The Synthesis of Biologically Relevant 4(5)-Phosphono-5(4)-aminoimidazoles Using a Pd-Catalyzed Coupling Reaction [1]

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Received June 7, 1994

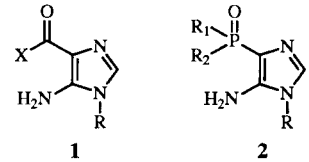
Regiochemically defined 1-benzyl-4-phosphono-5-carboalkoxyimidazoles were synthesized from the corresponding 4-bromoimidazoles using a tetrakis(triphenylphosphine)palladium(0)-catalyzed coupling reaction with diethyl phosphite. The corresponding Michaelis-Arbusov reaction failed to give a phosphonylated product. The carbomethoxy moiety was converted to an amino group using a Curtius rearrangement to afford 1-benzyl-4-phosphono-5-amino-imidazoles. Following deprotection and hydrolysis, phosphonic acid-linked aminoimidazoles were accessed that resemble intermediates formed during purine biosynthesis.

J. Heterocyclic Chem., **31**, 1701 (1994).

By virtue of structural and electronic similarity to carboxylic acid derivatives, phosphorus esters can simulate the transition state (TS) during hydrolysis or serve as an isostere group. The substitution of a phosphorus group for a carbon ester has been employed for many purposes including the preparation of stable TS analogs [3] or the production of catalytic antibodies [4]. A further advantage gained through substitution of a phosphorus moiety for a carboxyester is possible ^{31}P nmr application where certain chemical events or a biomolecule environment can be specifically probed or monitored. Many studies have also replaced the carboxamide moiety of peptides or acyclic carboxyesters for a phosphorus group but few have bridged the utility of phosphorus-based analogs with biologically interesting azaheterocycles.

The synthesis and chemistry of heterocyclic compounds bearing phosphorus substituents was first reviewed over twenty years ago by Redmore [5]. Many syntheses cited for the preparation of phosphorus-bearing heteroaromatic compounds were conducted *via* Arbusov or Michaelis-Becker (AMB) reactions. The displacement reaction likely occurs *via* addition-elimination, which explains enhanced reactivity when 2-halo-*N*-alkylpyridinium salts are used [6]. Therefore, synthetic routes to phosphorus-bearing heterocycles using an addition-elimination process should be productive when the electron pair can localize on a heteroatom following the addition step. Conversely, displacement processes should be less favored when the incoming lone pair cannot first localize on a heteroatom through direct addition or resonance delocalization. As a result, the juxtaposition of halogen and heterocyclic atom(s), and π-electron arrangement are important factors in reactivity as exemplified by nucleophilic displacement reactions of 2-haloimidazoles, which differ considerably from 4(5)-haloimidazoles. *N*-Alkyl-2-haloimidazoles undergo displacement with a variety of nucleophiles owing to assistance by the neighboring nitrogen. However, the corresponding 4(5)-haloimidazoles, which cannot stablize the incoming electron pair onto nitrogen require a strong electron-stabilizing group at C-4(5) (*e.g.*, nitro) to undergo reaction [7]. Thus, 4(5)-haloimidazoles with no adjacent electron-withdrawing group are expected to react poorly with nucleophiles, and are not expected to form phosphonoimidazoles.

In studies intended to prepare phosphorus analogs of purine biosynthesis intermediates **1** to be used as ^{31}P nmr probes, we required a route to 4-phosphono-5-aminoimidazoles **2**. Bartlett and coworkers [8] used a modification of Shaw's procedure [9] to prepare 1-benzyl-4-phosphonyl-5-aminoimidazole (**1** $R_1 = R_2 = OEt$) from diethyl cyanomethylphosphonate. A good yield and regiochemically pure product was obtained, but the method is limited only to variation in the *N*-alkyl group. A more general method that could access substituted C-4(5)-phosphonoimidazoles [and related heterocyclic systems] would be beneficial, specifically one that draws upon the more readily available haloimidazoles and phosphite esters. Since an AMB approach would require an adjacent electron-stabilizing group, we chose the Jones synthesis [10], which furnishes a carboalkoxy group at C-5. The Jones imidazoles can be halogenated at the available C-4 position [11], and syntheses of phosphorus-bearing imidazoles can be explored using the carboxyl moiety to stabilize the putative enolate formed during the Michaelis-Arbusov reaction. The carboxy group could be converted into an amino group *via* a Hofmann or Curtius rearrangement to provide the target molecules **2** and checked for structural identity through comparison to authentic material



