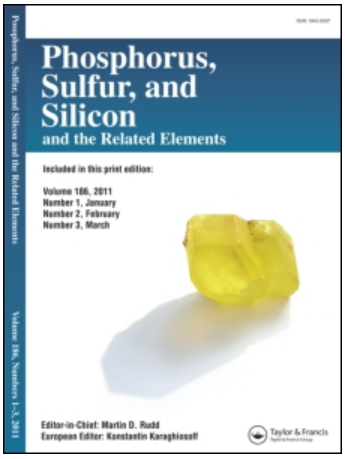

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REACTION OF KETOPHOSPHONIUM YLIDES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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The reaction of ketophosphonium ylides with dimethyl acetylenedicarboxylate in aprotic solvents gave mixtures of Z and E alkene products. Under protic conditions the initial Michael adduct was protonated and gave Z and E isomers of the alkene product as well. Depending on the alkyl group of the ketoylide, different product ratios were seen.

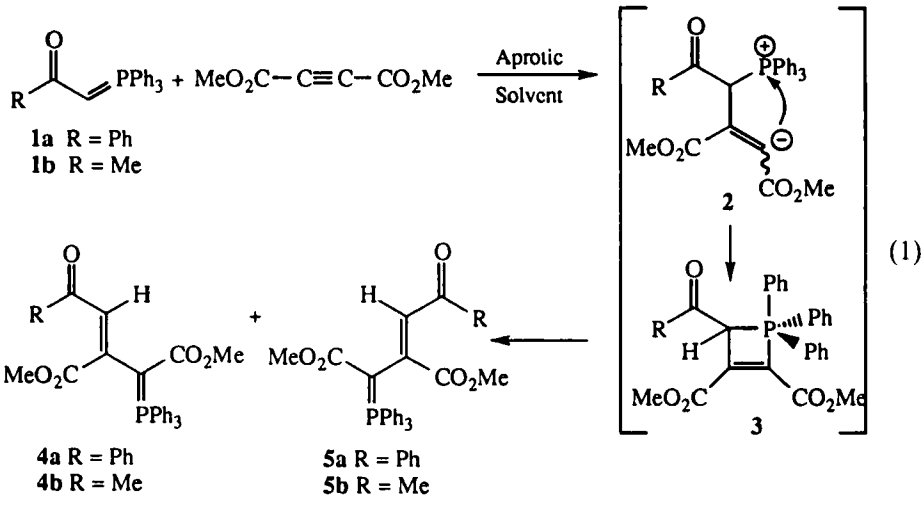
Key words: Ketophosphonium ylide, dimethyl acetylenedicarboxylate, rearrangement, Michael addition.

INTRODUCTION

Ketophosphonium ylides such as **1** are known to rapidly undergo O-alkylation when reacted with halides such as ethyl bromide to give β-ethoxy vinylphosphonium salts in high yields.[1] Reaction to afford the C-alkylated product was observed only when alkyl halides such as methyl iodide[2] and methoxymethyl chloride[3] were used. On the other hand, ketophosphonium ylides were found to react with activated acetylenes to give predominately C-alkylated products. For example, Hendrickson and coworkers found that the reaction of ketophosphonium ylide **1a** with dimethyl acetylenedicarboxylate (DMAD) resulted in a simple Michael adduct in protic solvents and a rearranged product (due to internal cyclization of the Michael adduct) in aprotic solvents.[4] These reactions were reported to afford only a single isomer of alkene product under either protic or aprotic conditions. In connection with studies on the C-alkylation of ketophosphonium ylides, we found that the reaction of **1a** and **1b** with dimethyl acetylenedicarboxylate gave a mixture of geometrical isomers. Furthermore, the steric nature of the R group of **1**, influenced the isomeric ratio of products obtained. These results will be discussed in this paper, along with corrected NMR values for the isomers obtained.

