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Direct Cyclopropanation of 1-Alkynylphosphonates by Cp_2ZrCl_2/2EtMgBr/$2AlCl_3$ To Afford Cyclopropylmethylphosphonates

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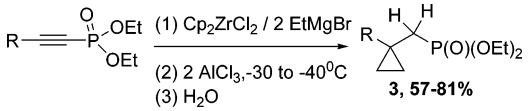
Received October 16, 2005



The reagent system Cp_2ZrCl_2/2EtMgBr/$2AlCl_3$ converts 1-alkynylphosphonates into cyclopropylmethylphosphonates **3** in good isolated yields. Ethers, chlorides, and other cyclopropyl groups are compatible with the reaction conditions. Deuterium labeling is consistent with the formation of stable cyclopropylmethylbimetallic phosphonates by ring contraction of the corresponding aluminacyclopentenylphosphonate. Temperature is crucial; apparently, the cyclopropylmethylbimetallic phosphonates are in equilibrium with the aluminacyclopentenylphosphonates. Low temperature favors the former. We surmise that the negative charges of the intermediate are stabilized by the phosphonate group. Thus, diphenylacetylene and 3-hexyne failed to give cyclopropyl products under the same reaction conditions.

Introduction

The proximity of cyclopropyl and phosphonate groups on the same molecule may endow it with pharmacological properties. For instance, cyclopropylphosphonates can act as *N*-methyl-D-aspartate (NMDA) receptor antagonists,[1] are selective anti-HBV agents,[2] are insecticides[3] and cytostatic agents,[4] possess antiproliferation properties,[5] are virostatics,[6] antidiabetics,[7] and antitumor agents,[8] and display antiviral activity.[9] The methods for synthesizing cyclopropylphosphonates depend on the relative placement of the cyclopropyl and phosphonates groups.[10]

Zirconium reagents have been used to prepare cyclopropanes from alkynes.[11] Dzhemilev reported that symmetrical alkynes reacted with excess $AlEt_3$ in the catalytic presence of Cp_2ZrCl_2 to afford aluminacyclopentenes that converted to 1,1-disubstituted cyclopropanes after workup with alkylsulfonates.[12] Szymoniak has used homoallylic ethers and Cp_2ZrCl_2/2 n-BuLi to produce substituted cyclopropanes,[13] and Taguchi has shown that γ,γ-dialkoxyallylic zirconium species react with aldehydes under neutral workup conditions to afford *gem*-dialkoxycyclopropyl alcohols.[14] Negishi reacted aluminacyclopentenes, obtained from the corresponding alkynes and excess of $AlEt_3$ in the presence of 10 mol % Cp_2ZrCl_2, with $BrCH_2OCH_3$ to give vinyl cyclopropanes.[15] Negishi also reported that cyclopropanation of enynes could be effected with the reagent system Et_2-Zn/0.1XTi(*i*-PrO)$_3$/0.2EtMgBr/$BrCH_2OCH_3$ to give fused vinylcyclopropanes;[16] however, simple alkynes did not undergo cyclopropanation. Kulinkovich-type[17] conversions of esters or acyl chlorides to cyclopropanols using zirconocene reagents have been reported.[18]

Vinylphosphonates are highly valued products and reagents.[19] Over the past few years we have been investigating the conversion of 1-alkynylphosphonate to highly substituted vinylphosphonates with group IV reagents.[20] We have shown that the intermediate metallocycles are very sensitive to the reaction conditions. Various substituted vinylphosphonates can be obtained from the same electrophile by changing both the quantities of reagents required to generate the reactive group IV species and the metal additives.[21] In this paper we report our results on the reaction of 1-alkynylphosphonates with Cp_2ZrCl_2/2EtMgBr in the presence of $2AlCl_3$. Although our initial aim was to obtain substituted vinylphosphonates, cyclopropylmethylphosphonates

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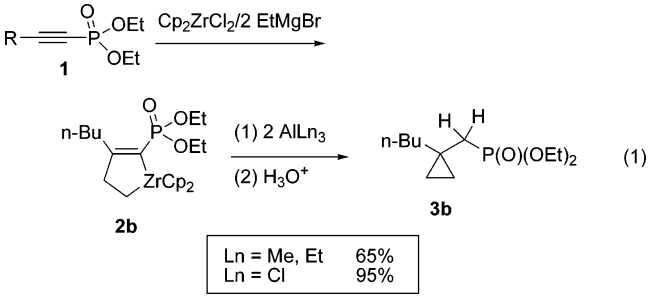
10.1021/jo052157l CCC: $33.50
Published on Web 12/22/2005

