Carbenes

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Transition-Metal-Free Intramolecular Carbene Aromatic Substitution/ Büchner Reaction: Synthesis of Fluorenes and [6,5,7]Benzo-fused Rings**

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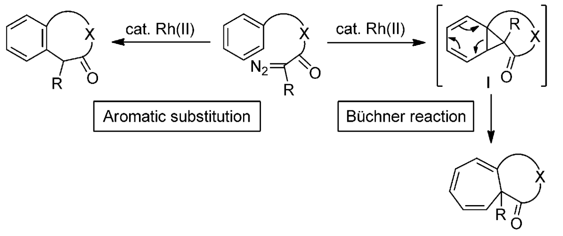
Dedicated to Professor Li-Xin Dai on the occasion of his 90th birthday

Abstract: *Intramolecular aromatic substitution and Büchner reaction have been established as powerful methods for the construction of polycyclic compounds. These reactions are traditionally catalyzed by Rh^{II} catalysts with α-diazocarbonyl compounds as the substrates. Herein a transition-metal-free intramolecular aromatic substitution/Büchner reaction is presented. These reactions use readily available N-tosylhydrazones as the diazo compound precursors and show wide substrate scope.*

The reaction of diazo compounds with arenes has been known for long time. In general, the diazo compounds stabilized by electron-withdrawing substituents, namely α-diazocarbonyl compounds, have been employed as the substrates.[1] Due to the lack of selectivity of free carbenes generated through photolysis or thermolysis, these reactions are usually catalyzed by transition metals or acids. Classical reactions of α-diazocarbonyl compounds with arenes include aromatic substitution[2] and Büchner ring expansion[3] (Scheme 1). These reactions provide a unique approach for the construction of ring systems. The Büchner reaction has been known to proceed through norcaradiene intermediate **I**. Since the early 1990s, Rh^{II}-catalyzed intramolecular Büchner reaction has been extensively studied by the groups of McKervey, Doyle, Moody, Maguire, and others.[4] This unique approach toward seven-membered carbocycles has been utilized in natural product synthesis.[5]

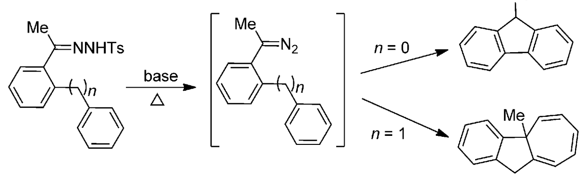


Scheme 1. Rh^{II}-catalyzed intramolecular reaction of aromatic α-diazocarbonyl compounds.

When the reaction leads to a highly strained five–six bicyclic system, the reaction usually follows a different path such as electrophilic aromatic substitution.[2] This type of reaction also finds applications in the synthesis of benzo-fused bicyclic systems. However, these reactions need transition metal catalysts or acid catalysts to achieve high reactivity and selectivity. Besides, α-diazocarbonyl compounds are used as the substrate, imposing some limitations on the substrate scope.

On the other hand, nonstabilized diazo compounds can be generated in situ from *N*-tosylhydrazones through the treatment with base (Bamford–Stevens reaction).[6] Recently, *N*-tosylhydrazones have been extensively explored as diazo compound precursors in transition-metal-catalyzed coupling reactions[7] and other related reactions.[8] However, to the best of our knowledge, the nonstabilized diazo compounds generated in situ from *N*-tosylhydrazones have only been sporadically studied for intramolecular aromatic substitution and Büchner reactions.[9] As a continuation of our own interest in this area, herein we report transition-metal-free reactions of the *N*-tosylhydrazones as shown in Scheme 2. Depending on the substrates, the reaction either undergoes intramolecular aromatic substitution or intramolecular Büchner reaction. Both reactions are highly efficient, thus constituting useful methods for the construction of aromatic polycyclic ring systems.

At the outset of this investigation, we employed *N*-tosylhydrazone **1a** (R = H) as the substrate with $Rh_2(OAc)_4$



Scheme 2. Transition-metal-free reaction of aromatic diazo compounds generated in situ from *N*-tosylhydrazones.

