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CYCLISATION OF ω-UNSATURATED β-DICARBONYLCOMPOUNDS CATALYZED BY A PALLADIUM HYDRIDE SPECIES

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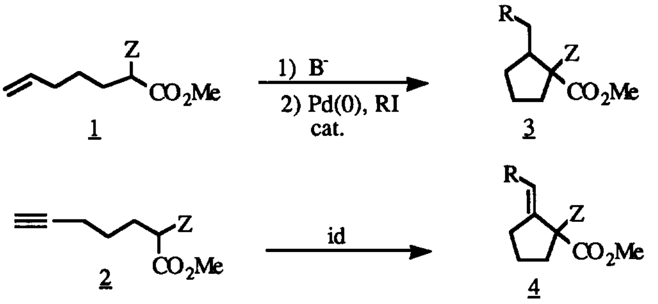
Abstract. When treated with potassium t-butoxide and then with a palladium(0) complex, the title compounds 1 , 2 , or 9 are smoothly cyclized by an attack of the enolates onto the unsaturation assisted by a palladium (II) species of tBuO-Pd-H type. The formation of a five-membered ring is particularly favored in such a process.

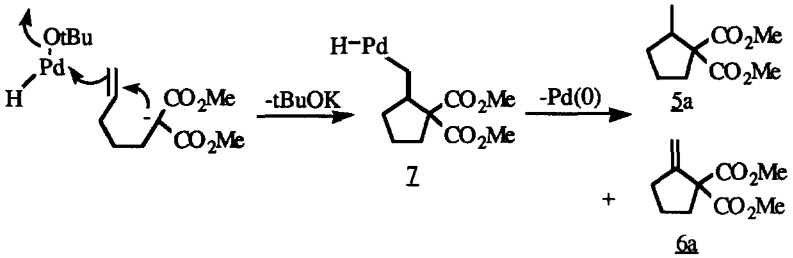
In the accompanying paper [1], we provided several lines of evidence for the mechanism of the cyclisation observed when the anions of compounds such as 1 and 2 were treated under the conditions of the Heck reaction, namely addition of a phenyl or a vinyl halide in the presence of a palladium(0) catalyst [2]. From the stereochemistry of the process as well as from the increased facility of the reaction with the increased nucleophilicity of the enolate, we deduced that these cyclisations could be considered as a nucleophilic attack of the enolate on the double or on the triple bond activated by the vinylic or the arylic σ-palladium species. There were precedents in the litterature for such processes but they have been described so far only for double bonds which were attacked by carbon nucleophiles and converted to cyclic functionnalized compounds in the presence of a stoichiometric amount of palladium II [3].



Z = CO_2Me , COMe , SO_2Ph R = phenyl or vinyl group

During the study of the cyclisation 1a → 3a (Z = CO_2Me , R = Ph) using potassium t-butoxide as the base, 3a was sometimes accompanied by traces (< 5%) of its homolog 5a having a hydrogen in the place of the phenyl group. We then considered the possibility that this product could be formed by the same kind of cyclisation initiated by a palladium (II) hydride species which would be issued from the oxidative addition of Pd(0) to t-butanol (scheme 1), identical to that proposed by Trost et al. in the case of acetic acid [4].

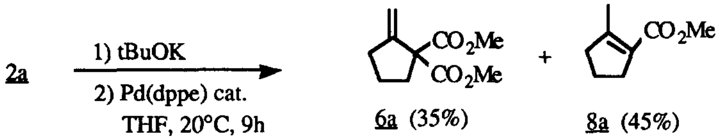
$$tBuOH + Pd(0) \longrightarrow tBuO-Pd-H$$



scheme 1

Consequently, we treated 1a successively by 1.1 equivalent of tBuOK and then by 0.05 equivalent of the Pd(dppe) complex [5] (solvent : THF). After 72 hours at 20°C, the starting material was fully and cleanly transformed to a mixture of two compounds 5a and 6a in a 4:1 ratio (yield : 60%). The formation of these two compounds is consistent with the intermediate formation of 7 which can evolve to 5a by reductive elimination or to 6a by β-elimination. Unfortunately, in spite of numerous attempts with different solvents (THF ; NMP ; toluene), catalysts ($Pd(P\emptyset_3)_4$; $Pd_2(dba)_3$, $CHCl_3$ + 1dppe or 1dppp) and temperature (up to 80°C), it was impossible to drive specifically the reaction towards 5a or 6a as well as to increase its yield.

