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Synthesis of α -Amino Nitriles from Carbonyl Compounds, Amines, and Trimethylsilyl Cyanide: Comparison between Catalyst-Free Conditions and the Presence of Tin Ion-Exchanged Montmorillonite

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In the absence of catalysts, the three-component, one-pot synthesis of a-amino nitriles proceeded using various aldehydes and ketones together with amines and trimethylsilyl cyanide (TMSCN) in high yields under neat conditions at room temperature. The addition order of the reagents had a significant influence on the yields of the desired α -amino nitriles. In contrast, when tin ion-exchanged montmorillonite (Sn-Mont), prepared by the ion-exchange of sodium montmorillonite (Na-Mont) with a tin tetrachloride solution, was used as a catalyst, the reaction rates significantly increased compared with those without catalysts, and the range of the applicable carbonyl compounds was also extended: structurally diverse aromatic, aliphatic and heteroatom-containing carbonyl compounds, including sterically hindered ketones

Introduction

There is growing interest in the one-pot Strecker synthesis of a-amino nitriles from carbonyl compounds, amines and trimethylsilyl cyanide (TMSCN) [Equation (1)], because of the significant importance of a-amino nitriles in preparing a wide variety of amino acids, amides, diamines, and nitrogen-containing heterocycles.^[1]



A broad spectrum of catalysts has been developed to promote the Strecker reactions, such as: metal complexes,^[2] Lewis acids,^[3-11] solid acids,^[12-14] base catalysts,^[15] and organic catalysts,^[16] etc.^[17] These protocols often require not only the use of valuable reagents, but also involve long reac-

as well as aliphatic and aromatic amines, were converted into the desired α -amino nitriles in good to excellent yields with short reaction times under mild conditions. Sn-Mont showed a better catalytic activity than proton or other metal ion-exchanged montmorillonites, supported SnO₂ catalysts and the previously reported homogeneous or heterogeneous catalysts. The recovered catalyst was reused several times without loss of catalytic performance. Along with the expansion of the interlayer space of Sn-Mont, the strong Brønsted acid and Lewis acid nature of Sn-Mont derived from protons and SnO₂ nanoparticles present in the interlayers of Sn-Mont likely played important and cooperative roles in the high catalytic activity.

tion times and tedious workup procedures. Moreover, Lewis acid catalysts such as nickel,^[4] thallium,^[5] copper,^[6] rhodium,^[7] niobium,^[8] indium,^[9] and zinc^[10] salts are prone to rapid hydrolysis and consequent deactivation by water released during the course of the reaction and hence are not reusable, resulting in the production of large quantities of inorganic waste. To overcome these disadvantages, the development of heterogeneous catalyst systems has been focused on. However, in spite of the evident advantages of catalyst recovery and recycling, there have been only a few heterogeneous catalysts reported, these include: montmorillonite KSF,^[12] supported heteropolyacids,^[13] Fe₃O₄ nanoparticles,^[18] H₂SO₄/silica gel,^[14] Nafion SAC-13,^[19] and PVP-SO₂ complex.^[20] Although effective, these systems have drawbacks such as low activity or require large amounts of catalyst. Moreover, these catalytic systems (and catalyst-free^[21] conditions) are only efficient for the synthesis of α -amino nitriles from active aldehydes, and are not suitable for ketone substrates. Thus, an improvement in the catalytic activity and a reduction in the amount of heterogeneous catalyst required, is still highly desirable.

Most three-component Strecker reactions have been performed with aldehydes. In contrast, successful examples with ketones are very few and are normally carried out either in two steps involving initial imine formation, fol-

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lowed by cyanide addition,^[22] or are performed in a onepot synthesis under high-pressure conditions.^[23] Recently Khan^[24] reported $Fe(Cp)_2PF_6$ as a homogeneous catalyst for the reaction with ketones, whereas Olah used Ga(III) triflate and $(CH_3)_3SiOSO_2CF_3$ in dichloromethane.^[11,25] More recently, Jung and coworkers reported using the Strecker reactions with ketones; in this case the reaction was catalyzed by palladium(II) complex and required 24 hours.^[26] Thus, the aim of this study was to develop a mild, efficient, heterogeneous catalytic system for performing Strecker reactions that is particularly suitable for ketones.

Montmorillonite, a naturally occurring clay, is composed of stacked, negatively charged two-dimensional aluminosilicate layers that hold exchangeable cationic species - mostly sodium ions - in the interlayers.^[27] After either multivalent metal cations or protons are substituted for the sodium ions in the montmorillonite, which is designated as M-Mont (M = metal or H) in this paper, [28-32] the clay becomes acidic and has been utilized in various acid-catalyzed organic reactions.^[33] We recently found that Sn-Mont, prepared by the ion-exchange of Na-Mont with aqueous SnCl₄, contained nanoparticles of SnO2 intercalated between the silicate layers.^[34] It has also been found that Sn-Mont worked as an effective acidic catalyst for the Michael reaction,^[29] the cyanosilylation of carbonyl compounds,^[35] and for the reduction of carbonyl compounds with hydrosilanes.[36] Among the various metal ion-exchanged montmorillonites, Sn-Mont was considered to be the most acidic and thus most suitable for the silvlation of alcohols.^[37] Very recently, we reported that a very small amount of Sn-Mont could be used as a highly active catalyst for the cyanosilylation of sterically congested ketones.^[38] To further determine the scope and limitations of Sn-Mont for acid catalysis, it is important to examine the catalytic potential of Sn-Mont for organic reactions involving basic substrates such as amines that, unsurprisingly, decrease the intrinsic acidity of the catalyst. Therefore, we extended our studies to the onepot, three-component Strecker synthesis of α-amino nitriles from carbonyl compounds, amines, and TMSCN using Sn-Mont.

