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RESEARCH ARTICLE

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 described[1]. 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 antibacterial[2].

The reaction of trimethyl phosphite and dimethyl acetylenedicarboxylate (DMAD) in the presence of alcohols is reported to produce phosphite ylide derivatives which are stable at low temperatures, but are converted to phosphonate derivatives by warming or by treatment with water[3]. 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 phosphite ylide intermediate[4-12]. In continuation of our works on the reaction between trivalent phosphorus nucleophiles and acetylenic esters in the presence of organic NH, OH, or CH-acids[5-13], 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_3PO_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 ^{o}C, IR (KBr)(ν_{max}, cm^{-1}): 3150 (NH), 1733 and 1705 (C=O, ester), Analyses: Calcd. for $C_{14}H_{17}N_4O_9PS_2$: 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 and3.73 (6 H, 2 s, 2 OCH_3), 3.76 and 3.81 (6 H, 2d ,$^{3}J_{PH}$=11 Hz, 2 $POCH_3$), 4.22 (1H, dd, $^{2}J_{HP}$=21 Hz, $^{3}J_{HH}$=11Hz, P-*C*H), 5.21 (1H, dd, $^{3}J_{HP}$=5 Hz, $^{3}J_{HH}$=11 Hz, P-C-CH),7.02-8.04 (m, H, aromatic), 8.10(d, 1H, NH, $^{3}J_{HH}$=11 Hz). ^{13}C NMR (125.8 M Hz, $CDCl_3$): δ 40.70 (d, $^{1}J_{cp}$=137 Hz, P-*C*), 43.01 (d, $^{2}J_{cp}$=3 Hz, CP), 52.89 and 53.38 (2O*C*H_3), 53.64 and 53.68 (2d, $^{2}J_{cp}$=11Hz, 2$POCH_3$), 123.17, 129.45, 137.38, 139.44, 141.04, 142.64 (6C, aromatic), 167.43 (d, $^{2}J_{CP}$=7 Hz, C=O), 172.88 (d, $^{3}J_{CP}$=21 Hz, C=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ 26.76.

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

Yield: 90%; Yellow powder, m.p.203-205 ^{o}C, IR (KBr)(ν_{max}, cm^{-1}): 3180 (NH), 1731 and 1711 (C=O, ester), Analyses: Calcd. for $C_{24}H_{21}N_4O_9PS_2$: 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 3.71and 3.96 (6 H, 2 s, 2 OCH_3), 4.01 (1 H, dd, $^{3}J_{HH}$ = 12 Hz, $^{2}J_{HP}$ = 21 Hz, CH), 4.32 (1 H, dd, $^{3}J_{HH}$ = 12 Hz, $^{2}J_{HP}$ = 5 Hz, CH), 7.13-8.04 (m, H, aromatic), 8.16 (1H, d, NH, $^{3}J_{HH}$=11Hz, NH).^{13}C NMR (125.8 M Hz, $CDCl_3$): δ 35.10 (d, $^{1}J_{cp}$=137 Hz, P-*C*), 53.41 and 53.76 (2 OCH_3), 55.16 (d, $^{2}J_{CP}$=3 Hz, CH), 122.27, 128.32, 131.43, 134.30, 139.04, 140.64 (6C, aromatic), 121.63 (d, $^{3}J_{CP}$=5 H_Z, 4 CH_{ortho}), 124.15 (s, 2 CH_{para}), 126.11 (d, $^{4}J_{cp}$=8 H_Z, 4 CH_{meta}), 153.22 (d, $^{2}J_{cp}$=10 H_Z, C_{ipso}), 156.16 (d, $^{2}J_{cp}$=10 H_Z, C_{ipso}), 168.56 (d, $^{2}J_{CP}$=7 Hz, C=O), 170.32 (d, $^{3}J_{CP}$=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 ^{o}C, IR (KBr)(ν_{max}, cm^{-1}): 3210 (NH), 1742 and 1705 (C=O, ester), Analyses: Calcd. for $C_{16}H_{21}N_4O_9PS_2$: 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, $^{3}J_{HH}$=7 Hz, 2CH_3), 3.62 and 3.71 (6 H, 2d, $^{3}J_{HP}$ = 11 Hz, 2 $POCH_3$), 4.22 and

