Novel Three-Component Route to Diastereoselective Synthesis of Trisubstituted Vinylphosphonates Using Phosphites, Acetylenic Esters, and Aroyl Chlorides

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Trisubstituted vinylphosphonates have been prepared via three-component reaction using phosphites, acetylenic esters, and aroyl chlorides in good yields. A variety of phosphites, activated acetylenes, and aroyl chlorides have been successfully employed in these reactions. In addition, three-component synthesis of vinylphosphonate provides exclusive *E*-olefin stereochemistry.

Introduction

In the past few years, combinatorial methods using multicomponent reactions have been closely examined as a fast and convenient solution for the synthesis of diverse classes of compounds.[1,2] Multicomponent reactions (MCRs), defined as one-pot reactions in which at least three functional groups join through covalent bonds, have been steadily gaining importance in synthetic organic chemistry.[1–4]

Organophosphonates have been used as substitutes of the corresponding esters and acids of high biological activity[5a,b] and as convenient probes for designing antibodies on the basis of transition state models. These investigations have been supported by organic synthesis; therefore, development of protocols for obtaining phosphonates of complex structures is inevitably important.[5c–e]

Vinylphosphonates are important synthetic intermediates[6] and have been investigated as biologically active compounds.[7] Vinylphosphonates have been used as intermediates in stereoselective synthesis of trisubstituted olefins[8,9] and in heterocycle synthesis.[10] They have been also extensively used in polymer sciences as additives or flame-retardants.[11] In medicinal chemistry, vinylphosphonates often exhibit interesting biological properties. This is the case for instance for nucleotide[12] or polyisoprenoid-derived[13] vinylphosphonates. In a recent example, a series of substituted vinylphosphonates has been recognized in vitro as excellent matrix metalloproteinase (MMP-2) inhibitors with potential anticancer implications.[14] The synthesis of vinylphosphonates has also been widely examined and a variety of noncatalytic and catalytic approaches have been described in the literature. Recent methods are limited by the requirement of highly reactive functional groups in the substrates.[15a–m] Several methods have been reported for the synthesis of vinylphosphonates.[16] However, they all rely on multistep reactions or their yields are low, and the reaction times are long. For example, diethyl 1-methyl-2-(trifluoromethyl)-4-phenyl-1,3-butadienyl phosphonate was synthesized through a multistep pathway in 71% with diastereoselectivity 1*E*,3*E*:1*E*,3*Z* 90:10, as illustrated by Scheme 1.[16a] Thus, development of new synthetic methods remains an attractive goal.

In this paper, as part of our ongoing studies on the multicomponent area,[17] we present herein our results of a novel discovery involving synthesis of vinylphosphonates, using commercially available starting materials in excellent yields and good stereoselectivities (Figure 1).

It is to be noted here that this is the first report of the synthesis of dialkyl (*E*)-2-(dialkoxyphosphoryl)-3-(aroyl)-2-butenedioate derivatives using multicomponent condition and this new reaction opens an important field to the use of MCR strategy in vinylphosphonic acid derivative synthesis.

Results and Discussion

Aroyl chlorides offer sp^2 carbon electrophilic sites, and therefore, it was of interest to examine the reactivity profile of the zwitterion toward (*E*)-vinylphosphonate derivatives. Thus, when aroyl chlorides **3** were treated with the in situ generated zwitterion, from trialkyl phosphites **1** and dialky acetylenedicarboxylate **2** in toluene at reflux condition, the (*E*)-vinylphosphonate derivatives **4** were obtained in 91−96% yield after 8 h. The structures of products are shown in Figure 2. The IR spectrum of **4a** exhibited absorption bands due to the carbonyl group of esters at 1724, ArC═O group at 1675, C═C group at 1611, Ar group at 1581 and 1441, and the absorption bands of the phosphonate moiety appeared at 1240 (P═O), 1101 and 1018 (PO−Me), and 844 cm^{-1} (P−O).

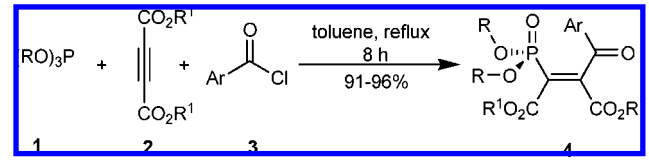

Figure 1. Synthesis of dialkyl (*E*)-2-(dialkoxyphosphoryl)-3-(aroyl)-2-butenedioate derivatives.

