

Cyanation of *N*-Acylhydrazones with Trimethylsilyl Cyanide Promoted by a Brønsted Base and a Lewis Acid

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Received: July 9, 2005; Accepted: September 8, 2005

Abstract: Cyanation of *N*-acylhydrazones using trimethylsilyl cyanide (TMSCN) proceeded well in the presence of an amine to afford the corresponding α -hydrazinonitriles in high yields. For less reactive substrates, the combined use of an amine and a catalytic amount of scandium triflate [Sc(OTf)₃] was effective to promote the reactions. The mechanistic study suggested that the amine worked as a Brønsted base.

Keywords: amines; cyanides; hydrazones; Lewis acids; nucleophilic addition; scandium

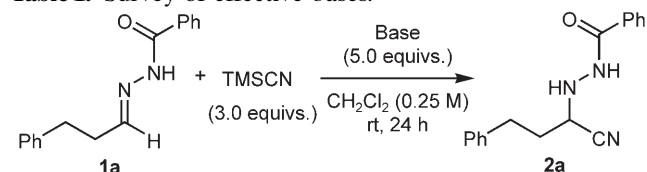
Cyanation of C=N double bonds is one of the most investigated reactions because it affords a variety of α -amino acid derivatives. Intensive studies have led to development of efficient reaction systems including catalytic enantioselective versions.^[1] Whereas preformed imines are used as substrates in most cases, several imines such as aliphatic aldehyde derivatives are often sensitive to hydrolysis. *N*-Acylhydrazones are advantageous as imine equivalents, since they can easily be prepared *via* condensation of the corresponding carbonyl compounds and acylhydrazines, can often be purified by simple recrystallization, and are stable at ambient temperature.^[2] The cyanation of *N*-acylhydrazones affords α -hydrazinonitriles, which can be converted into α -amino acids via an N–N bond cleavage^[3] and hydrolysis. α -Hydrazinonitriles are also an important class of compounds. They can be easily hydrolyzed to α -hydrazino acids, which consist of hydrazinopeptides and *N*-aminopeptides as pseudo amino acid analogues.^[4] It was reported that *N*-acylhydrazones reacted with various nucleophiles in the presence of Brønsted acids, Lewis acids, or Lewis bases to afford a wide variety of nitrogen-containing compounds.^[5] To the best of our knowledge, however, catalysis by Brønsted bases has not been covered before. Here, we report the first example of the cyanation of *N*-acylhydrazones promoted by a Brønsted base or the combination of a Brønsted base and a Lewis

acid catalyst. A mechanistic study to clarify the reaction pathway is also described.

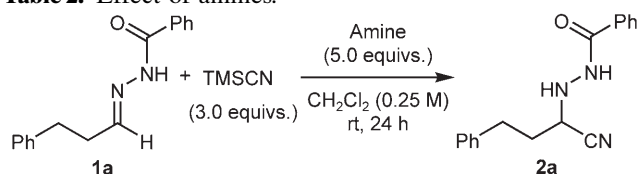
In the course of our investigations to examine effective Lewis base catalysts for cyanation of 3-phenylpropanal-derived *N*-benzoylhydrazone (**1a**) with trimethylsilyl cyanide (TMSCN), several Lewis bases (5.0 equivs.), which we found to be effective for allylation using allyltrichlorosilanes,^[6] were initially tested (Table 1). However, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine *N*-oxide, and phosphine oxides were ineffective (entries 1–5). On the other hand, triethylamine, which was less effective for the allylation, was found to promote the reaction well (entry 6). Triphenyl- or tributylphosphine, dimethyl sulfide, and triphenylarsine were also examined, but only tributylphosphine showed a slight activity resulting in low yield (entries 7–10).

Next, various amines were screened (Table 2). In general, aliphatic tertiary amines gave the desired product in high yields (entries 5, 6, 10 and 11), while primary or secondary amines were less effective (entries 1–4).^[7] 4-(Dimethylamino)pyridine (DMAP) and *N*-methylimidazole resulted in moderate to good yields, but pyridine

Table 1. Survey of effective bases.



