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STEREOSPECIFIC SYNTHESIS OF ARYLIDENE AND ALLYLIDENE CYCLOPENTANES BY A PALLADIUM-CATALYZED CYCLISATION

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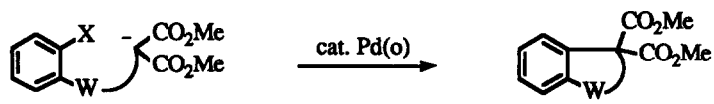
Abstract. Vinyl and aryl halides react with ε-acetylenic β-diesters, β-keto esters and β-sulfonylesters in the presence of a Pd(o) catalyst leading in good yields to the title compounds. The acetylenic homolog containing an additional carbon leads in the same conditions to a cyclohexane, but this process then competes with the arylation of the terminal acetylenic carbon.

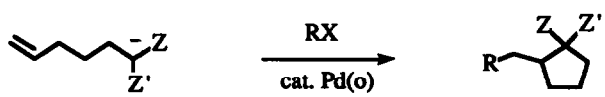
There is presently an increasing interest in the development of palladium-catalyzed cyclisations using either a π-allyl palladium route (1) or a process related to an intramolecular Heck reaction (2).

An other cyclisation process utilizes the displacement, via an arylic σ-palladium complex, of the halide of an aromatic substrate by a delocalized enolate (3), (scheme 1). Related to this reaction is our previous work concerning the carbopalladation of substrates such as 1 which are converted to cyclopentanic compounds 2 in a two carbon-carbon bond forming reaction (4) (scheme 2).



X = I, Br W = CH_2, -$(CH_2)_2$, SO_2, CO

Scheme 1

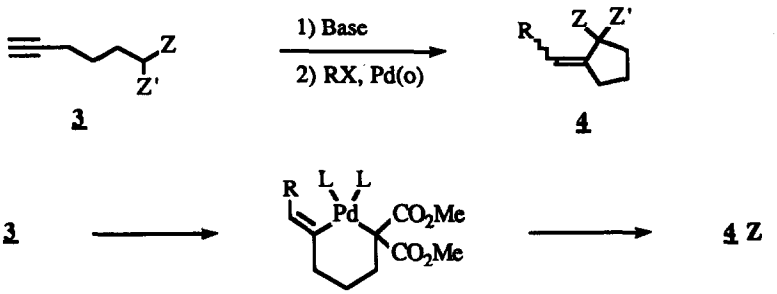


1 2

Z, Z' = -CN, -COR, -CO_2R R= phenyl or vinylic group

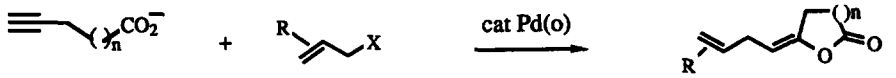
Scheme 2

We were interested in developing the same reaction in the case of the acetylenic homologs of 1. From a synthetic point of view this carbopalladation process would lead to arylidene or allylidene cyclopentane 4; on the other hand, the stereochemistry of the reaction could give information on the mechanism of the cyclisation by confirming or ruling out a palladacycle intermediate postulated in the reaction depicted in scheme 1. In the case of acetylenic substrates 3, this species would clearly leads to the Z isomer of the product 4 (scheme 3).



Scheme 3

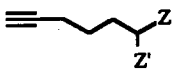
Only a related heterocyclisation process involving the carbopalladation of acetylenic substrates been previously described the carbopalladation species was a π-allyl palladium complex while a carboxylate was the internal nucleophile (5) (scheme 4).



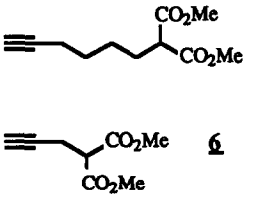
n = 1 or 2

Scheme 4

The substrates 3a, b, c necessary for this study were easily obtained by alkylation of methylmalonate, methylacetoacetate and α-phenylsulfonylmethylacetoacetate with the mesylate of commercially available pent-4-yne-1-ol . For the sake of comparison, we also prepared 5 and 6 respectively from the mesylate of hex-5-yne-1-ol and propargylbromide.



3a Z= Z'= CO_2Me
3b Z= CO_2Me, Z'= COMe
3c Z= CO_2Me, Z'= SO_2Ph



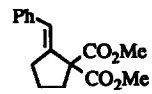
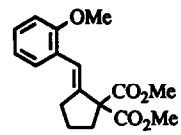
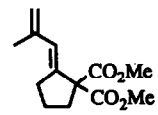
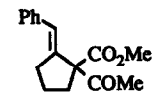
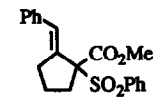
5

6

Initially, the carbopalladation of 3a was run in the conditions previously used for the ethylenic homologs 1 ; the preformed sodium enolate (3a + 1.1 mol.eq. of HNa) was heated in DMSO at 80°C with 1.1 mol. eq. of phenyliodide in the presence of 5 % mol. eq. of the complex palladium bis(dibenzylidene acetone) and 5 % of diphenylphosphinoethane, the evolution of the reaction being followed by GPC. After two hours, the starting 3a completely disappeared with the clean formation of a single isomer of 4a easily purified by flash-chromatography (table) (6). The E configuration of this isomer was deduced from differential NOE experiments in ^1H NMR : irradiation of the ethylenic proton (δ 6.7 ppm) had no effect on the allylic protons of the ring (δ 2.72 ppm) while irradiation of the aromatic hydrogens (δ 7.3 ppm) caused a neat Overhauser effect.

