

# Production of Quaternary $\alpha$ -Aminonitriles by Means of Indium-Catalyzed Three-Component Reaction of Alkynes, Amines, and Trimethylsilyl Cyanide

Yuta Hamachi, Moe Katano, Yohei Ogiwara, and Norio Sakai\*

Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science (RIKADAI), Noda, Chiba 278-8510, Japan

**S** Supporting Information

**ABSTRACT:** A novel synthesis of  $\alpha$ -aminonitriles is described via an indium-catalyzed three-component coupling reaction of alkynes, amines, and trimethylsilyl cyanide ( $\text{Me}_3\text{SiCN}$ ). Hydroamination of alkynes with a subsequent nucleophilic addition of  $\text{Me}_3\text{SiCN}$  resulted in a novel approach to quaternary  $\alpha$ -aminonitrile derivatives.

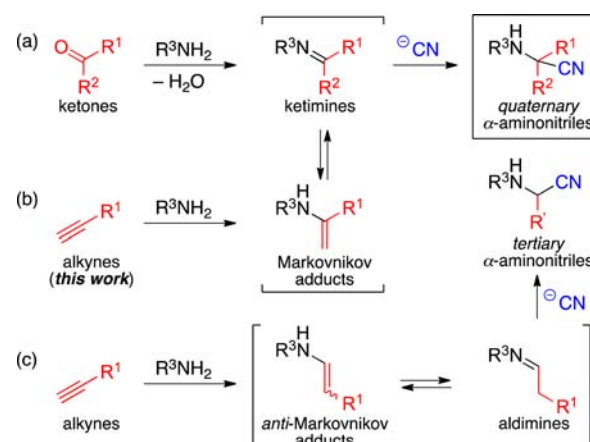


The Strecker reaction, which enables the one-pot synthesis of  $\alpha$ -aminonitriles by a three-component reaction of aldehydes, amines, and cyanides, is the classic method and still greatly important in organic chemistry.<sup>1</sup> The significance of this reaction is derived from the products,  $\alpha$ -aminonitriles, which constitute versatile precursors for the synthesis of both natural and non-natural amino acids and other nitrogen-containing heterocycles.<sup>2</sup> A large number of improvements to the original protocol have been reported over the years, such as the development of effective catalysts, a broadened scope of the amines, replacement of toxic cyanide with a safer cyanide source, and employment of ketones instead of aldehydes. In particular, the Strecker reaction using ketones has generally proven to be difficult because ketimine intermediates are less reactive to cyanide than aldimines. Therefore, although the Strecker products derived from ketones, quaternary  $\alpha$ -aminonitriles, are important compounds due to their synthetic potential for asymmetric applications, reliable and efficient procedures for their structures remain limited (Scheme 1a).<sup>3</sup>

Hydroamination of alkynes is another efficient approach to imines,<sup>4</sup> and a modified Strecker synthesis using alkynes via hydroamination, instead of aldehydes or ketones, is considered to be an alternative synthetic strategy. In particular, Markovnikov hydroamination is available to give good precursors, ketimines, for quaternary  $\alpha$ -aminonitriles (Scheme 1b). In 2006, Schafer and co-workers reported the titanium(IV)-catalyzed one-pot synthesis of  $\alpha$ -aminonitriles from terminal alkynes.<sup>5</sup> This method selectively provides only tertiary  $\alpha$ -aminonitriles due to the formation of aldimines via anti-Markovnikov regioselectivity in the initial hydroamination step and subsequent isomerization (Scheme 1c). As far as we could ascertain, however, the catalytic preparation of quaternary  $\alpha$ -aminonitriles from alkynes, amines, and cyanides via ketimine intermediates obtained via intermolecular Markovnikov hydroamination remains unexplored (Scheme 1b).

