Pyridine-Catalyzed Double C–N Coupling Reaction of an Isocyanate with Two Benzynes

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A pyridine-catalyzed double C-N bond cross-coupling reaction involving two benzynes with an isocyanate was carried out. The coupling reaction proceeded through a unique pathway involving the formation of an unstable carbamic acid intermediate and facile decarboxylation. Subsequent nucleo-

Introduction

Diaryl- and triarylamine derivatives are synthetically important compounds for their wide applications in biology^[1] and material science.^[2,3] Most of them are prepared through transition-metal-catalyzed C-N coupling methodology. Among the various transition-metal-catalyzed protocols reported to date, copper- and palladium-catalyzed Narylation are the most common and efficient conditions: for example, the copper-catalyzed Ullmann reaction^[4] involving the coupling of amines with aryl halides is convenient and air stable. Moreover, this reaction can be utilized for large-scale preparation. However, high catalyst loadings^[5] and operation at high reaction temperatures^[6] were usually required. The palladium-catalyzed N-arylations developed by Buchwald^[7] and Hartwig^[8] are effective for the laboratory-scale preparation of specific amines under milder conditions with low catalyst loadings, and the substrate scope is diverse. Nickel-catalyzed C-N coupling^[9] is an alternative process to the palladium- or copper-mediated reactions; however, the prerequisite for the preparation of the starting materials limits its application. The first transition-metalfree N-arylation involving benzynes and amines was reported by Larock.^[10,11] Although their choice of benzyne species was limited, their methodology provided a very simple procedure to generate diaryl- and triarylamine derivatives. This encouraged us to explore another possibility for the synthesis of diaryl- and triarylamines without the use of a transition metal. Herein, we wish to report a facile, transition-metal-free and low catalyst loading N-arylation involving isocyanates and benzynes. This is the first example of a double C-N cross-coupling reaction with a distinct philic addition/protonation of in situ prepared amines with benzynes afforded variously substituted diaryl- and triarylamines in moderate to good yields with tolerance of a variety of functional groups.

mechanism, and this method is efficient for the synthesis of diaryl- and triarylamine derivatives.

Results and Discussion

In our preliminary study, o-(trimethylsilyl)phenyl triflate $(1a)^{[12]}$ was treated with cyclohexylisocyanate (2a) in the presence of cesium fluoride (3.0 equiv.) in acetonitrile at 80 °C for 12 h to give the corresponding diphenylamine in 17% yield (Table 1, Entry 1). We observed that some of the isocyanates that did not participate in the C-N coupling

Table 1. Optimization of reaction conditions.[a]

$\begin{array}{c} & \overbrace{TMS}^{OTf} + \begin{array}{c} Cy_{NCO} \\ \mathbf{2a} (3.0 \text{ equiv.}) \end{array} \xrightarrow{\begin{array}{c} base/H_2O/CsF \\ CH_3CN, T \end{array}} \begin{array}{c} & \overbrace{OY}^{Cy} \\ & \overbrace{OY}^{N} \end{array}$					
1a (2.0 equiv.)				3a	
Entry	Base	H ₂ O [equiv.]	Temp [°C]	Yield [%] ^[b,c]	
1	none	none	80	17	
2	none	0.8	80	36	
3	none	1.0	80	41	
4	none	1.2	80	49	
5	none	1.4	80	46	
6	none	1.2	70	51	
7	none	1.2	60	41	
8	NEt ₃	none	80	21	
9	NEt ₃	1.2	70	71	
10	TMEDA	1.2	70	63	
11	pyridine	1.2	70	73	
12	2,6-lutidine	1.2	70	84	
13	2,6-lutidine	1.2	70	72 ^[d]	
14	DBU	1.2	70	62	
15	DABCO	1.2	70	66	
16	DIPEA	1.2	70	69	

[a] Reactions were carried out with o-(trimethylsilyl)phenyl triflate (1a; 0.1 mmol, 2.0 equiv.), cyclohexylisocyanate (2a, 0.15 mmol), base (2 mol-%), CsF (3.0 equiv.), and H₂O (0-1.4 equiv.) in CH₃CN (0.4 mL) for 12 h. [b] ¹H NMR yield based on internal standard mesitylene. [c] Yields were calculated based on 1a. [d] 5 mol-% base.

