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Synthesis of 2-Azaanthracenes via a Sequential Sonogashira Coupling/Alkynyl Imine−Allenyl Imine Isomerization/Aza-Diels−Alder/Elimination−Aromatization Reaction

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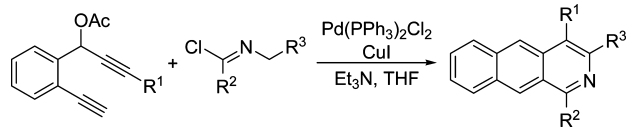
ABSTRACT



An interesting sequential Sonogashira coupling/alkynyl imine−allenyl imine isomerization/aza-Diels−Alder/elimination−aromatization reaction, providing a facile synthesis of substituted 2-azaanthracenes from 1,6-diynes and imidoyl chlorides, is reported. The easy procedure accessing the products efficiently from readily available starting materials may imply a potential synthetic application.

Anthracenes and azaanthracenes are core structures employed in a variety of practical applications, including potential therapeutics,[1] optical devices,[2] and polymeric materials.[3] Recently, Deiters et al. discovered that 2-azaanthracenes have very unique fluorescent properties in contrast to regular anthracenes.[4] Although several synthetic routes to anthracenes have been reported,[5] the method for the synthesis of 2-azaanthracenes is still limited.[4,6]

Allenes have shown impressive synthetic potentials in organic chemistry,[7] and many novel reactions were well established in the past decades.[8] Müller et al. pioneered the Sonogashira coupling/propargyl-allenyl isomerization reactions for the synthesis of a variety of useful compounds including chalcones, pyrazolines, pyrroles, fluorescent spirocycles, and some other pharmaceutically interesting heterocycles.[9] Several groups also

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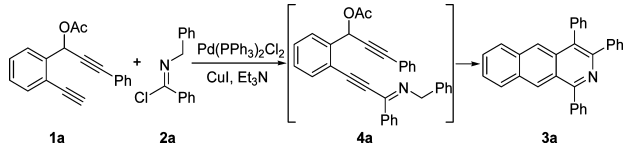
established a series of sequential reactions wherein an allene intermediate, generated in situ, underwent subsequent processes under mild conditions, providing an efficient synthesis of structurally complex polycycles.[10−12] In our continuous efforts to explore mild and efficient methodologies for the synthesis of heterocyclic compounds promoted by transition-metal catalysts,[13] we initially expected that reaction of diyne **1a** with imidoyl chloride **2a** via Sonogashira coupling reaction could afford the alkynyl imine **4a**.[14] To our delight, more valuable 2-azaanthracene **3a** was obtained rather than a simple coupling product (Scheme 1). Herein, we wish to

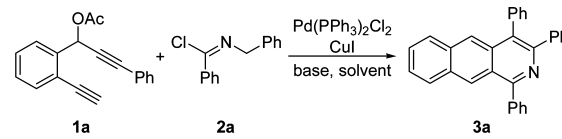
Scheme 1



report this convenient synthetic approach to substituted 2-azaanthracenes by utilizing a Pd-catalyzed tandem process via an allene intermediate.

Our preliminary studies focused on the reaction of diyne **1a** with imidoyl chloride **2a** in the presence of 5 mol % of $Pd(PPh_3)_2Cl_2$ and 5 mol % of CuI in Et_3N at room temperature. The 2-azaanthracene product **3a** was isolated in 62% yield after 10 h (Table 1, entry 1). Further studies showed that a 1:3 combination of Et_3N and THF as solvent was appropriate. Other common solvents such as CH_2Cl_2, CH_3CN, and toluene were effective as well, although lower yields were obtained (entries 2−5). The effect of the base was also investigated. An inorganic base, e.g., K_2CO_3 (entry 8), could also be applied to the reaction, while secondary amine diethylamine and pyridine were totally

Table 1. Optimization of the Reaction Conditions Base on the Synthesis of **3a** from **1a** and **2a**[a]



