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ORIGINAL ARTICLE

Chemoselective entry to 5-mercaptotriazoles by condensation of acetylenic esters with triphenylphosphine

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Triphenylphosphine

Abstract A new kind of 1,2,4-triazol derivatives containing ylide moiety were designed and synthesized. The reaction is performed by condensation of dialkyl acetylenedicarboxylate with 5-aryl-2H-1,2,4-triazol-3-thiol in the presence of Ph_3P. In these cases, the reactions take place on the sulfur atom in good to excellent yields via a chemoselective manner.

1. Introduction

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the goals in organic chemistry (Laszlo, 1995). Organophosphorus compounds are synthetic targets of interest, because of their applications in variety of industrial, biological, pharmacological activities and also in chemical synthetic uses (Corbridge, 1995). Among the phosphorus compounds, phosphorus ylides play an important role in the synthesis of organic molecules (Ramazani et al., 2008; Yavari and Islami, 1998), because these compounds give an elegant access to other functional groups and a number of these compounds were employed in the preparation of natural products such as β-carotene (Yuan et al., 2008). They can be prepared by the reaction of a phosphonium salt (Maeycker, 1965) with a base and synthesis of phosphonium salt often requires forcing conditions. Frequently, the phosphine and organic halide must be heated to reflux for several hours, and in some cases several days, to obtain the desired phosphonium salt (Cadogan, 1979). In recent years methods for the preparation of this class compounds has been developed by using a novel approach employing vinyl phosphonium salts (Yavari et al., 2003; Hassani et al., 2009). In addition, triazole compounds have been introduced as an important class of plant growth regulators (Davis, 1991; Kanno, 1987) along with fungicidal and herbicidal properties (El-Zemity et al., 2006). Triazoles containing fluorine atoms in the aryl ring have also shown some insecticidal activity against house mosquito larva (Liu et al., 2000). Our literature survey reveals that most of 5-aryl-2H-1,2,4-triazol-3-thiol derivatives in which the sulfur atom having a chain have exhibited antimicrobial, antifungal and anti-inflammatory activities (Seyhan et al., 1999; Ulusoy et al., 2001).

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Due to the usefulness of these compounds and their important applications in pharmaceutical industry now we wish to design molecules containing these functional groups. Herein, we present our investigation towards this goal.

2. Materials and methods

All common reagents and solvents were used as obtained from commercial suppliers without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 AVANCE (^{1}H NMR at 500 MHz, and ^{13}C at 125 MHz). Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. Elemental CHN analyses were performed by University of Tarbiat Moalem using a Heracus CHN-O Rapid analyzer. IR spectra were measured on a Mattson 1000 FT-IR spectrometer.

2.1. General procedure

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 3-fluoroaryl-5-mercapto-1,2,4-triazol (2 mmol) in 20 mL of a mixture of hexane–ethyl acetate (1:2). After the addition was complete (approximately 30 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 white powder.

2.1.1. Dimethyl-2-{[3-(3-fluorophenyl)-1H-1,2,4-triazol-5-yl]-sulfanyl}-3-(1,1,1-triphenyl-λ^5-phosphanylidene) succinate **3a**

(1.1 g, m.p. 156–158 °C, yield 91%); IR (KBr) (ν_{max}, cm^{-1}): 1760, 1716 and 1636 (C═O). Anal. Calcd. for $C_{32}H_{27}FN_3O_4PS$ (599.5): C, 64.11; H, 4.51; N, 7.01%. Found: C, 63.83; H, 4.43; N, 6.93%.