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reaction were converted into the corresponding isocyanurate 4^[13] (Scheme 1) through fluoride-promoted cyclotrimerization.^[14] Thus, we employed an excess amount of isocyanate to ensure that benzyne precursor 1a was completely consumed. We also noticed by GC-MS analysis that a small amount of phenanthridinone derivative $5^{[15,16]}$ was formed, and this renders our current target under investigation. To the best of our knowledge, this is the first C-N coupling reaction giving arylamines from benzynes and isocvanates.



Scheme 1. Side products of the cross-coupling reaction.

To optimize the reaction conditions, we first tested the reaction with different amounts of water at different temperatures (Table 1, Entries 2–7). We discovered that water was necessary to increase the yield of 3a and to inhibit the formation of 5. Another competitive reaction took place to afford product $6^{[10b,17]}$ (Scheme 1) from a molecule of H₂O and two benzyne molecules. Reactions carried out in CH₃CN at 70 °C were optimal; neither increased nor decreased temperatures improved the reaction yields. We noticed that an additional basic additive was effective in improving the yields of both 3a and 4 (Table 1, Entry 8). Among the investigated bases, we found that the pyridinepromoted reactions gave higher yields than those promoted by amines and imidazole (Table 1, Entries 9-16). It was found that 2,6-lutidine was the best for this coupling reaction, which exhibited a greatly improved yield of 84%. When a less-hindered pyridine was used as the catalyst, the formation of 7^[18] was also detected by GC-MS; however, the 2,6-dimethyl groups of 2,6-lutidine provided greater steric hindrance, thus preventing the approach of cyanomethanide. Moreover, a higher loading of 2,6-lutidine efficiently catalyzed the formation of product 4 and reduced the yield of **3a** (Table 1, Entry 13).

The scope of the pyridine-catalyzed C-N coupling reaction was evaluated with variously substituted isocyanates and benzynes (Table 2). All the alkyl isocyanates reacted smoothly with benzynes under the optimized conditions. Reactions with primary alkyl groups (Table 2, Entries 2 and 3) gave slightly poorer yields than the reaction with a secondary alkyl group (Table 2, Entry 1) due to their lower electron densities; however, the strongly hindered tertiary isocyanate (Table 2, Entry 4) showed poorer reactivity toward benzyne. Our results revealed that the performance of this coupling reaction strongly depends on the electronic effects of the aliphatic and aromatic substituted isocyanates. Thus, phenylisocyanate (2e) and p-tolylisocyanate (2f) worked well in this coupling reaction and produced the corresponding triarylamine derivatives 3e and 3f in 70 and 75% yield, respectively (Table 2, Entries 5 and 6). In addition, a phenyl ring with an electron-withdrawing group significantly reduced the yields (Table 2, Entries 7 and 8), especially for *p*-acetylphenylisocyanate (2h). Because strongly electron-withdrawing substituents weaken the nucleophilicity of the resulting secondary amine, single C-N bond coupling derivative 3h' predominated over the double

Table 2. Pyridine-catalyzed cross-coupling of benzynes with isocyanates.[a]

2,6-lutidine



[[]a] Reactions were carried out with benzyne precursor 1 (0.5 mmol, 2.0 equiv.), isocyanate 2 (0.75 mmol), 2,6-lutidine (2 mol-%), CsF (3.0 equiv.), and H_2O (1.2 equiv.) in CH₃CN (2.0 mL) at 70 °C for 12 h. [b] Isolated yields after column chromatography. [c] Yields were calculated based on benzyne precursor 1. [d] GC yields, detected and calculated by GC–MS. [e] Yields of 3'

C-N coupling compound **3h**. The triethoxysilyl group was also well tolerated in this coupling reaction to form compound **3i** (Table 2, Entry 9), which was difficult to obtain by other synthetic pathways, and this compound should be stored in the refrigerator due to its ease of decomposition at high temperatures.

