One-pot Synthesis of Novel α-Aminophosphonate Derivatives Containing a Pyrazole Moiety

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Abstract: Synthesis of novel *N*-protected *α*-aminophosphonates **6** were achieved with high yields through copper (II) triflate catalyzed one-pot three component reaction process. It involves the reaction of aryl substituted pyrazolaldehydes, methylcarbamate and trimethylphosphite or triphenylphosphite using copper (II) triflate as lewis acid catalyst in dry dichloromethane at room temperature. A mechanism for this condensation reaction is proposed. Cleavage of the *N*-methyloxycarbonly group under acid hydrolysis afforded the free *α*-aminophosphonates 8 in quantitative yields. The structures of all new compounds were established by elemental analysis IR, ^{1}HNMR and mass spectral data.

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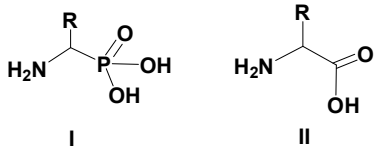
Key words: α-aminophosphonates, carbamates, Lewis acid, Pyrazolaldehydes.

1. Introduction:

Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates[1]. α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates[2–4]. Among α-functional phosphonic acids, α-aminophosphonic acids are an important class of compounds that exhibit a variety of interesting and useful properties. α-Aminophosphonic acids **I**, as structural mimics of α-amino acids **II** (Fig. 1), exhibit a broad spectrum of biological activities[5-12].



I II

Figure 1

These compounds have already been found to act as antibacterial agents, neuroactive compounds, anticancer drugs, and pesticides, with some of them already commercialized [13-18]. In this context, The therapeutic potential for modified α-aminophosphonates with improved pharmacokinetic properties, potency or spectrum, and lower side effects, prompted us to start a synthetic program to explore new pyrazole-aminophosphonate conjugates. We focused on pyrazole and its derivatives because it is an important class of compounds and attracted widespread attention due to their pharmacological properties, being reported to have a large spectrum of biological effects, especially analgesic, anticancer and anti-inflammatory properties. In this paper we would like to present the synthesis of novel pyrazole modified α-aminophosphonates conjugates.

2. Material and Methods

General Methods:

All ^{1}HNMR experiments (solvent DMSO and $CDCl_3$) were carried out with a 400 MHz Bruker Avance DRX-400 spectrometer at Okayama University, Japan. Chemical shifts are reported in part per million (ppm) relative to the respective solvent or tetramethylsilane (TMS). Melting points were recorded on Stuart scientific melting point apparatus and are uncorrected. The mass spectroscopy and the microanalysis were performed in microanalysis laboratory at Cairo University. All reactions were followed by thin layer chromatography (TLC) on kiesel gel F254 precoated plates (Merck). Anhydrous THF, MeOH and CH_2Cl_2 were obtained from Sigma-Aldrich. Starting materials were either commercially available or prepared as reported in literature.

General procedure for the preparation of formylpyrazole derivatives 2

To a mixture of methylaryl(heteroarly) ketone hydrazon, (0.01 mol), Vilsmeier reagent (14.6

mL DMF and 19.1 mL $POCl_3$) (0.01 mol) was added dropwise with stirring for one hour. The reaction mixture was refluxed for 6h at 70 – 80°C then hydrolyzed on ice/water mixture , neutralized by 5% NaOH solution till pH = 4, the solid formed was filtered , washed with water , dried and crystallized from isopropanol to yield the pure formyl hetero – cyclic pyrazole derivatives 2 in good yields.

1,3-Diphenylpyrazole4-carboxaldehyde 2a: Show the following data m.p = 142 – 143 °C, Yield = 95 %, ^{1}HNMR (DMSO): δ ppm = 7.5 – 8.2 (m.10 Harom) , 9.37 (s, 1 H , CH pyrazole) , 9.95 (s, 1H , CHO)

1 -Phenyl 3-tolyl pyrazole 4-carboxaldehyde 2b: Show the following data m.p = 118 – 120 °C , Yield = 90% , ^{1}HNMR (DMSO) δ ppm = 7.5 – 7.9 (m, 9 Harom) , 2.4 (s, 3H, cH_3) , 9.2 (s, 1H, CH) , 9.9 (s, 1H, CHO) , the mass spectra show the molecular ion peak at m/e = 262 (M^+, 19.4 %).

