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A Sterically Congested α-Cyanoamine as a Cyanating Reagent: Cyanation of Acetals and Orthoesters

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The cyanation of acetals and orthoesters by using a sterically congested α-cyanoamine as a cyanating reagent was investigated. The α-cyanoamine effectively facilitated cyanation in the presence of trichlorosilyl triflate to produce a variety of cyanated adducts in excellent yields. Analysis of the reaction mixture by ^{1}H NMR spectroscopy revealed that trichlorosilyl triflate produced an oxocarbenium cation species as an intermediate.

Introduction

The amines represent some of the most common and versatile reagents in organic synthesis. Amines are commonly used as Brønsted bases. In contrast, the Hantzsch ester acts as a hydride donor to mediate the reduction of organic compounds.[1] Several hydrogen-transfer reagents with aliphatic amines have been investigated.[2–6] Our research group recently demonstrated that a sterically congested tertiary amine facilitates the conjugate reduction of α,β-unsaturated ketones in the presence of trichlorosilyl triflate ($SiCl_3OTf$).[7,8] Therefore, a sterically congested amine can release a nucleophile, such as a hydride, from its α-position owing to steric restriction (Figure 1). Although several reports have described the development of hydride-releasable amines, little attention has been paid toward other nucleophile-releasable amines.[9] This communication reports that sterically congested α-cyanoamines act as cyanating reagents to realize the cyanation of acetals[10] and orthoesters[11,12] in high yields.

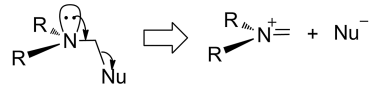

Figure 1. Tertiary amine as a nucleophile carrier.

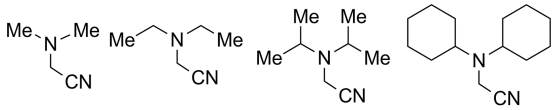

Figure 2. α-Cyanoamines **1** used in this work.

Results and Discussion

Cyanoamines **1** used in this study were readily prepared from the corresponding secondary amines and α-bromoacetonitrile (Figure 2).[13]

We initially examined the cyanation of acetals to evaluate the cyanating ability of α-cyanoamines **1**. The reaction was performed by treating acetal **2a** with cyanoamine **1** (2 equiv.) and $SiCl_3OTf$[14] in CH_2Cl_2 at 0 °C (Table 1). Dimethylcyanoamine (**1a**) did not produce cyanated adduct **3a** (Table 1, entry 1), whereas diethylcyanoamine (**1b**) gave **3a** in a promising yield of 50% (Table 1, entry 2). More hindered cyanoamine **1c** dramatically improved the product yield (93%; Table 1, entry 3).[15] These results indicated that the steric effects of α-cyanoamine **1** greatly influenced the yield of **3a** in the cyanation. A less-hindered amine might form an unfavorable complex with $SiCl_3OTf$, which thereby suppressed cyanation. The bulkiness of the cyanoamine can prevent the formation of the unfavorable complex and retain its cyanating functionality.[16,17] The use of dicyclohexylamine **1d** gave cyanated adduct **3a** in the highest yield (Table 1, entry 4).

With dicyclohexylcyanoamine (**1d**) in hand, we next investigated the substrate scope of various acetals (Table 2). The reactions of aromatic acetals **2b**–**f** proceeded smoothly, regardless of the electronic and steric effects of the aromatic ring, to produce corresponding products **3b**–**f** in excellent yields (Table 2, entries 2–6). Cinnamaldehyde derivative **2g** reacted suitably to provide product **3g** in 92% yield (Table 2, entry 7). Acetals **2h** and **2i** derived from aliphatic aldehydes gave corresponding cyanated adducts **3h** and **3i** in

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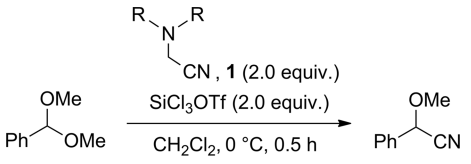
Table 1. Structural effects of cyanoamines **1**.[a]



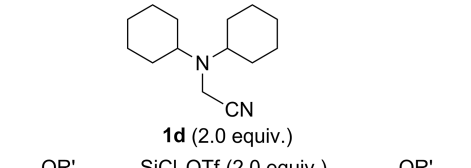
2a **3a**

Entry	α-Cyanoamine **1**	Yield [%]
1	**1a** (R = Me)	0
2	**1b** (R = Et)	50
3	**1c** (R = *i*Pr)	93
4	**1d** (R = Cy)	95

[a] All reactions were performed by adding a solution of 2 M $SiCl_3OTf$ in CH_2Cl_2 (2.0 equiv.) to a solution of acetal **2a** (0.5 mmol) and cyanoamine **1** (2.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C.

high yields (Table 2, entries 8 and 9). The reaction involving acetal **2j** at 0 °C produced a dimerized side product.[18] Reducing the reaction temperature to –78 °C improved the product yield (Table 2, entry 10). Diethyl acetal **2k** and dibenzyl acetal **2l** were also tolerated, and they afforded the corresponding products **3k** and **3l** in high yields (Table 2, entries 11 and 12). Cyanation of cyclic acetal **2m** opened the dioxolane ring to give cyano alcohol **3m** in 87% yield. Thus, α-cyanoamine **1d** promoted cyanation over a wide range of acetals.

