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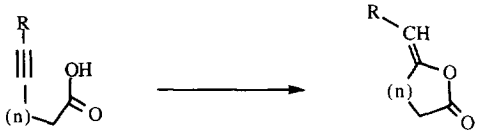
Palladium-Mediated Intramolecular Cyclization of Substituted Pentynoic Acids. A New Route to γ-Arylidenebutyrolactones.

M. Cavicchioli , D. Bouyssi , J. Goré and G. Balme*

Laboratoire de Chimie Organique I , associé au CNRS, Université Claude Bernard CPE-Lyon, 43 Bd. du 11 Novembre 1918, 69622 Villeurbanne, France.Fax 72 43 12 14

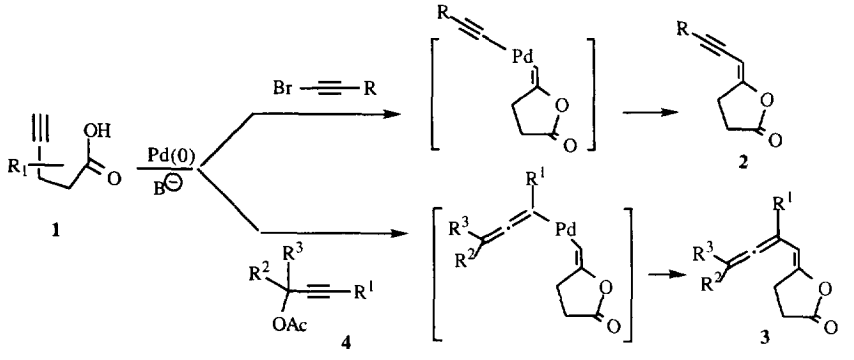
Abstract : Benzo-annulated enol lactones are obtained in good yields from pentynoic acids 3- or 5-substituted with an iodo-aryl moiety by palladium-catalyzed cyclization of their potassium carboxylates.

Over the last ten years, many synthetic efforts have been directed toward synthesis of exo-enol lactones because a number of natural products containing this moiety possess biological activity [1]. Due to their availability, cyclizations of pentynoic or hexynoic acids represent the most effective synthetic approaches to these enol lactone systems. [2]*(Scheme 1)*



(Scheme 1).

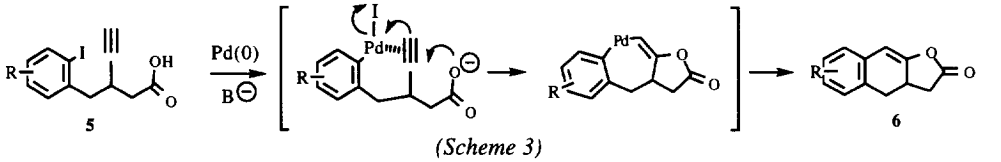
As part of an ongoing research project devoted to the study of palladium-catalyzed cyclization [3], we recently reported that biologically active ynenol- and allenenollactones **2** and **3** are stereoselectively obtained in high yields when γ-acetylenic carboxylates are reacted respectively with 1-bromo 1-alkynes and propargyl acetates **4.** [4,5]*(Scheme 2)*



(Scheme 2)

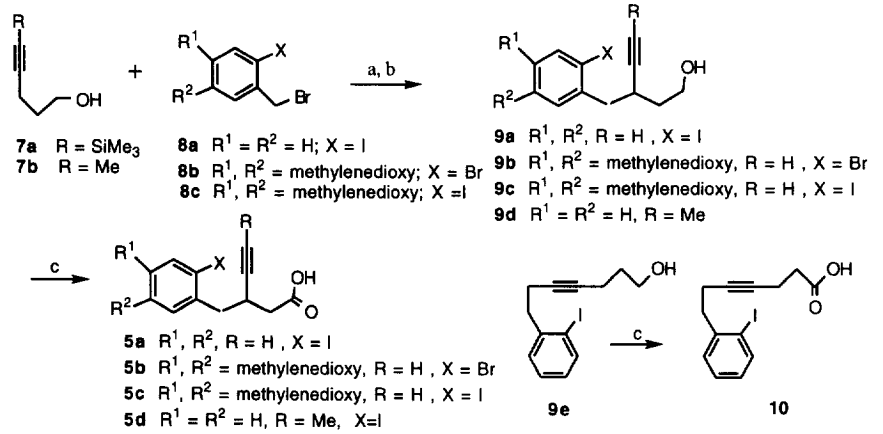
A recent report [6] has shown that alkenyl and aryl halides or triflates can also be used for the trapping in the Pd(0) catalyzed cyclization of acids **1.**

In pursuing a concept for the novel construction of tricyclic system [3] we now wish to report a simple extension of this methodology to the intramolecular version of this reaction which provides a simple synthetic method of γ-arylidenebutyrolactones of type **6** *(Scheme 3)*. These compounds are of interest as synthetic intermediates [7]. The reaction proceeds as expected via an intramolecular nucleophilic attack by the carboxylate anion on the σ-aryl palladium-coordinated carbon-carbon triple bond. Finally, a reductive elimination from the intermediate σ-bonded palladium species leads to the exocyclic enol lactone with regeneration of the catalyst. Various examples of this reaction are listed in Table I.



