Tetrahedron Letters, Vol. 33, No. 11, pp. 1403-1406, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

On the Palladium Catalyzed Reaction of Methallyl-1,1-Diacetate with Cyclic β-Ketoesters. Intervention of Hidden Mechanisms.

D. Gravel*, S. Benoît, S. Kumanovic, H. Sivaramakrishnan.

**Département de chimie, Université de Montréal,
Montréal, Québec, Canada, H3C 3J7.**

Abstract: *Palladium(0) catalysis in the title reaction causes the release of methacrolein which competes effectively with the π-allyl species in product formation, a bicycloannulated derivative, when DBU is used as base.*

In connection with a synthetic problem aimed at the rapid construction of various 1-carbomethoxy 3-methyl bicyclo[3.3.1] non-3-ene-9-ones (**1**) in order to generate analogs of huperzine-A (**2**) for testing[1], a palladium catalyzed bicycloannulation reaction attracted our attention. The latter involved the reaction of allylic 1,1-diol diacetates with the pyrrolidine enamine of cyclohexanone under the catalysis of palladium(0) to yield a bicycloannulated product in one step[2]. Although the mechanism proposed appeared surprising the reaction was nonetheless interesting and the yields acceptable[2]. We therefore attempted a similar reaction using substituted β-ketoesters and BSA or DBU as a base. Table **1** shows the results of the Pd(0) catalyzed reaction of the allylic 1,1-diacetate with various β-ketoesters[3]. In all cases using BSA as the base (entries 1-4), the reaction stopped at the monoalkylation product and, in all cases also, alkylation took place from the less hindered 3-position of the allylic 1,1-diacetate as observed by Trost and Vercauteren for related hindered systems[4]. On the other hand, results also show the marked influence of changing the base for a stronger one. Under the same reaction conditions, but using DBU as base (entries 5-8), a bicycloannulation reaction, analogous to that reported for enamines[2], is observed with unoptimized yields varying from 59% to 71%.

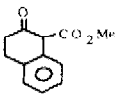
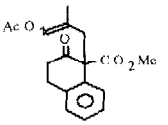
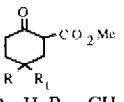
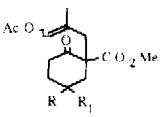
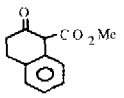
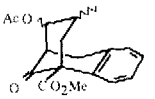
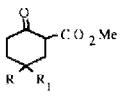
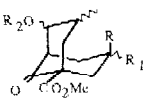
1

2

Much to our surprise, the monoalkylated compounds of entries 1 and 4 could be cyclized by treating them under the DBU conditions of entry 5 or simply in presence of DBU under refluxing toluene for 19.5 h. Therefore, the monoalkylation products of Table **1** are possible intermediates in the bicycloannulation reaction. Furthermore, the isolation of 18% of aldol in entry 7, suggested that methacrolein and acetic anhydride may be liberated under the reaction conditions and that these reagents may compete effectively with the π-allyl species in product formation when DBU is used as base.

This paper is dedicated to professor Zdenek Valenta on the occasion of his 65th birthday.

TABLE 1. Influence of the Base on the Reaction of β-Ketoesters with Methallyl-1,1-Diacetate in Presence of Palladium.

Entry	Model	Base[a]	Time (h)	Product	Yield (%)[b]
1		BSA	0.5 1.0[c] 29.0[c]		41 40[c] 86[c]
2	 R= H, R_1= CH_3	BSA	3.0		60
3	RR_1= -$O(CH_2)_2O$-	BSA	16.0	RR_1= -$O(CH_2)_2O$-	66
4	RR_1= CH_2	BSA	16.0	RR_1= CH_2	48
5		DBU	2.1		64
6	 R= H, R_1= CH_3	DBU	16.0		71 R_2= Ac
7	RR_1= -$O(CH_2)_2O$-	DBU	16.0	RR_1= -$O(CH_2)_2O$-	51 R_2= Ac 18 R_2= H
8	RR_1= CH_2	DBU	16.0	RR_1= CH_2	59 R_2= Ac

a: Solvent used is refluxing dioxane; refluxing toluene gives comparable results, see c in entry 1.
b: Yields (isolated) are not optimized. c: Solvent used is refluxing toluene.

A series of nmr experiments was therefore carried out to test this hypothesis and the results are presented below.

