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1,3-Dipolar cycloaddition of diazoalkanes onto dimethyl 1-(formylamino) ethylenephosphonate: a new route to 1-aminocyclopropanephosphonic acids and 3-phosphorylated pyrazoles

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ABSTRACT

Diazoalkanes regiospecifically react with dimethyl 1-(formylamino)ethylenephosphonate (**1a**) to afford 5-substituted dimethyl 3-(formylamino)-4,5-dihydro-3*H*-pyrazol-3-phosphonates **2** in high yields. Their thermal decomposition followed by hydrolysis provides a straightforward access to 2-substituted 1-aminocyclopropanephosphonic acids **4**. Aromatization of **2** under acidic conditions leads to 3-phosphorylated pyrazoles **5**.

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1. Introduction

Interest in 1-aminocyclopropanephosphonic acids began only in the middle of 1980s, and this class of compounds still remains poorly studied in comparison with both 1-aminocyclopropanecarboxylic acids[1] and acyclic 1-aminophosphonates.[2] Meanwhile, structural peculiarities of the 1-aminocyclopropanephosphonate unit are quite interesting. Indeed, the tetrahedral phosphonic acid functionality gives rise to important implications in the design of the transition state-analogue enzyme-inhibitors.[2a–d,3] 1-Aminocyclopropanephosphonic acids can be incorporated via an amide linkage into peptide sequences. Furthermore, the placement of the rigid cyclopropane ring into peptide chains is the most prominent pathway to conformationally constrained peptidomimetics, a modern drug-design tool.[1b,4]

The 1-aminocyclopropanephosphonic acid was found to be a potent inhibitor of 1-aminocyclopropanecarboxylate (ACC) deaminase from *Pseudomonas* sp. and alanine racemase from *Bacillus stearothermophilus*, its activity toward other pyridoxal 5′-phosphate linked enzymes being assumed.[5] Tight binding of the 1-aminocyclopropanephosphonic acid with ACC deaminase made it possible to determine the three-dimensional structure of the crystalline binary complex and hence elucidate the nature of the ring-cleaving enzyme active site and to clarify the catalytic mechanism of the biosynthesis of α-ketobutyrate and ammonia from ACC.[6] Several types of oligopeptides (including macrocyclic ones) comprising the 1-aminocyclopropanephosphonic moiety have been recently disclosed to be potent Hepatitis C virus (HCV) NS3 protease inhibitors and potential candidates for treating HCV infection.[7]

The reported syntheses of the 1-aminocyclopropanephosphonic acid can be divided into four principal strategies (Scheme 1). The first group of methods is based on the standard cyclodialkylation of convenient 1,1-biscarbanionic 1-aminomethanephosphonate equivalents with various 1,2-bidentate electrophiles.[7,8] The alternative approach involves the phosphonylation of cyclopropylideneiminium intermediates derived from cyclopropanone ethyl trimethylsilyl acetale.[9] The third, the most extensive and frequently utilized group of methods comprises Curtius or Hoffmann rearrangements of appropriate 1-(dialkoxyphosphoryl) cyclopropanecarboxylic acid derivatives as the crucial step.[10] A recently reported[11] reduction of 1-nitrocyclopropanephosphonates should be attributed to the last fourth group. These diverse methodologies have been lately surveyed by us in a short review.[12] All of them bear close analogies among synthetic routes to ACC.[1b,13]

The 1,3-dipolar cycloaddition of diazo compounds onto dehydroamino esters is one of the common practices in the ACC chemistry.[1b,13,14] As far as we are aware, a similar diazo addition method for 1-aminocyclopropanephosphonates preparation is still lacking. Meanwhile, it seems very attractive because 1-aminoethylenephosphonate derivatives are easily accessible[15] and there is no requirement for

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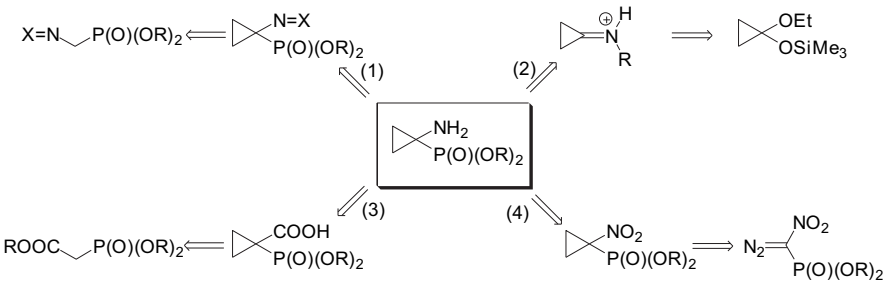
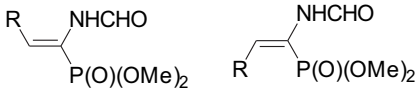


Scheme 1. Synthetic routes to 1-aminocyclopropanephosphonic acids.

further functional groups modification. The main limitation is caused by hazards associated with preparing and handling diazo compounds. Herein we would like to report our results on the investigation of 1,3-dipolar cycloaddition of diazo compounds onto dimethyl 1-(formylamino)alk-1-enephosphonates and further transformations of forming pyrazolines.