RESULTS AND DISCUSSION

In the presence of aprotic solvents such as THF, CH_3CN or DMSO the reaction of 1-triphenylphosphoranylidene-2-propanone (**1b**) with DMAD gave an oily mixture of two isomers **4b** and **5b** as shown in Equation (1). Presumably, initial Michael attack gives adduct **2** which can readily form the phosphorane **3**. Ring opening of this strained system resulted in formation of a 3:1 ratio of isomers **4b** and **5b** as determined by ^1H NMR. The separation of the isomers **4b** and **5b** was not possible



(1)

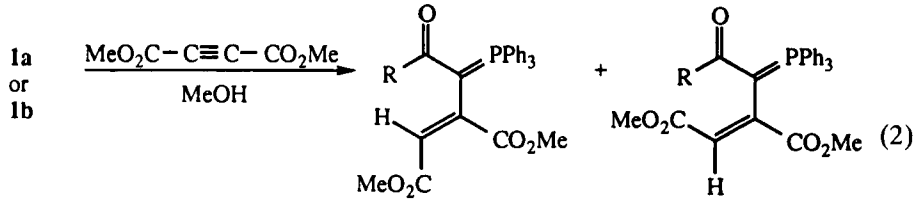
by either by chromatography or crystallization. The ratio of isomers formed was independent of the solvent utilized. Proton NMR of the major isomer **4b** showed a vinyl proton signal at 4.9 ppm while the minor isomer **5b** had a vinyl proton signal at 6.25 ppm.

Under similar conditions, when **1a** was reacted with DMAD in diethyl ether, a crystalline product formed. Analysis of the product mixture by ^{1}H NMR showed a 4.5:1 ratio of isomers **4a** and **5a**. The major isomer had a vinyl proton signal at 5.68 ppm and carbomethoxy signals at 3.85 ppm and 3.28 ppm. The minor isomer had a vinyl proton signal at 6.89 ppm and carbomethoxy shifts at 3.5 ppm and 3.25 ppm. These results are in contrast to the single isomer reported previously by Hendrickson and coworkers[4] for this system. They reported ^{1}H NMR signals at 5.61, 3.73 and 3.16 ppm, consistent with our major isomer. Since these original studies on the acetophenone ylide gave such a large amount of **4a**, the presence of **5a** could have easily been overlooked.

From our studies with the methyl and phenyl ketoylides **1b** and **1a**, it is clear that the steric nature of the R group affects the distribution of products formed after ring opening of the four membered ring phosphorane **3**. The opening of **3** can be compared to the thermal ring opening of substituted cyclobutenes. Thermally allowed conrotatory ring openings of substituted cyclobutenes may occur by either inward or outward rotation of the particular substituent. In the case of phosphorane **3**, outward rotation of the ketone group occurred predominately to afford the major E-isomer **4**, while inward rotation of the ketone accounted for minor amounts of the Z-isomer **5**. With the bulkier phenyl substituted ketone, the E isomer **4** is formed to a greater extent than when less bulky methyl substituted ketone is present. These results are consistent with the outward rotation reported for cyano,[5] ester[6] and ketone[7] substituted cyclobutenes.

When these reactions are conducted using a protic solvent, the initial Michael adduct **2** is protonated rather than cyclizing to form the four membered phosphorane **3** (Equation 1). The bulky triphenylphosphine group should be situated cis to the carbonyl group to avoid any interaction with the R group. Protonation

