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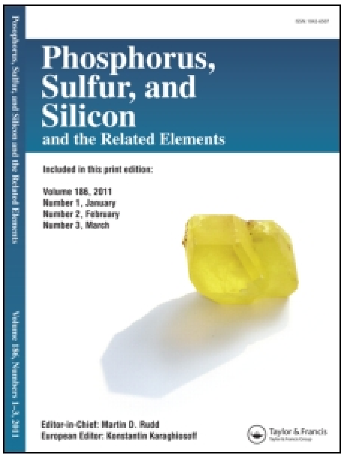

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One-Pot Synthesis of Dialkyl Succinates Containing an α -Amino Group and a β-Ylide Moiety Using Electron-Deficient Acetylenic Esters

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One-Pot Synthesis of Dialkyl Succinates Containing an α-Amino Group and a β-Ylide Moiety Using Electron-Deficient Acetylenic Esters

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The new succinic esters containing an α-amino group and a β-ylide moiety have been prepared in excellent yields by the three-components approach starting with the commercially available activated acetylenic esters and 2-aminothiazole or 4,5-dihydrothiazole-2-thiol in the presence of trivalent phosphine.

Keywords 2-Aminothiazole; 4,5-dihydrothiazole-2-thiol; acetylenic ester; succinic esters

INTRODUCTION

The use of substituted succinic acid derivatives as peptidomimetics and heterocyclic compounds such as 2-aminothiazole derivatives, which are a new class of an agonist allosteric enhancer (AE) of the human body, have found a number of applications in medicinal chemistry.[1–6] The fused thiazole ring with other aromatic rings has shown chemiluminescence by the reaction with hydrogen peroxide in the presence of potassium hexacyanoferrate in an alkaline medium.[7] With regard to the importance of these compounds, we wish to report here an efficient and simple synthetic strategy leading to novel dialkyl succinates containing an α-amino group and a β-phosphorus ylide moiety **3a–c** and **4a–b**.

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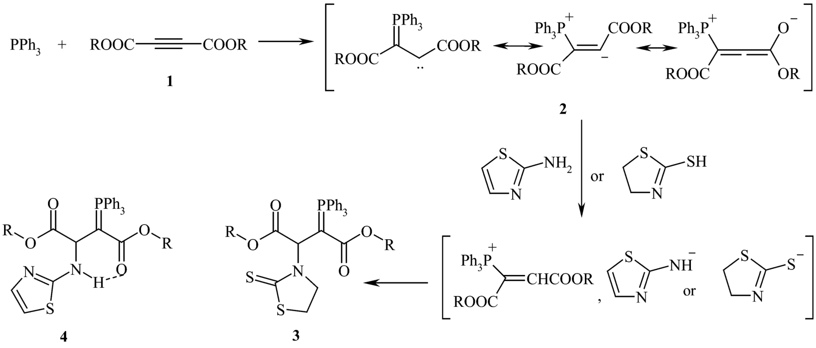
RESULTS AND DISCUSSIONS

It is known that the reaction of activated acetylenic esters and trivalent phosphine produced the carbene-ylide intermediate **2**, which is sufficiently stabilized by resonance.[8,9] Thus compounds **3a–c** and **4a–b** apparently are obtained from an initial addition of triphenylphosphine as a good nucleophile[10–14] to dialkyl acetylenedicarboxylate and a concomitant protonation of the carbene-ylide intermediate by the NH or SH-acid. The positively charged ion is attacked by the nitrogen of the conjugated base to form compounds **3** and **4** (Scheme 1).

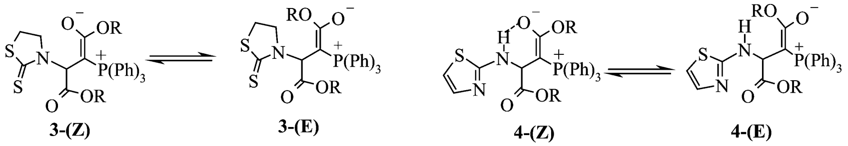


4	R	Yield (%)
a	Me	98
b	Et	88

3	R	Yield (%)
a	Me	90
b	Et	90
c	i-Pr	95

SCHEME 1

The structures of compounds **3a–c** and **4a–b** were deduced from their elemental analyses and their IR, high-field ^{1}H and ^{13}C NMR spectra (Table I). The ^{1}H NMR and ^{13}C NMR spectra of the new succinate esters **3a–c** and **4a–b** exhibited a mixture of two rotational isomers. The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group and the rotation about the partial double bond in **3**-(E), **3**-(Z) and **4**-(E), and **4**-(Z) geometrical isomer pairs is low on the NMR timescale at an ambient temperature (Scheme 2). Rotamer forms in phosphoranes have been previously established and reported in the literature.[15–17]



