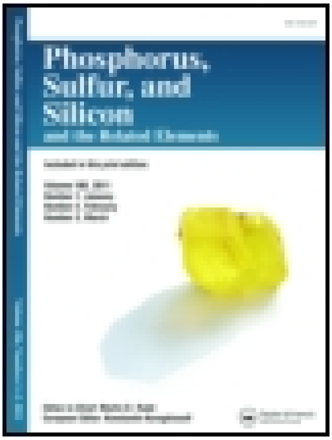

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Vinyltriphenylphosphonium Salt-Mediated Preparation of Fully Substituted Furans and Electron-Poor Imides from Benzoic acid, Cyclohexyl Isocyanide, and Acetylenic Esters

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Protonation of the reactive intermediates produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates by benzoic acid leads to vinyltriphenylphosphonium salts, which undergo complex reactions with cyclohexyl isocyanide to produce corresponding densely functionalized furans and imides in fairly good yields in neutral conditions. The formulas of the products were deduced from their IR, ^1H NMR, and ^{13}C NMR spectra. The reaction is completely stereoselective.

Keywords Acetylenic ester; densely functionalized furan; electron-poor imide; phosphorus ylide; triphenylphosphine

INTRODUCTION

Organophosphorus compounds[1,2] have been extensively employed in organic synthesis as useful reagents as well as ligands in a number of transition metal catalysts.[3] 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.[4] 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.[3,5] The nucleophilicity at the ylidic carbon is a factor of essential mechanistic importance in the

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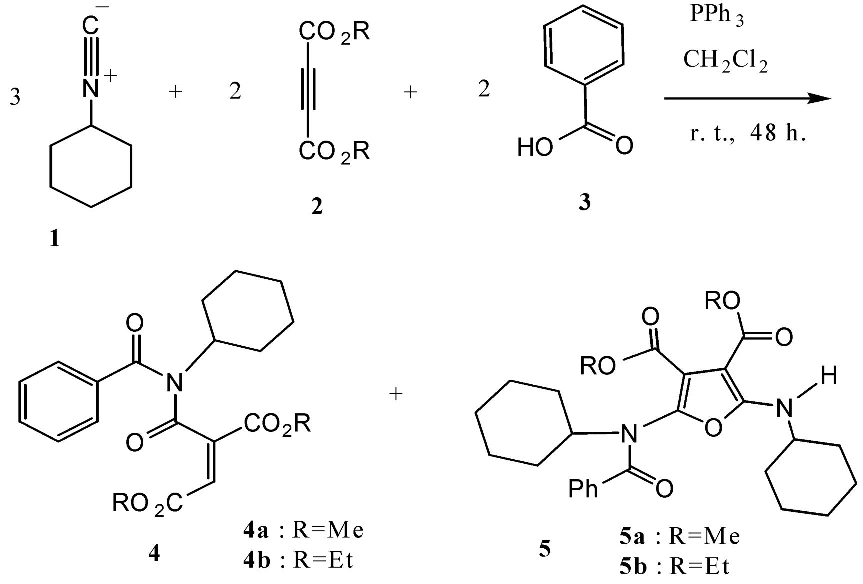
use of these ylides as Wittig reagents. Phosphorus ylides are important reagents in synthetic organic chemistry, especially in the synthesis of naturally occurring products, compounds with biological and pharmacological activity.[1,2] In recent years, we have established a one-pot method for the synthesis of stabilized ylides.[6–15]

For several years, acetylenic esters have attracted the attention of organic chemists and are reactive systems that can take part in many chemical syntheses,[16] almost as a Michael acceptor in the organic reactions.[17] In recent years, there has been increasing interest on the applications of acetylenic esters in the multi-component[16–19] synthesis. Due to the atom economy, convergent character and simplicity of one-pot procedures, multi-component condensation reactions (MCRs) have an advantageous position among other reactions. The development of novel MCRs is receiving growing interest from industrial chemistry research groups and represents a challenge for organic chemists.[20–23] As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[24–26] we sought to develop a convenient preparation of densely functionalized furans **5** and imides **4** in fairly good yields in neutral conditions.

