Inhibitors of Pyrimidine Biosynthesis. Part 2.† The Synthesis of Amidine Phosphonates as Potential Inhibitors of Carbamoyl Phosphate Synthase

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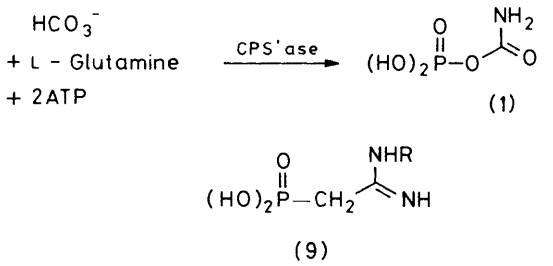
The synthesis of a series of amidine phosphonates (8) and (9) *via* a thioimidate intermediate is described.

EARLIER publications [1,2] from these laboratories have outlined the relevance of inhibition of *de novo* pyrimidine biosynthesis to chemotherapy. Our approach to the development of such inhibitors by exploiting information about the active sites of the constituent enzymes of the pathway has been illustrated by the design and synthesis of inhibitors of the second committed enzyme of pyrimidine biosynthesis, Aspartate Transcarbamylase (ATC'-ase).[2]

The first enzyme on the pathway, Carbamoyl Phosphate Synthase II (EC 2.7.2.5) (CPS'ase) is also a potential target for chemotherapy and this paper describes the synthesis of novel amidine phosphonates which are product analogues of the enzymic reaction.

RESULTS AND DISCUSSION

CPS'ase catalyses a mechanistically complex reaction sequence between hydrogencarbonate, ammonia (derived from L-glutamine), and two molecules of ATP to produce the labile product carbamoyl phosphate (1).[3] (Scheme 1). The analogues (9) described herein are formally

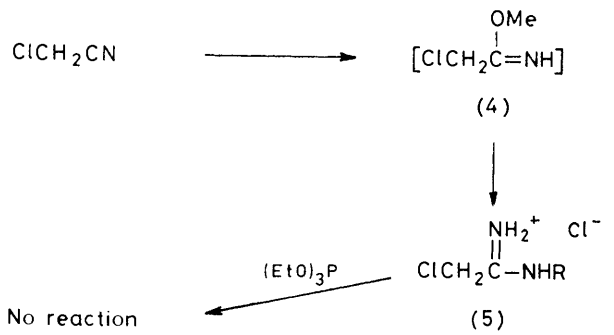


SCHEME 1

derived from carbamoyl phosphate (1) by replacement of the oxygen of the phosphate by methylene in order to give structures of greater stability than (1), and by replacement of the amide unit by the more basic amidine.

These amidine phosphonates (9) have not been described previously and all attempts at their synthesis from the readily available nitrile (2), *via* the imidate (3) or its hydrochloride, have failed because of our inability to make these latter compounds. The failure to make the imidate hydrochloride may simply reflect the fact that the product does not crystallise from the reaction mixture and hence does not shift the equilibrium position of the reaction towards product formation; however the base-catalysed formation of the imidate (3) is precluded by the competing ionisation of the methylene protons of the nitrile (2) under these reaction conditions.

An alternative approach, outlined in Scheme 2, using chloroacetonitrile as starting material, was also unsuccessful. Preparation of the amidines (5; R = H and



