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One-pot synthesis of stable phosphonium ylides using 2-aminothiophenol

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Abstract—Protonation of reactive 1:1 intermediates produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylate by 2-aminothiophenol leads to vinylphosphonium salts, which undergo Michael addition with thiophenolate anion to produce highly functionalized phosphonium ylides in excellent yields.

1. Introduction

Phosphorus ylides are reactive systems, which take part in many reactions of value in organic synthesis.[1–6] Several methods have been developed for the preparation of phosphorus ylides. These ylides are usually prepared by treatment of a phosphonium salt with a base and the salts are usually prepared from the phosphine and an alkyl halide.[2] Phosphonium salts can also prepared by Michael addition of phosphine to activated olefins.[2] Michael addition of phosphorus(III) compounds such as triphenylphosphine to acetylenic esters leads to reactive 1,3-dipolar intermediate betaines which are not detected even at low temperature.[6] These unstable species can be trapped by a protic reagent, ZH, such as methanol, amide, imide, etc. to produce various compounds e.g. ylides.

We wish to report an efficient synthetic route to sterically congested phosphorus ylides **3** using triphenylphosphine, dialkyl acetylenedicarboxylates **1** and 2-aminothiophenol **2**.

We found that isolated products from the reactions of 2-aminothiophenol, triphenylphosphine and dimethyl acetylenedicarboxylate (DMAD) or diethyl acetylenedicarboxylate (DEAD) are phosphorus ylides but the products obtained from the reactions of 2-aminothiophenol, triphenylphosphine and diisopropylacetylenedicarboxylate (DIAD) or ditert-butyl acetylenedicarboxylate (DTAD) are not phosphorus ylides. They were identified as derivatives of 1,4-benzothiazine[7–8] and at the end of the reaction the unreacted triphenylphosphine was recovered.

2. Results and discussion

On the basis of the well established chemistry of trivalent phosphorus nucleophiles[9–16] it is reasonable to assume that phosphorus ylides **4** result from the initial addition of triphenylphosphine to the acetylenic ester and a concomitant protonation of the 1:1 adduct by aminothiophenol. Then the positively charged ion is attacked by the thiophenoxy anion of the aminothiophenol to form phosphorane **4** (Scheme 1). The alkoxycarbonylmethylen-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazin derivative **6** may be considered as a product of a lactamization reaction (Scheme 2). Such an addition–cyclization product apparently results from the initial Michael addition of 2-aminothiophenol to the DIAD and DTAD (see Scheme 2). The reason for such a difference between products from DMAD or DEAD and products from the reaction mixture of DIAD or DTAD is not clear to us, but steric hindrance of DIAD and DTAD might play an important role in these reactions. Compounds **4a** and **4b** are stable solid powders whose structures are fully supported by elemental analyses, ^{1}H, ^{13}C NMR, ^{31}P NMR and IR spectral data. The ^{1}H NMR and ^{13}C NMR spectral data of phosphoranes **4a**–**b** exhibit a mixture of two rotational isomers. The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group and rotation about the partial double bond in **4**-(*E*) and **4**-(*Z*) geometrical isomer is slow on the NMR time scale at ambient temperature. The rotamer forms in phosphorus ylides have been previously established and reported in literatures.[17,18] The ^{1}H NMR spectrum of **4a**

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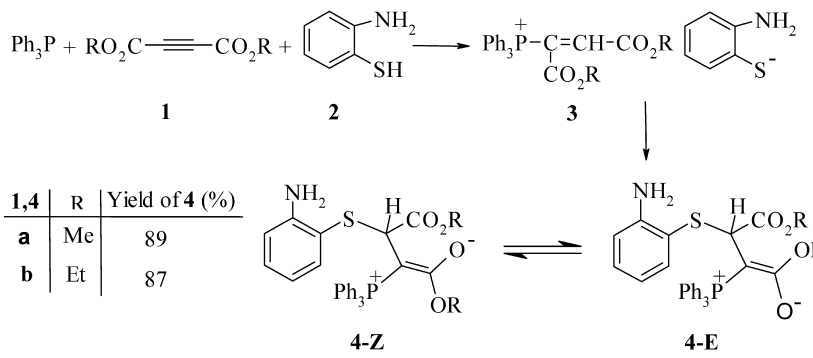
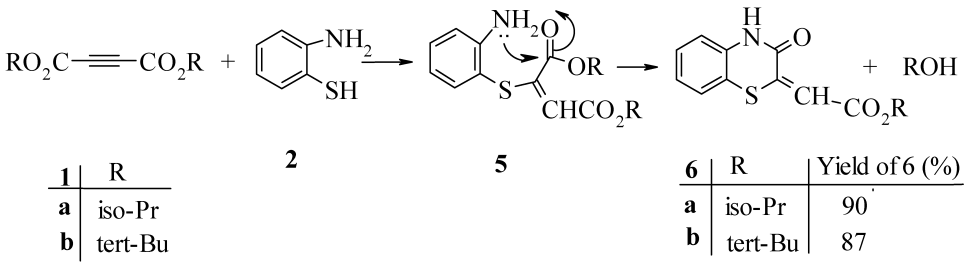


Scheme 1.



