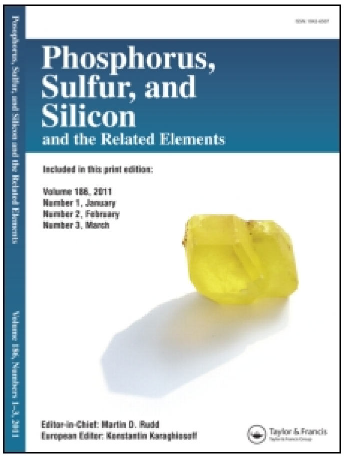

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Regio- and Stereoselective Addition of 1,2,3,6-Tetrahydrophthalimide to Electron-Poor Acetylenic Esters in the Presence of Triphenylphosphine

Amir Tofangchi Mahyari[a]; Nahid Shajari[ab]; Ebrahim Ahmadi[a]; Ali Ramazani[a]
[a] Chemistry Department, Zanjan University, Zanjan, Iran [b] Chemistry Department, Islamic Azad University-Zanjan Branch, Zanjan, Iran

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Amir Tofangchi Mahyari
Chemistry Department, Zanjan University, Zanjan, Iran

Nahid Shajari
Chemistry Department, Zanjan University, Zanjan, Iran
Chemistry Department, Islamic Azad University-Zanjan Branch,
Zanjan, Iran

Ebrahim Ahmadi
Ali Ramazani
Chemistry Department, Zanjan University, Zanjan, Iran

Protonation of the highly reactive 1:1 intermediates, produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates (or alkyl acetylenecarboxylates), by 1,2,3,6-tetrahydrophthalimide leads to vinyltriphenylphosphonium salts, which undergo Michael addition reaction with conjugate base to produce phosphorus ylides. Dipotassium hydrogen phosphate and silica gel were found to catalyze conversion of the phosphorus ylides to electron-poor N-*vinyl imides in solvent-free conditions under thermal (80–90°C, 40–50 min) conditions. The structural analysis of the products indicated that the reaction is regio- and stereoselective.*

Keywords Acetylenic esters; dipotassium hydrogen phosphate; electron-poor *N*-vinyl imide; regioselective, stereoselective; silica gel; vinyltriphenylphosphonium salt

INTRODUCTION

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

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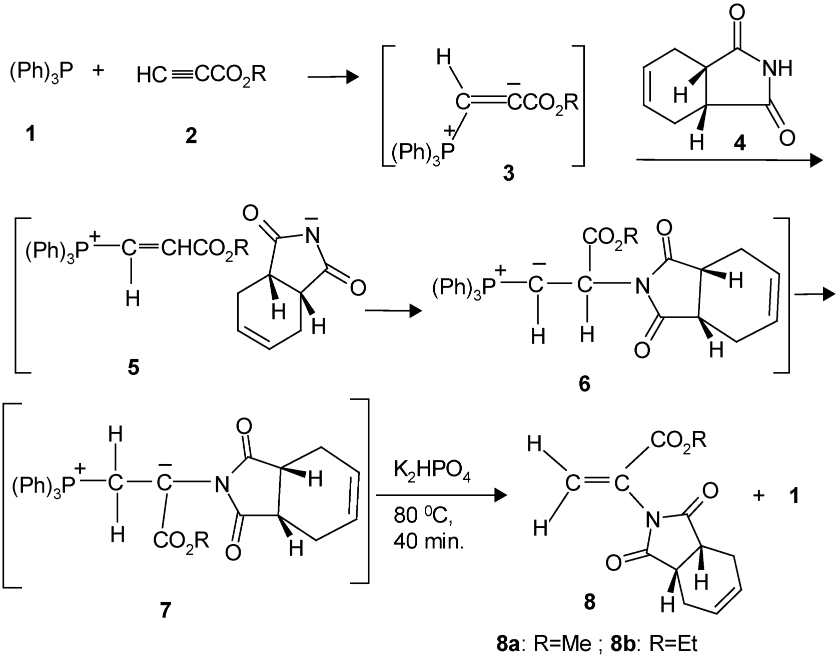
Address correspondence to Ali Ramazani, Department of Chemistry, Zanjan University, P.O. Box 45195-313, Zanjan, Islamic Republic of Iran. E-mail: aliramazani@yahoo.com