In the present study, we systematically investigated the one-pot synthesis of α-amino nitriles using carbonyl compounds (aldehydes and ketones), aromatic and aliphatic amines, and TMSCN, both in the presence of Sn-Mont and under catalyst-free conditions. In the absence of catalyst, a broad range of aldehydes, as well as a limited number of ketones, were successfully used. The reaction rates in the presence of Sn-Mont increased compared with those without the catalyst. Especially, it is striking that various types of ketones readily reacted with amines and TMSCN to give the α -amino nitriles. In addition, it was revealed that Sn-Mont showed a better catalytic performance when compared with the previously reported homogeneous and heterogeneous catalysts and, furthermore, Sn-Mont could be reused without loss of catalytic performance and simplified the workup procedure (no tedious chromatographic purification was needed in most cases).

Results and Discussion

One-Pot, Three-Component Synthesis of α -Amino Nitriles without Catalyst

Before starting the one-pot reactions using Sn-Mont as a catalyst, we first investigated the reactions of aldehydes without acidic catalysts under neat conditions. We observed a very interesting phenomenon that the addition order of the reagents directly influenced the yields. The reaction of o-tolualdehyde (1d), aniline (2a) and TMSCN in a 1:1:1.2 molar ratio was selected as a model reaction. As shown in Figure 1, when TMSCN was added to a mixture of 1d and 2a, the reaction proceeded very rapidly (15 min) and the yield of 2-(2-methylphenyl)-2-(phenylamino)acetonitrile (3d) was as high as 98% (Figure 1a). This addition process, in which TMSCN was added to a mixture of aldehyde and amine, was found to be the optimal procedure. Interestingly, when 2a was added to a mixture of 1d and TMSCN, the reaction proceeded relatively slowly and only half the starting reagents were transformed into 3d after 150 min (Figure 1b). The reaction concurrently gave the corresponding cvanohydrin trimethylsilyl ether (adduct of TMSCN to 1d) in about 8% yield based on ¹H NMR analysis, along with a trace amount of imine from the condensation of 1d and 2a.



Figure 1. Effects of the addition order of the reagents on the yield of the reaction of *o*-tolualdehyde (1d), aniline (2a), and TMSCN in the absence of catalyst at room temperature. (a) An optimal procedure: TMSCN was added to a mixture of 1d and 2a. (b) A sub-optimal procedure: 2a was added to a mixture of 1d and TMSCN.

The optimal and sub-optimal procedures for the one-pot synthesis of α -amino nitriles were compared using a series of aldehydes and amines under catalyst-free conditions at room temperature; the results are shown in Table 1. According to the optimal addition, all the reactions rapidly proceeded, and α -amino nitriles were isolated in 89 to 99% yields (odd entry numbers) except for entry 13 in which rapid condensation between tolualdehyde (1c) and *p*-bromoaniline (2c) produced a solid imine, followed by the relatively slow addition of TMSCN to the imine. Aromatic, benzylic and aliphatic amines were all suitable substrates for the reaction and gave good yields. Not only did the reac-



tions proceed smoothly to afforded good conversions, but the product isolation did not require any tedious chromatographic purification. Moreover, by using the optimal addition procedure, no cyanohydrin trimethylsilyl ether byproducts were detected.

Table 1. Comparison of the addition procedures for the one-pot synthesis of α -amino nitriles by the Strecker reactions of aldehydes, amines, and TMSCN in the absence of catalyst under neat conditions at room temperature.^[a]

	R ¹ —CHO + 1	H₂N• 2	- R ²	יד +	MSCN	neat, no c	r.t. ► at.		N ^{-R² 3}	
	H₂N-	┝┍	R R R	= H = CI = Br	2a 2b 2c		R ² = R ² =	<i>n-</i> butyl benzyl	2d 2e	
Entry	Aldehyde	A	mine		Produ	uct		Time (min)	Method ^[b]	Yield (%) ^[c]
1	сно	1a	2a		ÇN		3a	15	А	99
2	\bigcirc	1a	2a	Ć		~	3a	15	В	4
3	СНО	1b	2a		\sim^{c}	NN €) _{3b}	10	А	99
4 Me		1b	2a _N	leO	\$	H	3b	10	В	28
5		1c	2a			D	30	: 15	А	95
6	×9	1c	2a	Ĺ	Ĵ ŀ		30	: 15	В	6
7	СНО	1d	2a		CN 1		3d	I 15	А	98
8		1d	2a	C	X H	\sim	30	I 15	В	4
9	Сно	1e	2a				3e	20	А	91
10		1e	2a	Ĺ	X		3e	20	В	4
11	~ сно	1a	2b	•	ΓN [\mathbf{r}^{c}	3f	15	А	91
12	U	1a	2b	C		\sim	3f	15	В	4
13	сн о	1c	2c		ÇN (r 3g	30	А	95
14	\square	1c	2c	C	J	\sim	3g	30	В	5
15	~ сно	1c	2d	~		~	3h	10	А	89
16	\mathbf{V}	1c	2d 🔎	U	JH	• •	3h	10	в	0 ^[d]
17	~ сно	1a	2d	~		\sim	3i	10	А	90
18	V	1a	2d	C	JH	- `	3i	10	В	0 ^[d]
19	СНО	1a	2e	\sim		\sim	3j	15	А	91
20	V	1a	2e	U	JH	V	3j	15	В	39 ^[d]
21	СНО	1c	2e	~		\sim	, 3k	: 15	А	93
22	ノシ	1c	2e	人	J H	U	J _{3k}	15	В	34 ^[d]

