ORGANIC LETTERS

2011
Vol. 13, No. 19
5020–5023

Expeditious Synthesis of Phenanthrenes via $CuBr_2$-Catalyzed Coupling of Terminal Alkynes and *N*-Tosylhydrazones Derived from *O*-Formyl Biphenyls

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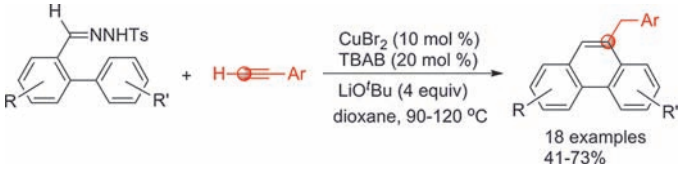
Received July 4, 2011

ABSTRACT



A new method for the synthesis of phenanthrenes via ligand-free $CuBr_2$-catalyzed coupling/cyclization of terminal alkynes with *N*-tosylhydrazones derived from *o*-formyl biphenyls has been developed. This new synthesis has wide range of functional group compatibility.

Phenanthrenes have attracted great attention because of their wide presence in natural products[1] as well as their applications in medicinal chemistry[2−4] and material sciences.[5] Hence, great efforts have been devoted to the development of synthetic methodologies for phenanthrenes. The most classical synthesis of phenanthrenes starts from the preparation of stilbene, followed by intramolecular aryl−aryl bond formation.[6] Another frequently utilized strategy is to connect the two aromatic rings through coupling reactions (in most cases by Suzuki−Miyaura cross-coupling), which is then followed by intramolecular cyclization to construct the phenanthrene structures.[7] To construct the phenanthrene frameworks directly, cycloisomerization of arynes with unsaturated compounds has also been developed.[8] Although great

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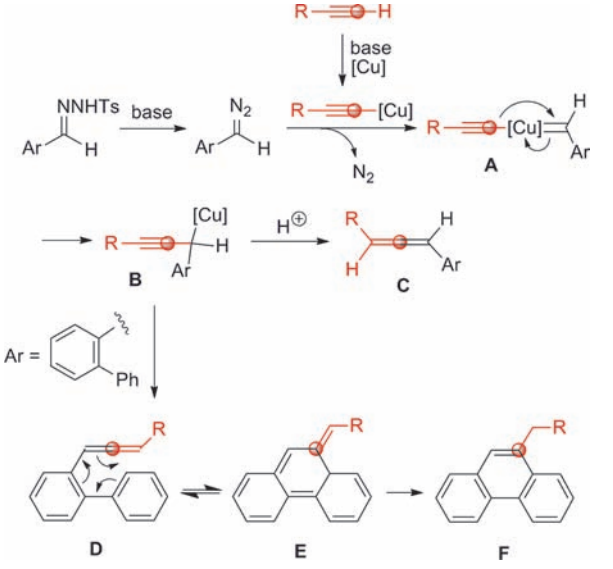
10.1021/ol201788v
Published on Web 08/29/2011

advances have been achieved in phenanthrene synthesis, many of these methods have limitations such as the lack of well-defined regioselectivity, low efficiency, harsh reaction conditions, and poor accessibility of the starting substrates.[9] Therefore, it is still highly desirable to develop new methods for phenanthrene synthesis.

In 2006, Wang and Burton reported a method for phenanthrene synthesis by base-promoted cyclization of 2-alkynyl-substituted biphenyls.[10] The reaction is proposed to involve a base-catalyzed rearrangement of the alkyne to allene, followed by 6π cycloaddition and isomerization to afford the final phenanthrene product. This mechanism is supported by the formation of phenanthrene from an isolated allene intermediate upon heating at high temperature.