Scheme 2.

exhibited two single sharp lines at 3.21 and 3.72 ppm for methoxy groups in the *Z* rotamer and two single sharp resonances at 3.66 and 3.73 ppm for methoxy groups in the *E* rotamer. The shift at 3.21 of methyl group of the *Z* rotamer is shielded, due to the anisotropic effect of phenyl groups of triphenylphosphine. Also the ^{1}H NMR spectrum of **4a** displayed signals for methine protons as two sets of doublets at δ 4.03 and 4.07 ppm, respectively ($^{3}J_{HP}$=16.9 Hz and 16.6 Hz), in agreement with the *E* and *Z* rotamers. The ^{1}H NMR spectrum of **4b** is similar to that of **4a** except for the ester group, which exhibits characteristic signals with appropriate chemical shifts. Further evidence was obtained from ^{31}P NMR spectra in addition to the evidence for two rotamers of **4a** and **4b** from the ^{1}H and ^{13}C NMR data.

In each ^{31}P NMR spectrum of **4a** and **4b** two siglets ^{31}P signals were observed at about 24 and 29 ppm (downfield from 85% H_3PO_4) for the *Z* and *E* rotamers, respectively. These shifts are similar to those observed for stable phosphorus ylides (Ph_3P=C).[19–21]

The ^{1}H NMR of **6a** displayed a signal as doublet at δ 1.41 ppm ($^{3}J_{HH}$=6.2 Hz) for methyl groups of isopropyl group and a signal as septet at δ 5.23 ppm ($^{3}J_{HH}$=6.2 Hz) for methine proton of isopropyl group, along with a multiplet in the aromatic region as well as a single sharp resonance at δ 7.27 ppm and a fairly broad peak at δ 10.97 ppm for olefinic proton and NH groups, respectively. The noise-decoupled ^{13}C NMR spectrum of **6a** showed 12 distinct resonances in agreement with the benzothiazine structure. The ^{1}H and ^{13}C NMR chemical shifts of **6b** are similar to those of **6a**, except for the ester moiety, which exhibited characteristic resonance pattern with appropriate chemical shift (see Section 3).

3. Experimental

3.1. General

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. IR spectra were measured on a Perkin–Elmer 783 Infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured with BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Triphenylphosphine and acetylenic esters **1** and 2-aminothiophenol **2** were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

3.1.1. Dimethyl 2-(2-amino thiophenoxy)-3-triphenylphosphoranylidene)-butanedioate 4a. To a magnetically stirred solution of 2-aminothiophenol (2 mmol) and triphenylphosphine (2 mmol) in ethyl acetate (5 mL) was added dropwise a solution of dimethyl acetylenedicarboxylate (2 mmol, 0.28 g) in ethyl acetate (2 mL) at −5°C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 1 h.

The precipitate was filtered off and washed with cold ethyl acetate and the product **4a** was obtained as white powder (0.94 g, mp 149°C, yield 89%); IR (KBr) (ν_{max}, cm^{-1}): 3440, 3320 (NH_2), 1735 and 1625 (2C=O); MS, (*m/z*, %): 405 (M−C_6H_4NS, 41), 262 (PPh_3, 100), 183 ($C_{12}H_8P$, 43). Anal. calcd for $C_{30}H_{28}NO_4SP$ (529.60); C, 68.04; H, 5.33; N, 2.64%. Found: C, 68.0; H, 5.4; N, 2.7%.

