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

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Abstract: Synthesis of novel \textit{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 \textit{N}-methyloxycarboxyl 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, \textsuperscript{1}HNMR and mass spectral data.


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\textsuperscript{[1]}. α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates\textsuperscript{[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\textsuperscript{[5 – 12]}.

![Figure 1](image-url)

These compounds have already been found to act as antibacterial agents, neuroactive compounds, anticancer drugs, and pesticides, with some of them already commercialized \textsuperscript{[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.

2. Material and Methods
General Methods:
All \textsuperscript{1}HNMR experiments (solvent DMSO and CDCl\textsubscript{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\textsubscript{2}Cl\textsubscript{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 methyaryl(heteroarly) ketone hydrazone, (0.01 mol), Vilsmeier reagent (14.6
mL DMF and 19.1 mL POCl₃ (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-Diphenylpyrazole-4-carboxaldehyde 2a: Show the following data m.p = 142 – 143 °C, Yield = 95 %, ¹H NMR (DMSO) δ ppm = 7.5 – 8.2 (m, 10 Harom), 9.37 (s, 1H, CH pyrazole), 9.95 (s, 1H, CHO)

1 -Phenyl 3-tolyl pyrazole 4-carboxaldehyde 2b: Show the following data m.p = 172 – 173 °C, Yield = 90 %, ¹H NMR (DMSO) δ ppm = 7.5 – 7.9 (m, 9 Harom), 2.4 (s, 3H, CH₃), 9.2 (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 = 1681 – 1691 °C, Yield = 85 %, ¹H NMR (DMSO) δ ppm = 7.5 – 7.9 (m, 9 Harom), 9.37 (s, 1H, CH pyrazole), 9.9 (s, 1H, CHO), the mass spectra show the molecular ion peak at m/e = 292 (M⁺, 66.7 %), the ion peak at m/e = 291 (M⁺+1, 64.4 %), the ion peak at m/e = 290 (M⁺+2, 65.7 %), the ion peak at m/e = 290 (M⁺+3, 44.4 %), the base ion peak at m/e = 63.

1-Phenyl 3-thiophenyl pyrazole 4-carboxaldehyde 2d: Show the following data m.p = 150 – 151 °C, Yield = 80 %, ¹H NMR (DMSO) δ ppm = 7.5 – 7.8 (m, 9 Harom), 9.37 (s, 1H, CH pyrazole), 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-thiophenyl pyrazole 4-carboxaldehyde 2f: Show the following data m.p = 190 – 192 °C, Yield = 78 %, ¹H NMR (CDCl₃) δ ppm = 7.2 – 7.8 (m, 8 Haromatic), 8.5 (s, 1H, CH pyrazole), 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-pyridyl pyrazole 4-carboxaldehyde 2g: Show the following data m.p = 182 – 184 °C, Yield = 82 %, ¹H NMR (CDCl₃) δ ppm = 7.2 – 7.8 (m, 8 Haromatic), 8.5 (s, 1H, CH pyrazole), 10.1 (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-pyridyl pyrazole 4-carboxaldehyde 2f: Show the following data m.p = 190 – 192 °C, Yield = 78 %, ¹H NMR (CDCl₃) δ ppm = 7.2 – 7.8 (m, 8 Haromatic), 8.5 (s, 1H, CH pyrazole), 10.1 (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-thiophenyl pyrazole 4-carboxaldehyde 2f: Show the following data m.p = 190 – 192 °C, Yield = 78 %, ¹H NMR (CDCl₃) δ ppm = 7.2 – 7.8 (m, 8 Haromatic), 8.5 (s, 1H, CH pyrazole), 10.1 (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-thiophenyl pyrazole 4-carboxaldehyde 2f: Show the following data m.p = 190 – 192 °C, Yield = 78 %, ¹H NMR (CDCl₃) δ ppm = 7.2 – 7.8 (m, 8 Haromatic), 8.5 (s, 1H, CH pyrazole), 10.1 (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-thiophenyl pyrazole 4-carboxaldehyde 2f: Show the following data m.p = 190 – 192 °C, Yield = 78 %, ¹H NMR (CDCl₃) δ ppm = 7.2 – 7.8 (m, 8 Haromatic), 8.5 (s, 1H, CH pyrazole), 10.1 (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-thiophenyl pyrazole 4-carboxaldehyde 2f: Show the following data m.p = 190 – 192 °C, Yield = 78 %, ¹H NMR (CDCl₃) δ ppm = 7.2 – 7.8 (m, 8 Haromatic), 8.5 (s, 1H, CH pyrazole), 10.1 (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-thiophenyl pyrazole 4-carboxaldehyde 2f: Show the following data m.p = 190 – 192 °C, Yield = 78 %, ¹H NMR (CDCl₃) δ ppm = 7.2 – 7.8 (m, 8 Haromatic), 8.5 (s, 1H, CH pyrazole), 10.1 (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.
1217 cm-1 corresponding to \( \nu \) (P = O), bands at 1024 cm-1 corresponding to \( \nu \) (POC) H1NMR (DMSO, 400 MHz): \( S = 3.43 \) (S, 3H, oCH3), 5.2 – 5.4 (m, 1H, CHP), 8.7 (d, 1H, 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 benzo 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 \( \nu_{CHOC} \) at 1700 cm\(^{-1}\) and at 1261 cm\(^{-1}\) corresponding to \( \nu_{POC} \), \( \nu \) (P = O), bands at 1700 cm\(^{-1}\) corresponding to \( \nu_{CHOC} \) at \( \nu \) (P = O). The ion peak at m/e = 233 (1,3 diphenyl benzyl phosphonate 6f), the ion peak at m/e = 233 (M+ - (oCH3)2 PO, 6.2%), the ion peak at m/e = 93 (C6H5O, 12.8%), the ion peak at m/e = 77 (C6H5Br, 1.8%), the ion peak at m/e = 77 (C6H5N, 7.5%).

The ion peak at m/e = 77 (C6H5N, 7.5%). Deprotection of the compounds 6 to the free aminophosphonate 8: To solution of methyloxy carbonyl aminophosphonates 6 (0.01 mol) in 5 mL dry CH2Cl2 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 Et3N was added and the mixture wa stirred at r.t. for 2 hours to liberate the free aminosphophonates 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%, \(^{1}\)H NMR (DMSO): \( \delta \) ppm = 3.34 – 3.47 (s, 3H, OCH3), 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 = 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+ - NH2, 1.8%). The base ion peak at m/e = 77 (C6H5), the ion peak at m/e = 80 (Br, 7.1), the ion peak at m/e = 91 (C6H5N, 7.5%).

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

**Diphenyl 1-amino[1-phenyl 3-chloro-benzen]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 \( \alpha \)-aminophosphonates 6 were accomplished in good yield using methyl carbamate, an pyrazoldehyde derivatives and triphenyl or trimethyl phosphite in the presence of a Lewis acid such as copper (II) trflate 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.
Having a diverse series of pyrazolaldehyde derivatives affording the opportunity to obtain a various structures diversity of α-aminophosphonates 6 by a fast and convenient one-pot three component reaction route according to 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.
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References

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