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Synthesis of Isoindolo[2,1-*a*]indoles by the Palladium-Catalyzed Annulation of Internal Alkynes

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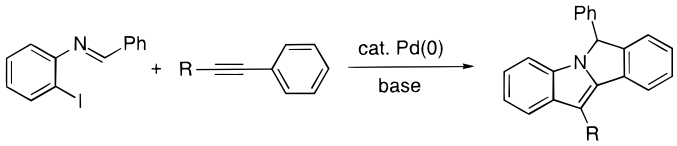
ABSTRACT



A wide variety of substituted isoindolo[2,1-*a*]indoles have been prepared in good to excellent yields by the palladium-catalyzed annulation of internal alkynes by imines derived from *o*-iodoanilines and benzaldehydes. The mechanism of this interesting annulation process appears to involve (1) oxidative addition of the aryl iodide to Pd(0), (2) alkyne insertion, (3) addition of the resulting vinylic palladium intermediate to the C–N double bond of the imine, (4) either electrophilic palladation of the resulting *σ*-palladium intermediate onto the adjacent aromatic ring originating in the internal alkyne or oxidative addition of the neighboring aryl carbon–hydrogen bond, and (5) reductive elimination of the tetracyclic product and Pd(0).

The development of efficient and selective synthetic transformations is a major challenge in organic synthesis. Consequently, tandem (domino) processes have been extensively investigated as they are among the most versatile reactions for the efficient, stereocontrolled synthesis of complex organic molecules.[1] It is not surprising, therefore, that transition metal-catalyzed alkyne annulation processes have received considerable attention for the synthesis of a variety of complex carbo- and heterocycles due to the synthetic efficiency of this methodology.[2] For example, the palladium-catalyzed annulation of internal alkynes has been employed by us for the synthesis of indoles,[3] benzofurans,[4] benzopyrans,[4] isocoumarins,[4] indenones,[5] isoquinolines,[6] α-pyrones,[7] and polycyclic aromatic hydrocarbons.[8]

Considerable attention has been directed toward the synthesis of compounds containing the indole nucleus, a structural subunit of a wide variety of biologically active natural products.[9] However, the synthesis of functionalized indoles still presents a major challenge in organic synthesis. Isoindolo[2,1-*a*]indoles are a class of these functionalized indoles that have been synthesized by employing classical synthetic organic,[10] photochemical,[11] radical,[12,13] and palladium-mediated methodologies.[13,14]

The classical synthetic, photochemical, and radical methods that have been reported all afford relatively low yields of the tetracyclic products and have yet to be employed on targets bearing much functionality. Efficient palladium-

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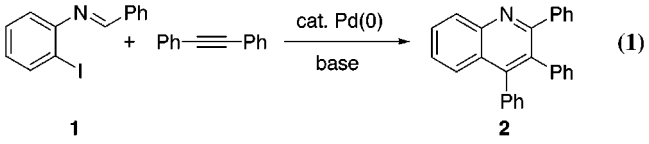
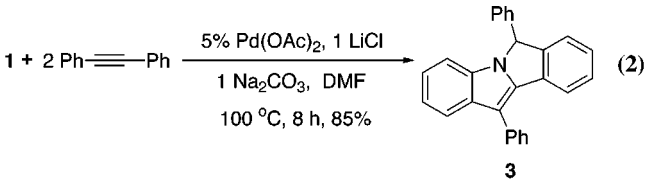
catalyzed cyclization methodology has been reported for the synthesis of these heterocycles. However, no reports of highly functionalized products or indoles containing functional groups other than a carbonyl at C-6 of the isoindole[2,1-*a*]-indole structure have appeared. Due to our continuing interest in the palladium-catalyzed annulation of internal alkynes, we have investigated the reaction of internal alkynes and imines derived from *o*-iodoanilines and aldehydes. Herein, we report that this annulation methodology very efficiently constructs the isoindolo[2,1-*a*]indole skeleton from readily prepared imines and internal aryl acetylenes.

