Lewis Base-catalyzed Cyanomethylation of Aldimines with Trimethylsilylacetonitrile

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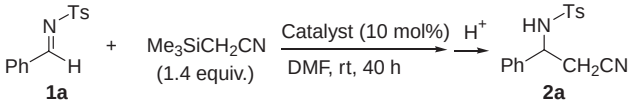
A catalytic cyanomethylation of various aldimines with trimethylsilylacetonitrile ($TMSCH_2CN$) in the presence of Lewis bases such as lithium acetate or benzoate proceeded smoothly to afford the corresponding cyanomethylated adducts in good yields.

β-Amino nitriles are the useful building blocks since they are easily converted into either β-aminocarboxylic acids or 1,3-diamino compounds.[1,2] General method for the synthesis of β-amino nitriles is the ring-opening reaction of 1,2-aziridines with nitriles in the presence of metal cyanides such as KCN, NaCN, and TMSCN.[3] The nucleophilic addition of a cyanomethyl group to imines is one of the most straightforward methods for the synthesis of β-amino nitriles. However, examples of the cyanomethylation of imines are fewer than those of Mannich-type reactions. Among them, Zhang et al. reported that the addition reactions to aldimines with bromoacetonitrile in the presence of tin powder gave the adducts in moderate yields.[4] Also, Shibasaki et al. recently reported a direct catalytic addition of acetonitrile to aldimines using a cationic Ru complex, DBU and $NaPF_6$.[5]

Table 1. Screening of various catalysts on cyanomethylation



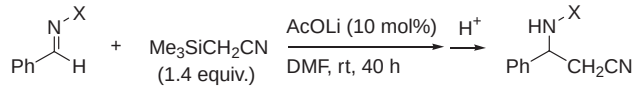
Entry	Catalyst	Yield[a]/%	Entry	Catalyst	Yield[a]/%
1	CF_3CO_2Li	N.D.[b]	7	BnOLi	60
2	$PhCO_2Li$	88	8	AcONa	76
3	AcOLi	96 (93)[c]	9	AcOK	72
4	*t*-$BuCO_2Li$	84	10	AcOCs	86
5	$(CF_3)_2CHOLi$	71	11	AcON(*n*-Bu)$_4$	72
6	PhOLi	68	12	none	N.D.

[a]Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]Not detected. [c]Isolated yield.

In our previous papers, the nitrogen- or oxygen-containing anions generated from amides, imides, carboxylic acids, or alcohols were shown to be effective Lewis base catalysts for the activation of trimethylsilyl (TMS) enolate in aldol, Michael and Mannich-type reactions.[6] Further, Strecker-type and trifluoromethylation reactions which proceeded under mild conditions by activating carbon–silicon bond of TMSCN or $TMSCF_3$ with AcOLi were recently reported from our laboratory.[7] In order to extend the synthetic utility of the above mentioned Lewis base catalyst, cyanomethylation reaction between $TMSCH_2CN$ and *N*-tosylaldimine was considered. In this communication, we would like to describe an effective method for the cyanomethylation of imines with $TMSCH_2CN$ by using a catalytic amount of Lewis base such as AcOLi under mild conditions.

In the first place, various Lewis base catalysts were examined by taking the reaction of *N*-tosylaldimines **1a** with $TMSCH_2CN$ as a model in the presence of 10 mol % of the catalyst at room temperature in DMF. Of the Lewis bases screened, lithium carboxylates such as benzoate, acetate, and pivalate turned out to promote this reaction most effectively while lithium phenoxides or alkoxides were less effective although these phenoxide or alkoxide anions were more nucleophilic than carboxylate ones (Entries 2–7). On the other hand, the cyanomethylated adduct was not detected in the absence of the catalyst (Entry 12). Thus, the lithium ion was the effective counter cation of the carboxylates for these reactions as shown in Table 1.

Table 2. Effects of substituents on the nitrogen of aldimine



Entry	X	Yield[a]/%	Entry	X	Yield[a]/%
1	4-$MeC_6H_4SO_2$	93	4	2-$NO_2C_6H_4SO_2$	94
2	4-$ClC_6H_4SO_2$	80	5	$P(O)Ph_2$	62[b]
3	4-$NO_2C_6H_4SO_2$	96	6	Ph	N.D.

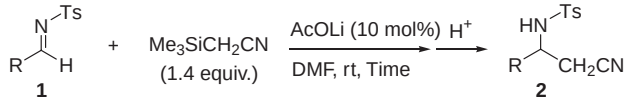
[a]Isolated yield. [b]2.0 equiv. of $TMSCH_2CN$ were used.

