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A facile synthesis of 2-oxo-cyclopentenylphosphonates by carbonylation of zirconacyclopentenylphosphonate with oxalyl chloride

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ABSTRACT

Addition of oxalyl chloride to zirconacycles prepared from 1-alkynylphosphonates **1** zirconocene dichloride, and two equivalents of EtMgBr smoothly produced novel 2-oxo-cyclopentenylphosphonates **6** in 58–81% isolated yields in the presence of a copper catalyst.

In addition to being important organic intermediates,[1–3] vinylphosphonates are potential pharmaceutical compounds.[4–6] In the last decade, we have investigated the synthesis of novel vinylphosphonates utilizing three-membered ring metallacycles of group 4 metals.[7–13] Zirconacyclopentenylphosphonates, prepared by the reaction of Cp_2ZrCl_2/2 EtMgBr with alkynylphopshonates, proved interesting to us and were used to obtain other novel vinylphosphonate products,[14] including cyclobutenylphosphonates **4**,[15] and methylcyclopropylphosphonates **3** (Scheme 1).[16]

One particular class of vinylphosphonates that has attracted our attention is the oxo-vinylphosphonates. Following on from the reported synthesis of 3-oxo-vinylphosphonate by the addition of acyl chlorides and nitriles to zirconacycles in the presence of a Cu catalyst,[17] and fused bicyclic 2-oxo-vinylphosphonate formation using the Pauson–Khand reaction,[18] herein the synthesis of another class of cyclic 2-oxo-vinylphosphonates, **6**, is reported. These novel compounds are potential synthetic intermediates. For instance, they can be used in the synthesis of thiazolehydroxyphosphonates and other heterocycles,[19] employed in asymmetric hydrogenations,[20] or in enantioselective reduction by Baker's yeast,[21] to provide interesting biologically active products.[22]

Surprisingly, despite their interesting chemical and biological properties, there are few methods in the literature reporting their synthesis. For example, they were obtained by reaction of the α-phosphonovinyl anion with phenyl isocyanate,[23] and by 1,3-dienyl phosphonate complexation to iron,[24] the Arbuzov reaction of α-halogenated ketones with trialkyl phosphates,[25] phosphorylation of cyclic ketones using electrophilic phosphorus reagents,[26] and by rearrangement of furyl-hydroxymethylphosphonate.[27]

Initially, the synthesis of diethyl 2-octyl-5-oxocyclopent-1-enylphosphonate (**6a**) was attempted by insertion of gaseous CO into zirconacyclopentenylphosphonate **2**, based on the reported reactivities of small molecules such as isocyanates, CO and CO_2 toward metallacycles.[28,29] However, unexpectedly, all efforts were unsuccessful either by bubbling CO into the reaction mixture or under a CO balloon atmosphere. Next, inspired by the research of Xi and co-workers on the synthesis of cyclopentenones and cyclopentadienones,[30] the oxocyclopent-1-enylphosphonate products **6** were obtained by reacting zirconacyclopentenylphosphonates **2** with oxalyl chloride in the presence of a catalytic amount of CuCl. Thus, zirconacyclopentenylphosphonates **2**, which were smoothly prepared by reacting two equivalents of the Cp_2ZrCl_2/2 EtMgBr reagent with 1-alkynylphosphonates, were treated with 10 mol % of CuCl and one equivalent of oxalyl chloride. In the absence of CuCl or when other metal catalysts (Ni, Zn, Pt, Ce, Pd, etc.) were used instead of CuCl, no traces of products **6** were detected, and only the ethylated product **5** was obtained (Scheme 1).

