NOVEL LACTAM SYNTHESIS *VIA* ENOL LACTONE

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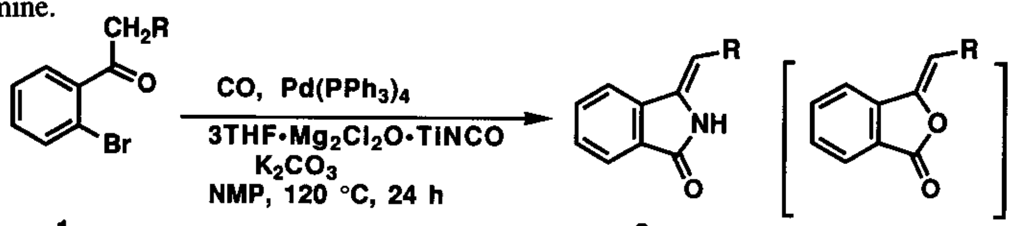
Abstract-----The lactams (**11**) and (**13**) were synthesized by the reaction of amine with the enol lactones (**12**), which were prepared from the enol triflates (**5**) using palladium catalyzed carbonylation.

We have already reported a novel lactam synthesis from **1** using the combination reaction of the nitrogenation and palladium catalyzed carbonylation.[1a] In this reaction, the intermediate is considered to be an enol lactone (**3**) and we also reported the synthesis of enol lactone from **1** using palladium catalyzed carbonylation.[1b,2] Namely, *o*-bromoacetophenone derivatives (**1**) were treated with the titanium isocyanate complex [3THF•Mg_2Cl_2O•TiNCO] in the presence of a palladium catalyst under carbon monoxide to give benzolactams (**2**) in good to excellent yield *via* the enol lactones (**3**). These results indicated that a novel lactam synthesis *via* enol lactone could be realized using palladium catalyzed carbonylation in the presence of an amine.



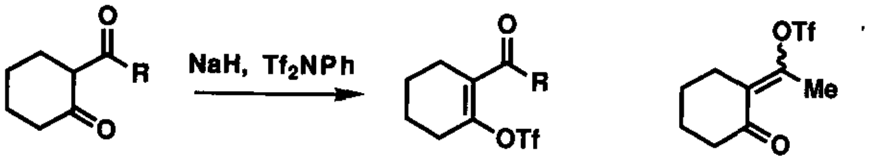
1 2 3

R=H, 55%
R=Ph, 77%

The enol triflates (**5**) of the keto ester (**4a**) or of the diketone (**4b**) were easily prepared usingthe known method.[3] For the latter case, the enol triflate (**5b**) was obtained along with (**6**) in the yields of 53% and 4%, respectively. The structure of **5b** was confirmed by the conversion of **5b** into **7** using palladium catalyzed hydrogenation in the presence of HCOOH-^{i}Pr$_2$EtN.

When a CH_3CN solution of compound (**5a**) was warmed with benzylamine at 60 °C in the presence of $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%) and K_2CO_3 under carbon monoxide for 15 h, the cyclized products (**8**) and (**9**) were obtained in 64% and 11% yields, respectively.

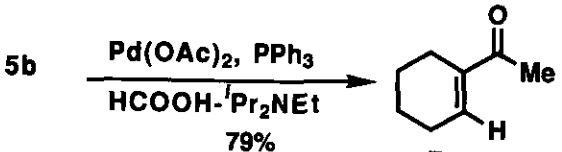
Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.