Recently, our research group reported the  $\text{InBr}_3$ -catalyzed reductive hydroamination of terminal alkynes with amines using  $\text{Me}_2\text{PhSiH}$  as a reducing reagent.<sup>6</sup> This reaction provides

**Scheme 1.** Strecker-Type Reaction of Ketimines Derived from (a) Ketones and (b,c) Alkynes



branched amines from ketimine intermediates via Markovnikov hydroamination. On the basis of this result, we envisioned that the addition of “Si-CN” rather than “Si-H” to the ketimines could achieve a sequential one-pot preparation of  $\alpha$ -aminonitriles including a quaternary carbon center with the indium catalytic system. Herein, we report a novel and straightforward approach to quaternary  $\alpha$ -aminonitriles by an indium(III)-catalyzed three-component coupling reaction of alkynes, amines, and  $\text{Me}_3\text{SiCN}$  through intermolecular Markovnikov hydroamination (Scheme 1b).

On the basis of our previous study,<sup>6</sup> when phenylacetylene and *p*-toluidine were initially treated with 10 mol % of  $\text{InBr}_3$  in toluene at 110 °C for 3 h, followed by the addition of 1.5 equiv of  $\text{Me}_3\text{SiCN}$  with further stirring at room temperature for 21 h, the expected  $\alpha$ -aminonitrile **1** was obtained in a 36% yield (Table 1, entry 1). To promote the addition of  $\text{Me}_3\text{SiCN}$ , the reaction

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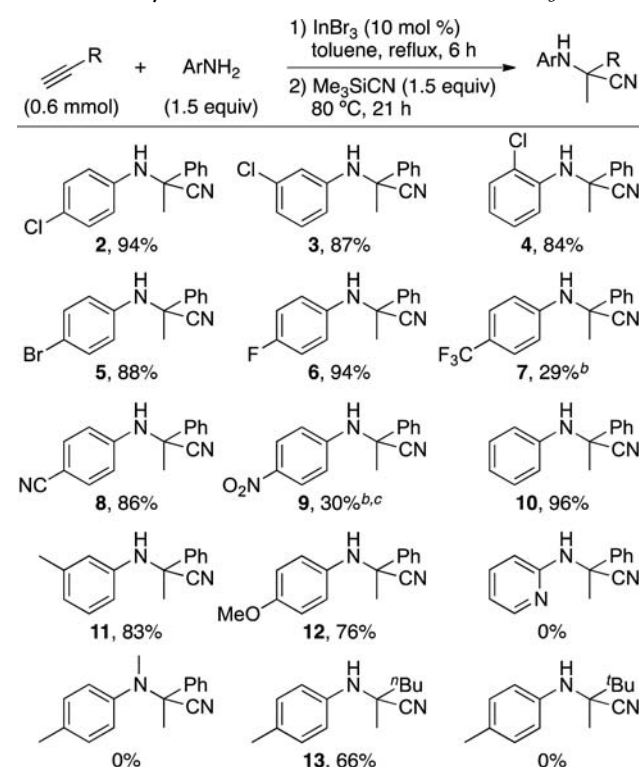
Table 1. Optimization of Reaction Conditions<sup>a</sup>

entry	catalyst	first step		second step	yield (%) <sup>b</sup>
		time (h)	temp (°C)	temp (°C)	
1	InBr <sub>3</sub>	3	rt	80	36
2	InBr <sub>3</sub>	3	60	80	50
3	InBr <sub>3</sub>	3	80	80	65
4	InBr <sub>3</sub>	3	reflux	80	27
5	InBr <sub>3</sub>	3	80	80	45 <sup>c</sup>
6	InBr <sub>3</sub>	3	80	80	55 <sup>d</sup>
7	InBr <sub>3</sub>	6	80	80	85
8	InCl <sub>3</sub>	6	80	80	43
9	In(OTf) <sub>3</sub>	6	80	80	44
10	InI <sub>3</sub>	6	80	80	85
11	AlCl <sub>3</sub>	6	80	80	0
12	GaCl <sub>3</sub>	6	80	80	0
13	Zn(OTf) <sub>2</sub>	6	80	80	80
14	none	6	80	80	0