By using the same protocol, we were able to carry out the C-N coupling reaction of isocyanates with variously substituted benzynes (Table 2, Entries 10-12). When benzynes **1b** and **1c** with electron-donating groups were employed, the corresponding diarylated products 3j and 3k were obtained in a moderate yield 59 and 54%, respectively (Table 2, Entries 10 and 11). Electron-deficient difluorobenzyne 1d under the same conditions also provided diarylated product 31 in moderate yield, but in good total yields including 3l'. Benzyne 1d and isocyanate 2h with strong electron-withdrawing substituents afford the resulting N-arylated secondary amines 3h' and 3l', which exhibit poor nucleophilicity; thus, the second coupling reaction is suppressed and the corresponding double C-N coupling adducts are not obtained.^[18,19] Compared with previous reports.^[10,11] these reaction conditions are closer to neutral and tolerate a wider scope of substituents because isocyanates were employed in the N-arylation instead of primary or secondary amines.

To understand the mechanism of this C–N coupling reaction, a control experiment was investigated by replacing H_2O with D_2O . It was observed that both phenyl groups were deuterated by D_2O (Scheme 2) and compound **3aa** was generated in 73% yield.



Scheme 2. Deuteration of 3a.

Although a more detailed study is required to fully understand the mechanism of this pyridine-catalyzed double C–N bond coupling reaction, a tentative pathway can be proposed. Active zwitterion $A^{[20]}$ was generated by nucleophilic addition of pyridine to isocyanate 2 (Scheme 3) and subsequent N-arylation then occurred by A with electron-deficient benzyne 1. The accompanied hydrolysis released pyridine and afforded a very unstable intermediate carbamic acid B,^[21] which underwent facile decarboxylation to form secondary amine derivative 3'. A second N-arylation of an additional benzyne with compound 3' provided diarylamine derivative 3. This proposed mechanism well explains the formation of 3aa, 3h', and 3l'.

In the absence of pyridine (Table 1, Entries 2–7), products **3** and **3'** were generated by fluoride-promoted nucleophilic addition of isocyanate to benzyne^[14] or through an alternative pathway involving the reaction of an isocyanate with a molecule of H₂O and the release of CO₂ to form the corresponding amine derivative (**2'**, Scheme 4). The subsequent addition to the benzynes afforded products **3'** and **3**.^[10] However, this suggestion failed to explain why pyr-



Scheme 3. Possible mechanism.

idine or fluoride was necessary to promote the reaction and the formation of compound **4**.^[22,23] Actually, alkyl isocyanates are inert under mild conditions and require a pre-nucleophile to assist its nucleophilic addition.^[14,22,23]



Scheme 4. An alternative pathway for the coupling reaction.

Conclusions

In conclusion, we have developed a novel pyridine-catalyzed method for the cross-coupling reaction of two benzynes with an isocyanate. This method can efficiently provide diaryl- and triarylamine derivatives in moderate to good yields and withstands a variety of functional groups. Further studies to extend the scope of the catalytic reactions as well as the cyclization of benzyne with isocyanate are currently underway.

Experimental Section

Typical Procedure for the C–N Cross-Coupling Reaction: To a screw-capped vial was added CsF (227 mg, 1.5 mmol). The vial was sealed with a septum and flushed several times with nitrogen. *o*-(Trimethylsilyl)phenyl triflate (1a; 0.5 mmol, 149 mg), cyclohexylisocyanate (2a; 0.75 mmol, 94 mg), 2,6-lutidine (0.01 mmol, 1.2 μ L), H₂O (0.6 mmol, 10.8 μ L), and acetonitrile (2.0 mL) were injected into the reaction mixture with a syringe. The septum was removed, and the vial was sealed with a screw cap. The reaction mixture was stirred at 70 °C for 12 h. The crude reaction mixture was diluted with CH₂Cl₂, filtered through a thin pad of Celite, and

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concentrated in vacuo. The resulting mixture was monitored by TLC and purified by column chromatography on silica gel to give pure product **3a** in 84% yield.

Supporting Information (see footnote on the first page of this article): General methods, experimental procedures, characterization data, spectroscopic data, and copies of the ¹H and ¹³C NMR spectra of all the new compounds.

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