Stereoselective Synthesis of Dialkyl 2-(dialkoxyphosphoryl)-1-[5-(5-nitrothiophen-2-yl)-1,3,4-Thiadiazol-2-yl amino] Ethanedioate

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Abstract: A three-component reaction between trialkyl(aryl) phosphites, dialkyl acetylene dicarboxylates and [5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-amine] is described as a simple and efficient route for the stereoselective synthesis of dialkyl 2-(dialkoxyphosphoryl)-1-[5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-yl amino] ethanedioate in high yields.

Keywords: Thiadiazole, Stereoselective synthesis, Dialkyl acetylenedicarboxylates, Trialkyl(aryl) phosphites, Phosphonates

Introduction

The 1,3,4-thiadiazole ring system is known to possess several biological activities and the antibacterial properties have been largely described1. It has also been reported that derivatives of 1,2,4-triazole and 1,3,4-thiadiazole condensed nucleus systems exert diverse pharmacological activities such as anti-inflammatory, antitumor, antifungal and antibacterial2.

The reaction of trimethyl phosphite and dimethyl acetylenedicarboxylate (DMAD) in the presence of alcohols is reported to produce phosphate ylide derivatives which are stable at low temperatures, but are converted to phosphonate derivatives by warming or by treatment with water3. There are some other recent reports on the reaction between phosphites and acetylenic esters in the presence of an acidic organic compound, all of them proceeding through a phosphate ylide intermediate4-12. In continuation of our works on the reaction between trivalent phosphorus nucleophiles and acetylenic esters in the presence of organic NH, OH, or CH-acids5-13, here we wish to report the results of our study on the reaction between dialkyl acetylenedicarboxylates (DAAD’s) and trialkyl(aryl) phosphites in the presence of [5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-amine].
Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. $^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded on Bruker DRX-300 Avance spectrometer in CDCl$_3$ using TMS as internal standard or 85% H$_3$PO$_4$ as external standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure for preparation of compounds 4a-d

To a magnetically stirred solution of trialkyl(aryl) phosphite (1 mmol) and [5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-amine] (1 mmol) in acetone (15 mL) was added dropwise a mixture of dialkyl acetylenedicarboxylate (1 mmol) in acetone (3 mL) at room temperature over 2 min. The reaction mixture was then stirred for 24 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (60, 230-400 mesh) using ethyl acetate-hexane (3:1) mixture as eluent.

Dimethyl 2-(dimethoxyphosphoryl)-1-(5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-yl amino) ethanedioate (4a)

Yield: 91%; Yellow powder, m.p.190-192 °C, IR (KBr)(ν$_{max}$, cm$^{-1}$): 3150 (NH), 1733 and 1705 (C=O, ester), Analyses: Calcd. for C$_{14}$H$_{17}$N$_4$O$_9$PS$_2$: C, 35.00; H, 3.57; N, 11.66; S, 13.35%. Found: C, 34.87; H, 3.35; N, 3.68%. MS (m/z, %): 480 (M$^+$, 7). $^1$H NMR (300 M Hz, CDCl$_3$): δ 3.62 and 3.73 (6 H, 2 s, 2 OCH$_3$), 3.76 and 3.81 (6 H, 2d, 3J$_{PH}$=11 Hz, 2POCH$_3$), 4.22 (1H, dd, 2J$_{HP}$=21 Hz, 3J$_{HH}$=11Hz, P-C$_H$), 5.21 (1H, dd, 3J$_{HP}$=5 Hz, 3J$_{HH}$=11 Hz, P-C-CH$\_2$), 7.02-8.04 (m, H, aromatic), 8.10 (d, 1H, NH, 3J$_{HH}$=11 Hz). $^{13}$C NMR (125.8 M Hz, CDCl$_3$): δ 40.70 (d, 1J$_{cp}$=137 Hz, P-C$_H$), 43.01 (d, 2J$_{cp}$=3 Hz, CP), 52.89 and 53.38 (2OCH$_3$), 53.64 and 53.68 (2d, 2J$_{cp}$=11 Hz, 2POCH$_3$), 123.17, 129.45, 137.38, 139.44, 141.04, 142.64 (6C, aromatic), 167.43 (d, 2J$_{cp}$=7 Hz, C=O), 172.88 (d, 3J$_{cp}$=21 Hz, C=O). $^{31}$P NMR (202.5 MHz, CDCl$_3$): δ 26.76.

