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Direct formation of cyclobutenylphosphonates from 1-alkynylphosphonates and Cp_2ZrCl_2/2EtMgCl/2CuCl

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ABSTRACT

Zirconacycles **2** prepared from 1-alkynylphosphonates **1**, zirconocene dichloride, and 2 equiv of EtMgCl are smoothly converted into cyclobutenylphosphonates **3** when treated with two equiv of CuCl in 65–81% isolated yield. The reaction is specific and general only for zirconacyclopentenyl phosphonates.

Cyclobutenes are a versatile group of compounds that are both pharmacologically active[1] and are also valuable synthetic intermediates that undergo many useful transformations[2] involving additions to the double bond (bromination,[3] hydrogenation[4] to the important cyclobutanes,[5] epoxidations,[6,7] haloselenylation,[6] hydroboration,[8] bromohydroxylation,[6] haloselenylation[9]) polymerization,[10] ring opening to dienes,[11] and ring contraction[12] to name a growing list of reactions. Accordingly, they have been prepared by various methods.[13] Organometallic routes include stannylcupration/epoxides[14] and ruthenium-catalysis/propargylic alcohols.[15] Various zirconium-mediated syntheses[16] of cyclobutenes consist of reaction of alkynyl halides with EtMgBr,[17] cross-coupling of terminal alkynes and vinyl bromides,[18] reaction of γ,γ-dialkoxyallylic zirconium species with acrylamide,[19] migratory insertion of an isocyanide into 1-zirconacyclopent-3-ynes,[20] cyclodimerization of alkynes,[21] by double carbonylation,[22] coupling of heteroaryl-substituted alkynes,[23] and coupling of 1,4-dicuprio-1,3-dienes,[24] diiodination of zirconacyclopentenes followed by treatment with *n*-BuLi,[25] and from symmetrical 1,3-diynes via zirconacyclopentenes.[26] The zirconium-mediated methods are tedious at best. Vinyl phosphonates are important chemically[27] and have been shown to possess pharmacological activity.[28] Therefore, in our opinion, juxtaposition of the cyclobutenyl and phosphonate groups should lead to interesting compounds. In fact, cyclobutenylphosphonates would represent an essentially unexplored class of compounds. Thus, Seyferth first reported the synthesis of only the parent compound in 1971 by copper-induced decomposition of α-diazo cyclopropylmethylphosphonate in 71% yield; but it could not be purified.[29] In a related procedure, α-diazo β-ketophosphonates were converted into cyclobutenone phosphonates.[30] The parent compound was also prepared by treating a polymer-supported cyclic phenylsulfonylmethylphosphonate with triethylamine.[31] Darling and Subramanian prepared two fused cyclobutenes by elimination of the corresponding β-aminophosphonates.[32]

In this Letter, we describe the preparation of cyclobutenylphosphonates from Cp_2ZrCl_2/2EtMgCl/2CuCl. We had previously reported the synthesis of the zirconacyclopentenyl phosphonates **2** by the addition of alkynylphosphonates using the reagent Cp_2ZrEt_2 prepared according to Takahashi and Negishi.[33] Various novel phosphonates were prepared by addition of aldehydes, allyl bromide, and propargylbromide to the zirconacyclopentenyl phosphonates **2**.[34] However, when **2b**, obtained from 1-hexynylphosphonate and 2EtMgCl, was treated with two equiv of CuCl, refluxed for 36 h, and worked up, cyclobutenylphosphonate **3b** was obtained as the sole product in 78% yield (Eq. 1, Table 1).[35]

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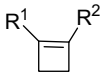
Table 1
Diethyl 2-alkylcyclobut-1-enylphosphonate **3** from diethyl alkynylphosphonate

