Facile Synthesis of α-Amino Nitriles Using Lanthanide Triflate as a Lewis Acid Catalyst

Shū Kobayashi,* Haruro Ishitani, Masaharu Ueno

Department of Applied Chemistry, Faculty of Science, Science University of Tokyo (SUT), Kagurazaka, Shinjuku-ku, Tokyo 162

Fax 3-3260-4726

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Abstract: In the presence of a catalytic amount of lanthanide triflate, imines reacted with cyanotrimethylsilane (TMSCN) to afford α-amino nitriles in excellent yields. Although some imines are difficult to prepare and purify, three-component reactions of aldehydes, amines, and TMSCN proceeded smoothly. Effects of water in these reactions and application to asymmetric synthesis are also discussed.

α-Amino nitriles are useful intermediates for the synthesis of amino acids[1] and nitrogen-containing heterocycles such as thiadiazoles, imidazole derivatives, etc.[2] Use of cyanotrimethylsilane (TMSCN) instead of HCN as a cyano anion source provides promising and safer routes to these compounds.[1] The synthetic routes to α-amino nitriles using TMSCN are divided into two categories: the reactions of O-silylated cyanohydrines (prepared from aldehydes and TMSCN) with amines,[3] and the reactions of imines with TMSCN.[4] While these methods have both merits and demerits, use of a Lewis acid is one of keys to performing the reactions efficiently in both cases. Recently, we have found a new type of Lewis acid, lanthanide triflates (Ln(OTf)$_3$), which are stable Lewis acids in water and are excellent catalysts in several synthetic reactions.[5] Moreover, the triflates are quantitatively recovered after the reactions are completed and can be reused. In the course of our investigations to develop useful reactions using Ln(OTf)$_3$ as a catalyst, we planned to use Ln(OTf)$_3$ in the above α-amino nitrile synthesis. Between the two main preparation methods, we focused on the reactions of imines with TMSCN, mainly due to the ease of their application to asymmetric synthesis.

First, *N*-benzylidenediphenylmethylamine was treated with TMSCN in the presence of 10 mol% Yb(OTf)$_3$ in dichloromethane at 0 °C. The reaction proceeded smoothly to afford the corresponding α-amino nitriles in a 99% yield. We then examined other typical imines and the results are summarized in Table 1. In all cases, the desired α-amino nitriles were obtained in high yields.

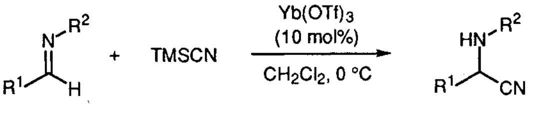
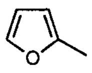
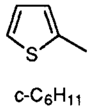


Table 1. Yb(OTf)$_3$-Catlyzed Reactions of Imines with TMSCN

Entry	R^1	R^2	Yield/%
1	Ph	Ph$_2$CH	99
2	Ph	p-ClPh	quant
3		Ph	94
4		Ph	97
5	c-C$_6$H$_{11}$	Ph$_2$CH	quant

In the reactions of imines, one drawback is their instability. Many imines are hygroscopic, unstable at higher temperatures, and difficult to purify by distillation or column chromatography. It is desirable from a synthetic point of view that imines, generated *in situ* from aldehydes and amines, immediately react with TMSCN and provide α-amino nitriles in a one-pot reaction.[6] However, most Lewis acids can't be used in this reaction because they decompose or deactivate in the presence of the amines and water that exist during imine formation. On the other hand, it was very recently reported that α-amino nitriles were prepared by simply mixing aldehydes, amines, and TMSCN without any catalysts.[7] The authors insisted that water which was produced in the imine formation catalyzed the reactions. We thought water would react with TMSCN immediately to form HCN and that HCN would react with the imines to give α-amino nitriles in these reactions.[8] Because the existence of water during the reactions caused the HCN problem, we carried out the reactions in the presence of a dehydration reagent such as MS 4A. It was found that the reaction of an aldehyde, an amine, and TMSCN proceeded sluggishly in the presence of MS 4A without any catalysts. On the other hand, the reaction proceeded smoothly in the presence of 10 mol% Yb(OTf)$_3$ under the same reaction conditions. We then carried out the reactions of several aldehydes, amines, and TMSCN in the presence of Yb(OTf)$_3$ and MS 4A, and the results are summarized in Table 2. In all cases, the three-component reactions proceeded smoothly to afford the corresponding α-amino nitriles in high yields.

