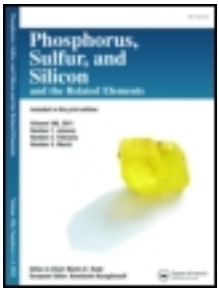

Phosphorus, Sulfur, and Silicon and the Related Elements

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One-Pot Synthesis of Alkyl 3-(Diphenylphosphoryl)-3-(10H-phenothiazin-10-yl)propanoates from Alkyl Acetylenecarboxylates, Phenothiazine, and Triphenylphosphine

Ali Ramazani [a] & Fariba Sadri [b]

[a] Department of Chemistry, Islamic Azad University-Zanjan Branch, Zanjan, Iran

[b] Chemistry Department, Payam Noor University (PNU), Abhar, Zanjan, Iran

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One-Pot Synthesis of Alkyl 3-(Diphenylphosphoryl)-3-(10*H*-phenothiazin-10-yl)propanoates from Alkyl Acetylenecarboxylates, Phenothiazine, and Triphenylphosphine

Ali Ramazani[1] and Fariba Sadri[2]
[1]Department of Chemistry, Islamic Azad University–Zanjan Branch, Zanjan, Iran
[2]Chemistry Department, Payam Noor University (PNU), Abhar, Zanjan, Iran

Protonation of the highly reactive 1:1 intermediates, produced in the reaction between triphenylphosphine and alkyl acetylenecarboxylates by phenothiazine, leads to vinyltriphenylphosphonium salts, which undergo a Michael addition reaction with conjugate bases to produce the corresponding phosphorus ylides. The phosphorus ylides react with water forming phenothiazine containing diphenylphosphine oxide derivatives in moderate yields.

Keywords Acetylenic ester; DEPT-135 experiment; phenothiazine; phenothiazine containing diphenylphosphine oxide derivatives; phosphorus ylide; triphenylphosphine; vinyltriphenylphosphonium salts

INTRODUCTION

The phosphorus ylides represent an outstanding achievement of the chemistry of the twentieth century.[1–16] They have found use in a wide variety of reactions of interest to synthetic chemists.[1–16] Phosphorus ylides are important reagents in synthetic organic chemistry,[1–16] especially in the synthesis of naturally occurring products, and compounds with biological and pharmacological activity.[6] The development of the modern chemistry of natural and physiologically active compounds would have been impossible without the phosphorus ylides.[1–16] These compounds have attained great significance as widely used reagents for

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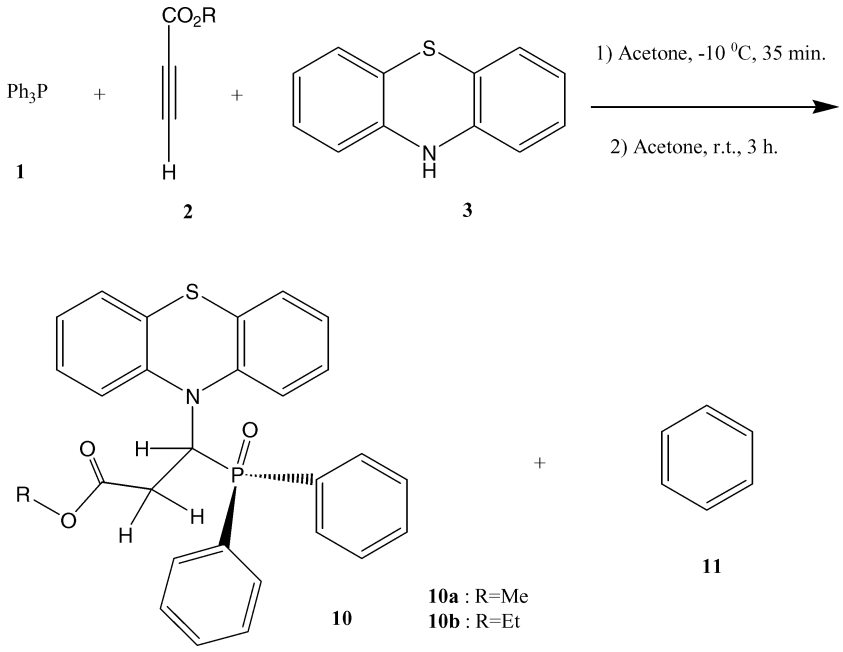
Address correspondence to Ali Ramazani, Department of Chemistry, Islamic Azad University–Zanjan Branch, P O Box 49195-467, Zanjan, Iran. E-mail: aliramazani@gmail.com

linking synthetic building blocks with the formation of carbon–carbon double bonds, and this has aroused much interest in the study of the synthesis, structure, and properties of P-ylides and their derivatives.[1–16] Several methods have been developed for preparation of phosphorus ylides.[1–16] These ylides are most often prepared by the treatment of a phosphonium salt with a base. Most of the phosphonium salts are usually made from phosphine and an alkyl halide,[1–16] and they are also obtained by the Michael addition of phosphorus nucleophiles to activated olefins.[1–16]