Entry	Base	Yield [%]
1	DMF	<2
2	pyridine <i>N</i> -oxide	7
3	Ph ₃ P=O	1
4	Bu ₃ P=O	<5
5	DMSO	4
6	Et ₃ N	85
7	Ph ₃ P	<1
8	Bu ₃ P	20
9	Me ₂ S	2
10	Ph ₃ As	2

Table 2. Effect of amines.

Entry	Amine	Yield [%]
1	<i>i</i> -PrNH ₂	30
2	aniline	5
3	Et ₂ NH	63
4	pyrrolidine	C.M. ^[a]
5	Et ₃ N	85
6	<i>i</i> -Pr ₂ NEt	64
7	pyridine	10
8	DMAP	73
9	<i>N</i> -methylimidazole	59
10	TMEDA	88
11	DABCO	74

^[a] C.M. = complex mixture.

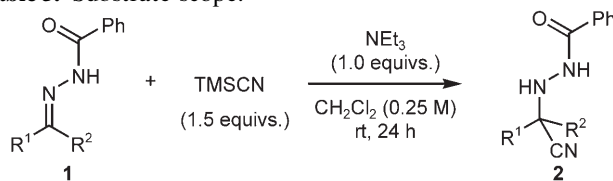
was poorly effective (entries 7–9). These results suggest that the basicities of the amines probably do not correspond to the promotional activities.^[8]

Further optimization was conducted after choosing triethylamine as a promoter. After several attempts, it was revealed that a slight excess amount of TMSCN and an equimolar amount of triethylamine were sufficient to promote cyanation of **1a** (Table 3, entry 1). We then investigated the substrate scope under these conditions. Aliphatic aldehyde-derived hydrazones reacted with TMSCN smoothly to afford the corresponding products in moderate to high yields (entries 1–7). A

sterically hindered pivalaldehyde derivative (**1f**) also reacted well (entry 7). It is noted that even aliphatic ketone-derived hydrazones were successfully converted into α,α -disubstituted hydrazinonitriles (entries 8 and 9). However, aromatic and α,β -unsaturated aldehyde-derived hydrazones remained almost intact resulting in recovery of the starting materials (entries 10–12).

In order to activate hydrazones with lower reactivities, the simultaneous addition of triethylamine and Lewis acid catalysts was next examined (Table 4). We previously reported that the cyanation of certain *N*-benzoylhydrazones was catalyzed by a Lewis acid,^[9] and Jacobsen et al. reported an enantioselective version using chiral rare earth metal complexes.^[10] To our delight, the combination of scandium triflate [Sc(OTf)₃, 0.20 equivs.] and triethylamine (1.0 equiv.) was found to promote the reaction (entry 2), while Sc(OTf)₃ (0.20 equivs.) alone afforded a trace amount of the product (entry 1).^[11] When the reaction was conducted for a longer time, considerable amounts of side products were formed and the yield of the desired product decreased (entry 3). The main side product proved to be a dehydrogenated product, [cyano(phenyl)methylene]benzohydrazide, whose structure was unambiguously determined by X-ray analysis.^[12] After several attempts, the formation of side products was effectively prevented by lowering the temperature (entries 4–6). Finally, a longer reaction time at –20 °C gave the best result (entry 7).

With the optimal conditions in hand, cyanation of less reactive *N*-acylhydrazones was tried (Table 5). Aromatic hydrazones with an electron-donating group at the *para* or *ortho* position reacted smoothly to afford the corresponding adducts in high yields (entries 2–4), while electron-withdrawing groups retarded the reaction (entry 5). α,β -Unsaturated substrates failed to give the products (entries 6 and 7). Significantly, alkyl aryl ketone-derivatives could be converted well to the products (entries 8–10). The combination of a catalytic

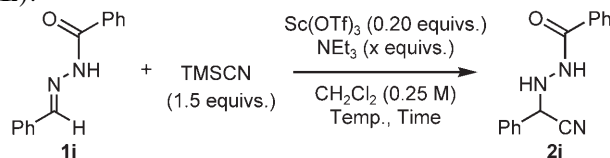
Table 3. Substrate scope.

