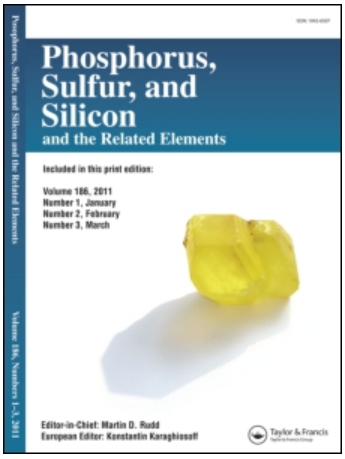

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Synthesis of Dimethyl 2-(2,4,6-Trimethylphenoxy)-3-triphenylphosphoniobutanedioate and its Application in Intramolecular Wittig Reactions

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SYNTHESIS OF DIMETHYL 2-(2,4,6-TRIMETHYLPHENOXY)-3-TRIPHENYLPHOSPHONIOBUTANEDIOATE AND ITS APPLICATION IN INTRAMOLECULAR WITTIG REACTIONS

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Protonation of the reactive 1:1 intermediate produced in the reaction between triphenylphosphine and dimethyl acetylenedicarboxylate by 2,4,6-trimethylphenol leads to a stable ylide in high yield, which is employed in intramolecular Wittig reactions.

Keywords: 2,4,6-Trimethylphenol; acetylenic ester; heterocyclic synthesis; stabilized ylide; triphenylphosphine

INTRODUCTION

A variety of methods are known for the synthesis of vinylphosphonium compounds, most of which utilize an appropriately substituted carbon skeleton, such as an alkene or alkyne. The most powerful of these methods is the efficient Pd-catalyzed preparation of Ph_3P-substituted vinylphosphonium compounds from vinyl triflates and triphenylphosphine.[1] We wish to report a direct, efficient and operationally convenient approach to the synthesis of dimethyl 2-(2,4,6-trimethylphenoxy)-3-triphenylphosphoniobutanedioate **1**. Thus reaction of triphenylphosphine with dimethyl acetylenedicarboxylate

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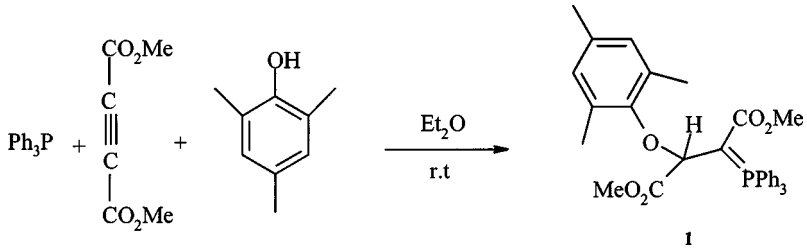
(DMAD) in the presence of 2,4,6-trimethylphenol leads to the corresponding vinylphosphonium derivatives **1** (Scheme 1).



1

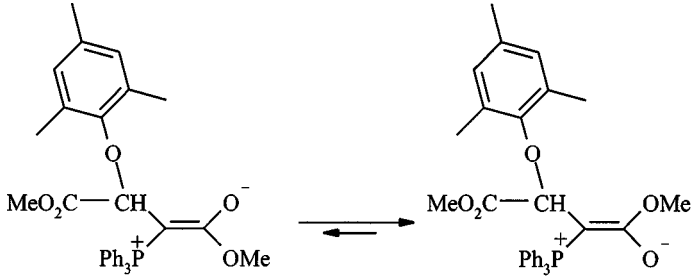
SCHEME 1

RESULTS AND DISCUSSION

The reaction of triphenylphosphine with DMAD in the presence of 2,4,6-trimethylphenol proceeded spontaneously at room temperature in diethyl ether, and is finished within a few minutes. ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of dimethyl 2-(2,4,6-trimethylphenoxy)-3-triphenylphosphoniobutanedioate **1**. Any product other than **1** could not be detected by NMR spectroscopy. The structure of compound **1** was deduced from its elemental analyses and its ^{1}H, ^{13}C, and ^{31}P NMR and IR spectra. The mass spectrum of **1** displayed a weak molecular ion peak at $m/z = 540$. Any initial fragmentation involved the loss of ester, Ph_3P, and $Me_3C_6H_2O$ moieties.

