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Preparation of α-vinylidene-γ-lactones by palladium-catalyzed carbonylation of 5-hydroxy-2-alkynyl methyl carbonates under mild conditions ☆

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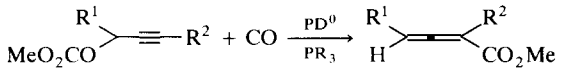
Abstract

Carbonylation of 5-hydroxy-2-alkynyl methyl carbonates catalyzed by $Pd(OAc)_2$ in the presence of a bidentate phosphine takes place under mild conditions to afford α-vinylidene-γ-lactones in good yields.

Keywords: Palladium; Carbonylation; Lactones; Propargylic carbonates

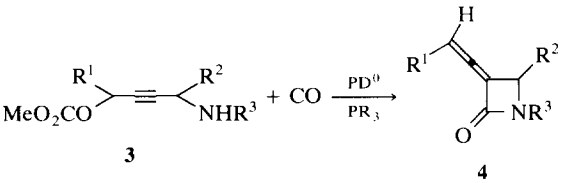
1. Introduction

We have found that facile carbonylation reaction of propargylic carbonates (**1**) proceeds under neutral conditions to give 2,3-alkadienoates (**2**), and have carried out extensive studies on the synthetic applications of this carbonylation reaction [1,2].

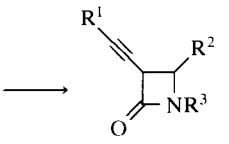


1 **2**

As one application, we found that the β-lactams (**4**) with an α-vinylidene group can be prepared by the carbonylation of 4-amino-2-alkynyl carbonates (**3**). Depending on the reaction conditions, the α-vinylidene group may isomerize to a 1-alkynyl group (**5**) [3].



3 **4**



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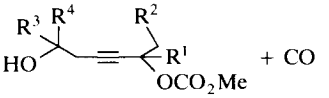
We then turned to the synthesis of γ-lactones from 5-hydroxy-2-alkynyl methyl carbonates (**6**) [4], and observed smooth formation of the γ-lactones (**7**) containing an α-vinylidene group or the isomerized 1,3-diene group, under very mild conditions in good yields. Such lactones were previously unknown. A full account of the carbonylation is presented in this paper.



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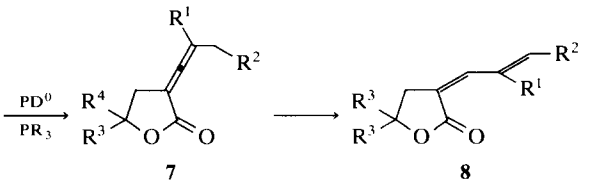

7 **8**

☆ This paper is dedicated to Professor Fausto Calderazzo on the occasion of his 65th birthday in recognition of his important contribution to organometallic chemistry.