2. Results

Starting dimethyl 1-(formylamino)alk-1-enephosphonates **1a**–**c** (Fig. 1) were synthesized by the Horner–Wadsworth–Emmons reaction of tetramethyl (formylamino)methanediphosphonate and aldehydes.[15a–c] Single (*E*)- and (*Z*)-isomers of **1b**,**c** were isolated by chromatography as described by R. Noyori et al.[15b] All the individual isomers exist as a mixture of two rotamers[15b] arising from the lack of free rotation around the C(O)–N bond[16] and reveal two sets of signals in NMR spectra.



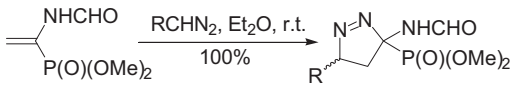
(*E*)-1 **(*Z*)-1**

a: R=H; **b**: R=Me; **c**: R=Ph

Fig. 1. Dimethyl 1-(formylamino)alk-1-enephosphonates 1.

We have found that the cycloaddition of diazomethane onto dimethyl 1-(formylamino)ethylenephosphonate (**1a**) smoothly proceeds in ether at room temperature to furnish dimethyl 3-(formylamino)-4,5-dihydro-3*H*-pyrazol-3-phosphonate (**2a**) after 24 h in a quantitative yield, as monitored by $^{31}P\{^{1}H\}$ NMR spectroscopy (Table 1, entry 1).

Table 1
The 1,3-dipolar cycloaddition reaction of diazo compounds with **1a**



1a, δ_P=15.00,13.60 **2a-c**

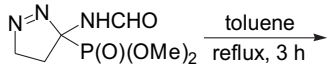
Entry	R	Time (h)	Product	Isolated yield (%)	$^{31}P\{^{1}H\}$ NMR, δ_P
1	H	24	**2a**	94	19.81, 18.61
2	Me	1.5	**2b**[a]	88	19.85, 18.58 and 18.72, 17.97
3	Ph	5	**2c**[b]	90	20.33, 19.71

[a] The diastereomers in the ratio (67:33).
[b] Single diastereomer.

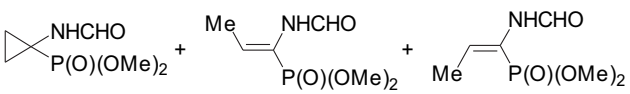
The structure of the product **2a**, isolated in 94% yield, was determined by the elemental analysis and spectral data. The IR spectrum shows P=O absorption at 1260 cm^{-1}. A prominent band at 1050 cm^{-1} and a medium-strong one at 795 cm^{-1} are assigned to the P–O–C stretch. The amide group absorbs strongly at 1695 (amide I) and 1535 cm^{-1} (amide II); a broad band of ν(NH) occurs at 3270 cm^{-1}. The weak endocyclic N=N vibration band appears at 1565 cm^{-1}.[17a,b] Tautomerization of 4,5-dihydro-3*H*-pyrazol-3-phosphonates to 4,5-dihydro-1*H*-pyrazol-5-phosphonates is known to be possible,[17b,18] but the absence of C=N stretching mode (usually at 1595–1635 cm^{-1})[17] indicates that this is not the case with the product **2a**.

Each of the ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra shows two sets of signals corresponding to two rotamers of **2a** (see Experimental part). $^{13}C\{^{1}H\}$ resonance of the distinctive quaternary carbon atom appears as a doublet at δ_C=100.1 ppm ($^{1}J_{CP}$=169.7 Hz) for the major rotamer and at δ_C=99.8 ppm ($^{1}J_{CP}$=171.7 Hz) for the minor one. Methoxy groups being equal in **1a** become diastereotopic in **2a** and give rise to a pair of signals in both ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra. The ^{1}H NMR spectrum reveals four multiplets due to the heterocycle ring protons for each rotamer of **2a**. The lower field signals (at δ_H=4.67, 5.07 ppm for the major rotamer and at δ_H=4.59, 4.95 ppm for the minor rotamer) can be most probably assigned to the strongly coupled CH_2N protons, whereas the high field multiplets (at δ_H=2.07–2.26 ppm for the major rotamer and at δ_H=1.67, 2.53 ppm for the minor rotamer) are attributable to CH_2CP protons.

4,5-Dihydro-3*H*-pyrazol-3-phosphonates can be fragmented with nitrogen extrusion through either photolysis[17b,18b,19] or thermolysis.[18b,20] We have found that in toluene at reflux the pyrazoline **2a** decomposes completely within 3 h affording dimethyl 1-(formylamino)cyclopropanephosphonate (**3a**) in 85% yield along with unsaturated isomeric by-products (*E*)-**1b** (14%) and (*Z*)-**1b** (1%), which were recognized by $^{31}P\{^{1}H\}$ NMR spectroscopy[15b] (Scheme 2).



2a
δ_P 19.81, 18.61



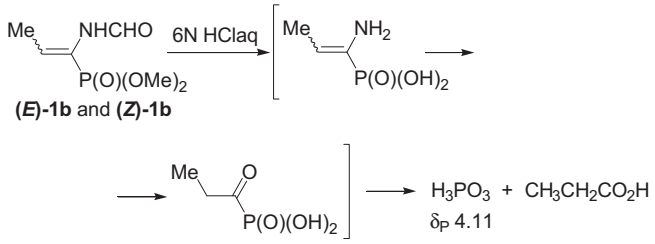
3a, 85% **(*E*)-1b**, 14% **(*Z*)-1b**, 1%
δ_P 27.15, 26.49 δ_P 16.35, 15.25 δ_P 16.77, 14.06

Scheme 2. Thermal deazetization of **2a**.