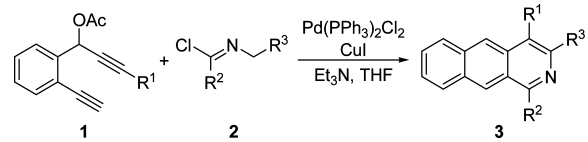
entry	solvent	base	temp	time (h)	yield of **3a**(%)
1	Et_3N	Et_3N	rt	10	62
2	THF	Et_3N	rt	10	74
3	CH_2Cl_2	Et_3N	rt	10	51
4	CH_3CN	Et_3N	rt	10	57
5	toluene	Et_3N	rt	10	43
6	THF	Et_2NH	rt	10	0
7	THF	pyridine	rt	10	0
8	THF	K_2CO_3[b]	rt	10	35
9	THF	Et_3N	60 °C	7	64
10	THF	*i*-Pr_2NEt	rt	10	70

[a] Unless otherwise specified, the reaction was carried out using **1** (0.5 mmol), **2** (0.6 mmol), $Pd(PPh_3)_2Cl_2$ (0.025 mmol), CuI (0.025 mmol), and base (1 mL) in solvent (3 mL). [b] 1.5 mmol of K_2CO_3 were added.

disfavored (entries 6, 7), indicating that the reaction was sensitive to the type of base. When the reaction was run at 60 °C, the product **3a** was obtained in lower yield (entry 9). Thus, we chose the following reaction conditions as optimum for all subsequent cyclizations: 0.5 mmol of **1**, 0.6 mmol of **2**, 0.025 mmol of $Pd(PPh_3)_2Cl_2$, and 0.025 mmol of CuI in Et_3N/THF (v/v 1:3) were stirred at room temperature for 10 h.

With the optimized conditions in hand, the scope of this Pd-catalyzed domino reaction was further investigated, and the results are summarized in Table 2.

Table 2. Synthesis of 2-Azaanthracenes **3**[a]



	substrate					yield of
entry	**1**	R^1	**2**	R^2	R^3	**3** (%)
1	**1a**	Ph	**2a**	Ph	Ph	74 (**3a**)
2	**1b**	4-$MeOC_6H_4$	**2a**	Ph	Ph	77 (**3b**)
3	**1c**	*n*-Hex	**2b**	Ph	4-MeC_6H_4	81 (**3c**)
4	**1d**	cyclopropyl	**2b**	Ph	4-MeC_6H_4	79 (**3d**)
5	**1a**	Ph	**2b**	Ph	4-MeC_6H_4	70 (**3e**)
6	**1d**	cyclopropyl	**2c**	4-MeC_6H_4	Ph	83 (**3f**)
7	**1d**	cyclopropyl	**2d**	4-$MeOC_6H_4$	Ph	75 (**3g**)
8	**1d**	cyclopropyl	**2e**	2-ClC_6H_4	Ph	52 (**3h**)
9	**1d**	cyclopropyl	**2f**	3-$NO_2C_6H_4$	Ph	59 (**3i**)
10	**1c**	*n*-Hex	**2g**	Ph	2,4-$Cl_2C_6H_3$	61 (**3j**)
11	**1c**	*n*-Hex	**2h**	Ph	vinyl	69 (**3k**)

[a] Unless otherwise specified, the reaction was carried out using **1** (0.5 mmol), **2** (0.6 mmol), $Pd(PPh_3)_2Cl_2$ (0.025 mmol), CuI (0. 025 mmol), and Et_3N (1 mL) in THF (3 mL) at room temperature for 10 h.

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The reactions proceeded smoothly to afford the corresponding 2-azaanthracenes **3** in moderate to good yields. Our preliminary results on these transformations showed that the reaction was successful when the R^1 group of diynes **1** was an alkyl or aryl group (Table 2, entries 1−4). The R^2 and R^3 group of imidoyl chlorides **2** can be a substituted phenyl group with either an electron-donating or electron-withdrawing group (entries 5−10). It should be noted that the presence of a substituent on the *ortho* position of aryl group R^2 and R^3 negatively affected the reaction (entries 8, 10). Furthermore, the reaction was also successful when R^3 was vinyl (entry 11). The structures of all these products were confirmed with the help of spectral and analytical data, and the structure of **3e** was further established by X-ray diffraction analysis[15] (Figure 1).

