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VINYLTRIPHENYLPHOSPHONIUM SALT-MEDIATED PREPARATION OF THIOPHENE-CONTAINING ELECTRON-POOR ALKENES FROM ACETYLENIC ESTERS, 2-THIENYLMETHANOL AND TRIPHENYLPHOSPHINE

Nahid Shajari[1*], Ali Ramazani[1] and Yavar Ahmadi[2]

[1]Department of Chemistry, Islamic Azad University-Zanjan Branch, P.O. Box 49195-467, Zanjan, Iran
[2]Chemistry Department, Zanjan University, P.O. Box 45195-313, Zanjan, Iran

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ABSTRACT. Protonation of the highly reactive 1:1 intermediates, produced in the reaction between triphenylphosphine and alkyl acetylenecarboxylates (methyl acetylenecarboxylate, ethyl acetylenecarboxylate and ethyl phenylacetylenecarboxylate) by 2-thienylmethanol leads to vinyltriphenylphosphonium salts, which undergo an addition-elimination reaction in CH_2Cl_2 at room temperature to produce the corresponding *O*-vinylated alkenes *via* thiophene-containing phosphorus ylides intermediates in fairly high yields. The structural analysis of all products indicated that the reactions are regio- and stereoselective.

KEY WORDS: 2-Thienylmethanol, Acetylenic ester, Vinyltriphenylphosphonium salt, *O*-Vinylation, Michael addition

INTRODUCTION

The phosphorus ylides represent an outstanding achievement of the chemistry of the twentieth century [1-16]. The development of the modern chemistry of natural and physiologically active compounds would have been impossible without the phosphorus ylides [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, compounds with biological and pharmacological activity [6]. These compounds have attained great significance as widely used reagents for 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 [1-6]. Several methods have been developed for preparation of phosphorus ylides [7-10]. 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 [10-16], and they are also obtained by the Michael addition of phosphorus nucleophiles to activated olefins [10-16]. 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]. In the past we have established a convenient, one-pot method for preparing stabilized phosphorus ylides utilizing an *in situ* generation of the phosphonium salts [18-20]. Stabilized phosphorus ylides, versatile intermediates in synthetic organic chemistry can be prepared by the novel reaction of dialkyl acetylenedicarboxylates (DAAD), triphenylphosphine (TPP) and acids

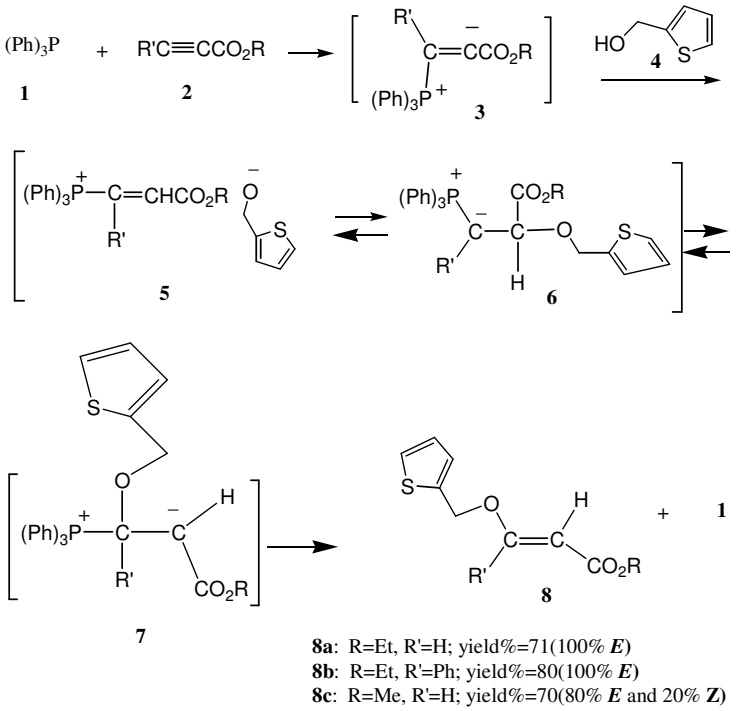
*Corresponding author. E-mail: n_shajari120@yahoo.com

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 converted to stabilized phosphorus ylides *via* a Michael addition reaction [18-28]. The stabilized phosphorus ylides are able to take part in the intramolecular Wittig reactions [32-39] but they are not generally able to participate in the intermolecular Wittig reactions [18-28]. 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 paper, we wish to describe stereoselective synthesis of thiophene-containing electron-poor alkenes from triphenylphosphine, acetylenic esters and 2-thienylmethanol.