4a R=OEt
4b R=Me

5a R=OEt 72%
5b R=Me 53%

6



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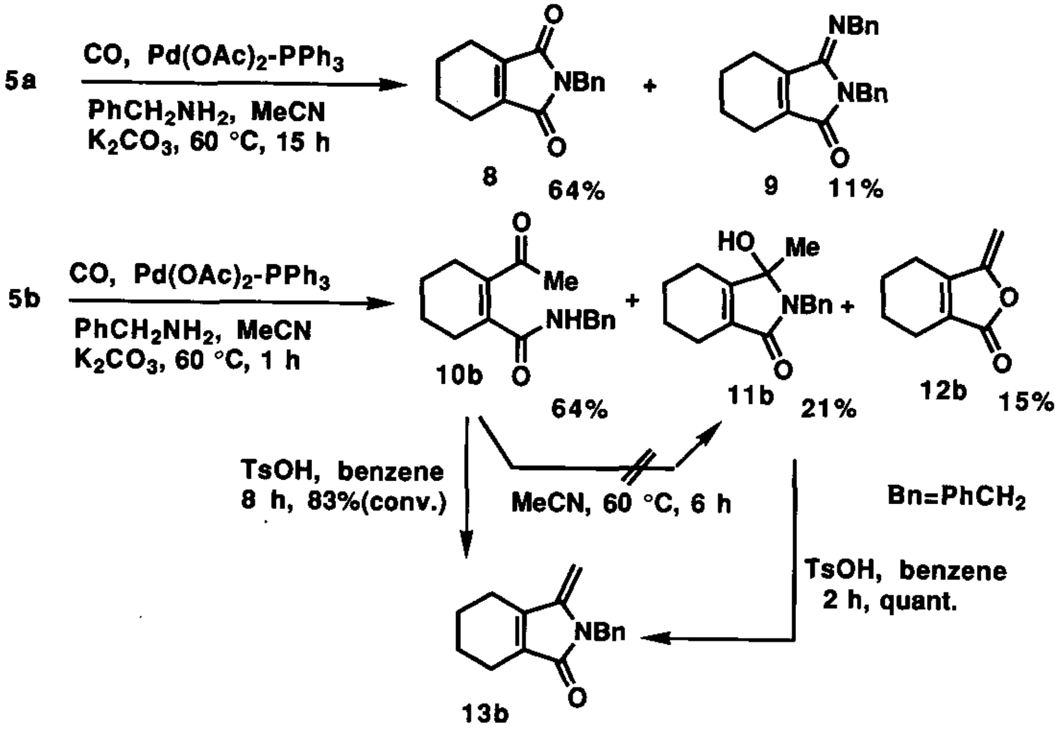
In a similar treatment of compound (**5b**) with benzylamine under carbon monoxide, the amide (**10b**), the lactam (**11b**), and the enol lactone (**12b**) were obtained in the yields of 64%, 21%, and 15%, respectively. Conversion of the main product (**10b**) into the hydroxylated lactam (**11b**) was unsuccessful and the starting material was completely recovered (93% yield) when a CH_3CN solution of **10b** was warmed at 60 °C for 6 h.

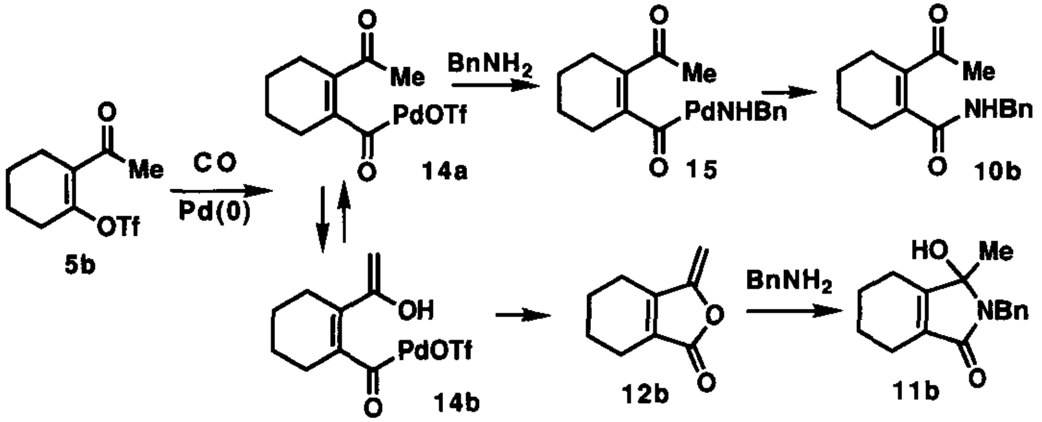


$$\mathbf{5b}\ \xrightarrow[\text{PhCH}_2\text{NH}_2,\ \text{MeCN, K}_2\text{CO}_3,\ 60\ ^\circ\text{C, 2 h}]{\text{CO, Pd(OAc)}_2\text{-PPh}_3}\ 90\%\quad \mathbf{12b}\ \xrightarrow[60\ ^\circ\text{C, 9 h}]{\text{BnNH}_2,\ \text{MeCN}}\ \mathbf{11b}\quad 57\%$$

However, a benzene solution of **10b** was refluxed in the presence of a catalytic amount of TsOH for 8 h to give the lactam (**13b**) (30% yield, 83% conversion yield). The same compound (**13b**) was obtained from **11b** in a quantitative yield by treatment with TsOH in benzene for 2 h. On the other hand, the enol lactone (**12b**) was obtained in 90% yield when the reaction was carried out without benzylamine. Treatment of the enol lactone (**12b**) with benzylamine in CH_3CN at 60 °C for 9 h gave the hydroxylated lactam (**11b**) in 57% yield. These results indicate that the lactam (**11b**) would be formed from the enol lactone (**12b**), but not derived from the amide (**10b**). Thus, it seems likely that two-step syntheses are reasonable for the synthesis of lactams from the enol triflate (**5b**) .