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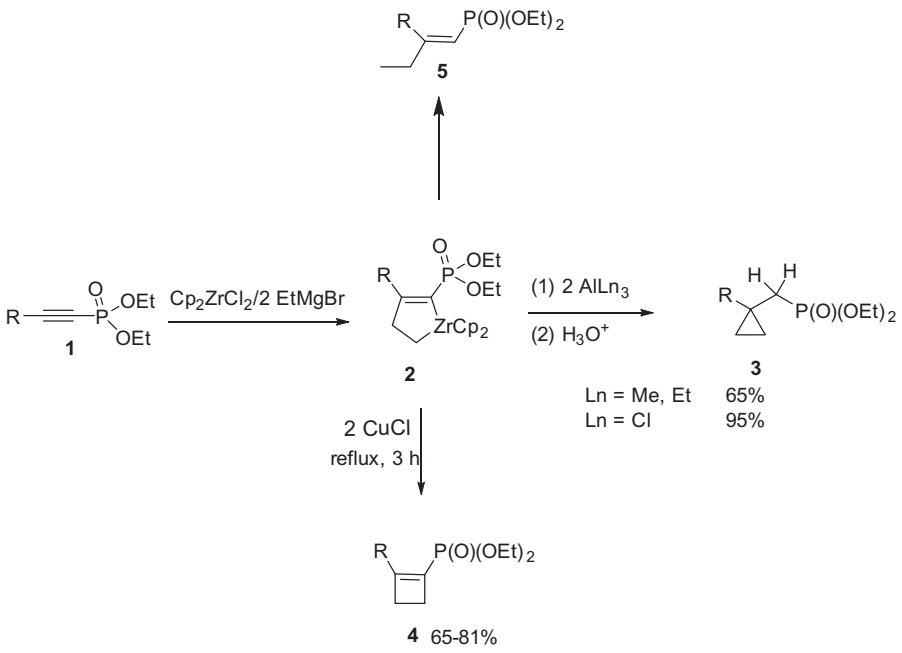
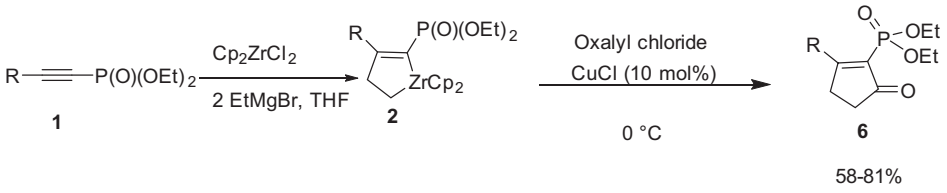


Scheme 1. Reactions of zirconacyclopentenylphosphonates.



Scheme 2. Oxalyl chloride addition to zirconacyclopentenylphosphonates **2**.

The oxocyclopent-1-enylphosphonate products **6** were isolated by silica gel column chromatography in good yields (58–81%) and were analyzed by NMR and GC/MS, and by elemental analysis (Scheme 2).[31] The broad triplet in the region ~2.9 and the multiplet at ~2.7 ppm in the ^{1}H NMR spectra of compounds **6**, along with vinylic carbons at 128.8 and 195.6 ppm, respectively, and the carbonyl carbon at 206.2 ppm in the ^{13}C NMR spectra were all indicative of oxocyclopentenylphosphonate structure **6**. In addition, the ^{31}P NMR chemical shifts of **6** in the region 11.0 ppm were consistent with phosphorus attached to an sp^{2} carbon rather than to an sp^{3} or sp carbon.

This process represents a general and facile one-pot method for the synthesis of novel cyclic 2-oxo-vinylphosphonates **6**, which are thermally- and air-stable compounds, and are soluble in most solvents. This efficient regio- and stereoselective intermolecular cyclization reaction is also tolerant to alkyl (**6a–d**), phenyl (**6h**) silyl (**6g**), and benzyloxy (**6e–f**) groups, as shown in Table 1.