(Scheme 3)

The starting materials **5** and **10** have not been prepared previously.Our preparation of these compounds [8] from the corresponding pentynols by a two or three step process is given in *Scheme 4*. When hex-4-yn-1-ol **7b** was treated with butyllithium (1 equiv.), t-butyllithium (1 equiv.), and TMEDA (2 equiv.), followed by **8a**, we obtained a mixture of **9d** and **9e** in a 1/1 ratio, both compounds beeing separated by flash chromatography and then oxidized respectively to the acid **5d** and **10** by Jones' reagent.



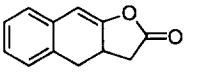
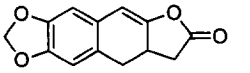
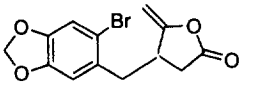
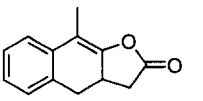
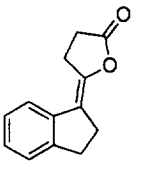
a) 1eq BuLi, 1eq tBuLi, TMEDA, 8a, 8b or 8c; b) when 7a is used : KF, H_2O, DMF; c) Jones' reagent

(Scheme 4)

In the first attempt, the derivative **5a** underwent palladium catalyzed cyclization under the conditions previously described by our group for the transformation **1**→ **2** [4] (entry 1). Thus, when treated with a catalytic amount of palladium acetate (5 mol %) and tri(2-furyl)phosphine (10 mol %) in DMSO, (room temperature, 30 min) in the presence of t-BuOK as base, **5a** gave **6a** in 78% yield (conditions A).

Replacement of tri(2-furyl)phosphine with triphenylphosphine resulted in very low conversion to **6a** and recovery of the starting material. The use of phase-transfer catalysis was also investigated. It was found that with

Table 1 : Palladium catalyzed cyclization of substituted pentynoic acids[a]

entry	pentynoic acid	reaction conditions [b]	catalyst	reaction time (min)	product	yield (%)[c]
1	**5a**	A	TFP[f]	30		78
2	**5a**	A	PPh_3			traces[e]
3	**5a**	B	PPh_3	45	**6a**	60
4	**5b**	A	TFP	60		50
5	**5c**	A	TFP	30	**6b**	50
6	**5b**	B	PPh_3			47
7	**5b**	B	PPh_3			27
8	**5b**	A[d]	TFP		**11**	8
9	**5d**	A	TFP	60	 **6c**	70
10	**10**	A	TFP	60	 **12**	77

a) Unless otherwise stated , the reactions were carried out at room temperature ; b) Conditions A : $Pd(OAc)_2$ (5 mol %) and ligand (10 mol %) in the presence of tBuOK as base (1.1 eq) Conditions B : $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) benzyltriethylammonium chloride (1.1 eq) in presence of Et_3N as base (1 eq.) ; c) isolated yields ; d) Reaction carried out in presence of K_2CO_3 (2 eq.) as base ; e) Starting **5a** was recovered in this experiment in 80% yield ; f) TFP tri(2-furyl)phosphine

the use of palladium acetate (5 mol %), triphenylphosphine (10 mol %), and benzyl triethyl ammonium chloride (TEBA) in DMSO in the presence of Et_3N as base (conditions B), the reaction can be carried at room temperature but the yield is only 60%. (entry 3).

Using conditions A, the aryl bromide **5b** cyclized to **6b** (50%) within 1 h at 40° C (entry 4). Essentialy the same result was obtained by changing the halogen from bromide to iodide (entry 5). In contrast, attempted palladium-catalyzed reaction of **5b** under conditions B resulted in no formation of **6b** but afforded the by-product **11** as the only cyclization product (47%); by switching to a catalyst derived from palladium acetate (5 mol %) and tri(2-furyl)phosphine (10 mol %) compound **11** was formed in only 8% yield. The mechanism of formation of **11** is not clear, but this compound is not an intermediate of **6b** since **11** is unchanged when replaced under conditions A .

The efficiency of this new route to exocyclic enol lactones was also tested by using the homologue of **5d** and linear pentynoic acid **10**. Using the former conditions, linear substrate **10** (entry 10) gave the 5-exo-dig product **12** as the only cyclization derivative in 70% yield (room temperature , 60 min). The enol butyrolactone was identified by its characteristic IR absorbances at 1800 cm^{-1} and 1680 cm^{-1} which are consistent with reported frequencies for five membered exocyclic enol lactone carbonyls [2a,2e] and with frequencies for **6a, 6b** and **6c.**

The present reaction was also applicable to the disubstituted alkyne **5d** and gave the corresponding enol lactone **6c** in 70% yield (conditions A).

In summary, a novel method for synthesis of γ-alkylidenebutyrolactones has been established. It is expected that the above described reaction will find application in the synthesis of biological products [9]. Further work in this area is now in progress in our laboratory.

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