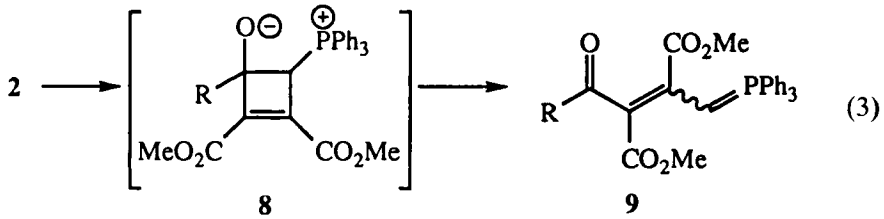
of the vinyl anion of **2** should occur to generate the least hindered E isomer **6** to a greater extent than the Z isomer **7** (Equation 2). Thus, when 1-triphenylphosphoranylidene-2-propanone **1b** was reacted with DMAD in the presence of methanol, a mixture of E and Z isomers **6b** and **7b** were obtained. The isomers were readily separated by preparative chromatography to give a 2:1 ratio of E and Z isomers. The configuration of these isomers was assigned based on the ^{1}H NMR chemical shifts of the products of similar sulfur ylides as reported by Trost.[8] The E isomer, **6b**, a bright red crystalline material, was identified by the vinyl proton singlet at 6.6 ppm and two carbomethoxy signals at 3.23 ppm and 3.7 ppm. On the other hand the minor Z isomer, **7b**, was a bright yellow crystalline compound and had a vinyl proton singlet at 5.4 ppm and carbomethoxy groups at 3.6 and 3.5 ppm. The phenyl substituted ketone **1a** actually yielded a higher proportion of the Z isomer, with a 1.4:1 ratio of isomers **6a** and **7a**, respectively, as determined by ^{1}H NMR. The major isomer, **6a**, had a vinyl proton signal at 6.13 ppm and carbomethoxy signals at 3.25 ppm and 3.45 ppm respectively. The minor isomer, **7a**, showed a vinyl proton signal at 5.3 ppm and carbomethoxy signals at 3.12 ppm and 3.5 ppm. Although a higher proportion of the Z isomer, **7**, was observed when R = Ph, reaction of both ketoylides **1a** and **1b** with DMAD, afforded the more stable E isomer **6** as the major product. This is in contrast to the report by Hendrickson which showed only the formation of the Z isomer, **7a**, when R = Ph.[4] It may be that the larger phenyl group may force approach of the solvent from the least hindered face to give greater amounts of the less stable Z isomer **7**.



6a R = Ph
6b R = Me

7a R =Ph
7b R = Me

Upon the reaction of the keto ylides **1** under aprotic conditions, the initial Michael adduct **2** could presumably also attack the carbonyl group giving rise to intermediate **8** and, subsequently, product **9** as shown in Equation (3). Under the standard conditions as reported above, we did not see any evidence of the attack on the carbonyl carbon. In an attempt to activate the carbonyl carbon by running the reaction in the presence of a Lewis acid catalyst such as $TiCl_4$, or to block the phosphorus from attack by forming hindered salts with LiBr or the sodium salt of



8 **9**

2,4,6-trinitrobenzenesulfonic acid, no evidence for the formation of product **9** was found. This result supports the argument that cyclobutenes are more strained than four membered phosphoranes and they are unlikely to be formed even when conditions favoring their formation are utilized.

In summary, the reactions of ketophosphonium ylides with DMAD in either protic or aprotic solvents formed product mixtures with complex NMR spectra, not in agreement with earlier reports by Hendrickson. Upon further investigation, it was found that geometrical isomers of the alkene products actually existed. Depending on the R group of the ketoylide, the isomeric ratio changed.

EXPERIMENTAL

General: Melting points were determined using an Electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a GE QE-300 300 MHz NMR in $CDCl_3$ using TMS as an internal standard. IR spectra were recorded on a Perkin Elmer Series 1600 FT IR. Column chromatography was performed on 230–400 mesh silica gel and preparative chromatography was performed utilizing Analtech silica gel 1000 micron plates. Chemicals were purchased from Aldrich Chemical Co. and were used as received, unless specified otherwise. Elemental Analysis were performed by Atlantic Microlabs, Norcross, Georgia.

