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Synthetic Development and Mechanistic Study on Pd(II)-Catalyzed Cyclization of Enediynes to Benzo[*a*]carbazoles

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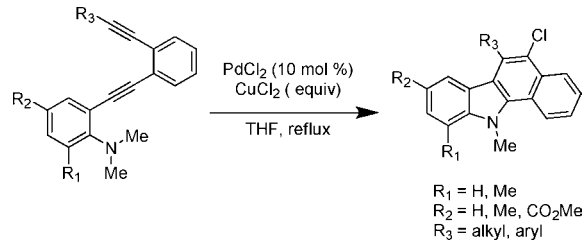
ABSTRACT



Treatment of *N,N*-dimethyl 2-[2-(2-ethynylphenyl)ethynyl]anilines (1) with 10 mol % of palladium chloride and 2 equiv of cupric chloride in refluxing THF gave benzo[*a*]carbazoles (6) in good yields. A mechanistic study showed that this reaction must proceed through formation of haloindole (7) followed by a palladium(II)-catalyzed atom transfer cyclization reaction to give the benzo[*a*]carbazoles.

The modes of cyclization of enediynes have attracted much attention since the discovery of enediyne antitumor antibiotics.[1] Initially research focused on the Bergman[2] and related cyclization of enediynes to generate biradical intermediates because they are the key intermediates for biological activities.[3] Recently, attention has been turned to the nonclassical thermal-type cyclization of enediynes to produce a variety of aromatic and highly π-conjugated molecules. These reactions involved the cyclization reaction of enediynes promoted by electrophiles,[4] nucleophiles,[5] radicals,[6] or organometallics.[7]

Carbazoles are pharmaceutically important heterocycles[8] and are attractive synthetic targets to many organic chemists.[9] Recently, we reported the palladium-catalyzed cyclization of enediynes to dibenzo[*b*,*d*]pyran-6-ones.[10] Although the reaction mechanism of that reaction is not clear, we anticipated that

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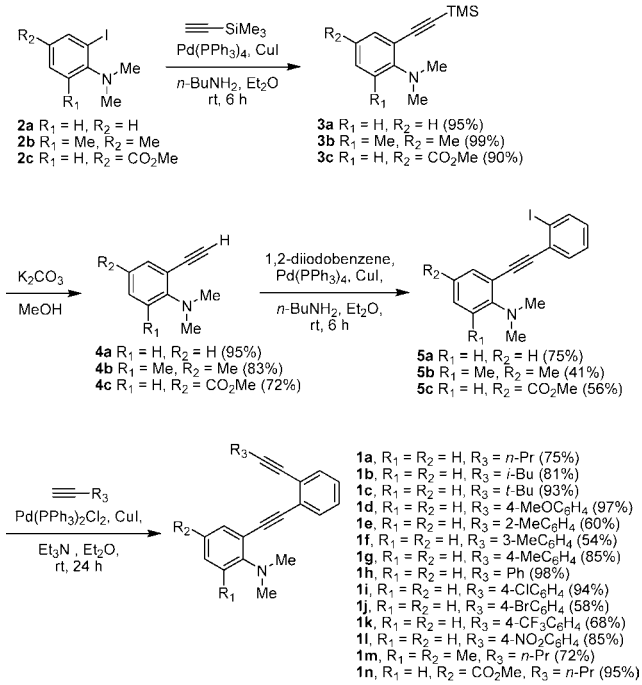
carbazoles could be synthesized by the same strategy starting from *N*,*N*-dimethyl 2-[6-substituted 3(*Z*)-hexen-1,5-diynyl]-anilines. Herein, we report the synthesis of benzo[*a*]carbazoles from *N*,*N*-dimethyl 2-[2-(2-ethynylphenyl)ethynyl]anilines catalyzed by palladium and a mechanistic study of this reaction.

The synthesis of *N*,*N*-dimethyl 2-[2-(2-ethynylphenyl)-ethynyl]aniline (**1a**) starting from *N*,*N*-dimethyl 2-iodoaniline (**2a**) is outlined in Scheme 1. A Sonogashira coupling

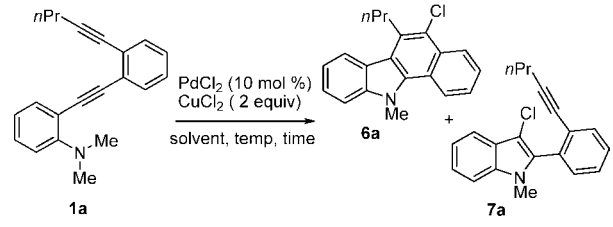
Scheme 1



reaction of **2a** with trimethylsilylacetylene using $Pd(PPh_3)_4$ as the catalyst gave compound **3a** in 95% yield. Desilylation of **3a** with methanol in the presence of potassium carbonate gave **4a** in 95% yield. Compound **4a** was then coupled with 1,2-diiodobenzene under the Sonogashira coupling reaction conditions to give **5a** in 75% yield. Finally, compound **5a** was coupled with 1-pentyne using $Pd(PPh_3)_2Cl_2$ as the catalyst to give the desired product **1a** in 75% yield.

