One-pot three-component Kabachnik–Fields reaction:
Synthesis of novel α-aminophosphonates containing thiazolylpyrazole moiety

Ashraf A. Sediek,1,2 Mohamed S. Mudarris1 and Abeer A. Shaddy2

1Chemistry Department, Faculty of Sciences and Arts, Al-Kamil Branch, King Abdulaziz University, Jeddah, Saudi Arabia
2Chemical Industries Division, National Research Centre, Dokki, Giza, Egypt

asediek@yahoo.com

Abstract: A novel series of thiazolylpyrazole α-aminophosphonate derivatives 4a-l have been synthesized by Kabachnik–Fields type reaction of equimolar quantities of 5-amino-3-(4-hydroxyphenyl)-1-(4-aryl-thiazol-2-yl)-1H-pyrazole-4-carbonitriles, aromatic aldehydes and alkyl phosphites, by using FeCl3 as Lewis acid catalyst. The reaction took place via imine formation followed by addition of dialkyl phosphate to furnish thiazolylpyrazole α-aminophosphonate derivatives in good yield.


Keywords: α-aminophosphonate; thiazolylpyrazole; Kabachnik-Fields reaction

Introduction
α-Aminophosphonates and their derivatives are an important class of bioactive molecules due to their biological importance and wide application in organic chemistry.1–3 A considerable number of α-aminophosphonate derivatives are known to be antiviral,4 antifungal, antibacterial5 and antitumor.6–12 A large number of studies on their synthesis and biological activities have been reported.13–18 From this point of view, our attention has been driven to the synthesis of biologically active α-aminophosphonates bearing N-heterocycles moieties.

In the present work we represented the synthesis of different dialkyl [3-(4-hydroxyphenyl)-4-cyano-1-(4-arylthiazol-2-yl)-1H-pyrazol-5-yl]-amino[aryl]methyl-phosphonate 4a-l derivatives via the reaction of 5-amino-3-(4-hydroxyphenyl)-1-(4-arylthiazol-2-yl)-1H-pyrazole-4-carbonitriles 1a,b with a variety of aromatic aldehydes and dialkyl phosphites (DAPs) 3a,b (Table-1) through three-component coupling based on Kabachnik-Fields reaction (Scheme A) using 10% mol FeCl3 as catalyst.

\[
\begin{align*}
\text{RCHO} + \text{R'NH}_2 + \text{HOR} & \rightarrow \text{RNR'O} \\
\text{R, R', R} & \text{ are Alkyl or Aryl}
\end{align*}
\]

Scheme A

General pathway of the Kabachnik-Fields reaction

In the framework of the scientific research of the project No. 204/856/1433, funded by King Abdulaziz University, the titled compounds and their structure were synthesized and investigated.

Chemistry
α-Aminomethylphosphonates 4a-l were synthesized by one-pot three component Kabachnik–Fields reaction, by heating a mixture of 5-amino pyrazole derivatives 1a,b with appropriate aromatic aldehyde 2a-c and dialkyl phosphates 3a,b in THF for 5-6 h. They were obtained in good yield (Scheme 1).

The structure of synthesized compounds have been confirmed by mass, infrared spectra (IR) and nuclear magnetic resonance (NMR) spectroscopy which displayed results agreed with the proposed structures 4a-l.
The spectroscopic data of compound 4a gave in IR spectra signals (cm⁻¹) at 3455 (OH-phenyl), 3,355 (NH), 2,198 (CN), 1,235 (P = O) and 1,055 (P–O–C); ¹H NMR showed two doublets at δ = 3.64, 3.74 ppm, and J_H-H = 6.9, J_H_c = 11.9 Hz, for 6H of (CH_3)_2P, doublet of doublet at δ = 5.8, 5.9, J_H-H = 8.8, J_H_c = 18.5 Hz, for 1H of HC–P and δ = 8.2 br, for NH; while ³¹C NMR spectra displayed signals at δ (ppm) = 152.6 (d, C–3), 78.3 (d, C–4), 159.3 (d, C–5), 51.6, 54.8 (d, J_H-c = 165.2 Hz, C–P), 155.2, 104.4 (C–4, C–5) of thiazole ring, 123.2 (CN), 53.51 (d, J_p-c = 12.2 Hz, (CH_3)2P); in ³¹P NMR, δ (ppm) = 23.4 for phosphonate and in MS spectra showed (m/z %): 541 (M⁺, 38).

