PALLADIUM-MEDIATED CARBOMACROLACTONIZATION OF TERMINAL HYDROXYACETYLENES AND ITS UTILIZATION FOR A SYNTHESIS OF EXALTOLIDE[†]

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Abstract —— Carbomacrolactonization took place to give macrolactone-acetylenes when terminal hydroxyacetylenes were stirred under atmospheric pressure of carbon monoxide at room temperature in the presence of palladium(II) acetate and triethylamine. Using 15-pentadecyn-2-olide obtained, exaltolide was synthesized on catalytic hydrogenation.

We report here a new method for macrolide ring formation that we believe is unprecedented. Tsuji and co-workers[1] previously reported that terminal acetylenes are facilely carboalkoxylated to give alkyl acetylenecarboxylates under atmospheric pressure of carbon monoxide in alkanols at room temperature in the presence of a catalytic amount of palladium(II) chloride and a stoichiometric amount of copper(II) chloride (**Scheme 1**). This procedure could be successfully employed by our hands in the preparation of some natural products and medicinally interesting compounds.[2] It, therefore, seemed to us that the palladium-mediated macrolactonization by using terminal acetylene substrates having an hydroxy group in an appropriate position should take place to furnish macrolides having α,β-acetylenic bond by intramolecular pathway.

$$\text{R}-\text{C}\equiv\text{CH} + \text{CO} + \text{R'OH} \xrightarrow[\text{CuCl}_2\text{-NaOAc}]{\text{PdCl}_2\text{ (cat.)}} \text{R}-\text{C}\equiv\text{C}-\text{CO}_2\text{R'}$$

Scheme 1

We first examined the reaction using the ether[3] (**1**), readily obtained by coupling of propargyl bromide with octan-1,8-diol, as preliminary experiment A 2% solution of **1** in THF was stirred with sodium acetate (1 equiv.) and copper(II) chloride (1 equiv.) under atmospheric pressure of carbon monoxide at room temperature for 12 h in the presence of a catalytic amount of palladium(II) chloride (3 mol %). The expected reaction did really take place to give, though in a low yield, the 14-membered lactone (**2**) in 4.8% yield accompanied by 44 6% of the unreacted starting material (**1**). Although we could not find any other better condition improving

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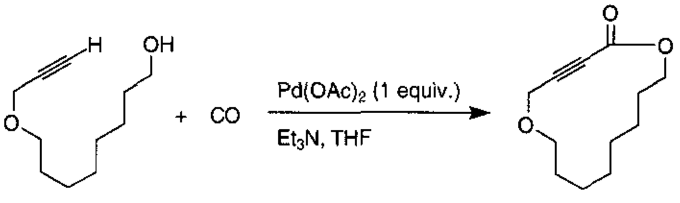
[†] Dedicated to Prof. Rolf Huisgen on the occasion of his 75th birthday.

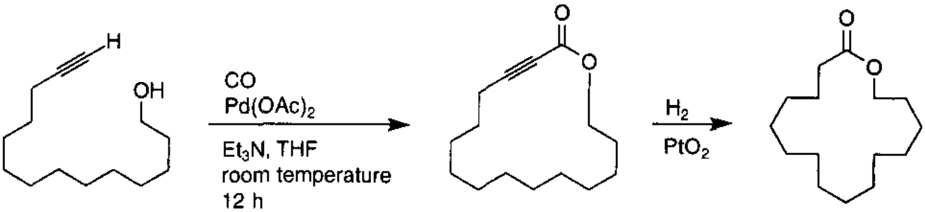
the yield of the carbomacrolactonization product under the catalytic conditions in the presence of the copper oxidants, we could obtain a little better yield of the macrolide (**2**) when a stoichiometric amount of palladium(II) acetate in place of palladium(II) chloride was used with an excess amount of triethylamine without presence of copper(II) chloride and sodium acetate. Thus, **1** in THF (2% w/v) was stirred with palladium(II) acetate (1 equiv) and triethylamine (10 equiv.) under atmospheric pressure of carbon monoxide at room temperature for 12 h to afford the 14-membered lactone (**2**) in 10.5% yield with recovery of the unchanged starting material in 44.5% yield (**Scheme 2**).



1 **2**

Scheme 2

To utilize the observed carbomacrolactonization reaction, we next subjected 14-hydroxy-1-tetradecyne[4] (**3a**) to the reaction conditions in the presence of palladium(II) acetate to generate 15-pentadecyn-2-olide (**4a**) which we expected to transform into exaltolide (**5**), contained in the vegetable musk oils and used as an ingredient of several perfumes,[5] on hydrogenation When **3a** was stirred in THF (2% w/v) under atmospheric pressure of carbon monoxide at room temperature in the presence of a catalytic amount of palladium(II) acetate (10 mol %) using *p*-benzoquinone (1 equiv.) as oxidant, the expected 16-membered product (**4a**) could be obtained in 7.6% yield with a recovery of 60% of the starting material. Further addition of more one molar equivalent of *p*-benzoquinone resulted in a little increase in an yield of **4a** to 12.4% accompanied by 4 8% of the 32-membered dimer lactone (**6a**) and 52.4% of the starting material.