Our first attempt for the cyclization of **1a** followed the reaction conditions used for the synthesis of dibenzo[*b*,*d*-]pyran-6-ones.[10] Thus, compound **1a** was treated with 10 mol % of $PdCl_2$ and 2 equiv of $CuCl_2$ in acetonitrile at room temperature for 24 h, and benzo[*a*]carbazole **6a** was obtained in 72% yield (entry 1, Table 1). Upon heating the reaction

Table 1. Optimization of Reaction Conditions



entry	solvent	temp(°C)	time(h)	products/yields (%)
1	CH_3CN	rt	24	**6a**/72
2	CH_3CN	reflux	1	**6a**/50
3	DMF	rt	24	**6a**/21, **7a**/24
4	THF	rt	24	**6a**/90
5	THF	reflux	1	**6a**/90
6	Toluene	rt	24	**6a**/52, **7a**/23
7	Toluene	reflux	1	**6a**/76
8[a]	CH_3CN	rt	24	**7a**/90
9[b]	CH_3CN	reflux	1	**6a**/trace

[a] Without $PdCl_2$ catalyst. [b] Without $CuCl_2$.

mixture at reflux, the yield of **6a** drops to 50% (entry 2, Table 1). To optimize the reaction conditions, we investigated the solvent effects on this cyclization reaction by employing different organic solvents. The results are summarized in Table 1. THF was found to be the most suitable solvent in this reaction. Upon heating the reaction mixture in refluxing THF for 1 h, compound **6a** was obtained in 90% yield (entry 5, Table 1). The structure of **6a** was unambiguously determined by X-ray crystallography (Figure 1).

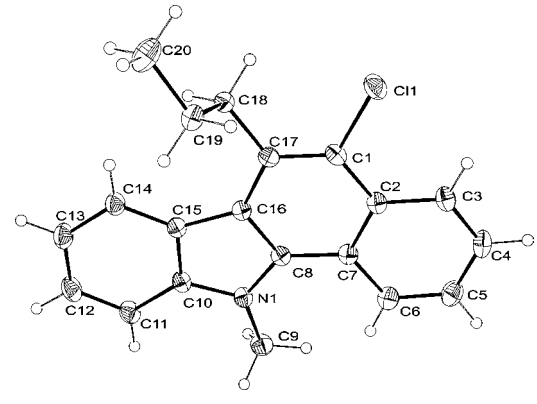


Figure 1. ORTEP drawing of compound **6a**.

Other *N*,*N*-dimethyl 2-[2-(2-ethynylphenyl)ethynyl]anilines **1b**−**m** bearing different substituents on the terminal alkynes

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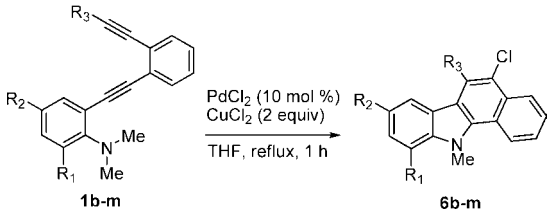
have also been synthesized (Scheme 1) and subjected to the cyclization reaction under the optimized reaction conditions. The results are summarized in Table 2. These reactions gave

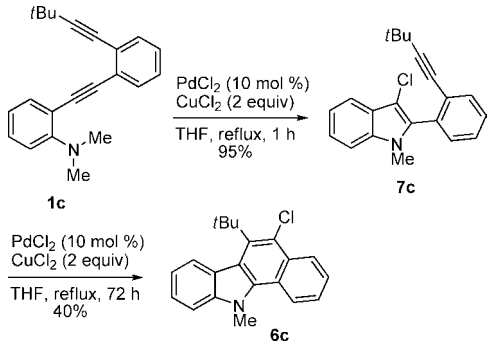
Table 2. Synthesis of Benzo[*a*]carbazoles by Optimized Reaction Conditions