RESULTS AND DISCUSSION

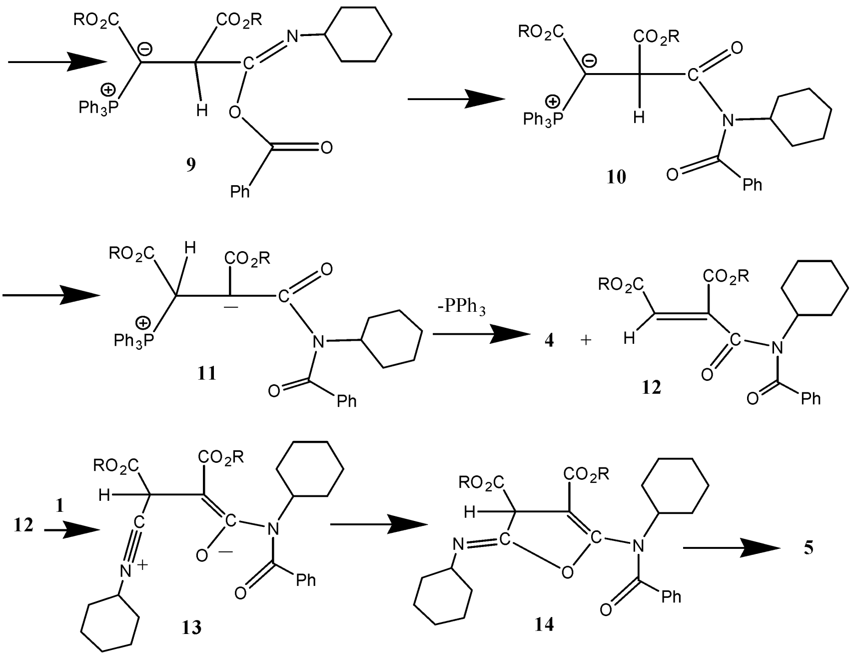
Protonation of the reactive intermediates produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates **2** by benzoic acid **3** leads to vinyltriphenylphosphonium salts **7**, which undergo complex reactions with cyclohexyl isocyanide **1** to produce corresponding densely functionalized furans **5** and imides **4** in fairly good yields in neutral conditions (Scheme 1 and Scheme 2). TLC indicated the formation of products **4** and **5** at room temperature. The reaction proceeds smoothly and cleanly under reaction conditions and no side reactions were observed. The reactions were completed in 48 h. and densely functionalized furans **5** observed as major products (Table I). In this reaction, triphenylphosphine acts as a catalyst. In the absence of the triphenylphosphine, the reactions were completed after 72 h in CH_2Cl_2 at room temperature and imides **4** observed as major products (Table I).[22,23] The ^{1}H NMR ($CDCl_3$) spectra of compounds **4** show the presence of one stereoisomer (*E*) for each imides **4**. *Z* isomers of the imides **4** were not isolated. It seems that *Z* isomers **12** are reactive than *E* isomers toward formation of adduct **13** with cyclohexyl isocyanide **1** and act as intermediate in the formation of furans **5** (Scheme 2). The reaction is completely stereoselective.

The mechanism of the reaction between the triphenylphosphine, cyclohexyl isocyanide (**1**), dialkyl acetylenedicarboxylates (**2**), and benzoic



SCHEME 1

acid (**3**) has not been established experimentally. However, a possible explanation is proposed in Scheme 2. The formulas of the products were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra (See Experimental section). The IR spectrum of **4a** showed strong adsorptions at 1730 (OCNCO), 1685 (CO_2Me), 1615 (C=C), 1538 and 1453 (Ph), and 1369, 1261, 1207, and 1161 (C—O) cm^{-1} indicating the presence of the mentioned functionalities in its formula. The ^{1}H NMR spectrum of **4a** compound exhibited five signals readily recognized as arising from cyclohexyl group ($\delta = 0.89$–2.40, m), two OMe groups ($\delta = 3.76$ and 3.81 ppm), NH ($\delta = 6.53$ ppm, s) and aromatic moieties ($\delta = 7.24$–7.72 ppm, m). The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 15 distinct resonances in agreement with the **4a** formula. Partial assignment of these resonances is given in the spectral analysis section (See experimental section). The ^{1}H and ^{13}C NMR spectra of compound **4b** are similar to those of **4a**, except for the ester groups (^{1}H and ^{13}C NMR), which exhibit characteristic signals with appropriate chemical shifts (see spectral analysis section).[22–26] The IR spectrum of **5a** showed strong adsorptions at 3461 (NH), 1738 (CO_2Me), 1676 (CO_2Me), 1607 (CON), 1238 (C—O) cm^{-1} indicating the presence of the mentioned functionalities in its formula. The ^{1}H NMR spectrum of **5a** compound exhibited five signals readily recognized as arising from cyclohexyl group ($\delta = 0.90$–2.40, m), two OMe groups ($\delta = 3.65$ and 3.70 ppm), NH ($\delta = 6.53$ ppm, d,



