Pergamon

Tetrahedron Letters, Vol. 37, No. 9, pp. 1429-1432, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00063-9

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

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

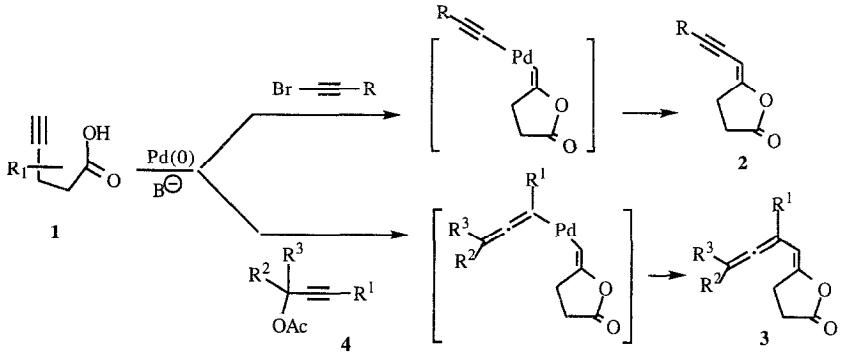
Laboratoire de Chimie Organique I , associé au CNRS, Université Claude Bernard CPE-Lyon, 43 Bd. du 11 Novembre 1918, 69622 Villeurbanne, France.Fax 72 43 12 14

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).

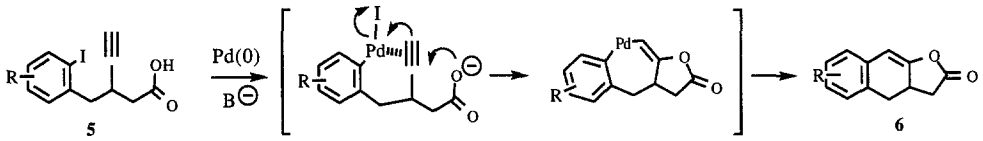
As part of an ongoing research project devoted to the study of palladium-catalyzed cyclization [3], we recently reported that biologically active ynenol- and allenenollactones **2** and **3** are stereoselectively obtained in high yields when γ-acetylenic carboxylates are reacted respectively with 1-bromo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



(Scheme 2)

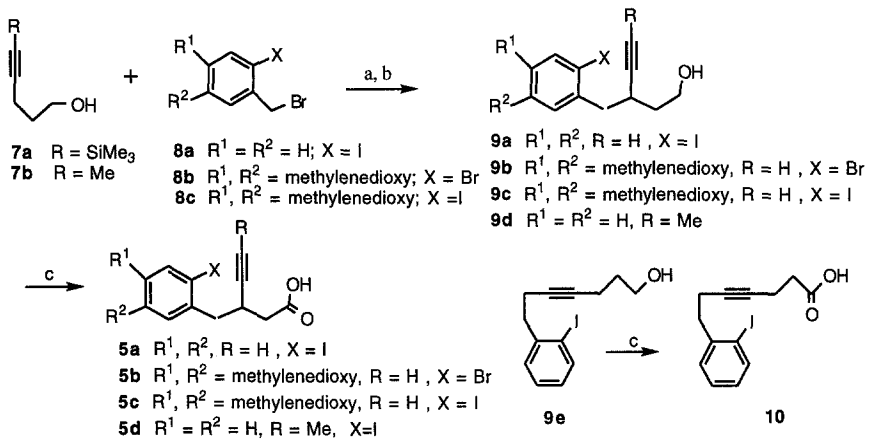
A recent report [6] has shown that alkenyl and aryl halides or triflates can also be used for the trapping in the Pd(0) catalyzed cyclization of acids **1.**

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.



7a R = $SiMe_3$
7b R = Me

8a R^1 = R^2 = H; X = I
8b R^1, R^2 = methylenedioxy; X = Br
8c R^1, R^2 = methylenedioxy; X = I

9a R^1, R^2, R = H , X = I
9b R^1, R^2 = methylenedioxy, R = H , X = Br
9c R^1, R^2 = methylenedioxy, R = H , X = I
9d R^1 = R^2 = H, R = Me

5a R^1, R^2, R = H , X = I
5b R^1, R^2 = methylenedioxy, R = H , X = Br
5c R^1, R^2 = methylenedioxy, R = H , X = I
5d R^1 = R^2 = H, R = Me, X=I

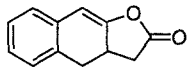
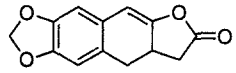
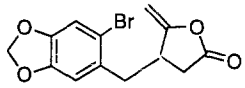
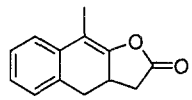
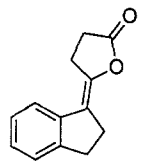
a) 1eq BuLi, 1eq tBuLi, TMEDA, 8a, 8b or 8c; b) when 7a is used : KF, H_2O, DMF; c) Jones' reagent

(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.