entry	compounds	product/yield (%)
1	**1b**, R_1 = H, R_2 = H, R_3 = *i*-Bu	**6b**/95
2	**1d**, R_1 = H, R_2 = H, R_3 = 4-$CH_3OC_6H_4$	**6d**/89
3	**1e**, R_1 = H, R_2 = H, R_3 = 2-$CH_3C_6H_4$	**6e**/85
4	**1f**, R_1 = H, R_2 = H, R_3 = 3-$CH_3C_6H_4$	**6f**/76
5	**1g**, R_1 = H, R_2 = H, R_3 = 4-$CH_3C_6H_4$	**6g**/75
6	**1h**, R_1 = H, R_2 = H, R_3 = Ph	**6h**/94
7	**1i**, R_1 = H, R_2 = H, R_3 = 4-ClC_6H_4	**6i**/88
8	**1j**, R_1 = H, R_2 = H, R_3 = 4-BrC_6H_4	**6j**/85
9	**1k**, R_1 = H, R_2 = H, R_3 = 4-$CF_3C_6H_4$	**6k**/78
10	**1l**, R_1 = H, R_2 = H, R_3 = 4-$NO_2C_6H_4$	**6l**/96
11	**1m**, R_1 = CH_3, R_2 = CH_3, R_3 = *n*-Pr	**6m**/93
12	**1n**, R_1 = H, R_2 = CO_2CH_3, R_3 = *n*-Pr	**6n**/92

the benzo[*a*]carbazoles in excellent yields (75−96%). However, under the optimized reaction conditions, cyclization of **1c** gave only the monocyclization product **7c** in 95% yield. No expected benzo[*a*]carbazole **6c** was formed. Compound **7c** was then dissolved in THF and stirred with 10 mol % of $PdCl_2$ and 2 equiv of $CuCl_2$ in refluxing THF for a prolonged time of 72 h; benzo[*a*]carbazole **6c** could then be obtained in 40% yield, and there is a significant amount (50%) of **7c** that was recovered (Scheme 2). The slow cyclization rate of

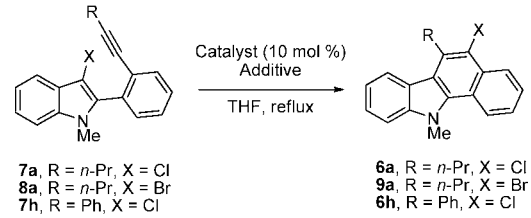
Scheme 2



compound **7c** must be because of the steric effect of the bulky *tert*-butyl substituent.

In our previous report,[10] the presence of $PdCl_2$ is crucial to obtain the double cyclization adduct; however, the reaction intermediates are not clear. We herein explore the reaction mechanism of this carbazole formation reaction. Thus, compound **1a** was first converted to **7a** using $CuCl_2$ as the halocyclization agent[11] in acetonitrile at room temperature for 24 h (eq 1). Compound **7a** was then dissolved in THF, and 10 mol % $PdCl_2$ was added. The reaction mixture was heated at reflux for 2 h. This led to the virtually complete conversion of **7a** to **6a** (entry 1, Table 3). Similar results

Table 3. Study of Conversion from Indole to Benzo[*a*]carbazoles



7a, R = *n*-Pr, X = Cl
8a, R = *n*-Pr, X = Br
7h, R = Ph, X = Cl

6a, R = *n*-Pr, X = Cl
9a, R = *n*-Pr, X = Br
6h, R = Ph, X = Cl

entry	compd	catalyst	additive	time (h)	products/ yields (%)
1	**7a**	$PdCl_2$	--	2	**6a**/92
2	**7a**	$Pd(OAc)_2$	--	2	**6a**/88
3	**7a**	$PdBr_2$	--	2	**6a**/85[a]
4	**7a**	PdI_2	--	2	**6a**/85[b]
5	**7a**	$Pd(PPh_3)_4$	--	24	**6a**/40[c]
6	**7a**	$PtCl_2$	--	2	**6a**/75
7	**8a**	$Pd(OAc)_2$	--	2	**9a**/90
8	**8a**	$Pd(OAc)_2$	$CuCl_2$(1 equiv)	2	**6a**/55, **9a**/18
9	**7h**	$PdCl_2$	--	2	**6h**/93
10	**7h**	$Pd(OAc)_2$	--	2	**6h**/93

[a] A trace amount of **9a** was observed by GC-MS. [b] A trace amount of **10a** (X = I) was observed by GC-MS. [c] Compound **7a** was recovered in 25% yield.