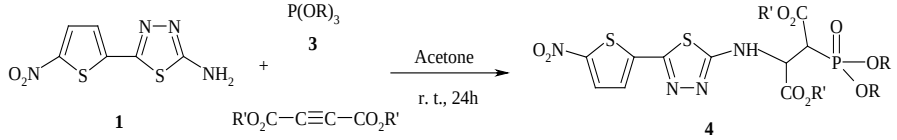
4.43 (4 H, 2q, $^3J_{HH}$=7 Hz , 2 OCH_2), 4.55(1H, dd, $^2J_{HP}$ = 21 Hz, $^3J_{HH}$ = 12 Hz, P-CH), 5.01(1H, dd, $^3J_{HP}$ = 5 Hz, $^3J_{HH}$ = 12Hz, P-C-CH), 6.98-8.01(m, H, aromatic), 8.12 (d, 1H, NH, $^3J_{HH}$=12Hz). ^{13}C NMR (125.8 M Hz, $CDCl_3$): δ : 14.16 and 14.47 ($2CH_3$), 43.41 (d, $^1J_{cp}$ = 137 Hz, P-*C*), 53.01 (d, $^2J_{cp}$ = 3 Hz, CH), 54.89 and 56.38 (2d, $^2J_{cp}$=7 Hz, 2 $POCH_3$), 63.64 and 63.78 ($2OCH_2$), 119.24, 123.45, 127.18, 135.24, 140.73, 142.63 (6C, aromatic), 166.03(d, $^2J_{CP}$=5 Hz, C=O), 172.43(d, $^3J_{CP}$ = 21 Hz, C=O).^{31}P NMR (202.5 MHz, $CDCl_3$): 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 ^{o}C, IR (KBr)(ν_{max}, cm^{-1}): 3180 (NH), 1739 and 1707 (C=O, ester), Analyses: Calcd. for $C_{26}H_{25}N_4O_9PS_2$: 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). ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.18 and 1.23 (6H, 2 t , $^3J_{HH}$ = 7 Hz, 2 CH_3), 3.45 and 3.67 and 4.11(5H, 2m, $2OCH_2$ and CH), 4.08 (1 H, dd, $^2J_{HP}$ = 21 Hz, $^3J_{HH}$ = 12 Hz, CH), 7.12-8.02 (m, H, aromatic), 8.15 (1H, d, NH, $^3J_{HH}$=12 Hz). ^{13}C NMR (125.8 M Hz, $CDCl_3$): δ 14.08 and 14.23 (2 CH_3), 45.90 (d, $^1J_{cp}$ = 137 Hz, P-*C*), 49.04 (d, $^2J_{cp}$ = 3 Hz, CH), 62.08 and 63.56 (2 OCH_2), 119.24, 123.39, 128.43, 133.60, 138.14, 142.84 (6C, aromatic), 120.63 (d, $^3J_{CP}$ = 5 Hz, 4 CH_{ortho}), 126.15 (s, 2 CH_{para}), 127.65 (d, $^4J_{cp}$ = 8 Hz, 4 CH_{meta}), 150.22 (d, $^2J_{cp}$ = 10 Hz, C_{ipso}), 151.16 (d, $^2J_{cp}$ = 10 Hz, C_{ipso}), 160.56 (d, $^2J_{CP}$ = 7 Hz, C=O), 170.88 (d, $^3J_{CP}$ = 21 Hz, C=O). ^{31}P NMR (202.5 MHz, $CDCl_3$): 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).



4	R	R'	Yield*
a	Me	Me	91
b	Ph	Me	90
c	Me	Et	87
d	Ph	Et	90

* Isolated yields

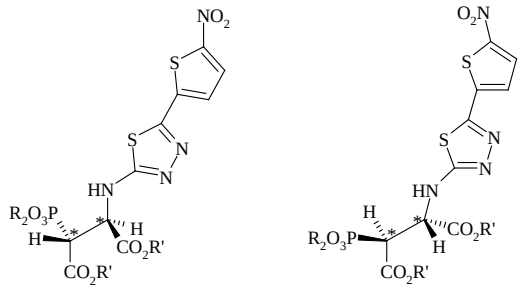
Figure 1. The reaction of [5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-amine] and DAAD's in the presence of trialkyl(aryl) phosphate

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 ^{1}H NMR spectrum of compound **4a** displayed two doublets ($^3J_{HP}$ = 11 Hz) at 3.76 and 3.81 ppm for two $POCH_3$ groups and two singlets at 3.62 and 3.73 ppm for two methoxycarbonyl groups. Two signals were observed at 4.22 (dd, $^3J_{HH}$ =11 Hz, $^2J_{HP}$ = 21 Hz) and 5.21 ppm (dd, $^3J_{HH}$ = 11Hz,

$^3J_{HP}$ = 5Hz) 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, $^3J_{HH}$ = 12Hz) and disappeared by addition of D_2O 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_{gauche} varies between 1.5 and 5 H_Z and J_{anti} between 10 and 14 Hz. Observation of $^3J_{HH}$ = 11Hz 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.

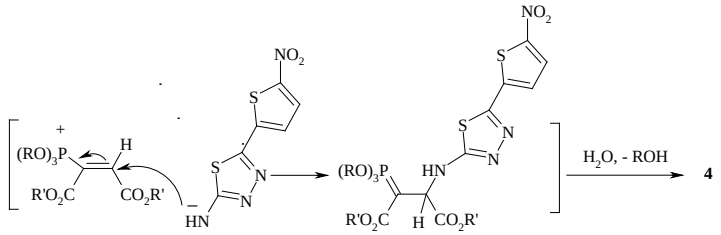
The three-bond carbon-phosphorus coupling, $^3J_{CP}$, depends on configuration, as expected, transoid couplings being larger than cisoid ones. The observation of $^3J_{CP}$ of 21 Hz for the ester C=O group is in agreement with the (*2R,3S*)- **4** and its mirror image (*2S,3R*)- **4** geometries (Figure 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).



(2R,3S) - 4 **(2S,3R)-4**

Figure 2. Two enantiomers

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 diionic 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 phosphite ylide **7** which then hydrolyzes to product **4**.



5 **6** **7**

Figure 3. Suggested mechanism for formation of compound **4**

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.

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