RESULTS AND DISCUSSION

Triphenylphosphine **1**, alkyl acetylenecarboxylates **2** and 2-thienylmethanol **4** were reacted in a 1:1:1 ratio in dichloromethane at room temperature to give electron-poor thiophene-containing *O*-vinyl ethers **8** (Scheme 1). TLC indicated the formation of products. The reaction proceeded smoothly and cleanly under mild conditions and no side reactions were observed. In the reaction, triphenylphosphine **1** acts as catalyst (Scheme 1). We reduced the amount of triphenylphosphine to 50% molar ratio. In all cases where we have used triphenylphosphine as a catalyst in the range of 50-100% molar ratio, the reaction time amounted to 24 h. In all cases where we have used triphenylphosphine as a catalyst in a molar ratio below 50%, the reaction time was longer than 24 h. In the absence of triphenylphosphine no product formation was observed. Reactions are known in which an α,β-unsaturated carbonyl compound is produced from a phosphorane and a carbonyl compound such as an aldehyde or ketone [19-21]. Thus, compounds **8** 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 **3**, followed by attack of the anion of 2-thienylmethanol **4** on the β-carbon atom of the vinylphosphonium cation **5** to form intermediates **6** and **7**. Elimination of triphenylphosphine **1** from intermediate **7** would lead to stereoselective formation of electron-poor thiophene-containing *O*-vinyl ethers (**8**) in fairly high yields (Scheme 1). The mechanism of the reaction outlined above has not been established experimentally. However, a possible explanation [19] is proposed in Scheme 1. The NMR spectra indicated that solutions of compounds (**8a–b**) ($CDCl_3$ as solvent) contained only the ***E*** isomer. However, in the case of (**8c**) the NMR spectra indicated that solutions of the compound ($CDCl_3$ as solvent) contained two stereoisomers (***E*** and ***Z***). The relative percentages of two stereoisomers of **8c** in $CDCl_3$ were determined from the ^{1}H NMR spectra and also *via* isolation of two stereoisomers of **8c** by flash column chromatography (see Scheme 1 and Experimental part). We also used ethanol, *tert*-butyl alcohol, butyl alcohol, *iso*-propyl alcohol, diethyl hydroxymethylphosphonate, 2-thienylethanol, 2-pyridilmethanol, 3-pyridilmethanol and 4-pyridilmethanol instead of the 2-thienylmethanol **4** in the reaction, but yields of corresponding products **8** were very low and several products and starting materials were observed based on TLC investigations. The weaker acidity of these alcohols as compared with alcohol **4** and high nucleophilicity of pyridine nitrogen may be responsible for the decrease of yields and observation of several products. We also used some of sulfonamide derivatives (*N*-(2-pyridyl)methanesulfonamide, N^1-(2-pyridyl)-1-benzenesulfonamide and 4-methyl-N^1-(2-pyridyl)-1-benzenesulfonamide) as NH-acids instead of the 2-thienylmethanol **4** in the reaction, but no products were observed and starting sulfonamide was recovered. The weaker acidity of these sulfonamide derivatives as compared with alcohol **4** may be responsible for the observation. The structures (**8a–c**) were deduced from their IR, ^{1}H and ^{13}C NMR spectra. For

example the ^{1}H NMR spectrum of **8a** exhibited distinct signals arising from a methyl group (δ_H = 1.26 ppm (3H, t, $^3J_{HH}$ = 7.3 Hz)), a methylene group (δ_H = 4.16 ppm (2H, q, $^3J_{HH}$ = 7.3 Hz)), a methylene group (δ_H = 5.03 (2H, s, OCH_2), a thienyl group (δ_H = 6.99–7.36 (3H, m, arom.)) and an AX system with $^3J_{HH}$ = 12.5 Hz (in agreement with disubstituted olefin with ***E*** configuration [19]) for the two =CH (δ_H = 5.32 and 7.65 ppm). The ^{13}C NMR spectrum of **8a** showed 10 distinct resonances arising from CH_3 of OEt (14.34 ppm), OCH_2 of OEt (59.89 ppm), 67.32 (OCH_2), 97.76 (=CH, alkene); 127.00, 127.18 and 127.95, (3 CH, arom.); 137.13 (1C, arom.); 161.30 (OCH=) and 167.51 (C=O of ester). The IR spectrum of **8a** showed C=O absorption at 1710 cm^{-1}.