Entry	R	^{31}P (ppm)	Yield (isolated)[a] (%)
3a	n-C_3H_7	10.70	75
3b	n-C_4H_9	10.75	78
3c	n-C_5H_{11}	10.67	73
3d	n-C_8H_{17}	11.01	81
3e	n-$C_{12}H_{25}$	12.78	76
3f	Phenyl	10.29	70
3g	$PhCH_2OCH_2CH_2$	10.35	65
3h	$(PhCH_2O)CHCH_2CH_2CH_2CH_3$	9.57	65

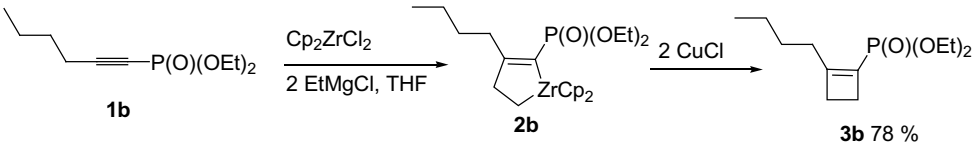
[a] After silical gel chromatography.

Table 3
Attempted cylization of disubstituted alkynes other than phosphonates



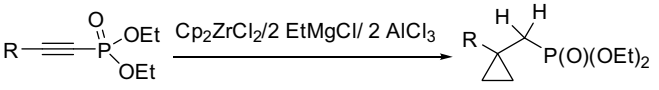
Entry	R^1	R^2	Yield[a]
a	n-Bu	$SiMe_3$	<2%
b	n-Bu	$Sn(n\text{-}Bu)_3$	<2%
c	Ph	Ph	7%
d	Ethyl	Ethyl	5%

[a] Estimated by GCMS.



(1)

This is very different from another reagent system we developed consisting of Cp_2ZrCl_2/2EtMgBr/2$AlCl_3$ which provided methylcyclopropylphosphonates from 1-alkynylphosphonates (Eq. 2).[36] Thus, the products of cyclization obtainable from zirconacylopentenylphosphonates are very sensitive to the metal in the transmetallation step.



(2)

After addition of 2 equiv of CuCl to zirconacyclopentenyl phosphonates **2** at room temperature, the reaction was refluxed for 36 h. It was quenched with dilute aqueous HCl. The reaction can be followed by ^{31}P NMR and GC/MS. The cyclobut-1-enylphosphonate products **3** were extracted with ethyl acetate and isolated by silica gel column chromatography in good yield (65–81%). This efficient inter-molecular cyclization reaction is tolerant to alkyl (**3a–e**), phenyl (**3f**), and benzyloxy (**3g–h**), groups. The addition of two equivalents of anhydrous CuCl was essential in order to reach the maximum yield.

The reaction did not proceed either under CuCl catalytic conditions or at room temperature. Other copper-containing compounds were investigated, and the yields were varied. Thiophene-2-carbonyloxy copper(I) (Table 2, entry b) afforded the highest yields after copper chloride and copper iodide (entry c) gave the lowest yields. On the other hand, when other metal chlorides such as $TiCl_4$, $CoCl_2$, $SnCl_2$ $SbCl_3$, $ZnCl_2$, $CeCl_3$, and $BaCl_2$ were used (Table 2, g–n), only the ethylated product was obtained, and no trace of cyclobutenylphosphonates **3** were detected. The reaction has limitations. Bulky substituted alkynylphosphonates, that is *t*-butylethynylphosphonate, did not afford the corresponding zirconacyclopentenylphosphonate, **2**, but rather the zirconacyclopropenylphosphonate which gave *cis*-*t*-butylvinylphosphonate after hydrolysis. Alkylhalide side chains are also not compatible. Thus, diethyl 5-chloro-1-pentynylphosphonate could not be converted to the corresponding cyclobutenylphosphonate. An intractable reaction mixture was obtained presumably due to various copper-induced coupling reactions.