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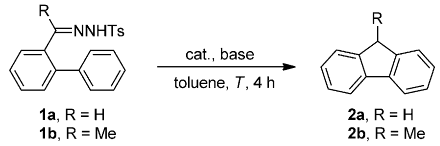
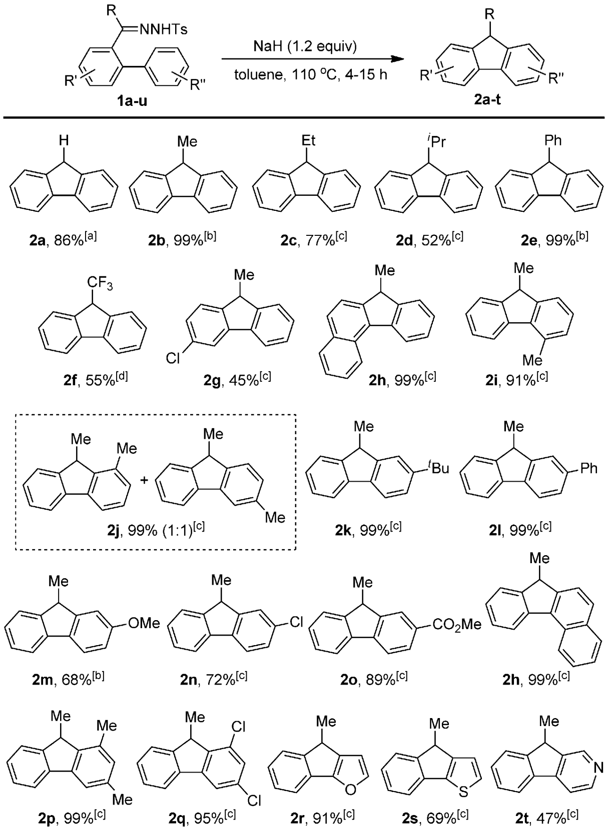
Table 1: Optimization of the reaction conditions.[a]



Entry	Substrate	Cat. (mol%)	Base	T [°C]	Yield [%][b]
1	**1a**	$Rh_2(OAc)_4$ (5)	LiO^{t}Bu	110	10
2	**1b**	$Rh_2(OAc)_4$ (5)	LiO^{t}Bu	110	96
3	**1b**	–	LiO^{t}Bu	110	91
4	**1b**	–	Cs_2CO_3	110	86
5	**1b**	–	NaOMe	110	45
6	**1b**	–	NaH	110	99
7	**1b**	–	NaH	90	50
8	**1b**	–	NaH	70	18

[a] All reactions were carried out with **1a** or **1b** (0.40 mmol), base (0.48 mmol) in 4.0 mL toluene for 4 h. [b] Yields of isolated product.



Scheme 3. Transition-metal-free synthesis of fluorene derivatives. All reactions were carried out with **1a–u** (0.40 mmol), NaH (0.48 mmol) in toluene (4.0 mL) at 110°C for 4–15 h. All yields refer to isolated products. [a] Reaction time was 11 h. [b] Reaction time was 4 h. [c] Reaction time was 15 h. [d] Reaction time was 6 h.

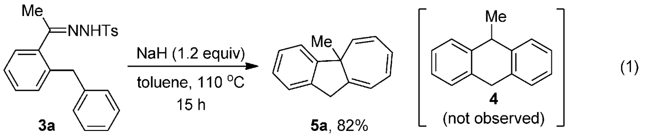
as the catalyst (Table 1). The reaction afforded the intramolecular aromatic C–H insertion product fluorene **2a** (R = H) in only 10% yield, with dimerization being the major side reaction (Table 1, entry 1). Switching the substrate to **1b** (R = Me) dramatically changed the reaction, affording the corresponding fluorene **2b** (R = Me) in 96% yield (Table 1, entry 2). Surprisingly, we found that the reaction could afford the product **2b** in 91% yield in the absence of $Rh_2(OAc)_4$ catalyst (Table 1, entry 3). Different bases were then examined and NaH was found to be the best one, affording fluorene **2b** in almost quantitative yield (Table 1, entry 6). The reaction was found to be significantly affected by the reaction temperature. The yields diminished dramatically at low temperature (Table 1, entries 7 and 8).

The results shown in Table 1 demonstrate an efficient synthesis of fluorene. Fluorene and its derivatives have found applications in various fields, especially in material sciences.[10] Traditional methods for the synthesis of the fluorene structure call for multistep reactions.[11] Recently, a transition-metal-catalyzed C–H activation strategy has been developed for the synthesis of fluorenes.[12] In contrast to the previous methods, the fluorene synthesis shown herein has some unique merits. First, the starting materials could be readily accessed through Suzuki–Miyaura coupling reaction and subsequent condensation with $TsNHNH_2$. Second, the transition metal catalyst is not involved in the reaction, thus avoiding the problem of heavy metal contamination. Thus, we proceeded to explore the substrate scope of the reaction (Scheme 3).

The scope of the reaction was first tested by varying a series of R groups in the substrates. When the R group is H, Me, Ph, (**1a**, **b**, **e**), the yields are good to excellent. For the substrates in which R is Et or ^{i}Pr (**1c**, **d**), the yields are slightly diminished due to the 1,2-H shift side reaction. In the case of **1f** (R = CF_3), the diminished yield is presumably attributed to the low reactivity of the corresponding carbene.

