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Easy Access to 5-(E)-Alkynylidene Tetrahydro-2 Furanones by a Palladium Catalyzed Process

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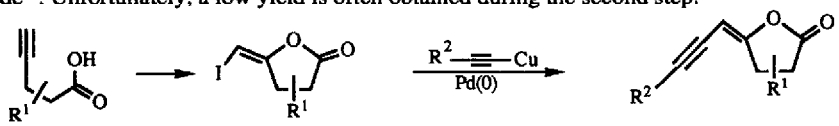
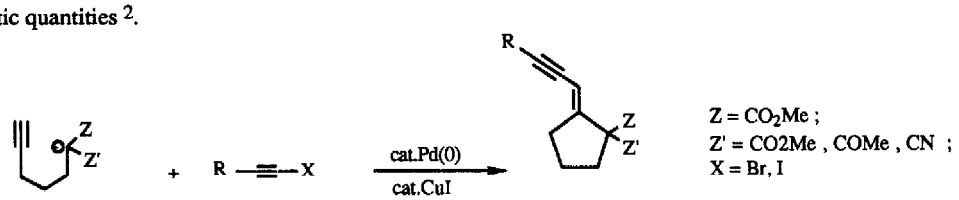
Abstract.: Biologically active ynenol lactones **1** are stereospecifically obtained when γ-acetylenic carboxylates are reacted with 1-bromo 1-alkynes in the presence of a palladium(0)-phosphine complex. The reaction is effective only with the potassium carboxylate and the nature of the phosphine is essential for the cyclisation process.

Ynenol lactones of general formulæ **1** display interesting biological properties mainly as suicide inhibitors of serine proteases. They were prepared previously from pentynoic acids by a two step-process, an iodolactonisation followed by a palladium-catalyzed coupling of the intermediate iodovinyllactone with a copper acetylide [1]. Unfortunately, a low yield is often obtained during the second step.



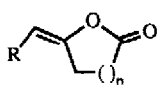
1

Recently, we have shown that ynenylcyclopentanes **2** were easily and stereospecifically prepared from alkynes **3** and acetylenic bromides or iodides in the presence of both a palladium(0) complex and copper iodide in catalytic quantities [2].



3 **2**

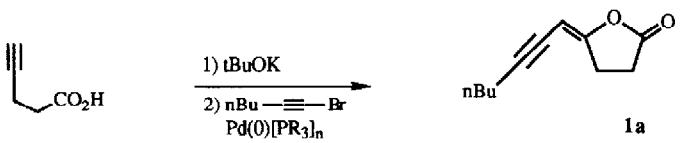
It was therefore possible to envisage the direct access to **1** from pentynoic acids or their carboxylates by applying the same experimental conditions. In this context some recent reports have described the palladium-catalyzed cyclisation of ω-acetylenic acids which gives rise in a single step to lactones **4** where R is an aryl and vinyl [3] or an allyl group [4,5].



4
n = 1 or 2

In the first attempt, we treated the potassium carboxylate of 5-pentynoic acid with 1-bromo 1-hexyne in the presence of palladium tetrakistriphenylphosphine (0.03 mol.eq.) and cuprous iodide (0.06 mol.eq.) under the conditions previously described for the transformation **3**→**2** [2]. This reaction was completely unsuccessfull as were others performed when the components of the reaction mixture were modified. Among these modifications were the addition of potassium bromide which slightly increases the solubility of the carboxylate, the use of the lithium or sodium salts of pentynoic acid, the replacement of triphenylphosphine by diphenylphosphinoethane as ligand of palladium, the absence of the cuprous salt etc...

Fortunately, Tsuda *et al.* made an intensive study of the effect of the metal ligands and, have also examined, though not as thoroughly, the effect of the solvent in the cyclisation of 5-pentynoates promoted by a π-allylpalladium complex [4]. This reaction is mechanistically related to the expected transformation of the same pentynoates to the ynenol lactones **1** under the influence of a σ-ethynylpalladium complex. Effectively, the same dramatic influence of the ligand was noticeable since it was possible to obtain the lactone **1a** in variable yields by using other palladium-phosphine complexes [6]. Some results are listed table 1 and were obtained by reacting 1 molar equivalent of potassium 5-pentynoate with 1-bromo 1-hexyne in the presence of 0.5 mol.eq. of potassium bromide.



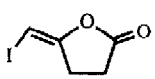
1a

R in PR_3	Solvent	temperature	reaction time (h)	yield [a] (%)
o-tolyl	THF	25°	48	30
"	CH_3CN	"	40	37
"	THF/CH_3CN 1/1	"	48	41
"	"	55°	72	14
p-Cl phenyl	"	25°	71	26
p-F phenyl	"	"	48	0
2-furyl	"	"	18	27

[a] The reactions were followed by G.C. and stopped after disappearance of the pentynoic acid, the reaction product being formed of **1a** and the starting acetylenic bromide. The yields are based on the quantity of **1a** purified by flash-chromatography.