The ^{1}H NMR spectrum of the reaction mixture shows two complicated multiplets due to the cyclopropane ring protons at δ_H=1.08–1.16 and 1.39–1.47 ppm. A doublet due to the equal methoxy groups at δ_H=3.74 ppm ($^3J_{PH}$=11.3 Hz), a broad singlet due to NH proton at δ_H=7.09 ppm, and a singlet due to formyl proton at δ_H=8.09 ppm are corresponding to the major rotamer of **3a**. For the minor rotamer of **3a**, a doublet due to OCH_3 protons is observed at δ_H=3.81 ppm ($^3J_{PH}$=11.2 Hz); doublets due to NH and CHO protons appear at δ_H=7.20 and 8.21 ppm, respectively, revealing a coupling constant of 11.5 Hz ($^3J_{HH}$). The ^{1}H NMR analysis also unambiguously confirms the admixture of geometric isomers of **1b**.[15b]

The similar ratio of the products of the pyrazoline **2a** thermolysis was observed when the reaction was carried out in *o*-xylene at reflux. Attempts to diminish the undesirable alkenephosphonates formation by photodecomposition of the pyrazoline **2a** were also unsuccessful.

We have failed to purify the cyclopropanephosphonate **3a** by distillation or chromatography. Treating of the crude product with potassium permanganate in aqueous acetone[20] for oxidizing the alkenes led also to the appreciable degradation of **3a**. Fortunately, the impurities turned out to be easily removable by simple acidic hydrolysis. Thus, the treatment of the unseparated mixture with 6 N hydrochloric acid under reflux[5,9a] results in the formation of two products as indicated by the ^{31}P{^{1}H} NMR spectrum of the crude reaction mixture (two signals at δ_P=13.33 and 4.11 ppm in the ratio ca. 86:14 that precisely enough corresponds to a parity of the main and by-products after thermolysis). Simultaneously, the ^{1}H NMR spectrum discloses a set of signals due to the protons of 1-aminocyclopropanephosphonic acid (**4a**) as well as a doublet at δ_H 6.77 ppm with typical coupling constant of 665.2 Hz ($^1J_{PH}$) denoting formation of phosphorous acid as a result of hydrolysis of by-products **1b** (Scheme 3).



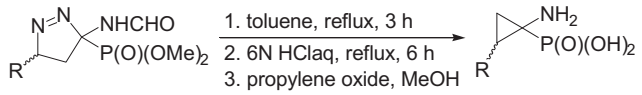
Scheme 3. Possible transformations of **1b** under hydrolysis.

Final treatment of the crude product with propylene oxide in methanol leads to pure acid **4a** in 85% overall yield (Table 2, entry 1). The spectral data are consistent with those reported in the literature.[5,8a,9a]

Attempted widening of the scope of the aforesaid cycloaddition reaction on dimethyl 1-(formylamino)alk-1-enephosphonates **1b**,**c** met with failure. When we have tested the action of diazomethane on (*Z*)- or (*E*)-**1b**,**c** the ^{31}P{^{1}H} NMR spectra of the reaction mixtures did not indicate the formation of the corresponding pyrazolines. This is most likely due to electronic or steric factors.[21]

In principle, there are two possible synthetic pathways to 2-substituted 1-aminocyclopropanephosphonates based on 'diazo addition' method (Scheme 4). The first one is the [2+3]-cycloaddition reaction of diazomethane with 1-(formylamino) alk-1-enephosphonates followed by deazetization of the intermediate 4-substituted 3-(formylamino)-4,5-dihydro-3*H*-pyrazol-3-phosphonate. The second one is the 1,3-dipolar cycloaddition of the diazoalkanes onto unsubstituted 1-(formylamino) ethylenephosphonate with subsequent decomposition of isomeric 5-substituted 3-(formylamino)-4,5-dihydro-3*H*-pyrazol-3-phosphonate. Having failed on the first path, we turned to alternative possibility.

Table 2
1-Aminocyclopropanephosphonic acids **4** prepared



2a-c **4a-c**

Entry	R	Product	Isolated yield[a] (%)	*Z*/*E*-ratio[b,c]	^{31}P{^{1}H} NMR, δ_P	
					(*Z*)	(*E*)
1	H	**4a**	85	—	13.33	
2[d]	Me	**4b**	75	55:45	12.15	14.01
3	Ph	**4c**	63	Only (*Z*)	17.27	—

[a] The yields were calculated from **2a**–**c**.
[b] The (*Z*)- and (*E*)-notation is based on the relationship of R to the dihydroxyphosphoryl group.
[c] The ratios were determined by integral values of ^{31}P{^{1}H} NMR.
[d] The treatment with propylene oxide in EtOH.

