

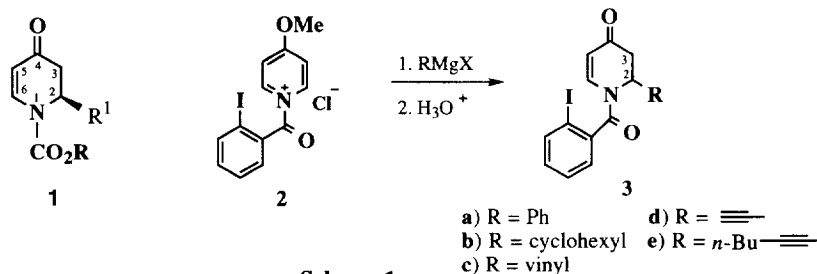
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Regio- and Stereoselective Intramolecular Heck Reactions of *N*-Acyl-2,3-dihydro-4-pyridones

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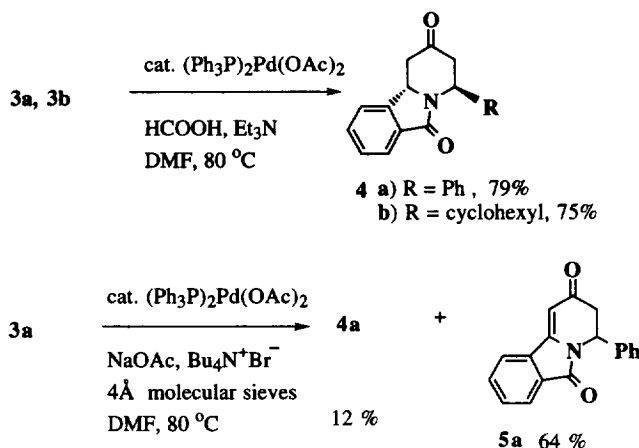
Abstract: Intramolecular Heck reactions of *N*-acyl-2,3-dihydro-4-pyridones provide polycyclic heterocycles with high regio- and stereoselectivity.

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 enantiopure³ forms has allowed concise syntheses of indolizidine,^{4a} quinolizidine,⁵ piperidine,^{4,6} and *cis*- and *trans*-decahydroquinoline⁷ 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 structures⁹, 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 reaction¹⁰.



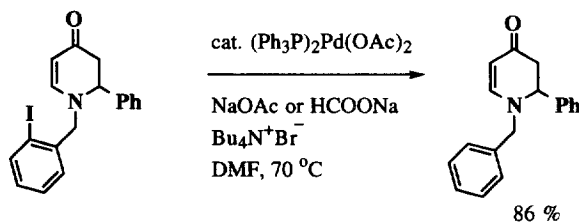
Scheme 1

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 ¹H 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) strain¹² 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



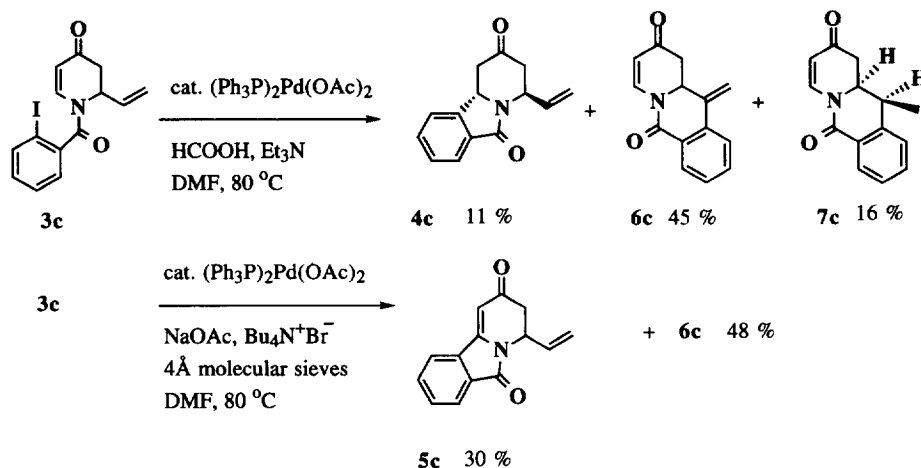
Scheme 2

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

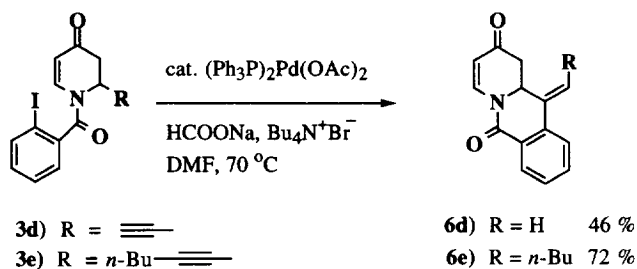


Scheme 3

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}

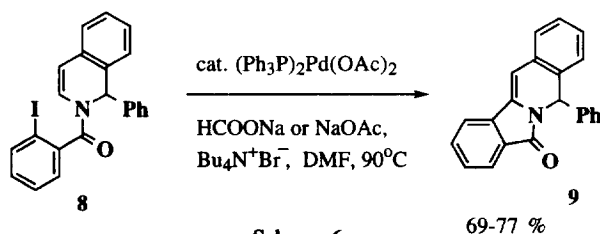


Scheme 4



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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