Lewis Base-catalyzed Strecker-type Reaction between Trimethylsilyl Cyanide and *N*-Tosylimines in Water-containing DMF

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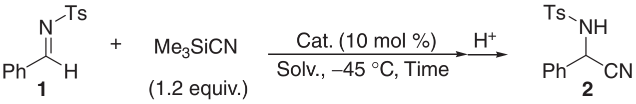
Lewis base-catalyzed Strecker-type reaction between trimethylsilyl cyanide and *N*-tosylimines proceeded smoothly in dry DMF or water-containing DMF and the corresponding α-amino compounds were obtained in good to high yields.

Strecker-type reaction between trimethylsilyl cyanide (TMSCN) and imines is one of the most important tools for the construction of α-amino nitriles.[1] This reaction is generally performed through activation of the acceptor imines with Lewis acid, for which various methods have been reported. It is known that fluoride anion activates TMSCN, however, a stoichiometric amount of fluoride anion is generally required.

It was reported in the previous communication that trimethylsilyl (TMS) enolates were activated with Lewis base catalysts such as the nitrogen and oxygen containing-anions generated from amides, imides, or carboxylic acids, and they worked as a promoter of aldol and Michael reactions.[2,3] These Lewis bases also worked as useful catalysts for Mannich-type reaction between *N*-tosylaldimines and TMS enolates because they are neither deactivated nor decomposed by a basic nitrogen contained in an aldimine, a starting material, and an amine, a product.[4]

In order to show more examples of the synthetic utility of a Lewis base catalyst, Strecker-type reaction between TMSCN and *N*-tosylimines was considered. In this communication, we would like to report on efficient Strecker-type reactions using a catalytic amount of AcOLi in dry or water-containing DMF.

Table 1.



Entry	Cat.	Solv.	Time/h	Yield[a]/%
1	—	DMF	12	36
2	—	THF	12	n.d.
3	AcOLi	THF	6	20
4	AcOLi	DMF	6	97
5	AcOLi	DMF	6	96[b,c]
6	AcONa	DMF	6	quant.
7	AcOK	DMF	6	quant.
8	Phthalimide-K	DMF	6	98
9	AcONn-Bu$_4$	DMF	6	quant.
10	AcONMe$_4$	DMF	6	quant.
11	AcONMe$_4$	THF	6	98
12	PhCO$_2$Nn-Bu$_4$	DMF	6	93
13	PhCO$_2$Nn-Bu$_4$	CH$_2$Cl$_2$	6	quant.
14	PhCO$_2$Nn-Bu$_4$	Toluene	6	98
15	PhCO$_2$Nn-Bu$_4$	THF	12	97[d]

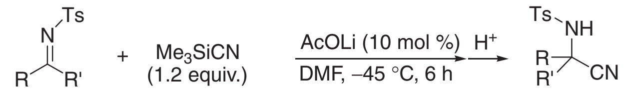
[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]Cat.: 1 mol %. [c]Isolated yield. [d]Reaction temp.: −78 °C.

In the first place, reactions between *N*-tosylaldimine **1** and TMSCN were tried in the presence of a catalytic amount of AcOLi in DMF at −45 °C (Table 1). Then, the reactions were found to proceed smoothly to afford the corresponding α-amino nitriles **2** in high yields (Entries 4 and 5).[5] In these reactions, various counter cations of carboxylate anion such as sodium, potassium, and ammonium turned out to be effective. When the reaction was carried out in the presence of AcOLi in THF, **2** was obtained only in 20% yield (Entry 3). On the other hand, the adduct **2** was afforded in a high yield in various solvents such as CH$_2$Cl$_2$, toluene, and THF when ammonium carboxylates such as AcONMe$_4$ or PhCO$_2$Nn-Bu$_4$ were used (Entries 11, 13–15).