<sup>a</sup>Reaction conditions. First step: alkyne (0.6 mmol), ArNH<sub>2</sub> (0.9 mmol), catalyst (0.06 mmol), toluene (1.2 mL), reflux. Second step: Me<sub>3</sub>SiCN (0.9 mmol), 21 h. <sup>b</sup>Isolated yield. <sup>c</sup>InBr<sub>3</sub> (5 mol %). <sup>d</sup>Me<sub>3</sub>SiCN (2 equiv).

temperature in the second step was examined. Although the increase in temperature to 80 °C promoted the addition (entries 2 and 3), the reflux condition resulted in a drastic decrease in the yield of **1** (entry 4). When the reaction was conducted with either 5 mol % of InBr<sub>3</sub> or 2 equiv of Me<sub>3</sub>SiCN at 80 °C, both yields were slightly reduced (entries 5 and 6). When the reaction time at the first step was prolonged to 6 h, the yield of **1** was improved to 85% (entry 7). During the screening of the catalysts (entries 8–13), InI<sub>3</sub> and Zn(OTf)<sub>2</sub> showed catalytic activity that compared favorably to InBr<sub>3</sub>. Also, when the reaction was conducted in the absence of a catalyst, the first hydroamination did not occur, and the starting alkyne and amine were completely recovered (entry 14).

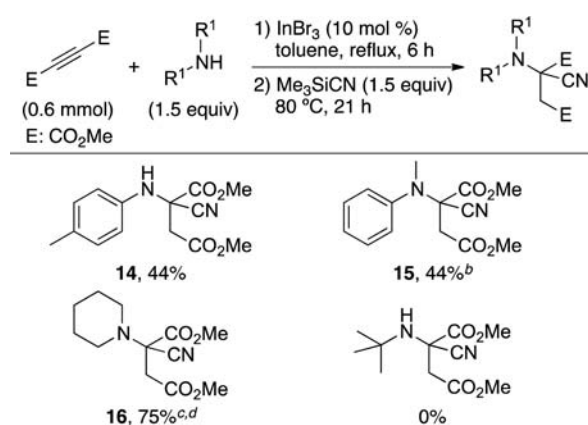
Using the optimal conditions, the scope of both alkynes and amines was next investigated (Scheme 2). Primary aromatic amines bearing a chlorine atom on the benzene ring at the 4-, 3-, or 2-positions were applied to a three-component coupling reaction with phenylacetylene and Me<sub>3</sub>SiCN, giving  $\alpha$ -aminonitriles **2–4** in excellent yields. Anilines containing the other halogens at the 4-position, bromine and fluorine, were also converted into the corresponding products **5** and **6** in 88 and 94% isolated yields, respectively. The reactions of anilines with an electron-withdrawing group, such as 4-trifluoromethyl, 4-cyano, and 4-nitro, were also applicable to this transformation to afford **7–9**, although the yield of the substrate with a CF<sub>3</sub> or NO<sub>2</sub> group was remarkably decreased. When the reaction was conducted with aniline, *m*-toluidine, or 4-anisidine, the corresponding  $\alpha$ -aminonitriles **10–12** were obtained in 96, 83, and 76% yields, respectively. When the reaction was performed with 2-aminopyridine or a secondary *N*-methylaniline, the desired products were not obtained under these conditions. An extension to aliphatic alkynes was then examined. When 1-hexyne and *p*-toluidine were employed, the corresponding product **13** was obtained in a practical yield. Unfortunately, the

Scheme 2. Indium-Catalyzed Three-Component Reaction of Terminal Alkynes and Aniline Derivatives with Me<sub>3</sub>SiCN<sup>a</sup>

<sup>a</sup>Reaction conditions. First step: alkyne (0.6 mmol), ArNH<sub>2</sub> (0.9 mmol), InBr<sub>3</sub> (0.06 mmol), toluene (1.2 mL), reflux, 6 h. Second step: Me<sub>3</sub>SiCN (0.9 mmol), 80 °C, 21 h. Isolated yields are shown. <sup>b</sup>First step is 24 h. <sup>c</sup>ArNH<sub>2</sub> (2 equiv).

first hydroamination did not proceed when employing a sterically hindered alkyne, 3,3-dimethyl-1-butyne.