SCHEME 2

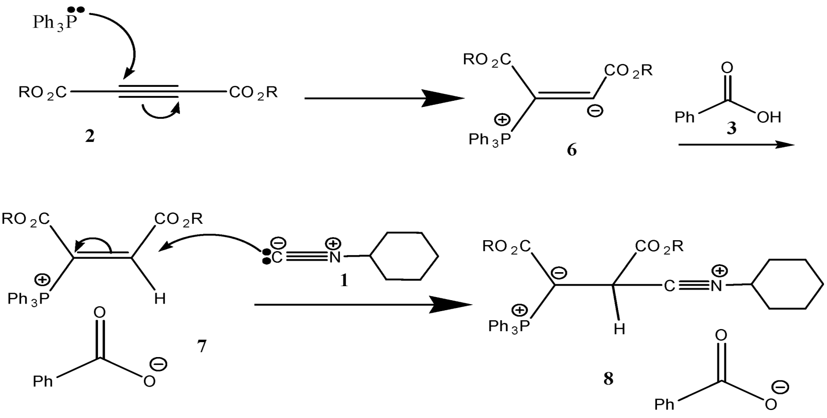
$^3J_{HH} = 8.0$) and aromatic moieties ($\delta = 7.24$–7.72 ppm, m). The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed 18 distinct resonances in agreement with the **5a** formula. Partial assignment of these resonances is given in the spectral analysis section (See Experimental section). The ^{1}H and ^{13}C NMR spectra of compound **5b** are similar to those of **5a**, except for the ester groups (^{1}H and ^{13}C NMR), which exhibit characteristic signals with appropriate chemical shifts (see spectral analysis section).[22–26]

CONCLUSION

In summary, we have found a new and efficient method for preparing electron-poor imides (**4**) and fully substituted furans (**5**) from triphenylphosphine, cyclohexyl isocyanide (**1**) dialkyl acetylenedicarboxylates (**2**) and benzoic acid (**3**) in neutral conditions (Scheme 1, Scheme 2, and Table I). We believe the reported method offers a simple and efficient route for the preparation of electron-poor imides (**4**) and fully substituted furans (**5**) (Scheme 1). Its ease of work up and fairly good yields make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

TABLE I Synthesis of Imides 4 and Furans 5 (See Scheme 1)

Entry	Products	In the presence of PPh_3 (r. t., 48 h.): Total isolated yield % (**4** + **5**); Ratio of **4/5**	In the absence of PPh_3 (r. t., 72 h.): Total isolated yield % (**4** + **5**); Ratio of **4/5**
1	**4a/5a**	88; 30/70	83; 83/17
2	**4b/5b**	82; 35/65	83; 85/15



EXPERIMENTAL

^1H (250.13 MHz) and ^{13}C (62.90 MHz) NMR measurements were recorded on a Brucker 250 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. IR spectra were measured on a Mattson-1000 FTIR spectrophotometer. Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Flash chromatography columns were prepared from Merck silica gel powder.

General Procedure for the Preparation of Compounds 4a–b and 5a–b

To a magnetically stirred solution of triphenylphosphine (0.262 g, 1.00 mmol) and benzoic acid **3** (0.140 g, 1.00 mmol) in dry CH_2Cl_2 (1.00 ml) was added dropwise a solution of **2** (1.00 mmol) in CH_2Cl_2 (2.00 ml) at −10°C over 15 min. The mixture was allowed to warm to room temperature and added dropwise a solution of cyclohexyl isocyanide **1** (1.00 mmol) in CH_2Cl_2 (1.00 ml) over 10 min. The mixture was allowed to stirred for 48 h. The solvent was removed under reduced pressure, and the viscous residue was purified by flash column chromatography (silica gel; light petroleum ether-ethyl acetate). Characterization data are given below:

Dimethyl (E)-2-{[benzoyl(cyclohexyl)amino]carbonyl}-2-butenedioate 4a

Viscose yellow oil, IR (KBr) (υ_{max}, cm^{-1}): 1730 (OCNCO), 1685 (CO_2Me), 1615 (C=C), 1538 and 1453 (Ph), 1369, 1261, 1207, and 1161 (C—O). ^1H NMR (250.13 MHz, $CDCl_3$): δ_H 0.89–2.4 (11 H, m, cyclohexyl), 3.76 (3 H, s, OMe), 3.81 (3 H, s, OMe), 6.53 (1 H, s, NH), 7.24–7.72 (5 H, m, arom).^{13}C NMR (62.90 MHz, $CDCl_3$): δ_C24.71 (CH_2 of cyclohexyl), 26.33 (CH_2 of cyclohexyl), 29.29 (CH_2 of cyclohexyl), 52.33 (OMe), 52.97 (OMe), 60.39 (CH of cyclohexyl), 128.44 (2 CH_{ortho} of C_6H_5), 128.58 (C=CH), 132.55 (CH_{para} of C_6H_5), 135.34 (C_{ipso} of C_6H_5), 142.46 (C=CH), 163.14 (PhCONCO), 164.58 (CO_2Me), 165.72 (CO_2Me), 175.12 (PhCON).