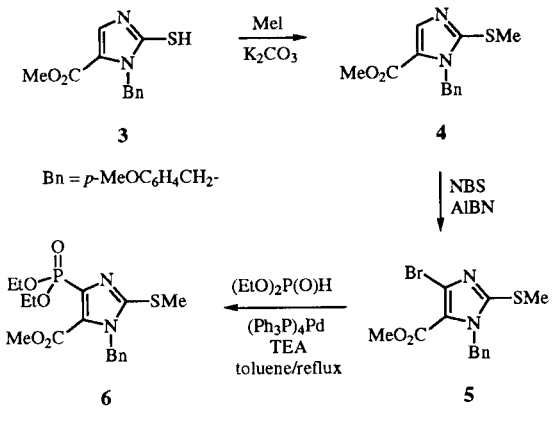
1 **2**

Figure 1. Structures of purine biosynthesis precursors; **1a**: 4-carboxy-5-aminoimidazole ribonucleotide (CAIR); **1b**: 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), and **2**: target phosphonoimidazoles.

obtained by Bartlett's procedure. Therefore, this study first aims to test if an AMB reaction could be conducted at the C-4 of a 1-alkyl-4-halo-5-carboalkoxyimidazole.

The requisite haloimidazole was prepared as follows (Scheme 1): Methyl 2-mercapto-1-*p*-methoxybenzyl-5-imidazolylcarboxylate (**3**) [10] was alkylated at the sulfur atom with methyl iodide to form methyl 1-*p*-methoxybenzyl-2-thiomethyl-5-imidazolylcarboxylate (**4**) in 93% yield. Bromination at the C-4 position was accomplished with *N*-bromosuccinimide [1:1 chloroform/carbon tetrachloride and catalytic 2,2'-azobis(2-methylpropionitrile)]

Scheme 1



at reflux to give the desired precursor, methyl 4-bromo-2-thiomethyl-5-imidazolecarboxylate (**5**) in 40-45% yield. It should be noted that the thiomethyl group serves to block the C-2 position, which undergoes preferential halogenation under these conditions. Minor amounts of aryl ring and benzylic bromination (15%) was found during conversion of **4** to **5** that was confirmed through nmr analysis. Electrophilic sources of bromine (for example, Br_2) led to significant decomposition of the starting material.

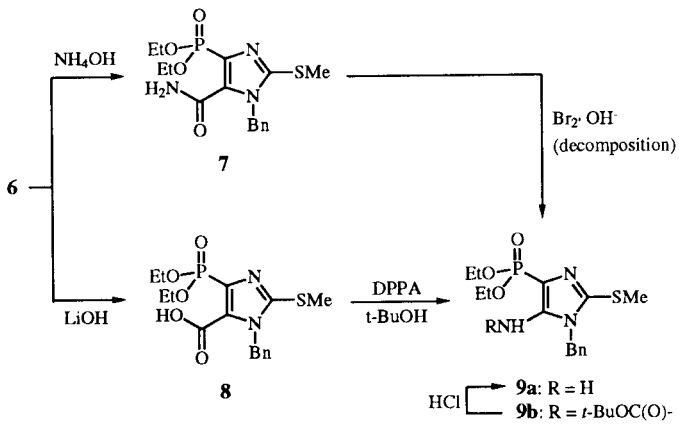
The bromoimidazole **5** was subjected next to a variety of AMB conditions. However, all attempts to react the bromo group with a phosphorus moiety by reaction with trivalent phosphorus compounds failed even under forcing conditions. For example, reaction of **5** with triethylphosphite at reflux (neat) for 48 hours gave quantitative recovery of starting material. Since the thiomethyl group acts as an electron donor, the imidazole reactivity may have been reduced by this group and an effort to conduct the AMB reaction without this group was undertaken. Unfortunately, attempts to reductively remove (*e.g.*, Ra-Ni) this moiety led to preferential loss of the 4-bromo group.