Table 2. Cyanation of acetals **2** with α-cyanoamine **1d**.[a]



2a–m **3a–m**

Entry	Acetal			Product	Yield
	2	R	R′		[%]
1	**2a**	Ph	Me	**3a**	95
2	**2b**	4-Me-C_6H_4	Me	**3b**	95
3[b]	**2c**	4-MeO-C_6H_4	Me	**3c**	97
4	**2d**	4-Br-C_6H_4	Me	**3d**	95
5	**2e**	1-naphthyl	Me	**3e**	97
6	**2f**	2-naphthyl	Me	**3f**	87
7	**2g**	PhCH=CH	Me	**3g**	92
8	**2h**	Cy	Me	**3h**	95
9	**2i**	$PhMe_2C$	Me	**3i**	96
10[c]	**2j**	$PhCH_2CH_2$	Me	**3j**	90
11	**2k**	Ph	Et	**3k**	87
12	**2l**	Ph	Bn	**3l**	95
13	**2m**	Ph	–CH_2CH_2–[d]	**3m**	87

[a] Unless otherwise noted, reactions were performed by adding a solution of 2 M $SiCl_3OTf$ in CH_2Cl_2 (2.0 equiv.) to a solution of acetal **2** (0.5 mmol) and cyanoamine **1d** (2.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C. [b] Amine **1d** (3.0 equiv.) and $SiCl_3OTf$ (3.0 equiv.). [c] At –78 °C. [d] 2-Phenyl-1,3-dioxolane.

We next directed our attention toward elucidating the reaction mechanism. The intermediates in the reaction mixture were characterized by conducting ^1H NMR spectroscopy experiments (Figure 3). Acetal **2a** gave two types of singlets at δ = 5.3 (H^a) and 3.3 ppm (H^b) (Figure 3, I). The addition of $SiCl_3OTf$ (2.0 equiv.) produced several new signals in place of these signals (Figure 3, II). The observed characteristic signals at δ = 9.8 ($H^{a'}$) and 5.1 ppm ($H^{b'}$) corresponded to oxocarbenium cation **4**.[19–21] Oxocarbenium cations are generally difficult to detect owing to the rapid equilibrium that is established between the oxocarbenium cation and the tetrahedral carbon center accompanied by a counterion. The observed sharp signals indicated that $SiCl_3OTf$ efficiently produced an oxocarbenium cation. The subsequent addition of cyanoamine **1d** completely removed these signals, whereas new resonances at δ = 5.2 ($H^{a''}$) and 3.5 ppm ($H^{b''}$) corresponding to product **3a** increased in intensity, and another signal appeared at δ = 8.2 ppm (H^c), corresponding to iminium cation **6** (Figure 3, III).

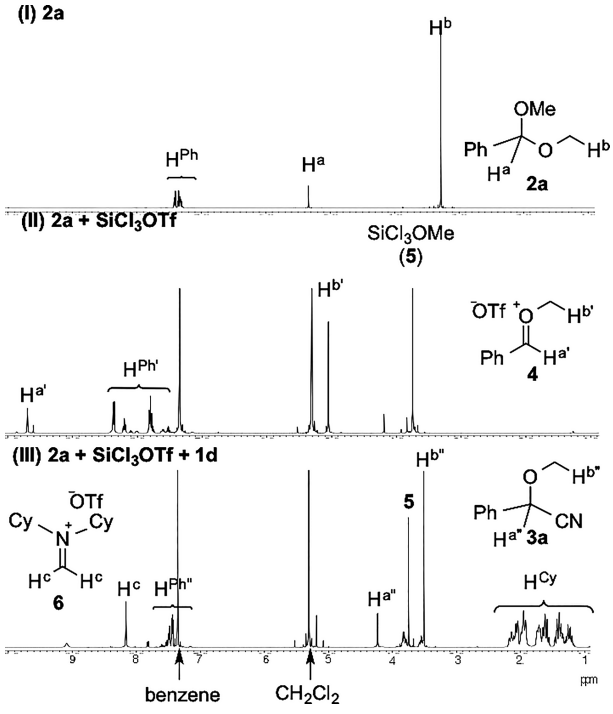


Figure 3. ^1H NMR spectroscopy experiments.

