuk, and A. A. Tolmachev, *Synth. Commun.*, **28**, 2355 (1998).
8. A. A. Yurchenko, A. N. Huryeva, E. V. Zarudnitskii, A. P. Marchenko, G. N. Koidan, and A. M. Pinchuk, *Heteroatom Chem.*, **20**, 289 (2009).
9. J. Lin and Ch. M. Thompson, *J. Heterocycl. Chem.*, **31**, 1701 (1994).
10. M. A. Poss, US Pat. 5208234 (1993); *Chem. Abstr.*, **119**, 139549 (1993).
11. F. Palacios, A. M. O. de Retana, J. Oyarzabal, and J. M. Ezpeleta, *Tetrahedron*, **54**, 2281 (1998).
12. W. Huang and C. Yan, *Synthesis*, 511 (1996).
13. M. Schnell, M. Ramm, and A. Kockritz, *J. Prakt. Chem.*, **336**, 29 (1994).
14. M. Vuilhorgne, J. Malpart, S. Mutti, and S. Mignani, *J. Heterocycl. Chem.*, **40**, 159 (2003).
15. B. Iddon and R. I. Ngochindo, *Heterocycles*, **38**, 2487 (1994).
16. R. I. Ngochindo, *J. Chem. Soc., Perkin Trans. 1*, 1645 (1990).
17. G. Shapiro and B. Gomez-Lor, *J. Org. Chem.*, **59**, 5524 (1994).
18. B. H. Lipshutz, B. Huff, and W. Hagen, *Tetrahedron Lett.*, **29**, 3411 (1988).