NMR EXPERIMENTS (remarks and conclusions)

Exp 1. $(Pd(OAc)_2 + Ph_3P + Tol\text{-}d_8)_{30\ min\ R.T.}$ + (DBU + diacetate + β-ketoester of entry 4 + Tol-d_8)

After 10 min reflux, ^1H nmr of aliquot shows starting β-ketoester, methacrolein, signals characteristic of R-$CH_2CH(CH_3)CHO$ and almost complete disappearance of the starting diacetate. After 60 min reflux, nmr shows diminished starting β-ketoester and methacrolein signals, some R-$CH_2CH(CH_3)CHO$, the bicycloannulated product and a small amount of the monoalkylated product. The spectrum of course shows a number of other unidentified peaks and unfortunately, the region around 2 ppm is too complex to ascertain whether acetic anhydride is also present as hypothesized. A ^{13}C spectrum however allows unambiguous characterization of this anhydride in the mixture.

In order to probe the potential role of DBU in the release of methacrolein and acetic anhydride, experiments 2 and 3 were performed.

Exp 2. $(Pd(OAc)_2 + Ph_3P + Tol\text{-}d_8)_{30\ min\ R.T.}$ + (diacetate + Tol-d_8)

After heating the mixture at 75°C for 5 min, no change appears in the ^1H and ^{13}C nmr spectra. After 5 min of refluxing, traces of methacrolein and acetic anhydride appear in the ^1H and ^{13}C spectra. After 24 h of reflux, the amount of 1,1-diacetate has greatly diminished with respect to methacrolein and acetic anhydride and the latter two are in a ratio of ~1:2 which suggests that acetic anhydride accumulates as the 1,1-diacetate decomposes and methacrolein polymerises, probably under the influence of Ph_3P. A number of unidentified peaks may be due to this reaction.

Exp 3. $(Pd(OAc)_2 + Ph_3P + Tol\text{-}d_8)_{30\ min\ R.T.}$ + (diacetate + Tol-d_8)

After refluxing for 10 min a mixture identical to that of experiment 2, ^1H and ^{13}C spectra show small amounts of methacrolein and acetic anhydride, and mostly the starting 1,1-diacetate. Then, one equivalent of DBU is added and the mixture heated to reflux for an additional 10 min period; ^1H and ^{13}C spectra show large amounts of methacrolein and acetic anhydride and almost no more 1,1-diacetate. This therefore shows the implication of DBU in the methacrolein releasing reaction; it was further ascertained that palladium is necessary for this reaction to take place.

Exp 4. $(Pd(OAc)_2 + Ph_3P + Tol\text{-}d_8)_{30\ min\ R.T.}$ + (BSA + diacetate + β-ketoester of entry 4 + Tol-d_8)

Experiment 4 was done in order to establish whether methacrolein and acetic anhydride are also formed in the case of BSA as base. After 10 min of reflux, ^1H and ^{13}C nmr spectra establish the presence of methacrolein and the monoalkylated product but no acetic anhydride; also, as expected, no free starting β-ketoester is present, it seems to have been completely converted to the corresponding silylenol ether. After 55 min of reflux, methacrolein is always present as well as the monoalkylated product. No trace of annulated product or other alkylated aldehyde is present.

Exp 5. (β-ketoester of entry 1 + $CH_2{=}C(CH_3)CHO$ + BSA + Ac_2O + Tol-d_8)

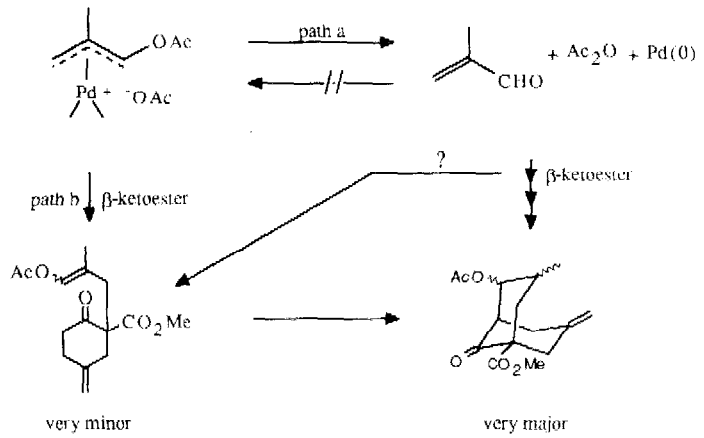
Experiment 5 was done in order to verify whether methacrolein could be involved in the formation of the monoalkylated product. After 18 h of reflux, a ^1H nmr spectrum shows the silylenol ether corresponding to the starting β-ketoester and no other new product corresponding to alkylated starting material.