β-Additions of nucleophiles to the vinyl group of vinylic phosphonium salts leading to the formation of new alkylidenephosphoranes has attracted much attention as a very convenient and synthetically useful method in organic synthesis.[18–30] Phosphorus ylides are a class of special type of zwitterions, which bear strongly nucleophilic, electron-rich carbanions. The electron distribution around the P^+–C^- bond and its consequent chemical implications had been probed and assessed through theoretical, spectroscopic, and crystallographic investigations.[30] The proton affinity of these ylides can be used as a molecular guide to assess their utility as synthetic reagents and their function as ligands in coordination and organometallic chemistry.[17,30]

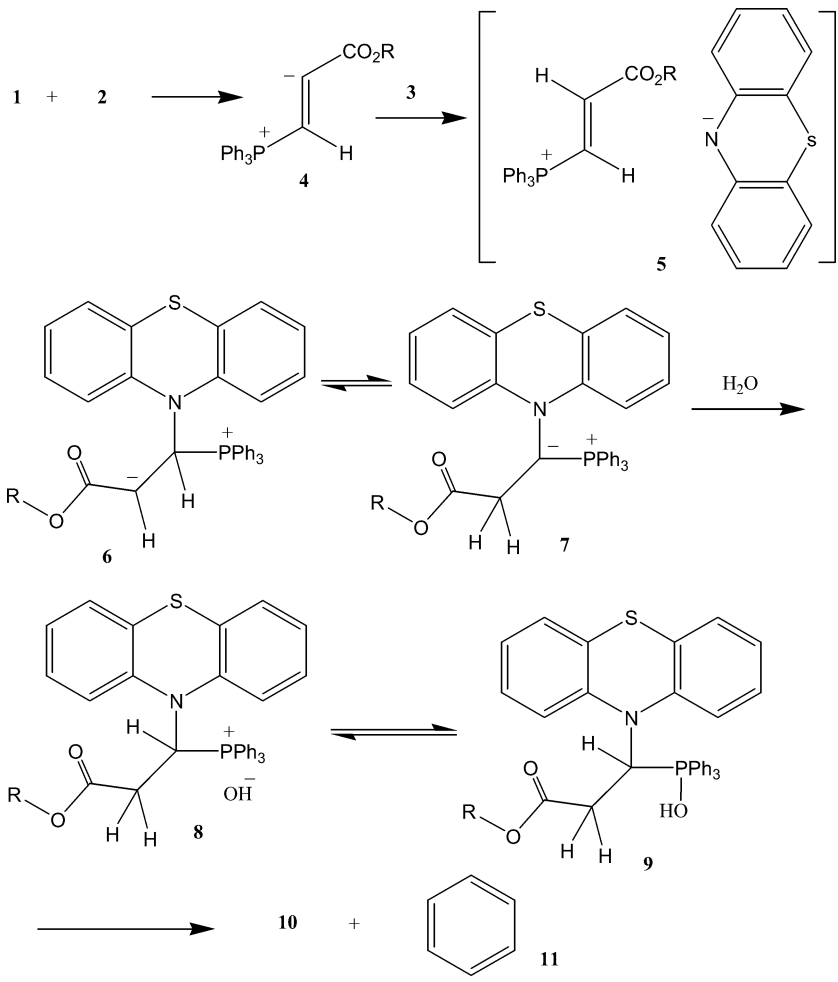
Previously we have established a convenient, one-pot method for preparing stabilized phosphorus ylides utilizing in situ generation of the phosphonium salts.[18–28] Stabilized phosphorus ylides, versatile intermediates in synthetic organic chemistry, can be prepared by the novel reaction of dialkyl acetylenedicarboxylates (DAAD), triphenylphosphine (TPP), and acids such as phenols, imides, amides, enols, oximes, and alcohols.[18–28] The reaction[31] involves an intermediate formed by the 1:1 conjugate addition reaction of the TPP to DAAD, and concomitant protonation of the intermediate by an acid leads to vinyltriphenylphosphonium salts.[18–28] The salts are unstable intermediates and are converted to stabilized phosphorus ylides via a Michael addition reaction.[18–28] The stabilized phosphorus ylides are able to take part in the normal intramolecular Wittig reactions, but they are not generally able to participate in the normal intermolecular Wittig reactions.[18–28] Intermolecular Wittig reactions of the ylides are observed only with highly electron-poor carbonyl groups such as indane-1,2,3-trione.[31] The ylides are converted to electron-poor alkenes via elimination of TPP in solvent-free conditions.[31] Almost all of the final products are valuable families of compounds.[31] In this article, we wish to describe a simple one-pot method for the preparation of alkyl 3-(diphenylphosphoryl)-3-(10*H*-phenothiazin-10-yl)propanoates **10** from alkyl acetylenecarboxylates, phenothiazine, and triphenylphosphine (Scheme 1).