The carbopalladation-cyclisation reaction proves easier than in the ethylenic serie : the same clean conversion of 3a to 4a can be also observed when the reaction mixture is stirred overnight at 30°C. On the contrary, the change of the counter-ion of the enolate, if slightly improving the yield, does not exerce a marked effect on the rate of the transformation (7).

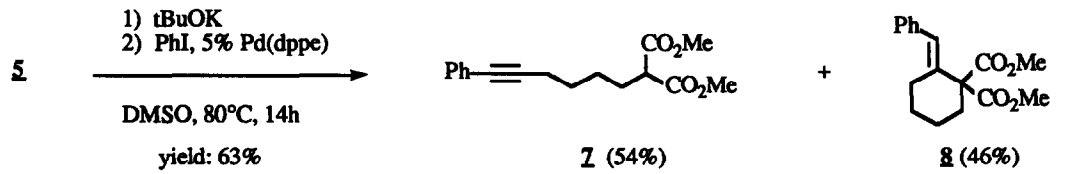
Table

Starting matérial	Entering Halide	Experimental conditions* base-t°.-time	Product	isolated yield**
3a	Iodo benzene	NaH-80°C-2h NaH-30°-14h tBuOK-30°C-14h	 4a	78% 70% 80%
3a	2-iodo anisole	tBuOK-30°C-14h		70%
3a	2-bromopropene	tBuOK-30°C-14h		75%
3b	iodobenzene	tBuOK-30°C-14h	 4h	88%
3c	iodobenzene	tBuOK-30°C-14h	 4c	57%

* all the reactions were performed on a 10^{-3} mole scale.
** products were isolated by chromatography on silica gel.

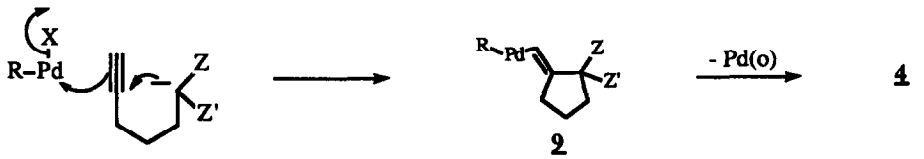
Considering these first results, the carbopalladations of 3a with different entering halides and of 3b and 3c with phenyl iodide were run under the latter conditions : in every case the cyclopentanic compound was obtained in fairly good yields and with a single configuration, assumed to be E by spectral comparison with 4a (Table).

The one additional carbon homolog 5 is only engaged when the reaction is run at 80°C and is transformed in 14 h to a mixture of 7 and 8. The formation of 8 is a novelty, compared to the ethylenic series where a cyclisation to a six-membered ring was never observed (4). Again, only one isomer of 8 is formed, the ^{13}C NMR spectrum of which is, with one more signal, almost superimposable to that of 4a. Consequently, the same E configuration was attributed to 8.



Finally, no reaction was observed in the case of 6, even when the mixture was heated for 12 h at 80° and then 6 h at 110°. A large amount of the starting material was then recovered in addition to polymerized products.

In conclusion, this study provides an easy access to cyclopentanes 4 obtained in high yield from easily prepared substrates 3. From a mechanistic point of view, it seems that the stereochemistry of the process rules out a palladacycle as the intermediate. The more plausible pathway is depicted in scheme 5 and involves i) electrophilic assistance by the σ-aryl or σ-vinyl palladium of the attack by the carbon nucleophile of the acetylenic linkage (5-exo-dig process) ; ii) reductive elimination of the σ-vinylic palladium species 9. This process is in competition in the case of 5, with a normal palladium catalyzed arylation of the terminal acetylenic carbon.



Scheme 5

References and notes

1. For review, see Trost B.M., *Angew.Chem.Int.Ed.Engl.*, **1989**, 28, 1173.
2. For review, see Thebtaranonth C and Thebtaranonth Y., *Tetrahedron*, **1990**, 46, 1385 ; see also Ref.4b.
3. Ciufolini M.A. , Qi H.B. and Browne M.E., *J. Org. Chem.*, **1988**, 53, 4149.
4. Fournet G., Balme G. and Gore J. a) *Tetrahedron Lett.*, **1988**, 30 , 69.
   b) *Tetrahedron*, in press.
5. a) Tsuda T., Chujo Y. and Saegusa T., *Synth.Comm.*, **1981**, 11, 775.
   b) Yanagihara N., Lambert C., Iritani K., Utimoto K. and Nozaki H., J.Amer.Chem.Soc., **1986** , 108 , 2753.
   c) Tsuda T., Ohashi Y, Nagahama N., Sumiya R. and Saegusa T., J.Org.Chem., **1988**, 53, 2650.
6. NMR spectra of 4a ^1H (300 MHz, $CDCl_3$ - TMS) : 1.84 (2H, quint J=7Hz) , 2.39 (2H, t, J=7Hz) , 2.72 (2H, dt, J=2.5 and 7Hz) , 3.77 (6H, s) , 6.70 (1H, t, J=2,5Hz) , 7.18-7.40 (5H, m). ^{13}C (75 MHz, $CDCl_3$ - TMS) : 24.94 (t) , 32.13 (t) , 35.84 (t) , 52.90 (q) , 65.49 (s) , 126.94 (d) , 127.56 (d) , 128.28 (d) , 128.80 (d) , 137.67 (s) , 141.08 (s) , 171.54 (s).
7. In the case of the ethylenic homologs, the replacement of HNa by tBuOK has a dramatic effect on the rate of the reaction which can be run at room temperature in place of 80°C : Balme G., Bouyssi D., Fournet G., Gore J. and Monteiro N. to be published.

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