SCHEME 2

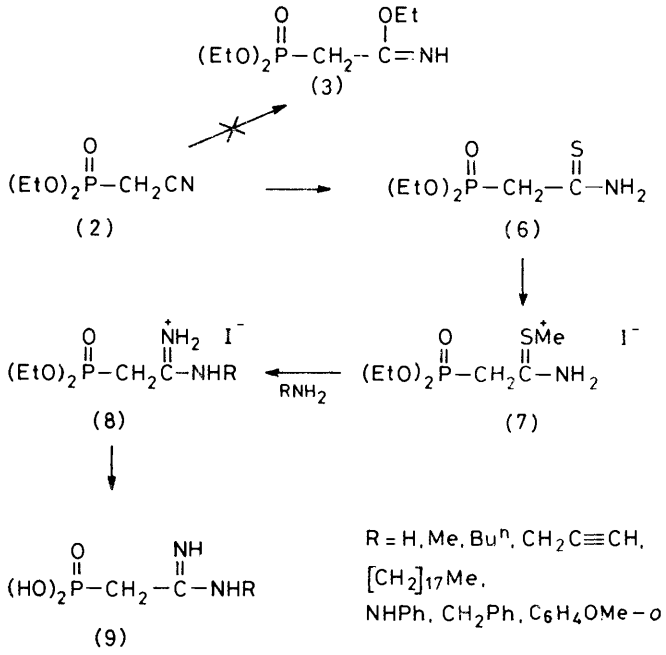
CH_2Ph) from the unisolated imidate (4) was achieved in 89% and 5% yields, respectively, but the Michaelis–Arbuzov reaction of (5; R = H) with triethyl phosphite failed under all conditions examined.

In contrast the thioimidate route shown in Scheme 3 proved successful. Generation of the novel thioamide (6) and the unstable thioimidate (7) followed standard methods. The substitution reactions with (7) which produce the amidines (8) proceed in low yields and appear to be limited in scope to the alkyl-substituted amines and the more nucleophilic of the aromatic substituted amines. The presence of electron-withdrawing substituents in the aromatic amines (*e.g. o-* and *p*-nitroanilines) precluded any reaction. The low isolated yields in the syntheses of (8) require some comment in relation to a recent paper by Schnur,[4] which shows that so-called 'retronitrile formation' may occur in reactions between thioimidates and strongly basic aliphatic amines. During routine monitoring of these reactions by t.l.c., no nitrile (2) formation was observed; however, it would be of interest to investigate the effect on the yields of these reactions by applying the remedy of a buffered organic reaction medium as advocated by Schnur.

The reaction of (7) with the diamine *p*-phenylenediamine, at all stoicheiometric ratios attempted, produced only the bis-substituted product (10) and unreacted diamine.

† Part 1 is ref. 2.

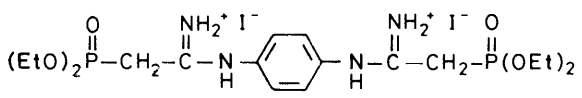
Hydrolysis of the esters (8) to the phosphonic acids (9) proved difficult; eventually two methods were developed which were satisfactory for all cases except for (8; R = H or prop-2-ynyl); these were resistant to hydrolysis under the conditions examined. Vigorous hydrolysis conditions, using refluxing concentrated hydrochloric acid for long periods, were used when the alternative milder procedure using trimethylsilyl bromide [5] failed.



SCHEME 3

This failure [for (8; R = Me, Bu , and NHPh)] was due, in some part at least, to insolubility of these substrates in the reagent, resulting in only partial conversion to the intermediate bis(trimethylsilyl)phosphonate esters.

During the routine characterisation of the phosphonate esters (8) it was observed that exchange of the methylene protons adjacent to phosphorus occurred in D_2O solution. This process did not occur in the acids (9), the nitrile (2), the thioamide (6), simple amidines (without the phosphonate group), 2-(diethoxyphosphinyl)acetamide, or in triethylphosphonoacetate. This neutral



(10)

exchange process can be ascribed, therefore, to a combination of mesomeric and inductive effects operating from the combination of the amidine and phosphonate ester functions, which is suppressed by competing ionisation in the phosphonic acids (9).