Next, AcOLi-catalyzed Strecker-type reaction was examined by using various *N*-tosylimines and TMSCN in the presence of 10 mol % of AcOLi in DMF at −45 °C (Table 2). Reactions of aromatic aldimines that have an electron-withdrawing or -donating group proceeded smoothly and afforded the corresponding α-amino nitriles in good to high yields (Entries 1–6). When an aromatic aldimine containing another basic part such as dimethylamino-function was used, the corresponding α-amino nitrile was also obtained in high yields (Entry 7). The cases were the same when aliphatic aldimine and ketimine were used and the desired products were obtained in high yields (Entries 8 and 9).

Then, Lewis base-catalyzed Strecker-type reaction was tried in a water-containing solvent by using the above Lewis base catalysts which were stable in water (Table 3). When the reaction between aldimine **1** and TMSCN was carried out by using

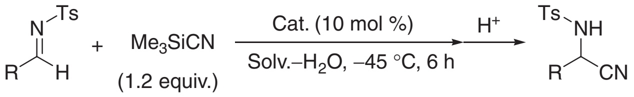
Table 2.



Entry	R	R′	Yield[a]/%
1	4-ClC$_6$H$_4$	H	98
2	4-BrC$_6$H$_4$	H	95 (90[b])
3	4-NCC$_6$H$_4$	H	73
4	4-MeC$_6$H$_4$	H	quant.
5	4-MeOC$_6$H$_4$	H	quant.
6	2-Naphthyl	H	87
7	4-Me$_2$NC$_6$H$_4$	H	quant. (95[b])
8	c-Hexyl	H	quant. (95[b])
9	Ph	Me	quant.

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]Isolated yield.

Table 3.



Entry	R	Cat.	Solv.	Solv.:H_2O[a]	Yield[b] /%
1	Ph	—	DMF	50:1	n.d.
2	Ph	AcOLi	DMF	50:1	98
3	Ph	AcOLi	DMF	10:1	95
4	Ph	AcOLi	DMF	5:1	92
5	Ph	AcOLi	THF	10:1	n.d.
6	Ph	$PhCO_2Nn\text{-}Bu_4$	THF	10:1	84
7	4-ClC_6H_4	AcOLi	DMF	10:1	quant.
8	4-$MeOC_6H_4$	AcOLi	DMF	10:1	96
9	4-$Me_2NC_6H_4$	AcOLi	DMF	50:1	98
10	2-Naphthyl	AcOLi	DMF	10:1	83
11	C_6H_{11}	AcOLi	DMF	10:1	89

[a]Volume ratio. [b]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

10 mol % of AcOLi at −45 °C, it proceeded smoothly to afford **2** in high yields (Entries 2–4) while no reaction took place in the absence of a catalyst. Further, no reaction was observed in water-containing THF too when AcOLi was used (Entry 5). On the other hand, when ammonium salts such as $PhCO_2$-N*n*-Bu_4 were used instead of AcOLi, it proceeded smoothly and afforded **2** in high yield (Entry 6). Next, reactions of various *N*-tosylimines with TMSCN in water-containing DMF were tried and these reactions proceeded smoothly by using AcOLi (Entries 9–11), which afforded the corresponding α-amino nitriles in high yields.

Thus, Lewis base-catalyzed Strecker-type reaction between TMSCN and *N*-tosylimines in dry or water-containing DMF was established. This method is quite practical and is applicable to the synthesis of various α-amino nitriles since the reaction proceeded smoothly in the presence of a mild, readily available yet inexpensive Lewis base catalyst in a not-strictly-anhydrous solvent. Further development of this reaction is now in progress.

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References and Notes

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5 General experimental procedure is as follows: To a stirred solution of AcOLi (0.02 mmol) in DMF (0.3 mL) were added successively a solution of TMSCN (0.24 mmol) in DMF (0.6 mL) and a solution of *N*-tosylimine (0.2 mmol) in DMF (0.6 mL) at −45 °C. After the mixture was further stirred for 6 h at the same temperature, it was quenched with saturated aqueous NH_4Cl. The mixture was extracted with AcOEt. Organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified by preparative TLC to give the corresponding α-amino nitriles. Products and yields were as reported in the text.

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