The palladium-catalyzed reaction of imine **1** and diphenylacetylene was chosen as the model system for our initial investigation of this annulation process. We anticipated that imine **1** might undergo a reaction with an internal alkyne in the presence of a palladium catalyst to produce the highly substituted quinoline derivative **2** (eq 1). However, when



1 **2** **(1)**

reaction conditions were employed that have been used in much of our previous alkyne annulation chemistry (1 equiv of the aryl imine, 2 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 1 equiv of Na_2CO_3, and 1 equiv of LiCl in DMF at 100 °C),[3−8] none of the anticipated quinoline derivative was observed. Instead, isoindole **3** was isolated in 85% yield after an 8 h reaction time (eq 2). This surprising result encouraged us to define the scope and limitations of this intriguing new isoindole synthesis.



3 **(2)**

Although the reaction of imine **1** and diphenylacetylene proceeded in high yield in a short reaction time under the reaction conditions that were initially employed, other annulations of **1** with alkynes of differing functionality failed to give yields as good as those of diphenylacetylene. For example, the reaction of imine **1** and 1-phenyl-1-butyne afforded none of the desired indole. Therefore, several optimization reactions were run in order to improve this isoindole synthesis. The results of these optimization studies have led to the use of three general reaction procedures. Procedure A: 0.5 mmol of the aryl imine, 2.0 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 1 equiv of Na_2CO_3, and 1 equiv of LiCl in 10 mL of DMF at 100 °C. Procedure B: 0.5 mmol of the aryl imine, 1.2 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 1 equiv of *i*-Pr_2NEt, and 1 equiv of *n*-Bu_4NCl in 5 mL of DMF at 100 °C. Procedure C: 0.5 mmol of the aryl imine, 1.2 equiv of the acetylene, 5 mol % of $Pd(OAc)_2$, 1 equiv of *i*-Pr_2NEt, and 1 equiv of *n*-Bu_4NCl in 10 mL of DMF at 100 °C. The procedure used for these reactions is dependent upon the alkyne that is employed, as one procedure may not give any of the desired indole and another affords high yields. For example, alkyl-substituted acetylenes afford better yields when procedure B is employed and diaryl acetylenes afford better yields when procedure C is employed. The other substituted alkynes (ester, hydroxyl) that were employed afford better yields when procedure A is used. The isoindoles that have been synthesized are shown in Table 1.

The reaction of imine **1** with a variety of functionalized alkynes has afforded the desired indoles in good to excellent yields. For example, the reaction with diphenylacetylene gave indole **3** in 94% yield by employing procedure C (entry 1). The reaction of **1** with alkyl-substituted alkynes afforded the desired heterocycles in excellent yields by employing procedure B (entries 2 and 3). Using procedure A, the annulation with ethyl phenylpropiolate afforded **6** in 80% yield (entry 4). 6-Phenyl-5-hexyn-1-ol was also employed in the reaction with imine **1** to afford indole **7** in 72% yield (entry 5).

We have also investigated the regiochemistry of ring closure onto the aryl group of the acetylene (entries 6−9). This has been done by employing aryl alkynes which bear substituents *meta* to the alkynyl substituent. In the case of the aryl acetylene bearing a methyl group, the single regioisomer **8** was obtained in 81% yield (entry 6). By ^1H NMR spectral analysis, the regioisomer **8** bearing a methyl substituent in the 9-position of the isoindole was obtained. The single regioisomer **9** was also isolated in 78% yield from the annulation using an aryl acetylene bearing an electron-donating methoxy group (entry 7). However, indole **9** has the electron-donating methoxy substituent in the 7-position. The excellent regioselectivity of this ring closure and the reversal of regioselectivity upon switching from the electron-donating methoxy group to the relatively neutral methyl group were rather surprising, so we therefore investigated the use of alkynes bearing electron-withdrawing substituents.