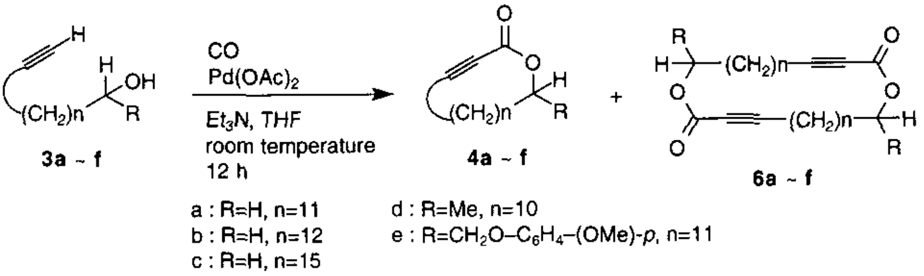
3a **4a** **5**

Scheme 3

On the other hand, when a stoichiometric amount of palladium(II) acetate was used in the absence of the oxidant, the macrolactone (**4a**) was formed in 17.5% yield accompanied by the dimer lactone (**6a**) in 1.8% yield with a recovery of 64.8% of the starting material. The yield of **4a** increased by addition of more 0.5

molar equivalent of palladium(II) acetate which afforded the macrolide (**4a**) in 27.1% yield with 6.4% of the dimer lactone (**6a**) and 31% of the starting material. The starting material was found to be consumed completely in the presence of two molar equivalents of the palladium catalyst, but the yield of the macrolide (**4a**) not much increased (**Table 1**; Entries 3~5) Exaltolide[5c] (**5**) could be obtained from the 16-membered macrolide (**4a**) in quantitative yield on catalytic hydrogenation on Adams catalyst (**Scheme 3**).

We also examined the carbomacrolactonization using other hydroxyacetylene substrates under the conditions in



Scheme 4

Table 1. Carbomacrolactonization of Terminal Hydroxyacetylenes[a)]

Entry	substrate	Pd catalyst (equiv.)	additive (equiv)	macrolide (ring size): yield (%)	dimer (ring size): yield (%)	recovery (%)
1	**3a**	$Pd(OAc)_2$ (10 mol %)	Et_3N (10) *p*-benzoquinone (1)	**4a** (16):7.6	b)	**3a** (60)
2	**3a**	$Pd(OAc)_2$ (10 mol %)	Et_3N (10) *p*-benzoquinone (2)	**4a** (16):12.4	**6a** (32):4.8	**3a** (52.4)
3	**3a**	$Pd(OAc)_2$ (1)	Et_3N (10)	**4a** (16):17.5	**6a** (32):1.8	**3a** (64.8)
4	**3a**	$Pd(OAc)_2$ (1.5)	Et_3N (10)	**4a** (16):27.1	**6a** (32):6.4	**3a** (31.4)
5	**3a**	$Pd(OAc)_2$ (2)	Et_3N (10)	**4a** (16):28.8	**6a** (32):7.6	c)
6	**3b**	$Pd(OAc)_2$ (1)	Et_3N (10)	**4b** (17):20.9	b)	**3b** (36.7)
7	**3c**	$Pd(OAc)_2$ (1)	Et_3N (10)	**4c** (20):18.5	b)	**3c** (46.6)
8	**3c**	$Pd(OAc)_2$ (2)	Et_3N (10)	**4c** (20):39.0	**6c** (40):2.4	c)
9	**3d**	$Pd(OAc)_2$ (1)	Et_3N (10)	**4d** (15):9.7	b)	**3d** (48.6)
10	**3d**	$Pd(OAc)_2$ (2)	Et_3N (10)	**4d** (15):32.2	**6d** (30):7.6	**3d** (30.2)
11	**3e**	$Pd(OAc)_2$ (1)	Et_3N (10)	**4e** (16):7.5	b)	**3e** (53.9)
12	**3e**	$Pd(OAc)_2$ (2)	Et_3N (10)	**4e** (16):11.2	b)	**3e** (19.0)

a) Reaction was carried out in THF (2% w/v) at room temperature for 12 h.
b) Dimer could not be isolated.
c) Starting material was consumed.

the presence of a stoichiometric amount and more of palladium(II) acetate. Although we could not find optimal conditions for a practical use of the present reaction, 15- to 20-membered macrolides[6] were generated under these conditions in the presence of palladium(II) acetate (**Scheme 4**). Particularly interesting was the formation of the macrolides from the substrates having a secondary alcoholic group. Thus, **3d** afforded the 15-membered lactone (**4d**) having a secondary carboxyl center in 9.7% yield in the presence of a stoichiometric amount of the palladium catalyst and 32.2% yield in the presence of two equivalents of the catalyst, respectively. Similarly, **3e** afforded the 16-membered lactone (**4e**) in yields of 7.5 and 11.2% in the presence of 1 and 2 equivalents of the catalyst, respectively (**Table 1**; Entries 9~12).

In conclusion, although a considerable improvements are required for practical use, the present unprecedented macrolide synthesis[7] based on the palladium-mediated carbomacrolactonization reaction is synthetically promising and has high potential utility.

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