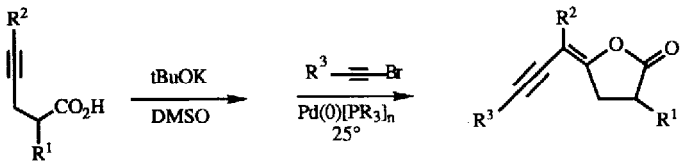
Table 1

It is noteworthy that only the potassium carboxylate (resulting from the reaction of either tBuOK or KH with the acid) is effective in this cyclisation to ynenol lactone **1a**, the lithium salt (formed with n-BuLi) or the sodium salt (formed with HNa) giving less that 5% of **1a**. Further, the presence of KBr consistently increases the yield by about 15-20%, while the use od 1-iodo 1-hexyne is less effective, the formation of **1a** being accompanied by that of the iodolactone **5**. For example, in the presence of tri-o-tolyl phosphine as ligand, the reaction product (room temperature -66h) is composed of **1a** (17%) and **5** (42%) in addition to unreacted starting acid and polymers.



5

Finally, we found that the yield of **1a** is increased even further if DMSO is used as the solvent and if an excess of the unsaturated acid (1.5 mol.eq.) is engaged since this compound has a marked tendency to polymerize under the reaction conditions. Two phosphines have been found capable of promoting an efficient transformation : tri o-tolyl phosphine and primarily tri (2-furyl) phosphine which was previously described as being able to decrease the electronic density on palladium and consequently to increase the electrophilicity of the palladium complex [7]. The results of reactions involving three different γ-acetylenic acids and diverse 1-bromo 1-alkynes are listed in the table table 2. They provide evidence for the efficiency of the reaction for forming stereo specifically [8] the enynol lactone **1** in one step [9].



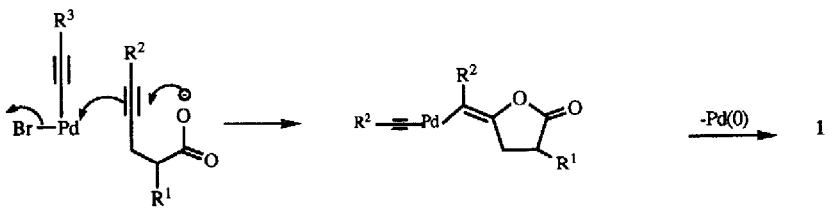
1a $R_1=R_2=H$; $R_3=nBu$
1b $R_1=R_2=H$; $R_3=Ph$
1c $R_1=R_2=H$; $R_3=(CH_2)_3Cl$
1d $R_1=H$; $R_2=CH_3$; $R_3=nBu$
1e $R_1=CH_3$; $R_2=H$; $R_3=nBu$

R^1	R^2	R^3	R in phosphine	time	lactone	Yield[a] (%)
H	H	nBu	o-tolyl 2-furyl	15 h 5 h	**1a**	68 84
H	H	Ph	o-tolyl 2-furyl	22 h 16 h	**1b**	35 55
H	H	$(CH_2)_3Cl$	o-tolyl 2-furyl	17 h 5 h	**1c**	60 73
H	CH_3	nBu	2-furyl	5 h 30	**1d**	58
CH_3	H	nBu	o-tolyl 2-furyl	22 h 6 h	**1e**	42 90

[a] see note table 1, but here the reactions were stopped after disappearance of the acetylenic bromide.

Table 2

As far as the mechanism is concerned, we can propose again that this cyclisation occurs by nucleophilic attack of the carboxylate onto the triple bond activated by the σ-ethynylpalladium complex. This cyclisation is followed by reductive elimination giving **1** and regenerating the palladium(0) complex.



The success of this cyclisation compared to the ineffectiveness of the transformation **3**→**2** in the absence of catalytic quantities of cuprous iodide reflects the importance of the use of tri(2-furyl)phosphine [10] as a palladium ligand. With this catalyst, the transformation **3**→**2** (Z=Z'=CO_2Me, R=nBu, potassium enolate) is

observed in 24h (yield : 45%) under the best experimental conditions used here [9]. This provides confirmation for the increased electrophilicity of the σ-ethynyl palladium species in the presence of this phosphine [7].