When alkynes bearing electron-withdrawing substituents were employed with imine **1**, single regioisomers were also obtained. For example, indole **10** was obtained in which the trifluoromethyl substituent appears in the 9-position, analogous to the alkyne bearing the methyl group (entry 8). Surprisingly, the alkyne bearing the electron-withdrawing ester reacted in such a manner as to place the ester

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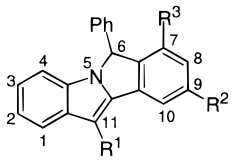
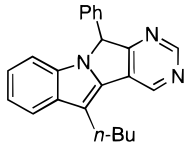
Table 1. Synthesis of Isoindolo[2,1-*a*]indoles by the Pd-Catalyzed Annulation of Imine **1** and Internal Alkynes[a]

entry	procedure, time (h)	product			compound, % yield
					
		R^1	R^2	R^3	
1	C, 12	Ph	H	H	**3**, 94
2	B, 36	Et	H	H	**4**, 81
3	B, 24	*n*-Bu	H	H	**5**, 81
4	A, 4	CO_2Et	H	H	**6**, 80
5	B, 10	$(CH_2)_4OH$	H	H	**7**, 72
6	B, 36	*n*-Bu	Me	H	**8**, 81
7	B, 36	*n*-Bu	H	OMe	**9**, 78
8	B, 18	*n*-Bu	CF_3	H	**10**, 95
9	B, 18	*n*-Bu	H	CO_2Et	**11**, 74
10	B, 10				93

1 2

[a] See the text for experimental procedures A-C.

functionality in the 7-position, analogous to the alkyne bearing the electron-donating methoxy group (entry 9).

From these results, it appears that certain substituents on the aryl ring of the alkyne are able to control the regioselectivity of ring closure by chelation of the palladium in the σ-palladium intermediate that is formed during the reaction (see the latter mechanistic discussion). Thus, potentially chelating oxygen substituents such as the alkoxy or ester functionalities afford exclusively products with the substituent in the 7-position. However, when alkynes were employed that contained trifluoromethyl or methyl substituents, products were isolated with these substituents in the 9-position, presumably due to steric inhibition to ring closure at the position *ortho* to these nonchelating substituents. Thus, it appears that by the appropriate choice of functionality, it is possible to exclusively prepare a single isoindole isomer.

Finally, ring closure onto a heterocyclic ring has been investigated. Thus, 5-pyrimidyl-1-hexyne afforded the desired tetracyclic indole in a short reaction time and 93% yield (entry 10).

We propose a mechanism for this remarkable isoindole synthesis involving (1) reduction of $Pd(OAc)_2$ to the actual catalyst Pd(0), (2) oxidative addition of the aryl iodide to Pd(0), (3) coordination and subsequent insertion of the acetylene, (4) 5-exo addition of the vinylpalladium intermediate across the carbon−nitrogen double bond, (5) either electrophilic palladation of the resulting σ-palladium intermediate onto the adjacent aromatic ring or oxidative addition of the neighboring aryl carbon−hydrogen bond of the aromatic ring to the σ-palladium intermediate to form a Pd(IV) intermediate, and subsequent elimination of HI by base, and (6) regeneration of the Pd(0) catalyst by reductive elimination to form the isoindole. To our knowledge, this is the first example of a vinylic palladium species adding to a C−N double bond.[15] Consistent with our recent work on the addition of organopalladium compounds to the C−N triple bond of nitriles, this step is no doubt favored by the intramolecular nature of this process.[16]

In conclusion, we have developed an efficient, palladium-catalyzed synthesis of isoindolo[2,1-*a*]indole heterocycles from readily available starting materials. A wide variety of aryl acetylenes in which the aromatic ring of the alkyne contains either a phenyl or a heterocyclic ring undergo this process in moderate to excellent yields with high regioselectivity.

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Supporting Information Available: General experimental procedure, ^1H and ^{13}C spectra for compounds **6**, **7**, **8**, **9**, **10**, **11**, and **12**, and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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