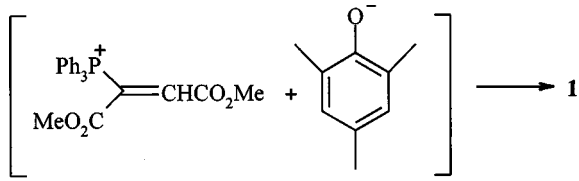
The stabilized phosphorance **1,** in $CDCl_3$ solution, resolves at room temperature into two isomeric forms (in 3:1 ratio) which are identified as (*Z*)-**1** and (*E*)-**1** (see Scheme 2). Thus, the ^{1}H NMR spectrum of **1** exhibited four single sharp lines readily recognizable as arising from the methoxy group in the two isomers of **1** [major isomer (*E*)-**1** $\delta = 3.67$ and 3.85, and minor isomer (*Z*)-**1** $\delta = 3.18$ and 3.81], along with two doublets at $\delta = 4.22$ ($^{3}J_{HP} = 15.5$ Hz) and $\delta = 4.39$ ($^{3}J_{HP} = 15.0$ Hz) for the OCH proton in (*E*) and (*Z*) isomers respectively. Assignment of configuration (*Z*) to the minor geometrical isomer is based on the ^{1}H chemical shift of the OCH_3 group, which is expected to be shielded as a result of the anisotropic effect of the phenyl groups (see Scheme 2). The methine protons of the phenolic residue in both isomers give rise to a single peak at $\delta = 6.62$, and the Ph_3P group exhibits a fairly complex multiplet at $\delta = 7.3$–7.7.

We have not yet established the mechanism of the reaction between triphenylphosphine and DMAD in the presence of



SCHEME 2

2,4,6-trimethylphenol in an experimental manner, but a possible explanation is proposed in Scheme 3. On the basis of the chemistry of trivalent phosphorus nucleophiles, it is reasonable to assume that compound **1** results from the initial addition of triphenylphosphine to the acetylenic ester and a subsequent protonation of the reactive 1:1 adduct by 2,4,6-trimethylphenol. Then, the positively charged ion might be attacked by the conjugate base of the phenol to produce the stabilized phosphorane **1** (see Scheme 3).

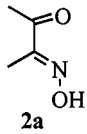
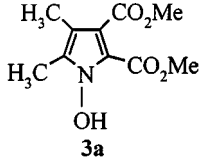
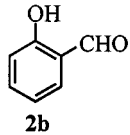
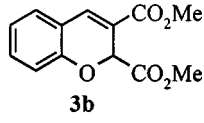
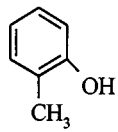
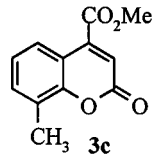
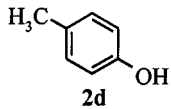
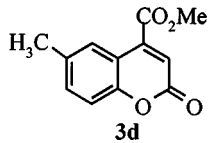
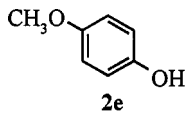
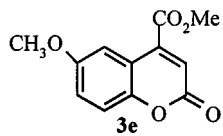
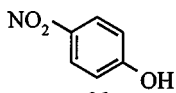
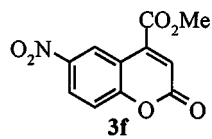
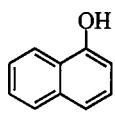
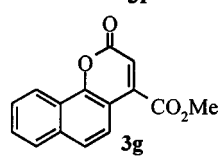
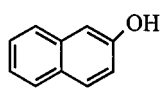
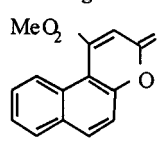


SCHEME 3

Dimethyl 2-(2,4,6-trimethylphenoxy)-3-triphenylphosphoniobutanedioate **1** may be used as a reagent in intramolecular Wittig reactions.[2,3] We have recently described the synthesis of functionalized heterocyclic derivatives of 2*H*-chromenes,[4–6] *N*-hydroxypyrroles,[7–9] and coumarines,[10–13] from the reaction of triphenylphosphine, dialkyl acetylenedicarboxylates and hydroxy-containing compounds. Now, we wish to report the use of the stable vinyltriphenylphosphonium derivative **1**, as a reagent, in the synthesis of these heterocyclic systems. Thus mixing an equimolar amount of compound **2** and reagent **1**, in dichloromethane at room temperature, leads to product **3** in fairly high yields together with 2,4,6-trimethylphenol (see Table I).