EXPERIMENTAL

I.r. spectra were determined with a Perkin-Elmer 157G or 297 instrument for KBr discs, Nujol mulls, or liquid films. ^{1}H N.m.r. spectra were recorded using a Perkin-Elmer R12B (60 MHz) or a JEOL JNM-PMX60 (60 MHz) spectrometer operating in the continuous-wave mode and a Bruker WP-80 (80 MHz) or a Bruker HFX-90 (90 MHz) instrument operating in the Fourier-transform mode [tetramethylsilane or sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate, as internal standard]. Resonances are reported as p.p.m. from $SiMe_4$, positive numbers indicating downfield shifts (*i.e.* δ scale).

All products were routinely checked for homogeneity by t.l.c. on silica-gel plates (E Merck, 60F254, 0.25 mm) using the solvents indicated in the text. The spots were visualised either by filtered u.v. light, ($\lambda_{max.}$ 254 and 365 nm), iodine, or 1% t-butyl hypochlorite in cyclohexane followed by 1% starch–1% potassium iodide in water.

(Diethylphosphono)acetonitrile (2). —(Diethylphosphono)-acetonitrile (2) was prepared from triethyl phosphite and chloroacetonitrile in 82% yield following the literature procedure,[6] b.p. 88—94 °C (0.02 Torr), t.l.c., R_F 0.75 in chloroform–methanol (1 : 1) with trace impurity at R_F 0.6; $\nu_{max.}$ (liquid film) 2 265 cm^{-1}; δ ($CDCl_3$) 1.40 (t, 6 H, *J* 7 Hz, $MeCH_2$), 2.92 (d, 2 H, *J* 21 Hz, P–CH_2), and 4.27 (m, 4 H, CH_2Me). No exchange of signal at δ 2.92 on treatment with D_2O, but complete exchange on treatment with NaOD.

Attempted Synthesis of O-Ethyl 2-(Diethylphosphono)-acetimidate (3).—(Diethylphosphono)acetonitrile (2) (10.05 g, 0.05 mol) was added to a solution of sodium ethoxide [prepared from sodium (1.15 g, 0.05 mol) dissolved in ethanol (50 ml)] and stirred overnight at room temperature with exclusion of atmospheric moisture. Benzylamine hydrochloride (7.18 g, 0.05 mol) was then added and the suspension stirred for 6.5 h at room temperature, then for 9 h at reflux. T.l.c. of the reaction mixture indicated the presence of both starting materials and three minor products, which were not further investigated.

An attempted preparation of (3)-hydrochloride from (diethylphosphono)acetonitrile (2) (5.31 g, 0.03 mol) in dry ethanol (1.75 ml, 0.03 mol) with dry hydrogen chloride bubbled through the reaction mixture for 9 h gave no solid. Addition of benzylamine (3.22 g, 0.03 mol) and stirring produced only benzylamine hydrochloride as shown by t.l.c.

N^1-Benzyl-2-chloroacetamidine Hydrochloride (5; R = CH_2Ph).—Chloroacetonitrile (7.55 g, 0.1 mol) was added to a solution of sodium methoxide [prepared from sodium (0.04 g, 1.74 mmol) in dry methanol (40 ml)] and the mixture stirred overnight with exclusion of atmospheric moisture to produce a solution of *O*-methyl 2-chloroacetimidate (4).[7] Glacial acetic acid (0.104 g, 1.74 mmol) was then added, followed by addition of benzylamine hydrochloride (14.35 g, 0.1 mol) and the reaction mixture was refluxed for 6 h. Filtration and evaporation of the filtrate gave a solid which was recrystallised twice from ethyl acetate–ethanol to give (5; R = CH_2Ph) (1.08 g, 5%), m.p. 117 °C (decomp.) (Found: C, 49.7; H, 5.4; N, 12.4. $C_9H_{12}Cl_2N_2$ requires C, 49.32; H, 5.48; N, 12.79%); $\nu_{max.}$ (KBr disc) 3 020, 1 686, 1 640, 737, and 695 cm^{-1}; δ ([$^2H_6$]DMSO) 4.6—4.92 (m, 4 H, $ClCH_2$ and $PhCH_2$), 7.44 (s, 5 H, aromatics), and 10.30 (br s, *ca.* 2 H, partly exchanged NH protons).

