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# SYNTHESIS OF ETHYNYLIDENE CYCLOPENTANES BY A CYCLISATION CATALYZED BY THE SIMULTANEOUS PRESENCE OF PALLADIUM (0) AND COPPER (I)

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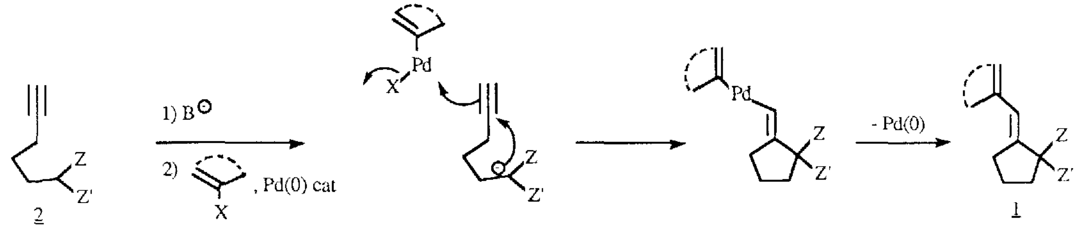
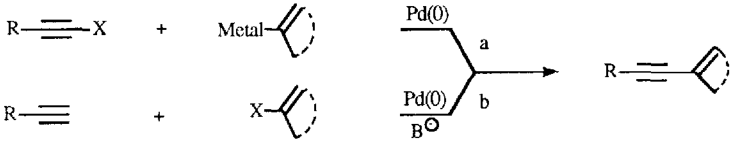
Abstract. Ethynylidene cyclopentanes 3 can be formed in 35-71% yield from the reaction of the enolates of compounds such as δ-acetylenic malonates with 1-halogeno-1-alkynes. This reaction requires catalysis by both palladium (0) and copper (I) species.

We recently showed that arylidene and allylidene cyclopentanes 1 can be stereospecifically formed by a palladium-catalyzed process involving the cyclisation of the enolates of the easily accessible compounds 2 (1). A nucleophilic attack of the enolate onto the unsaturation activated by the electrophilic palladium (II) complex was proposed for this cyclisation (scheme 1) that can be also promoted by a palladium hydride species (2).



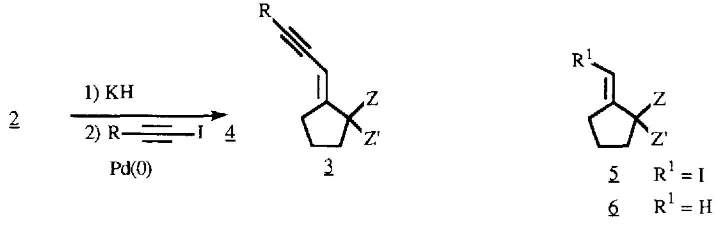
Scheme 1

Considering that some natural products have an ethynylidene-cyclopentanic skeleton (3), we wondered whether the same process would occur with an acetylenic halide as the source of the palladium(II) complex. If enynes have been made by the coupling of acetylenic and ethylenic partners catalyzed by a palladium(0) complex, only a few reports mention acetylenic halides as the precursors of σ-palladic intermediates (scheme 2, process a) (4). In the majority of such couplings, vinylic halides are reacted with acetylenic compounds in the presence of a base (process b) (5). The main reason for this is that σ-ethynylpalladium species are prone to homocoupling giving 1,3-diynes (6).



Scheme 2

Our first attempts to transform the enolate of the acetylenic starting material 2 to the expected products 3 using acetylenic iodides 4 (R = butyl or phenyl) in the presence of $Pd(PØ_3)_4$ were unsuccessfull : in addition to intense polymerisation, we were able to isolate only small quantities of the corresponding 1.3-diynes and(or) the cyclized vinylic iodide 5 and(or) the methylene compound 6 previously isolated under other conditions (2) (scheme 3).

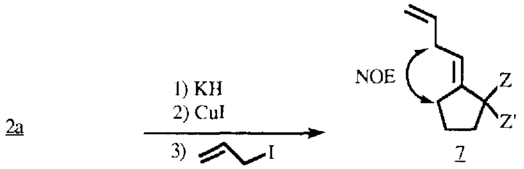


Scheme 3

After a systematic study of some of the experimental parameters of the reaction we found that the expected transformation 2 ⟶ 3 can take place in THF at room temperature by adding slowly the halide 4 to a solution of the preformed potassium enolates in the presence of 0.03 molar equivalent of $Pd(PØ_3)_4$ and 0.06 equivalent of cuprous chloride or iodide. The results of some of these transformations with modifications of the starting material and(or) of the acetylenic halide are given in the table. In all cases, the stereospecific formation of 3 occured but the yields were variable depending on the nature of R, Z and Z'. Generally, the enyne 3 is accompanied by polymeric materials and by some traces of the methylenecyclopentane 6 (easily separated by flash-chromatography).