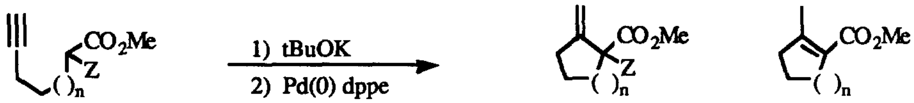
We then turned our attention to the acetylenic series and treated 2a ($Z = CO_2Me$) in THF at 20°C with i) 1 equivalent of potassium t-butoxide and ii) 0.05 equivalent of the Pd(dppe) complex. After 9 hours, 2a was transformed to a mixture of the cyclised products 6a and 8a.



After flash-chromatographic separation of both compounds, 6a treated by one equivalent of tBuOK in refluxing THF was cleanly transformed to 8a in quantitative yield. Consequently, 2a was exclusively converted to 8a with a 75% yield by reacting it successively with one equivalent of tBuOK and then 0.05 equivalent of the catalyst during 3 hours at 80°C.

As the transformation of 2a to 6a could be catalytic, not only in palladium(0) but also in alkoxide, and as it has been proven that this last reagent promotes the transformation 6a → 8a , the same reaction was performed with only 0.2 equivalent of base. It then became a slow and sluggish process. Taking into account our previous results showing that an increase of the nucleophilicity of the enolate greatly accelerates the cyclisation, we ran the same reaction in the presence of 0.2 equivalent of 18-crown-6 and observed the exclusive formation of 6a in 76% yield after refluxing for 18 hours in THF [6]. The same specific transformations were also observed in the case of the β-keto-ester 2b which can be transformed either to 6b or to 8a with excellent yields (Table).

In the case of the one-more carbon starting materials 9a and 9b , the cyclisations proved more difficult and needed both longer times and the presence of 18-crown-6. Even in the presence of molar quantities of tBuOK, the cyclized products 10 proved to be stable under the reaction conditions but the yields were modest due to polymerisation and to the formation in all cases of about 20% of dimeric compounds 11a,b [7].

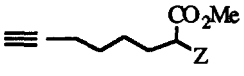


starting material	conditions [a]			products and yields %			
	Base [b]	T(°C)	t(h)				
2a (n=1 , Z=CO_2Me)	A	0	24	6a	40	8a	43
	"	20	9		35		45
	"	78	3		0		75
	B	"	18		76		0
2b (n=1 , Z=COMe)	A	20	6	6b	0	8a	91
	B	"	16		80		0
9a (n=2 , Z=CO_2Me)	C	78	48	10a	40		
9b (n=2 , Z=COMe)	C	78	30	10b	42		

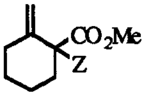
Table

[a] All the reactions were performed on a 1 mmole scale using THF as solvent and 5% of catalyst. Yields refer to quantities of products isolated by flash-chromatography after total transformation of the starting material (TLC).

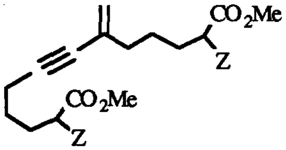
[b] A = 1.1 eq tBuOK
B = 0.2 eq tBuOK ; 0.2 eq 18cr6
C = 1.1 eq tBuOK ; 0.2 eq 18cr6



9 a $Z = CO_2Me$
b $Z = COMe$



10 a $Z = CO_2Me$
b $Z = COMe$



11 a $Z = CO_2Me$
b $Z = COMe$

Finally, in the case of 2a the same transformations to 6a or 8a were also observed when methanol was used in place of t-butanol. The treatment of 2a successively by one equivalent of potassium hydride and then by 0.05 equivalent of the Pd(dppe) catalyst in the presence of two equivalents of methanol leads to 8a (90%) after 3 hours at 50°C while 6a (61%) is exclusively formed if the reaction is performed with 0.2 equivalent of both hydride and methanol during 15 hours at the same temperature.

In conclusion, it appears that the cyclisation of stabilized enolates to a double or a triple bond can be effectively promoted by a palladium hydride species formed by reaction of an alcohol with a palladium(0) catalyst. Again, this type of cyclisation is greatly favored and exclusive when it leads to five-membered rings but competitive processes are observed in other cases.

References and notes

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