Certain metal catalysts (*e.g.*, $NiBr_2$) are known to enhance the reactivity toward phosphites, and have been used to construct phosphorus-bearing heterocycles [5]. Tetrakis(triphenylphosphine)palladium(0) is an excellent transition metal catalyst for coupling carbon-carbon bonds [12], and also has been used to couple haloarenes with dialkyl phosphites [13] or phosphinates [14]. Unlike the AMB reaction, the Pd-promoted reaction proceeds *via* initial oxidative addition of the aryl halide to the Pd(0) complex, followed by elimination of HBr from the complex. Reductive elimination furnishes the arylphosphonyl compound and regenerates the Pd(0). Because the Pd(0) method is not as reliant upon the nucleophilicity of the phosphorus reagent, it was an attractive alternative.

We were pleased to find that the Pd-catalyzed phosphonylation of **5** with diethyl phosphite led to formation of methyl 4-diethylphosphonyl-1-*p*-methoxybenzyl-2-thiomethyl-5-imidazolylcarboxylate (**6**) in 62% yield. There are several noteworthy aspects of this reaction. First, this experiment represents one of the few reported Pd(0)-promoted coupling of phosphites to heterocycles, which previously included 3-bromopyridine [13] and 2-bromothiophene [14]. Second, to our knowledge, no example of a successful Pd(0)-promoted phosphonylation has been conducted in the presence of an exocyclic thioether group, which would be expected to poison the catalyst. We suspect some complexation did occur, however, since 20 mole % of catalyst was needed rather than 10% as used in prior studies [6]. Last, we also were gratified that the neighboring carboalkoxy group did not deter the reaction since *ortho* substituents on aryl halides were shown to reduce the yield [13]. Dimethyl phosphite did not give the corresponding dimethoxyphosphonate imidazole.

The next step toward the preparation of **2** required a rearrangement of the 5-carbomethoxy moiety into an amine group (Scheme 2). The carboxyester was converted into the carboxamide **7** in low yield by stirring with ammonium hydroxide. The amide was subjected to Hofmann rearrangement conditions (bromine, sodium hydroxide) but only destruction of the starting material was noted. The rearrangement to diethyl 5-amino-1-*p*-methoxybenzyl-2-thiomethyl-4-imidazolylphosphonate

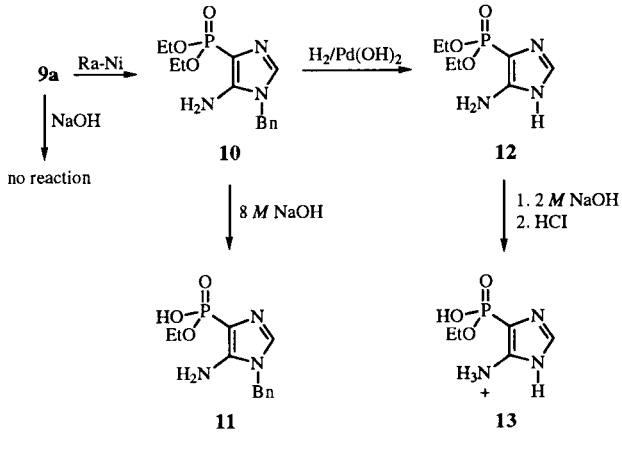
Scheme 2



(**9a**) was accomplished in 68-70% yield using modified Curtius reaction conditions (Scheme 2). The carboxyester **6** was first hydrolyzed to the carboxylic acid **8** then reacted with diphenylphosphorylazide [15] in triethylamine/*t*-butyl alcohol at reflux to give **9a**. Some of the intermediate *tert*-butyl carbamate **9b** was isolated following silica gel chromatography and was quantitatively converted to the amine with dilute hydrochloric acid.