Isomer (Z) (68%) ^{1}H NMR (500 MHz, Me_2SO): δ 3.0 and 3.7 (s, $2OCH_3$), 5.7 (d, $^{3}J_{PH}$ = 22.4 Hz, P═C–13CH), 7.4–7.8 (38H, m, arom),[1] 13.9 (1H, brs, NH). ^{13}C NMR (125.77 MHz, Me_2SO): δ 50.3 (d, $^{1}J_{PC}$ = 141.4 Hz, C═P),[1] 51.9 and 52.2 ($2OCH_3$), 61.3 (d, $^{2}J_{PC}$ = 14.1 Hz, P═C–CH), 112.0 (d, $^{2}J_{FC}$ = 20.9 Hz, C^{ortho}), 117.3 (d, $^{2}J_{Fc}$ = 21 Hz, C═C–F),[1] 121.4 (s, C^{para}), 125.4 (d, $^{1}J_{PC}$ = 92 Hz, C^{ipso}), 128.8 (d, $^{3}J_{PC}$ = 12.2 Hz, C^{meta}), 131.3 (s, C^{meta}), 132.2 (d, $^{4}J_{PC}$ = 2.5 Hz, C^{para}), 132.9 (s, C^{meta}), 133.2 (d, $^{2}J_{PC}$ = 10.9 Hz, C^{ortho}), 162.2 (d, $^{1}J_{FC}$ = 244 Hz, C^{ipso}), 164.7 (s, C═N),[1] 166.1 (s, C═N),[1] 168.2 (d, $^{2}J_{PC}$ = 13.4 Hz, C═O), 169.11 (d, $^{3}J_{PC}$ = 11.3 Hz, C═O). Isomer (E) (32%) ^{1}H NMR (500 MHz, Me_2SO): δ 3.4 and 3.69 (s, $2OCH_3$), 5.7 (d, $^{3}J_{PH}$ = 17.8 Hz, P═C–13CH, 13.8 (1H, brs, NH). ^{13}C NMR (125.77 MHz, Me_2SO): δ 51.7 and 52.0 ($2OCH_3$), 60.3 (d, $^{2}J_{PC}$ = 14.3 Hz, P═C–CH), 112.4 (d, $^{2}J_{FC}$ = 24.3 Hz, C^{ortho}), 121.7 (s, C^{para}), 126.1 (d, $^{1}J_{PC}$ = 91.6 Hz, C^{ipso}), 128.6 (d, $^{3}J_{PC}$ = 12.1 Hz, C^{meta}), 131.4 (s, C^{meta}), 131.9 (d, $^{4}J_{PC}$ = 2.5 Hz, C^{para}), 133.1 (s, C^{meta}), 133.3 (d, $^{2}J_{PC}$ = 11.3 Hz, C^{ortho}), 169.2 (d, $^{3}J_{PC}$ = 12.2 Hz, C═O), 169.8 (d, $^{2}J_{PC}$ = 17.4 Hz, C═O).

2.1.2. Diethyl-2-{[3-(2-fluorophenyl)-1H-1,2,4-triazol-5-yl]sulfanyl}-3-(1,1,1-triphenyl-λ^5-phosphanylidene) succinate **3b**

(1.0 g, m.p. 134–136 °C, yield 81%); IR (KBr) (ν_{max}, cm^{-1}): 1741, 1716 and 1617 (C═O). Anal. Calcd. for $C_{34}H_{31}FN_3O_4PS$ (627): C, 65.07; H, 4.94; N, 6.69%. Found: C, 64.70; H, 4.84; N, 6.62%.