Next, the present method was evaluated (Scheme 3) using an activated alkyne, dimethyl acetylenedicarboxylate (DMAD). The reaction of DMAD with *p*-toluidine afforded the desired product **14** in a 44% yield. It is noteworthy that when employing a

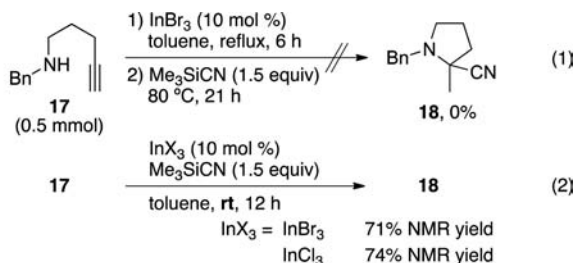
Scheme 3. Reaction of DMAD and Amines with Me<sub>3</sub>SiCN<sup>a</sup>

<sup>a</sup>Reaction conditions. First step: DMAD (0.6 mmol), amine (0.9 mmol), InBr<sub>3</sub> (0.06 mmol), toluene (1.2 mL), reflux, 6 h. Second step: Me<sub>3</sub>SiCN (0.9 mmol), 80 °C, 20 h. Isolated yields are shown. <sup>b</sup>Second step is 30 h. <sup>c</sup>Yield of **16** was determined by <sup>1</sup>H NMR analysis as the mixture with enamine intermediate **16'** due to decomposition of **16**. <sup>d</sup>Three days in the second step.

secondary amine, *N*-methylaniline, which is not compatible with a classic Strecker synthesis, the corresponding  $\alpha$ -aminonitrile **15** was obtained. This result implies that the pathway for the reaction with DMAD is different from that with inactivated alkynes, as shown in Scheme 2. In addition, the use of piperidine afforded the corresponding  $\alpha$ -aminonitrile **16** in a good yield. In contrast, when the reaction was carried out with *t*-butylamine, the enamine intermediate was obtained in a quantitative yield without the formation of cyanide addition products. In this case, it seemed that steric hindrance prevented the intermediate from undergoing a subsequent cyanosilylation.

On the other hand, for other unactivated internal alkynes or aliphatic amines as a substrate, the desired  $\alpha$ -aminonitriles were not detected at all. Thus, we next attempted to apply this protocol to intramolecular hydroamination. Recently, Hammond et al. reported the one-pot synthesis of  $\alpha$ -CN *N*-heterocycles from alkynylamines with  $\text{Me}_3\text{SiCN}$  using a copper(I) or a gold(I) catalyst under microwave conditions.<sup>7</sup> It was assumed that the reaction would proceed via the intramolecular hydroamination of alkynylamines, followed by the addition of  $\text{Me}_3\text{SiCN}$  to form  $\alpha$ -cyanated heterocycles. On the basis of this example, we anticipated that our indium catalytic system could also be applied to the reaction of 4-alkynylamines with  $\text{Me}_3\text{SiCN}$ .