The final steps to the target molecules and structural proof included ring deprotection and manipulation of the phosphonyl moiety (Scheme 3). Desulfurization of **9a** with Raney-nickel [11] furnished diethyl 5-amino-1-*p*-methoxybenzyl-4-imidazolylphosphonate (**10**) the structure of which was confirmed by spectral and elemental analyses and comparison of spectral features with material prepared by a literature procedure [8]. Hydrolysis and debenzylation reactions were unexpectedly difficult. The phosphonate moiety of **9** was completely reluctant to alkaline or acidic hydrolysis, but **10** was converted to the phosphorus monoester **11** with 8 *N* sodium hydroxide. Likely, the inductive effect imparted by the thiomethyl group reduced the reactivity at the phosphoryl group. The hydrolysis of the phosphorus ester became more facile when the second protecting group was removed. The *N*-benzyl group of compound **10** was removed by hydrogenolysis using Perlman's catalyst to give diethyl 5-amino-4-imidazolylphosphonate (**12**) in 59% yield. Hydrolysis to the phosphorus monoester **13** now proceeded using 2 *N* sodium hydroxide. The structure of the phosphate monoester **13** was consistent with all spectral data, specifically a ^{31}P shift from 12.8 ppm for **12** to 1.2 ppm for **13**.

Scheme 3



In conclusion, we have shown that a phosphonyl group can be installed at the C-4(5) position of imidazoles using a Pd(0)-promoted reaction in place of unsuccessful AMB methodology. The study indicates that this procedure is amenable to highly substituted systems, and can be used in the preparation of compounds of biological interest. Also uncovered in this work was the influence of substituents upon C-4(5) phosphonyl reactivity, namely, electron donor groups dramatically reduce phosphonyl reactivity. Future studies will couple compounds **12** and **13** to a ribose moiety [16] and examine the biological activity.

EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and were uncorrected. The ^1H and ^{13}C nmr spectra were taken in deuteriochloroform at 300 and 75.6 MHz using tetramethylsilane as a standard. The ^{31}P nmr spectra were taken in deuteriochloroform at 121.5 MHz using phosphoric acid as an external standard. Chemical shifts are reported in ppm (δ) and J values in Hz. Elemental analyses were performed by Midwest Microlab, Indianapolis, Indiana. Analytical thin layer chromatography was conducted with aluminum-backed silica plates. Visualization was first accomplished with an ultraviolet lamp, followed by ninhydrin, ammonium molybdate, or phosphomolybdic acid stain. All solvents and reagents were purified by standard literature methods. Air- or water-sensitive reactions were conducted under an argon atmosphere by utilizing standard techniques. All reagents were purchased from Aldrich Chemical Company (Milwaukee, WI).

Methyl 1-*p*-Methoxybenzyl-2-thiomethyl-5-imidazolylcarboxylate (**4**).

A mixture of 14.250 g (0.05 mole) of methyl 2-mercapto-1-*p*-methoxybenzyl-5-imidazolylcarboxylate (**3**) and 14.19 g (0.10 mole) of iodomethane were dissolved in 100 ml of anhydrous methanol and chilled to 0°. The reaction mixture was placed under argon and 13.800 g (0.10 mole) of potassium carbonate was added and the reaction mixture stirred for 1.5 hours at 0°. The insoluble inorganic salts were removed by filtration, and the methanol was evaporated *in vacuo*. To the residue was added 100 ml of diethyl ether and 100 ml of distilled water. The organic layer was dried over anhydrous sodium sulfate and evaporated to afford 13.150 g (0.045 mole, 90% yield) of a light yellow, powdery solid. Methyl 1-*p*-methoxybenzyl-2-thiomethyl-5-imidazolylcarboxylate (**4**) was obtained pure following one recrystallization from ether-petroleum ether to give 10.914 g (83% recovery, and 75% overall yield), mp 89-90°; R_f = 0.20 (diethyl ether); ^1H nmr (deuteriochloroform): δ 2.64 (s, 3H, SCH_3), 3.74 (s, 3H, CO_2CH_3), 3.78 (s, 3H, $ArOCH_3$), 5.42 (s, 2H, $ArCH_2$), 6.80 (d, J = 8.8 Hz, 2H, ArH), 7.13 (d, J = 8.6 Hz, 2H, ArH), 7.74 (s, 1H, imidazole-H); ^{13}C nmr (deuteriochloroform): δ 15.1 (SCH_3), 48.0, 51.3, 55.2, 113.8 (phenyl-CH), 123.5, 128.2, 128.5 (phenyl-CH), 137.8, 150.4, 158.9 (C=O), and 160.2.

