SHORT COMMUNICATION

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Three-Component Synthesis of α-Amino-α-aryl Carbonitriles from Arynes, Aroyl Cyanides, and *N*,*N*-Dimethylformamide

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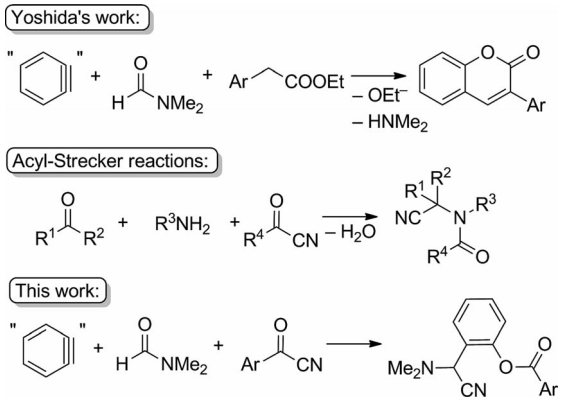
A general and efficient synthesis of α-amino-α-aryl carbonitriles through the three-component reaction of arynes, aroyl cyanides, and DMF in a single step is described. DMF was not only used as the solvent, but it also participated in the reaction as a component. Used as the cyanide sources, the aroyl cyanides solved the toxicity and solubility problems associated with the use of HCN or metal cyanides in the Strecker synthesis. This procedure furnished α-amino-α-aryl carbonitriles in moderate to good yields with broad substrate scope. Moreover, this reaction could be performed under mild conditions with high atom economy.

Introduction

Since the first multicomponent reaction (MCR) was disclosed by Strecker in 1850,[1] MCRs have been widely developed and utilized in modern organic synthesis.[2] These reactions combine three or more components in one pot and provide a major product through a sequential route with high atom economy and high bond-formation efficiency.[3–8] In this blooming field, Yoshida's elegant design in which an aryne and DMF were used as two components attracted our attention (Scheme 1).[9]



Scheme 1. Our work leading to α-amino carbonitriles.

Bifunctional α-amino carbonitriles are not only key intermediates in the preparation of α-amino acids, but they also play important roles in constructing various heterocycles because of their dual functionality.[10] One of the most practical methods for the preparation of α-amino carbonitriles is the classical Strecker synthesis, which combines an aldehyde/ketone, ammonia, and hydrogen cyanide in one pot to provide α-amino carbonitriles in a single step.[1] Much effort has been devoted to the enantiomeric synthesis of chiral α-amino carbonitriles[11] and to the disclosure of new cyanide surrogates.[12] Only a few contributions are related to new methodologies in constructing α-amino carbonitriles, such as the acyl-Strecker reactions in Scheme 1.[13]

Three kinds of cyanide sources are normally applied in the Strecker synthesis. One is HCN, which is classically used, but it has extremely high toxicity. The second one is metal cyanides,[14] which are highly toxic and show low solubility in common organic solvents. The third one is organic compounds that contain a CN group that can release the cyanide anion uring the reaction process. In these cases, TMSCN,[15] acetone cyanohydrin,[16] acetyl cyanide,[13] ethyl carbonocyanidate,[17] and cyanobis(dibenzylamino)borane[18] are extensively used. As the cyanide anion is in situ generated and consumed during these reaction processes, these reactions are environmentally more benign and operationally safer than those that use HCN or metal cyanides. Herein, we would like to report a three-component reaction that uses benzoyl cyanide as the cyanide source (Scheme 1).

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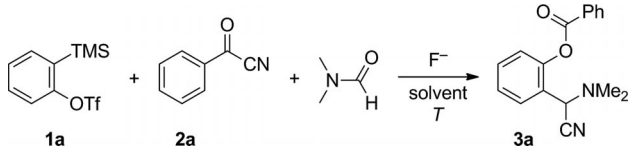
Results and Discussion