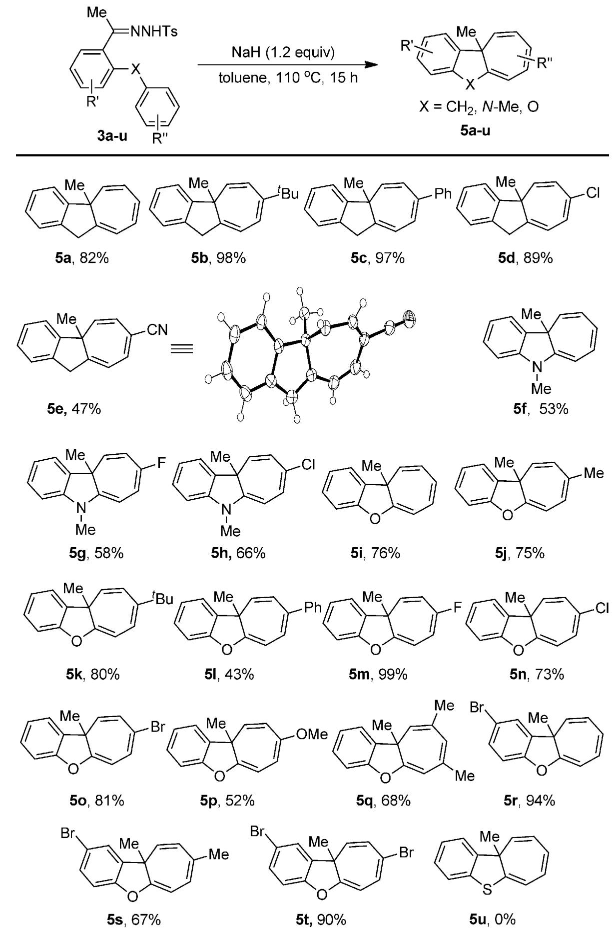
Next, the effect of substituents on the aromatic rings was investigated. The *p*-Cl substituent on the phenyl ring bearing a tosylhydrazone moiety (**1g**) showed a detrimental effect on the reaction giving **2g**. The naphthyl-substituted substrate gave 99% yield (**2h**). Next, we examined the effect of the substituent on the other aryl ring. When one of the insertion positions was blocked (**1i**), the product **2i** was isolated in 91% yield. For **1j**, there were two different insertion positions, and the products were found to be 1:1 mixtures of the isomers **2j**. When the two insertion positions were symmetrical, it was found that the yields were not significantly affected by the substituents. Both electron-rich (**1k–m**) and electron-poor substituents (**1n–o**) afforded the corresponding products **2k–m** and **2n–o** in good to excellent yields. Moreover, the reaction with substrates bearing a heteroaromatic ring (**1s–u**) also proceeded smoothly to give **2r–t**, albeit with diminished yields in the case of **2t**.

It has been well documented that the chemoselectivity of the Rh^{II}-catalyzed intramolecular reaction of α-diazocarbonyl compounds is drastically affected by the substrate structure. We have thus anticipated that by extending the linker between two aromatic rings, the intramolecular Büchner reaction may become the dominant reaction path. This was indeed shown to be the case. When *N*-tosylhydrazone **3a** was submitted to the same reaction conditions, 4*b*-methyl-4*b*,10-dihydrobenzo[*a*]azulene **5a** was isolated in 82% yield. The intramolecular aromatic substitution product **4** was not detected [Eq. (1)].



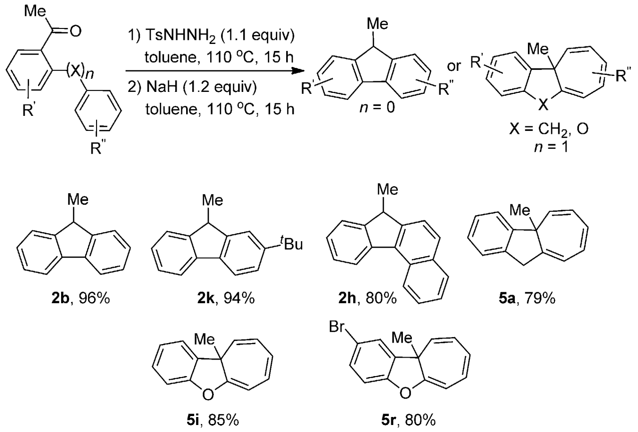
Since this highly efficient intramolecular Büchner reaction can serve as a straightforward method for the construction of the 4*b*,10-dihydrobenzo[*a*]azulene structure, we then proceeded to study the substrate scope. As shown in Scheme 4, the reaction with methylene-bridged substrates (**3a–e**), which could also be easily prepared by Suzuki–Miyaura cross-coupling, proceeded smoothly to afford the corresponding products **5a–e**. The structure of **5e** was confirmed by X-ray crystallography.[13]