1-Phenyl 3-bromo benzene pyrazole 4-carboxaldehyde 2c:

Show the following data m.p = 172 – 173 °C , Yield = 85 %^{1}H NMR (DMSO) δ ppm = 7.5 – 7.9 (m, 9 Harom) , 9.2 (s, 1H, CH) , 9.96 (s, 1H, CHO).

1-Phenyl 3-chlorobenzene pyrazole carbox-adehyde 2d: Show the following data m.p = 162 – 163 °C, Yield = 87% , ^{1}H NMR (DMSO) δ ppm = 7.5 – 7.9 (m, 9 H, arom.) , 9.2 (s, 1H, CH pyrazolo) , 9.8 (s, 1H, CHO), the mass spectra show The molecular ion peak at m/e = 64 (M^+ - $C_{15}H_{10}N$, 11.2 %).

1-Phenyl 3-nitrobenzene pyrazole 4-carboxadehyde 2e: Show the following data m.p = 165 – 167 °C, Yield = 80 % ^{1}HNMR (DMSO) show: δ ppm = 7.5 – 8.2 (m.9 Harom) , 9.37 (S, 1 H , CH pyrazele) , 9.95 (s, 1H , CHO). The mass spectra show the molecular ion peak At m/e = 293 (22. 2 %) , the ion peak at m/e = 292 (M^+-1, 66.7 %) , the ion peak at m\e = 291 (M^+-2, 66.7 %) , the ion peak at m/e = 290 (M^+-3, 44.4 %) , the base ion peak at m/e = 63.

1-Phenyl 3-thinylpyrazole 4-carboxaldehyde 2f: Show the following data m.p = 182 – 184 Yield = 82 % ,^{1}HNMR ($CDCI_3$) : δ ppm = 7.2 – 7.8 (m, 8 Haromatic), 8.5 (S, 1H, CH pyrazolo) , 10.05 (S, 1H, CHO) the mass spectra show the molecular ion peak at m\e = 254 (35.7 %) and the base peak at m/e = 51

1-Phenyl 3-pyridylpyrazole 4-carbox- aldehyde 2g: : Show the following data m.p = 190 – 192 °C, Yield = 78 % , The Infra- red spectra of compound exhibit it high intensity absorption bands for ν_{CHO} at 1681 cm^{-1} bands at 1600 cm^{-1} corresponding to $\nu_{C=N}$, a band at 1500 cm^{-1} corresponding to $\nu_{C=N}$, a band at 756 cm^{-1} corresponding to ν_{C-N} ^{1}HNMR (DMSO) show : s = 7.4 – 7.6 (d, 2H pyridine) , 7.9 – 8.01 (m, Haromatic) , 9.3 (S, 1H , CH pyrazole), 9.9 (S, 1H , CHO). The mass spectra show The molecular ion peak at m/e = 249 (M^+ , 26.5 %).

Reaction of Aldehydes with Methyl Carbamate; General Procedure:

Aldehyde (1.2 mmol), methyl carbamate (1 mmol) and triphenylphosphite or trimethylphosphite were dissolved in well dried anhyd. CH_2Cl_2 (5 ml). The lewis acid, copper (II) triflate (10 mol%) was added in one portion. The mixture was stirred at RT , until TLC analysis showed the complete consumption of methyl carbamate. Then CH_2Cl_2 was evaporate and the residue dissolved in MeOH (10 mL) the product was percipitated from this solution by storing at – 20 °C for 3 – 6hrs in case of aldehyde and 24 hours in case of ketones, followed by the collection of the precipitate by filteration afford the protected aminophosphonates **6** in good to excellent yields.

Diphenyl [(methyloxycarbonyl) amino] (1, 3 diphenyl pyrazole) methyl phosphonate 6a:

Show the following data m.p = 185 – 186 °C, Yield = 90 % ^{1}HNMR (DMSO) δ ppm = 3.6 (s , 3 H , OCH_3) , 5.4 – 5.5 (m, 1H , CHP) , 8.8 (d , 1H , NH) , 7.1 – 7.4 (m , 9 Harom), 8.5 (s, 1H , CH pyrazole) , 7.5 – 7.8 (m , 10 Harom)

Diphenyl[(methyloxycarbonyl)amino](1- phenyl 3-tolyl pyrazole) methyl phosphonate 6b:

