Synthesis of Isoquinolines and Pyridines via Palladium-Catalyzed Iminoannulation of Internal Acetylenes

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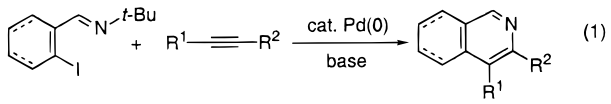
Annulation processes have found numerous applications in organic synthesis, primarily due to the ease with which a wide variety of complicated hetero- and carbocycles can be rapidly constructed.[1] In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methodology can be effectively employed for the synthesis of indoles,[2] benzofurans,[3] isocoumarins,[3] indenones,[4] and polycyclic aromatic hydrocarbons.[5]

Substituted isoquinolines have previously been synthesized by employing palladium methodology. For instance, Pfeffer reported the formation of a disubstituted isoquinoline derivative from a cyclopalladated *N*,*N*-dimethylbenzylamine complex,[6] and Heck observed the formation of 3,4-diphenylisoquinoline in 22% yield by the reaction of cyclopalladated *N*-*tert*-butylbenzaldimine tetrafluoroborate with diphenylacetylene.[7] Widdowson has also reported an isoquinoline synthesis based on cyclopalladated *N*-*tert*-butylarylaldimines.[8] These examples, however, suffer the major disadvantage that they are stoichiometric with respect to palladium, and in the latter synthesis, a final pyrolysis step greatly limits the synthetic utility.

Our own interest in these types of annulation reactions has prompted us to investigate a catalytic version of these isoquinoline syntheses. We now report that the palladium-catalyzed iminoannulation of internal alkynes readily affords a wide variety of nitrogen heterocycles, including isoquinolines, tetrahydroisoquinolines, pyrindines, and pyridines. Our preliminary results are summarized in Table 1.

Our initial studies focused on the palladium-catalyzed annulation of internal alkynes employing the methyl imine of *o*-iodobenzaldehyde. However, this substrate failed to produce any of the desired isoquinoline even at elevated temperatures. Furthermore, use of the corresponding isopropyl, allyl, and benzyl imines also afforded none of the desired heterocyclic products. The reaction of the α-methylbenzyl imine with diphenylacetylene did produce the desired product, 3,4-diphenylisoquinoline, albeit in low yields (6−11%). By employing the *tert*-butylimine, however, we obtained substantially improved results with a variety of alkynes, after optimization of the reaction conditions (eq 1).



(1)

The reaction conditions employed in the present heterocycle synthesis are similar to those that we previously reported for the annulation of alkynes.[2−5] The reaction of the *tert*-butylimines with 2 equiv of an alkyne in the presence of 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, and 1 equiv of Na_2CO_3 in DMF as the solvent at 100 °C affords the desired heterocyclic products in good to excellent yields in short reaction times.

The annulation of a variety of aryl-substituted alkynes by the *tert*-butylimine of *o*-iodobenzaldehyde (**1**) affords the desired disubstituted isoquinoline heterocycles in moderate to excellent yields with high regioselectivity (Table 1, entries 1−4). The regiochemistry of the products is based on analogy with our previous alkyne annulation chemistry[2−5] and comparison of the spectral and physical data for compounds **3**[6] and **4**[9] with those already in the literature.

The annulation of a relatively unhindered diyne and enyne by imine **1** also affords the anticipated isoquinoline products in good yields, although mixtures of regioisomers are obtained (Table 1, entries 5 and 6). This is interesting due to the fact that the products **2**−**5** are all isolated as single regioisomers. In addition, the diyne annulation gives an unexpected major product bearing the more hindered phenyl group in the 4-position (Table 1, entry 5).

It is interesting to note that the attempted annulation of many alkyl-substituted alkynes, namely 4-octyne, 3-hexyne, 4,4-dimethyl-2-butyne, and 3,3-dimethyl-1-phenyl-1-butyne, by imine **1** fails to produce any of the desired heterocycles. On the basis of the observations of Heck,[7] it is presumed that multiple alkyne insertion products are being formed from these alkynes, although none of these products have been identified. Alternatively, the presumed vinylpalladium intermediate generated upon alkyne insertion (see the latter mechanistic discussion) may simply be undergoing β-hydride elimination to afford allenes.