Isomer (Z) (58%) ^{1}H NMR (500 MHz, Me_2SO): δ 0.35 and 1.20 (T, 6H, $^{3}J_{HH}$ = 7.0 and 7.1 Hz, $2CH_3$), 3.5–3.9 (8H, m, OCH_2),[1] 5.4 (d, $^{3}J_{PH}$ = 20.5 Hz, P═C–13CH), 7.4–7.8 (38H, m, arom),[1] 13.6 (1H, brs, NH).[1] ^{13}C NMR (125.77 MHz, Me_2SO): δ 14.2 and 14.5 ($2CH_3$), 57.7 (d, $^{1}J_{PC}$ = 84.8 Hz, C═P),[1] 60.8 (d, $^{2}J_{PC}$ = 15.9 Hz, P═C–CH), 61.0 and 61.1 ($2OCH_2$), 114.6 (d, $^{2}J_{FC}$ = 11.3 Hz, C═C–F),[1] 117.2 (d, $^{2}J_{Fc}$ = 21 Hz, C═C–F), 125.5 (s, C^{para}),[1] 127.0 (d, $^{1}J_{PC}$ = 91.7 Hz, C^{ipso}), 129.3 (d, $^{3}J_{PC}$ = 11.9 Hz, C^{meta}), 129.6 (s, C^{meta}), 132.7 (s, C^{para}),[1] 133.2 (d, $^{3}J_{FC}$ = 11.4 Hz, C^{meta}), 133.8 (d, $^{2}J_{PC}$ = 9.7 Hz, C^{ortho}),[1] 159.6 (d, $^{1}J_{FC}$ = 253 Hz, C^{ipso}),[1] 166.4 (C═N),[1] 168.3 (d, $^{2}J_{PC}$ = 13.2 Hz, C═O), 169.2 (d, $^{3}J_{PC}$ = 10.9 Hz, C═O). Isomer (E) (42%) ^{1}H NMR (500 MHz, Me_2SO): δ 1.0 and 1.22 (T, 6H, $^{3}J_{HH}$ = 7.0 and 7.1 Hz, $2CH_3$), 5.6 (d, $^{3}J_{PH}$ = 18.9 Hz, P═C–13CH). ^{13}C NMR: δ 14.5 and 15.1 ($2CH_3$), 61.0 (d, $^{2}J_{PC}$ = 14.1 Hz, P═ C–CH), 61.8 and 61.9 ($2OCH_2$), 117.3 (d, $^{2}J_{Fc}$ = 20.8 Hz, C═C–F), 128.3 (d, $^{1}J_{PC}$ = 92 Hz, C^{ipso}), 129.3 (d, $^{3}J_{PC}$ = 12.0 Hz, C^{meta}), 131.9 (d, $^{3}J_{FC}$ = 9.8 Hz, C^{meta}), 169.3 (d, $^{2}J_{PC}$ = 12.3 Hz, C═O), 170.2 (d, $^{3}J_{PC}$ = 18.4 Hz, C═O).

2.1.3. Dimethyl-2-{[3-(2-fluorophenyl)-1H-1,2,4-triazol-5-yl]sulfanyl}-3-(1,1,1-triphenyl-λ^5-phosphanylidene) succinate **3c**

(1.12 g, m.p. 157–158 °C, yield 93%); IR (KBr) (ν_{max}, cm^{-1}): 1760, 1716 and 1640 (C═O). Anal. Calcd. for $C_{32}H_{27}FN_3O_4PS$ (599.5): C, 64.11; H, 4.51; N, 7.01%. Found: C, 63.63; H, 4.38; N, 6.93%.

Isomer (Z) (52%) ^{1}H NMR (500 MHz, Me_2SO): δ 3.4 and 3.5 (s, $2OCH_3$), 5.5 (d, $^{3}J_{PH}$ = 19.5 Hz, P═C–13CH),[1] 7.4–7.8 (38H, m, arom),[1] 13.6 (1H, brs, NH). ^{13}C NMR (125.77 MHz, Me_2SO): δ 49.7 (d, $^{1}J_{PC}$ = 150 Hz, C═P),[1] 52.5 and 52.77 ($2OCH_3$), 62.5 (d, $^{2}J_{PC}$ = 14.1 Hz, P═C–CH),[1] 117.4 (s, C^{ortho}, C═C–F),[1] 125.5 (s, C^{ortho}, C═C–F),[1] 126.7 (d, $^{1}J_{PC}$ = 82.0 Hz, C^{ipso}), 129.4 (d, $^{3}J_{PC}$ = 12.2 Hz, C^{meta}), 129.63 (s, C^{para}), 132 (s, C^{meta}, C═C–C–F), 132.7 (d, $^{4}J_{PC}$ = 2.6 Hz, C^{para}), 133.8 (d, $^{2}J_{PC}$ = 10.1 Hz, C^{ortho}), 166.6 (s, C═N),[1] 174.6 (d, $^{2}J_{PC}$ = 13.5 Hz, C═O),[1] 175.2 (d, $^{3}J_{PC}$ = 11.9 Hz, C═O).[1]

Isomer (E) (48%) ^{1}H NMR (500 MHz, Me_2SO): δ 2.9 and 3.6 (s, $2OCH_3$), 13.8 (1H, brs, NH). ^{13}C NMR (125.77 MHz, Me_2SO): δ 52.4 and 52.6 ($2OCH_3$), 126.0 (d, $^{1}J_{PC}$ = 82.7 Hz, C^{ipso}), 129.2 (d, $^{3}J_{PC}$ = 11.8 Hz, C^{meta}), 130.0 (s, C^{para}), 131.9 (s, C^{meta}, C═C–C–F), 132.5 (d, $^{4}J_{PC}$ = 8.8 Hz, C^{para}), 133.8 (d, $^{2}J_{PC}$ = 14.0 Hz, C^{ortho}).