We briefly investigated other disubstituted alkynes (Table 3). None gave satisfactory results. The reason for this is unclear but not surprising. In the past, we have noticed that the phosphono group enhances the stability of zirconacycles. For instance, zirconacyclopropenylphosphonates do not dimerize and do not require stabilization by adding phosphine ligands.[37] Be that as it may, the present method of preparing 2-substituted cycobutenylphosphonates is general, conceptually simple, and is far superior to any methodology, whether organometallic or other, reported to date.

Table 2
Effect of various metal complexes on cyclization of zirconacyclopentenyl phosphonates **2**

Entry	Metal complex	Yield of **3d** (%)
a	CuCl	81
b	$C_4H_3SC(O)OCu$[a]	70
c	CuI	8
d	Cu(II)triflate	10
e	CuCN	15
f	$CuIP(OCH_3)_3$	45
g	$TiCl_4$	0[b]
h	$CoCl_2$	0[b]
i	$SnCl_2$	0[b]
j	$SbCl_3$	0[b]
k	$ZnCl_2$	0[b]
l	$CeCl_3$	0[b]
m	$BaCl_2$	0[b]
n	$Mo(CO)_6$	0[b]

[a] Thiophene-2-carbonyloxy copper(I).
[b] Only ethylated product obtained.

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References and notes

1. (a) Chao, J.; Taveras, A. G.; Aki, C.; Dwyer, M.; Yu, Y.; Purakkattle, B.; Rindgen, D.; Jakway, J.; Hipkin, W.; Fosetta, J.; Fan, X.; Lundell, D.; Fine, J.; Minnicozzi, M.; Phillips, J.; Merritt, J. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3778–3783; (b) Gonsiorek, W.; Fan, X. D.; Hesk, D.; Fossetta, J.; Qiu, H. C.; Jakway, J.; Billah, M.; Dwyer, M.; Chao, J. H.; Deno, G.; Taveras, A.; Lundell, D. J.; Hipkin, R. W. *J. Pharmacol. Exp. Ther.* **2007**, *322*, 477–485.
2. Gauvry, N.; Huet, F. *J. Org. Chem.* **2001**, *66*, 583–588.
3. Brune, H. A.; Rottele, H.; Horlbeck, G. *Z. Naturforsch., B* **1972**, *B27*, 505–510.
4. Tufariello, J. J.; Milowsky, A. S.; Alnuri, M.; Goldstein, S. *Tetrahedron Lett.* **1987**, *28*, 267–270.
5. Ortuno, R. M.; Moglioni, A. G.; Moltrasio, G. Y. *Curr. Org. Chem.* **2005**, *9*, 237–259.
6. Mevellec, L.; Evers, M.; Huet, F. *Tetrahedron* **1996**, *52*, 15103–15116.
7. Freccero, M.; Gandolfi, R.; Sarzi-Amade, M. *Tetrahedron* **1999**, *55*, 11309–11330; Leyhane, A. J.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 5183–5186.
8. (a) Marsac, Y.; Nourry, A.; Legoupy, S.; Pipelier, M.; Dubreuil, D.; Aubertin, A. M.; Bourgougnon, N.; Benhida, R.; Huet, F. *Tetrahedron* **2005**, *61*, 7607–7612; (b) Knapp, K. M.; Goldfuss, B.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 5259–5265;

