Tetrahedron Letters, Vol. 33, No. 11, pp. 1407-1410, 1992
Printed in Great Britain

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

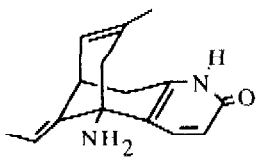
Novel Palladium Catalyzed Bicycloannulation of Monoactivated Cyclic Ketones Using a 1,3-Allylic Diacetate and an Enolyzing Catalyst.

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

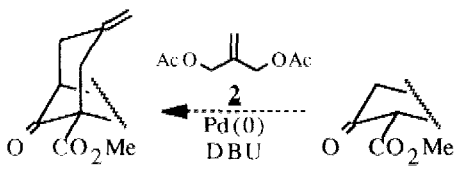
**Département de chimie, Université de Montréal,
Montréal, Québec, Canada, H3C 3J7.**

Abstract: *A novel procedure is reported whereby polysubstituted bicyclo[3.3.1] nonane derivatives are prepared in one step from β-ketoesters providing an adequate enolyzing catalyst is used.*

In the previous communication[1], we showed that methallyl-1,1-diacetate in conjunction with palladium catalysis, DBU and a β-ketoester, may be used to generate, albeit by unsuspected pathways, bicycloannulated products pertinent to the synthesis of huperzine A (**1**) and its analogs[2]. This observation suggests that under the same reaction conditions but using a 1,3-allylic diacetate, 2-hydroxymethyl-2-propene-1-ol diacetate (**2**), it should be possible to generate bicycloannulated products bearing an exo methylene group on the three-carbon bridge. The latter should further be readily isomerisable for the purpose of synthetising huperzine A (**1**) or some analogs for testing (vide infra).



1



It is important to note here that the first report of bicycloannulation using the above 1,3-allylic diacetate **2** is that of Lu and Huang[3] where they described the reaction of **2** with (equivalents of) "dicarbanions" such as 2,6-dicarbomethoxycyclohexanone and the pyrrolidine enamines of cyclohexanone, 2-methylcyclohexanone or 4-methylcyclohexanone. Unfortunately, none of these derivatives can be used in the synthesis of **1** or its analogs which require one carbomethoxy group as precursor to an amino function. Hence, following our earlier observations we studied the reactivity of 2-carbomethoxycyclohexanones (monoactivated ketones) with the 1,3-allylic diacetate **2** in presence of Pd(0) and a base or acid as enolyzing catalyst[4]. Table **1** shows the influence of the nature of the enolyzing catalyst on the reaction of **2** with cyclic β-ketoesters.

As expected from our previous observations, entry 1 shows that the palladium catalyzed condensation in presence of DBU does indeed lead to bicycloannulation while entry 2, in presence of BSA, shows that the

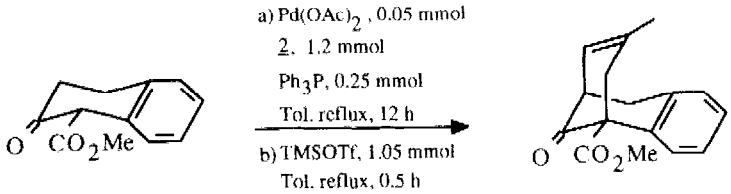
This paper is dedicated to professor Zdenek Valenta on the occasion of his 65th birthday.

weaker base leads only to monoalkylation at the activated α-position of the ketone. Furthermore, it was shown that the monoalkylated product of entry 2 can be cyclized in 59% yield to the annulated product of entry 1 upon treatment with Pd(0) in refluxing dioxane in presence of DBU for 4 hours. On the other hand, entry 3 shows that the annulation reaction also works very well in presence of an insoluble base such as potassium carbonate in refluxing toluene. The latter, in fact, allowed us to prepare in a 76% yield the bicyclo[3.3.1] derivative of entry 3 which was difficultly obtained in a synthetic approach to selagine which we reported[5]. The same comment applies in the case of entry 4 which shows that efficient access to the carbon skeleton of the benzoanalog of huperzine A (1) can be achieved in high yield with our procedure (see below). Finally as shown in entry 5, the same conditions applied to the ketoester of entries 1 and 2 also leads to bicycloannulation. This therefore means that the potassium carbonate conditions are sufficiently basic to enolyze the monoalkylated β-ketoester of entry 2 despite the fact that it does not possess an unsaturation γδ to the ketone as in the case of entries 3 and 4 which should make the latter more acidic.

The results of entries 3, 4 and 5 therefore suggest that in absence of base, the equivalent of acetic acid produced by alkylation of the α-position of the β-ketoester by the π-allyl derivative might be sufficient to enolyze some of the ketones and particularly those of entries 3 and 4 to give bicycloannulation product. This is borne out by the results of entries 6 and 7 which show that the annulation process takes place in the case of the more acidic ketone, the β-tetralone system of entry 6 but not in the case of the simple cyclohexanone of entry 7. This conclusion is supported by the fact that BSA prevents the annulation reaction, as shown in entry 8, by silylating the acetic acid formed in the reaction thereby preventing it from acting as enolyzing catalyst; BSA itself is not a strong enough base to enolyze the monoalkylated β-ketoesters.

Two other pertinent observations are reported in entries 9 and 10. First it was found that, although alkylation and annulation can proceed in absence of base *i.e.* in presence of the acetic acid progressively liberated during the reaction, one equivalent of acetic acid introduced at the beginning of the reaction largely inhibits its progress, (entry 9) probably by decomposing the π-allyl complex by protonolysis. Secondly, the observation reported in entry 10 pertains to the instability of the 1,3-allylic diacetate in presence of DBU[6] under the refluxing reaction conditions and the possibility of raising yields substantially by introducing the DBU progressively with a syringe pump during the reaction.