[a] Aldehydes (1 mmol), amines (1 mmol), TMSCN (1.2 mmol), neat, room temperature. [b] A: optimal procedure; B: sub-optimal procedure (see the Experimental Section). [c] Isolated yields for the optimal procedure and ¹H NMR-based yields for the sub-optimal procedure. [d] The remaining aldehyde completely reacted with TMSCN to give the corresponding cyanohydrin trimethylsilyl ethers.

Following the sub-optimal procedure, however, the yields of the corresponding α -amino nitriles significantly decreased (Table 1, even entry numbers). For example, the one-pot reactions of benzaldehyde (**1a**) or its methyl-substituted analogues, aniline or its halogenated equivalent, and TMSCN proceeded very slowly (Table 1) and the yields were as low as 4–6%, with the exception that 4-methoxybenzaldehyde (**1b**), which gave a slightly better yield of 28% (entry 4). Notably, for the reactions with *n*-butylamine (**2d**), no corresponding α -amino nitriles were produced and the cyanohydrin trimethylsilyl ethers were formed exclusively (entries 16 and 18). For the one-pot reactions with benzylamine (**2e**), α -amino nitriles were produced in low yields, and the remaining aldehydes were completely transformed into the corresponding cyanohydrin trimethylsilyl ethers (entries 20 and 22).

For such simple three-component, one-pot reactions in the absence of catalysts, we wanted to address the question of why the order of addition of the starting reagents had such a significant impact on the yields of the target α amino nitriles shown in Figure 1 and Table 1. Scheme 1 shows the plausible reaction pathways that can be followed when adopting different orders of reagent addition. Following the optimal procedure, as soon as the aldehyde and amine are mixed, prompt condensation reactions of the aldehyde with the amine takes place to produce the corresponding imines, releasing $H_2O^{[39]}$ TMSCN addition to the imines can then occur, which is catalyzed by a trace amount of hydrogen cyanide included in the TMSCN or derived from the hydrolysis of TMSCN and water,^[40] followed by hydrolysis with water to give the α -amino nitriles (Scheme 1a).^[41] However, when amines, and especially anilines, are added to a mixture of aldehyde and TMSCN in the sub-optimal procedure, weakly basic anilines could coordinate to TMSCN to form hypervalent silicate intermediates,^[42,43] giving rise to significantly reduced levels of condensation with the aldehyde and leading to reduced yields of a-amino nitriles (Scheme 1b). Instead, the hypervalent silicate intermediates could react with aldehydes to give cvanohydrin trimethylsilyl ethers, though in poor yields.^[42] When primary aliphatic amines, which are more basic than anilines, are used, they may actually promote the nucleophilic addition of TMSCN to aldehydes through the formation of reactive hypervalent silicate intermediates (Scheme 1c) to predominantly give cyanohydrin trimethylsilvl ethers; this is similar to the catalytic use of tertiary or secondary amines such as Et₃N, or *i*Pr₂NH.^[42]



Scheme 1. Plausible reaction pathways for the three-component Strecker reactions in the absence of catalysts: (a) The optimal addition order; (b) the sub-optimal addition of anilines, and (c) the sub-optimal addition of aliphatic amines.

One-Pot Strecker Synthesis of α-Amino Nitriles with Sn-Mont Catalyst

The reaction of benzaldehyde (1a) and aniline (2a) with TMSCN in the presence of Sn-Mont was selected as a model. First, the reaction was performed in a range of solvents, as summarized in Figure 2. Among the solvents tested, dimethylformamide (DMF), toluene, and dichloromethane gave the product in poor yields of only 10-42%, whereas moderate yields were obtained when the reaction was performed in acetonitrile or even in water. More interestingly, when the reaction was performed with no solvent, the liquid substrate mixture suddenly solidified within 6 min, indicating the rapid formation of 2-phenyl-2-(phenylamino)acetonitrile (3a) in an extremely high yield of 96%(Table 2, entry 1). This indicated that the use of a solvent significantly retarded the Strecker reaction with Sn-Mont. Compared with the same reaction under catalyst-free conditions (Table 1, entry 1), the reaction with Sn-Mont was complete in less than half the time. Thus, neat conditions and a small amount of Sn-Mont (10 mg; Sn: 1.9 mol-%) are optimal for the synthesis of α -amino nitriles.^[44]



Figure 2. Solvent effects on the Strecker reactions catalyzed by Sn-Mont: benzaldehyde (1a; 1 mmol), aniline (2a; 1 mmol), TMSCN (1.2 mmol), Sn-Mont (10 mg; Sn: 1.9 mol-%), room temperature, 30 min for the reactions in various solvents, and 6 min under neat conditions.