Bassindale, M. J.; Hamley, P.; Harrity, J. P. A. *Tetrahedron Lett.* **2001**, *42*, 9055–9057.
9. Lescop, C.; Mevellec, L.; Huet, F. *J. Org. Chem.* **2001**, *66*, 4187–4193.
10. (a) Kitayama, T.; Kawauchi, T.; Nakamura, M.; Sufi, B.; Padias, A. B.; Hall, H. K. *Polymer* **2004**, *45*, 5085–5093; (b) Chen, X. P.; Sufi, B. A.; Padias, A. B.; Hall, H. K. *Macromolecules* **2002**, *35*, 4277–4281; (c) Perrott, M. G.; Novak, B. M. *Macromolecules* **1996**, *29*, 1817–1823; (d) Wu, Z.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 3502–3508; (e) Casey, P. K.; Mathias, L. J. *Polym. Commun.* **1991**, *32*, 27–29; (f) Hall, H. K.; Padias, A. B. *J. Polym. Sci., A1* **2003**, *41*, 625–635.
11. (a) Ingham, S.; Turner, R. W.; Wallace, T. W. *Chem. Commun.* **1985**, 1664–1666; (b) Binns, F.; Hayes, R.; Ingham, S.; Saengchantara, S. T.; Turner, R. W.; Wallace, T. W. *Tetrahedron* **1992**, *48*, 515–530; (c) Hayes, R.; Ingham, S.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron Lett.* **1991**, *32*, 2953–2954; (d) Binns, F.; Hayes, R.; Hodgetts, K. J.; Saengchantara, S. T.; Wallace, T. W.; Wallis, C. J. *Tetrahedron* **1996**, *52*, 3631–3658; (e) Hodgetts, K. J.; Saengchantara, S. T.; Wallis, C. J.; Wallace, T. W. *Tetrahedron Lett.* **1993**, *34*, 6321–6324; (f) GourdelMartin, M. E.; Huet, F. *Tetrahedron Lett.* **1996**, *37*, 7745–7748; (g) Youcef, R. A.; Boucheron, C.; Guillarme, S.; Legoupy, S.; Dubreuil, D.; Huet, F. *Synthesis* **2006**, 633–636.
12. Mevellec, L.; Huet, F. *Tetrahedron Lett.* **1995**, *36*, 7441–7444.
13. (a) de Meijere, A. Ed. Carbocyclic Four-Membered Ring Compounds; Thieme: Stuttgart, **1997**; *17f*, E17e-E17f.; (b) Jiang, X. F.; Ma, S. M. *Tetrahedron* **2007**, *63*, 7589–7595; (c) Murakami, M.; Matsuda, T. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; pp 727–815; (d) Ma, S. M. *Chem. Rev.* **2005**, *105*, 2829–2871.
14. Barbero, A.; Cuadrado, P.; Garcia, C.; Rincon, J. A.; Pulido, F. J. *J. Org. Chem.* **1998**, *63*, 7531–7533.
15. Le Paih, J.; Derien, S.; Bruneau, C.; Demerseman, B.; Toupet, L.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2912–2915.
16. Hartley, R. C.; Caldwell, S. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 477–501.
17. Kasai, K.; Liu, Y. H.; Hara, R.; Takahashi, T. *Chem. Commun.* **1998**, 1989–1990.
18. Barluenga, J.; Rodriguez, F.; Alvarez-Rodrigo, L.; Fananas, F. J. *Chem. Eur. J.* **2004**, *10*, 101–108.
19. Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 3217–3220.
20. Bach, M. A.; Beweries, T.; Burlakov, V. V.; Arndt, P.; Baumann, W.; Spannenberg, A.; Rosenthal, U. *Organometallics* **2007**, *26*, 4592–4597.
21. Liu, Y. H.; Liu, M. N.; Song, Z. Q. *J. Am. Chem. Soc.* **2005**, *127*, 3662–3663.
22. Mito, S.; Takahashi, T. *Chem. Commun.* **2005**, 2495–2496.