Recently, we have developed a novel allene synthesis by Cu(I)-catalyzed coupling of *N*-tosylhydrazones with terminal alkynes (Scheme 1).[11] Furthermore, if a suitable intramolecular nucleophile, such as hydroxy or amino group, is introduced to the substrate, the initially formed allene can undergo a subsequent cyclization to afford benzofurans or indoles.[12] In these reactions, Cu carbene is generated from the in situ formed diazo substrate, which is followed by a migratory insertion process (**A** to **B**). To further expand this chemistry, we have conceived that if allene intermediate **D**, which is similar to those reported by Wang and Burton, is generated through Cu-catalyzed coupling of *N*-tosylhydrazone and terminal alkyne, then 6π cycloaddition and isomerization should occur to afford a phenanthrene product. In this paper, we report an efficient and straightforward phenanthrene synthesis based on this rationale.

Scheme 1. Phenanthrene Synthesis from *N*-Tosylhydrazone and Terminal Alkyne



The *N*-tosylhydrazones **2a**–**i** can be easily prepared by a two-step transformation in good yields from *o*-halo-substituted benzaldehydes and aromatic boronic acids, as outlined in Scheme 2.

Scheme 2. Two-Step Preparation of *N*-Tosylhydrazones **2a**–**i**

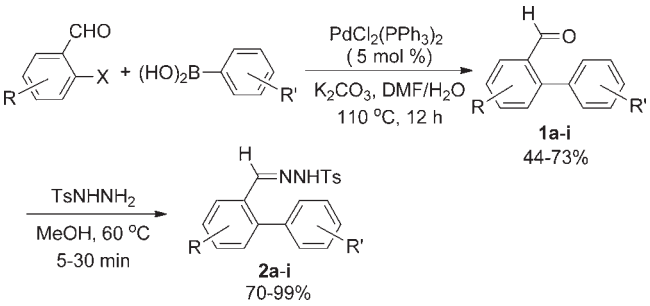
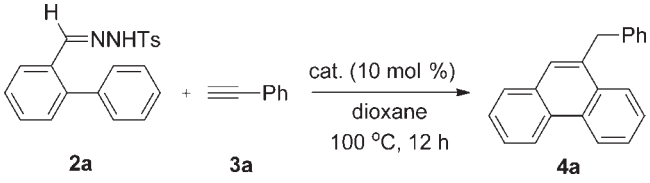


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	base	additive	yield[b] (%)
1	CuI	Cs_2CO_3	none	27
2	CuI	LiO^{t}Bu	none	34
3	$Cu(MeCN)_4PF_6$	LiO^{t}Bu	none	44
4[c]	$Cu(MeCN)_4PF_6$	LiO^{t}Bu	none	52
5[c]	$CuBr_2$	LiO^{t}Bu	none	57
6[c,d]	$Cu(MeCN)_4PF_6$	LiO^{t}Bu	none	19
7[c,e]	$Cu(MeCN)_4PF_6$	LiO^{t}Bu	none	7
8[c]	$Cu(MeCN)_4PF_6$	LiO^{t}Bu	TBAB	58
9[c]	$CuBr_2$	LiO^{t}Bu	TBAB	66
10[c]	$CuBr_2$	NaOMe	TBAB	trace
11[c]	$CuBr_2$	K_2CO_3	TBAB	0
12[c,f]	**$CuBr_2$**	**LiO^{t}Bu**	**TBAB**	**74**

[a] Unless otherwise noted, reactions were carried out with **2a** (0.2 mmol), **3a** (1.2 equiv), 10 mol % catalyst, and base (3.5 equiv) in 2 mL of solvent at 100 °C for 12 h. [b] Yield was determined by GC using dodecane as an internal standard. [c] **2a** to **3a** ratio was 1.2:1, and the reaction was carried out at 90 °C for 4 h and then at 120 °C for 24 h. [d] The reaction was carried out in DMF. [e] The reaction was carried out in toluene. [f] **2a** to **3a** ratio was 2:1.