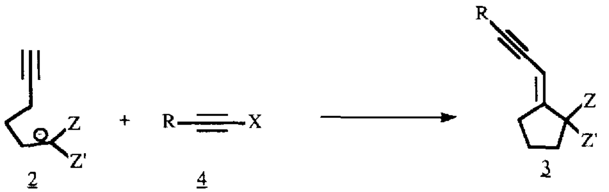
It is noteworthy that the transformation needs to occur in the presence of both palladium and cuprous catalysts : in the reaction of the anion of 2a and 1-iodo-hex-1-yne 4a under the same conditions but in the presence of only 0.05 mol.eq. of $Pd(PØ_3)_4$ (addition time 4 hours ; reaction time 24 hours), the product formed consisted primarily of polymers, starting material (18%) and the vinylic iodide 5a ($Z=Z'=CO_2Me$) (10%). With only 0.1 mol.eq. of CuI, the starting material slowly disappeared (96 hours for total consumption) giving a complex mixture in which 3a is completely absent.

The mechanism of the transformation 2 ⟶ 3 can be deduced from a supplementary experiment : when 2a was treated sequentially in THF at room temperature with potassium hydride (1 mol.eq.), cuprous iodide (1 mol.eq.) and the immediate addition of allyl iodide (1 mol.eq.) the 1,4-dienic compound 7 was also stereospecifically formed in 65% yield (scheme 4).



Scheme 4

The configuration of the trisubstituted double bond of 7 was deduced from a differencial NOE experiment that showed the proximity of the two designated methylene groups.



| Starting [a] 2 | Halide [b] 4 | reaction [c] time (hours) | Product | Yield [d] |
|---|---|---|---|---|
| 2a<br>$Z=Z'=CO_2Me$ | 4a R=nBut<br>X=I | 7 | 3a $Z=Z'=CO_2Me$<br>R=nBut | 71% |
| | 4b $R=Cl(CH_2)_3$<br>X=I | 22 | 3b $Z=Z'=CO_2Me$<br>$R=Cl\text{-}(CH_2)_3\text{-}$ | 68% |
| | 4c $R=MeOCH_2$<br>X=I | 19 | 3c $Z=Z'=CO_2Me$<br>$R=MeOCH_2$ | 40% |
| | 4d R=Ph<br>X=Br | 16 | 3d $Z=Z'=CO_2Me$<br>R=Ph | 49% |
| | 4e R=Ph<br>X=I | 6 | 3d (17%) + 5a (15%) | - |
| 2b<br>$Z=CO_2Me$<br>Z'=COMe | 4a | 19 | $Z=CO_2Me$<br>3e Z'=COMe<br>R=nBut | 35% |
| 2c<br>$Z=CO_2Me$<br>$Z'=SO_2Ø$ | 4a | 22 | $Z=CO_2Me$<br>3f $Z'=SO_2Ø$<br>R=nBut | 50% |
| 2d<br>$Z=CO_2Me$<br>Z'=CN | 4a | 7 | $Z=CO_2Me$<br>3g Z'=CN<br>R=nBut | 71% |

Table

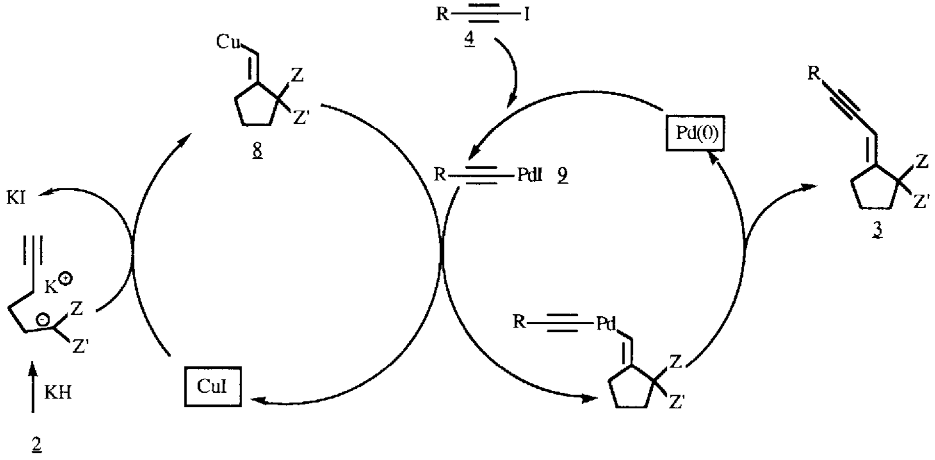
[a] all the reactions were performed on a one millimole scale

[b] slow addition in 4 hours (except for 4c, 6 hours) with an automatic syringe

[c] The reactions are followed by TLC and stopped after disappearance of the starting material

[d] based upon quantities of 3 isolated by flash-chromatography

Consequently, it appears that cuprous iodide is able to promote the stereospecific cyclisation of the enolate of 2a to the E vinylic species 8 which reacts with the $\sigma$-ethynylpalladium complex 9 produced by the oxidative addition of the acetylenic halide 4 to palladium(0) (scheme 5). This complex 9 is not electrophilic enough to assist the attack of the enolate onto the double bond as previously shown for its vinylic or arylic homologs.



Scheme 5

The E stereochemistry of the double bond of 3 was deduced mainly from that of 7 which has the same vinylic copper intermediate 8 and from the fact that the irradiation of the vinylic proton of 3a has no effect on the signal of the allylic methylene group in a differencial NOE experiment.

In conclusion, we have shown that the cyclisation of the enolates of $\delta$-acetylenic malonates and congeners can be accomplished by using acetylenic halides but for this reaction to occur, catalysis by both a cuprous salt and a palladium(0) complex is necessary.

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