Diethyl (E)-2-{[benzoyl(cyclohexyl)amino]carbonyl}-2-butenedioate 4b

Viscose yellow oil, IR (KBr) (υ_{max}, cm^{-1}): 1731 (OCNCO), 1669 (CO_2Me), 1608 (C=C), 1530 and 1453 (Ph), 1373, 1261, 1200 and 1161 (C-O). ^1H NMR (250.13 MHz, $CDCl_3$): δ_H 1.25 (3 H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.32 (3 H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.5–2.4 (11 H, m, cyclohexyl), 4.2 (2 H, q, $^3J_{HH}$ = 7.0 Hz, OCH_2), 4.28 (2 H, q, $^3J_{HH}$ = 7.0 Hz, OCH_2), 6.52 (1 H, s, NH), 7.2–8.1 (5 H, m, arom).^{13}C NMR (62.90 MHz, $CDCl_3$): δ_C 13.94 (CH_3), 14.04 (CH_3), 24.61 (CH_2 of cyclohexyl), 26.35 (CH_2 of cyclohexyl), 29.29 (CH_2 of cyclohexyl), 60.35 (OCH_2), 61.40 (OCH_2), 62.17 (CH of cyclohexyl), 128.45 (2 CH_{ortho} of C_6H_5), 128.52 (C=CH), 129.51 (CH_{para} of C_6H_5), 135.49 (C_{ipso} of C_6H_5), 142.65 (C=CH), 162.65 (PhCONCO), 164.22 (CO_2Me), 165.91 (CO_2Me), 175.05 (PhCON).

Dimethyl 2-[Benzoyl(cyclohexyl)amino]-5-(cyclohexylamino)-3,4-furandicarboxylate 5a

Viscose yellow oil, IR (KBr) (υ_{max}, cm^{-1}): 3461 (NH), 1738 (CO_2Me), 1676 (CO_2Me), 1607 CON), 1238 (C—O). ^1H NMR (250.13 MHz, $CDCl_3$): δ_H 0.9–2.4 (11 H, m, cyclohexyl), 3.65 (3 H, s, OMe), 3.70 (3 H, s, OMe), 6.53 (1 H, d, $^3J_{HH}$ = 8.0, NH), 7.24–7.72 (5 H, m, arom).^{13}C NMR (62.90 MHz, $CDCl_3$): δ_C 24.45 (CH_2 of cyclohexyl), 25.37 (CH_2 of cyclohexyl), 33.29 (CH_2 of cyclohexyl), 50.96 (CH of cyclohexyl), 51.54 (OMe), 51.81 (OMe), 56.73 (CH of cyclohexyl), 85.48 (C4 of furan), 114.05 (C3 of furan), 127.28 (CH_{para} of C_6H_5), 127.62 (2 CH_{ortho} of C_6H_5), 130.14 (2 CH_{meta} of C_6H_5), 136.45 (C_{ipso} of C_6H_5), 138.73 (C5 of furan), 159.46 (C2 of furan), 162.29 (CO_2Me), 164.96 (CO_2Me), 171.23 (NCO).

Diethyl 2-[Benzoyl(cyclohexyl)amino]-5-(cyclohexylamino)-3,4-furandicarboxylate 5b

Viscose yellow oil, IR (KBr) (υ_{max}, cm^{-1}): 3353 (NH), 1723 (CO_2Me), 1669 (CO_2Me), 1607 (CON), 1238 (C—O). ^1H NMR (250.13 MHz, $CDCl_3$): δ_H 1.21 (3 H, t, $^3J_{HH} = 7.3$ Hz, CH_3), 1.26 (3 H, t, $^3J_{HH} = 7.3$ Hz, CH_3), 0.8–2.4 (11 H, m, cyclohexyl), 3.49–4.51 (4 H, m, OCH_2), 6.64 (1 H, d, $^3J_{HH} = 8.3$, NH), 7.2–8.2 (5H, m, arom). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ_C 14.05 (CH_3), 14.22 (CH_3), 24.44(CH_2 of cyclohexyl), 24.59 (CH_2 of cyclohexyl), 24.70 (CH_2 of cyclohexyl), 25.38 (CH_2 of cyclohexyl), 51.49 (CH of cyclohexyl), 56.77 (CH of cyclohexyl), 59.68 (OCH_2), 61.01 (OCH_2), 85.76 (C4 of furan), 114.54 (C3 of furan), 127.43 (CH_{para} of C_6H_5), 127.73 (2 CH_{ortho} of C_6H_5), 130.11 (2 CH_{meta} of C_6H_5), 136.35 (C_{ipso} of C_6H_5), 137.99 (C5 of furan), 159.36 (C2 of furan), 162.20 (CO_2Me), 164.62 (CO_2Me), 171.26 (NCO).

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