crystallographic investigations.[1] They are excellent ligands and excel in their ligating functions the unstabilized ylides because of their ambidentate and chemically differentiating character. 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.[2] The nucleophilicity at the ylidic carbon is a factor of essential mechanistic importance in the use of these ylides as Wittig reagents. Phosphorus ylides are important reagents in synthetic organic chemistry, especially in the synthesis of naturally occurring products, compounds with biological and pharmacological activity.[3] These ylides are usually prepared by treatment of a phosphonium salt with a base, and phosphonium salts are usually obtained from a phosphine and an alkyl halide. Phosphonium salts are also prepared by Michael addition of phosphorus nucleophiles to activated olefins and in other ways.[4] The phosphonium salts are most often converted to the ylide by treatment with a strong base, though weaker bases can be used if the salt is acidic enough. In recent years, we have established a one-pot method for the synthesis of stabilized ylides.[5–10] In this article, we attempt to describe the regio- and stereoselective preparation of electron-poor *N*-vinyl imides from the dialkyl acetylenedicarboxylates (or alkyl acetylenecarboxylates) and 1,2,3,6-tetrahydrophthalimide in the presence of triphenylphosphine in fairly good yields.

RESULTS AND DISCUSSION

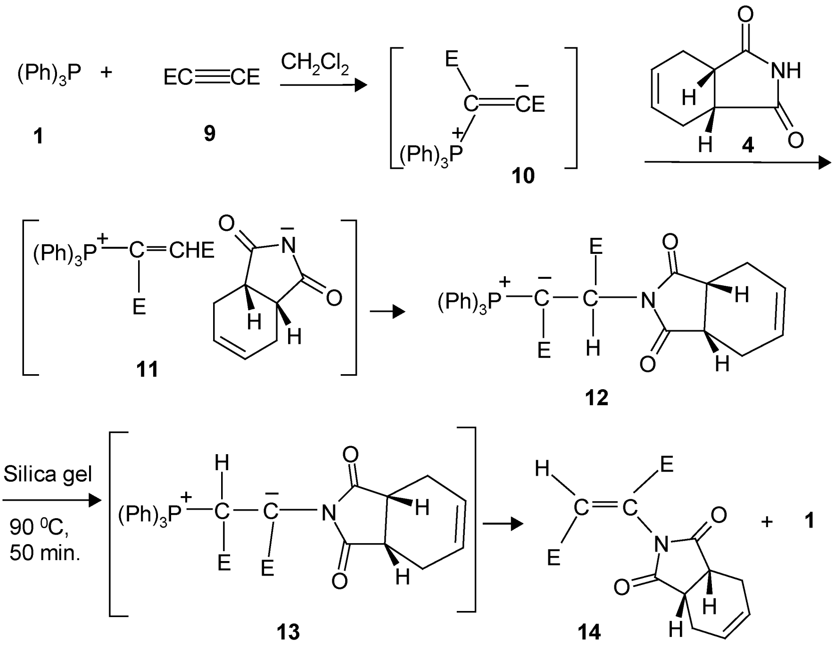
The zwitterionic intermediate **7** may result from initial addition of triphenylphosphine (**1**) to the alkyl acetylenecarboxylate **2** and concomitant protonation of the 1:1 adduct **3**, followed by attack of the NH-acid anion on the vinyltriphenylphosphonium cation to form the phosphorane **6** (Scheme 1) that undergo intramolecular protontransfer[11] leads to formation of zwitterionic intermediate **7**. TLC indicated formation of zwitterionic intermediate **7** in CH_2Cl_2. Dipotassium hydrogen phosphate and potassium carbonate powders were found to catalyze conversion of the zwitterionic intermediate **7** to electron-poor *N*-vinyl imides (**8**) in solvent-free conditions[12] under thermal (80°C, 40 min.) conditions. In the absence of the K_2HPO_4 (or K_2CO_3) powder, the conversion of the zwitterionic intermediate **7** to electron-poor *N*-vinyl imides (**8**) were not observed and decomposition of the starting materials were observed (Scheme 1). The reaction 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[11] is proposed in Scheme 1. We have also used MgO, KI,



SCHEME 1

KH_2PO_4, Al_2O_3, SiO_2, NH_4Cl, ZnO, and Na_2CO_3 in this reaction, but no product were observed (or in the some cases the conversions were very low) and in all cases decomposition were observed.