Dimethyl 2-(diphenylophosphoryl)-1-(5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-yl amino) ethanedioate (4b)

Yield: 90%; Yellow powder, m.p.203-205 °C, IR (KBr)(ν$_{max}$, cm$^{-1}$): 3180 (NH), 1731 and 1711 (C=O, ester), Analyses: Calcd. for C$_{24}$H$_{21}$N$_4$O$_9$PS$_2$: C, 47.68; H, 3.50; N, 9.27%. Found: C, 47.63; H, 3.32; N, 9.19%. MS (m/z, %): 604 (M$^+$, 11). $^1$H NMR (300 M Hz, CDCl$_3$): δ 3.71 and 3.96 (6 H, 2 s, 2 OCH$_3$), 4.01 (1 H, dd, 3J$_{HH}$=12 Hz, 2J$_{HP}$=21 Hz, CH), 4.32 (1 H, dd, 3J$_{HH}$=12 Hz, 2J$_{HP}$=11 Hz, CH), 7.13-8.04 (m, H, aromatic), 8.16 (1H, d, NH, 3J$_{HH}$=11 Hz, NH). $^{13}$C NMR (125.8 M Hz, CDCl$_3$): δ 35.10 (d, 1J$_{cp}$=137 Hz, P-C$_H$), 53.41 and 53.76 (2 OCH$_3$), 55.16 (d, 2J$_{CP}$=3 Hz, CH), 122.27, 128.32, 131.43, 134.43, 134.30, 139.44, 140.64 (6C, aromatic), 121.63 (d, 2J$_{CP}$=5 Hz, 4 CH$_{ortho}$), 124.15 (s, 2 CH$_{para}$), 126.11 (d, 4J$_{CP}$=8 Hz, 4 CH$_{meta}$), 153.22 (d, 2J$_{CP}$=10 Hz, C$_{ipso}$), 156.16 (d, 2J$_{CP}$=10 Hz, C$_{ipso}$), 168.56 (d, 2J$_{CP}$=7 Hz, C=O), 170.32 (d, 3J$_{CP}$=21 Hz, C=O). $^{31}$P NMR (202.5 MHz, CDCl$_3$): δ 27.08.

Diethyl 2-(dimethoxyphosphoryl)-1-(5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-yl amino) ethanedioate (4c)

Yield: 87%; Yellow powder, m.p.197-199 °C, IR (KBr)(ν$_{max}$, cm$^{-1}$): 3210 (NH), 1742 and 1705 (C=O, ester), Analyses: Calcd. for C$_{16}$H$_{21}$N$_4$O$_9$PS$_2$: C, 37.79; H, 4.16; N, 11.02%. Found: C, 37.65; H, 4.23; N, 10.98 %. MS (m/z, %): 508 (M$^+$, 3). $^1$H NMR (300 M Hz, CDCl$_3$): δ 1.15 and 1.25 (6H, 2t, 3J$_{HH}$=7 Hz, 2CH$_3$), 3.62 and 3.71 (6 H, 2d, 3J$_{HP}$=11 Hz, 2POCH$_3$), 4.22 and
4.43 (4 H, 2q, J_HH = 7 Hz, 2 OCH2), 4.55 (1H, dd, J_HP = 21 Hz, J_HH = 12 Hz, P-CH), 5.01 (1H, dd, J HP = 5 Hz, J_HH = 12 Hz, P-C-CH), 6.98-8.01 (m, H, aromatic), 8.12 (d, 1H, NH, J_HH = 12 Hz). 13C NMR (125.8 MHz, CDCl3): δ: 14.16 and 14.47 (2CH3), 43.41 (d, J_cp = 137 Hz, P-C), 53.01 (d, J_cp = 3 Hz, CH), 54.89 and 56.38 (2d, J_cp = 7 Hz, 2 POCH3), 63.64 and 63.78 (2OCH2), 119.24, 123.45, 127.18, 135.24, 140.73, 142.63 (6C, aromatic), 166.03 (d, J_cp = 5 Hz, C=O), 172.43 (d, J_cp = 21 Hz, C=O). 31P NMR (202.5 MHz, CDCl3): δ: 26.06.