The NMR spectroscopy results suggest the reaction mechanism shown in Figure 4. First, acetal **2a** is activated by $SiCl_3OTf$, and the resulting complex eliminates $SiCl_3OMe$ (**5**) to give oxocarbenium cation species **4**.[22] Once highly electrophilic cation species **4** is formed, the cyano group in **1d** is transferred to afford cyanated product **3a**, accompanied by iminium cation **6**. Notably, trichlorosilyl triflate kinetically generates highly reactive intermediate **4** to promote the cyano group transfer reaction to the acetals.

Cyanoamine **1d** was also found to be useful in the cyanation of orthoesters (Figure 5).[11] The cyanation of orthoester **7a** with cyanoamine **1d** and $SiCl_3OTf$ gave corre-

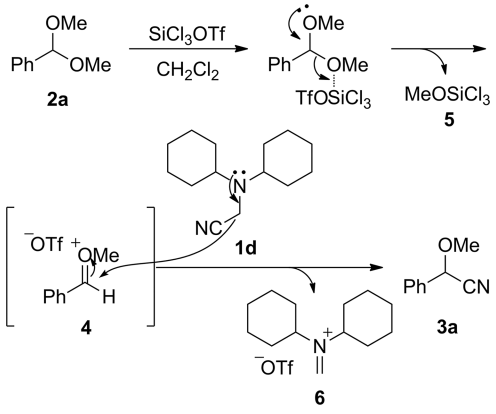


Figure 4. Proposed reaction mechanism.

sponding cyanoacetal **8a** in excellent yield.[23] A variety of orthoesters **7b–d** were also transformed into cyanoacetals **8b–d** in good yields.

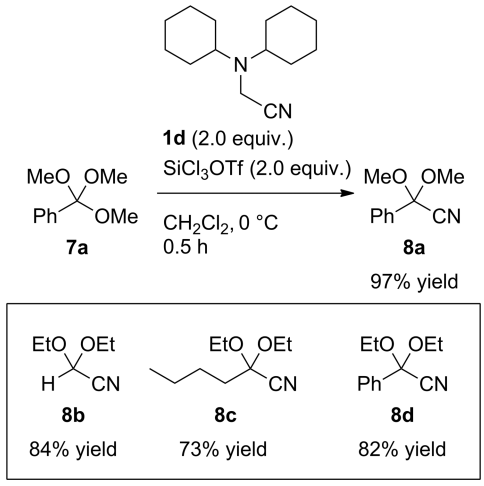


Figure 5. Cyanation of the orthoesters **7**. For the preparation of **8c** and **8d**, cyanoamine **1d** (3.0 equiv.) and $SiCl_3OTf$ (3.0 equiv.) were used.

Conclusions

In conclusion, we demonstrated that sterically hindered α-cyanoamines could effectively promote the cyanation of acetals and orthoesters in the presence of trichlorosilyl triflate to produce cyanated adducts in high yields. In addition, we detected oxocarbenium cations as intermediates through analysis of the reaction mixtures by NMR spectroscopy. We are currently investigating the development of useful reactions by using sterically congested tertiary amines as nucleophile carriers.

Experimental Section

Typical Procedure for the Cyanation with Tertiary Amine 1d: A solution of 2.0 M trichlorosilyl triflate in dichloromethane (0.5 mL, 1.0 mmol, 2.0 equiv.) was added dropwise to a solution of **1d** (220 mg, 1.0 mmol, 2.0 equiv.) and acetal **2a** (76.1 mg, 0.5 mmol) in dichloromethane (5.0 mL) at 0 °C. After stirring for 0.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and stirred for another 0.5 h at room temperature. After filtration through Celite, the filtrate was extracted with EtOAc (3 × 10 mL), and the combined organic layer was washed with brine (30 mL) and dried over Na_2SO_4. After filtration and concentration, the obtained crude product was purified by column chromatography (hexane/EtOAc, 10:1) to afford product **3a**.

Acknowledgments

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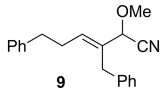
[15] The handling of α-cyanoamine **1c** was difficult owing to its low boiling point.

[16] Cyanated product **3a** was obtained in 91% yield upon using 1.2 equivalents of **1d**.

[17] $SiCl_4$ and $BF_3{\cdot}OEt_2$ were ineffective as Lewis acid promoters. Me_3SiOTf and $TiCl_4$ gave product **3a**, but in lower yields.

[18] Dimerized side product **9** was obtained in 4% yield.



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[20] A singlet for $SiCl_3OMe$ (**5**) was observed at δ = 3.8 ppm.

[21] The ^{13}C NMR spectrum also exhibited a signal at δ = 207.8 ppm attributable to the methine carbon atom of oxocarbenium cation **4**.

[22] Oxocarbenium cation **4** in the mixture was stable for at least 24 h. Even if cyanoamine **1d** was treated with **4** after 24 h, **3a** was obtained in 87% yield.

[23] With the use of Cy_2NiBu as a hydride donor, benzyl methyl ether was obtained in 42% yield.

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