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A New Tandem Reaction of Benzyne: One-Pot Synthesis of Aryl Amines Containing Anthracene

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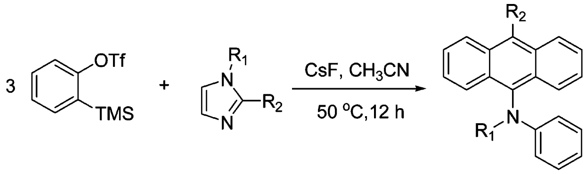
ABSTRACT



The reaction of benzyne with N-substituted imidazoles affords a novel way to prepare arylamines containing anthracene under very mild conditions. This transformation is assumed to proceed via a tandem reaction involving a Diels–Alder reaction and an intermolecular nucleophilic coupling reaction.

Aryl amines are fundamental building blocks in natural products and functional materials.[1,2] However, the classical methods for the synthesis of aryl amines often suffer from the harsh reaction conditions, which lead to severe limitations in the general use of the reactions.[3,4] As a consequence, considerable attention has been paid to the development of novel methods for the synthesis of aryl amines,[5,6] and currently, transition-metal-catalyzed C−N bond-forming reactions have become the direct routes in the synthesis of aryl amines.[7,8]

Arynes are one of the most important classes of organic species[9] and have been frequently used as the substrates in a variety of reactions.[10,11] In particular, their use in Diels−Alder processes with heterocyclic compounds affords the unique straightforward methods for the preparation of a wide range of aromatic ring-containing heterocycles.[12] Among the reactions of aryne with various heterocyclic compounds, few reports are available on the reaction of N-substituted imidazoles with aryne in the cycloaddition processes. In the studies of N-substituted imidazoles with benzyne generated in situ from *o*-trimethylsilyl aryltriflates, Yoshida et al. found that *N*-alkyl-*N*′-aryl imidazolium salts, instead of cycloaddition products, were produced.[13]

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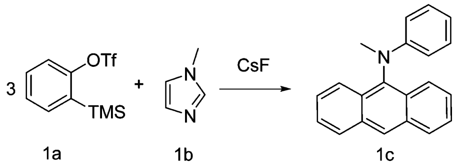
Herein, we describe our findings on the investigation of benzyne with N-substituted imidazoles. The reaction was assumed to proceed via a tandem Diels−Alder reaction of benzyne with N-substituted imidazole and intermolecular nucleophilic coupling reaction. The ratio of benzyne and imidazole was crucial for the direction of the reaction, and two important building blocks, aryl amine and anthracene, were constructed in a single step under optimized conditions. The aryl amines containing anthracene[14] were separated as the final products. This method provides a novel transition-metal-free access to aryl amines containing anthracene under very mild conditions.

We first examined the reaction of benzyne and *N*-methylimidazole using the same reaction conditions reported by Yoshida et al.,[13] and *N*-methyl-*N*′-phenyl imidazolium triflate was obtained. We noticed that in their experiments the ratio of N-substituted imidazole and benzyne was 3:1. We reasoned that the large excess of imidazole might make the rate of nucleophilic addition of a nitrogen atom to benzyne fast and lead to the production of imidazolium salt. Accordingly, we carried out the reaction using benzyne and imidazole in a 1:1 ratio at room temperature. As we expected, the benzyne/imidazole ratio had a decisive influence on the direction of the reaction, and the interesting tandem product *N*-methyl-*N*′-phenylanthracen-10-amine (**1c**) was isolated in 23% yield after 24 h. The increase of the reaction temperature was found to be beneficial to the tandem reaction, and the best yield was obtained when the reaction temperature achieved 50 °C for 12 h (Table 1, entries 1−3 and 6). Further increase of the temperature resulted in a lower yield (Table 1, entry 6). Among the solvents tested, CH_3CN was found to be the best (Table 1, entries 2 and 7−10).

Table 1. Optimization Studies[a]



entry	conditions	yield[b] (%)
1	30 °C, 24 h, CH_3CN	26
2	50 °C, 24 h, CH_3CN	53
3	50 °C, 12 h, CH_3CN	56
4	50 °C, 8 h, CH_3CN	38
5	50 °C, 4 h, CH_3CN	19
6	80 °C, 24 h, CH_3CN	43
7	80 °C, 24 h, toluene	36
8	110 °C, 24 h, toluene	42
9	80 °C, 24 h, DME	36
10	67 °C, 24 h, THF	28

[a] Reaction conditions: **1a** (0.5 mmol), **1b** (0.5 mmol), CsF (1.0 mmol). [b] Isolated yield.

