Synthesis of Highly Functionalized Cyclobutene Derivatives

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Summary. Protonation of the reactive 1:1 intermediates produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates with CH-acids, such as ethyl 2,4-dioxo-hexanoate and ethyl 2,4-dioxo-5-methylhexanoate, lead to vinyltriphenylphosphonium salts, which undergo an intramolecular Wittig reaction to produce cyclobutene derivatives in fairly high yields.

Keywords. Cyclobutene derivatives; CH-acid; Intramolecular Wittig reaction; Acetylenic esters.

Introduction

Although several strategies for the synthesis of cyclobutenes have been developed in the past [1–3], this class of cyclenes is generally not easily accessible. In recent years, several routes to cyclobutenes via cycloaddition reactions have been described [4–6]. However, the general applicability of these methods is limited. We previously have described the synthesis of cyclobutene derivatives from the stereoselective intramolecular Wittig reaction of a vinyltriphenylphosphonium salt [7–9]. As part of our current studies on the development of new routes to heterocyclic and carbocyclic systems, we now report a convenient and facile synthesis of functionalized cyclobutene derivatives via intramolecular Wittig reaction.

Results and Discussion

The reactions of triphenylphosphine and dialkyl acetylenedicarboxylates 1 in the presence of a strong CH-acid, such as ethyl 2,4-dioxopentanoate (2a), lead to diastereomeric cyclobutene isomers 3 in high yields (Scheme 1).

We have not yet established a mechanism for the formation of 3 in an experimental manner, but a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of trivalent phosphorus nucleophiles [10–14], it is reasonable to assume that 3 results from initial addition of triphenylphosphine to
the acetylenic ester and subsequent protonation of the 1:1 adduct by 2. Then, the positively charged ion might be attacked by the conjugate base of the CH-acid to form the phosphorane 4, which is converted to 3 under the reaction conditions employed.

Compounds 3 possess two stereogenic centers, and two diastereoisomers are expected. In fact, the NMR spectra of 3a–3i show the presence of both isomers. The $^3J_{HH}$ values of the two adjacent methine groups have been employed to assign the relative configuration.

The structures of 3a–3i were deduced from their elemental analyses and their IR, $^1$H, and $^{13}$C NMR spectra. The $^1$H NMR spectra of the cyclobutene derivatives display signals at about $\delta = 3.80–4.02$ ppm for the two methine groups (doublets, $^3J_{HH} = 3.0–6.0$ Hz), in agreement with the cis geometry of these protons together