Show the following data m.p = 196 – 198 °C, Yield = 85 % ^{1}HNMR (DMSO) δ ppm = 2.34 (s , 3H , CH_3) , 3.43 (s , 3 H , OCH_3) , 5.2 – 5.3 (m, 1H , CHP) , 8.7 (d , 1H , NH) , 7.0 – 7.3 (m , 9 Harom), 8.4 (s, 1H , CH pyrazole) , 7.3 – 7.8 (m , 10 Harom)

Diphenyl[(methyloxycarbonyl)amino](1- phenyl 3-bromobenzene pyrazole)methyl- phosphonate

6c: Show the following data m.p = 209 – 210 °C Yield = 82 % , ^{1}HNMR (DMSO): δ ppm = 3.4 (s , 3H , OCH_3) , 5.6 – 5.7 (m, 1H , CHP) . 8.8 (d , 1H , NH) , 8.5 (s, 1H , CH pyrazole) , 6.9 – 7.2 (m, 9 Harom) , 7.25 – 7.70 (m , 10 arom), 8.4 (s, 1H , CH pyrazole), 6.9 – 7.3 (m, 9 Harom) , 7.5 – 7.7 (m, 10 Harom). The ion peak at m/e = 77 (C6H5) (M^+ - $C_{13}H_{14}N_2O_5P$, 74.7 %)

Diphenyl[(methyloxycarbonyl)amino](1- phenyl 3-Chlorobenzene pyrazole)methyl- phosphonate 6d:

Show the following data m.p = 200 – 201 °C. Yield = 80 % ,The Infra- red spectra of compound show a characteristic bands for V (CH3OC) at 1710 cm-1 bands at 3410 cm-1 corresponding to V NH, bands at

1217 cm-1 corresponding to V (P = O), bands at 1024 cm-1 corresponding to V (POC) H1NMR (DMSo , 400 MHZ) : S = 3.43 (S , 3H , oCH3) , 5.2 – 5.4 (m , 1H , CHP) , 8.7 (d , 1 H , NH) , 8.4 (S, 1H, CH pyrazole) 6.9 – 7.3 (m, 9 Harom) , 7.5 – 7.7 (m, 10 Harom)

Diphenyl [(methyloxy carbonyl) amino] (1- phenyl 3- nitro benzene pyrazole) methyl phosphonate 6e:

Show the following data m.p = 280- 281 ˚C. Yield = 80 % , The Infra- red spectra of compound show characteristic bands for ν_{CH3OC} at 1700 cm^{-1} and at 1261 cm^{-1} corresponding to $\nu_{P=O}$, absorption at 1033 cm^{-1} corresponding to ν_{POC}. ^{1}HNMR (DMSO): δ ppm = 3.34 – 3.47 (s, 3H , OCH_3) , 5.6 – 5.7 (m , 1H , CHP) , 8.8 (d , 1H , NH) 8.4 (s, 1H , CH pyrazole), 6.9 – 7.3 (m , 9 Harom) , 7.4 – 8 (m , 10 Harom). The mass spectra show the molecular ion peak at m/e = 584 (M^+, 26%).

Diphenyl[(methyloxycarbonyl)amino](1- phenyl 3-thinyl pyrazole)methyl- phosphonate6f:

Show the following data m.p = 220 – 221 ˚C Yield = 82 % , ^{1}HNMR (DMSO): δ ppm = 3.5 (s , 3H , OCH_3) , 5.8 – 5.9 (m, 1H , CHP) . 8.9 (d , 1H , NH) , 8.6 (s, 1H , CH pyrazole) , 6.9 – 7.5 (m, 9 Harom) , 7.3 – 7.8 (m , 10 arom), 8.6 (s, 1H , CH pyrazole), 6.9 – 7.3 (m, 9 Harom) , 7.5 – 7.7 (m, 10 Harom).

Diphenyl[(methyloxycarbonyl)amino](1- phenyl 3-pyridyl pyrazole)methyl- phosphonate 6g:

Show the following data m.p = 230 – 232 ˚C Yield = 80 %, ^{1}HNMR (DMSO): δ ppm = 3.7 (s , 3H , OCH_3) , 5.8 – 5.9 (m, 1H , CHP) . 8.9 (d , 1H , NH) , 8.4 (s, 1H , CH pyrazole) , 6.9 – 7.2(m, 9 Harom) , 7.1 – 7.3 (m , 10 arom), 8.6 (s, 1H , CH pyrazole), 6.9 – 7.3 (m, 9 Harom) , 7.5 – 7.7 (m, 10 Harom).