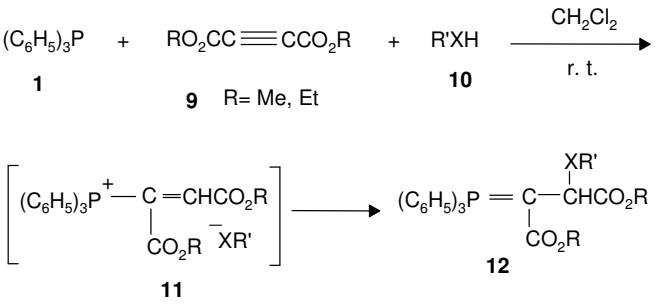


8a: R=Et, R'=H; yield%=71(100% ***E***)
8b: R=Et, R'=Ph; yield%=80(100% ***E***)
8c: R=Me, R'=H; yield%=70(80% ***E*** and 20% **Z**)

Scheme 1. Stereoselective synthesis of thiophene-containing electron-poor alkenes from acetylenic esters and 2-thienylmethanol in the presence of triphenylphosphine.

We have also used dialkyl acetylenedicarboxylates (**9**) (Scheme 2) instead of alkyl acetylenecarboxylates (**2**) and several OH- and SH-acids in this reaction, but based on TLC investigations, the corresponding ylides [32] **12** were fairly stable in dichloromethane solvent for several days at room temperature and were not converted to corresponding electron-poor *O*-vinylethers *via* losing of triphenylphosphine. We also used ethanol, *tert*-butyl alcohol, butyl alcohol, *iso*-propyl alcohol, 2-thienylethanol, 2-pyridilmethanol, 3-pyridilmethanol, 4-pyridilmethanol, diethyl hydroxymethylphosphonate, *N*-(2-pyridyl)methanesulfonamide, N^1-(2-pyridyl)-1-benzenesulfonamide and 4-methyl-N^1-(2-pyridyl)-1-benzenesulfonamide instead of the R'XH **10** (Scheme 2) in the reaction, but yields of corresponding products **12** were very low and starting OH- and NH-acids were observed based on TLC investigations. The weaker acidity of these OH- and NH-acids as compared with R'XH **10** (Scheme 2) may be responsible for the

decrease of yields. As stated in recent reports [31, 40], the reaction (Scheme 2) proceeds smoothly and cleanly under mild conditions and no side reactions were observed. The mechanism of the reaction has not been established experimentally. However, a possible explanation is proposed in Scheme 2.



Scheme 2. Synthesis of highly stabilized phosphorus ylides **12** from dialkyl acetylenecarboxylates, R'XH **10** and triphenylphosphine [31, 40].

CONCLUSIONS

In conclusion, we believe that the reported method offers a mild, simple, and efficient route for the stereoselective synthesis of thiophene-containing electron-poor alkenes **8**. The ease of workup, good yields, and fairly mild reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

EXPERIMENTAL

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods were used to follow the reactions are TLC and NMR. TLC and NMR indicated that there is no side product. IR spectra were measured on a Jasco 6300 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-250 Avance spectrometer at 250.0 and 62.5 MHz, respectively. Flash chromatography columns were prepared from Merck silica gel powder.

*General procedure for the preparation of thiophene-containing electron-poor alkenes **8a-c***

To a magnetically stirred solution of triphenylphosphine (0.262 g, 1 mmol) and 2-thienylmethanol (1 mmol) in dichloromethane (10 mL) was added dropwise a mixture of acetylenic ester **2** (1 mmol) in dichloromethane (4 mL) at -10 °C over 15 min. The mixture was allowed to warm up to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the viscous residue was purified by flash column chromatography (silica gel; ethyl acetate-light petroleum ether (1:10)). The solvent was removed under reduced pressure and the products were obtained as viscous light yellow oils (**8a–c**) (Scheme 1). The characterization data of the compounds (**8a**–**c**) are given below.