The suggested mechanism for the reaction is depicted in Scheme 2, according to the Kabachnik–Fields reaction, the first step of this mechanism assumed to be the formation of Schiff bases 5a-f by the condensation between heterocyclic amines 1a,b and aromatic aldehydes 2a-c, followed by addition of DAPs 3a,b in the presence of FeCl₃ and heating to give dialkyl [3-(4-hydroxyphenyl)-4-cyano-1-(4-arylthiazol-2-yl)-1H-pyrazol-5-yl]-amino]aryl)methyl-phosphonate 4a-l.

On the other hand Schiff bases 5a-f obtained in a good yield by heating amines 1a,b with aryl aldehydes 2a-c in ethanol/acetic acid. α-Aminomethylphosphonates 4a-l can be synthesized in higher yield (~70%) by reacting Schiff bases 5a-f with DAPs 3a,b in THF containing 10% mol FeCl₃ (Scheme 3).

![Scheme 2](image)

![Scheme 3](image)

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Experimental
All chemicals used were purchased from Aldrich. Solvents were distilled and dried by standard techniques. The reactions were monitored by thin layer chromatography (TLC) on Merck precoated silica GF254 aluminum plates. Melting points were measured on Stuart scientific melting point apparatus SMP30 and are uncorrected. $^1$H NMR, $^{31}$P NMR and $^{13}$C NMR spectra were recorded on Bruker spectrometer 400 MHz. $^1$H and $^{13}$C NMR spectra were measured using TMS as the internal standard, whereas $^{31}$P NMR spectra were recorded relative to external H$_3$PO$_4$ (85%). Mass spectrometry was performed on a Konik MS Q12 spectrometer. IR spectra were recorded on a Thermo Scientific Nicolet IS 10 spectrophotometer using KBr pellets. 5-amino-3-(4-hydroxyphenyl)-1-(4-arylthiazol-2-yl)-1H-pyrazole-4-carbonitriles 1a–l were prepared as reported in literature.20

General procedure for the one-pot preparation of 4a–l
A mixture of 5-Amino-3-(4-hydroxyphenyl)-1-(4-arylthiazol-2-yl)-1H-pyrazole-4-carbonitriles 1a (1.717 g, 0.005 mol) or 1b (1.889 g, 0.005 mol), aldehyde 2a–c (0.005 mol) and trimethyl phosphate 3b (0.008 mol in tetrahydrofuran (10 ml) and FeCl$_3$ (10 mol %) was heated at 70 °C for appropriate reaction time, After completion of the reaction (TLC), EtOAc (10 ml) was added to the mixture. The mixture was washed with H$_2$O (10 ml). The organic phase was separated and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under vacuum and the resulting α-aminophosphonates were collected and crystallized from the proper solvent.

dimethyl [4-cyano-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-ylamino][phenyl)methylphosphonate 4a
Pale-yellow crystals; yield = 61%; m.p. = 218-219 °C (AcOEt); IR (KBr): ν = 3455 (OH), 3355 (NH), 2,198 (CN), 1,235 (P – O), 1,055 (P – O – C) cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ (ppm) = 3.64, 3.74 (2d, $J_{H-H}$ = 6.9, $^3$J$_{P-H}$ = 11.9 Hz, 6H, (CH$_3$O)$_2$P), 5.8, 5.9 (dd, $J_{H-H}$ = 8.8, $^3$J$_{P-H}$ = 18.5 Hz, 1H, HC–P), 8.2 (br, 1H, NH), 7.07–8.26 (m, 15H, Ar–H, thiazole–H), 9.55 (s, 1H, OH); $^{13}$C NMR (CDCl$_3$): δ (ppm) = 152.6 (d, C–3), 78.3 (d, C–4), 159.3 (d, C–5), 51.6, 54.8 (d, $^3$J$_{P,C}$ = 165.2 Hz, C–P), 152.8, 141.3, 139.2, 129.4, 128.5, 127.5, 130.1, 128.1 (C–Ar) 155.2, 104.4 (C–4′, C–5′–thiazole), 123.2 (CN), 16.6 (d, $^3$J$_{P,C}$ 7.2 Hz, (CH$_3$CO)$_2$P). $^{31}$P NMR (CDCl$_3$): δ (ppm) = 23.4; MS (m/z %): 557 (M*, 38), 448 (100).