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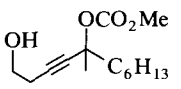
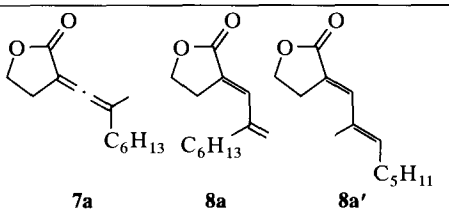
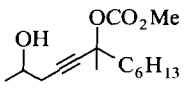
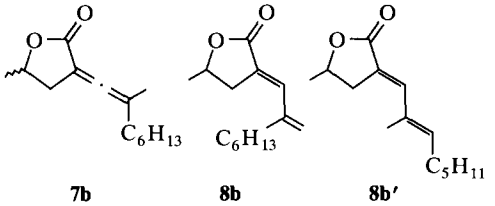
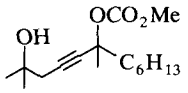
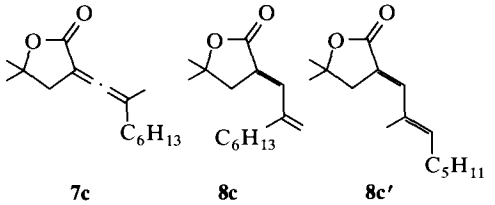
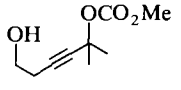
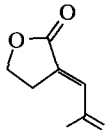
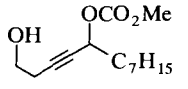
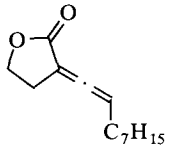
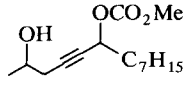
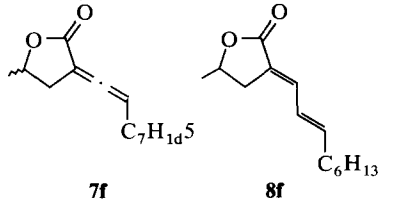
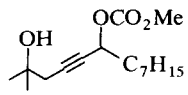
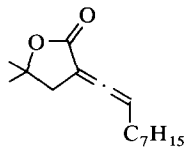
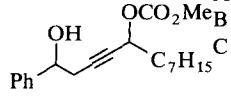
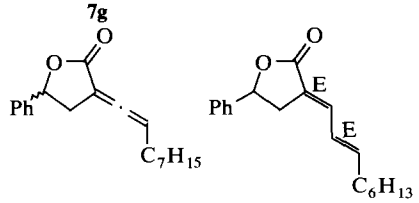
Table 1
Results of carbonylation with a range of substrates

Entry	Carbonates 6	Pd/PR_3	CO (atm)	Time (h)	γ-Lactones 7 and/or 8	Yield (%)	Ratio
1	 **6a**	A	1	1	 **7a** **8a** **8a′**	70:	**7a/8a** = 97/3
		A	10	14		81:	**8a/8a′** = 73/27
		B	1	2		75:	**7a/8a** = 98/2
		C	1	27		69:	**7a**
		C	10	14		84:	**7a**
2	 **6b**	A	1	2	 **7b** **8b** **8b′**	82:	**7b/8b/8b′** = 93/52
		A	10	14		78:	**8b/8b′** = 63/37
		B	1	2		76:	**7b/8b** = 98.5/1.5
		C	10	14		80:	**7b**
3	 **6c**	A	1	1	 **7c** **8c** **8c′**	86:	**7c**
		A	1	24		87:	**7c/8c/8c′** = 71/24/5
		A	10	24		81:	**8c/8c′** = 83/17
		B	1	5		83:	**7c**
		C	10	24		86:	**7c**
4	 **6d**	A	10	15	 **8d**	75:	**8d**
		C	10	15		78:	**8d**
5	 **6e**	A	10	19	 **7e**	67:	**7e**
		C	10	12		64:	**7e**
6	 **6f**	A	1	21	 **7f** **8f**	79:	**7f**
		A	10	24		59:	**7f**
		B	1	21		66:	**7f/8f** = 53/47
		C	10	24		71:	**7f**
		D	10	24		68:	**7f/8f** = 78/22
7	 **6g**	A	10	24	 **7g**	65:	**7g**
		C	10	24		25:	**7g**
8	 **6h**	A	10	14	 **7h** **8h**	69:	**7h**
		B	10	14		75:	**8h**
		C	10	20		41:	**7h**

The reactions were carried out in toluene at room temperature. A: $Pd(OAc)_2$/dppp (5mol%/5mol%) B: $Pd(OAc)_2$/dppp (5mol%/10mol%) C: $Pd(OAc)_2$/dppf (5mol%/5mol%). D: $Pd(OAc)_2$/dppf (5mol%/10mol%).