Encouraged by these results, we continued to investigate the Strecker reactions with a wider variety of aldehydes and amines under neat conditions at room temperature. As shown in Table 2, a variety of aldehydes were condensed at room temperature with amines and TMSCN in a one-pot operation in the presence of a catalytic amount of Sn-Mont (10 mg; Sn: 1.9 mol-%) to afford the corresponding α amino nitriles in excellent yields. All the reactions proceeded faster than those without catalysts to give the expected products within very short reaction times (2-6 min). For comparison, the reactions reported in entries 1, 5, 7 and 8, which were conducted without Sn-Mont for 6 min, gave yields (in brackets) that were far lower than those obtained from reactions catalyzed by Sn-Mont. The present method works very effectively regardless of the electronic nature of the substituents on the benzene ring. Reactions with aliphatic amines also gave good results (entries 8-13).

Table 2. One-pot synthesis of α -amino nitriles by the Strecker reaction of aldehydes, amines, and TMSCN in the presence of Sn-Mont under neat conditions.^[a]

	R ¹ –CH 1	0+	H₂N − R ² 2	+ TMSCN	Sn-M neat	1ont ;, r.t.	► 3	
Entry	Aldehy	de	Amine	Produ	ict		Time (min)	Yield (%) ^[b]
1	1a		2a	3a			6	96 (57)
2	1b		2a	3b			6	97
3	1c		2a	3c			6	92
4	1d		2a	3d			6	94
5	1e		2a	3e			6	89 (21)
6	1a		2b	3f			6	90
7	1c		2c	3g			6	91 (18)
8	1c		2d	3h			6	95 (68)
9	1a		2d	3i			6	95
10	1a		2e	Зј			6	92
11	1c		2e	3k			6	91
12	CC H	^O 1d	2e		Ô	31	6	94
13		0 1f	2e		\bigcirc	3m	6	90
14	© C⊢	10 1g	2a		Ĵ	3n	2	93
15	S () CH	^O 1h	2a	s M M	Ĵ	30	3	92
16	КССН	0 1i	2e		Ô	Зр	3	95

[a] Aldehydes (1 mmol), amines (1 mmol), TMSCN (1.2 mmol), Sn-Mont (10 mg; Sn: 1.9 mol-%), neat, room temperature. [b] Isolated yields; the yields in brackets were obtained in the absence of Sn-Mont.

The Sn-Mont-catalyzed system was also applicable to acidsensitive heterocyclic aldehydes such as furfuraldehyde (1g), thiophenaldehyde (1h), and 4-pyridinecarboxaldehyde (1i) (entries 14–16). The results in Table 2 thus show that the present protocol has wide applicability for a range of aldehydes and amines.

Conventional heterogeneous and homogeneous catalysts such as metal salts, supported acids, montmorillonite KSF, and iodine are all effective in the one-pot reaction of 1a, 2a and TMSCN. However, these systems normally require large amounts of catalysts, long reaction times, and/or high reaction temperatures to obtain **3a** (see Table S1 in the Supporting Information). In contrast, the Sn-Mont-catalyzed Strecker reactions smoothly proceeded at room temperature with a very small amount of Sn-Mont (10 mg; Sn: 1.9 mol-%) in only 6 min. The turnover frequency (TOF) of 505 h^{-1} was clearly higher than those of the previously reported catalysts (1.1-376 h⁻¹) (see Table S1 in the Supporting Information). At the same time, the reaction rate (960 mmol h^{-1} g_{cat}^{-1}), based on the weight of Sn-Mont, was also far higher than those $(0.2-450 \text{ mmol h}^{-1} \text{ g}_{cat}^{-1})$ for the previously reported catalysts (See Table S1 in the Supporting Information).



Inspired by the results obtained with aldehydes, we then investigated whether these simple protocols were also valid for the Strecker reaction with ketones. To reveal any differences in the catalytic activity among the heterogeneous catalysts, the one-pot reaction of propiophenone (4a), 2a, and TMSCN was used as a model, and the reaction was conducted under neat conditions as shown in Table 3. No formation of 2-phenyl-2-(phenylamino)butyronitrile (5a) was observed even when the reaction time was extended to 15 h in the absence of a catalyst (entry 1), indicating that ketones were much less reactive than aldehydes under these conditions. Sn-Mont (10 mg; Sn: 1.9 mol-%), however, gave 5a in an 84% isolated yield within three hours (entry 2). The TOF reached 67.4 h^{-1} , which is higher than that obtained with $Ga(OTf)_3$ (3.92 h⁻¹)^[25] and comparable to that using $Fe(Cp)_2PF_6$ (57 h⁻¹)^[24] as homogeneous catalysts.

Table 3. Strecker reaction of propiophenone (4a), 2a, and TMSCN with various catalysts under neat conditions.^[a]

	+ 2a + TM:	SCN <u>cat.</u> r.t., neat	
Entry	Catalyst	Time (h)	Yield (%) ^[b]
1	No catalyst	15	0
2	Sn-Mont	3	84
3	Na-Mont	3	0
4	Sn(OH) ₄	3	0
5	SnO ₂	3	0
6 ^[c]	Sn-MCM-41	3	0
7 ^[d]	Al-MCM-41	3	0
8	SnO ₂ /silica	3	7.2
9	SnO ₂ /MCM-41	3	22
10	SnO ₂ /SiO ₂ -Al ₂ O ₃	3	37
11	Al-Mont	3	62
12	H-Mont	3	50
13	K-10	3	51
14	Ti-Mont	3	39
15	Fe-Mont	3	26
16	Cu-Mont	3	12

[a] 4a (1 mmol), 2a (1 mmol), TMSCN (1.2 mmol), catalyst (10 mg), neat, room temperature. [b] Isolated yields. [c] Si/Sn = 20. [d] Si/A1 = 20.