Entry	R ¹	R ²	Substrate	Product	Yield [%]
1	PhCH ₂ CH ₂	H	1a	2a	77
2 ^[a]	PhCH ₂ CH ₂	H	1a	2a	69
3	<i>n</i> -C ₇ H ₁₅	H	1b	2b	97
4	<i>i</i> -Bu	H	1c	2c	87
5	<i>i</i> -Pr	H	1d	2d	92
6	<i>c</i> -Hex	H	1e	2e	82
7	<i>t</i> -Bu	H	1f	2f	62
8 ^[b]	PhCH ₂ CH ₂	Me	1g	2g	60
9	–(CH ₂) ₅ –	H	1h	2h	94
10	Ph	H	1i	2i	2
11	PhCH=CH	H	1j	–	N.R. ^[c]
12	PhC≡C	H	1k	–	N.R. ^[c]

^[a] 0.10 equivalents of NEt₃ were used for 168 h.

^[b] For 48 h.

^[c] N.R. = no reaction.

Table 4. Cyanation of benzaldehyde *N*-benzoylhydrazone (**1i**).

Entry	x [equivs.]	Temp. [°C]	Time [h]	Yield [%]
1	0	rt	14	2
2	1.0	rt	24	34
3	1.0	rt	48	10
4	1.0	0	24	52
5	1.0	–10	24	56
6	1.0	–20	24	68
7	1.0	–20	72	86

Table 5. Cyanation using Sc(OTf)₃ and NEt₃.

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1\text{C}=\text{N}-\text{NH}-\text{C}-\text{Ph} \\ \parallel \\ \text{R}^2 \end{array} + \text{TMSCN} \xrightarrow[\text{NEt}_3 (1.0 \text{ equiv.})]{\text{Sc(OTf)}_3 (0.20 \text{ equiv.})} \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1\text{C}=\text{N}-\text{NH}-\text{C}-\text{Ph} \\ \parallel \\ \text{R}^2 \\ \\ \text{CN} \end{array} $						
Entry	R ¹	R ²	Substrate	Time [h]	Product	Yield [%] ^[a]
1	Ph	H	1i	72	2i	86 (2)
2	(4-Me)C ₆ H ₄	H	1l	48	2l	91 ^[b]
3	(4-MeO)C ₆ H ₄	H	1m	48	2m	92 ^[b]
4	(2-MeO)C ₆ H ₄	H	1n	48	2n	87
5	(4-Cl)C ₆ H ₄	H	1o	48	2o	60 ^[b]
6	PhCH=CH	H	1j	24	—	C.M. ^[c]
7	PhC≡C	H	1k	48	—	C.M. ^[c]
8	Ph	Me	1p	48	2p	65 ^[b] (23) ^[b]
9	Ph	<i>n</i> -Bu	1q	48	2q	64
10	Ph	<i>i</i> -Pr	1r	48	2r	65
11 ^[d]	<i>t</i> -Bu	H	1f	24	2f	85 (60)

^[a] Isolated yield. The yield of the product obtained without using Sc(OTf)₃ (rt for 24 h) is given in parenthesis.

^[b] Yield determined by ¹H-NMR analysis (durene as an internal standard).

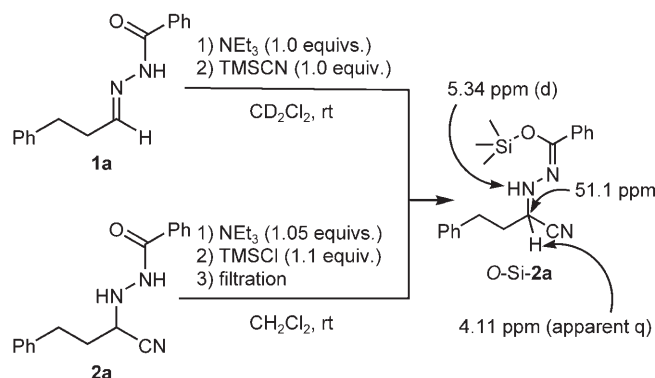
^[c] C.M. = complex mixture.

^[d] The reaction was carried out at rt.