Attempts to prepare this compound *via* *O*-ethyl 2-chloroacetimidate hydrochloride (prefered by the method of ref. 8) by treatment with benzylamine produced only benzylamine hydrochloride.

2-Chloroacetimidine Hydrochloride [7] (5; R = H).—2-Chloroacetamidine hydrochloride (5; R = H) was prepared in 89% yield in an identical manner to (5; R = CH_2Ph),

m.p. 85—89 °C (lit.,[7] 95—99 °C) (Found: C, 18.05; H, 4.55; N, 21.6. Calc. for $C_2H_6Cl_2N_2$; C, 18.60; H, 4.65; N, 21.71%); $\nu_{max.}$ (KBr disc) 3 320, 3 100, 1 700, and 661 cm^{-1}; δ ([$^2H_6$]DMSO) 4.52 (s, 2 H, CH_2) and 9.46 (br s, 4 H, NH).

All attempts at the Michaelis–Arbuzov reaction with triethyl phosphite on (5; R = H) gave starting materials at low temperatures and extensive decomposition at reflux temperature.

2-(*Diethylphosphono*)*thioacetamide* (6).—(Diethylphosphono)acetonitrile (2) (10.62 g, 0.06 mol), pyridine (11 g), and triethylamine (12.14 g, 0.12 mol) were mixed and hydrogen sulphide was passed through the mixture with stirring at room temperature for 5 h. After standing overnight, the reaction mixture was purged with nitrogen and then cooled at 4 °C for several hours. Filtration of the resulting yellow solid and recrystallisation from diethyl ether gave the product (6) (2.93 g, 23%), m.p. 62—64 °C; t.l.c., R_F 0.4 in chloroform–methanol (8 : 1) (Found: C, 34.35; H, 6.7; N, 6.65. $C_6H_{14}NO_3PS$ requires C, 34.12; H, 6.64; N, 6.64%); $\nu_{max.}$ (Nujol mull) 3 200, 1 030, 970 cm^{-1}; δ ($CDCl_3$) 1.35 (t, 6 H, *J* 8 Hz, CH_2Me), 3.45 (d, 2 H, *J* 21 Hz, PCH_2), 4.20 (m, 4 H, CH_2Me), and 8.35 (s, 1 H) and 8.65 (s, 1 H, exchangeable NH protons).

2-(*Diethylphosphono*)-S-*methylthioacetamidium Iodide* (7).—2-(Diethylphosphono)thioacetamide (6) (2.11 g, 0.01 mol) was dissolved in acetone (11 ml) and methyl iodide (5.68 g, 0.04 mol) was added with stirring at room temperature, with exclusion of moisture. After 25 min a white solid crystallised from the reaction mixture; this was filtered, washed with dry ether, and dried at room temperature *in vacuo* over phosphorus pentaoxide to give the air-unstable product (7) (2.65 g, 75%), m.p. 103—105 °C; δ ($CDCl_3$) 2.84 (t, 6 H, *J* 6 Hz, CH_2Me), 3.10 (s, 3 H, MeS), 4.10 (d, 2 H, *J* 24 Hz, CH_2P), 4.24 (m, 4 H, CH_2Me), and 11.24 (s, 2 H, NH_2). Because of the lability of this material it was not characterised further and was stored *in vacuo* until immediately before use.