Effects of substituents on the nitrogen atom of aldimine were examined by using various aldimines in the presence of a catalytic amount of AcOLi in DMF (Table 2). It was found that the reactivity of this reaction was dependent on the electrophilicities of these imines. When *N*-sulfonylimines and *N*-phosphinoylimines were used as substrates, it proceeded smoothly under the same reaction conditions and the desired products were obtained in good to moderate yields (Entries 1–5). On the other hand, no desired products were detected when a weak electrophile such as *N*-phenylaldimine was used (Entry 6).

Next, the reaction of various *N*-tosylaldimines with $TMSCH_2CN$ was tried by using 10 mol % of AcOLi in DMF (Table 3). Aromatic aldimines having electron-donating or -withdrawing group reacted smoothly to afford the cyanomethylated adducts in good yields. While aliphatic aldimines having no α-protons adjacent to the imino group reacted smoothly to afford the desired adduct in high yields, those with α-protons did not undergo the cyanomethylation because the competitive abstraction of α-proton took place.[8]

Finally, Lewis base-catalyzed cyanomethylation reaction was studied by using several trimethylsilylacetonitriles (Table 4). When the above derivative **3** or **4** was employed as a substrate, the corresponding β-amino nitrile was obtained in good yield with low diastereoselectivity. On the other hand, the reaction with the nitrile derivative **5** did not proceed because of the insufficient activation of carbon–silicon bond to react with aldimines. Then, various Lewis bases were screened and reaction

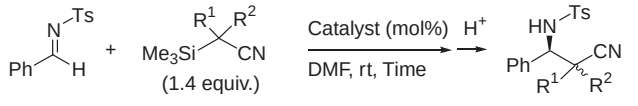
Table 3. Cyanomethylation of various aldimines



Entry	R		Time/h	Yield[a]/%
1	4-$MeOC_6H_4$	**(1b)**	40	90
2	4-MeC_6H_4	**(1c)**	40	90
3	4-ClC_6H_4	**(1d)**	40	88
4	4-BrC_6H_4	**(1e)**	24	92
5	4-$NO_2C_6H_4$	**(1f)**	24	86
6	2-Naphthyl	**(1g)**	40	81
7	2-Furyl	**(1h)**	40	94
8	3-Pyridyl	**(1i)**	40	75
9	(*E*)-PhCH=CH	**(1j)**	40	65[b]
10	*t*-Bu	**(1k)**	40	89
11	*c*-C_6H_{11}	**(1l)**	40	N.D.

[a]Isolated yield. [b]2.0 equiv. of $TMSCH_2CN$ were used.

Table 4. Cyanomethylation with various trimethylsilylacetonitrile derivatives



Entry	Reagent		Catalyst (mol %)	Yield[a]/%	d.r.
1	R^1= Me, R^2= H	**3**	AcOLi (10)	84	59:41[b]
2	R^1= Et, R^2= H	**4**	AcOLi (10)	81	59:41[b]
3	R^1= Me, R^2= Me	**5**	AcOLi (10)	N.D.	—
4	R^1= Me, R^2= Me	**5**	AcOCs (20)	71	—

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]The relative configuration was not determined.

conditions were optimized so as to improve the yields. Consequently, it was found that the corresponding cyanomethylated adduct was obtained in moderate yield when the reaction was carried out in the presence of AcOCs (Entry 4).

In conclusion, a catalytic cyanomethylation of various aldimines with $TMSCH_2CN$ by using Lewis base catalysts such as lithium acetate or benzoate proceeded smoothly via the activation of carbon–silicon bond of $TMSCH_2CN$. Further investigation on this reaction is now in progress.

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References and Notes

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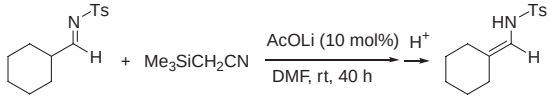
8 The enamine derived from **1l** was confirmed by ^{1}H NMR: ^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.73 (d, $J = 8.1$ Hz, 2H), 7.28 (d, $J = 8.1$ Hz, 2H), 6.41 (d, $J = 9.2$ Hz, 1H), 5.75 (d, $J = 8.1$ Hz, 1H), 2.41 (s, 3H), 2.20–1.60 (4H, m), 1.48–1.36(4H, m), 1.18–1.32 (m, 2H).



9 Typical experimental procedure is as follows (Table 1, Entry 3): To a stirred solution of AcOLi (2.0 mg, 0.03 mmol) in DMF (0.8 mL) were added successively a solution of *N*-tosylbenzaldimine (77.8 mg, 0.3 mmol) in DMF (0.2 mL) and $TMSCH_2CN$ (57.5 μL, 0.42 mmol) at room temperature. The mixture was stirred for 40 h at the same temperature and quenched with saturated aqueous NH_4Cl. The mixture was extracted with AcOEt and organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the resulted residue was purified by preparative TLC to give the desired product (83.8 mg, 93%) as a white powder.

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