Diethyl 2-(diphenoxyphosphoryl)-1-(5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-yl amino) ethanedioate (4d)

Yield: 90%; Yellow powder, m.p. 211-213 °C, IR (KBr) (νmax, cm⁻¹): 3180 (NH), 1739 and 1707 (C=O, ester), Analyses: Calcd. for C26H25N4O9PS2: C, 49.36; H, 3.98; N, 8.86%. Found: C, 49.23; H, 4.04; N, 8.77%. MS (m/z, %): 632 (M +, 8). 1H NMR (300 MHz, CDCl3): δ: 1.18 and 1.23 (6H, 2 t, J_HH = 7 Hz, 2 CH3), 3.45 and 3.67 and 4.11 (5H, 2m, 2OCH2 and CH), 4.08 (1H, dd, J_HP = 21 Hz, J_HH = 12 Hz, CH), 7.12-8.02 (m, H, aromatic), 8.15 (1H, d, NH, J_HH = 12 Hz). 13C NMR (125.8 MHz, CDCl3): δ: 14.08 and 14.23 (2CH3), 45.90 (d, J_cp = 137 Hz, P-C), 49.04 (d, J_cp = 3 Hz, CH), 62.08 and 63.56 (2OCH2), 119.24, 123.39, 128.43, 133.60, 138.14, 142.84 (6C, aromatic), 120.63 (d, J_cp = 5 Hz, 4 CHortho), 126.15 (s, 2 CHpara), 127.65 (d, J_cp = 8 Hz, 4 CHmeta), 150.22 (d, J_cp = 10 Hz, Cipso), 151.16 (d, J_cp = 10 Hz, Cipso), 160.56 (d, J_cp = 7 Hz, C=O), 170.88 (d, J_cp = 21 Hz, C=O). 31P NMR (202.5 MHz, CDCl3): δ: 27.18.

Results and Discussion

The reaction of DAAD’s 2 with trialkyl(aryl) phosphite 3 in the presence of [5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-amine] 1 leads to dialkyl 2-(dialkoxyphosphoryl)-1-[5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-yl amino]ethanedioate 4 in high yields (Figure 1).

![Figure 1. The reaction of [5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-amine] and DAAD’s in the presence of trialkyl(aryl) phosphate](image)

Products 4a-d were all new compounds and their structures were deduced from their elemental analyses and spectral data. The mass spectrum of compound 4a showed the molecular ion peak at 480. The 1H NMR spectrum of compound 4a displayed two doublets (J_HH = 11 Hz) at 3.76 and 3.81 ppm for two POCH3 groups and two singlets at 3.62 and 3.73 ppm for two methoxycarbonyl groups. Two signals were observed at 4.22 (dd, J_HH = 11 Hz, J HP = 21 Hz) and 5.21 ppm (dd, J_HH = 11 Hz,
$3J_{HP} = 5\text{Hz}$) for two vicinal methine protons. Aromatic protons resonated between 7.02-8.04 ppm. A doublets signal was observed at 8.10 ppm (d, 1H, NH, $3J_{HH} = 12\text{Hz}$) and disappeared by addition of D$_2$O to solution of 4a. The $^{13}$C NMR spectrum of compound 4a showed fourteen distinct resonances in agreement with the proposed structure. The structural assignments made on the basis of the NMR spectra of compound 4a were supported by its IR spectrum, the ester carbonyl groups exhibited strong absorption bands at 1733 cm$^{-1}$. The $^{31}$P NMR spectrum of compound 4a displayed a signal at 26.76 ppm.

The vicinal proton-proton coupling constants can be obtained from the Karplus equation$^{14,15}$. Typically, $J_{\text{gauche}}$ varies between 1.5 and 5 Hz and $J_{\text{anti}}$ between 10 and 14 Hz. Observation of $3J_{HH} = 11\text{Hz}$ for the vicinal protons in compound 4a indicates an anti arrangement for these protons. Since compound 4a possesses two stereogenic centers, two diastereoisomers with anti HCCH arrangements are possible.

The three-bond carbon-phosphorus coupling, $3J_{CP}$, depends on configuration, as expected, transoid couplings being larger than cisoid ones. The observation of $3J_{CP}$ of 21 Hz for the ester C=O group is in agreement with the (2R,3S)- 4 and its mirror image (2S,3R)-4 geometries (Figure 2)$^{16}$. The same diastereomers were observed for compounds 4b-d any traces of the other diastereomer were not detected by the NMR spectra of compounds 4a-d (Figure 2).

![Figure 2. Two enantiomers](image)

A reasonable mechanism for the formation of compound 4a is presented in Figure 3. The initial addition of trialkyl(aryl) phosphite on DAAD’s leads to a dionic intermediate that is protonated by and [5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-amine] to produce the vinyl phosphonium 5. The conjugate addition of anion 6 to cation 5 afforded the phosphate ylide 7 which then hydrolyzes to product 4.

![Figure 3. Suggested mechanism for formation of compound 4](image)
Conclusion
In summary, we report herein that three-component reaction between trialkyl(aryl) phosphites, dialkyl acetylenedicarboxylates and [5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-amine] provides a simple and efficient one pot route for the synthesis of dialkyl 2-(dialkoxyphosphoryl)-1-[5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-yl amino]ethanedioate in good yields.

References