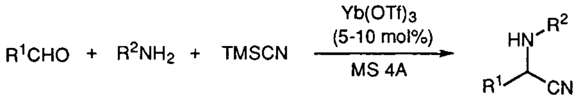


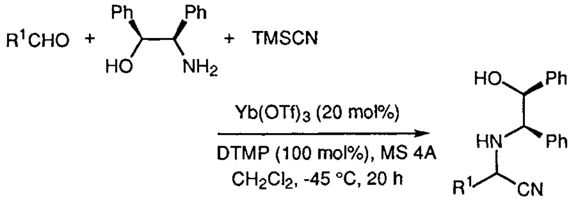
Table 2. Yb(OTf)$_3$-Catlyzed Three-Component Reactions of Aldehydes, Amines, and TMSCN

Entry	R^1	R^2	Conditions[a]	Yield/%
1	Ph	MeOPh	A	92
2	Ph	Ph$_2$CH	A	88
3	α-Nap	MeOPh	A	91
4	α-Nap	Ph$_2$CH	A	85
5	c-C$_6$H$_{11}$	MeOPh	A	86
6	c-C$_6$H$_{11}$	Ph$_2$CH	A	85
7	C$_3$H$_7$	Ph$_2$CH	B	91
8	(CH$_3$)$_2$CHCH$_2$	Ph$_2$CH	B	84
9	(CH$_3$)$_2$CH	Ph$_2$CH	B	91

[a] Conditions A: Yb(OTf)$_3$ 5 mol%, CH$_3$CN, rt; B: Yb(OTf)$_3$ 10 mol%, C$_2$H$_5$CN, -78 °C to 0 °C.

A typical experimental procedure is as follows: To a suspension of Yb(OTf)$_3$ (0.05 mmol, 10 mol%) and MS 4A (100 mg) in CH$_2$Cl$_2$ (1.0 ml) were added an aldehyde (0.5 mmol) in CH$_2$Cl$_2$ (0.5 ml) and an amine (0.5 mmol) in CH$_2$Cl$_2$ (0.5 ml) at room temperature. The mixture was stirred for 0.5 h and TMSCN (0.75 mmol) in CH$_2$Cl$_2$ (0.5 ml) was added to the same pot. After the mixture was further stirred for 20 h, water was added[9] and the product was extracted with dichloromethane. After the organic layer was dried and evaporated, the crude product was chromatographed on silica gel to afford the α-amino nitrile. The catalyst was quantitatively recovered from the aqueous layer and could be reused for further runs. We tested other lanthanide triflates such as $Sc(OTf)_3$, $Y(OTf)_3$, $Er(OTf)_3$, $Tm(OTf)_3$, etc. and found that they were also effective.

Finally, asymmetric reactions using a chiral amine were examined.[7b,10] In the presence of 10 mol% of $Yb(OTf)_3$ and 100 mol% of 2,6-di-*t*-butyl-4-methylpyridine (DTMP),[11] the three-component reaction of benzaldehyde, (*1S,2R*)-(+)-2-amino-1,2-diphenylethanol, and TMSCN proceeded smoothly at -45 °C, to afford the corresponding α-amino nitrile in an excellent diastereoselectivity. In the reaction using cyclohexanecarboxaldehyde, the selectivity decreased slightly.



R^1 = Ph, 78% yield, ds = 16:1
R^1 = c-C_6H_{11}, 87% yield, ds = 7.5:1

In summary, lanthanide triflates were found to be efficient catalysts both in the reactions of imines with TMSCN and in the three-component reactions of aldehydes, amines, and TMSCN, to afford α-amino nitriles in high yields. The reactions were carried out under anhydrous conditions, and decomposition of TMSCN to HCN did not occur under these conditions. Further application of these reactions to asymmetric synthesis is now in progress.

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