In contrast, when the reaction was performed with pristine Na-Mont, Sn(OH)₄ prepared from SnCl₄ with aqueous NH₃, or crystalline SnO₂, almost no reaction occurred (Table 3, entries 3-5). The Sn- and Al-doped MCM-41 materials with high specific surface areas and ordered mesopores (entries 6 and 7), which have been applied in a diverse range of reactions,^[45] also had no catalytic activity. Use of various supported SnO₂ catalysts, such as SnO₂/SiO₂, SnO₂/ MCM-41 and SnO₂/SiO₂-Al₂O₃, also resulted in very poor yields (7.2-37%, entries 8-10). Al-Mont (62%) and H-Mont (50%), as well as commercially available montmorillonite K-10^[46] (51%), were effective for this reaction and gave the expected product in moderate yields (entries 11-13). The catalytic activities of Ti-Mont^[47,48] (39%), Fe-Mont^[31] (26%) and Cu-Mont^[32] (12%) under the same conditions were low (entries 14-16). Similar trends in the acid catalysis were also observed for the silylation of alcohols^[37] and the cyanosilylation of ketones^[38] using various heterogeneous catalysts.

To demonstrate the practical applicability of Sn-Mont, a series of Strecker reactions was performed with different ketones at room temperature. For comparison, the reactions were also conducted without catalyst; the results are listed

Table 4. One-pot synthesis of α -amino nitriles from various ketones, amines, and TMSCN under neat conditions, either catalyzed by Sn-Mont or performed without catalyst.^[a]

	0 L		3	TMSCI	cat	_	NC. N	H - R ³	
	$R^1 R^2 T$		<u>2</u> - K ' 2	TWOOL	neat,	r.t.	$R^1 \mathbf{X}_{\mathbf{F}}$	₹ ²	5
Entry	Ketone		Amine	Pro	oduct		Cat. ^[b]	Time (h)	Yield (%) ^[c]
1	Å	4b	2a			5b	А	3	84
2	$\int \int$	4b	2a	\mathcal{I}	\smile	5b	В	15	12
3 4	$\rightarrow^{"}$	4c 4c	2a 2a		\neg	5c 5c	A B	1 15	83 12
5	Å	4d	2a		\\	5d	А	0.2	96
6	\sum_{α}	4d	2a	Ť Ĥ		5d	В	15	95
7	Å	4e	2a	$\sum_{i=1}^{n}$		5e	A	0.2	94
8	\sim	4e	2a	NC		5e	в	15	91
9 10		4f ⊿f	2a 2a			5f 5f	A B	0.75	96 96
11		4n	2a	NC		50	A	1	92
12	Man	4g	2a _M	Ĵ	∼ _N -<∠∕	5g	В	15	24
13		4h	2a _F			5h	А	4	63
14	T)	4h	2a	U		5h	В	15	0
15	Å	4i	2a		=\</td <td>5i</td> <td>А</td> <td>3</td> <td>66</td>	5i	А	3	66
16	Br	4i	2a E			5i	В	15	0
17		4a	2a	NC		5a	А	3	84
18	C ĭ	4a	2a			5a	В	15	0
19	ക്	4j	2a	\sim	×	5j	А	3	91
20	MeO	4j	2a _{Me}		н	5j	В	15	93
21	ſ∧ [™]	4k	2a	\sim		5k	А	3	89
22	Me	4k	2a №		н	5k	В	15	30
23	Ŕ	4f	2b		- (~)- ci	51	A	0.75	95
24	<u>م</u>	4f	2b 1			51	в	15	89
25 26		4f	2c		- Br	5m	A	0.75	99 05
20	o o	41	20 .	NC.HN	-Ph	500	D	15	90 70[[]
27		41] 41	2a 2a	$\hat{\mathbb{O}}^{\times}$		on 5n	B	4 15	78 ¹³ 9
20[0]		4m	20	NC	^{>h}	50	∆[e]	8	76 ^[1]
20 ^[d]	\bigcirc	4m	2a 2a			50 50	B	15	0
31[9]		4n	22	NC, H	N-Ph	5n	A[e]	10	45[f]
32 ^[g]	(11)	4n	2a		$\hat{\mathbb{O}}$	5p	В	15	0
33 ^[d]	~~~~	4o	2a	NC HM	N-Ph	5q	A ^[e]	10	60 ^[f]
34 ^[d]	UU) ₄₀	2a	\bigcirc	(\mathbf{D})	5q	В	15	0

[a] Ketones (1 mmol), amines (1 mmol), TMSCN (1.2 mmol), neat, room temperature. [b] A: use of Sn-Mont (10 mg; Sn: 1.9 mol-%), B: without catalyst. [c] Isolated yield. [d] Ketone (1 mmol), **2a** (1.5 equiv.), TMSCN (3 equiv.), 60 °C. [e] Sn-Mont (20 mg; Sn: 3.8 mol-%). [f] The main by-products were cyanohydrin trimethyl-silyl ethers. [g] Ketone (1 mmol), **2a** (2 equiv.), TMSCN (4 equiv.), 80 °C.