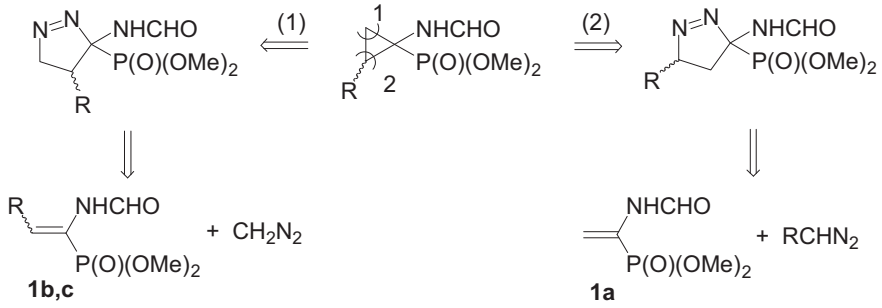
Phosphonate **1a** was found to react rapidly with diazoethane in ether to afford two diastereomers (or, more precisely, two diastereomeric racemates) of dimethyl 3-(formylamino)-5-methyl-4,5-dihydro-3*H*-pyrazol-3-phosphonate (**2b**) in the ratio 67:33 without formation of any by-products (^{31}P{^{1}H} NMR monitoring) (Table 1, entry 2). The composition of inseparable mixture isolated in 88% yield and the structure of the diastereomers were confirmed by the elemental analysis and spectroscopic methods (see Experimental part). At the same time, when phosphonate **1a** reacted with phenyldiazomethane (Table 1, entry 3) in ether, a single diastereomer of dimethyl 3-(formylamino)-5-phenyl-4,5-dihydro-3*H*-pyrazol-3-phosphonate (**2c**) was formed quantitatively as indicated by the ^{31}P{^{1}H}, ^{1}H, and ^{13}C{^{1}H} NMR spectra of the crude product, although its stereochemistry is not determined.

Thermolysis of the pyrazolines **2b**,**c** followed by hydrolysis leads to corresponding 2-substituted 1-aminocyclopropanephosphonic acids **4b**,**c** (Table 2, entries 2 and 3). 1-Amino-2-methylcyclopropanephosphonic acid (**4b**) was isolated in 75% overall yield as a 55:45 *Z*/*E* mixture. The relative stereochemistry of the diastereomers **4b** was deduced from ^{31}P NMR data based on the known correlation $^3J_{P/cis\text{-}H} > {}^3J_{P/trans\text{-}H}$ for the coupling constants between cyclopropane protons and phosphorus atom. In both ^{1}H and ^{13}C{^{1}H} NMR spectra the sets of signals from minor (*E*)-diastereomer (phosphorus analogue of racemic *allo*-norcoronamic acid) as well as from major (*Z*)-diastereomer are in agreement with the reported data.[8b,9b–d,10a] Luckily, (*Z*)- and (*E*)-diastereomers are easily separable by simple precipitation from water solution by addition of ethanol, (*Z*)-isomer being more insoluble. Pure (*Z*)-**4b** was thus obtained after two crystallizations from H_2O/EtOH.

The variation in diastereomers ratio in the starting pyrazolines mixture **3b** (67:33) and in the obtained mixture **4b** (55:45) is noteworthy. The thermolysis leads to a perceptible equalizing of the reaction mixture composition with a slight predominance of the thermodynamically less stable (*Z*)-isomer with methyl and dihydroxyphosphoryl groups located on the one side of the ring plane.

The same methodology was also adopted to prepare 1-amino-2-phenylcyclopropanephosphonic acid (**4c**), which was isolated in 63% yield for two steps as a single diastereomer. The relative configuration at C-1 and C-2 atoms in **4c** was assigned by ^{31}P and ^{1}H NMR spectroscopy to be *Z*. The ^{1}H–^{31}P coupling constants were measured as $^3J_{P/cis\text{-}3\text{-}H}$=11.7 Hz, $^3J_{P/trans\text{-}3\text{-}H}$=4.2 Hz, $^3J_{P/trans\text{-}2\text{-}H}$=6.2 Hz. These values are in agreement with those reported for similar structures.[9b–d]

Pyrazoline **2a** is quite stable when stored in a refrigerator for several months, but at room temperature it turned out to be slowly converting into dimethyl 3-(1*H* or 2*H*)pyrazolphosphonate (**5a**),



Scheme 4. Possible synthetic approaches to 2-substituted 1-aminocyclopropanephosphonates based on [2+3]-cycloaddition reaction.

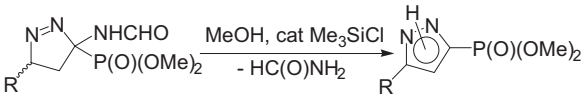
which was isolated by column chromatography and identified. The IR spectrum reveals a set of characteristic bands confirming the retention of dimethoxyposphoryl moiety along with a strong broad band of NH stretch at 3127 cm^{-1}. In the ^1H NMR spectrum the NH proton resonates at δ_P 13.64 ppm. The structure of the pyrazole skeleton was also readily confirmed by characteristic chemical shifts of the signals from aromatic protons and carbon atoms in ^1H and $^{13}C\{^1H\}$ NMR spectra, respectively. It should be also mentioned that tautomerism[22a–c] for **5a** was not observed by ^1H and $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR.