diethyl [4-cyano-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-ylamino][phenyl)methylphosphonate 4b
Pale-yellow crystals; yield = 60%; m.p. = 229-230 °C (AcOEt); IR (KBr): ν = 3450 (OH), 3,350 (NH), 2,200 (CN), 1,233 (P = O), 1,050 (P – O – C) cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ (ppm) = 1.15, 1.17 (2d, $J_{H-H}$ = 5.9, $^3$J$_{P-H}$ = 3.9 Hz, 6H, (CH$_3$CO)$_2$P), 3.9, 4.1 (2dq, $^3$J$_{P,H}$ = 9.8 Hz, 4H (CH$_3$O)$_2$P), 5.8, 5.9 (dd, $J_{H,H}$ = 8.8, $^3$J$_{P,H}$ = 18.5 Hz, 1H, HC–P), 8.2 (br, 1H, NH), 7.07–8.26 (m, 15H, Ar–H, thiazole–H), 9.56 (s, 1H, OH); $^{13}$C NMR (CDCl$_3$): δ (ppm) = 152.6 (d, C–3), 78.3 (d, C–4)
Pale yellow crystals; yield = 57%; m.p. = 207-208 °C (AcOEt); IR (KBr): $\nu = 3450$ (OH), 3360 (NH), 2210 (CN), 1230 (P = O), 1050 (P–O–C) cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ (ppm) = 3.6, 3.7 (2d, $J_{P,H} = 6.9, J_{P,H} = 3.9$ Hz, 6H, (CH$_2$)$_2$, CN), 1,235 (P = O), 1,055 (P–O–C) cm$^{-1}$; $^3$P NMR (CDCl$_3$): $\delta$ (ppm) = 51.6, 54.8 (d, $J_{P,H} = 165.2$ Hz, C–P), 152.8, 141.3, 139.2, 132.2, 129.4, 128.5, 127.5, 130.2, 130.1, 128.1 (C–Ar) 155.2, 104.4 (C–4’, C–5’–thiazole), 123.2 (CN), 53.51 (d, $J_{P,C} = 12.2$ Hz, (CH$_2$O)$_2$P), 55.6 (d, $J_{P,C} = 8.4$ Hz, (CH$_3$O)$_2$P); MS (m/z %): 585 (M$^+$, 35), 448 (100).
diethyl [1-(4-(4-chlorophenyl)thiazol-2-yl)-4-cyano-3-(4-hydroxyphenyl)-1H-pyrazol-3-ylaminol[2-chlorophenyl)methyl-phosphonate 4j

Pale-yellow crystals; yield = 59%; m.p. = 212–213 °C (AcOEt); IR (KBr): v = 3455 (OH), 3340 (NH), 2190 (CN), 1230 (P = O), 1045 (P–O–C) cm⁻¹; ¹H NMR (CDCl₃): δ (ppm) = 1.16, 1.17 (2d, Jₚ₋ₓ = 5.9, Jᵧ₋ₓ = 3.9 Hz, 6H, (CH₂)₃P), 3.8, 4.1 (2dq, Jᵧ₋ₓ = 9.6 Hz, 4H (CH₂O)₂P), 5.6, 5.8 (dd, Jₓ₋ᵧ = 8.8, Jᵧ₋ₓ = 18.3 Hz, 1H, HC–P), 8.2 (br, 1H, NH), 7.1–8.26 (m, 13H, Ar–H, thiazoil-H), 9.72 (s, 1H, OH); ¹³C NMR (CDCl₃): δ (ppm) = 152.4 (d, C–C), 78.2 (d, C–C), 159.4 (d, C–C), 51.4, 54.5 (d, Jₓ₋ᵧ = 165.1 Hz, C–C), 152.6, 141.4, 139.2, 132.2, 129.2, 128.5, 127.3, 130.1, 128.1 (C–Ar) 155.2, 104.4 (C–C’, C–5’–thiazoil), 123.2 (CN), 16.4 (d, Jₓ₋ᵧ = 7.1 Hz, (CH₂O)₂P), 55.4 (d, Jₓ₋ᵧ = 8.4 Hz, (CH₂O)₂P); MS (m/z %): 654 (M⁺, 30), 518 (100).

dimethyl [1-(4-(4-chlorophenyl)thiazol-2-yl)-4-cyano-3-(4-hydroxyphenyl)-1H-pyrazol-5-ylaminol[2-chlorophenyl)methyl-phosphonate 4k