The reaction was first performed by mixing 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1a**, 1 mmol) and benzoyl cyanide (**2a**, 1 mmol) in DMF (10 mL) in the presence of 4 Å molecular sieves. If CsF (2 mmol) was added to the mixture and the resulting mixture was heated at 60 °C for 3 h, α-amino-α-(2-benzoyloxy)phenyl carbonitrile **3a** was formed and isolated by column chromatography in 55% yield. Spectroscopy analysis of **3a** indicated that DMF participated in the reaction as a component.[19] Delighted by this result and the potential use of α-amino-α-aryl carbonitriles as effective sphingomyelin synthase inhibitors,[20] we optimized the reaction conditions for the formation of **3a**, and the results are listed in Table 1. Without the 4 Å molecular sieves, the yield dramatically decreased to 10% (Table 1, Entry 2). Keeping the reaction mixture dry was critical for a better transformation. Screening the fluoride source, it was found that CsF was superior to all others tested, including KF, LiF, and tetrabutylammonium fluoride (TBAF; Table 1, Entries 3–5). Upon using 10 equiv. of DMF with the supplementary addition of acetonitrile as the solvent, **3a** was not isolated, although it was detectable by TLC analysis. By changing the solvent from acetonitrile to THF and toluene, **3a** was not detected (Table 1, Entries 6–8). Either raising or lowering of the reaction temperature decreased the yields (Table 1, Entries 9 and 10). By changing the amount of DMF to 3 mL, the yield of **3a** decreased to 15% (Table 1, Entry 11). Increasing the amount of **1a** significantly increased the yield. If the ratio of **1a**/**2a** was altered to 2:1, **3a** was isolated in 70% yield. Conversely, increasing the amount of **2a** decreased the yield markedly (Table 1, Entries 12 and 13). The yield was improved if the reaction was conducted under N_2 (Table 1, Entry 14). Thus, the optimal reaction conditions were established.

Table 1. Screening of the reaction conditions.[a]

