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Regio- and Stereoselective Intramolecular Heck Reactions of *N*-Acyl-2,3-dihydro-4-pyridones

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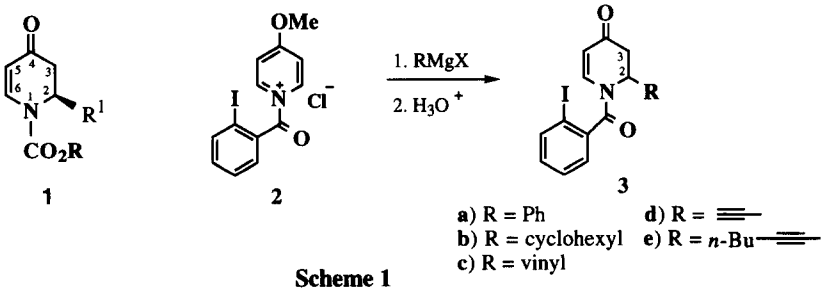
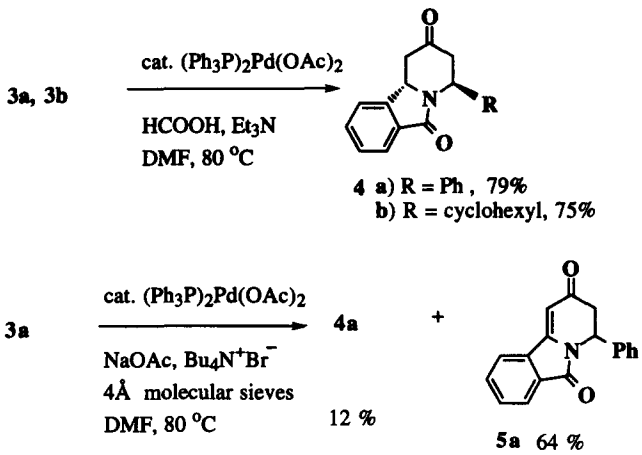
Abstract: *Intramolecular Heck reactions of N-acyl-2,3-dihydro-4-pyridones provide polycyclic heterocycles with high regio- and stereoselectivity.*

In recent years *N*-acyl-2,3-dihydro-4-pyridones **1** have proven to be useful building blocks for alkaloid synthesis. Their ease of preparation[1,2] in racemic[2b] or enantiopure[3] forms has allowed concise syntheses of indolizidine,[4a] quinolizidine,[5] piperidine,[4,6] and *cis*- and *trans*-decahydroquinoline[7] alkaloids. As a part of our ongoing effort to expand the synthetic utility of *N*-acyl-2,3-dihydro-4-pyridones, we have been investigating intramolecular cyclizations of these heterocycles. Ionic cyclizations via a haloalkyl tether at the C-2 position have led to indolizidine and quinolizidine alkaloids.[2b,4a,5] Radical cyclization of a haloalkyl chain attached at nitrogen to the enone moiety at C-6 of a dihydropyridone ring has been reported to occur with high stereoselectivity.[8] Since the Heck reaction has been shown to be a powerful tool for the synthesis of complex structures[9], we decided to investigate its utility as a method for annulating heterocycles of the type **1.** Herein we report our initial studies of a stereoselective annulation of *N*-acyl-2,3-dihydro-4-pyridones using an intramolecular Heck reaction[10].



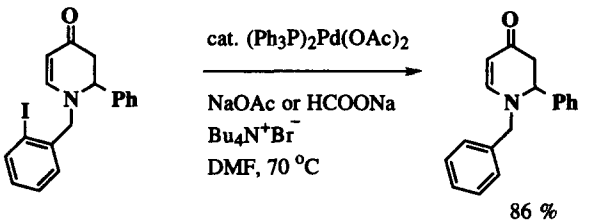
Scheme 1

Dihydropyridones **3** were prepared in good yield (56-92%) in one step by the addition of a Grignard reagent to *N*-acyl-4-methoxypyridinium salt **2** (Scheme 1).[1,2] Intramolecular Heck reaction of **3a** and **3b** gave **4a** and **4b** in 79% and 75% yield, respectively (Scheme 2).[11] Only the trans diastereomer was observed in the ^{1}H NMR spectrum of the crude product. This stereoselectivity has also been observed in a radical cyclization of the identical substrate.[8] The C-2, C-6 trans stereochemistry obtained in the product **4** can be explained through $A^{(1,3)}$ strain[12] arguments. In a transition state leading to the cis diastereomer, the C-2 substituent is sterically hindering due to its *pseudo*-axial orientation. This steric hindrance is absent in the transition state leading to the



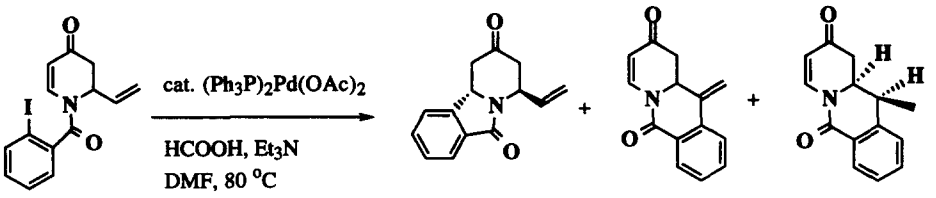
Scheme 2

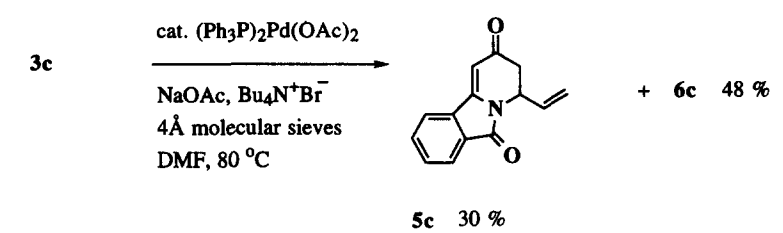
trans diastereomer **4**. In the absence of a hydride source, dihydropyridone **3a** provided **4a** and **5a** in 12% and 64% yield (Scheme 2). The presence of **4a** even in the absence of a hydride source may be due to an unfavorable geometry for the *syn* elimination of HPdI.[10] The amide carbonyl plays an important role in these reactions; in its absence, only dehalogenated products were isolated (Scheme 3). Similar cyclizations to form six-membered rings via an amide tether, as well as a carbamate tether, failed to give reasonable amounts of desired products.[13]