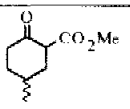
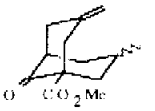
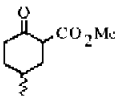
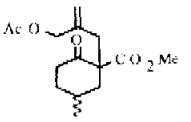
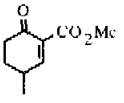
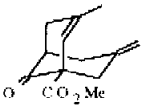
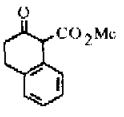
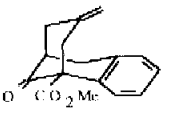
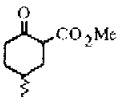
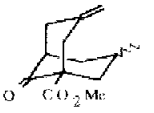
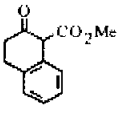
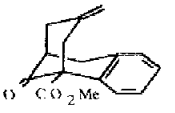
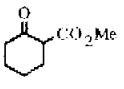
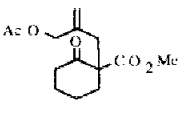
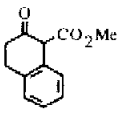
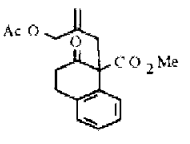
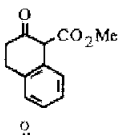
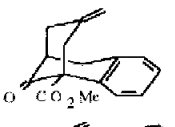
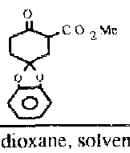
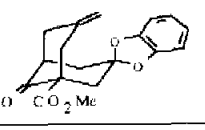
Finally, as alluded to in the comments on entry 4, our procedure allows the preparation in 87% yield of the carbon skeleton of the benzoanalog of huperzine A (1) providing however, that the exocyclic double bond can be isomerized regioselectively to the proper position. This, it was found, can be achieved with 100% regioselectivity using acid catalysis. In fact, in one instance, using a one pot procedure, a 96% yield of the benzoanalog of huperzine A (1) was obtained (equation 1) starting from 2-carbomethoxy-β-tetralone.



(1)

The 96% yield obtained for the combined annulation-isomerization sequence is a remarkable improvement over the reported yields for the synthesis of the benzoanalog of huperzine A[7] or huperzine A itself[8,9] which are 30%, 31% and 30% respectively.

Table 1. Influence of the Nature of the Enolyzing Catalyst on the Course of the Pd(0) Catalyzed Reaction of 2 with Cyclic β-ketoesters.

Entry	Model	Base	Solvent[a]	Time[b] (h)	Product(s)	Yield[c] (%)
1		DBU	A	16.0		46
2		BSA	A	1.0		66[d]
3		K_2CO_3	B	16.0		76
4		K_2CO_3	B	16.0		87
5		K_2CO_3	B	16.0		50
6		---	B	48.0		70[e]
7		---	B	16.0		trace
8		BSA	A	16.0		70
9		AcOH (1 eq.)	B	16.0		30[f]
10		DBU	A	4.5 5.0		53 77[g]

a: Solvent A= dioxane, solvent B= toluene; b: Prolonged heating sometimes gives dehydrogenation products; c: Yields (isolated) are not optimized. d: This monoalkylated product may be cyclized under the DBU conditions (*vide infra*); e: There is also obtained a 7% yield of the endocyclic olefin which corresponds to the benzoanalog of huperzine A (see below); f: The major products are starting material, 62% and monoalkylated product, 8%; g: The 77% yield is obtained when DBU is added with a syringe pump.

In conclusion, the procedure reported herein, taking advantage of the influence of the enolyzing catalyst on the course of the reaction, allows the specific alkylation or bicycloannulation of cyclic β-ketoesters. Furthermore, it was found that, in the case of the synthesis of the benzoanalog of huperzine A (1), isomerization of the exomethylene is totally regioselective thereby constituting by far the most efficient method of accessing these systems.

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. See preceding communication, this issue.
2. 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.
3. Huang, Y.; Lu, X. *Tetrahedron Lett.* **1988**, *29*, 5663-5664. See also Huang, Y.; Lu, X. *Tetrahedron Lett.* **1987**, *28*, 6219- 6220 and Trost, B.M.; Tometzki, G.B.; Hung, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 2176-2177.
4. General procedure for the reaction of ketoesters with diacetate and a base. Palladium diacetate (0.05 mmol) and triphenylphosphine (0.2 mmol) were stirred at room temperature in 3 ml. of solvent for 30 minutes. To the complex thus obtained, a solution of the diacetate (1.1 mmol) in 1 ml of solvent was added. After 15 minutes, a solution of the ketoester (1.0 mmol) and base (2.1 mmol) in 1 ml of solvent was added, and the resulting solution was heated at reflux. Removal of the solvent *in vacuo* and purification of the residue by flash chromatography gave the reaction product.
5. Gravel, D.; Bordeleau, L.; Ladouceur, G.; Rancourt, J.; Thoraval, D. *Can. J. Chem.* **1984**, *62*, 2945-2947.
6. See preceding communication, experiment 3, for a pertinent observation.
7. Xia, Y.; Reddy, E.R.; Kozikowski, A.P. *Tetrahedron Lett.* **1989**, *30*, 3291-3294.
8. Xia, Y.; Kozikowski, A.P. *J. Am. Chem. Soc.* **1989**, *111*, 4116-4117.
9. Qian, L.; Ji, R. *Tetrahedron Lett.* **1989**, *30*, 2089-2090.

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