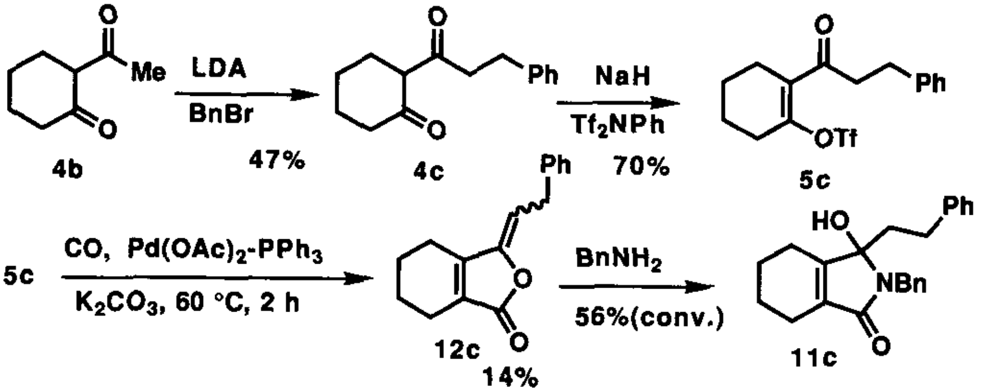
On the basis of these results, the reaction would proceed as follows. The enol triflate (**5b**) oxidatively adds to the low-valent palladium complex to give a vinyl palladium complex, which converts into the acylpalladium complex (**14a**) under carbon monoxide. In the presence of benzyl amine, the acylpalladium complex (**14a**) would react with the amine to produce the amide (**10b**) *via* **15**.[4] Since the acylpalladium complex (**14a**) is in equilibrium with **14b**, the acyl carbonyl group would be intramolecularly attacked by the enol moiety of **14b** to give the enol lactone (**12b**), which would react with benzylamine to produce **11b**.

Possible Reaction Course



Subsequently, the lactam that has the substituents on the double bond was prepared. The diketone (**4b**) was converted into **4c**, which was treated with Tf_2NPh to give the triflate (**5c**). When compound (**5c**) was treated with $Pd(OAc)_2$ and PPh_3 in the presence of K_2CO_3 in CH_3CN, the desired enol lactone (**12c**) was obtained in 76% yield, which was then treated with benzylamine to give the lactam (**11c**) (34% yield, 56% conversion yield).[5]

The enol lactones are useful intermediates for the synthesis of the lactams, which are easily obtained by palladium catalyzed carbonylation.



Further studies concerning the synthesis of the lactams are now in progress.

REFERENCES AND NOTES

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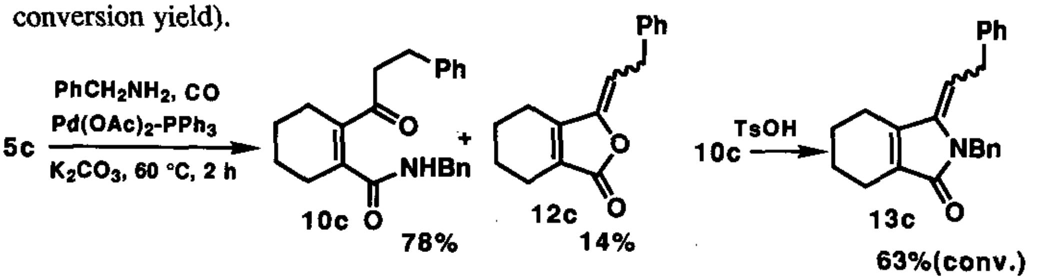
2. Enol lactone or enol ester formation by palladium catalyzed carbonylation has been reported as a by-product of the synthesis of the ketone. T. Kobayashi and M. Tanaka, *Tetrahedron Lett.*, **1986**, *27*, 4745. E. Negishi and J. M. Tour, *Tetrahedron Lett.*, **1986**, *27*, 4869 .
3. P. J. Stang, M. Hanack, and L. R. Subramanian, *Synthesis*, **1982**, 85.
4. The amide (**10b**) may be produced from the carbamoyl complex by reductive elimination, generated by the attack of benzylamine on the coordinated carbon monoxide. a) F. Ozawa, H. Soyama, H. Yanagihara, I Aoyama, H. Takino, K. Izawa, T. Yamamoto, and A. Yamamoto, *J. Am. Chem. Soc.*, **1985**, *107*, 3235 . b) F. Ozawa, T. Sugimoto, Y. Yuasa, M. Santra, T. Yamamoto, and A. Yamamoto, *Organometallics*, **1987**, *6*, 1640.
5. Compound(5c)was treated with $Pd(OAc)_2$ and PPh_3 in the presence of benzylamine and K_2CO_3 under carbon monoxide at 60 °C for 2 h, producing the amide (**10c**) in 78% yield along with the enol lactone (**12c**) (14% yield). The former compound (**10c**) was refluxed with TsOH in benzene for 19 h to give the lactam (**13c**) in 30% yield (63% conversion yield).



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