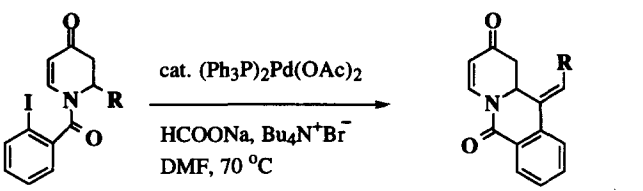
Scheme 3

In the presence of a hydride source, *N*-acyl-2,3-dihydro-4-pyridone **3c** gave **4c**, **6c**, and **7c**[14] in 11%, 45%, and 16% yield, respectively (Scheme 4). It is interesting to note that the major products resulted from the reaction on the C-2 vinyl substituent rather than reaction on the enone. In the absence of a hydride source, **6c** and **5c** were obtained in 48% and 30% yield, respectively. In either case, six-membered ring formation by cyclization to the vinyl substituent is favored over reaction at C-6 of the enone moiety. Because of the interesting regioselectivity observed with **3c**, we subjected *N*-acyl-2-alkynyl-2,3-dihydro-4-pyridones **3d** and **3e** to the same reaction conditions (Scheme 5). This resulted in the products **6d** and **6e** in 46% and 72% yield, respectively. The low yield of **6d** may be due to the acidity of the terminal alkyne proton. The cis geometry of the product alkene **6e** was confirmed by NOE experiments and was anticipated via the cis-addition of an arylpalladium to the alkyne.[10,15]



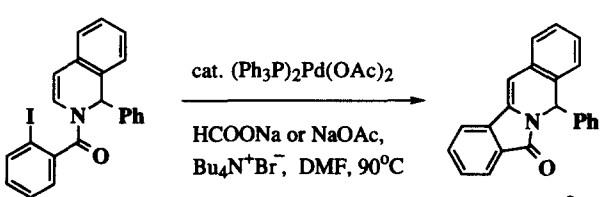


Scheme 4



Scheme 5

In a similar manner, **8** was subjected to the Heck reaction conditions, either in the presence or absence of a hydride source, and **9** was the only product isolated (Scheme 6). This reaction may be driven to a single product due to the extensive conjugation in **9**.[10]



Scheme 6

These intramolecular Heck reactions provide interesting heterocycles with high regio- and stereoselectivity. The regioselective reactions of **3c,d,e** to preferentially form a six-membered ring, instead of reaction with the enone to form a five membered ring, is interesting. Efforts are underway to further develop this reaction for use in alkaloid synthesis.

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References and Notes

1. (a) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549. (b) Comins, D. L.; Killpack, M. O. *J. Am. Chem. Soc.* **1992**, *114*, 10972. (c) Comins, D. L.; Chung, G.; Foley, M. A. *Heterocycles* **1994**, *37*, 1121 and references cited therein.
2. For reviews covering the addition of organometallics to 1-acylpyridinium salts, see: (a) Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199.; (b) Comins, D. L.; Joseph, S. P. Advances in Nitrogen Heterocycles; Moody, C. J., Ed.; JAI Press: Greenwich, Vol. 2, in press.
3. (a) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574. (b) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.
4. (a) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1991**, *113*, 6672. (b) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1993**, *115*, 8851. (c) Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035.
5. Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807 and references cited therein.
6. Comins, D. L.; Radi Benjelloun, N. *Tetrahedron Lett.* **1994**, *35*, 829.
7. (a) Comins, D. L.; Dehghani, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1838. (b) Comins, D. L.; Dehghani, A. *J. Org. Chem.* **1995**, *60*, 794.
8. Beckwith, A. L. J.; Joseph, S. P.; Mayadunne, R. T. A. *J. Org. Chem.* **1993**, *58*, 4198.
9. For recent reviews on the Heck reaction, see: de Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379.; Grigg, R. *J. Heterocyclic Chem.* **1994**, *31*, 631. Hegedus, L. S. in Organometallics in Synthesis ; Schlosser M., Ed.; Wiley, Chichester, **1994**, 383. Heck, R. F. in Comprehensive Organic Synthesis ; Trost, B. M. ; Fleming, I., Eds.; **1991**, Vol 4, 833.
10. For intramolecular Heck reactions of tetrahydropyridines, see: Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003.
11. In a typical experiment, a mixture of the substrate (1 mmol), triethylamine (4 mmol), formic acid (4 mmol) and DMF (5 mL) were heated at 80 °C for 6 to 15 h. In some cases better yields of the products were obtained by replacing triethylamine and formic acid with tetrabutylammonium bromide and sodium formate (1 eq).
12. Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.; Johnson, F. *Chem. Rev.* **1968**, *68*, 375.; Foley, M. A.: Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445 and references cited therein.
13. For recent work on intramolecular Pd-catalyzed aryl-enone conjugate additions, see: Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1995**, *36*, 7047 and references cited therein.
14. The relative stereochemistry was determined by comparing the coupling constants with theoretical values obtained from PC-MODEL (Serena Software).
15. Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505.; Thorn, D. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 2079.

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