With *N*-tosylhydrazone **2a** and phenylacetylene **3a** as model substrates, we started to examine the effectiveness of copper catalysts in phenanthrene synthesis (Table 1). To our delight, with 10 mol % of CuI and Cs_2CO_3 as base, the expected phenanthrene product **4a** was formed in 27% GC

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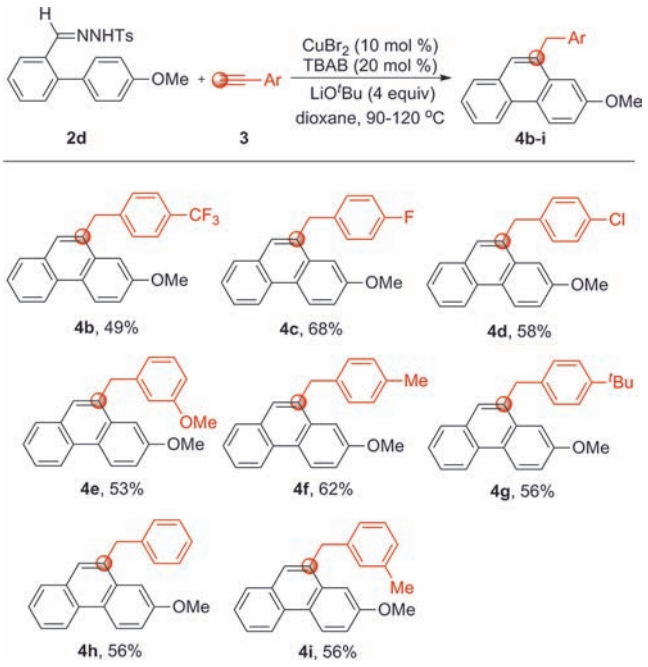

Figure 1. Reaction of *N*-tosylhydrazone **2d** with various terminal alkynes. (a) Reaction conditions: *N*-tosylhydrazone **2** (0.8 mmol), 1-alkyne **3** (0.4 mmol), $CuBr_2$ (10 mol %), LiO^tBu (1.6 mmol), TBAB (20 mol %), dioxane (4 mL), 90 °C, 4 h; 120 °C, 24 h. (b) Isolated yield by column chromatography.

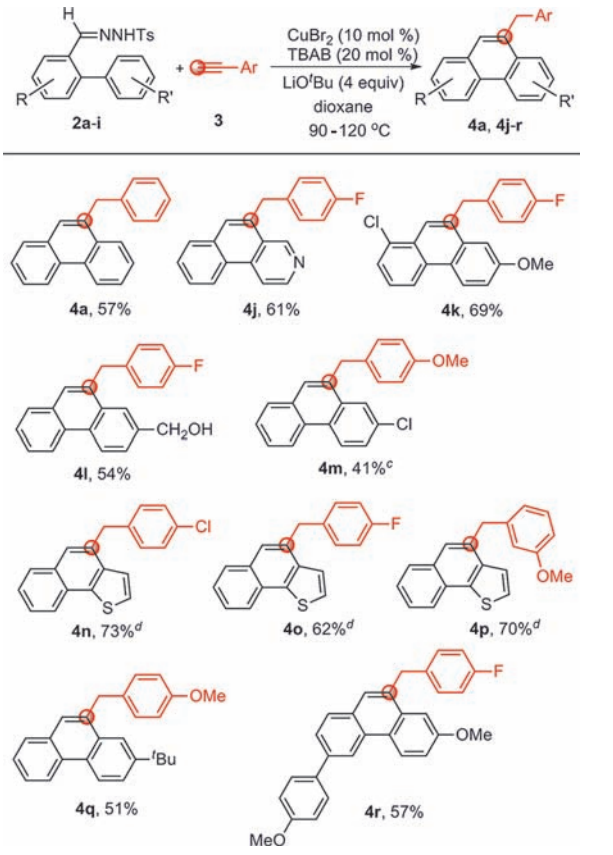

Figure 2. Reaction of *N*-tosylhydrazone **2a**–**i** with terminal alkynes. (a) Reaction conditions: *N*-tosylhydrazone **2** (0.8 mmol), 1-alkyne 3 (0.4 mmol), $CuBr_2$ (10 mol %), TBAB (20 mol %), LiO^tBu (1.6 mmol), dioxane (4 mL), 90 °C, 4 h; 120 °C, 24 h. (b) Isolated yield by column chromatography. (c) 20% yield of alkyne was recovered. (d) The reaction was carried out at 90 °C for 4 h and then at 120 °C for 36 h.