N^1-*Benzyl*-2-(*diethylphosphono*)*acetamidine Hydriodide* (8; R = CH_2Ph).— 2-(Diethylphosphono)-S-methylthioacetamidium iodide (7) (2.65 g, 0.075 mol) and benzylamine (0.8 g, 0.075 mol) were stirred in ethanol (17 ml) at room temperature for 3 h with the exclusion of atmospheric moisture. On cooling the reaction mixture overnight at −20 °C, a colourless solid crystallised; this was filtered off and washed with diethyl ether to give the product (8; R = CH_2Ph) (2.18 g, 71%), m.p. 128 °C (Found: C, 37.85; H, 5.35; N, 6.65. $C_{13}H_{22}IN_2O_3P$ requires C, 37.86; H, 5.34; N, 6.80%); $\nu_{max.}$ (KBr disc) 3 216, 3 060, 1 670, 1 223, 1 030, 758, and 652 cm^{-1}; δ ([$^2H_6$]DMSO) 1.26 (t, 6 H, *J* 8 Hz, CH_2Me), 3.26 (d, 2 H, *J* 25 Hz, CH_2P, exchange occurs in D_2O), 4.10 (m, 4 H, CH_2Me), 4.60 (s, 2 H, CH_2Ph), 7.43 (s, 5 H, $PhCH_2$), and 9.34 (br s, NH, exchange in D_2O).

The other *N*-substituted amidine hydriodides (8) were prepared in an analogous manner. The reaction times, yields, m.p.s and microanalytical data for these compounds are shown in the Table.

N.m.r. studies on all the compounds (8) have shown a rapid and complete exchange of the signal from the methylene adjacent to phosphorus, on treatment of the [$^2H_6$]DMSO solution with D_2O.

p-*Phenylenebis*-{N^1-[2-(*diethylphosphono*)*acetamidine*]} *Dihydriodide* (10).—2-(Diethylphosphono)-S-methylthioacetamidium iodide (7) (7.06 g, 0.02 mol) and *p*-phenylenediamine (1.08 g, 0.01 mol) were dissolved in ethanol (44 ml) and stirred for 24 h at room temperature with the exclusion of moisture. Filtration of the reaction mixture and ice-cooling of the filtrate gave a crystalline solid (10) which was recrystallised from ethyl acetate–ethanol (1.27 g, 17%), m.p. 194 °C (decomp.) (Found: C, 29.95; H, 4.75; N, 7.65. $C_{18}H_{34}I_2N_4O_6P_2$ requires C, 30.08; H, 4.74; N, 7.80%); $\nu_{max.}$ (KBr disc) 3 015, 1 672, 1 250, and 1 012 cm^{-1}; δ ([$^2H_6$]DMSO) 1.34 (t, 12 H, *J* 7 Hz, CH_2Me), 3.20 (d, 4 H, *J* 21 Hz, CH_2P, exchange occurs in D_2O), 4.20 (m, 8 H, CH_2Me), 7.48 (s, 4 H, aromatic H), and 9.8 (br s, NH, exchange occurs in D_2O).

Preparation of *N*-substituted-2-(diethylphosphono)acetamidine hydriodides (8)

R	Reaction time/h	Yield (%)	M.p. (°C)	Formula	Analysis (%) Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
H	7	21	104.5—105.5	$C_6H_{16}IN_2O_3P$	22.0	5.1	8.55	22.36	4.97	8.70
Me	48	16	90—93	$C_7H_{18}IN_2O_3P$	25.35	5.5	8.05	25.00	5.36	8.33
Bu^n	16	48	129—131	$C_{10}H_{24}IN_2O_3P$	31.6	6.45	7.5	31.77	6.35	7.41
HC≡C-CH_2	24	19	109—110	$C_9H_{18}IN_2O_3P$	30.05	5.2	7.85	30.00	5.00	7.78
$Me(CH_2)_{17}$	16	11	83	$C_{24}H_{52}IN_2O_3P$	50.35	9.35	4.8	50.17	9.06	4.88
$PhCH_2$	3	71	128	$C_{13}H_{22}IN_2O_3P$	37.85	5.35	6.65	37.86	5.34	6.80
PhNH	24	38	75	$C_{12}H_{21}IN_3O_3P{\cdot}0.5H_2O$	34.1	5.4	10.15	34.12	5.21	9.95
C_6H_4OMe-*o*	24	44	126—127	$C_{13}H_{22}IN_2O_4P$	36.4	5.3	6.3	36.45	5.14	6.54

Hydrolysis of the diethylphosphonoamidines (8) to the phosphonic acids (9) was carried out using two alternative methods.