Major rotamer (*Z*)-**4a** (57%). ^{1}H NMR, δ: 3.21, 3.72 (6H,

2s, 2O–CH_3), 4.03 (1H, d, $^3J_{HP}$=16.9 Hz, P=C–CH), 4.55 (4H, br s, $2NH_2$),† 6.40 (1H, dd, $^3J_{HH}$=7.4 and 7.3 Hz, CH_{para} to NH_2),† 6.61 (1H, d, $^3J_{HH}$=7.9 Hz, CH_{ortho} to NH_2),† 7.00 (1H, dd, $^3J_{HH}$=7.9 and 7.4 Hz, CH_{meta} to NH_2),† 7.02 (1H, d, $^3J_{HH}$=7.3 Hz, CH_{ortho} to S–CH),† 7.45–7.65 (30H, m, 6 C_6H_5).† ^{13}C NMR, δ: 42.39 (d, $^1J_{CP}$=128.2 Hz, P=C), 48.83 and 52.22 (2s, 2O–CH_3), 54.75 (d, $^2J_{PC}$=13.6 Hz, P=C–CH), 114.32, 117.12, (4CH), 126.63 (d, $^1J_{PC}$=82.9 Hz, C_{ipso}), 128.29 (d, $^2J_{PC}$=11.5 Hz, C_{meta} of C_6H_5),† 131.65 (CH_{para} of C_6H_5),† 133.59 (d, $^3J_{PC}$=9.8 Hz, CH_{ortho} of C_6H_5),† 137.24 (C–NH_2 of C_6H_4), 149.40 (C–S of C_6H_4),† 170.18 (d, $^2J_{PC}$=16.2 Hz, C=O), 173.18 (d, $^3J_{PC}$=17 Hz, C=O ester). ^{31}P NMR, δ: 24.45 (s, Ph_3P=C).

Minor rotamer (*E*)-**4a** (43%). ^{1}H NMR, δ: 3.66 and 3.72 (6H, 2s, 2O–CH_3), 4.07 (1H, d, $^3J_{HP}$=16.6 Hz, P=C–CH). ^{13}C NMR, δ: 43.73 (d, $^1J_{pc}$=134.6 Hz, P=C), 50.02 and 52.23 (2s, 2O–CH_3), 54.18 (d, $^2J_{PC}$=13.4 Hz, P=C–CH), 114.33, 117.14 (4CH), 125.9 (d, $^1J_{PC}$=82.2 Hz, C_{ipso}), 137.39 (C–NH_2 of C_6H_4), 168.48 (d, $^2J_{PC}$=12.1 Hz, C=O ester), 172.94 (d, $^3J_{PC}$=17.5 Hz, C=O ester). ^{31}P NMR, δ: 24.49 (s, Ph_3P=C).

3.1.2. Diethyl 2-(2-amino thiophenoxy)-3-triphenylphosphoranylidene)-butanedioate 4b. White–yellow powder (0.69 g, mp 152°C, yield 88.5%); IR (KBr) (ν_{max}, cm^{-1}): 3410, 3320 (NH_2), 1730, 1605 (2C=O); MS, (*m*/*z*, %): 433 (M−C_6H_6NS, 40), 262 (PPh_3, 100), 183 ($C_{12}H_8P$, 45). Anal. calcd for $C_{32}H_{32}NO_4SP$ (557.65); C, 68.92; H, 5.78; N, 2.51%. Found: C, 68.9; H, 5.8; N, 2.5%.

Major rotamer (*Z*)-**4b** (57%). ^{1}H NMR, δ: 0.51 (3H, t, $^3J_{HH}$=6.2 Hz, CH_3–CH_2O), 1.30 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3–CH_2O), 3.76 and 4.10 (4H, m, 2O–CH_2), 3.95 (1H, d, $^3J_{HP}$=18.4 Hz, P=C–CH), 4.56 (4H, br s, $2NH_2$),† 6.41 (1H, dd, $^3J_{HH}$=6.6 and 6.9 Hz, CH_{para} to NH_2),† 6.61 (1H, d, $^3J_{HH}$=7.9 Hz, CH_{ortho} to NH_2),† 7.00 (1H, dd, $^3J_{HH}$=6.6 and 7.9 Hz, CH_{meta} to NH_2),† 7.03 (1H, d, $^3J_{HH}$=6.9 Hz, CH_{ortho} to S–CH),† 7.49–7.70 (30H, m, 6 C_6H_5).† ^{13}C NMR, δ: 13.69 and 13.92 (2s, $2CH_3$), 42.12 (d, $^1J_{PC}$=129.5 Hz, P=C), 54.88 (d, $^2J_{PC}$=14 Hz, P=C–CH), 57.36 and 61.03 (2s, 2O–CH_2), 114.29, 117.07 (4CH), 126.84 (d, $^1J_{PC}$=89 Hz, C_{ipso}), 128.33 (d, $^3J_{PC}$=12.8 Hz, CH_{meta}, of C_6H_5),† 131.58 (C_{para} of C_6H_5),† 133.65 (d, $^2J_{PC}$=9.6 Hz, C_{ortho} of C_6H_5),† 137.21 (C–NH_2 of C_6H_4), 149.41 (C–S of C_6H_4),† 168.42 (d, $^2J_{PC}$=15 Hz, C=O), 172.40 (d, $^3J_{PC}$=5.2 Hz, C=O). ^{31}P NMR, δ: 29.56 (s, Ph_3P=C).