In presence of DBU, nmr experiments 1-3 therefore demonstrate the intervention of a competing mechanism (path **a**), whereby methacrolein and acetic anhydride liberated via the initial π-allyl derivative[5] lead, by base catalyzed 1,4-addition followed by aldolization and acetylation, to the observed bicycloannulated product as shown in Scheme **1**. This was substantiated by treating the β-ketoester of entry 5 with corresponding amounts of methacrolein, acetic anhydride and DBU, mimicking the conditions of entry 5, and refluxing the mixture in dioxane for 2.1 hours and obtaining 79% of bicycloannulated product. Path **b**, on the other hand, should normally lead to the monoalkylation product which is observed to the extent of a few percent under DBU conditions, but, as indicated above, this product cyclizes under those conditions and therefore is an intermediate. The relative contribution of both pathways to product formation remains to be established but, as observed, release of methacrolein and acetic anhydride appears very rapid.

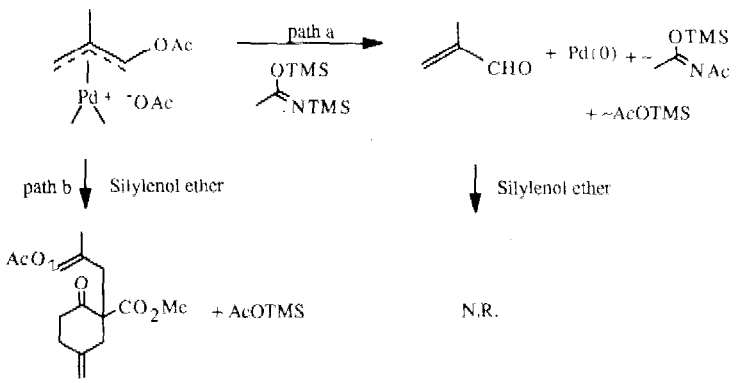
On the other hand, in presence of the weaker base BSA, nmr experiments 4 and 5 show that: although methacrolein is formed in a side reaction (path **a**), it does not react with the silylenol ether of the β-ketoester and therefore the monoalkylation product, the sole product observed, results from the normal reaction involving the π-allyl derivative (path **b**) as shown in Scheme **2**.

CONCLUSION: The above demonstration of the methacrolein release in the reaction of methallyl-1,1-diacetate with Pd(0) and the intervention of a hidden mechanism of alkylation under DBU catalysis suggests avenues for future work and caution in the application and interpretation of the title reaction.

Scheme 1. Partial mechanism of bicycloannulation in presence of DBU.



Scheme 2. Partial mechanism of alkylation in presence of BSA.



Acknowledgements: Financial support from NSERC and FCAR is gratefully acknowledged. We also acknowledge Bio-Méga and NSERC for predoctoral fellowships to S.B. and S.K. respectively.

References

1. a) Liu, J.S.; Zhu, Y.L.; Yu, C.M.; Zhou, Y.Z.; Han, Y.Y.; Wu, F.W.; Qi, B.F. *Can. J. Chem.* **1986**, *64*, 837-839. b) Kozikowski, A.P.; Xia, Y.; Reddy, E.R.; Tückmantel, W.; Hanin, I.; Tang, X.C. *J. Org. Chem.* **1991**, *56*, 4636-4645 (and references cited therein).
2. Lu, X.; Huang, Y. *Tetrahedron Lett.* **1986**, *27*, 1615-1616.
3. General procedure for the reactions of ketoesters with diacetate and a base. Palladium diacetate (0.05 mmol) and triphenylphosphine (0.2 mmol) are stirred at room temperature in 5 mL of solvent for 30 minutes. A solution of the ketoester (1.0 mmol), the base (2.1 mmol) and the diacetate (1.5 mmol) is added to the complex thus obtained over a period of 5 minutes. The resulting mixture is then heated at reflux. Removal of the solvent *in vacuo* and purification of the residue by flash chromatography gives the reaction product.
4. Trost, B.M.; Vercauteren, J. *Tetrahedron Lett.* **1985**, *26*, 131-134.
5. See Lu, X.; Huang, Y. *J. Organomet. Chem.* **1984**, *268*, 185-190 and ref. 2 for related discussions.

(Received in USA 15 August 1991; accepted 2 January 1992)