This reaction thus represents a cleavage of formamide, rather than nitrogen, from pyrazoline **2a**. Formamide formation was undoubtedly confirmed by the observation of the corresponding signals[23] in the ^1H and $^{13}C\{^1H\}$ NMR spectra of the crude product.

The similar conversion of pyrazolines into pyrazoles with formal elimination of acetamide or benzamide,[14a] hydrogen bromide,[22d] hydrogen cyanide,[22e–g] diethyl phosphite,[22f] methanesulfinic,[22f] *p*-toluenesulfinic,[17c,22h] *p*-toluenesulfenic[22i] or nitrous[22a–c] acids, or SO_2 and diethylcyanamide[22j] are known processes, being also adopted for preparation of phosphonylated pyrazoles.[22a–c,e,f,i,j] These latter are of special interest in different fields, such as agrochemical and medicinal chemistry and also as efficient coordinating ligands.[22a,e,24] Nevertheless, methods for 3(5)-pyrazolphosphonates preparation are few in number and often involve multistep reaction sequences.[25] In this context, the revealed aromatization reaction may be of benefit.

In Table 3, the results on the transformation of pyrazolines **2a**–**c** into corresponding pyrazoles **5a**–**c** are shown. The reaction takes place at room temperature in methanol in the presence of catalytic additive of Me_3SiCl. The products **5a**–**c** were isolated in moderate to excellent yields and totally characterized.

Table 3
Dimethyl pyrazol-3(5)-phosphonates **5** prepared



2 **5**

Entry	R	Time (h)	Product	Yield[a] (%)	$^{31}P\{^1H\}$ NMR, δ_P
1	H	5	**5a**	78 (61)	14.00
2	Me	48	**5b**	73 (37)	13.12
3	Ph	12	**5c**	98 (93)	11.85

[a] Determined by $^{31}P\{^1H\}$ NMR spectroscopy of the crude reaction mixture; isolated yields are given in the parentheses.

For base-assisted transformation of Δ^1-pyrazolines into pyrazoles a mechanism implying initial elimination of a leaving group followed by intramolecular proton transfer has been postulated.[22a,e–g,i] For acidic reaction conditions, such as in our case, it is reasonable to assume a preliminary tautomerization of the Δ^1-pyrazolin **2** into isomeric Δ^2-pyrazolin.[14a] This latter eliminates formamide to give pyrazole **5**. A high yield in the case of pyrazole **5c** (Table 3, entry 3) can be explained by the conjugation of the aromatic π-system with the double bond in the molecule of corresponding Δ^2-pyrazoline, which may contribute to the motive force of the reaction.

3. Conclusion

In conclusion, we have shown that phosphonate **1a** and diazoalkanes undergo [2+3]-cycloaddition reactions regiospecifically. The 1,3-dipolar cycloadducts **2** thus obtained in high yields can serve as versatile synthones not only for the 1-aminocyclopropanephosphonic acids **4**, but also for 3-phosphonylated pyrazoles **5**.

4. Experimental

4.1. General information

All chemicals, except commercial products of a satisfactory quality, were purified by literature procedures prior to use. Solvents were dried according to standard methods. Phosphonates **1** were obtained as described earlier.[15a] The ethereal solutions of diazomethane, diazoethane, and phenyldiazomethane were prepared from corresponding mono-substituted ureas according to the known procedures[26] (CAUTION! diazo compounds are poisonous and potentially explosive); the concentration being determined by titration with the benzoic acid.

^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker Avance-400 instrument at 400, 101 and 162 MHz, respectively. Chemical shifts (δ) are reported in parts per million relative to TMS (0 ppm for ^1H NMR), solvent $CDCl_3$ (77.0 for ^{13}C NMR), residual $CHCl_3$ (7.25 for ^1H NMR) or HDO (4.75 for ^1H NMR), and external 85% H_3PO_4 (0 ppm for ^{31}P NMR). Infrared spectra were obtained using SPECORD 75 IR and Carl Zeiss UR-20 spectrophotometers. HRMS (ESI) were measured on a Bruker micrOTOF II instrument in both positive and negative ion modes. Elemental analyses were done on an Elementar Vario MICRO Cube analyzer. Column chromatography was performed using Chemapol Silicagel LL_{254} 5/40. TLC was carried out using 0.20 mm thick Macherey-Nagel plates (ALUGRAM® SIL G/UV254).

4.2. Synthesis of dimethyl 3-(formylamino)-4,5-dihydro-3*H*-pyrazol-3-phosphonates 2

*4.2.1. Dimethyl 3-(formylamino)-4,5-dihydro-3H-pyrazol-3-phosphonate (**2a**).* To a foil-covered flask containing phosphonate **1a** (0.450 g, 2.51 mmol) at room temperature the 0.07 M ethereal solution of diazomethane (75 mL, 5 mmol) was added dropwise with stirring over 2 h. The mixture was stirred for 22 h. Volatile