23. Song, Z. Q.; Li, Y. X.; Liu, M.; Cong, L. Q.; Liu, Y. H. *Organometallics* **2006**, *25*, 5035–5044.
24. Chen, C.; Xi, C.; Lai, C.; Wang, R.; Hong, X. *Eur. J. Org. Chem.* **2004**, 647–650.
25. Negishi, E.; Liu, F.; Choueiry, D.; Mohamud, M. M. *J. Org. Chem.* **1996**, *61*, 8325–8328.
26. Liu, Y.; Sun, W.-H.; Nakajima, K.; Takahashi, T. *Chem. Commun.* **1998**, 1133–1134.
27. (a) Maffei, M. *Curr. Org. Synth.* **2004**, *1*, 355–375; Minami, T.; Okauchi, T.; Kouno, R. *Synthesis* **2001**, 349–357; (b) Kouno, R.; Tsubota, T.; Okauchi, T.; Minami, T. *J. Org. Chem.* **2000**, *65*, 4326–4332.
28. (a) Quntar, A. A.; Gallily, R.; Katzavian, G.; Srebnik, M. *Eur. J. Pharmacol.* **2007**, *556*, 9–13; (b) Al-Quntar, A. A.; Baum, O.; Reich, R.; Srebnik, M. *Arch. Pharm.* **2004**, *337*, 76–80.
29. Marmor, R. S.; Seyferth, D. *J. Org. Chem.* **1971**, *36*, 128–136.
30. Andriamiadanarivo, R.; Chantegrel, B.; Deshayes, C.; Doutheau, A. *Tetrahedron Lett.* **1993**, *34*, 7923–7924.
31. Liu, X.-L.; Sheng, S.-R.; Zhou, W.; Wang, Q.-Y.; Zhang, X.-L.; Gong, B. *Synth. Commun.* **2007**, *37*, 119–127.
32. Darling, S. D.; Subramanian, N. *Tetrahedron Lett.* **1975**, 3279–3282.
33. Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266–6268.
34. Ben-Valid, S.; Quntar, A. A.; Srebnik, M. *J. Org. Chem.* **2005**, *70*, 3554–3559.
35. *Procedure for the synthesis of* **3b**: To 0.306 g (1.05 mmol) of zirconocene dichloride dissolved in 6 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-bottomed flask. After stirring for 5 min at −78 °C, 1 mmol of alkynylphosphonate was added and the reaction was gradually warmed to 25 °C, and stirred for 2 h. Then, 0.20 g (2 mmol) of CuCl was added under N_2. After stirring at reflux for 36 h, the reaction was quenched with dilute aqueous HCl. The oily product was extracted with Et_2O (2 × 10 ml), separated on silica gel column (70% petroleum ether: 30% ethyl acetate). ^{1}H NMR (300 MHz): δ 0.91 (t, 3H, J_{HH} = 4.2 Hz), 1.31 (t, 6H, J_{HH} = 4.2 Hz), 1.28–1.38 (overlap m, 2H), 1.43 (m, 2H), 2.35 (br t, 2H, J_{HH} = 4.8 Hz), 2.54 (br s, 4H), 4.04–4.10 (m, 4H). ^{31}P NMR (121.4 MHZ): δ 10.75; ^{13}C NMR (75.5 MHz): δ 13.81, 16.39 (d, $^3J_{PC}$ = 3.7 Hz), 22.52, 27.18 (d, $^2J_{PC}$ = 5.1 Hz), 29.15, 30.41, 31.04 (d, $^3J_{PC}$ = 19.3 Hz), 61.31 (d, $^2J_{PC}$ = 3.7 Hz), 127.19 (d, $^1J_{PC}$ = 109.1 Hz), 168.53 (d, $^2J_{PC}$ = 4.2 Hz); MS(EI):*m*/*z* (%) 246 (6.5), 231 (8.8), 217 (48.0), 204 (83.4), 189 (28.2), 176 (24.7), 161 (82.2), 148 (62.0), 129 (8.9), 107 (56.1), 93 (50.8), 79 (100), 65 (62.7), 53 (20.1); Anal. Calcd for $C_{12}H_{23}O_3P$: C, 58.52; H, 9.41; P, 12.58. Found: C, 58.69; H, 9.47; P, 12.44.
36. Quntar, A. A.; Srebnik, M. *J. Org. Chem.* **2006**, *71*, 730–733.
37. Quntar, A. A.; Srebnik, M. *Org. Lett.* **2001**, *3*, 1379–1381.