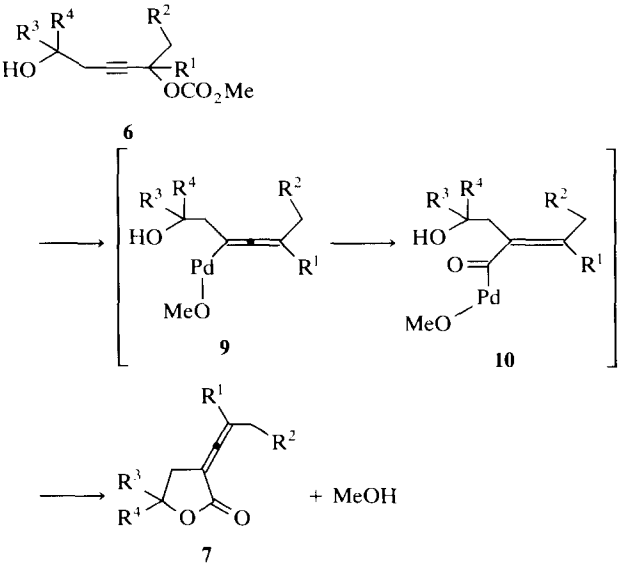
2. Results and discussion

Formation of lactone was found to proceed under mild conditions, namely at room temperature under 1–10 atm of CO. Benzene, toluene and THF were found to be good solvents and toluene was used in most cases. As the phosphine ligand, the widely used triphenylphosphine is not suitable, the reaction proceeding very slowly. Bidentate phosphines show a much higher activity, the most suitable ligands were found to be dppp [1,3-bis(diphenylphosphino)propane] and dppf [1,1′-bis(diphenylphosphino)ferrocene]. Mixtures of $Pd(OAc)_2$ and dppp or dppf in ratios of 1:1 and 1:2 were used as catalysts. The primary products of the carbonylation are α-vinylidene-γ-lactones (**7**), but depending on reaction conditions, partial or complete isomerization of the α-vinylidene group to the conjugated 1,3-diene took place to give **8**.

The extent of the isomerization depends on the structure of the carbonates, the reaction time, and the type of ligand. Extensive isomerization took place when the tetrasubstituted allene system is produced (entries 1–4), rather than the trisubstituted (entries 5–8). As for the ligands, the isomerization is slower when dppf was used, but isomerization is facilitated by dppp and the complete isomerization was observed with longer reaction time. For example, the vinylidene-γ-lactone (**7a**) was obtained in 69% yield in 27 h using $Pd(OAc)_2$ and dppf in 1:1 ratio under 1 atm of CO, and the same lactone was obtained in 84% yield with the same catalyst under 10 atm of CO in 14 h (entry 1). On the other hand, a mixture of the lactones **7a** and **8a** with the isomerized 1,3-diene system was obtained in 70% yield in a ratio of 97:3 in one hour with $Pd(OAc)_2$ and dppp as the catalyst. Only a mixture of **8a** and **8a′** was obtained in 81% yield in 14 h (entry 1). It is interesting to note that isomerization to the alkyne bond was not observed.

In the formation of α-vinylidene-β-lactams (**4**), the isomerization of the 1,2-diene took place to give the alkyne bond **5** in the presence of a base, but not to 1,3-dienes [3]. The present γ-lactone formation proceeded smoothly with the various substituted propargylic carbonates **6a–h** in good yields. Reaction was particularly rapid with the tertiary carbonates (**6a–6d**). The reaction was somewhat slower with the secondary carbonates (**6e–h**), and the lactone could not be isolated cleanly when a primary carbonate group was used. Results of the carbonylation with various substituted substrates are shown in Table 1.

The mechanism of formation of the lactone is as follows. The first step is the formation of the allenylpalladium complex **9**, and CO insertion then generates the acylpalladium complex **10**. Finally the preferential intramolecular attack of the hydroxy group gives the lactone **7**. No methyl ester was formed by the reductive elimination of **10**.



3. Experimental section

3.1. General

^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded for solutions in $CDCl_3$. Chemical shifts are given in δ units relative to tetramethylsilane as an internal standard. High resolution mass spectra (HRMS) were recorded on a JEOL-JMS-DX 303HF. The elemental analyses were carried out with a Perkin Elmer 2400 CHN elemental analyzer.