Minor rotamer (*E*)-**4b** (43%). 1.26 (3H, t, $^3J_{HH}$=6.9 Hz, CH_3–CH_2O), 1.34 (3H, t, $^3J_{HH}$=6.6 Hz, CH_3–CH_2O), 3.62 and 4.19 (4H, m, 2O–CH_2), 3.94 (1H, d, $^3J_{HP}$=18.2 Hz, P=C–CH). ^{13}C NMR, δ: 13.93 and 14.74 (2s, $2CH_3$), 43.84 (d, $^1J_{PC}$=137 Hz, P=C), 54.50 (d, $^2J_{PC}$=13.8 Hz, P–C–CH), 58.11and 61.05 (2s, 2O–CH_2), 114.31, 117.12 (4CH), 126.15 (d, $^1J_{PC}$=85 Hz, C_{ipso}), 137.43 (C–NH_2 of C_6H_4), 169.83 (d, $^2J_{PC}$=17 Hz, C=O), 172.69 (d, $^3J_{PC}$=5.5 Hz, C=O). ^{31}P NMR, δ: 29.60 (s, Ph_3P=C).

† For two rotamers.

3.1.3. Isopropoxycarbonylmethylene-3,4-dihydro-3-oxo-2H-benzo-1,4-thiazin 6a. To a magnetically stirred solution of 2-aminothiophenol (2 mmol) in 40% ethyl acetate/hexane (5 mL) was added dropwise a solution of dimethyl acetylenedicarboxylate (2 mmol, 0.282 g) in 40% ethyl acetate/hexane (2 mL) at −10°C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for about 3 h. The precipitate was filtered off and washed with cold 40% ethyl acetate/hexane and the product **6** was obtained as yellow powder.

Data for **6a**. Yellow powder (0.47 g, mp 215°C, yield 90%); IR (KBr) (ν_{max}, cm^{-1}): 3190 (NH), 1695, 1670 (2C=O); MS, (*m*/*z*, %): 263 (M, 70), 221 (M-Propene, 30), 204 (M-OPr^i, 35), 177 ($MH^+-CO_2Pr^i$, 100). Anal. calcd for $C_{13}H_{13}NO_3S$ (263.32); C, 59.30; H, 4.98; N, 5.32%. Found: C, 59.4; H, 5.0; N, 5.2%. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.41 (6H, d, *J*=6.2 Hz, $CHMe_2$), 5.23 (1H, septet, *J*=6.2 Hz, O–CH), 7.27 (1H, s, CH=), 7.15–7.36 (4H, m, $4CH_{arom}$), 10.97 (1H, br s, NH). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=21.65 ($CHMe_2$), 68.19 (O–^{13}CHMe$_2$), 116.31 (CH=), 116.60 (C=), 117.12, 123.88, 125.03 and 126.80 ($4CH_{arom}$), 131.67 and 139.52 ($2C_{arom}$), 156.63 and 165.65 (2C=O).

Data for **6b**. Yellow powder (0.48 g, mp 216°C, yield 87%); IR (KBr) (ν_{max}, cm^{-1}): 3180 (NH), 1680 and 1650 (2C=O); MS, (*m*/*z*, %): 277 (MH^+, 75), 221 (M-isobutene, 30), 204 (M-O–Bu^t, 30), 175 ($M^+-CO_2Bu^t$, 40); $C_{14}H_{15}NO_3S$ (277.34); C, 60.63; H, 5.45; N, 5.05%. Found: C, 60.64; H, 5.5; N, 5.0%. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.63 (9H, s, CMe_3), 7.27 (1H, s, CH=), 7.11–7.32 (4H, m, $4CH_{arom}$), 11.21 (1H, br s, NH). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=27.96 (CMe_3), 81.28 (O–*C*Me$_3$), 116.68 (C=), 117.17 (CH=), 117.73, 123.83, 124.93 and 126.70 ($4CH_{arom}$), 131.66 and 138.58 (2C), 156.87 and 165.64 (2C=O).

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