Surprisingly, when a more electron-rich imine **10** is employed in a reaction that previously gave only a single regioisomer, a mixture of regioisomers is observed (compare Table 1, entries 3 and 7). In the case of the imine **13** bearing an electron-withdrawing group, only a single regioisomer is obtained, with hydrolysis of the imine presumably occurring during the workup of the reaction.

This annulation chemistry has also been extended to vinylic imines. For example, the tetrahydroisoquinoline derivative **16** and the pyrindine derivative **18** have been synthesized by annulation with the cyclic vinylic imines **15** and **17**, respectively (Table 1, entries 9 and 10). Acyclic vinylic imines have also been successfully employed in this annulation process to produce highly substituted pyridine derivatives (Table 1, entries 11 and 12). It is interesting to note that the compounds derived from the vinylic imines are all isolated as single regioisomers. Surprisingly, the imine **21** works quite well in this pyridine synthesis, whereas the corresponding ethyl ester (*Z*-PhCI=$CHCO_2$Et) fails to undergo annulation of this same alkyne to produce the corresponding pyrone, a process with which we have recently had considerable success.[10]

We propose a mechanism for this process that is similar to our other alkyne annulation chemistry. Specifically, oxidative addition of the aryl or vinylic halide to Pd(0)

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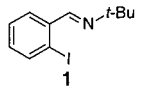
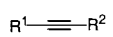
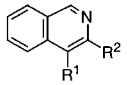
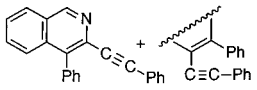
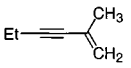
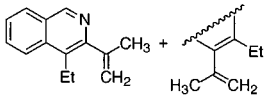
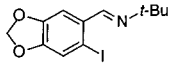
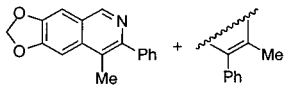
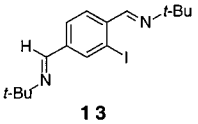
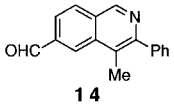
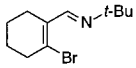
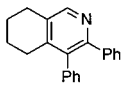
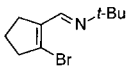
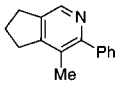
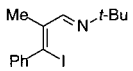
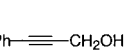
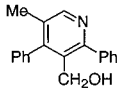
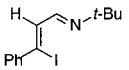
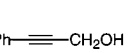
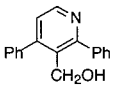
Table 1. Synthesis of Nitrogen Heterocycles by the Pd-Catalyzed Annulation of Internal Acetylenes[a]

entry	imine	alkyne	time (h)	product	% yield
	 **1**	 R¹ R²			
1		Ph Ph	24	**2**	96
2		CO_2Et Ph	5	**3**	99
3		Me Ph	21	**4**	84
4		CH(Me)OH Ph	4	**5**	65
5			25	 **6** **7**	72 + 13
6			21	 **8** **9**	69[b]
7	 **10**		44	 **11** **12**	77 + 14
8	 **13**		36	 **14**	69
9	 **15**		16	 **16**	72
10	 **17**		3	 **18**	96
11	 **19**		2	 **20**	95
12	 **21**		2	 **22**	79

[a] A representative procedure for the annulation of internal acetylenes: 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, Na_2CO_3 (0.5 mmol), the acetylene (1.0 mmol), the imine (0.5 mmol), and DMF (10 mL) were placed in a 4 dram vial and were heated at 100 °C for the indicated time. [b] Isolated in an 85:15 ratio of **8** to **9** as an inseparable mixture of isomers.

produces an organopalladium intermediate, which then inserts the acetylene, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a seven-membered palladacyclic ammonium salt. Subsequent reductive elimination produces a *tert*-butylisoquinolinium salt and regenerates Pd(0). As previously suggested by Heck,[7] the *tert*-butyl group apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position.

In conclusion, we have developed an efficient, palladium-catalyzed synthesis of nitrogen heterocycles, including isoquinolines, tetrahydroisoquinolines, pyrindines, and pyridines. A wide variety of aryl acetylenes undergo this process in moderate to excellent yields, with high regioselectivity being observed in most cases. Further detailed studies into the scope and limitations of this annulation process are currently under investigation.

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Supporting Information Available: General experimental procedure, copies of ^1H and ^{13}C spectra for compounds **5**−**9**, **12**, and **14**, and characterization data for all products (18 pages).

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