Dimethyl [(methyloxycarbonyl) amino] (1.3 diphenyl pyrazole) methylphosphonate 6h:

Show the following data m.p = 175-176C^o yield 91%

H1NMR (DMSO , 300 MHZ) ; S = 1.4 (S , 3H, CH3O) , 3.67(S, 3H , OCH3) , 4.7 (D m 1H , CHP) , 7.5 – 7.9 (m , 10 Harom) , 8.5 (S , 1H , CHpyrazole) , 9.3 (S , 1H , NH) .

The mass spectra show the molecular ion peak at mle = 417 (M+ , 26.9 %) , the ion peak at mle = 63 ((oCH3)2 H)(M+ - C18H15N3O3P , 23.1 %) , the ion peak at mle = 74 (CH3oCNH) (M+ - C18H18N2O3P, 61.5 %) , the ion peak at mle = 77 (C_6H_5) (M^+ - $C_{14}H_{17}N_3O_5P$, 65.4 %). The base ion peak at mle = 94 $(OCH_3)_2$ PH. (M^+- $C_{18}H_{14}N_3O_3$, 100 %), The ion peak at m/e = 233 (1,3 diphenyl pyrazole 4-CH) (M^+ - $C_4H_{10}NO_5P$, 19.5%).

Deprotection of the compounds 6 to the free aminophosphonate 8: To solution of methyloxycarbonyl aminophosphonates **6** (0.01 mol) in 5 mL dry CH_2Cl_2 was added perchloric acid (0.01 mol), stirred the mixture for 2 hrs at room temperature, filter the solid and wash it with methanol. The dried perchlorate salt was dissolved in 10 mL dry THF and few drops of Et_3N was added and the mixture wa stirred at r.t. for 2 hours to liberate the free aminophosphonates **8**. Filter the solid and dry it under reduced pressure to afford compounds **8** in good yields.

Diphenyl 1-amino (1,3 diphenyl pyrazole) 1-methyl phosphonate 8a:

Show the following data m.p = 200-201˚C, Yield = 80 % , ^{1}HNMR (DMSO): δ ppm = 5.0 – 5.1 (m, 1H, CHP), 5.8 – 6 (d, 2H, NH_2), 7.0 – 7.2 (m,10 Harom), 7.4 – 7.8 (m, 10 Harom). 8.6 (s, 1H, CH pyrazole). the mass spectra show the molecular ion peak at m/e = 480 (M^+, 5.1%).

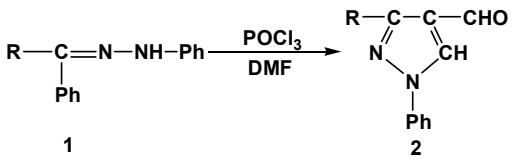
Diphenyl 1-amino [1-phenyl 3- Bromo- benzene) pyrazole] 1-methyl phosphonate 8c: Show the following data m.p =195-196 ˚C , Yield = 75 % The mass spectra show the molecular ion peak at m/e = 545 (M^+ - NH_2 , 1.8 %). The base n peak at m/e = 77 (C_6H_5), the ion peak at m/e = 80 (Br , 7.1) , the ion peak at m/e = 91 (C_6H_5N , 7.5 %)

The ion peak at m/e = 93 (C6H5O , 12.8 %) , the ion peak at mle = 233 ((oph)2po , 6.2 %) , the ion peak at (mle = 299 (C15H10N2Br , 4.0 %)

Diphenyl 1-amino[(1-phenyl 3-chloro-benzene)pyrazole]1-methyl phosphonate 8d: Show the following data m.p = 210-211◦C, Yield = 78 % , the mass spectra show the molecular ion peak at m/e = 514 (M^+, 0.5 %).

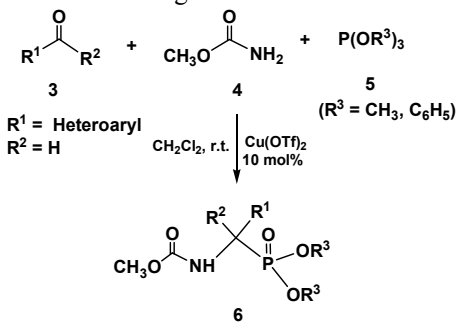
3. Results and Discussion:

The synthesis of mono- and disubstituted diphenyl and dimethyl α-aminophosphonates **6** were accomplished in good yield using methyl carbamate, an pyrazolaldehyde derivatives and triphenyl or trimethyl phosphite in the presence of a Lewis acid such as copper (II) triflate according to scheme 2. The required aldehyde needed for this study were synthesized according to published method[19] using Vilsmeier reagent as shown in scheme 1.