Anal. Calcd. for $C_{14}H_{16}N_2SO_3$: C, 57.54; H, 5.52; N, 9.59. Found: C, 57.37; H, 5.37; N, 9.49.

Methyl 4-Bromo-1-*p*-methoxybenzyl-2-thiomethyl-5-imidazolylcarboxylate (**5**).

A mixture of 10.227 g (0.035 mole) of methyl 1-*p*-methoxybenzyl-2-thiomethyl-5-imidazolylcarboxylate (**4**), 15.574 g

(0.088 mole) of *N*-bromosuccinimide, and a catalytic amount of 2,2'-azobis(2-methyl-propionitrile) were dissolved in a solution of 180 ml of chloroform (dried over anhydrous magnesium sulfate prior to use) and 180 ml of carbon tetrachloride (dried over activity I alumina prior to use). The mixture was brought to reflux under argon and continued with stirring for 18-20 hours. The mixture was cooled to room temperature, washed with 50% saturated sodium bicarbonate solution, and the organic layer dried over anhydrous sodium sulfate. An orange, sticky oil was obtained following removal of the solvent that was purified using silica gel chromatography (diethyl ether:petroleum ether, 1:1) to give 5.702 g (0.015 mole, 44% yield) of **5** as a white powdery solid, mp 100-101.5°; R_f = 0.40 (diethyl ether:petroleum ether, 1:1); ^{1}H nmr (deuteriochloroform): δ 2.66 (s, 3H, SCH_3), 3.76 (s, 3H, CO_2CH_3), 3.82 (s, 3H, $ArOCH_3$), 5.41 (s, 2H, $ArCH_2$), 6.81 (d, 2H, J = 8.8 Hz, ArH), 7.10 (d, 2H, J = 8.9 Hz, ArH); ^{13}C nmr (deuteriochloroform): δ 15.2 (SCH_3), 49.3, 51.6, 55.2, 113.9 (phenyl-CH), 121.4, 124.4, 127.7, 128.4 (phenyl-CH), 150.0, 159.0 (C=O), and 159.5.

Anal. Calcd. for $C_{14}H_{15}N_2SO_3Br$: C, 45.31; H, 4.07; N, 7.55. Found: C, 45.37; H, 4.26; N, 7.61.

Methyl 4-Diethylphosphonyl-1-*p*-methoxybenzyl-2-thiomethyl-5-imidazolylcarboxylate (**6**).

A mixture of 1.94 g (0.014 mole) of diethyl phosphite, 1.95 ml (0.014 mole) of triethylamine, 2.311 g (0.0020 mole) tetrakis(triphenylphosphine)palladium (0), and 3.711 g (0.010 mole) of methyl 4-bromo-1-*p*-methoxybenzyl-2-thiomethyl-5-imidazolylcarboxylate (**5**) were dissolved in 20 ml of toluene and stirred for 8 hours at 90° under argon. Ethyl acetate (20 ml) was added and the solid material removed by filtration through a frit containing a 1 centimeter layer of Celite. The solution was dried over anhydrous sodium sulfate, and concentrated to afford a yellow, sticky oil that was chromatographed on silica gel (diethyl ether) to yield 2.673 g (0.006 mole, 62% yield) of **6** as a colorless or light yellow oil, R_f = 0.09 (diethyl ether); ^{1}H nmr (deuteriochloroform): δ 1.36 (t, 6H, J = 7.1 Hz, $POCH_2CH_3$), 2.64 (s, 3H, SCH_3), 3.74 (s, 3H, OCH_3), 3.85 (s, 3H, $ArOCH_3$), 4.19-4.28 (m, 4H, J = 7.1 Hz, $POCH_2$), 5.38 (s, 2H, $ArCH_2$), 6.80 (d, 2H, J = 8.7, ArH), 7.10 (d, 2H, J = 8.6 Hz, ArH); ^{13}C nmr (deuteriochloroform): δ 15.1 (SCH_3), 16.4 (d, J = 6.6 Hz, P-O-C-C), 48.6, 52.0, 55.2, 62.9 (d, J = 6.0 Hz, P-O-C), 113.9 (phenyl-CH), 127.4, 128.6 (phenyl-CH), 135.9, 139.1, 150.0 (d, J = 25 Hz, P-C), 159.1 (C=O), 159.5; ^{31}P nmr (deuteriochloroform): δ 10.1.