2.1.4. Dimethyl-2-{[3-phenyl-1H-1,2,4-triazol-5-yl]sulfanyl}-3-(1,1,1-triphenyl-λ^5-phosphanylidene) succinate **3d**

(0.94 g, m.p. 157–159 °C, yield 80%); IR (KBr) (ν_{max}, cm^{-1}): 1740, 1716 and 1617 (C═O). Anal. Calcd. for $C_{32}H_{28}N_3O_4PS$ (581): C, 65.9; H, 4.82; N, 7.23%. Found: C, 65.39; H, 4.73; N, 7.16%. Isomer (Z) (53%) ^{1}H NMR (500 MHz, Me_2SO): δ 2.99 and 3.5 (s, $2OCH_3$), 5.6 (d, $^{3}J_{PH}$ = 17 Hz, P═C–13CH),[1] 7.5–7.9 (40H, m, arom),[1] 13.73 (1H, brs, NH). ^{13}C NMR (125.77 MHz, Me_2SO): δ 49.8 (d, $^{1}J_{PC}$ = 143.5 Hz, C═P),[1] 52.4 and 52.8 ($2OCH_3$), 61.7 (d, $^{2}J_{PC}$ = 14.5 Hz, P═C–CH), 125.8 (s, C^{ortho}), 126.8 (d, $^{1}J_{PC}$ = 82.7 Hz, C^{ipso}), 129.4 (d, $^{3}J_{PC}$ = 12.1 Hz, C^{meta}), 129.6 (S, C^{para}), 131.9 (s, C^{meta}), 132.7 (d, $^{4}J_{pc}$ = 2.6 Hz, C^{para}), 133.5 (s, C^{ipso}), 133.8 (d,

[1] For two rotamers.

$^{2}J_{PC}$ = 10.4 Hz, C^{ortho}), 147.6 (s, C=N), 168.8 (d, $^{2}J_{PC}$ = 13 Hz, C=O), 169.8 (d, $^{3}J_{PC}$ = 15 Hz, C=O). Isomer (E) (47%) ^{1}H NMR (500 MHz, Me_2SO): δ 3.4 and 3.5 (s, $2OCH_3$), 13.8 (1H, brs, NH). ^{13}C NMR (125.77 MHz, Me_2SO): δ 52.3 and 52.6 ($2OCH_3$), 60.7 (d, $^{2}J_{PC}$ = 14.8 Hz, P=C–CH), 125.7 (s, C^{ortho}), 126.0 (d, $^{1}J_{PC}$ = 82.9 Hz, C^{ipso}), 129.2 (d, $^{3}J_{PC}$ = 11.8 Hz, C^{meta}), 129.7 (s, C^{para}), 132.0 (s, C^{meta}) 132.5 (d, $^{4}J_{pc}$ = 2.5 Hz, C^{para}), 133.7 (s, C^{ipso}), 133.9 (d, $^{2}J_{PC}$ = 10.5 Hz, C^{ortho}), 147.7 (s, C=N), 169.9 (d, $^{2}J_{PC}$ = 11 Hz, C=O), 170.4 (d, $^{3}J_{PC}$ = 17.3 Hz, C=O).

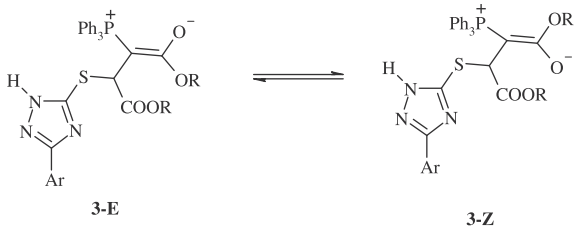
3. Results and discussion

As a continuous work we examined the reaction of 5-aryl-2H-1,2,4-triazol-3-thiol and dialkyl acetylenedicarboxylate in order to prepare synthetically useful heterocyclic compounds containing phosphorus atom. Combination of equimolar quantities of **1** with dimethyl or diethyl acetylenedicarboxylate and Ph_3P in ambient temperature resulted in 80–93% yield of S-substituted triazoles containing succinic esters chain **3a–d** (Scheme 1). In the basis of chemistry of trivalent phosphorus nucleophiles (Becker, 1980; Kolodiazhnyi, 1998), it is reasonable to assume that treatment of triphenylphosphine with acetylenic esters in ethyl acetate as a solvent generated the corresponding zwitter ion in situ which, on further reaction with SH group of triazoles, led to the formation of a salt. Then the positively charged ion is attacked by the conjugated base of SH group to form compounds **3**.