components were removed on a rotary evaporator and then under high vacuum. The crude product was crystallized from ether to give pyrazoline **2a** (0.523 g, 94%) as white solid that turned yellow in air; 87:13 mixture of two rotamers in $CDCl_3$. Found: C, 32.33; H, 5.34; N, 18.61. $C_6H_{12}N_3O_4P$ requires C, 32.59; H, 5.47; N, 19.00%; IR ν_{max} (Nujol) 3270, 3220 sh, 1695, 1565, 1535, 1260, 1195, 1050, 855, 795 cm^{-1}; $^{31}P\{^1H\}$ NMR ($CDCl_3$) 19.81 (major), 18.61 (minor); ^1H NMR ($CDCl_3$) 1.67 (0.13H, m, CH_2CP, minor), 2.07–2.26 (1.74H, m, CH_2CP, major), 2.53 (0.13H, m, CH_2CP, minor), 3.86 (3H, d, J=10.7 Hz, OCH_3), 3.90 (3H, d, J=10.7 Hz, OCH_3), 4.59 (0.13H, m, CH_2N, minor), 4.67 (0.87H, m, CH_2N, major), 4.95 (0.13H, m, CH_2N, minor), 5.07 (0.87H, m, CH_2N, major), 7.42 (1H, br, NH), 8.19 (0.87H, s, CHO, major); 8.52 (0.13H, d, J=11.6 Hz, CHO, minor); $^{13}C\{^1H\}$ NMR ($CDCl_3$) 23.7 (major), 29.5 (minor), 54.3 (J=6.7 Hz, major), 54.5 (J=6.7 Hz, major), 54.4 (J=6.7 Hz, minor), 54.6 (J=6.1 Hz, minor), 78.2 (minor), 79.3 (major), 99.8 (J=171.7 Hz, minor), 100.1 (J=169.7 Hz, major), 160.5 (J=12.1 Hz, major), 163.9 (J=11.8 Hz, minor).

*4.2.2. Dimethyl 3-(formylamino)-5-methyl-4,5-dihydro-3H-pyrazol-3-phosphonate (**2b**).* Compound **2b** was obtained in 88% yield analogous to **2a** from phosphonate **1a** (0.400 g, 2.23 mmol) in 4 mL of ether and diazoethane (6.0 mL of 0.75 M solution in ether, 4.50 mmol) as white solid; a 67:33 mixture of two diastereomers. Found: C, 35.92; H, 6.11; N, 17.89. $C_7H_{14}N_3O_4P$ requires C, 35.75; H, 6.00; N, 17.87%; IR ν_{max} (Nujol) 3285, 3280 sh, 1695, 1565, 1525, 1260, 1210, 1055, 850, 800 cm^{-1}. The major diastereomer is a 89:11 mixture of two rotamers in $CDCl_3$. $^{31}P\{^1H\}$ NMR ($CDCl_3$) 19.85 (major), 18.58 (minor); ^1H NMR ($CDCl_3$) (only for the major rotamer) 1.54 (3H, d, J=7.3 Hz, CH_3), 1.63 (1H, m, CH_2), 2.36 (1H, m, CH_2), 3.86 (3H, d, J=10.7 Hz, OCH_3), 3.92 (3H, d J=10.7 Hz, OCH_3), 5.20 (1H, m, CHN), 7.70 (1H, d, J=9.1 Hz, NH), 8.16 (1H, s, CHO); $^{13}C\{^1H\}$ NMR ($CDCl_3$) (only for the major rotamer) 18.0, 30.5, 54.4 (J=5.9 Hz), 54.5 (J=6.7 Hz), 87.6 (J=5.0 Hz), 100.6 (J=172.0 Hz), 160.2 (J=12.0 Hz). The minor diastereomer is a 81:19 mixture of two rotamers in $CDCl_3$. $^{31}P\{^1H\}$ NMR ($CDCl_3$) 18.72 (major), 17.97 (minor); ^1H NMR ($CDCl_3$) (only for the major rotamer) 1.68 (3H, d, J=7.1 Hz, CH_3), 1.80 (1H, m, CH_2), 2.59 (1H, m, CH_2), 3.85 (3H, d, J=10.7 Hz, OCH_3), 3.86 (3H, d, J=10.7 Hz, OCH_3), 4.65 (1H, m, CHN), 7.83 (1H, d, J=6.8 Hz, NH), 8.24 (1H, s, CHO); $^{13}C\{^1H\}$ NMR ($CDCl_3$) (only for the major rotamer) 18.0, 33.0, 54.3 (J=6.7 Hz), 54.4 (J=6.7 Hz), 87.2, 95.4 (J=175.1 Hz), 163.4 (J=25.8 Hz).

*4.2.3. Dimethyl 3-(formylamino)-5-phenyl-4,5-dihydro-3H-pyrazol-3-phosphonate (**2c**).* Compound **2c** was obtained analogous to **2a** from phosphonate **1a** (107 mg, 0.60 mmol) in 1 mL of ether and phenyldiazomethane (2.4 mL of 0.5 M solution in ether, 1.20 mmol). The crude product was purified by column chromatography (EtOAc, R_f 0.12) to give **2c** (0.160 g, 90%) as white solid; a 78:22 mixture of two rotamers in $CDCl_3$. $^{31}P\{^1H\}$ NMR ($CDCl_3$) 20.33 (major); 19.71 (minor); ^1H NMR ($CDCl_3$) (only for the major rotamer) 3.26–3.83 (3H, m, CH_2 and CH), 3.87 (3H, d, J=10.1 Hz, OCH_3), 3.89 (3H, d, J=10.7 Hz, OCH_3), 7.35 (3H, m, ArH), 7.48 (1H, br, NH), 7.64 (2H, m, ArH), 8.14 (1H, s, CHO); $^{13}C\{^1H\}$ NMR ($CDCl_3$) (only for the major rotamer) 42.3, 54.4 (J=7.1 Hz), 54.9 (J=6.6 Hz), 75.2, 100.8 (J=172.0 Hz), 126.2, 128.6, 129.4, 140.2, 161.9.