References and notes

1. a. Tam, T.F. ; Spencer, R.W. ; Thomas, E.M. ; Copp. L.J. and Krantz, A. ; J.Amer.Chem.Soc., **1984**, 106, 6849.
   b. Spencer, R.W. ; Tam, T.F. ; Thomas, E.M. ; Robinson, V.J. and Krantz, A. ; J.Amer.Chem.Soc., **1986**, 108, 5589.
2. Bouyssi, D. ; Balme, G. and Gore, J. ; Tetrahedron Lett., **1991**, 32, 6541.
3. Arcadi, A. ; Burini, A. ; Cacchi, S. ; Delmastro, M. ; Marinelli, F. ; Pietroni, B.R. ; sent for publication as announced in : Arcadi, A. ; Cacchi, S. ; Burini, A. ; Delmastro, M. Marinelli, F. Pietroni, B.R., Synlett , **1991**, 407
   We thank Professor S. Cacchi for communication of his manuscript prior to publication.
4. Tsuda, T. ; Ohashi, Y. ; Nagahama, N. ; Sumiya, R. and Saegusa, R. ; J.Org.Chem., **1988** , 53 ,2650 .
5. Yanagihara, N. ; Lambert, C. ; Iritani, K. ; Utimoto, K. and Nozaki, H. ; J.Amer.Chem.Soc., **1986**, 108, 2753.
6. The palladium(0) complexes used in this study were preformed in the appropriate solvent by reaction of 1-heptene with palladium acetate (0.5 mol.eq.) in the presence of the selected phosphine (2 mol.eq.). Generally the reactions were run with 0.05 mol. eq. of the catalyst.
7. Farina, V. ; Baker, S.R. ; Benigni, D.A. and Sapino, Jr. C. ; Tetrahedron Lett. ; **1988**, 29, 5739 and references there-in...
8. In every case, only one isomer of **1** was detected ; its configuration is proposed by reference to all the other related cyclisations [2-5].
9. Typical experiment : The anion is formed by adding 1.5 eq. of pentynoic acid, 0.75 eq. of KBr and 1.55 eq. of tBuOK in 4 ml of DMSO at R.T. Then, the addition of the Pd(0) solution prepared according to ref.6 is made via a canula and is followed by that of 1 eq. of the acetylenic bromide in 3 ml of DMSO. The mixture is stirred until the acetylenic bromide is consumed (GC) Classical work-up followed by chromatography on silica-gel gives **1a-e**.
   All these compounds **1a-e** are characterized by spectroscopic methods (^1H and ^{13}C NMR, IR, MS). As an example, the spectral data of **1c** and **1e** are given.
   Compound **1c** : IR (neat) : 3040, 2960, 2220, 1810, 1660, 1110 and 910 cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) : δ 1.98 (q, 2H, J=6.5) ; 2.54 (txd, 2H, J=6.5 ; 2.3) ; 2.71 (m, 2H) ; 3.0 (m, 2H) ; 3.66 (t, 2H, J=6.5) ; 5.32 (q, 1H, J=2.3). ^{13}C NMR ($CDCl_3$) : δ 17.01, 24.5, 27.17, 30.39, 43.61, 75.05, 86.94, 92.85, 160.42, 174,15. Mass spectrum m/z (%) : 198 ($M^{+\cdot}$, 71) ; 170(42) ; 135(38) ; 107(67) ; 77(87) ; 51(100) ; 39(66) ; 27(63).
   Compound **1e** : IR (neat) : 2960, 2920, 2860, 2205, 1800, 1670 and 1120 cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) : δ 0.92 (t, 3H, J=7) ; 1.34 (d, 3H, J=8) ; 1.4-1.55 (m, 4H) ; 2.32 (txd, 2H, J=6.8 ; 2) ; 2.59 (dxdxd, 1H, J=16.7 ; 7.8 ; 2.5) ; 2.86 (dxdxq, 1H, J=9.7 ; 7.8 ; 8) ; 3.27 (dxdxd, 1H, J=16.7 ; 9.7 ; 1.7) ; 5.3 (dxtxq, 1H, J=2.5 ; 2.0 ; 1.7). ^{13}C NMR ($CDCl_3$) : δ 13.61 ; 16.15 ; 19.25 ; 21.98 ; 30.96 ; 32.82 ; 34.15 ; 74.06 ; 87.25 ; 94.98 ; 158.62 ; 177.25. Mass spectrum m/z (%) : 192 ($M^{+\cdot}$, 70) : 149(33) ; 135(13) ; 121(32) ; 107(44) ; 79(100) ; 51(89) ; 39(58) ; 23(33).
10. This phosphine, which is not commercially available, can be prepared according to : Allen, D.W. ; Hutley, B.G. ; Mellor, M.T.J. ; J.Chem.Soc. Perkin II, **1972**, 63.

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