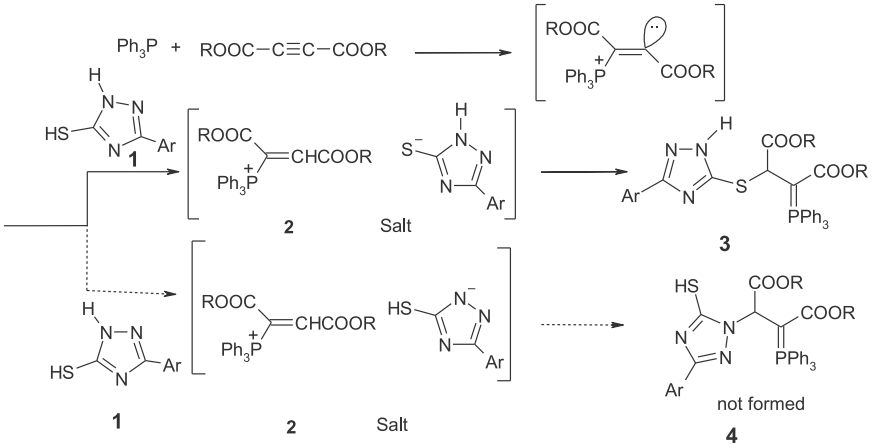
It is important to note that in the protonation step the SH group acts as a stronger acid than the NH group. Thus, under the present reaction condition compound **3** is formed as the only product in a chemoselective manner and the compound **4** is not formed (Scheme 1).

Compounds **3a–d** were deduced on the basis of their spectroscopic data such as the ^{1}H NMR, ^{13}C NMR, IR and elemental analyses data. These data are consistent with the presence of two rotational isomers (Bestmann et al., 1966; Hooper et al., 1994). The ylide moiety in these compounds is strongly conjugated with adjacent carbonyl group and rotation about the partial double bond in **3**-(**E**) and **3**-(**Z**) geometrical isomers slows at room temperature (Scheme 2).

The ^{1}H NMR spectrum of **3a** showed four sharp lines (δ = 2.99, 3.43, 3.69 and 3.75 ppm) due to methoxy protons along with signals for methine protons at δ = 5.66 and 5.71 ppm, which appear as two doublets ($^{3}J_{PH}$ = 22.4 Hz) and ($^{3}J_{PH}$ = 17.8 Hz), respectively, for the major and minor geometrical isomers and two fairly broad signals at δ = 13.80 and 13.78 ppm for protons of NH groups. The fully proton decoupled ^{13}C NMR spectrum of **3a** displayed 31 distinct resonances in agreement with the mixture of two rotamers. Although the presence of the ^{31}P nucleus complicates both the ^{1}H and ^{13}C NMR spectra of **3a**, it helps in assignment of signals by long-range spin–spin couplings with ^{1}H and ^{13}C nuclei. Fluorine nucleus coupled with some hydrogen and carbon atoms of the aromatic rings thus, the ^{1}H and ^{13}C spectra of this region were complicated. For example, in the fully proton decoupled ^{13}C NMR spectrum of **3a**, the signal due to the carbon carrying F atom was appeared as a doublet with a coupling constant equal to 244 Hz. The ^{1}H and ^{13}C NMR



Scheme 2



3	R	Ar	Yield (%)
a	Me	3-FC_6H_4	91
b	Et	2-FC_6H_4	81
c	Me	2-FC_6H_4	93
d	Me	C_6H_5	80

Scheme 1

spectra of triazoles **3b**–**d** are similar to those of **3a**, except for the signals from the ester groups or aromatic rings, which appear as characteristic resonance lines with the corresponding chemical shifts.

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