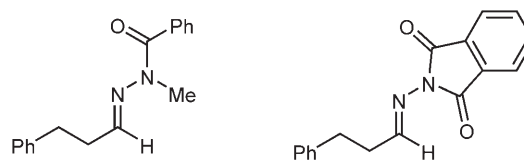
amount of Sc(OTf)₃ and one equivalent of NEt₃ accelerated the reaction rate more than NEt₃; the sterically hindered pivalaldehyde-derived *N*-benzoylhydrazone **1f** gave a high yield after 24 h (entry 11).

To get mechanistic insights into the reaction pathway, the reaction of **1a** with TMSCN (1.0 equiv.) and NEt₃ (1.0 equiv.) in deuterated dichloromethane at room temperature was monitored by ¹H NMR. As the reaction proceeded, new quartet and doublet signals gradually appeared at 4.11 ppm and at 5.34 ppm, respectively. After *ca.* 18 h, the reaction showed almost no change and was quenched by deuterated methanol (CD₃OD). These new two peaks were completely converted to a triplet at 4.08 ppm and a broad singlet at 5.32 ppm, respectively. ¹³C NMR analysis of the reaction was also conducted at the same time and a characteristic new peak emerged at 51.1 ppm, which was shifted to 52.8 ppm when quenched by CD₃OD. The initial product could be assigned to an *O*-trimethylsilylated cyanation product (*O*-Si-**2a**), whose structure was further confirmed by silylation of **2a** with TMSCl and NEt₃ (Scheme 1).

To account for the formation of *O*-Si-**2a** and that general Lewis bases such as phosphine oxides were ineffective for the current reaction, it is likely that triethylamine works as a Brønsted base. A possible mechanism is shown in Scheme 2. The reaction is initiated by deprotonation of the amide hydrogen of an *N*-acylhydrazone, while the oxy anion is trapped by TMSCN to release cyanide ion (CN[−]). Then the *O*-silylated substrate *O*-Si-**1** is attacked by CN[−] and protonated by the ammonium salt to form an *O*-silylated cyanation product (*O*-Si-**2**)

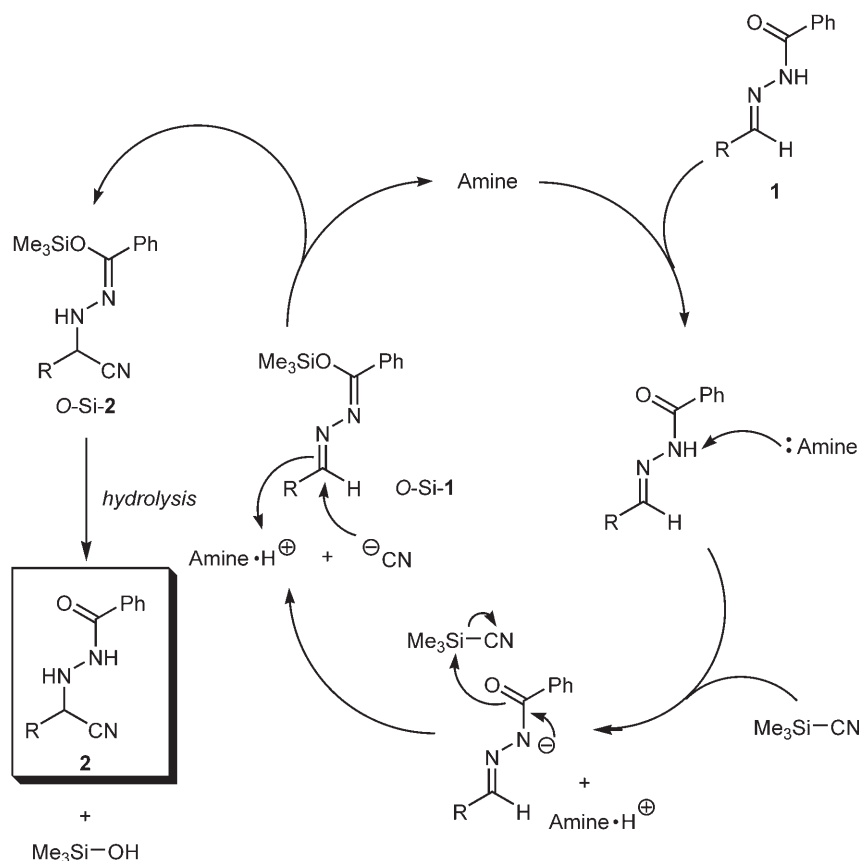
**Scheme 1.** Formation of the assumed intermediate *O*-Si-**2a**.