yield after heating the dioxane solution at 100 °C for 12 h (entry 1). By changing the base from Cs_2CO_3 to LiO^tBu, the yield could be slightly improved (entry 2). The yield was further improved by employing $Cu(MeCN)_4PF_6$ as catalyst (entry 3). A significant amount of byproduct, mostly derived from homocoupling of *N*-tosylhydrazone, was observed. To minimize the homocoupling of *N*-tosylhydrazone, the reaction temperature was first set at 90 °C for 4 h. After the allene intermediate (**D** in Scheme 1) was formed, the reaction temperature was raised to 120 °C in order to facilitate the 6π cycloaddition and isomerization. Moreover, the ratio of **2a** to **3a** was switched from 1:1.2 to 1.2:1. Under such conditions, the yield of **4a** was improved to 52% (entry 4). $CuBr_2$ was also found to be effective to give **4a** in comparable yield (entry 5). Two solvents, DMF and toluene, were investigated, but both were found to be ineffective for the reaction (entries 6 and 7). Next, the effect of additive was investigated, and TBAB (tetrabutylammonium bromide) was found to facilitate the reaction (entries 8 and 9). Finally, with $CuBr_2$ as catalyst two commonly used bases, NaOMe and K_2CO_3, were examined, and both were found ineffective for the reaction (entries 10 and 11). On the basis of the above experiments, the optimized reaction conditions are summarized as follows: **2a**/**3a** = 2:1, $CuBr_2$ (10 mol %), TBAB, dioxane, 90 °C for 4 h and then 120 °C for 24 h (entry 12).

With the optimized reaction conditions in hand, we next investigated the scope of the reaction with a series of *N*-tosylhydrazones **2a**–**i** and terminal alkynes. The results are summarized in Figures 1 and 2, respectively.

As shown in Figure 1, the reaction was found to be not significantly affected by the substituents on the aromatic ring of the terminal alkynes. Aryl-substituted alkynes with both electron-donating and electron-withdrawing groups, such as methoxyl, alkyl, halogen, and trifluoromethyl, could be smoothly transformed into the corresponding phenanthrene products.

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Next, we studied the scope of *N*-tosylhydrazone. Various substituted *N*-tosylhydrazones were employed as substrates to react with aryl terminal alkynes (Figure 2). In all cases, the reaction proceeded smoothly to afford the corresponding phenanthrenes in moderate to good yields. It is noteworthy that the *N*-tosylhydrazones containing heterocycles, such as pyridine and thiophene, can also undergo a cyclization process with the allene moiety to afford the corresponding phenanthrene products (**4j**,**n**−**p**). To our delight, the free hydroxyl group could tolerate the reaction condition to afford the phenanthrene product in comparable yield (**4l**).

In conclusion, we have developed a new method for the synthesis of phenanthrene derivatives, which employs easily accessible *N*-tosylhydrazones derived from *O*-formyl biphenyls and terminal alkynes as substrates and $CuBr_2$ as catalyst. The reaction involves a sequence of $CuBr_2$-catalyzed coupling/allenylation/6π electron cycloaddition/aromatization. The advantages of this new method involve the easy preparation of the *N*-tosylhydrazone derivatives and the use of inexpensive $CuBr_2$ as catalyst without use of ligand. Further investigation of this method is ongoing in our laboratory, and the results will be reported in due course.

Acknowledgment. Financial support from 973 Program (No. 2009CB825300), National Natural Science Foundation of China (Grant No. 20902005, 20832002, 20772003, 20821062), GSK R&D China, and China Postdoctoral Science Foundation is gratefully acknowledged.

Supporting Information Available. Procedures for synthesis and characterization of products (^1H and ^{13}C NMR data). This material is available free of charge via the Internet at http://pubs.acs.org.