SCHEME 2

TABLE I Proton and Carbon-13 NMR Data for Major Isomer of Compounds 3a–c and 4a–b

Compound	$^1H/^{13}C$	δ(ppm) ($CDCl_3$-Me_4Si)
3a	$^1H/^{13}C$	Major isomer, **3a**-(Z) (65%), 3.18 and 3.83 (6H, 2s, 2 OCH_3), 3.31–3.43 (2H, m, NCH_2), 4.41–4.50 (2H, m, SCH_2), 5.47 (1H, d, $^3J_{PH}$ 17.5 Hz, P=C–CH), 7.54–7.72 (30H, m, arom).* ^{13}C NMR: δ 27.86 (NCH_2), 41.11 (d, $^1J_{PC}$ 126.3 Hz, P=C), 48.97 and 52.28 (2 OCH_3), 61.07 (d, $^2J_{PC}$17.8 Hz, P=C–CH), 126.02 (d, $^1J_{PC}$ 92.1 Hz, C^{ipso}), 128.83 (d, $^3J_{PC}$ 12.3 Hz, C^{meta}), 132.05 (d, $^4J_{PC}$ 2.0 Hz C^{para}), 133.16 (d, $^2J_{PC}$ 9.7 Hz, C^{ortho}), 165.05 (2C),* 169.53 (d, ^{2} J_{PC} 12.8 Hz, 2C=O),* 170.75 (d, $^3J_{PC}$ 12.5 Hz, 2C=O),* 194.84 (C=S). Minor isomer, **3a**-(E) (35%),^1H NMR: δ 3.19-3.26 (2H, m, NCH_2), 3.60 and 3.79 (6H, 2s, 2 OCH_3), 4.59–4.65 (2H, m, SCH_2), 5.45 (1H, d, $^3J_{PH}$ 18.9 Hz, P=C–CH). ^{13}C NMR: δ 27.69 (NCH_2), 42.17 (d, $^1J_{PC}$ 134.5 Hz, P=C), 49.93 and 52.04 (2 OCH_3), 60.65 (d, $^2J_{PC}$ 18.5 Hz, P=C–CH), 125.36 (d, $^1J_{PC}$ 92.3 Hz, C^{ipso}), 128.23 (d, $^3J_{PC}$12.2 Hz, C^{meta}), 131.68 (d, $^4J_{PC}$ 2.1 Hz C^{para}), 131.78 (d, $^2J_{PC}$ 9.8 Hz, C^{ortho}), 194.95 (C=S).
3b	$^1H/^{13}C$	Major isomer, **3b**-(Z) (68%), ^1H NMR: δ 0.52 (3H, t, $^3J_{HH}$7.0 Hz, CH_3), 1.37 (3H, t, $^3J_{HH}$ 7.3 Hz, CH_3), 3.21–4.66 (16 H, m, 8 CH_2).* ^{13}C NMR: δ 13.78 and 14.17 (2CH_3), 57.80 and 61.16 (2 OCH_2).[a]
3c	$^1H/^{13}C$	Major isomer, **3c**-(Z) (74%), ^1H NMR: δ 0.48 (3 H, d, $^3J_{HH}$ 5.7 Hz, CH_3), 0.75 (3 H, d, $^3J_{HH}$ 5.9 Hz, CH_3), 1.34 (3 H, d, $^3J_{HH}$5.9 Hz, CH_3), 1.37 (3 H, d, $^3J_{HH}$6.2 Hz, CH_3), 4.76–4.80 (1H, m, CH), 5.12–5.17 (1H, m, CH).^{13}C NMR: δ 21.22, 21.47, 21. 82 and 22.03 (4 CH_3), 64.64 and 68.46 (2CH).[a]
4a	$^1H/^{13}C$	Major isomer, **4a**-(Z) (63%), ^1H NMR: δ 3.19 and 3.76 (6H, 2s, 2 OCH_3), 4.55 (1H, dd, $^3J_{PH}$ 15.2 Hz,$^3J_{HH}$ 6.5 Hz, P=C–CH), 6.29 (1H, br. d,$^3J_{HH}$ 7.2 Hz, NH), 6.41–7.76 (34H, m, arom).* ^{13}C NMR: δ 42.71 (d, $^1J_{PC}$ 126.7 Hz, P=C), 48.75 and 52.03 (2 OCH_3), 57.43 (d, $^2J_{PC}$ 17.8 Hz, P=C–CH),* 106.06 (2CH),* 126.40 (d, $^1J_{PC}$ 91.6 Hz, C^{ipso}), 128.31 (d, $^3J_{PC}$ 13.6 Hz, C^{meta}), 131.64 (C^{para}), 133.53 (d, $^2J_{PC}$ 9.9 Hz, C^{ortho}), 138.37 (CH), 165.09 (2C),* 169.75 (d, $^2J_{PC}$ 12.8 Hz, 2C=O),* 173.45 (d, $^3J_{PC}$ 7.9 Hz, 2C=O).* Minor isomer, **4a**-(E) (37%),^1H NMR: δ 3.65 and 3.74 (6H, 2s, 2 OCH_3), 4.39 (1H, dd, $^3J_{PH}$ 16.7 Hz,$^3J_{HH}$ 7.2 Hz, P=C–CH), 6.85 (1H, br. d,$^3J_{HH}$ 6.5 Hz, NH). ^{13}C NMR: δ 44.00 (d, $^1J_{PC}$ 135.4 Hz, P=C), 49.89 and 51.95 (2 OCH_3), 126.08 (d, $^1J_{PC}$ 94.3 Hz, C^{ipso}), 128.47 (d, $^3J_{PC}$ 12.6 Hz, C^{meta}), 132.16 (C^{para}), 132.80 (d, $^2J_{PC}$ 10.3 Hz, C^{ortho}), 138.40 (CH).
4b	$^1H/^{13}C$	Major isomer, **4b**-(Z) (66%), ^1H NMR: δ 0.50 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_3), 1.29 (3H, t, $^3J_{HH}$ 6.9 Hz, CH_3), 3.74–4.34 (8 H, m, 4 CH_2).* ^{13}C NMR: δ 14.02 and 14.11 (2CH_3), 57.47 and 60.92 (2 OCH_2).[a]