Pale-yellow crystals; yield = 56%; m.p. = 224–225 °C (AcOEt); IR (KBr): v = 3460 (OH), 3355 (NH), 2200 (CN), 1245 (P = O), 1050 (P–O–C) cm⁻¹; ¹H NMR (CDCl₃): δ (ppm) = 3.62, 3.72 (2d, Jₓ₋ᵧ = 6.7, Jᵧ₋ₓ = 11.8 Hz, 6H, (CH₂O)₂P), 3.88 (s, 3H, Phenyl-OCH₃), 5.7, 5.8 (dd, Jₓ₋ᵧ = 8.6, Jᵧ₋ₓ = 18.1 Hz, 1H, HC–P); 8.1 (br, 1H, NH), 7.1–8.26 (m, 13H, Ar–H, thiazoil-H), 9.7 (s, 1H, OH); ¹³C NMR (CDCl₃): δ (ppm) = 152.5 (d, C–C), 78.2 (d, C–C), 159.4 (d, C–C), 51.4, 54.4 (d, Jₓ₋ᵧ = 165.1 Hz, C–C), 152.4, 141.1, 139.2, 132.2, 129.2, 128.3, 127.2, 130.1, 128.1 (C–Ar) 155.2, 104.2 (C–C’, C–5’–thiazoil), 123.2 (CN), 56.2 (Phenyl-OCH₃), 53.49 (d, Jₓ₋ᵧ = 11.8 Hz, (CH₂O)₂P); MS (m/z %): 622 (M⁺, 35), 513 (100).
3.86 (s, 3H, Phenyl), 9.5 (s, 1H, HC=N, exocyclic), 1,610 (C=N) cm$^{-1}$; 13C NMR (CDCl$_3$): δ (ppm) = 161.2 (HC=N, exocyclic), 146.3 (C–3), 167.1 (C–5), 82.1 (C–4), 143.3, 138.2, 132.2, 129.4, 128.5, 127.5, 128.1, 126.1, 120.2 (C–Ar), 153.2, 107.8 (C–4’, C–5’–thiazole), 121.6 (CN); MS (m/z %): 482 (M$^+$, 38), 357 (25), 77 (100).

(E)-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-5-(4-methoxyphenyl-methyleneamino)-1H-pyrazole-4-carbonitrile 5e

m.p. = 196–197 °C; IR (KBr): ν = 3450 (OH), 2,198 (CN), 1,620 (C=O) cm$^{-1}$; 1H NMR (CDCl$_3$): δ (ppm) = 9.4 (s, 1H, OH), 8.48 (s, 1H, HC=N, exocyclic), 3.82 (s, 3H, Phenyl-OCH$_3$), 7.17–8.1 (m, 14H, Ar–H), thiazole-H; 13C NMR (CDCl$_3$): δ (ppm) = 163.2 (HC=N, exocyclic), 55.8 (Phenyl-OCH$_3$), 148.4 (C–3), 167.1 (C–5), 81.6 (C–4), 143.3, 138.4, 132.6, 129.4, 128.5, 127.5, 128.1, 126.1, 121.2 (C–Ar), 154.2, 106.4 (C–4’, C–5’–thiazole), 121.4 (CN); MS (m/z %): 477 (M$^+$, 38), 357 (18), 77 (100).

(E)-[1-(4-chlorophenyl)-thiazol-2-yl]-3-(4-hydroxyphenyl)-5-(2-chlorophenyl-methyleneamino)-1H-pyrazole-4-carbonitrile 5d

m.p. = 182–183 °C; IR (KBr): ν = 3460 (OH), 2,195 (CN), 1,615 (C=O) cm$^{-1}$; 1H NMR (CDCl$_3$): δ (ppm) = 9.3 (s, 1H, OH), 8.42 (s, 1H, HC=N, exocyclic), 7.3–8.4 (m, 14H, Ar–H), thiazole-H; 13C NMR (CDCl$_3$): δ (ppm) = 162.2 (HC=N, exocyclic), 143.2, 137.6, 133.2, 129.4, 128.4, 127.5, 128.1, 126.1, 120.8 (C–Ar), 154.2, 106.4 (C–4’, C–5’–thiazole), 121.4 (CN); MS (m/z %): 482 (M$^+$, 38), 392 (22), 77 (100).

(E)-[1-(4-chlorophenyl)-thiazol-2-yl]-3-(4-hydroxyphenyl)-5-(2-chlorophenyl-methyleneamino)-1H-pyrazole-4-carbonitrile 5e

m.p. = 179–180 °C; IR (KBr): ν = 3450 (OH), 2,195 (CN), 1,620 (C=O) cm$^{-1}$; 1H NMR (CDCl$_3$): δ (ppm) = 9.4 (s, 1H, OH), 8.45 (s, 1H, HC=N, exocyclic), 7.2–8.3 (m, 13H, Ar–H), thiazole-H; 13C NMR (CDCl$_3$): δ (ppm) = 162.2 (HC=N, exocyclic), 143.2, 137.6, 133.2, 129.4, 128.4, 127.5, 128.1, 126.1, 122.2 (C–Ar), 154.2, 106.4 (C–4’, C–5’–thiazole), 121.4 (CN); MS (m/z %): 515 (M$^+$, 38), 392 (22), 77 (100).

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References


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