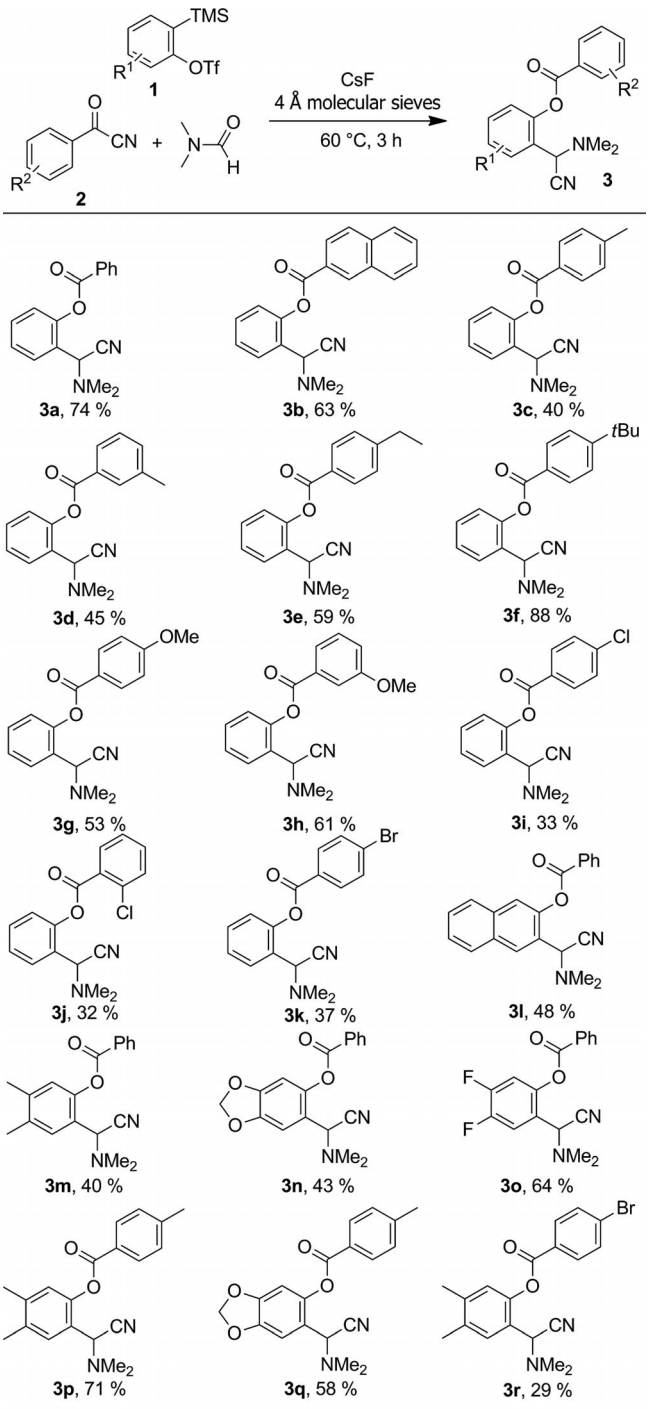


1a **2a** **3a**

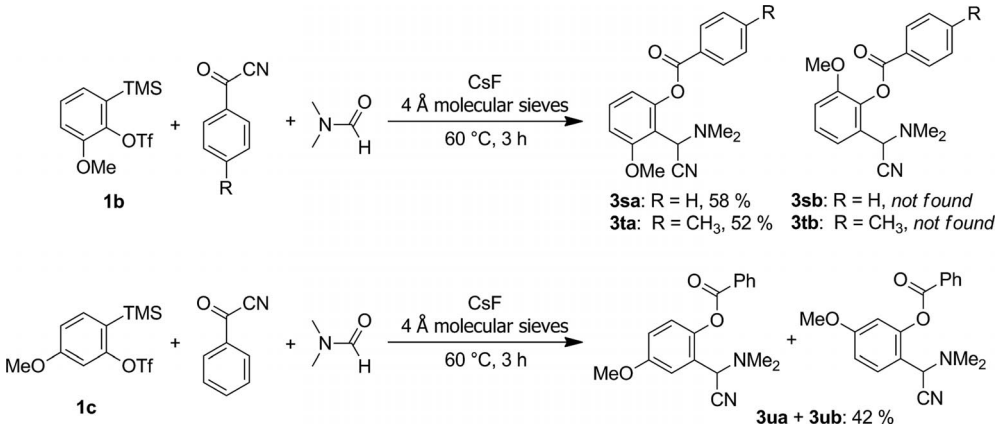
Entry	Reagent (2.0 equiv.)	DMF [equiv.]	Solvent	*T* [°C]	Yield[b] [%]
1	CsF	–	DMF	60	55
2[c]	CsF	–	DMF	60	10
3	KF	–	DMF	60	20
4	LiF	–	DMF	60	15
5	TBAF	–	DMF	60	<5
6	CsF	10	MeCN	60	<5
7	CsF	10	THF	60	n.d.[d]
8	CsF	10	toluene	60	n.d.[d]
9	CsF	–	DMF	55	47
10	CsF	–	DMF	70	46
11[e]	CsF	–	DMF	60	15
12[f]	CsF	–	DMF	60	70
13[g]	CsF	–	DMF	60	23
14[h]	CsF	–	DMF	60	74

[a] Unless otherwise specified, all reactions were performed with **1a** (1.0 mmol), **2a** (1.0 mmol), CsF (2.0 mmol) and 4 Å molecular sieves (1 g) in DMF (10 mL) at 60 °C for 3 h. Tf = trifluoromethylsulfonyl. [b] Yield of isolated product after silica gel column chromatography. [c] Without 4 Å molecular sieves. [d] n.d. = not detected. [e] DMF (3 mL). [f] **1a** (2.0 mmol). [g] **2a** (1.5 mmol). [h] Under nitrogen.

Table 2. Substrate scope of this three-component reaction.[a]



[a] Reaction conditions: A mixture of **1** (1.0 mmol), **2** (0.5 mmol), CsF (2.0 mmol), and 4 Å molecular sieves (1.0 g) in DMF (5 mL) was heated to 60 °C for 3 h under nitrogen.



Scheme 2. A regioselectivity problem arises from unsymmetrical benzynes.

With the optimized reaction conditions in hand, we tested the substrate scope (Table 2). Naphthoyl cyanide produced **3b** in 63% yield. Benzoyl cyanides with aliphatic groups on the benzene ring, such as methyl, ethyl, and *tert*-butyl, furnished **3c**, **3e**, and **3f** in 40, 59, and 88% yield, respectively. Altering the position of the methyl group on the benzene ring of the benzoyl cyanide from the *para* position to the *meta* position slightly raised the yield of α-amino carbonitrile **3d**. Single crystal analysis of **3d** further confirmed that the product contained the α-amino carbonitrile substructure (Figure 1).[21] However, the yields were significantly affected by the presence of a chlorine or bromine atom on the benzene ring. Thus, **3i**, **3j**, and **3k** were obtained in 33, 32, and 37% yield, respectively. By changing the benzyne surrogate, we isolated **3l**, **3m**, **3n**, and **3o** in 48, 40, 43, and 64% yield, respectively. Further application of these benzyne surrogates furnished **3p**, **3q**, and **3r** in 71, 58, and 29% yield, respectively. Aliphatically substituted **3p** and **3q** were obtained in higher yield than bromine-substituted **3r**.

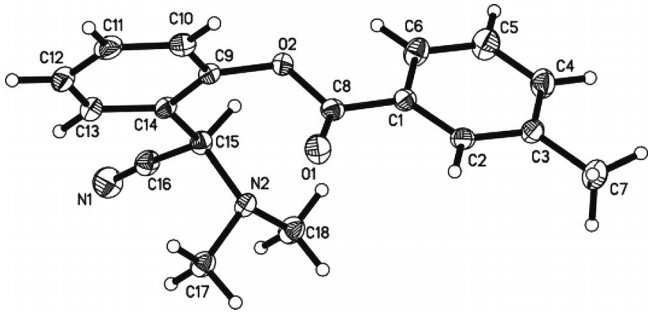
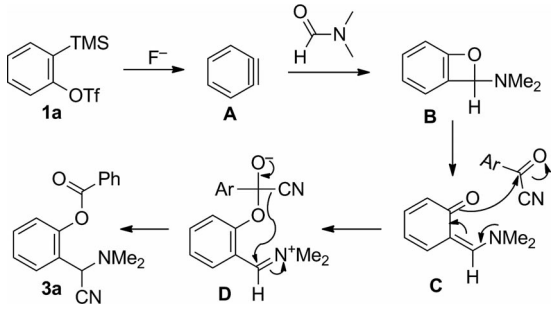


Figure 1. Crystal structure of **3d**.