4.3. Synthesis of 1-aminocyclopopanephosphonic acids 4

*4.3.1. 1-Aminocyclopropanephosphonic acid (**4a**).* The solution of pyrazoline **2a** (340 mg, 1.54 mmol) in anhydrous toluene (17 mL) was heated to reflux for 3 h. The solvent was thoroughly evaporated at reduced pressure. The residue was dissolved in aqueous 6 M HCl (16 mL) and heated at reflux for 6 h. The volatile materials were removed at reduced pressure to dryness. The residue was dissolved in the minimum amount of MeOH, and an excess of propylene oxide was added dropwise while heating to 30 °C. The precipitate formed was filtered off and washed with MeOH. The acid **4a** (180 mg, 85%) was obtained as white solid. Found: C, 26.18; H, 5.90; N, 10.15. $C_3H_8NO_3P$ requires C, 26.29; H, 5.88; N, 10.22%; IR ν_{max} (Nujol): 2700 vbr, 2300 vbr, 1630 br, 1557, 1210, 1170, 1060, 1035, 970, 870 cm^{-1}; $^{31}P\{^1H\}$ NMR (D_2O) 13.33; ^1H NMR (D_2O) 1.01–1.14 (4H, m, cycle). $^{13}C\{^1H\}$ NMR (D_2O) 8.9, 28.9 (J=198.1 Hz).

*4.3.2. 1-Amino-2-methylcyclopropanephosphonic acid (**4b**).* Compound **4b** was synthesized in 75% yield similar to **4a** from pyrazoline **2b** (250 mg, 1.06 mmol) as white solid; a 55:45 mixture of *Z*/*E* isomers. Found: C, 31.39; H, 6.64; N, 8.99. $C_4H_{10}NO_3P$ requires C, 31.80; H, 6.67; N, 9.27%; IR ν_{max} (Nujol): IR ν_{max} (Nujol): 2680 vbr, 2350 vbr, 1735 br, 1640 sh, 1610, 1545, 1250, 1185, 1097, 1030, 955, 855 cm^{-1}. Pure (*Z*)-**4b** was isolated by crystallization from the mixture H_2O/EtOH (7:2). $^{31}P\{^1H\}$ NMR (D_2O) 12.15; ^1H NMR (D_2O) 1.00 (1H, ddd, J_{gem}=6.5 Hz, J_{cis}=11.7 Hz, $^3J_{P/trans\text{-}3\text{-}H}$=7.2 Hz, 3-$H_{cycle}$), 1.19 (1H, ddd, J_{gem}=6.5 Hz, J_{trans}=4.5 Hz, $^3J_{P/cis\text{-}3\text{-}H}$=10.5 Hz, 3-$H_{cycle}$), 1.25 (3H, d, J=6.4 Hz, CH_3), 1.42 (1H, dddq, J_{cis}=11.7 Hz, J_{trans}=4.5 Hz, $^3J_{P/trans\text{-}2\text{-}H}$=7.2 Hz, J=6.4 Hz, 2-H_{cycle}); $^{13}C\{^1H\}$ NMR (D_2O) 12.5 (J=3.0 Hz), 16.5, 17.7, 33.9 (J=192.2 Hz). For (*E*)-**4b**: $^{31}P\{^1H\}$ NMR (D_2O) 14.01; ^1H NMR (D_2O) 0.77 (1H, ddd, J_{gem}=6.4 Hz, J_{trans}=6.8 Hz, $^3J_{P/trans\text{-}3\text{-}H}$=6.9 Hz, 3-$H_{cycle}$), 1.20 (3H, d, J=6.5 Hz, CH_3), 1.27 (1H, ddd, J_{gem}=6.4 Hz, J_{cis}=9.4 Hz, $^3J_{P/cis\text{-}3\text{-}H}$=12.7 Hz, 3-$H_{cycle}$), 1.49 (1H, dddq, J_{cis}=9.4 Hz, J_{trans}=6.8 Hz, J=6.5 Hz, $^3J_{P/cis\text{-}2\text{-}H}$=12.7 Hz, 2-$H_{cycle}$); $^{13}C\{^1H\}$ NMR (D_2O) 10.7, 14.6, 15.9, 33.5 (J=192.2 Hz).