were observed by employing electrophilic palladium salts, such as $Pd(OAc)_2$, $PdBr_2$, and PdI_2 (entries 2−4, Table 3). When $Pd(PPh_3)_4$ was employed in this reaction, the reaction took place very slowly. After stirring in refluxing THF for 24 h, carbazole **6a** was isolated in only 40% yield and the starting indole **7a** was recovered in 25% yield (entry 5, Table 3). Platinum(II) was also employed in this reaction as a catalyst, and **6a** was obtained in 75% yield (entry 6, Table 3). The bromoindole **8a** was prepared by the reaction of **1a** with $CuBr_2$ in 85% yield (eq 1). Treatment of **8a** with 10 mol % of $Pd(OAc)_2$ in refluxing THF for 2 h gave **9a** in 90% yield (entry 7, Table 3). In the presence of 1 equiv of $CuCl_2$, the above reaction led to the formation of **6a** in 55% yield and **9a** in 18% yield (entry 8, Table 3). The phenyl substituted compound **7h** was also treated with 10 mol % of $PdCl_2$ and $Pd(OAc)_2$, respectively. Both reactions gave benzo[*a*]carbazole **6h** in 93% yield (entries 9 and 10, Table 3).

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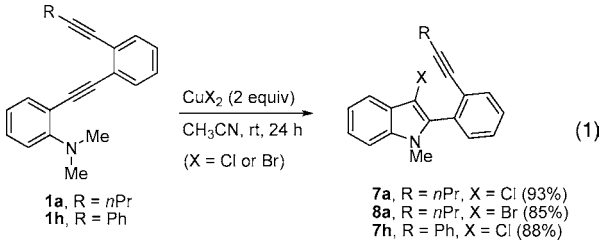
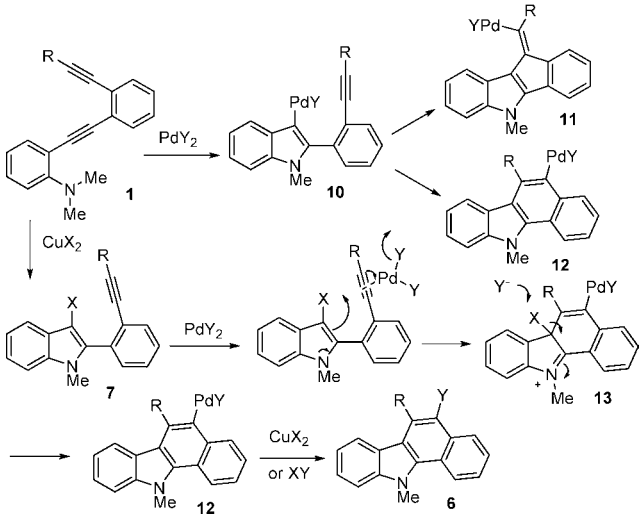


(1)

Based upon the above experimental results, a proposed reaction mechanism is outlined in Scheme 3. Since Pd(II) and Cu(II) both can catalyze the cyclization of 2-alkynylanilines to give indole derivatives,[11,12] two possible intermediates **10** and **7** could be formed in the first cyclization step. If the palladated indole **10** is the case, the second step cyclization should favor the 5-exodig pathway to give the vinylpalladium **11** based on previous reports.[4d,13] We therefore excluded the possibility of this pathway. We believe that compound **1** should react with CuX_2 to form the halogenated indole **7** initially. The Pd(II) could then coordinate to the triple bond, followed by intramolecular Friedel−Crafts cyclization to give **13**. The released nucleophilic ligand would come back to kick out the halogenium ion to give the palladated carbazole **12**. Finally, intermediate **12** could be coverted to the final product **6** by reaction with either CuX_2 or XY. In entry 8 of Table 3, the reaction of bromoindole **8a** with $Pd(OAc)_2$ in the presence of 1 equiv of $CuCl_2$ gave a mixture of bromocarbazole **9a** and chlorocarbazole **6a**, establishing the possibility of this reaction pathway.

Scheme 3



In conclusion, we have not only developed an efficient synthetic method to convert *N*,*N*-dimethyl 2-[2-(2-ethynylphenyl)ethynyl]anilines to halogenated benzo[*a*]carbazoles but also proposed a unique electrophilic palladium- or platinum-catalyzed atom transfer cyclization reaction of 1-halodienynes. Based upon this new type of cyclization reaction, we should be able to develop new synthetic methods to many carbocycles. These studies are currently under investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures and full spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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