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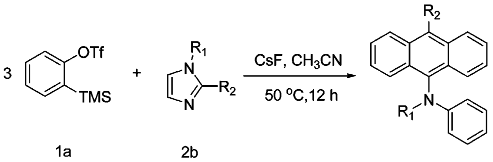
Table 2. Tandem Reaction of Benzyne with Imidazoles[a]



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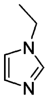
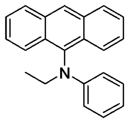
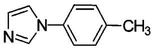
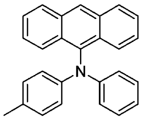
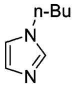
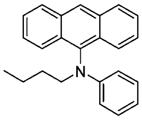
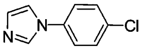
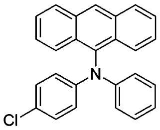
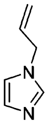
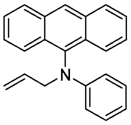
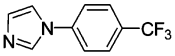
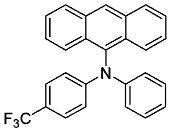
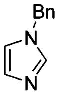
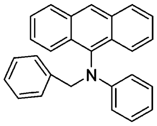
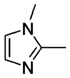
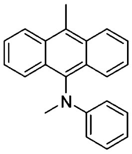
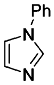
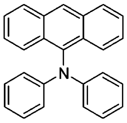
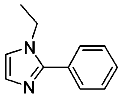
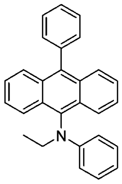
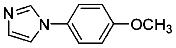
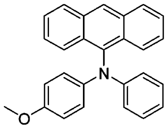
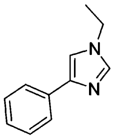
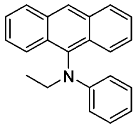
1			60	7			57
2			62	8			45
3			55	9			40
4			47	10			70
5			47	11			66
6			57	12			61

[a] Reaction conditions: the reaction was conducted in N_2 using 0.5 mmol of **1a**, 1.0 mmol of CsF, and 0.5 mmol of imidazole at 50 °C (bath temperature) for 12 h. [b] Isolated yield.

We next examined the scope of the tandem reaction, and a variety of aryl amines containing anthracene were obtained as described in Table 2. The *N*-alkyl-substituted imidazoles, such as *N*-ethylimidazole and *N*-butylimidazole, were found to readily undergo the tandem reaction, and *N*-ethyl-*N*-phenylanthracene-10-amine as well as *N*-butyl-*N*-phenylanthracene-10-amine were afforded in 60% and 62% yields, respectively (Table 2, entries 1 and 2). *N*-Benzylimidazole and *N*-allylimidazole carried out the reaction smoothly and delivered the desired product in 62% and 55% yields (Table 2, entries 3 and 4). Besides the *N*-alkyl-substituted imidazoles, the *N*-aryl-substituted imidazoles also reacted with benzyne, and asymmetric triaryl amines containing anthracene were produced (Table 2, entries 5−9). The electron-releasing substituents on aryl facilitated the reaction, and higher yields were obtained (Table 2, entries 6 and 7). On the other hand, the lower yields were obtained with the *N*-arylimidazoles bearing electron-withdrawing substituents on aryl (Table 2, entries 8 and 9). It should be noted that 1,2-disubstituted imidazoles reacted smoothly with benzyne and afforded the aryl amines with substituents on anthracene (Table 2, entries 10 and 11).

On the basis of our results, an alternative mechanism is proposed as shown in Scheme 1. The benzyne generated from flourine-induced elimination of *o*-trimethylsilyl aryltriflate undergoes the Diels−Alder reaction with substituted imidazole to produce the nitrogen-bridged isoquinoline intermediate **A**. Subsequent retro Diels−Alder reaction leads to the loss of nitrile and generates the intermediate **B**, which undergoes the second Diels−Alder reaction with benzyne to give the intermediate **C**. The intermolecular nucleophilic addition of intermediate **C** to benzyne affords the final product of aryl amine containing anthracene.[15]

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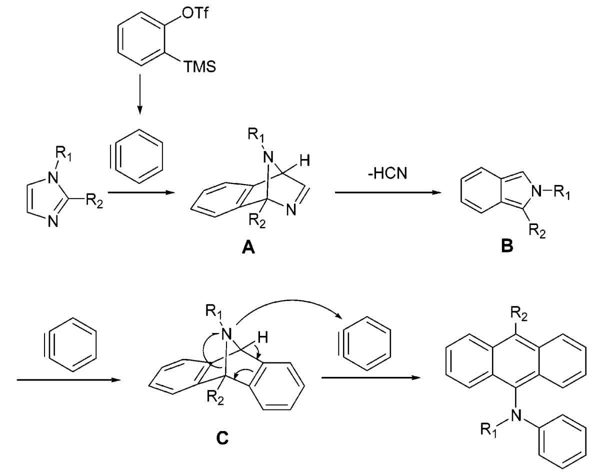
(15) Liu, Z. J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198−3209.

Scheme 1



To obtain further evidence to support the mechanism, we allowed 1-ethyl-4-phenyl-1*H*-imidazole to react with benzyne, and the desired product of *N*-ethyl-*N*-phenylanthracene-10-amine was generated in 61% yield (Table 2, entry 12). The reaction solution was analyzed by GC-MS, and benzonitrile was indeed detected (shown in Supporting Information), which showed the implications of the expulsion of benzonitrile from intermediate **A** to **B** from the retro Diels−Alder reaction.

In conclusion, we have developed a mild, direct, and transition-metal-free process for the synthesis of aryl amines containing anthracene, which would otherwise be difficult to obtain. The reaction is believed to undergo an unusual tandem process of benzyne with N-substituted imidazoles to produce the aryl amines in a single step. Further studies on other heterocycles are in progress.

Acknowledgment. We thank the support of the Natural Science Foundation of China (No. 20571063).

Supporting Information Available: The experimental procedures and spectroscopic data (^{1}H NMR, ^{13}C NMR, FTIR, and HRMS) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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