SCHEME 1 Synthesis of phenothiazine containing diphenylphosphine oxide derivatives (**10**).

RESULTS AND DISCUSSION

Triphenylphosphine **1**, alkyl acetylenecarboxylates **2**, and phenothiazine **3** were reacted in a 1:1:1 ratio in acetone at room temperature to give alkyl 3-(diphenylphosphoryl)-3-(10*H*-phenothiazin-10-yl)propanoates **10** and benzene **11** (Scheme 1). The reactions were monitored with using of TLC technique. The reaction proceeded smoothly and cleanly under mild conditions, and no side reactions were observed. Reactions are known in which an organophosphorus compound is produced from an acid (CH, NH, OH, and SH-acids), a acetylenic ester, and a phosphine such as a tributylphosphine or triphenylphosphine.[19–21] Thus, compounds **10** may be regarded as the product of an addition-elimination reaction. Such addition-elimination products may result from an initial addition of triphenylphosphine **1** to the acetylenic ester **2** and concomitant protonation of the 1:1 adduct **4**, followed by attack of the anion of phenothiazine **5** on the vinylphosphonium cation **5** to form intermediates **6** and **7**. Hydrolysis of the intermediates **6** and **7** via intermediates **8** and **9**, along with loss of benzene **11** leads to

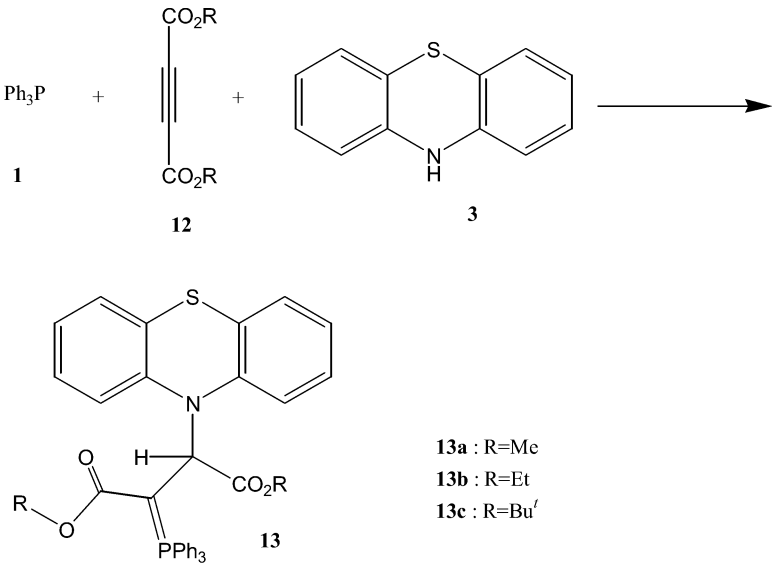


SCHEME 2 Proposed mechanism for the formation of alkyl 3-(diphenylphosphoryl)-3-(10*H*-phenothiazin-10-yl)propanoates (**10**).

formation of alkyl 3-(diphenylphosphoryl)-3-(10*H*-phenothiazin-10-yl) propanoates **10** (Scheme 2).

The mechanism of the reaction outlined above has not been established experimentally. However, a possible explanation[19] is proposed in Scheme 2.

The structure of products **10** was proven by their ^{1}H NMR and ^{13}C NMR spectral data (see the Experimental section**).** The ^{1}H NMR spectrum of compound **10b** exhibited six signals readily recognized as arising from its appropriate functional groups [1.02 (3 H, t, $^{3}J_{HH}$



SCHEME 3 Synthesis of phenothiazine-containing stabilized phosphorus ylides (**13**).