*For two rotamers.

[a] We have listed all the chemical shifts due to compounds **3a** and **4a** but for compounds **3b–c** and **4b**, Only new signals from the esters groups in the major isomer of these compounds are listed.

The ^1H NMR spectrum of **3a** showed four sharp lines ($\delta = 3.18, 3.19, 3.26$, and 3.83 ppm) due to methoxy protons along with signals for methine protons at $\delta = 5.47$ and 5.45 ppm, which appear as two doublets ($^3J_{PH}$ 17.5 Hz) and $^3J_{PH}$ 18.9 Hz, respectively), for the major and minor geometrical isomers and four multiplet signals at $\delta = 3.19$–3.43 and 4.41–4.65 ppm for protons of NCH_2 and SCH_2 groups in the two rotamers, respectively. The aromatic region appeared as a multiplet at δ 7.54–7.72 ppm. The ^{13}C NMR spectrum of **3a** displayed 23 distinct resonances in agreement with the mixture of two rotamers. Although the presence of the ^{31}P nucleus complicates both the ^1H and ^{13}C NMR spectra of **3a**, it helps in the assignment of signals by long-range spin–spin couplings with ^1H and ^{13}C nuclei. The ^1H and ^{13}C NMR spectra of **3b** are similar to those of **3a**, except for the signals from the ester groups, which appear as characteristic resonance lines with the corresponding chemical shifts (see Table I).