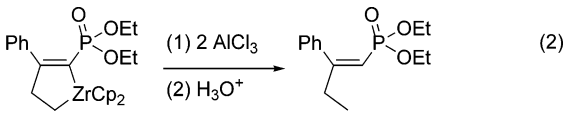
were formed instead. While Cp_2ZrCl_2/2EtMgBr is a known reagent,[22] Cp_2ZrCl_2/2EtMgBr/2$AlCl_3$ has been recently reported.[23]

Results and Discussion

The zirconacyclopentenylphosphonate **2b** was obtained in >97% (based on GCMS and NMR analysis) from Cp_2ZrCl_2/2EtMgBr. Intermediates **2** are thermally stable at room temperature and smoothly insert various electrophiles.[24] Surprisingly, during our present effort to insert other functional groups to **2b**, we found that addition of 2 equiv of $AlMe_3$ or $AlEt_3$ led to the exclusive formation of cyclopropylmethyl phosphate **3b** in 65% yield (based on ^{31}P NMR). Optimization of the reaction conditions by using $AlCl_3$ rather than AlR_3 improved the yield of **3b** to 95% (eq 1).



The temperature is crucial for the course of the reaction. We found that $AlCl_3$ must be added to **2b** at −30 to −40 °C, after which the reaction is maintained at the same temperature for 1 h and is quenched with dilute HCl. Adding $AlCl_3$ at a higher temperature or allowing the temperature to rise above −30 °C resulted in the formation of predominantly ethylated vinylphosphonates (eq 2). Also, 2 equiv of $AlCl_3$ is essential for optimum



yield; using less than 2 equiv of $AlCl_3$ substantially decreased the yield of **3b**. The products **3** were extracted, separated on

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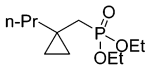
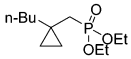
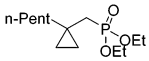
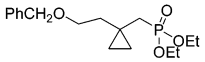
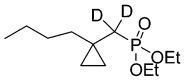
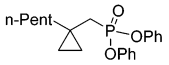
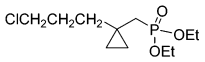
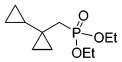
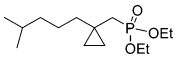
TABLE 1. Formation of Cyclopropylmethylphosphonates, 3

Entry	3	Conversion[a]/Yield[b]
3a		95/75
3b		95/81
3c		95/72
3d		95/72
3e		95/73
3f		95/68
3g		80/57
3h		95/71
3i		95/68

[a] Determined by ^{31}P NMR. [b] Isolated yield after chromatography.

silica gel chromatography, and analyzed by NMR spectroscopy, GCMS, and elemental analysis. For instance, in the ^{1}H NMR spectrum of **3b**, the two multiplets in the region 0.3−0.5 ppm, and the ^{13}C peaks in ^{13}C NMR spectrum in the region ∼12 ppm are indicative of a cyclopropyl structure. The doublet in the region 1.43−1.77 ppm ($^{2}J_{PH}$ = 14.7−18.0 Hz) corresponds to the methylene hydrogens α to phosphorus. Furthermore, ^{31}P NMR of **3b** in the region 25.9−31.9 ppm is consistent with phosphorus attached to sp^3 carbon rather than to a sp^2 or sp carbon. The reaction is sensitive to the R group of the 1-alkynylphosphonate. When R was phenyl, no cyclopropane product was observed, but rather the respective ethylated vinyl phosphonate was obtained (eq 2).

The ester moiety affects the rate of the reaction. The diphenyl phosphonate required overnight stirring to achieve an 85% yield of the zirconacyclopentenediphenyl phosphonate (**3f** intermediate), apparently due to stiric effect. In addition, the present cyclopropanation procedure seems to be restricted to aluminum reagents. Other metals (Ni, Cu, Zn, Pt, Ce, Pd etc) were unsuccessful. Various substituents are tolerated by the reaction conditions, such as ethers (Table 1, **3d**) or chlorides (Table 1, **3g**). Another cyclopropyl group may also be incorporated (Table 1, **3h**). The conversion, based on starting 1-alkynylphosphonate is essentially complete (^{31}P NMR). Isolated yields after silica gel chromatography are good. These novel cyclopropylmethylphosphonates are thermally and air stable compounds and are soluble in most solvents. Results are summarized in Table 1.