In summary, the reaction of triphenylphosphine and electron-deficient acetylenic esters in the presence of 2,4,6-trimethylphenol

TABLE I Preparation of Heterocyclic Compounds **3a–h** by Reaction Between Phosphorus Ylide **1** and Compounds **2a–h**

Entry	Compounds	Products	Yield (%)
1	 **2a**	 **3a**	76
2	 **2b**	 **3b**	81
3	 **2c**	 **3c**	64
4	 **2d**	 **3d**	69
5	 **2e**	 **3e**	89
6	 **2f**	 **3f**	92
7	 **2g**	 **3g**	85
8	 **2h**	 **3h**	83

provides a simple one-pot synthesis of the stable reagent **1** of potential synthetic interest.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured with a Bruker DRX-500 AVANCE instrument with $CDCl_3$ as solvent at 500.1, 125.7, and 202.5 MHz respectively. The mass spectra were recorded on a Finningan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

Preparation of Dimethyl 2-(2,4,6-trimethylphenoxy)-3-triphenylphosphoniobutanedioate 1

To a magnetically stirred solution of triphenylphosphine (0.52 g, 2 mmol) and 2,4,6-trimethylphenol (0.27 g, 2 mmol) in diethyl ether (8 mL) was added dropwise dimethyl acethylendicarboxylate (0.28 g, 2 mmol) at −10°C over 3 min. After 10 min., the product was filtered and washed with 5 mL of cold diethyl ether to yield 1.07 g, yellow powder, m.p. 134–135°C, 96% of **1**. IR (KBr) (ν_{max}, cm^{-1}): 1754 and 1724 (C=O, ester). Analysis: Calc. for $C_{30}H_{33}O_3P$ (540.60): C, 73.32, H, 6.15; found: C, 73.0, H, 6.2.(*E*)-**1**(75%): δ_H 1.90 (6 H, s, 2 CH_3); 2.20 (3 H, s, CH_3); 3.67, 3.87 (6 H, 2 s, 2 OCH_3); 4.22 (1 H, d, $^{3}J_{PH}$ 15.5 Hz); 6.62 (2 H, s, 2 CH); 7.35–7.75 (15 H, m, Ar); δ_C 16.7 (2 CH_3); 20.68 (CH_3); 52.3 and 52.38 (2 OCH_3); 46.0 (C, $^{1}J_{PH} = 134.4$ Hz, P=C); 79.27 (d, $^{2}J_{PC} = 17.5$ Hz, P=C–*C*H); 52.34 and 52.42 (2 OCH_3). ^{31}P NMR (202.4 MHz; $CDCl_3$): δ23.80 (Ph_3P^+–C).

^{1}H, ^{13}C, and ^{31}P NMR data for the minor (25%) isomer (*Z*)-**1**: δ_H 1.90 (6 H, s, 2 CH_3); 2.20 (3 H, s, CH_3); 3.18, 3.81 (6 H, 2 s, 2 OCH_3); 4.39 (1 H, $J = 15.0$ Hz); 6.89 (2 H, s, 2 CH); 7.35–7.75 (15 H, m, Ar); δ_C 15.98 (2 CH_3); 20.68 (CH_3); 50.31 and 52.38 (2 OCH_3); 44.46 (C, $J = 127.1$); 52.23 (CH, $J = 16.6$); 79.9 (C, $J = 16.1$); 127.0 (C, $J = 93.4$); 128.37–133.89 (Ar), 150.22 (C); 169.42 (C, $J = 14.5$); 173.89 (C, $J = 9.8$); ^{31}P NMR (202.4 MHz; $CDCl_3$): δ23.20 (Ph_3P^+–C).

General Procedure for Preparation of 3

Typical reaction process for the preparation of dimethyl 2,3-dimethyl-*N*-hydroxypyrrole-4,5-dicarboxylate (entry 1 in Table I) is described below as an example. To a magnetically stirred solution of **2a** (2 mmol)

in diethyl ether (5 mL) was added 1.02 gr (2 mmol) of **1**. The reaction mixture was stirred for 24 hr. The solvent was removed under reduced pressure and the residue was purified by silica gel (Merck silica gel 60, 230–400 mesh) column chromatography using ethyl acetatehexane (1:3) as eluent to yield compound **3a** (see Table I).

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