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in Table 4. Interestingly, even in the absence of catalyst, several reactions with the cyclic ketones 4d and 4e, acetophenone (4f), 4-methoxypropiophenone (4j) (entries 6, 8, 10 and 20), and the halogen-substituted anilines (entries 24 and 26) proceeded smoothly, although they required relatively long reaction times of 15 h to reach completion. In other cases, poor yields (9–30%) were observed for the reaction with linear aliphatic ketones (entries 2 and 4), 4-methylpropiophenone (4k; entry 22), and chalcone (4l; entry 28) under catalyst-free conditions. Moreover, bromoacetophenones 4h and 4i (entries 14 and 16), 4a (entry 18), and the more sterically bulky ketones such as 4m, 4n, and 4o, gave no products in the absence of catalyst even after 15 h (entries 30, 32, and 34).

In the presence of Sn-Mont, the reaction outcomes were greatly improved compared to those without catalysts. Various aliphatic and aromatic ketones, regardless of differences in the electronic characters and steric bulk, smoothly reacted with aniline and TMSCN to give the corresponding products in fair to excellent yields after short reaction times (0.2-4 h). For instance, linear aliphatic ketones [5-nonanone (4b) and 3.3-dimethylbutan-2-one (4c)] were selectively converted into the corresponding α -amino nitriles with good yields of 84% and 83% in 3 h and 1 h, respectively (Table 4, entries 1 and 3). Cyclopentanone (4d) and cyclohexanone (4e) both rapidly underwent the condensation within 0.2 h in almost quantitative yields (entries 5 and 7). The reaction rates were far higher than those observed in reactions performed without catalyst. The introduction of a methoxy group to the para-position of 4f did not significantly change the reaction rate (entries 9 and 11), whereas a bromo-substituent at either the *meta* or *para* position resulted in the poorer yields of 63 and 66% yields of the α -amino nitriles, respectively, along with concurrent ketimine formation (entries 13 and 15). The Strecker reactions with halogenated anilines catalyzed by Sn-Mont were also accelerated when compared with those in the absence of catalyst (entries 23– 26). Chalcone (41) was also suitable for the reaction, and afforded the product in 78% yield (entry 27). Sterically hindered ketones, such as benzophenone (4m), 9-fluorenone (4n) and 2-benzoylnaphthalene (4o), also reacted with 2a and TMSCN to give the corresponding products in good yields, although the reactions proceeded relatively slowly (entries 29, 31, and 33). In entries 27, 29, 31, and 33, the main side products were the cyanohydrin trimethylsilyl ethers, i.e. the adducts of TMSCN to the ketones. Except for these cases, no cyanohydrins were produced in any of the other reactions reported in Table 2 and Table 4. It can be concluded that Sn-Mont provides the best catalytic activity for the one-pot Strecker reactions and that this catalyst can be applied in the reaction of a broad range of aldehydes, ketones and aromatic amines.

In contrast to the reactions with aromatic amines, the products of reactions of ketones with TMSCN and aliphatic amines, such as *n*-butylamine (**2d**), benzylamine (**2e**) and piperidine, were exclusively cyanohydrin trimethylsilyl ethers (TMSCN addition products to ketones) instead of α -amino nitriles. The direction of the overall reaction depends

on the relative rates of the two pathways; the addition of amines to ketones (hemiaminal/imine formation) or TMSCN addition to ketones (cyanohydrin formation).^[25] With aromatic amines such as aniline, in the presence of Sn-Mont, the imine formation is far faster than that of cyanohydrin, preferentially producing α -amino nitrile. However, with aliphatic amines and aromatic ketones, the more basic aliphatic amines act as homogeneous base catalysts to promote the nucleophilic addition of TMSCN to ketones to provide the cyanohydrin derivatives,^[42] the formation rate of which is much higher than that of the corresponding imine from ketones and aliphatic amines catalyzed by Sn-Mont.

In the Sn-Mont-catalyzed Strecker reactions, the solid catalysts were easily recovered from the reaction mixture by filtration and could be reused at least four times without any obvious loss of catalytic activity in the reaction with **4f**, **2a** and TMSCN (Figure 3). In addition, Sn-Mont can be stored in a glass vial under ambient conditions for six months without any decrease in catalytic activity.



Figure 3. Reusability of Sn-Mont for the reaction with **4f**, **2a**, and TMSCN.

Reaction Mechanism for the One-Pot Strecker Reactions in the Presence of Sn-Mont

One of the important characteristics of montmorillonites is the ability to intercalate various organic molecules into the interlayer spaces, resulting in an increase in the interlayer distance (see the Supporting Information). Indeed, the basal spacing of Sn-Mont expanded from 1.30 to 2.51 nm when Sn-Mont was soaked with acetophenone (4f) for 10 min, as confirmed by XRD analysis (Figures 4a and b). The total expansion was about 1.21 nm, which confirms the intercalation of 4f into the layered Sn-Mont. The possibility that Sn-Mont-intercalated 4f could react with 2a and TMSCN was supported by the observation that the mixture completely solidified after stirring for 20 min, which implies the formation of 5f. Also, the basal spacing of Sn-Mont was found to decrease to 2.04 nm compared with that of the 4fintercalated Sn-Mont (Figure 4c). 4f was completely consumed and not included in the final product. Moreover, mechanical mixing of the product 5f and Sn-Mont by grinding with a mortar did not increase the basal spacing of Sn-Mont, as shown in Figure 4d. After the reaction, the basal spacing of the recovered Sn-Mont readily reverted to that of the original Sn-Mont by washing with dichloromethane, which removed the products, indicating that the layered structure of Sn-Mont was maintained during the reaction (Figure 4f). Together, these results support the proposal that **4f** intercalates into the interlayers of Sn-Mont during the reaction with amine and TMSCN. The finding also indicates that the catalytically active sites of Sn-Mont exist in the interlayers. Similar observations concerning expanded basal spacing of Sn-Mont upon one-pot Strecker reactions were also observed with other ketones (see Figure S3 in the Supporting Information).