Anal. Calcd. for $C_{18}H_{25}N_2O_6SP$: C, 50.46; H, 5.88; N, 6.54. Found: C, 50.42; H, 5.88; N, 6.49.

4-Diethylphosphonyl-1-*p*-methoxybenzyl-2-thiomethyl-5-imidazolylcarboxylic Acid (**8**).

A mixture of 2.5 g (5.84 mmoles) of methyl 4-diethylphosphonyl-1-*p*-methoxybenzyl-2-thiomethyl-5-imidazolylcarboxylate (**6**) and 20 ml of 1.0 *N* lithium hydroxide were dissolved in 15 ml of tetrahydrofuran. The mixture was stirred at room temperature for 2-3 hours then extracted with ether. The aqueous solution was neutralized with 1.0 *N* hydrochloric acid, and extracted twice with ether. The organic layers were dried over anhydrous sodium sulfate and evaporated to afford 2.088 g (5.04 mmoles, 86% yield) of 4-diethylphosphonyl-1-*p*-methoxybenzyl-2-thiomethyl-5-imidazolylcarboxylic acid (**8**) as a light yellow semi-solid. After one recrystallization from ether, white crystals were obtained in 82% yield, R_f = 0.16 (20% methanol/ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 1.35 (t, 6H, J = 7.1 Hz, $POCH_2CH_3$), 2.65 (s, 3H, SCH_3), 3.75 (s, 3H, $ArOCH_3$), 4.14-4.26 (m, 4H, J = 7.1 Hz, $POCH_2$), 5.6 (s, 2H, $ArCH_2$), 6.81 (d, 2H, J = 8.8 Hz, ArH), 7.21 (d, 2H, J = 8.8 Hz, ArH); ^{13}C nmr (deuteriochloroform); 16.4 (d, J = 6.7 Hz, $POCH_2CH_3$), 16.8 (SCH_3), 50.7, 55.4, 62.4 (d, J = 5.9 Hz, $POCH_2$), 114.3 (phenyl-CH), 125.7, 129.4 (phenyl-CH), 133.0, 135.5, 150.2 (d, J = 25 Hz, P-C), 158.2 (C=O), 159.8; ^{31}P nmr (deuteriochloroform): δ 12.4.

Anal. Calcd. for $C_{17}H_{23}N_2O_6SP$: C, 49.27; H, 5.59; N, 6.76. Found: C, 49.14; H, 5.59; N, 6.70.

Diethyl 5-Amino-1-*p*-methoxybenzyl-2-thiomethyl-4-imidazolylphosphonate (**9a**).

A mixture of 1.763 g (6.40 mmoles) diphenylphosphoryl azide (DPPA) and 1.1 ml (7.68 mmoles) triethylamine were added to a solution of 2.038 g (4.92 mmoles) of 1-*p*-methoxybenzyl-2-thiomethyl-4-diethylphosphonyl-5-imidazolylcarboxylic acid (**8**) in 15 ml of *tert*-butyl alcohol. The mixture was brought to reflux for 24 hours, cooled to room temperature, and the solvent evaporated. The product diethyl 5-amino-1-*p*-methoxybenzyl-2-thiomethyl-4-imidazolylphosphonate (**9a**) and the *tert*-butylcarbamate (**9b**, below) were obtained in 60-65% and 5-8% yield, respectively, following silica gel chromatography (ethyl acetate), R_f = 0.18 (in ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 1.29 (t, 6H, J = 7.0 Hz, $POCH_2CH_3$), 2.45 (s, 3H, SCH_3), 3.76 (s, 3H, $ArOCH_3$), 4.03-4.12 (m, 4H, J = 7.1 Hz, $POCH_2$), 4.49 (br s, 2H, NH_2), 4.97 (s, 2H, $ArCH_2$), 6.84 (d, 2H, J = 8.7 Hz, ArH), 7.07 (d, 2H, J = 8.7 Hz, ArH); ^{13}C nmr (deuteriochloroform); δ 16.28 (d, J = 6.5 Hz, P-O-C-C), 17.1 (SCH_3), 46.4, 55.3, 62.10 (d, J = 5.2 Hz, P-O-C), 114.5 (phenyl-CH), 126.7, 128.3 (phenyl-CH), 131.9, 138.7 (d, J = 23.1 Hz, C-NH_2), 149.3 (d, J = 25.7 Hz, P-C), 159.4; ^{31}P nmr: δ 14.5.