Next, aromatic *N*-tosylhydrazones bearing a heteroatom bridge were investigated. N-Me-bridged substrates afforded the dihydrocyclohepta[*b*]indole derivatives (**5f–h**) in moderate yields. Similarly, a series of O-bridged substrates were examined in the reaction. The reaction proceeded smoothly and most of the yields were moderate to good (**5i–l, 5n–q, 5s**). In some cases the yields were excellent (**5m, r, t**). However, for the S-bridged substrate the reaction failed to afford the expected product **5u**.



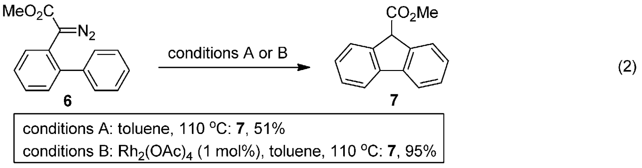
Scheme 4. Transition-metal-free synthesis of [6,5,7]benzo-fused ring compounds. All reactions were performed with **3a–u** (0.40 mmol), NaH (0.48 mmol) in 4.0 mL toluene at 110 °C for 15 h. All the yields refer to isolated products.

Since the conversion of ketone to *N*-tosylhydrazone is highly efficient, we next performed the experiments in a one-pot reaction directly starting from the ketones (Scheme 5). To our delight, the reaction with 2-biphenyl methyl ketones worked smoothly under the one-pot conditions (**2b**, **2k**, **2h**). The reaction with methylene and O-bridged methyl ketones also proceeded well.

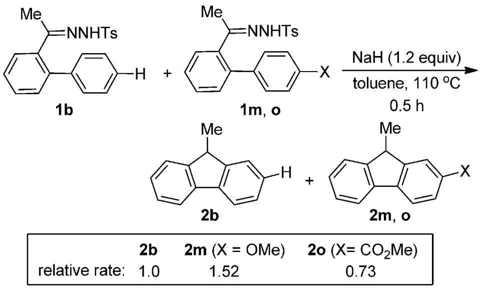


Scheme 5. One-pot reactions of methyl ketones. All reactions were performed with methyl ketones (0.40 mmol), $TsNHNH_2$ (0.44 mmol) in toluene (1.0 mL) at 110 °C for 15 h, then NaH (0.48 mmol) and toluene (3.0 mL) were added to the reaction mixture, and stirring was continued at 110 °C for 15 h. All yields refer to isolated products after two steps.

To gain some insights into the reaction, we have compared the corresponding intramolecular reaction of α-diazoester **6** under the metal-free and Rh^{II}-catalyzed conditions. As shown in Equation (2), the metal-free reaction afforded the intramolecular aromatic substitution product **7** in 51 % yield (conditions A). However, the $Rh_2(OAc)_4$-catalyzed reaction afforded the same product in 95 % yield (conditions B).[12f] In contrast, both transition-metal-free and $Rh_2(OAc)_4$-catalzyed reaction of *N*-tosylhydrazone **1b** afforded the corresponding intramolecular aromatic substitution product **2b** in similarly high yields (Table 1, entries 2 and 3). The results indicate the effect of the α-substituent on the reactivity of the carbene intermediate.



Moreover, the results in Scheme 3 illustrate that the reaction time is dependent on the substituents. To more precisely determine the rate influences by the substituents, intermolecular competition experiments were carried out as



Scheme 6. Intramolecular competition experiments.

depicted in Scheme 6. The results show that the reaction is weakly electrophilic in nature. We thus suggest that the reactions in Scheme 3 follow a free-carbene electrophilic substitution pathway, which is comparable with the corresponding metal-catalyzed reactions.[14] However, rigorous studies are needed to unambiguously establish the reaction mechanism.

In summary, we have developed a simple and efficient method to access fluorenes and [6,5,7]benzo-fused rings through transition-metal-free intramolecular aromatic substitution/Büchner reaction, using *N*-tosylhydrazones as non-stabilized diazo compound precursors. A literature survey indicates that there are few synthetically useful methods for the construction of these structures.[15] Considering the ready availability of the aromatic *N*-tosylhydrazone substrates and the high efficiency of the transition-metal-free reaction, this method may turn into a general methodology for preparing these types of compounds.

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