The mechanism of this reaction is proposed to involve transmetallation of zirconacyclopentene **2** with CuCl followed by the formation of a seven-membered ring by coordination with oxalyl chloride and intramolecular cyclization with the elimination of CO gas.[30]

In conclusion, a facile, general, regio-, and stereoselective synthesis of novel oxocyclopentenylphosphonates has been accomplished in good yields by the addition of oxalyl chloride to zirconacyclopentenylphosphonates in the presence of catalytic CuCl. These products are of potential biological activity as anti-inflammatory,[5] and anticancer agents.[4]

Table 1
Diethyl oxocyclopentenylphosphonate products **6** obtained by carbonylation of zirconacyclopentenylphosphonates

Product	R	^{31}P NMR (ppm)	Conversion[a] (%)	Yield[b] (%)
6a	n-C_8H_{17}	11.0	>95	81
6b	n-C_5H_{11}	11.3	>95	80
6c	n-C_4H_9	11.4	>95	78
6d	n-$C_{10}H_{21}$	10.9	90	62
6e	$PhCH_2OCH_2CH_2$	11.0	>90	68
6f	$PhCH_2OCHCH_2CH_2CH_2CH_2$	11.0	>90	58
6g	$(CH_3)_3Si$	11.1	90	70
6h	Ph	10.8	93	78

[a] Based on ^{31}P NMR (121.4 MHz) and GC/MS analysis of the reaction mixture.
[b] Yield of isolated product.

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31. *Typical procedure and spectroscopic data for* ***6a***: To zirconecene dichloride (0.306 g, 1.05 mmol) dissolved in dry THF (6 ml) at −78 °C was added EtMgBr (2 M, 1.05 ml, 2.1 mmol) dropwise in a 25 ml round-bottomed flask. After stirring for 5 min at −78 °C, 1-decynylphosphonate (1 mmol) was added and the mixture was gradually warmed to room temperature and stirred for 2 h. Then, after cooling to −30 °C, CuCl (10 mol%) and oxalyl chloride (0.127 g, 1.0 mmol) were added successively. The reaction was again allowed to warm to 0 °C and stirred for 1 h before being quenched with dilute HCl. The oily products were extracted with EtOAc (2 × 10 ml) and the combined organic layers dried and evaporated. The residue was purified silica gel column chromatography (70% petroleum ether: 30% EtOAc) to give the product in 81% yield, which was analyzed by GC/MS, elemental analysis, and NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, 3H, J_{HH} = 7.2 Hz), 1.10–1.40 (overlap, 10H), 1.31 (t, 6H, J_{HH} = 6.9 Hz), 1.55–1.65 (m, 2H), 2.44 (br t, 2H, J_{HH} = 5.4 Hz), 2.71 (m, 2H), 2.88 (br t, 2H, J_{HH} = 8.4 Hz), 3.99 (m, 4H); ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 11.02; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.3, 16.6 (d, $^{3}J_{PC}$ = 6.6 Hz), 22.8, 29.4, 29.6, 32.0, 32.4, 32.7, 32.5 (d, $^{3}J_{PC}$ = 18.7 Hz), 33.4 (d, $^{3}J_{PC}$ = 2.5 Hz), 35.5 (d, $^{3}J_{PC}$ = 11.2 Hz), 62.4 (d, $^{2}J_{PC}$ = 5.7 Hz), 128.8 (d, $^{1}J_{PC}$ = 192.5 Hz), 195.6 (d, $^{2}J_{PC}$ = 15.0 Hz), 206.2 (d, $^{2}J_{PC}$ = 12.7 Hz); MS(EI): *m*/*z* (%) 330 (5.3), 301 (0.1), 287 (0.9), 259 (3.0), 245 (100), 232 (4.8), 217 (27.5), 204 (6.8), 189 (50.9), 171 (33.1), 133 (5.5), 106 (10.4), 91 (10.9), 79 (12.2), 55 (12.5); Anal. Calcd for $C_{17}H_{31}O_4P$: C, 61.80; H, 9.46; P, 9.37. Found: C, 62.03; H, 9.53; P, 9.25.