accompanied with regeneration of the amine. In fact, the amine can be catalytic as demonstrated in Table 3, entry 2. When *N*-acylhydrazones having no amide hydrogen (Figure 1) were subjected to the reaction, no product was obtained at all. This strongly supports that deprotonation of the amide hydrogen by a base is an indispensable process in this reaction.

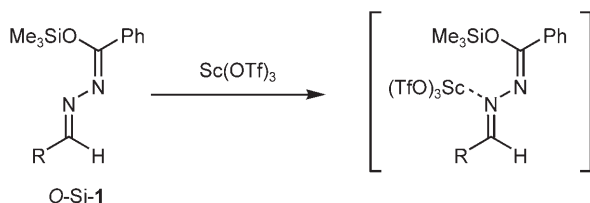
**Figure 1.** Unreactive *N*-acylhydrazones.

In the case of aromatic aldehyde- or ketone-derived substrates, the addition of a catalytic amount of Sc(OTf)₃ was necessary to promote the reaction. This might be ascribed to the fact that the addition of cyanide requires deconjugation of the stable intermediates *O*-Si-**1**. Thus, Sc(OTf)₃ might act as a Lewis acid to activate *O*-Si-**1** (Scheme 3). The higher reactivity of hydrazones with electron-donating substituents might be attributed to facile protonation or Lewis acid coordination of *O*-Si-**1**, which was possibly rate-determining.

In summary, we have found that aliphatic aldehyde- and ketone-derived *N*-acylhydrazones reacted with TMSCN to afford α -hydrazinonitriles in the presence of an amine. In addition, a catalytic amount of Sc(OTf)₃ was found to promote the reaction of less reactive *N*-acylhydrazones in cooperation with the amine base. A mechanistic study indicated that the amine worked as a Brønsted base, which initiated the reaction by abstraction of the amide hydrogen of the substrate. This method is a rare example of the cyanation of C=N bonds promoted by both Brønsted base and Lewis acid.^[13] Further investigations to develop enantioselective versions of this reaction are now in progress.



Scheme 2. Assumed reaction mechanism.



Scheme 3. Plausible role of $\text{Sc}(\text{OTf})_3$.

Experimental Section

General Procedure for Cyanation of *N*-Benzoylhydrazones **1** using NEt_3

To a mixture of **1** (0.25 mmol) and NEt_3 (0.25 mmol) in dichloromethane (1.0 mL) was added TMSCN (50 μL , 0.38 mmol) at room temperature. After stirring at room temperature for the indicated time, the reaction was quenched by adding saturated aqueous NH_4Cl (3.0 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (three times). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by preparative TLC on silica gel to afford product **2**.

General Procedure for Cyanation of *N*-Benzoylhydrazones **1** using NEt_3 and $\text{Sc}(\text{OTf})_3$

A mixture of **1** (0.25 mmol) and $\text{Sc}(\text{OTf})_3$ (24.6 mg, 0.050 mmol) in dichloromethane (1.0 mL) was stirred at room temperature for 15 min. NEt_3 (35 μL , 0.25 mmol) was added to the mixture and then the whole was cooled at -20°C . To the mixture was added dropwise TMSCN (50 μL , 0.38 mmol) at -20°C . After stirring at -20°C for the indicated time, the reaction was quenched by adding saturated aqueous NH_4Cl (3.0 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (three times). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by preparative TLC on silica gel to afford product **2**.

Acknowledgements

This work was partially supported by CREST, SORST, and ERATO, Japan Science and Technology Agency (JST), and Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Sciences (JSPS).

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- [12] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-277486. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax.: (internat.) +44 1223/336–033; e-mail: deposit@ccdc.cam.ac.uk].
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