Anal. Calcd. for $C_{16}H_{24}N_3O_4SP$: C, 49.86; H, 6.28; N, 10.90. Found: C, 50.00; H, 6.31; N, 10.81.

Diethyl 5-*tert*-Butoxycarbonylamino-1-*p*-methoxybenzyl-2-thiomethyl-4-imidazolylphosphonate (**9b**).

This compound was isolated as the non-polar eluting material along with the aminoimidazole **9a** from the experiment above, R_f = 0.31 (ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 1.34-1.39 (t, 6H, J = 7.1 Hz, $POCH_2CH_3$), 1.52 (s, 9H, $C(CH_3)_3$), 2.58 (s, 3H, SCH_3), 3.82 (s, 3H, $ArOCH_3$), 4.15-4.21 (m, 4H, J = 7.1 Hz, $POCH_2$), 5.12 (s, 2H, $ArCH_2$), 6.87 (d, 2H, J = 8.7 Hz, ArH), 7.05 (s, 1H, NH), and 7.11 (d, 2H, J = 8.7 Hz, ArH); ^{13}C nmr (deuteriochloroform): δ 15.8 (SCH_3), 16.35 (d, J = 5.4 Hz, P-O-C-C), 28.1 ($C(CH_3)_3$), 47.6, 55.3, 62.5 (d, J = 5.5 Hz, P-O-C), 81.7 ($C(CH_3)_3$), 114.0 (phenyl-CH), 127.6, 128.7 (phenyl-CH), 132.0, 137.0 (d, J = 23.1 Hz, C-NH), 144.0 (d, J = 25.7 Hz, P-C), 153.8 (d, J = 1 Hz, C=O), 159.2: ^{31}P nmr (deuteriochloroform): δ 11.2.

Anal. Calcd. for $C_{21}H_{32}N_3O_6PS$: C, 51.95; H, 6.64; N, 8.65. Found: C, 52.05; H, 6.60; N, 8.57.

Diethyl 5-Amino-1-*p*-methoxybenzyl-4-imidazolylphosphonate (**10**).

To a room temperature solution of 0.652 g (1.69 mmoles) of diethyl 5-amino-1-*p*-methoxybenzyl-2-thiomethyl-4-imidazolylphosphonate (**9a**) in 30 ml of a 1:1 methanol:tetrahydrofuran was added a large excess of Raney-Nickel in ethanol. The

reaction mixture was brought to reflux for 10 hours. The reaction mixture was cooled, filtered through Celite, the solvents evaporated *in vacuo*, and the residue dissolved into 20 ml of dichloromethane. A solution of 1.0 *N* hydrochloric acid was added to the dichloromethane solution, and the organic layer was discarded. To the aqueous layer was added carefully 2 *N* sodium hydroxide until the *p*H was greater than 10. The aqueous layer was extracted twice with 15 ml of dichloromethane, the combined dichloromethane layers dried over anhydrous sodium sulfate, and concentrated by rotary evaporation to afford 0.458 g (1.35 mmoles, 80% yield) of **10** as a white solid. White crystals of **10** were obtained following recrystallization from chloroform/diethyl ether, mp 134-135°; R_f = 0.14 (in ethyl acetate): ^{1}H nmr (deuteriochloroform): δ 1.30 (t, 6H, J = 7.1 Hz, $POCH_2CH_3$), 3.80 (s, 3H, $ArOCH_3$), 4.01-4.17 (m, 4H, J = 7.1 Hz, $POCH_2$), 4.30 (bs, 2H, NH_2), 4.90 (s, 2H, $ArCH_2$), 6.87 (d, 2H, J = 8.5 Hz, ArH), 7.08 (d, 2H, J = 8.6 Hz, ArH), 7.18 (d, 1H, J = 1.9 Hz, imidazole-CH); ^{13}C nmr (deuteriochloroform): δ 16.3 (d, J = 6.5 Hz, P-O-C-C), 47.3, 55.4, 62.1 (d, J = 5.4 Hz, P-O-C), 114.7 (phenyl-CH), 119.6, 126.2, 128.4 (phenyl-CH), 133.7 (d, J = 8.9 Hz), 149.0 (d, J = 25 Hz, P-C), 159.7; ^{31}P nmr (deuteriochloroform): δ 15.0.