We have also used dialkyl acetylenedicarboxylates (**9**) (Scheme 2) instead of alkyl acetylenecarboxylate (**2**) in this reaction. The stabilized phosphorus ylides **12** may result from initial addition of triphenylphosphine (**1**) to the acetylenic esters **9** and concomitant protonation of the 1:1 adduct **10**, followed by attack of the NH-acid anion[11] on the vinyltriphenylphosphonium cation to form the phosphorane **12** (Scheme 1). TLC indicated formation of the stabilized phosphorus ylides **12** in CH_2Cl_2. Silica gel, KH_2PO_4 and NH_4Cl powders were found to catalyze conversion of the stabilized phosphorus ylides **12** to electron-poor *N*-vinyl imides (**14**) in solvent-free conditions[11] under thermal (90°C, 50 min) conditions. In the absence of the Silica gel (or KH_2PO_4 and NH_4Cl) powder, the conversion of the stabilized phosphorus ylides **12** to electron-poor *N*-vinyl imides (**14**) were not observed and decomposition of the starting materials were observed (Scheme 2). The reaction proceeds smoothly and cleanly under mild conditions and no side reactions were observed. The mechanism of the reaction has not been



14a: E=CO$_2$Me ; **14b**: E=CO$_2$Et

SCHEME 2

established experimentally. However, a possible explanation[11] is proposed in Scheme 1. We have also used MgO, KI, K_2HPO_4, Al_2O_3, ZnO, K_2CO_3, and Na_2CO_3 in this reaction, but no products were observed (or in the some cases the conversions were very low), and in all cases decomposition was observed. The NMR spectra indicated that solutions of compound **14a–b** ($CDCl_3$ as solvent) contain only *Z* isomer. The structures **8a–b** and **14a–b** were deduced from their IR, ^{1}H, and ^{13}C NMR spectra. The ^{1}H NMR spectra of compounds **8a–b** exhibited two slightly broad single peaks at $\delta = 5.79$–5.81 and $\delta = 6.56$–6.57 for the two diastereotopic protons of the olefinic methylene group.[11] The alkoxy groups and the heterocyclic moieties give characteristic signals at appropriate chemical shifts (see Experimental section). Further evidence was obtained from the ^{13}C NMR spectra which displayed a methylene carbon resonance at about $\delta = 127.52$ and carbonyl carbons at about $\delta = 161.57$–178.25 (see Experimental section). The ^{1}H NMR spectra of compounds **14a–b** exhibited single peak at $\delta = 7.04$–7.05 for the olefinic proton of the electron-poor double bond, that are well consistent with their *Z* stereochemistry.[13,14] The alkoxy groups and the heterocyclic moieties give characteristic signals at the appropriate chemical shifts (see Experimental section). Further evidence was obtained from the ^{13}C NMR spectra which displayed carbonyl carbons at about $\delta = 161.21–177.50$ (see Experimental section), that are well consistent with their structures.[13,14]

CONCLUSION

In conclusion, we have developed a convenient, one-pot regio-, and stereoselective method for preparing electron-poor *N*-vinyl imides (**8a–b** and**14a–b**) utilizing in situ generation of the phosphonium salts. Other aspects of this process are under investigation.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker Spectrospin spectrometer at 250 and 62.5 MHz, respectively.

Preparation of Alkyl 2-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl)acrylates 8a–b

To a magnetically stirred solution of triphenylphosphine (0.262 g, 1 mmol) and 1,2,3,6-tetrahydrophthalimide (0.151 g, 1 mmol) in dichloromethane (10 ml) was added dropwise to a mixture of alkyl acetylenecarboxylates **2** (1 mmol) in dichloromethane (4 ml) at −10°C over 15 min. The mixture was allowed to warm up to room temperature. Dipotassium hydrogen phosphate powder (1.5 g) was added, and the solvent was evaporated. Dry silica gel and the residue were heated (yield for **8a**, 57%; yield for **8b**, 70%) for 40 min at 80°C and then placed over a column of silica gel powder (12 g). The column chromatography was washed using ethyl acetate-light petroleum ether (1:10) as eluent. The solvent was removed under reduced pressure and products were obtained as viscous yellow oils (**8a–b**) (Scheme 1). The characterization data of the compounds (**8a–b**) are given below.

Selected Data for Methyl 2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl)acrylate 8a

IR(neat)($\upsilon_{\max}$, cm^{-1}): 2953, 1723, 1646, 1207.^{1}H NMR (CDCl$_3$), δ_{H}: 2.24 and 2.63 (2 m, 4H, 2 CH$_2$), 3.18 (m, 2H, 2CH), 3.74 (s, 3H, OCH$_3$), 5.92 (m, 2H, HC=CH), 5.81 and 6.56 (2 s, 2 H, =CH).^{13}C NMR (CDCl$_3$)$\delta_{\mathrm{C}} = 23.44$ (2 CH$_2$), 39.38 (2 CH), 52.72 (OCH$_3$), 127.52 (=CH$_2$), 128.11 (2CH), 129.61 (1C), 162.06 (C=O of ester), 178.27 (2 C=O of imide).