3.2. The carbonylation

The way the carbonylation was typically carried out is described for entry 1 in Table 1 as follows: $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and dppf (13.9 mg, 0.025 mmol) were mixed in toluene (1 ml) in a round bottom flask. A toluene solution (2 ml) of the carbonate **6a** (128 mg, 0.50 mmol) was added, and a rubber balloon filled with CO was attached. The mixture was stirred at room temperature for 27 h. The mixture was filtered through Florisil and the filtrate was concentrated under reduced pressure to give crude lactone **7a** as a yellow oil (122 mg). The product was purified by silica gel column chromatography (hexane-ethyl acetate 3:1) to give the pure lactone **7a** as a colourless oil. (87 mg, 69%). Its identity was determined by elemental analysis, ^{13}C and ^1H NMR spectroscopy as follows:

α-(2-methyloctenylidene)-γ-butyrolactone (**7a**) (entry 1). Anal. Calcd. for $C_{13}H_{20}O_3$: C, 74.96; H, 9.68. Found: C, 74.67; H, 10.05%. ^1H NMR: δ 0.86 (t, $J = 6.6$ Hz, CH_3), 1.20–1.35 (m, 6H, CH_2), 1.35–1.48

(m, 2H, CH_2), 1.80 (s, 3H, CH_3), 1.90–2.15 (m, 2H, C=CCH_2), 2.89–3.03 (m, 2H, C=CCH_2), 4.36 (t, J = 7.7 Hz, 2H, OCH_2).

^{13}C NMR: δ 14.0, 18.1, 22.5, 26.5, 27.0, 28.7, 31.5, 33.5, 65.8, 92.3, 108.2, 170.9, 203.7.

The carbonylation of **6a** was carried out under 10 atm of CO for 14 h using $Pd(OAc)_2$ and dppp. An inseparable mixture of the isomerized products **8a** and **8a′** was obtained in 81% yield in a ratio of 73:27. The identities and ratios of the products were determined from the ^{1}H NMR spectra: ^{1}H NMR: δ 0.80–0.90 (m 3H, CH_3), 1.20–1.46 (m, 8H, CH_2), 1.87 (s, 3H, CH_3), 2.10–2.18 (m, 0.54H, C=CCH_2 in **8a′**), 2.18–2.26 (m, 1.46H, C=CCH_2 in **8a**), 3.01–3.10 (m, 1.46H, C=CCH_2 in **8a**), 3.10–3.18 (m, 0.54H, C=CCH_2 in **8a′**), 4.31 (t, J = 15.4 Hz, 0.81H, OCH_2 in **8a′**), 4.35 (t, J = 15.0 Hz, 2.19H, OCH_2 in **8a**), 5.29 (s, 0.73H, C=CH in **8a**), 5.32 (s, 0.73H, C=CH in **8a**), 5.91 (t, J = 7.5 Hz, 0.27H, C=CH in **8a′**), 7.01–7.06 (m, 1H, C=CH).

The carbonylation of other propargyl carbonates **6b–h** was carried out similarly and the spectroscopic data for the lactones shown in Table 1 are as follows:

α-(2-Methyloctenylidene)-γ-methyl-γ-butyrolactone (**7b**) (entry 2). Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.38; H, 10.35%. ^{1}H NMR: δ 0.80–0.88 (m, 3H, CH_3), 1.18–1.45 (m, 11H, CH_2, CH_3), 1.77 (s, 3H, CH_3), 1.95–2.14 (m, 2H, C=CCH_2), 2.45–2.55 (m, 1H, CH_2), 2.97–3.10 (m, 1H, CH_2), 4.58–4.70 (m, 1H, OCH). ^{13}C NMR: δ, 14.0, 18.1, 21.86, 21.9, 22.5, 27.0, 28.7, 31.5, 33.5, 34.2, 34.3, 74.2, 93.4, 93.44, 107.8, 170.5, 203.7.