Mechanistic Insights. Both Negishi[15] and Dzhemilev[12] have reported cyclopropanation reactions of alkynes with group IV metals. Negishi has investigated the mechanism of formation and subsequent reactions of aluminacyclopentenes derived from simple alkynes and 3AlEt$_3$/Cp$_2$ZrCl$_2$ 10 mol %.[25] XCH$_2$OCH$_3$ is required to convert aluminacyclopentenes to vinylcyclopropanes. Dzhemilev, using an almost identical reagent system as

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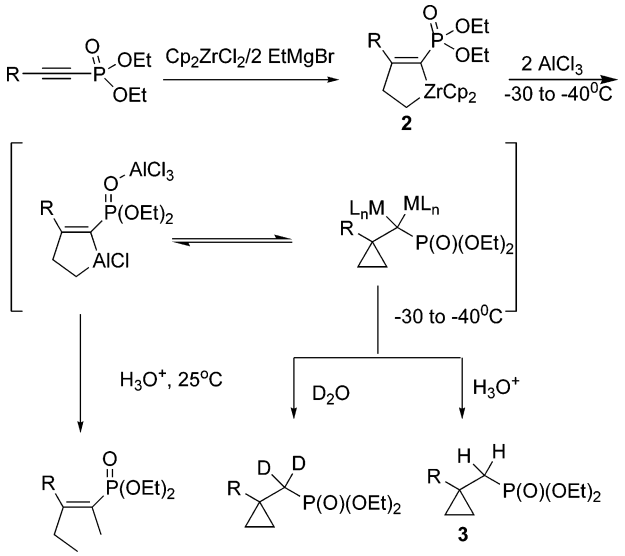
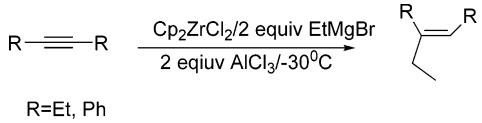
SCHEME 1



that of Negishi, 3AlEt$_3$/Cp$_2$ZrCl$_2$ 10 mol %, reported that workup with dialkylsulfonates of aluminacyclopentenes derived from simple alkynes gave *gem*-dialkylcyclopropanes.[12] In the absence of this workup procedure, cyclopropanation did not occur. Workup with tosylates afforded diethylated alkenes. Clearly, the system, 3AlEt$_3$/Cp$_2$ZrCl$_2$ 10 mol % is capable of reacting differently by slight modification of the reaction conditions. Using the Negishi/Dzhemilev protocol with 1-alkynylphosphonates, no cyclopropanation products were observed and only the starting material was recovered. Apparently, the phosphonate oxygens coordinate with the AlEt$_3$ and Cp$_2$ZrCl$_2$. Indeed when hex-1-ynylphosphonate was stirred with 1 equiv of AlCl$_3$ in CDCl$_3$, an upfield shift in the ^{31}P NMR was observed from ca. δ −4 to ca. δ −8 ppm, which is indicative of Lewis acid complexation with the phosphonate oxygens. Thus, it is necessary to form the much more reactive zirconacyclopentene, which subsequently can be transmetalated with AlCl$_3$ to afford the aluminacyclopentenes. Even with preformed zirconacyclopentenes **2**, 2 equiv of AlCl$_3$ are required. One equivalent reacts with **2** to form the aluminacyclopentenylphosphonate, and we conjecture that the other equivalent remains coordinated to the phosphonate oxygens. The aluminacyclopentenylphosphonate apparently is in equilibrium with the ring-contracted cyclopropylmethylbimetallic phosphonate. Low temperature favors the latter. Deuteriolysis of the reaction mixture at −30 °C gave a 2 [^{2}H] species, which is consistent with formation of a cyclopropylmethylbimetallic phosphonate prior to workup (Scheme 1). Hydrolysis of the same reaction mixture at 25 °C led to the ethylated product. That low temperature favors the cyclopropylmethylbimetallic species must be due to the phosphonate group's ability to stabilize the adjacent negative charges. To verify this observation, diphenyl acetylene and 3-hexyne were reacted under the same conditions as for the 1-alkynylphosphonates (eq 3). No cyclopropanation occurred under our



(3)

standard conditions. Only the ethylated products could be detected.