4.3.3. (1S,2S*)-1-Amino-2-phenylcyclopropanephosphonic acid (**4c**).* Compound **4c** was synthesized in 63% yield similar to **4a** from **2c** (250 mg, 0.84 mmol) as white solid. Found: C, 50.43; H, 5.72; N, 6.35. $C_9H_{12}NO_3P$ requires C, 50.71; H, 5.67; N, 6.57%; IR ν_{max} (Nujol): 2700 vbr, 2350 vbr, 1730 br, 1640, 1610, 1535, 1230, 1140 br, 1030, 960, 870, 780, 757, 710 cm^{-1}. $^{31}P\{^1H\}$ NMR (D_2O/K_2CO_3) 17.27; ^1H NMR (D_2O/K_2CO_3) 0.94 (1H, ddd, J_{gem}=4.7 Hz, J_{cis}=9.4 Hz, $^3J_{P/trans\text{-}3\text{-}H}$=4.2 Hz, 3-$H_{cycle}$), 1.37 (1H, ddd, J_{gem}=4.7 Hz, J_{trans}=6.8 Hz, $^3J_{P/cis\text{-}3\text{-}H}$=11.7 Hz, 3-$H_{cycle}$), 2.20 (1H, ddd, J_{cis}=9.4 Hz, J_{trans}=6.8 Hz, $^3J_{P/trans\text{-}2\text{-}H}$=6.2 Hz, 2-$H_{cycle}$), 7.17 (1H, t, J=7.4 Hz, ArH), 7.26 (2H, t, J=7.4 Hz, ArH), 7.36 (2H, d, J=7.4 Hz, ArH).

4.4. Synthesis of 3-phosphonylated pyrazoles 5

*4.4.1. Dimethyl 3-(1H or 2H)pyrazolphosphonate (**5a**).* To a solution of pyrazoline **2a** (116 mg, 0.52 mmol) in anhydrous methanol (2 mL) three drops of Me_3SiCl was added, and the reaction mixture was stirred at room temperature for 5 h. After completion of the reaction (TLC monitoring, EtOAc) the volatile components were removed on a rotary evaporator and the residue was treated with saturated aqueous $NaHCO_3$ (1 mL). The product was extracted with $CHCl_3$ (3×3 mL). The organic extracts were dried over anhydrous Mg_2SO_4 and concentrated at reduced pressure. The residue was washed several times with hexane to give **5a** (56 mg, 61%) as colorless solid. Found: C, 33.94; H, 4.77; N, 15.29. $C_5H_9N_2O_3P$ requires C, 34.10; H, 5.15; N, 15.91%; IR ν_{max} (film): 3127, 3006, 2915, 1222, 1037, 846, 788 cm^{-1}; $^{31}P\{^1H\}$ NMR ($CDCl_3$) 14.00; ^1H NMR ($CDCl_3$); 3.81 (6H, d, J=11.4 Hz, OCH_3), 6.77 (1H, dd, J_{PH}=1.3 Hz, J=2.0 Hz, CH), 7.90 (1H, dd, J_{PH}=2.2 Hz, J=2.0 Hz, CH), 13.64 (1H, br s, NH); $^{13}C\{^1H\}$ NMR ($CDCl_3$) 53.0 (J=6.1 Hz), 110.9 (J=23.3 Hz), 131.6 (J=11.8 Hz), 137.6 (J=231.0 Hz).

*4.4.2. Dimethyl 5-methyl-3-(1H or 2H)pyrazolphosphonate (**5b**).* Compound **5b** was obtained in 37% yield analogous to **5a** from **2b** (100 mg, 0.43 mmol) as colorless transparent oil. $^{31}P\{^1H\}$ NMR ($CDCl_3$) 13.12; ^1H NMR ($CDCl_3$) 2.34 (3H, s, CH_3), 3.76 (6H, d, J=11.4 Hz, OCH_3), 6.45 (1H, s, CH), 8.16 (1H, br s, NH); $^{13}C\{^1H\}$ NMR

($CDCl_3$) 11.2, 53.0 (J=5.9 Hz), 110.4 (J=21.9 Hz), 137.3 (J=232.7 Hz), 143.0 (J=14.3 Hz). HRMS MH^+, found 191.0582. $C_6H_{12}N_2O_3P$ requires 191.0586.

*4.4.3. Dimethyl 5-phenyl-3-(1H or 2H)pyrazolphosphonate (**5c**).* Compound **5c** was obtained analogous to **5a** from **2c** (160 mg, 0.54 mmol). The crude product was purified by silica gel column chromatography (EtOAc, R_f 0.26) to give **5c** (126 mg, 93%) as a pale yellow oil. Found: C, 52.37; H, 5.54; N, 10.81. $C_{11}H_{13}N_2O_3P$ requires C, 52.38; H, 5.2; N, 11.11%; IR ν_{max} (film): 3150, 2940, 2875, 1255, 1045, 850, 797, 770, 700 cm^{-1}; $^{31}P\{^1H\}$ NMR ($CDCl_3$) 11.85; ^1H NMR ($CDCl_3$) 3.86 (6H, d, J=11.5 Hz, OCH_3), 7.03 (1H, d, J=1.9 Hz, CH), 7.37 (1H, t, J=7.4 Hz, ArH), 7.45 (2H, t, J=7.4 Hz, ArH), 7.77 (2H, d, J=7.4 Hz, ArH), 12.27 (1H, br s, NH); $^{13}C\{^1H\}$ NMR ($CDCl_3$) 52.4 (J=6.0 Hz), 108.3 (J=22.8 Hz), 125.2, 126.9, 127.1, 127.8, 128.2, 130.2 (J=201.5 Hz).

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.10.010.

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