α-(2-Methyloctenylidene)-γ,γ-dimethyl-γ-butyrolactone (**7c**) (entry 3). Anal. Calcd. for $C_{15}H_{24}O_2$: C. 76.22, H. 10.24, Found: C. 76.18, H. 10.60%. ^{1}H NMR: δ 0.83 (t, J = 6.6 Hz, 3H, CH_3), 1.16–1.32 (m, 6H, CH_2), 1.32–1.45 (m, 2H, CH_2), 1.40 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.95–2.11 (m, 2H, C=CCH_2), 2.67 (d, J = 15.4 Hz, 1H, CH_2), 2.73 (d, J = 15.4 Hz, 1H, CH_2). ^{13}C NMR: δ 13.9, 18.2, 22.4, 26.9, 28.2, 28.6, 31.5, 33.4, 40.1, 81.6, 94.4, 107.5, 170.1, 203.8.

α-Isobutenylidene-γ-butyrolactone (**8d**) (entry 4). HRMS: Calcd. for $C_8H_{10}O_2$: 138.0681. Found: 138.0643. ^{1}H NMR: δ 1.99 (s, 3H, CH_3), 3.10–3.18 (m, 2H, C=CCH_2), 4.35 (t, J = 7.3 Hz, 2H, OCH_2), 5.32 (s, 1H, C=CH), 5.34 (s, 1H, C=CH), 7.08 (t, J = 2.9 Hz, 1H, C=CH). ^{13}C NMR: 21.0, 26.6, 65.3, 122.9, 124.7, 138.8, 140.3, 172.5.

α-Nonenylidene-γ-butyrolactone (**7e**) (entry 5). HRMS: Calcd. for $C_{13}H_{20}O_2$: 208.1463. Found: 208.1468. ^{1}H NMR: δ 0.85 (t, J = 6.8 Hz, 3H, CH_3), 1.10–1.50 (m, 10H, CH_2), 2.10–2.18 (m, 2H, C=CCH_2), 2.95–3.05 (m, 2H, C=CCH_2), 4.37 (t, J = 7.5 Hz, 2H, OCH_2), 5.72–5.80 (m, 1H, C=CH). ^{13}C NMR: 14.0, 22.5, 26.4, 27.7, 28.5, 28.8, 28.9, 31.7, 65.8, 93.3, 98.6, 170.6, 205.6.

α-Nonenylidene-γ-methyl-γ-butyrolactone (**7f**) (entry 6). HRMS: Calcd. for $C_{14}H_{22}O_2$: 222.1619. Found: 222.1600. ^{1}H NMR: δ 0.80–0.96 (m, 3H, CH_3), 1.15–1.60 (m, 13H, CH_2, CH_3), 2.05–2.20 (m, 2H, C=CCH_2), 2.50–2.65 (m, 1H, C=CCH_2), 3.05–3.15 (m, 1H, C=CCH_2), 4.60–4.75 (m, 1H, OCH), 5.70–5.80 (m, 1H, C=CH).

^{13}C NMR 14.0, 21.8, 22.5, 27.6, 28.5, 28.8, 28.9, 31.6, 34.1, 74.4, 74.42, 94.4, 98.3, 170.2, 205.5,

α-Nonenylidene-γ,γ-dimethyl-γ-butyrolactone (**7g**) (entry 7). HRMS: Calcd. for $C_{15}H_{24}O_2$: 236.1776. Found: 236.1747. ^{1}H NMR: δ 0.86 (t, J = 6.8 Hz, 3H, CH_3), 1.20–1.50 (m, 10H, CH_2), 1.43 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.10–2.20 (m, 2H, C=CCH_2), 2.77 (d, J = 4.8 Hz, 2H, C=CCH_2), 5.70–5.78 (m, 1H, C=CH).

^{13}C NMR δ, 14.0, 22.6, 27.8, 28.3, 28.6, 28.7, 28.9, 29.0, 29.1, 29.5, 31.7, 40.2, 82.0, 98.2, 169.8, 205.7.