Method A. Using concentrated hydrochloric acid. N^1-*Methyl*-2-*phosphonoacetamidine* (9; R = Me). N^1-Methyl-2-(diethylphosphono)acetamidine hydriodide (8; R = Me) (0.5 g, 0.001 5 mol) was dissolved in concentrated hydrochloric acid (2 ml) and refluxed for 72 h with exclusion of atmospheric moisture. Evaporation afforded a white solid which was recrystallised twice from ethanol–diethyl ether (0.031 g, 14%), m.p. 268 °C (decomp.) (Found: C, 23.5; H, 6.15; N, 18.15. $C_3H_9N_2O_3P$ requires C, 23.68; H, 5.92; N, 18.42%); $\nu_{max.}$ (KBr disc) 3 080, 2 900, 1 704, 1 656, 1 275, 1 170, and 1 050 cm^{-1}; δ ([$^2H_6$]DMSO) 2.88 (s, 3 H, Me), 2.94 (d, 2 H, *J* 15 Hz, PCH_2), 8.03 (br s), 8.82 (s, 1 H), 9.03 (s, 1 H), and 9.56 (s, 1 H) (all exchangeable).

N^1-*Butyl*-2-*phosphonoacetamidine hydrochloride* (9; R = Bu^n)·HCl. This was prepared in a similar manner by refluxing the reaction mixture for 60 h. Evaporation and recrystallisation from ethanol–diethyl ether gave the product (9; R = Bu^n)·HCl (17%), m.p. 70—73 °C (Found: C, 28.95; H, 7.55; N, 11.2. $C_6H_{16}ClN_2O_3P{\cdot}1H_2O$ requires C, 28.97; H, 7.24; N, 11.27%); $\nu_{max.}$ (KBr disc) 3 080, 1 670, and 1 628 cm^{-1}; δ ([$^2H_6$]DMSO) 0.92 (t, 3 H, *J* 5 Hz, Me), 1.5 (m, 4 H, $MeCH_2CH_2$), 2.93 (d, 2 H, *J* 20 Hz, PCH_2), 3.33 (t, 2 H, *J* 4 Hz, NCH_2), 5.5 (br s, exchangeable protons + H_2O), 8.75 (br s, 1 H), 9.0 (br s, 1 H), and 9.5 (br s, 1 H) (all exchangeable).

N^1-*Benzyl*-2-*phosphonoacetamidine Hydrochloride* (9; R =

CH_2Ph)·HCl. This was prepared in a similar manner by refluxing the reaction mixture for 10 h. Evaporation and recrystallisation from ethanol–diethyl ether gave the product (9; R = CH_2Ph)·HCl (26%), m.p. 148 °C (decomp.) (Found: C, 40.7; H, 5.5; N, 10.2. $C_9H_{14}ClN_2O_3P$ requires C, 40.83; H, 5.29; N, 10.59%); $\nu_{max.}$ (KBr disc) 3 120, 1 671, 1 630, 1 220, and 940 cm^{-1}; δ ([$^2H_6$]DMSO) 3.15 (d, 2 H, *J* 20 Hz, PCH_2), 4.56 (d, 2 H, *J* 4 Hz, NH–CH_2), 7.56 (s, 5 H, Ph), 9.28 (br s, 4 H, exchangeable protons), and 10.19 (t, 1 H, *J* 4 Hz, N*H*CH_2).