Upon changing the benzyne surrogate to unsymmetrical **1b**, **3sa** and **3ta** were regioselectively prepared in 58 and 52% yield, respectively, and **3sb** and **3tb** were not found in these cases (Scheme 2). The regioselectivity was confirmed by HMBC spectroscopy (see the Supporting Information). However, if unsymmetrical benzyne surrogate **1c** was used, **3ua** and **3ub** were obtained in 42% yield. The ratio of **3ua**/**3ub** was determined to be 1:2 on the basis of the ^{1}H NMR spectrum. Notably, this three-component reaction is scalable. If a mixture of 10 mmol of **1a**, 5 mmol of 4-(*tert*-butyl)benzoyl cyanide, and 20 mmol of CsF was heated at 60 °C for 6 h in 50 mL of DMF in the presence of 10 g of 4 Å molecular sieves, 1.23 g of **3f** was isolated in 73% yield.

Notably, the possibility of using *N*,*N*-dimethylacetamide in place of DMF was investigated for **1a**, but we did not isolate any of the desired product from the complex reaction mixture.

On the basis of the above reactions and literature reports, we postulate a possible mechanism for the formation of the α-amino carbonitriles (Scheme 3). First, benzyne intermediate **A** is in situ generated by treatment of benzyne surrogate **1a** with the fluoride anion. Then, a [2+2] cycloaddition between benzyne and the carbonyl group of DMF occurs to form oxetene ring **B**. Some oxetenes are stable and can be isolated.[22] In this case, the benzene-fused oxetene ring is unstable, and its fragmentation leads to the formation of α-amino-α-unsaturated ketone **C**.[9,23] Through effective push–pull of the lone pair of electrons of the dimethylamino group in intermediate **C**, benzoyl cyanide is incorporated into the product through reasonable intermediate **D**.



Scheme 3. Proposed mechanism for the formation of α-amino carbonitrile.

Conclusions

We developed a three-component reaction that efficiently constructed α-amino-α-aryl carbonitriles from benzyne surrogates, aroyl cyanides, and *N*,*N*-dimethylformamide under

mild reaction conditions in a single step. DMF not only worked as a component, but it also served as the solvent in this reaction. Aroyl cyanides slowly released the cyanide anion during the course of the reaction, which solved the toxicity and solubility problems arising from the use of classical HCN and metal cyanides in the Strecker reaction. Other multicomponent reactions based on benzyne and DMF are underway.

Experimental Section

General Methods: Unless otherwise indicated, NMR spectra were obtained with a Bruker Avance DMX400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C in $CDCl_3$. Melting points were recorded with a Büchi 535 apparatus. All HRMS measurements were performed upon electron ionization (EI or ESI) with a mass spectrometer. Flash column chromatography was performed by employing 300–400 mesh silica gel. Thin layer chromatography (TLC) was performed with silica gel HSGF254.

Typical Experimental Procedure for the Preparation of 2-[Cyano(dimethylamino)methyl]phenyl Benzoate (3a): A solution of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (298 mg, 1.0 mmol), benzoyl cyanide (65 mg, 0.5 mmol), and 4 Å molecular sieves (1000 mg) in DMF (5 mL) was prepared under nitrogen. After the reaction mixture had been stirred for 2 min, CsF (302 mg, 2.0 mmol) was added. The reaction mixture was stirred at 60 °C for 3 h. After cooling the reaction mixture to room temperature, the excess amount of DMF was removed under reduced pressure. The residue was purified by column chromatography (silica gel; 5% triethylamine in hexane/ethyl acetate, 10:1) to afford **3a** (104 mg, 74%) as a yellow solid. M.p. 89–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, J = 7.1 Hz, 2 H), 7.65 (dd, J = 7.2, 6.5 Hz, 2 H), 7.55–7.46 (m, 3 H), 7.35 (dd, J = 7.6, 0.8 Hz, 1 H), 7.29–7.26 (m, 1 H), 5.01 (s, 1 H), 2.12 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 149.5, 133.9, 130.6, 130.3, 129.6, 129.5, 128.9, 126.4, 126.2, 124.3, 114.7, 59.5, 41.6 ppm. HRMS (EI): calcd. for $C_{17}H_{16}N_2O_2$ $[M]^+$ 280.1212; found 280.1209.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures; characterization data; copies of the NMR spectra of **1a**–**1f**, **2b**–**2j**, and **3a**–**3ub**; crystallographic information of **3d**.

Acknowledgments

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