Acknowledgment: M.C thanks the EC for the award of a postdoctoral fellowship under the framework of the Human Capital and Mobility Initiative.

References and notes

1. See for example : (a) Kupchan, S.M. ; Britton, R.W. ; Ziegler, M.F. ; Gilmore, C.J. ; Restivo, R.J. ; Bryan, R.F. *J.Am.Chem.Soc.* **1973,** *95*, 1335-1336 and references cited therein; (b) Niwa, M. ; Iguchi, M. ; Yamamura, S. *Chem.Lett.* **1975,** 655; (c) Niwa, M. ; Iguchi, M. ; Yamamura, S. *Tetrahedron Lett.* **1975**, *16* , 4395-4398; (d) Mason, C.P. ; Edwards, K.R. ; Carlson, R.E. ; Pignatello, J. ; Gleason, F.K. ; Wood, J.M. Science (*Washington, D.C.*) **1982**, *215*, 400; e) Jong, T.T. ; Williard, P.G. ; Porwoll. J.P. *J.Org.Chem.* **1984**, *49*, 735-736 ; f) Mali, R.S. ; Jagtap, P.G. *J. Chem. Research* (S) **1993**, 184-185 ; g) Shing, T.K.M. ; Tai, V.W.F. ; Tsui H.C. *J. Chem. Soc. Chem. Comm.* **1994**, 1293-1294.
2. (a) Castaner, B.J. ; Pascual, J. *J. Chem. Soc.* **1958**, 3962-3964. (b) Amos, R.A. ; Katzenellenbogen J.A. *J.Org.Chem.* **1978,** 43, 560-564; (c) Yamamoto, M.J. *J. Chem. Soc., Perkin Trans 1,* **1981**, 582-587 ; (d) Jellal, A. ; Grimaldi, J. ; Santelli, M. *Tetrahedron Lett.* **1984,** *30*, 3179-3182. (e) Spencer, R.W. ; Tam, T.F. ; Thomas, E. ; Robinson, V.J. ; Krantz A. *J. Am. Chem. Soc.* **1986**, *108*, 5589-5597; (f) Lambert, C. ;Utimoto, K. ; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323-5326 ;(g) Marder, T.B. ; Chan, D.M.T. ; Fultz, W.C. ; Calabrese J.C. ; Milstein, D. ; *J. Chem. Soc., Chem. commun.* **1987**, 1885.(h) Chan, D.M.T. ; Marder, T.B. ; Milstein, D. ;Taylor, N.J. *J. Am. Chem. Soc.* **1987**, *109*, 6385-6388. (i) Rollinson, S.W. ; Amos, R.A. ; Katzenellenbogen, J.A. *J.Am.Chem.Soc.* **1981**, *103*, 4114-4125. (j) Sofia, M.J. ; Katzenellenbogen, J.A. *J. Org. Chem.* **1985**, *50*, 2331-2336. (k) Baek, D.J. ; Daniels, S.B. ; Reed, P.E. ; Katzenellenbogen, J.A. *J. Org. Chem.* **1989**, *54*, 3963-3972.
3. Balme, G. ; Bouyssi, D. *Tetrahedron* **1994**, *50*, 403-414 and references therein.
4. Bouyssi, D. ; Goré, J. ; Balme , G. ; *Tetrahedron Lett.* **1992**, *33*, 2811-2814.
5. Bouyssi, D. ; Goré, J. ; Balme , G. ; Louis D. ; Wallach, J. *Tetrahedron Lett.* **1993**, *34*, 3129-3130.
6. Arcadi, A. ; Burini, A. ; Cacchi, S. ; Delmastro, M. ; Marinelli, F. ; Pietroni, B.R. *J. Org. Chem.* **1992,** *57* ,976-982.
7. Review : Becker, K.B. *Tetrahedron* **1980**, *36*, 1717-1745.
8. All new isolated products yielded satisfactory ^{1}H and ^{13}C NMR and IR spectra as well as elemental analyses.
9. a) Aristoff, P.A. ; Jonhson,P.D. ; Harrison,A.W. *J. Am. Chem. Soc.* **1985**, 107, 7967-7974 ; b)Wu, G. ; Shimoyama, I. ; Negishi, E. ; *J. Org. Chem.* **1991**, 56, 6505-6506.

(*Received in France* 14 *November* 1995; *accepted* 8 *January* 1996)