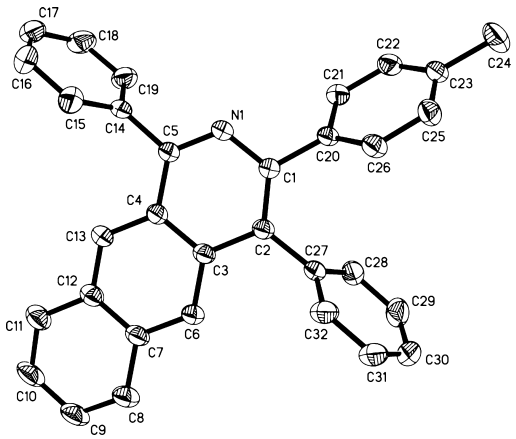
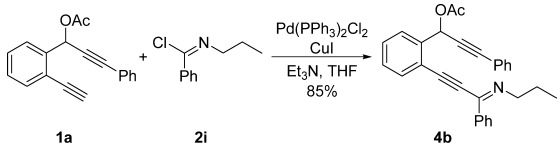


Figure 1. ORTEP representation of **3e**.

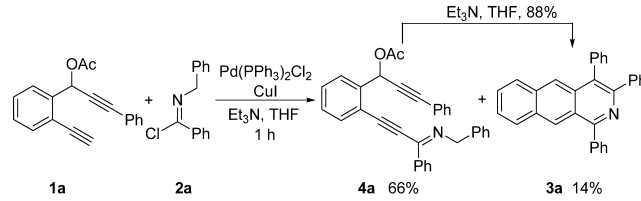
Interestingly, when R^3 was an alkyl group the reaction stopped at the alkynyl imine **4b**, thus indicating the importance of the phenyl or vinyl group on the R^3 position in the subsequent cyclization reaction (Scheme 2).

Scheme 2



To have more insight into the reaction, we performed the following reactions as shown in Scheme 3. The reaction of

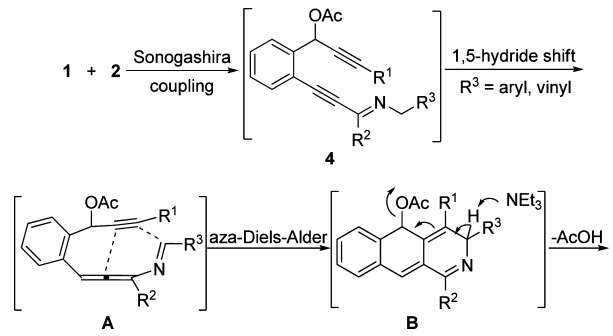
Scheme 3



1a and **2a** under the standard conditions was stopped at 1 h, and alkynyl imine **4a** and 2-azaanthracene **3a** were isolated in 66% and 14% yields, respectively. Further investigation demonstrated that the conversion from **4a** to **3a** required only Et_3N and no reaction occurred upon heating of **4a** in the absence of base.

Thus, based on the above results, we propose the following plausible mechanism for this reaction (Scheme 4): (i) the

Scheme 4



Sonogashira coupling reaction of 1,6-diyne **1** and imidoyl chloride **2** affords the intermediate alkynyl imine **4**; (ii) the intermediate **4**, in which R^3 is an aryl or vinyl group, undergoes a base-assisted 1,5-hydride shift[16] to form allene intermediate **A**; (iii) that reaction is followed by an aza-Diels−Alder reaction to form tricyclic intermediate **B**; (iv) subsequently, elimination of a molecule of AcOH gives the final product 2-azaanthracene **3**.

In conclusion, we have developed an interesting sequential reaction consisting of Pd-catalyzed coupling, alkynyl imine−allenyl imine isomerization, aza-Diels−Alder, and elimination−aromatization, leading to an efficient method to construct 2-azaanthracene derivatives. The wide tolerance of various substituents in the substrates and easy procedure to access the products efficiently from readily available starting materials may imply a potential synthetic application.

(15) Crystal data for **3e**: $C_{32}H_{23}N$, MW = 421.51, Orthorhombic, space group $P\bar{1}$, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0383, wR2 = 0.1008; *R* indices (all data), R1 = 0.0508, wR2 = 0.1170; a = 17.827(4) Å, b = 11.746(2) Å, c = 11.045(2) Å, α = 90°, β = 90°, γ = 90°, V = 2312.8(8) Å^3, T = 296(2) K, Z = 4 reflections collected/unique 8505/3893 (R_{int} = 0.0257), number of observations [$I > 2\sigma(I)$] 3893, parameters: 299. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 800881.

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Supporting Information Available: Spectroscopic data for **3a**−**k**, **4a**, and **4b**. X-ray crystal data for **3e**. Detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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