α-Nonenylidene-γ-phenyl-γ-butyrolactone (**7h**) (entry 8). HRMS: Calcd. for $C_{19}H_{24}O_2$: 284.1776. Found: 284.1814. ^{1}H NMR: δ 0.80–0.94 (m, 3H, CH_3), 1.10–1.50 (m, 10H, CH_2), 2.10–2.22 (m, 2H, C=CCH_2), 2.90–2.98 (m, 1H, C=CCH_2), 3.36–3.45 (m, 1H, C=CCH_2), 5.50–5.58 (m, 0.6H, C=CH), 5.75–5.84 (m, 0.4H, C=CH).

^{13}C NMR: δ 14.0, 22.5, 27.8, 28.6, 28.9, 31.7, 35.2, 78.5, 94.0, 98.7, 125.3, 128.4, 128.7, 139.8, 170.0, 205.5.

α-(2-Nonenylidene)-γ-phenyl-γ-butyrolactone (**8h**) (entry 8). ^{1}H NMR: δ 0.88 (t, J = 6.8 Hz, 3H, CH_3), 1.20–1.50 (m, 8H, CH_2), 2.15–2.25 (m, 2H, C=CCH_2), 2.82–2.91 (m, 1H, C=CCH_2), 3.37–3.45 (m, 1H, C=CCH_2), 5.54 (dd, J = 8.4 and 6.2 Hz, 1H, OCH), 6.10 (dd, J = 15.4 and 11.0 Hz, 1H, γ-C=CH), 6.22 (dt, J = 15.4 and 7.0 Hz, 1H, δ-C=CH), 7.13 (dt, J = 11.0 and 2.8 Hz, 1H, β-C=CH). ^{13}C NMR δ 13.9, 22.4, 28.5, 28.7, 31.5, 33.2, 34.3, 77.9, 122.4, 125.2, 125.9, 128.2, 128.6, 136.5, 140.4, 146.6, 171.5. The stereochemistry of the 1,3-diene system was found by NOE experiments to be E, E.

References and notes

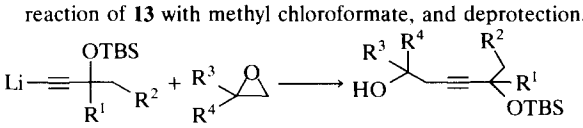
1 Review: J. Tsuji and T. Mandai, *J. Organomet. Chem.*, *451* (1993) 15.

2 J. Tsuji, T. Sugiura and I. Minami, *Tetrahedron Lett.*, *27* (1986) 731; T. Mandai, H. Kunitomi, K. Higashi, M. Kawada and J. Tsuji, *Synlett*, (1991) 697; T. Mandai, S. Susuki, A. Ikawa, T. Murakami, M. Kawada and J. Tsuji, *Tetrahedron Lett.*, *32* (1991) 7687; T. Mandai, J. Tsuji, Y. Tsujiguchi and S. Saito, *J. Am. Chem. Soc.*, *115* (1993) 5865.

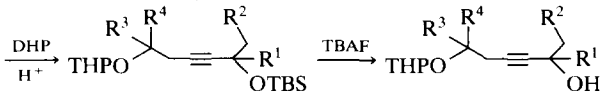
3 T. Mandai, K. Ryoden, M. Kawada and J. Tsuji, *Tetrahedron Lett.*, *32* (1991) 7683.

4 5-Hydroxy-2-alkynyl methyl carbonates **6a–h** used for the carbonylation were prepared by the following sequence of reactions. The coupling of propargylic alcohols **11** bearing a protective ^{t}BuMe$_2$Si group, with substituted ethylene oxide **12** followed by protection and selective deprotection of the hydroxy groups gave free propar-

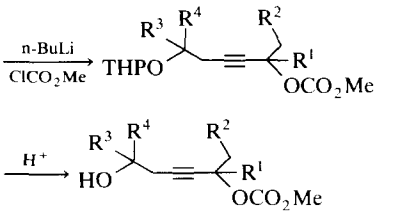
gylic alcohol **13**. The carbonates **6a–h** were prepared by the reaction of **13** with methyl chloroformate, and deprotection.



11 **12**



13



6a–h