Scheme 1

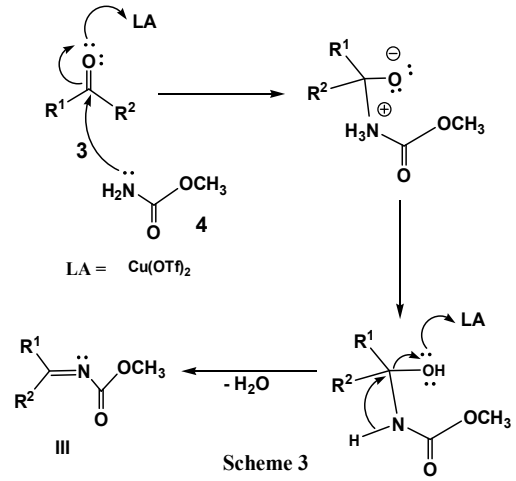
Having a diverse series of pyrazolaldehyde derivatives affording the opportunity to obtain a various structures diversity of α-amino- phosphonates **6** by a fast and convenient one-pot three component reaction route according to scheme 2.

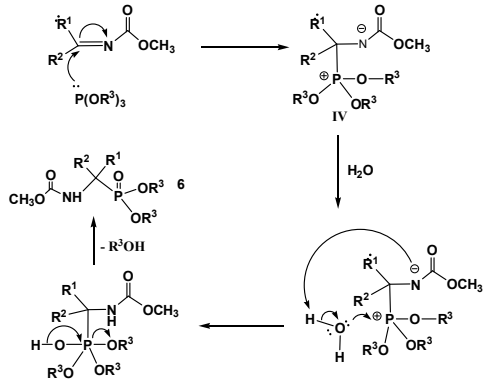


Scheme 2

Optimal conditions for the Lewis acid were found to be 10 mol% in dichloromethane (Scheme 2). At 5 mol%, the reaction afforded the same yield but required longer reaction times. The reactions are clean and complete within hours. The reaction conditions are very mild and α-aminophosphonates are exclusively formed without the formation of any undesired side products. Another important feature of this reaction is the survival of a variety of functional groups such as ester under the reaction conditions. Moreover, the mechanism of this reaction has not been investigated in detail. We suppose that after reaction of the carbonyl compound with the carbamate in presence of lewis acid catalyst, the acylimine intermediate **III** is attacked by nucleophilic phosphite with the formation of a phosphonium intermediate **IV** and that both reactions are catalyzed by the Lewis acid. Reaction of phosphonium intermediate **IV** with water affords the target compound 6 after elimination of phenol/methanol as shown in scheme **4**.

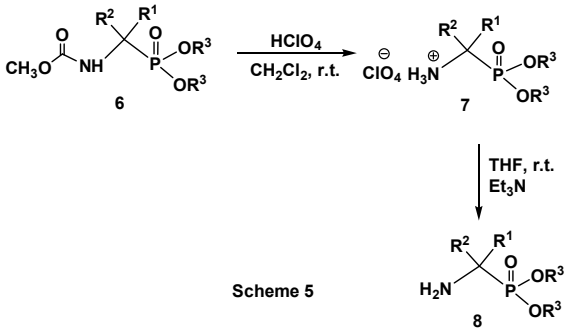
In all cases, the reaction proceeded smoothly at ambient temperatures with high selectivity**.** In summary, we found that a Lewis acid such as $Cu(OTf)_2$ effectively promoted the condensation of heterocyclic aldehydes bearing pyrazole moiety with methylcarbamate and triphenylphosphite or trimethylphosphite at room temperature. In addition to we have demonstrated a novel and efficient protocol for the synthesis of α-aminophosphonates which can serve as peptide mimetics. The method is effective for heterocyclic aldehydes such as pyrazolaldehyde and provides excellent yields of the products, which makes it useful and attractive process for the synthesis of α-aminophosphonates. It is believed that this method presents a better and more practical alternative to the existing methodologies[20] for the synthesis of α-aminophosphonates.





Scheme 4

Finally, deprotection or cleavage of the methyloxycarbonly group by acidic hydrolysis using perchloric acid cleanly affords the free α-aminophosphonates **8** in high yields.



Scheme 5

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