These results support the notion that the phosphonate group must stabilize the negative charge of the intermediate cyclopropylmethylbimetallic phosphonates, whereas alkyl and phenyl groups do not. Our method is unique in that it gives cyclopropylmethyl compounds directly without requiring additional alkylating reagents.

Conclusion

We have described a new utility for the reagent system Cp_2ZrCl_2/2EtMgBr/2$AlCl_3$ that can transform 1-alkynylphosphonates to cyclopropylmethylphosphonates in good isolated yields. Temperature is crucial to the success of the reaction. We have found that −30 to − 40 °C is optimal for generating **3**. Working up the same reaction mixture at 25 °C results only in the formation of ethylated vinylphosphonates. Apparently there is equilibrium between the aluminacyclopentenylphosphonates and the cyclopropylbimetallic phosphonates. Low temperature favors the latter. This must be due to the presence of the phosphonate group, which can stabilize the adjacent negative charges of the cyclopropylbimetallic phosphonates. Though diphenylacetylene and 3-hexyne failed to give cyclopropylmethyl derivatives under the same reaction conditions, it was successful for 1-alkynylphosphonates. The reaction is compatible with ethers, chlorides, and other cyclopropyl groups. We conjecture that other EWGs (electron-withdrawing groups) stable under the conditions of the reaction should also provide the corresponding cyclopropylmethyl derivatives.

Experimental Section

General Procedure for the Synthesis of 3b. To 0.306 g (1.05 mmol) of zirconocene dichloride dissolved in 7 mL of dry THF at −78 °C was added 1.05 mL of 2 M EtMgBr (2.1 mmol) dropwise in a 25 mL round-bottom flask. After 5 min of stirring at −78 °C, 1 mmol (0.22 g) of diethyl hex-1-ynylphosphonate was added. The reaction was gradually warmed to 25 °C and stirred for 2 h. The reaction was cooled to −30 °C and maintained at −30−40 °C while 2 equiv of $AlCl_3$ was added. The reaction was stirred for 1 h at −30 °C and was worked up with dilute HCl. The product was extracted with diethyl ether (2 × 15 mL), separated on silica gel column (80% petroleum ether/20% ethyl acetate), and analyzed by GCMS, elemental analysis, and NMR spectroscopy.

Diethyl (1-Butylcyclopropyl)methylphosphonate (3b). ^{1}H NMR (300 MHz): δ 0.35 (m, 2H), 0.42 (m, 2H), 0.86 (t, 3H, J_{HH} = 6.6 Hz), 1.30 (dt, 6H, J_{HH} = 6.9, $^4J_{PH}$ = 0.3 Hz), 1.30−1.45 (overlap, 6H), 1.75 (d, 2H, $^2J_{PH}$ = 18.0 Hz), 4.00−4.18 (m, 4H). ^{31}P NMR (121.4 MHz): δ 31.89. ^{13}C NMR (75.5 MHz): δ 12.7, 12.8, 14.1, 15.0 (d, $^2J_{PC}$ = 4.3 Hz), 16.4 (d, $^3J_{PC}$ = 6.0 Hz), 22.8, 28.7, 32.3 (d, $^1J_{PC}$ = 140.1 Hz), 36.7, 61.3 (d, $^2J_{PC}$ = 6.6 Hz). MS *m*/*z*: 248 (28.4), 233 (16.7), 219 (66.7), 205 (25.5), 191 (29.5), 163 (49.8), 149 (50.0), 138 (44.1), 125 (35.3), 111 (100), 97 (43.1), 81 (82.4), 67 (47.1), 57 (43.1), 41 (71.6), 29 (48.0). Anal. Calcd for $C_{12}H_{25}O_3P$: C, 58.05; H, 10.15; P, 12.47. Found: C, 58.24; H, 10.21; P, 12.52.

Acknowledgment. We thank the Israel Science Foundation (grant 138/01) for supporting this work A.A.Q. thanks the Israel Ministry of Science for providing financial support.

Supporting Information Available: General experimental procedures; ^{1}H, ^{13}C, and ^{31}P spectra; GCMS spectra; and elemental analysis for compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052157L