= 7.1 Hz, CH_3); 2.81–2.99 and 3.06–3.19 (2 H, 2 m, CH_2); 3.88 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2); 4.00–4.10 (1 H, m, CH-P); 7.10–7.99 (m, 18 H, aromatic)]. The ^{13}C NMR spectrum of the compound **10b** showed four distinct resonances in the aliphatic region, as was expected. The functionality of CH_2-CH-P of compound **10b** was established by a DEPT-135 experiment [δ = 34.89 (s, CH_2, negative signal) and δ = 42.93 (d, $^1J_{PC}$ = 67.93 Hz, CH, positive signal)]. Partial assignment of these resonances is given in the Experimental section. The ^1H and ^{13}C NMR of compound **10a** are similar to those of the compound **10b**, except in the alkyl moiety of ester group that appears in an appropriate chemical shift (see the Spectral Analysis section).[28,32] The ^{31}P NMR spectra of the compounds **10** exhibited signals readily recognized as arising from their $Ph_2P{=}O$ functional group (δ = 33.34 for the compound **10a** and δ = 33.12 for the compound **10b**). Synthesis of phenothiazine containing stabilized phosphorus ylides **13** from from dialkyl acetylenedicarboxylates **12**, phenothiazine **3**, and triphenylphosphine **1** have been reported (Scheme 3).[33]

CONCLUSION

In summary, we have found a new and efficient method for the synthesis of alkyl 3-(diphenylphosphoryl)-3-(10*H*-phenothiazin-10-yl)

propanoates (**10**) from triphenylphosphine (**1**), alkyl acetylenecarboxylates (**2**), and phenothiazine (**3**) (Scheme 1). We believe the reported method offers a simple and efficient route for the preparation of the phenothiazine-containing diphenylphosphine oxide derivatives **10** (Scheme 1 and Scheme 2). Its easy work-up and acceptable yields make it a useful method. Possible extensions are under investigation.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Mattson 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker Spectrospin spectrometer at 250 and 62.5 MHz, respectively.

General Procedure for the Preparation of Alkyl 3-(Diphenylphosphoryl)-3-(10H-phenothiazin-10-yl)propanoates 10a–b

To a magnetically stirred solution of triphenylphosphine **1** (0.262 g, 1.00 mmol) and phenothiazine **3** (0.199 g, 1.0 mmol) in acetone (4 mL), a mixture of alkyl acetylenecarboxylate **2** (0.10 mL, 1.0 mmol) in acetone (1 mL) at $-10^{\circ}C$ was added dropwise over 15 min, and the mixture was stirred for 35 min at $-10^{\circ}C$. The mixture was allowed to warm up to room temperature and stirred for 3 h. The product precipitated as white crystals. The crystals were separated from acetone by simple filtration and washed with cold diethyl ether (3×15 mL). The product was dried at room temperature.

Methyl 3-(Diphenylphosphoryl)-3-(10H-phenothiazin-10-yl) propanoate (10a)

White crystals; mp: 185–186°C; Yield: 43.2%. IR (KBr) (υ_{max}, cm^{-1}): 3062 (C–H, aromatic); 2954 (C–H, aliph); 1739 (C=O, ester); 1443 (arom.); 1200 (P=O and C-O). ^{1}H NMR ($CDCl_3$) δ: 2.85–3.00 and 3.05–3.20 (2 H, 2 m, CH_2); 3.45 (3 H, s, OCH_3); 4.02–4.15 (1 H, m, CH-P); 7.12–8.00 (18 H, m, aromatic). ^{13}C NMR ($CDCl_3$) δ: 34.72 (s, CH_2); 43.32 (d, $^{1}J_{PC} = 68.37$ Hz, CHP); 51.89 (s, OCH_3); 127.25–135.90 (fairly complex, arom.); 161.72 (d, $^{3}J_{PC} = 3.15$ Hz, CO of ester). ^{31}P NMR ($CDCl_3$) δ: 33.34.

Ethyl 3-(Diphenylphosphoryl)-3-(10H-phenothiazin-10-yl) propanoate (10b)

White crystals; mp: 190–191°C; Yield: 51.4%. IR (KBr) (υ_{max}, cm^{-1}): 3046 (C–H, aromatic); 2985 and 2915 (C–H, aliph.); 1739 (C=O, ester);

1439 (arom.); 1185 (P=O and C-O). ^{1}H NMR ($CDCl_3$) δ: 1.02 (3 H, t, $^3J_{HH}$ = 7.1 Hz, CH_3); 2.81–2.99 and 3.06–3.19 (2 H, 2 m, CH_2); 3.88 (2 H, q, $^3J_{HH}$ = 7.1 Hz, OCH_2); 4.00–4.10 (1 H, m, CH-P); 7.10–7.99 (m, 18 H, aromatic). ^{13}C NMR ($CDCl_3$) δ: 13.91 (s, CH_3); 34.89 (s, CH_2); 42.93 (d, $^1J_{PC}$ = 67.93 Hz, CH); 60.74 (s, OCH_2); 127.20–135.10 (fairly complex, arom.); 171.31 (d, $^3J_{PC}$ = 16.98 Hz, CO of ester). ^{31}P NMR ($CDCl_3$) δ: 33.12.

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