The ^1H and ^{13}C NMR spectroscopic data for compounds **4a–b** are also consistent with the presence of two geometrical isomers (see Table I). The structural assignments made for phosphoranes **3a–c** and **4a–b** on the basis of the ^1H and ^{13}C NMR spectra were also supported by their IR spectra. In the IR spectra of **3a–c**, three absorption bands at 1770–1628 cm^{-1} were detected due to the CO and CS groups, respectively. The IR spectra of compounds **4a** and **4b** are similar to those of compounds **3a–c**, except for the absorption band from the NH group, which appears at 3200–3280 cm^{-1}, and no CS group was detected. Of special interest is the ester absorption at 1660–1628 cm^{-1} for these compounds. Conjugation with the negative charge accounts for the reduction of the wave numbers of the carbonyl absorption bands.

EXPERIMENTAL

Dialkyl acetylenedicarboxylats, 2-aminothiazole, and 4,5-dihydrothiazole-2-thiol were obtained from Fluka and were used without further purification. Melting points were obtained on an Electrothermal 9100 melting point apparatus and are uncorrected. Elemental analyses for C, H, and N were performed by the Iranian Research Institute of Petroleum Industry using a Heracus CHN-O-Rapid analyzer. IR spectra were measured on a Perkin-Elmer 783 Infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively.

Dimethyl-2-(thiazol-2-ylamino)-3-triphenylphosphoranylidene) Succinate 3a

At ambient temperature, dimethyl acetylenedicarboxylate (0.24 mL, 2 mmol) was added dropwise to a stirred solution of triphenylphosphine

(0.53 g, 2 mmol) and 4,5-dihydrothiazole-2-thiol (0.23 g, 2 mmol) in ethyl acetate (6 mL). After the addition was complete (approximately 5 min), the mixture was stirred for an additional 1 h and was subsequently filtered. The solid collected in the filter was washed thoroughly with ethyl acetate to give a pale yellow powder. (0.95 g, m.p. 154–155°C. yield 90%); IR (KBr) (ν_{max}, cm^{-1}): 1765 and 1648 (C=O). Anal. calcd. for $C_{27}H_{26}NSO_4P$ (523.61): C, 61.93; H, 5.00; N, 2.68%. Found: C, 61.5; H, 5.0; N, 2.4%

Diethyl-2-(thiazol-2-ylamino)-3-triphenylphosphoranylidene) Succinate 3b

(1.0 g, pale yellow powder, m.p. 130–132°C, yield 90%); IR (KBr) (ν_{max}, cm^{-1}): 1760 and 1642 (C=O). Anal. calcd. for $C_{29}H_{30}NO_4PS$ (551.66): C, 63.14; H, 5.48; N, 2.54%. Found: C, 62.8; H, 5.6; N, 2.4%

Diisopropyl-2-(thiazol-2-ylamino)-3-triphenylphosphoranylidene) Succinate 3c

(1.1 g, pale yellow powder, m.p. 200–201°C. yield 95%); IR (KBr) (ν_{max}, cm^{-1}): 1770 and 1660 (C=O). Anal. calcd. for $C_{32}H_{34}NO_4PS$ (591.73): C, 66.30; H, 5.91; N, 2.42%. Found: C, 66.4; H, 5.8; N, 2.50%.

Dimethyl-2-(2-thioxo-thiazolidin-3-yl)-3-triphenylphosphoranylidene) Succinate 4a

(1.1 g, pale brown powder, m.p. 160–162°C, yield 98%); IR (KBr) (ν_{max}, cm^{-1}): 3405 (NH), 1760 and 1638 (C=O). Anal. calcd. for $C_{27}H_{25}N_2O_4PS$ (504.55): C, 64.28; H, 4.99; N, 5.55%. Found: C, 65.0; H, 5.0; N, 5.70%.

Diethyl-2-(2-thioxo-thiazolidin-3-yl)-3-triphenylphosphoranylidene) Succinate 4b

(1.0 g, pale brown powder, m.p. 155–157°C, yield 88%); IR (KBr) (ν_{max}, cm^{-1}): 3408 (NH), 1742 and 1628 (C=O). Anal. calcd. for $C_{29}H_{29}N_2O_4PS$ (532.60): C, 65.40; H, 5.49; N, 5.26%. Found: C, 65.1; H,5.5; N, 5.1%.

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