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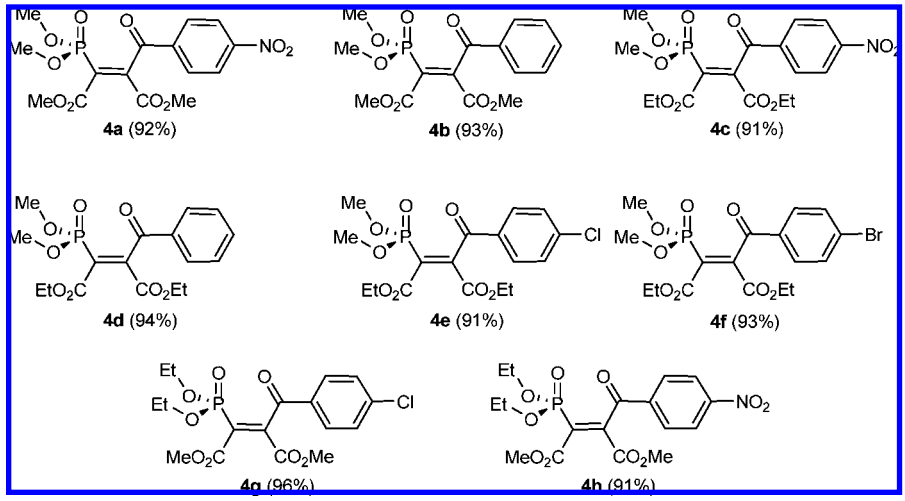
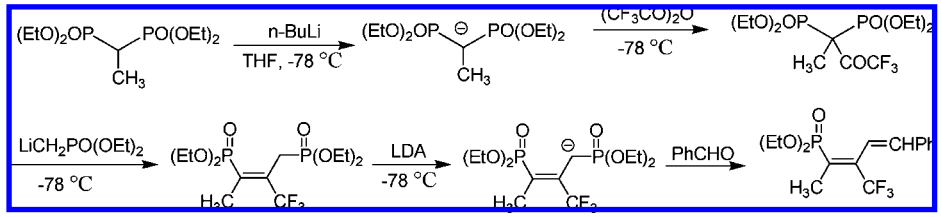


Figure 2. Structure of products **4a**−**h**.

Scheme 1. Preparation of Substituted Trifluoromethylated 1,3-Dienylphosphonates via a Multistep Pathway



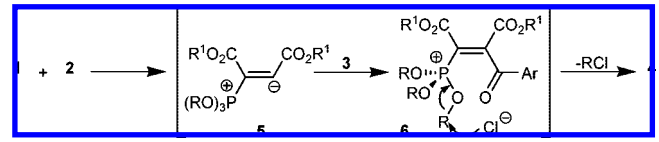
The ^{1}H NMR spectrum of **4a** exhibited one sharp doublet readily recognized as arising from methoxies (δ = 3.69, $^{3}J_{HP}$ 12.7 Hz, P(OMe)$_2$ and two sharp singlets from methoxy groups (δ = 3.70 and 3.90). The aryl moiety exhibited characteristic signals in the aromatic region of the spectrum.

The ^{1}H and ^{13}C-decoupled ^{31}P NMR spectrum of **4a** exhibited one sharp singlet readily recognized as arising from phosphonate (δ = 10.19). The relative stereochemistry of **4a** was determined on the basis of coupling constants of the ^{31}P—^{13}C of the vinylphosphonate. Vicinal ^{31}P—^{13}C coupling through a π bond is a useful tool for assigning *Z* and *E* structure. In general, ^{3}J (PC)-trans is much larger than ^{3}J (PC)-cis.[18] In the ^{13}C NMR spectrum of **4a**, the $^{3}J_{PC}$ value of 6.1 Hz for P—C (δ = 189.08, ArC═O) was diagnostic for their *E* relationship as attested by ref 18. The ^{1}H, ^{13}C, and ^{31}P NMR spectra of compounds **4b**−**h** are similar to those of **4a** except for the alkoxy group, ester groups, and the aryl moiety which exhibit characteristic signals with appropriate chemical shifts. X-ray crystallographic analysis revealed the relative configuration of the isomer **4a** as depicted in Figure 3 (see the Supporting Information).

Although we have not established the mechanism of the reaction between the phosphites **1** and the acetylenic esters **2** in the presence of the aroyl chloride **3** in an experimental manner, a possible explanation is proposed in Scheme 2.

On the basis of the well-established chemistry of acetylenic esters,[17a–c,g,19] it is reasonable to assume that the functionalized vinylphosphonate derivatives **4** apparently result from initial addition of the phosphite to the acetylenic ester and subsequent attack of the resulting zwitterion **5** to the aroyl

Scheme 2. Possible Mechanism for the Formation of Products **4a**−**h**



chloride **3** to yield ion pair **6**. Then, attack of the chloride ion would yield the vinylphosphonates **4** (Scheme 2).

Conclusion

In summary, the reaction between phosphites and dialkyl acetylenedicarboxylates in the presence of aroyl chlorides provides a simple one-pot entry into the synthesis of vinylphosphonate derivatives of potential synthetic and pharmacologically interest. The present method carries the advantage of being performed under the one-pot multicomponent conditions, and requiring no activation or modification

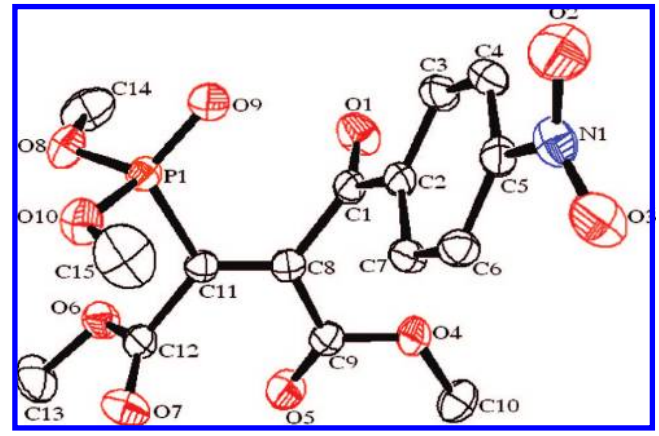


Figure 3. ORTEP diagram of **4a**.

of the educts. In addition, vinylphosphonate derivatives using commercially available starting materials are synthesized.

Supporting Information Available. Experimental procedures, IR, mass, ^{1}H, ^{13}C, and ^{31}P NMR for all compounds, crystallographic data, and ORTEP/X-ray structures for **4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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