Selected Data for Ethyl 2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl)acrylate 8b

IR(neat)(υ_{max}, cm^{-1}): 2961, 1723, 1646, 1207.^{1}H NMR ($CDCl_3$)δ_H: 1.26 (t, 3 H, $^3J_{HH}$ = 7.0 Hz, CH_3 of Et), 2.22 and 2.63 (2 m, 4 H, 2 CH_2), 3.19 (m, 2 H, 2 CH), 4.20 (q, 2 H,$^3J_{HH}$ = 7.0 Hz, OCH_2 of OEt), 5.91-5.96 (m, 2 H, HC=CH), 5.79 and 6.57 (2 s, 2 H, =CH).^{13}CNMR ($CDCl_3$)δ_C: 14.01 (CH_3), 23.41 (2 CH_2), 39.36 (2 CH), 61.91 (OCH_2 of OEt), 127.52 (=CH_2), 127.72 (2 CH), 129.92 (1 C), 161.57 (C=O of ester),178.25 (2 C=O of imide).

Preparation of Dialkyl (Z)-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl)-2-butenedioates 14a-b

To a magnetically stirred solution of triphenylphosphine (0.262 g, 1 mmol) and 1,2,3,6-tetrahydrophthalimide (0.151 g, 1 mmol) in dichloromethane (10 ml) was added dropwise to a mixture of dialkyl acetylenedicarboxylates **9** (1 mmol) in dichloromethane (4 ml) at −10°C over 15 min. The mixture was allowed to warm up to room temperature. Silica gel powder (1.5 g) was added and the solvent was evaporated. Dry silica gel and the residue were heated (yield for **14a**, 72%; yield for **14b**, 66%) for 50 min at 90°C and then placed over a column of silica gel powder (12 g). The column chromatography was washed using ethyl acetate-light petroleum ether (1:10) as eluent. The solvent was removed under reduced pressure and products were obtained as viscous yellow oils (**14a–b**) (Scheme 2). The characterization data of the compounds (**14a–b**) are given below.

Selected Data for Dimethyl (Z)-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl)-2-butenedioate 14a

IR(neat)(υ_{max}, cm^{-1}): 2953, 1730, 1661, 1276.^{1}H NMR ($CDCl_3$)δ_H: 2.28 and 2.59 (2 m, 4 H, 2 CH_2), 3.20 and 3.22 (2 m, 2 H, 2 CH), 3.71 and 3.80 (2 s, 6 H, OCH_3), 5.93 and 5.94 (2 m, 2 H, HC=CH), 7.05 (s, 1 H, =CH).^{13}C NMR ($CDCl_3$)δ_C: 23.08 and 23.3 (2 CH_2), 39.62 and 40.31 (2 CH), 52.44 and 53.41 (2 OCH_3), 127.72 (2 CH),127.24 (=CH), 128.65 (1C), 161.68, and 162.85 (2 C=O of 2 esters), 177.49 (2 C=O of imides).

Selected Data for Diethyl (Z)-2-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl)-2-butenedioate 14b

IR (neat) (υ_{max}, cm^{-1}): 2930, 1723, 1669, 1269.^{1}H NMR ($CDCl_3$)δ_H: 1.25 and 1.27 (2 t, 6 H, $^3J_{HH}$ = 7.0 Hz, 2 CH_3 of 2 Et), 2.29–2.61 (2 m, 4 H, 2 CH_2), 3.18–3.26 (m, 2 H, 2 CH), 4.18 and 4.26 (q, 4 H,$^3J_{HH}$ = 7.0 Hz, 2 OCH_2 of 2 OEt), 5.93–5.90 (m, 2 H, HC=CH), 7.04 (s, 1 H, =CH).^{13}C NMR ($CDCl_3$)δ_C: 13.97 and 14.01 (2 CH_3), 23.09 (2 CH_2), 39.69 (2 CH), 61.51 and 62.72 (2 OCH_2 of 2 OEt), 127.24 (2 CH), 127.24 (=CH), 128.83 (1C), 161.21, and 162.47 (2 C=O of 2 esters), 177.50 (2 C=O of imide).

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