Ethyl (E)-3-(2-thienylmethoxy)-2-propenoate ***8a***

Light yellow oil; yield (71 %). IR (neat, ν_{max}, cm^{-1}): 2983, 1710, 1645, 1628, 1464 and 1327 cm^{-1}. ^1H NMR ($CDCl_3$) δ_H: 1.26 (3H, t, $^3J_{HH}$ = 7.3 Hz, CH_3 of OEt); 4.16 (2H, q, $^3J_{HH}$ = 7.3 Hz, OCH_2 of OEt); 5.03 (1H, s, OCH_2); 5.32 (1H, d, $^3J_{HH}$ = 12.5 Hz, =CH); 6.99–7.36 (3H, m, arom.) and 7.65 (1H, d, $^3J_{HH}$ = 12.5 Hz, OCH=). ^{13}C NMR ($CDCl_3$) δ_C: 14.34 (CH_3); 59.89 (OCH_2 of Et); 67.32 (OCH_2); 97.76 (=CH); 127, 127.18 and 127.95 (3CH, arom.); 137.13 (1C, arom.); 161.30 (OCH=) and 167.51 (C=O of ester).

Ethyl (E)-3-phenyl-3-(2-thienylmethoxy)-2-propenoate ***8b***

Light yellow oil; yield (80 %). IR (KBr, ν_{max}, cm^{-1}): 2982, 1721, 1625, 1494 and 1116 cm^{-1}. ^1H NMR ($CDCl_3$) δ_H: 1.16 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3 of OEt); 4.07 (2H, q, $^3J_{HH}$ = 7.0 Hz, OCH_2 of OEt); 5.17 (1H, s, OCH_2); 5.41 (1H, s, =CH); 6.97–7.51 (8H, m, arom.). ^{13}C NMR ($CDCl_3$) δ_C: 14.17 (CH_3); 59.73 (OCH_2 of OEt); 65.81 (OCH_2); 93.98 (=CH); 126.63; 126.79; 127.56; 127.68; 128.97 and 129.80 (6CH arom); 134.82 and 137.52 (2C, arom.); 161.65 (1C, OC=) and 169.76 (C=O of ester).

Methyl (E)-3-(2-thienylmethoxy)-2-propenoate ***8c*** *(E)*

Light yellow oil; yield (56%). IR (neat, ν_{max}, cm^{-1}): 2953, 1713, 1626, 1436 and 1140 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ_H: 3.69 (3H, s, OCH_3), 5.04 (2H, s, OCH_2), 5.33 (1H, d, $^3J_{HH}$ = 12.5 Hz, =CH); 6.96–7.36 (3H, m, arom.) and 7.61 (1H, d, $^3J_{HH}$ = 12.5 Hz, OCH=). ^{13}C NMR ($CDCl_3$) δ_C: 51.19 (OCH_3), 67.41 (OCH_2), 97.44 (=CH) and 161.47 (OCH=), 127.01, 127.22 and 127.99 (3CH, arom.), 137.07 (1 C, arom.) and 167.91 (C=O of ester).

Methyl (Z)-3-(2-thienylmethoxy)-2-propenoate ***8c*** *(Z)*

Light yellow oil; yield (14%). IR (neat, ν_{max}, cm^{-1}): 2930, 1720, 1646, 1439 and 1168 cm^{-1}. ^1H NMR ($CDCl_3$) δ_H: 3.68 (3H, s, OCH_3), 4.90 (1H, d, $^3J_{HH}$ = 7.5 Hz, =CH); 5.18 (2H, s, OCH_2), 6.60 (1H, d, $^3J_{HH}$ = 7.5 Hz, OCH=) and 6.98–7.70 (3H, m, arom.). ^{13}CNMR ($CDCl_3$) δ_C: 50.96 (OCH_3), 70.41 (OCH_2), 97.05 (=CH) and 161.50 (OCH=); 127.04, 127.40 and 128.19 (3CH, arom.), 137.15 (1 C, arom.) and 167.91 (C=O of ester).

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