N^1-*Anilino-2-phosphonoacetimidine* (9; R = NHPh). N^1-Anilino-2-(diethylphosphono)acetimidine hydriodide (8; R = NHPh) (1.0 g, 2.4 mmol) was dissolved in concentrated hydrochloric acid (2 ml) and refluxed for 4 d with exclusion of atmospheric moisture. Evaporation of the reaction mixture and recrystallisation of the residue from ethanol gave a white solid (0.055 g, 10%) which was dried for 2 d at 80 °C and 0.1 Torr, m.p. 229 °C (decomp.) (Found: C, 41.45; H, 5.05; N, 18.0. $C_8H_{12}N_3O_3P$ requires C, 41.92; H, 5.24; N, 18.34%); $\nu_{max.}$ (KBr disc) 3 405, 2 996, 1 678, 1 640, 1 491, 1 180, and 1 030 cm^{-1}; δ ([$^2H_6$]DMSO) 2.95 (d, 2 H, *J* 20 Hz, PCH_2), 6.75—7.43 (m, 4 H, aromatics), and 8.38 (br s) and 9.0—9.5 (br s) (both exchangeable).

Method B. Using trimethylsilyl bromide. N^1-*Octadecyl-2-phosphonoacetamidine* [9; R = $(CH_2)_{17}Me$]. N^1-Octadecyl-2-(diethylphosphono)acetamidine hydriodide [8; R = $(CH_2)_{17}Me$] (0.100 g, 0.175 mmol) and trimethylsilyl bromide (0.5 ml) were stirred overnight in a stoppered vial at room temperature. Evaporation at 40 °C and subsequent treatment of the residue with water (3 ml) gave a solid which was recrystallised from methanol and air-dried to give the product [9; R = $(CH_2)_{17}Me$] (0.050 g, 73%), m.p. 194—196 °C (Found: C, 60.85; H, 11.05; N, 7.1. $C_{20}H_{43}N_2O_3P·0.25H_2O$ requires C, 60.71; H, 11.34; N, 6.69%); δ ([$^2H_6$]DMSO) 0.85 (t, 3 H, Me), 1.00—1.67 [m, 32 H, Me(CH_2)$_{16}$], 2.72 (d, 2 H, *J* 20 Hz, CH_2P), 3.20 (t, 2 H CH_2N), and 3.40 (br s, exchangeables and water).

N^1-(2-*Methoxyphenyl*)-2-*phosphonoacetamidine Hydrobromide* (9; R = *o*-$MeOC_6H_4$)·HBr. N^1-(2-Methoxyphenyl)-2-(diethylphosphono)acetamidine hydriodide (8; R = *o*-$MeOC_6H_4$) (0.642 g, 1.5 mmol) was dissolved in chloroform (5 ml) and trimethylsilyl bromide (2.0 ml) was added. The reaction mixture was stirred and refluxed for 9 h with exclusion of moisture and then set aside overnight at room temperature. The reaction mixture was evaporated at 40 °C and water (3 ml) was added to the residue. The solid which formed was filtered and air-dried at room temperature (0.362 g, 74%), m.p. 169—170 °C (decomp.) (Found: C, 33.25; H, 4.3; N, 8.6. $C_9H_{14}BrN_2O_4P$ requires C, 33.36; H, 4.53; N, 8.48%); $\nu_{max.}$ (KBr disc) 3 480, 3 170, 3 050, 2 900, 2 740, 1 670, 1 610, 1 595, 1 495, 1 260, 1 040, 1 020, and 765 cm^{-1}; δ ([$^2H_6$]DMSO) 3.12 (d, 2 H, *J* 22 Hz, CH_2P), 3.84 (s, 3 H, MeO), 6.90—7.68 (m, 4 H, aromatics), and 8.46 (br s, 1 H), 9.20 (br s, 3 H), and 10.90 (br s, 1 H) (all exchangeable).

All attempts to cleave the unsubstituted, and the 2-(diethylphosphono)-N^1-(prop-2-ynyl)acetamidine hydriodides (8; R = H and $CH_2C{\equiv}CH$) with concentrated hydrochloric acid or trimethylsilyl bromide were unsuccessful.

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