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Palladium-Catalyzed Synthesis of New Unsaturated Exo-Enol Lactones with Potential Biological Activity.

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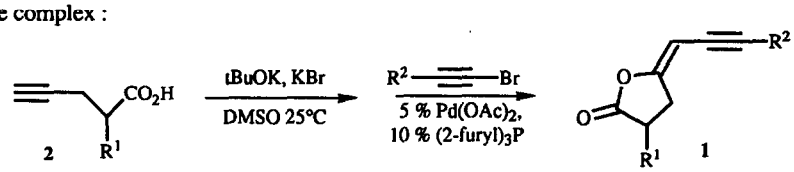
Abstract : Various allenenols lactones [5(E)-(2-allenylidene)-tetrahydro-2-furanones] have been synthesized by reacting 4-pentynoic acid and 2-alkynyl acetate in dimethyl sulfoxide in the presence of K_2CO_3, $Pd(OAc)_2$ as the catalyst and tri(2-furyl) phosphine as the ligand. The biological activity of these compounds as protease inhibitors has been proven.

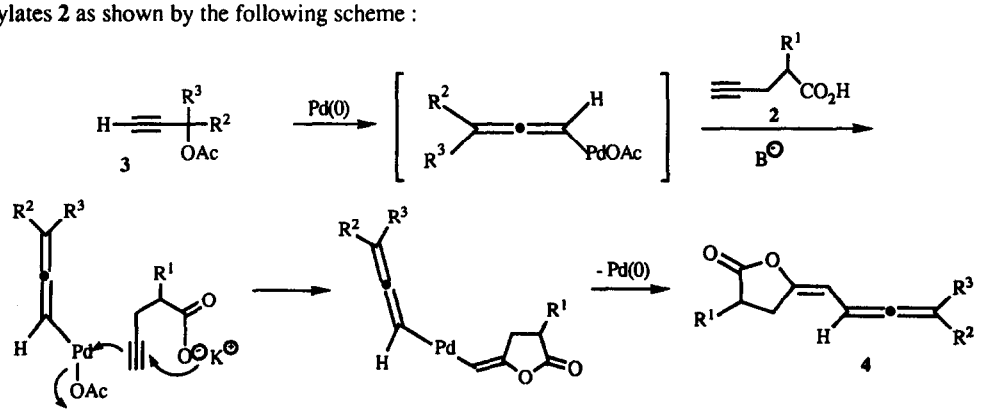
In recent years, significant attention has been focused on the synthesis of exo-enol lactones because many naturally occurring products containing this moiety possess biological activity[1].

Ynenol lactones **1** are known to display interesting biological properties mainly as suicide inhibitors of serine proteases[2]. In an earlier publication[3] we reported that these compounds are stereoselectively obtained when γ acetylenic carboxylates **2** are reacted with 1-halogeno-1 alkynes in the presence of a palladium(0) phosphine complex :



Since the reaction appeared promising for the preparation of heterocyclic compounds, we decided to examine the possibility of extending this methodology to the synthesis of allenenol lactones **4** [(5E)-2 allenylidene-tetrahydro-2-furanones]. Indeed mechanistic considerations suggest that these unknown allenyl derivatives could also produce electrophilic Michael acceptors at protease active sites [2,4].

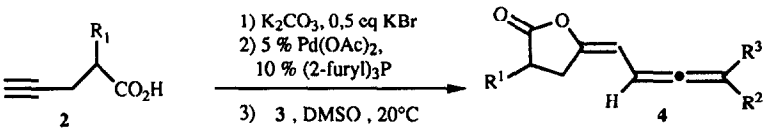
Several groups have provided many examples showing[5] that the palladium-catalyzed reaction of propargyl derivatives offers novel synthetic methods for various allenyl compounds. Therefore a direct access to allenenol lactones **4** could be the palladium catalyzed reaction of 2-alkynyl acetate **3** with pentynoic acid carboxylates **2** as shown by the following scheme :



The proposed mechanism involves an intramolecular nucleophilic attack of the carboxylate anion on the triple bond activated by a σ-allenyl palladium intermediate and subsequent reductive elimination of Pd(0) species from the resulting σ-vinyl palladium complex giving **4** and regenerating the palladium(0) complex.

The attempted reaction of 2-alkynyl acetate **3a** (R^2=R^3=CH_3) with the potassium carboxylate generated by the reaction of 4-pentynoic acid **2a** (R^1=H) with tBuOK under the conditions previously described for the transformation **2**⟶**1**[3] was successfull. We obtained the expected allenenol lactone **4a** in 43% yield.

Best results were observed when K_2CO_3 was used instead of tBuOK to prepare the potassium carboxylate of **2a** (yield 61%). Other representative results of this reaction are shown in table 1.



Acid	Acetate	Time	Lactone	Yield % [a]
R^1 = H **2a**	R^2 = R^3 = CH_3 **3a**	14 h	R^1 = H R^2 = R^3= CH_3	61 **4a**
R^1 = H **2a**	R^2 = H ; R^3 = Ph **3b**	22 h	R^1 = H R^2 = H ; R^3 = Ph	50 **4b**
R^1 = H **2a**	R^2 = R^3 =$(CH_2)_5$ **3c**	2 h	R^1 = H R^2 = R^3 = $(CH_2)_5$	54 [b] **4c**
R^1 = CH_3 **2b**	R^2 = R^3 = CH_3 **3a**	7 h	R^1 = CH_3 R^2 = R^3 = CH_3	62 **4d**

[a] : the yields are based on the quantity of isolated **4** purified by flash chromatography ; [b] : this reaction is carried out at 50°C.

Table 1

As noted above, allenenol lactones are potential mechanism based inactivators (suicide inactivators) of serine hydrolases, since acyl transfer to the active site of the enzyme releases a dienone that can react with nucleophilic sites by the same type of Michaël addition that was suggested for compounds **1**[2].

Our first assay using Succ-$(Ala)_3$-pNA as a substrate[6] proved, as anticipated, that **4a** is an inhibitor of Human Leukocyte Elastase (E.C 3.4.21.37) though it was less potent that compounds of type **1**. Experiments to determine the selectivity of this activity for serine proteases as well as the inhibitory capacity of diversely substituted compounds **4** are currently in progress.

References and notes

1. See for example :
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