Anal. Calcd. for $C_{15}H_{22}N_3O_4P$: C, 53.10; H, 6.54; N, 12.38. Found: C, 53.14; H, 6.61; N, 12.25.

Diethyl 4(5)-Amino-5(4)imidazolylphosphonate (**12**).

A mixture of 1.00 g (2.95 mmoles) of diethyl 5-amino-1-*p*-methoxybenzyl-4-imidazolylphosphonate (**10**) and 10 mg of palladium hydroxide on carbon were dissolved in 40 ml of methanol and reacted with hydrogen gas in a Paar reactor for 24-30 hours at 40 psi. The reaction mixture was filtered through Celite, the solvent evaporated, and 0.377 g of compound **12** was obtained (1.73 mmoles, 59% yield) following silica gel chromatography (10% methanol/ethyl acetate), mp 110-111°; R_f = 0.12 (in 10% methanol/ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 1.28 (t, 6H, J = 7.1 Hz, $POCH_2CH_3$), 4.01-4.09 (m, 4H, J = 7.1 Hz, $POCH_2$), 5.10-5.90 (br, 3H, NH and NH_2), and 7.37 (d, 1H, J = 3.1 Hz, imidazole-CH); ^{13}C nmr (deuteriochloroform): δ 16.3 (d, J = 6.8 Hz, P-O-C-C), 62.2 (d, J = 5.0 Hz, P-O-C), 135.6 (d, J = 17.1 Hz), 154.0 (d, J = 21.8 Hz, P-C), 154.6; ^{31}P nmr (deuteriochloroform): δ 12.8.

Anal. Calcd. for $C_7H_{14}N_3O_3P$: C, 38.36; H, 6.44. Found: C, 38.59; H, 6.48.

Ethyl 4(5)-Amino-5(4)-imidazolylphosphonic Acid (**13**).

A solution of 0.500 g (2.29 mmoles) of diethyl 4(5)-amino-5(4)-imidazolylphosphonate (**12**) in 3 ml of methanol was added to 2 ml of 2 *N* sodium hydroxide. The mixture was brought to reflux overnight, cooled to room temperature then neutralized with 1.0 *N* hydrochloric acid to a *p*H < 4, and 10 ml of ethanol was added to the mixture and re-concentrated to a solid. A mixture of the product **13** and the remaining inorganic salts were dissolved into deuterium oxide and the ^{1}H and ^{31}P nmr spectrum were recorded; ^{1}H nmr (deuterium oxide): δ 1.14 (t, 3H, J = 7.1 Hz, $POCH_2CH_3$), 3.75-3.85 (m, 2H, J = 7.1 Hz, $POCH_2$), and 8.32 (s, 1H, imidazole-CH): ^{13}C nmr (deuterium oxide with d_6-acetone as reference): 15.7 (d, J = 6.8 Hz, $POCH_2CH_3$), 62.1 (d, J = 4.9 Hz, $POCH_2CH_3$), 130.4 (d, J = 8.7 Hz), 132.2 (d, J = 10.1 Hz, P-C), and 143.8 (d, J = 1.8 Hz); ^{31}P nmr (deuterium oxide): δ 1.20.

Acknowledgment.

The authors wish to acknowledge the financial support of the NIH (ES04434) to whom we are grateful. We also wish to thank Loyola University for the purchase of the VXR 300 MHz nmr used in this study and Dr. J. M. Gerdes (Zeneca AG, USA) for helpful suggestions.

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