Figure 4. XRD patterns of (a) Sn-Mont, (b) Sn-Mont intercalating 4f, (c) Sn-Mont after one-pot reaction of 4f, 2a, and TMSCN, (d) a mechanically mixed sample of Sn-Mont and α -amino nitrile 5f, (e) α -amino nitrile 5f, and (f) the recovered Sn-Mont.

The presence of the Brønsted and Lewis sites in Sn-Mont was confirmed by FTIR spectroscopy after pyridine adsorption. As shown in Figure 5a, fresh Sn-Mont showed no absorption peaks between 1400 and 1600 cm⁻¹. Upon contact with pyridine (Figure 5b), Sn-Mont exhibited a band at 1548 cm⁻¹, which is clearly due to the pyridinium ions, showing that Sn-Mont has Brønsted acid sites that are strong enough to protonate pyridine. Treatment of Na-Mont with pyridine did not gave rise to any adsorption band at 1548 cm⁻¹.^[49] Besides the Brønsted acidity, the formation of a Lewis acid-type adduct with pyridine was observed at 1455 cm⁻¹.^[50,51] A stronger adsorption band at 1490 cm⁻¹ may result from the interaction of both Lewis and Brønsted acid sites on Sn-Mont with pyridine.^[50]

Considering the XRD and IR findings described above, the efficient catalysis by Sn-Mont of the one-pot Strecker reactions can be related to the facile and reversible expansion of the interlayer spaces and to the strong Brønsted and Lewis acid sites in the montmorillonite interlayers. The strong acid sites interact and activate carbonyl compounds,



Figure 5. FTIR spectra of (a) Sn-Mont and (b) Sn-Mont after pyridine adsorption.

and enable the iminium intermediate to be generated by attack of an amine. The intermediate then undergoes attack by TMSCN at the carbon–nitrogen double bond, which is followed by hydrolysis with water to afford the a-amino nitrile (Scheme 2).



Scheme 2. Proposed mechanism for the one-pot synthesis of α -amino nitriles in the presence of Sn-Mont.

Conclusions

On the basis of the observations and results described above, α -amino nitriles can be easily obtained in excellent yields by simply mixing aldehydes as well as some ketones, amines, and TMSCN without acidic catalysts under neat conditions. The order of addition of the reagents, however, strongly affects the one-pot condensation.

The addition of Sn-Mont results not only in significant increases in reaction rates, especially in the case of ketones, but also extends the applicability of the reaction to a wide range of substrates, including several sterically hindered ketones. Compared with the previously reported protocols, the Sn-Mont catalyst system has several merits, such as: (1) operational simplicity, (2) short reaction times, and (3) the very small amount of catalyst required. Furthermore, Sn-Mont is easy to prepare, environmentally sound, nontoxic, noncorrosive, water-tolerant, and reusable. Our method avoids not only the use of easily hydrolyzed, expensive, or toxic Lewis acids, but also eliminates the need for tedious chromatographic separation and consequent loss of products during the purification. In most cases, the products are obtained in excellent yields with high purity.

Experimental Section

Instruments: ¹H and ¹³C NMR spectra were recorded at 500 MHz and 126 MHz, respectively, with a JEOL a500 NMR spectrometer; samples were dissolved in CDCl₃. The ¹H NMR chemical shifts were determined relative to the internal tetramethylsilane (δ = 0.0 ppm). The ¹³C NMR chemical shifts were determined relative to the internal tetramethylsilane ($\delta = 0.0$ ppm) or to the ¹³C NMR signal of CDCl₃ (δ = 77.0 ppm). The coupling constants (J) are given in Hz. Software used to processes the NMR data was from MestRenova (Mestrelab Research S. L.). X-ray powder diffraction patterns were collected with a Rigaku Multiflex instrument using $Cu-K_{\alpha}$ ($\lambda = 0.15406$ nm) radiation at 40 kV and 40 mA. The BET surface area, pore diameter, and pore volume of the materials were determined by a multi-point N₂ adsorption-desorption method at liquid N₂ temperature (77 K) with a Belsorp-mini instrument (BEL JAPAN, Inc). The IR spectra were measured with a JASCO IR-630 spectrophotometer (NaCl, film). High-resolution mass spectra were obtained with a JEOL GCmate (EI) mass spectrometer. Melting points were measured in open capillaries with an electrothermal model IA 9100 digital melting point apparatus. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel; plates were visualized under short-wavelength UV light (254 nm).

Reagents: Sodium montmorillonite (Na-Mont) was supplied by Kunimine Industry Co., Ltd., as Kunipia F (Na, 2.69; Al, 11.8; Fe, 1.46; Mg, 1.97%. Cation-exchange capacity = 1.19 mequiv g⁻¹). Na-Y (Si/Al = 3.5), SiO₂ (CARiACT Q-3) and SiO₂-Al₂O₃ (JRC-SAL-2, Al₂O₃ = 13.75%) as catalyst supports were supplied by Tosoh Corporation, Fuji Silysia Chemical, Ltd., and the Catalysis Society of Japan, respectively. All organic chemicals were purchased from commercial sources [Toyko Chemical Industry or Kanto Chemical (reagent grade)] and used without purification, except for benzaldehyde, which was purified by distillation. Silica gel 60 (70–230 mesh, ASTM) was used for column chromatography and was obtained from Merck Japan Limited.