To evaluate the initial intramolecular hydroamination and subsequent cyanosilylation of 4-alkynylamine **17** with  $\text{Me}_3\text{SiCN}$ , several screenings of the reaction conditions were conducted. On the basis of the optimal conditions of the three-component coupling reaction above, when the one-pot stepwise protocol was initially examined, no desired  $\alpha$ -cyanation product **18** was detected (eq 1). On the other hand, in the presence of  $\text{Me}_3\text{SiCN}$ ,

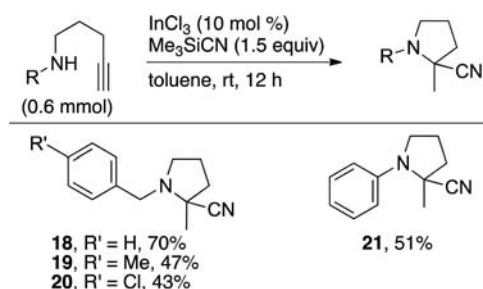


a similar one-pot reaction employing the indium catalyst at room temperature afforded the expected pyrrolidine **18** in a 71% NMR yield. Also, similar catalytic activity for this procedure was observed using  $\text{InCl}_3$ , which is more stable under air and is less expensive than  $\text{InBr}_3$  (eq 2).

Therefore, we chose  $\text{InCl}_3$  as the catalyst, and the intramolecular hydroamination/cyanosilylation of several 4-alkynylamines with  $\text{Me}_3\text{SiCN}$  was examined (Scheme 4). With the optimal conditions, the  $\alpha$ -CN pyrrolidine **18** could be isolated in a 70% yield. Reactions of secondary alkynylamines bearing benzylic *N*-substituents with  $\text{Me}_3\text{SiCN}$  afforded the corresponding products **19** and **20** in 47 and 43% yields, respectively. The substrate containing a phenyl-substituted nitrogen was also applicable to this reaction, although the yield of product **21** was slightly decreased to 51%.

To confirm the catalytic effect of the indium catalyst, several control experiments were then conducted. When phenylacetylene and 4-anisidine were treated with 10 mol % of  $\text{InBr}_3$  in toluene at 110 °C for 6 h, hydroamination proceeded to produce imine **22** in an 80% yield (eq 3). Next, when the imine intermediate **22** was treated with the optimal conditions at the

**Scheme 4.** Cyclization and Cyanation of 4-Alkynylamines with  $\text{Me}_3\text{SiCN}$ <sup>a</sup>



<sup>a</sup>Reaction conditions: substrate (0.6 mmol),  $\text{InCl}_3$  (0.06 mmol), toluene (1.2 mL), rt, 12 h. Isolated yields are shown.



second step, though no products were obtained in the absence of the catalyst, the corresponding  $\alpha$ -aminonitrile **12** was obtained in a 75% yield (eq 4). These results indicate that the indium catalyst was effective for both hydroamination and cyanation.<sup>8</sup>

In summary, we have demonstrated a one-pot preparation of quaternary  $\alpha$ -aminonitrile derivatives by an indium-catalyzed three-component reaction of alkynes, amines, and trimethylsilyl cyanide. The reaction proceeded via the hydroamination of an alkyne with a subsequent addition of trimethylsilyl cyanide. Since the hydroamination approach is considered to be an alternative route to access the ketimine as a Strecker intermediate, it would be a potentially powerful synthetic strategy for a variety of quaternary  $\alpha$ -aminonitriles as a complementary tool of a classic Strecker synthesis. Further substrate scope, asymmetric application, and other silicon-based nucleophilic versions of this transformation are now in progress.

## ■ ASSOCIATED CONTENT

### § Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00508.

Experimental procedures and characterization data (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: sakachem@rs.noda.tus.ac.jp.

### Notes

The authors declare no competing financial interest.

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(8) Since the indium salt showed catalytic activity for the cyanation of ketimine, we envisioned that the indium catalyst could also be acceptable for the typical Strecker reaction of a ketone. When acetophenone (0.6 mmol) and aniline (0.9 mmol) were treated with  $\text{InBr}_3$  (10 mol %) and  $\text{Me}_3\text{SiCN}$  (1.5 equiv) in toluene, as expected, the corresponding quaternary  $\alpha$ -aminonitrile **10** was obtained in a 96% yield.