Reaction of 1-triphenylphosphoranylidene-2-propanone **1b** *in tetrahydrofuran*: The ketoylide **1b** (126 mg, 0.396 mmol) was dissolved in dry THF at room temperature. Dimethylacetylene dicarboxylate (49 μL, 0.399 mmol) was added in one portion. The mixture went from a yellow color to a dark orange as it stirred overnight. The solvent was removed to yield a dark orange-brown oil. Purification by preparative chromatography (1:1 EtOAc:CH_2Cl_2) gave a 3:1 ratio of isomers (170 mg, 0.369 mmol, 93%). Anal. Calcd. for $C_{27}H_{25}O_2P$: C, 70.43; H, 5.43. Found: C, 70.55; H, 5.66. IR: 3057, 2991, 2946, 1731, 1673, 1514, 1436, 1337, 1243, 1178, 1104, 1081, 978, 739, 694, 544 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) Major isomer **4b**: δ 7.8 (m, 6 H), 7.5 (m, 9 H), 4.9 (s, 1 H), 3.84 (s, 3 H), 3.3 (s, 3 H), 1.6 (s, 3 H). Minor isomer **5b**: δ 7.8 (m, 6 H), 7.5 (m, 9 H), 6.25 (s, 1 H), 3.44 (s, 3 H), 3.35 (s, 3 H), 2.0 (s, 3 H).

Reaction of 1-triphenylphosphoranylidene-acetophenone **1a** *in DMSO*: Phenacyltriphenylphosphonium bromide (0.427 mg, 0.926 mmol) was dissolved in warm DMSO and added to a round bottom flask containing oil free KH (37 mg, 0.925 mmol). After several minutes the solution turned yellow and was allowed to stir for 1.5 h. To this mixture was added dimethyl acetylenedicarboxylate (114 μL, 0.927 mmol). The mixture immediately turned orange-red and was stirred overnight. The dark red solution was quenched with H_2O, and the product extracted into CH_2Cl_2. The organic extracts were washed with H_2O, sat'd $NaHCO_3$, dried over $MgSO_4$. The product was recrystallized from CH_2Cl—Et_2O to yield a 4.5:1 ratio of E and Z isomers **4a** and **5a**, respectively (346 mg, 0.663 mmol, 72%). mp = 228–230°C (lit. mp = 230–231°C).[4] IR: 3058, 2945, 1732, 1672, 1631, 1502, 1484, 1435, 1346, 1232, 1178, 1103, 1083, 898, 738, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) Major isomer **4a**: δ 7.7 (m, 6 H), 7.5 (m, 9 H), 7.4–7.1 (m, 5 H), 5.68 (s, 1 H), 3.85 (s, 3 H), 3.28 (s 3 H). Minor isomer **5a**: δ 7.7 (m, 6 H), 7.5 (m, 9 H), 7.4–7.1 (m, 5 H), 6.89 (s, 1 H), 3.5 (s, 3 H), 3.25 (s, 3 H).

Reaction of 1-triphenylphosphoranylidene-2-propanone **1b** *in methanol*: Triphenylphosphoranylidene-2-propanone (123.4 mg, 0.421 mmol) was dissolved in dry methanol under nitrogen. Dimethyl acetylenedicarboxylate (52 μL, 0.422 mmol) was added dropwise and the mixture turned yellow. The reaction was allowed to stir overnight. The solvent was removed to generate orange crystals. Anal. Calcd. for $C_{27}H_{25}O_5P$: C, 70.43; H, 5.43. Found: C, 70.37; H, 5.47. The isomers were separated by preparative chromatography (1:1 EtOAc:CH_2Cl_2) to generate a 2:1 ratio of **6b** (59 mg) and **7b** (32 mg) in 87% yield based on unrecovered starting material (58 mg, 0.182 mmol). E isomer, **6b**: mp = 165–166°C, red crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.8–7.4 (m, 15 H), 6.6 (s, 1 H), 3.7 (s, 3 H), 3.25 (s, 3 H), 2.0 (s, 3 H). IR: 3057, 2948, 1715, 1528, 1436, 1314, 1239, 1199, 1172, 1105, 1032, 720, 692 cm^{-1}. Z isomer **7b**: mp = 129–131°C, yellow crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.8–7.4 (m, 15 H), 5.4 (s, 1 H), 3.6 (s, 3 H), 3.5 (s, 3 H), 2.1 (s, 3 H). IR: 3057, 2946, 1716, 1528, 1437, 1196, 1119, 750, 721, 695 cm^{-1}.

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