Preparation of Sn-Mont: Sn-Mont was prepared according to our previously reported protocol;^[36] Na-Mont (8 g) was ion-exchanged with aq. SnCl₄·5H₂O (0.3 M, 80 mL) at r.t. for 2 h, and the exchange process was repeated. The collected clav was then washed with H₂O $(2 \times 80 \text{ mL})$, with a mixture of H₂O (40 mL) and MeOH (40 mL) 6 times, and with absolute methanol (80 mL). Finally Sn-Mont was dried in vacuo (0.5 Torr) at r.t. for 12 h, followed by grinding in a mortar with a pestle. The powder was passed through a 60-mesh screen and stored in a general glass bottle under ambient conditions. XRD analysis of Sn-Mont showed that the layered structure was maintained after the ion-exchange, with a basal spacing of 0.34 nm (see Figure S1 in the Supporting Information). According to the nitrogen sorption data, the specific surface area significantly increased from 12 m²g⁻¹ for Na-Mont to 280 m²g⁻¹ for Sn-Mont (see Figure S2 in the Supporting Information). Elemental analysis of Sn-Mont by inductively coupled plasma (ICP) showed the degree of exchange for the Na cations in Sn-Mont was 97.1%. The Sn content of Sn-Mont is 22.9 wt.-%.

Preparation of SnO₂/MCM-41, SnO₂/SiO₂ and SnO₂/SiO₂–Al₂O₃: These composite catalysts were prepared by the direct impregnation method. MCM-41 (1 g) was added to aq. SnCl₄·5H₂O (8.2×10^{-2} M, 30 mL). The obtained slurry was stirred at r.t. until the water was completely evaporated to afford a white solid, which was then dried under vacuum for 6 h to give SnO₂/MCM-41 (Sn, 22.9 wt.-%). The same treatment using SiO₂ (Q-3) and SiO₂-Al₂O₃ (JRC-SAL-2) afforded SnO₂/SiO₂ (Sn, 22.9 wt.-%) and SnO₂/SiO₂-Al₂O₃ (Sn, 22.9 wt.-%), respectively.

Preparation of Other Control Catalysts: Fe-Mont,^[30,36,37] Sn-MCM-41 (Si/Sn = 20)^[38] and Al-MCM-41 (Si/Al = 20)^[38] were prepared according to our previous procedures. H-Mont,^[52] Al-Mont,^[52] Ti-Mont,^[47] and Cu-Mont^[32] were synthesized according to the ion-exchange methods reported by Prof. Kaneda.

IR Measurements of Sn-Mont with Pyridine Adsorption: The IR spectra of the pyridine-adsorbed Sn-Mont were obtained at r.t. in the transmission mode with a JASCO IR-630 spectrophotometer. Sn-Mont (0.1 g) was treated with pyridine (1 mmol) for 1 h. The excess pyridine was removed by heating the sample at 150 °C in vacuo for 5 h. The pyridine-adsorbing Sn-Mont was mixed with KBr (3 mg Sn-Mont and 100 mg KBr) and then pressed into a disc (10 mm diameter). The IR spectrum of Sn-Mont after heating in vacuo at 150 °C for 5 h was also obtained using a KBr pellet.

One-Pot Synthesis of a-Amino Nitriles under Catalyst-Free Conditions: (a) Optimal Procedure: 1a (1 mmol) and **2a** (1 mmol) were added to a flask and the mixture was stirred at r.t. for 5 min. TMSCN (1.2 mmol) was then added to the mixture, which was vigorously stirred. After 15 min, the stirring bar was removed and the mixture was washed with dichloromethane. The combined solution was evaporated under reduced pressure to give the crude products. Further purification was carried out by rinsing the products with excess hexane, followed by evaporation of the residual hexane^[25] to afford 2-phenyl-2-(phenylamino)acetonitrile **3a** (206 mg, 99%) as a white solid.

(b) Alternative Procedure: 2a (1 mmol) and TMSCN (1.2 mmol) were added to a flask and the mixture was stirred at r.t. for 5 min. 1a (1 mmol) was then added to the mixture, which was vigorously stirred for 15 min. The yield (4%) was determined by ¹H NMR spectroscopy.

Typical Procedure for the One-Pot Synthesis of a-Amino Nitriles Catalyzed by Sn-Mont: 4a (0.103 mL, 1 mmol) and 2a (0.091 mL, 1 mmol) were added to a 30-mL flask containing Sn-Mont (10 mg; Sn: 1.9 mol-%) that had been heated in vacuo at 120 °C for 1 h. The mixture was vigorously stirred and TMSCN (0.160 mL, 1.2 mmol) was added to the mixture at 25 °C in a thermocontrolled water bath. After completion of the reaction (monitored by TLC), the catalyst was removed by filtration through a Celite plug, which was washed with dichloromethane, and the combined solution was evaporated under reduced pressure to obtain the crude product. Further purification was carried out by rinsing the products with excess hexane,^[25] followed by evaporation of the hexane to afford 2phenyl-2-(phenylamino)butyronitrile (5a; 199 mg, 84%) as a white solid. Products in entries 1 and 30 of Table 4 were purified by silica chromatography (hexane/ethyl acetate). The products were identified by comparison with reported IR, MS, melting points, and ¹H and ¹³C NMR spectroscopic data as shown in the Supporting Information.

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

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