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Lewis base-catalyzed transformation of α,β-unsaturated aldehydes to saturated carboxylic acids, esters and amides

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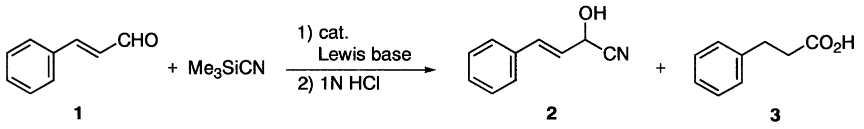
Abstract—The reactions of α,β-unsaturated aldehydes such as (*E*)-cinnamaldehyde and 2- or 4-methoxycinnamaldehyde with trimethylsilyl cyanide in the presence of a catalytic amount of a Lewis base such as TTMPP and DBU afforded the corresponding saturated carboxylic acids after hydrolysis. © 2002 Elsevier Science Ltd. All rights reserved.

In 1991, Mukaiyama and his co-workers reported Lewis base-catalyzed formation of cyanohydrin trimethylsilyl ethers by the reaction of trimethylsilyl cyanide with some aldehydes.[1] The Lewis bases they employed were amines (Et_3N, *i*-Pr_2NEt, *i*-Pr_2NH, 1-ethylpiperidine, *N*,*N*,*N′*,*N′*-tetramethylethylenediamine, 2,2,6,6-tetramethylpiperidine), phosphines (*n*-Bu_3P, Ph_3P), arsine (Ph_3As) and antimony (Ph_3Sb). In all cases they examined, the reaction products were trimethylsilyl ethers of cyanohydrin.

Here we would like to report that some strong Lewis bases such as tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP)[2–4] and 1,8-diazabicyclo[5,4,0]undec-7-ene

Table 1. Reaction of (*E*)-cinnamaldehyde with Me_3SiCN catalyzed by a variety of Lewis bases[a]



Entry	Catalyst (mol%)	Conditions		Products (% yield)[b]	
		Temp (°C)	Time (h)	2	3
1	PhP_3 (20)	28	3.5	46	0
2	TMPP (20)	31	3.5	87	0
3	TDMPP (20)	31	3.5	23	70
4	TTMPP (5)	32	2	10	86
5	TTMPP (10)	32	2	7	87
6	TTMPP (20)	29	3.5	0	90
7	*n*-Bu_3P (20)	31	2.5	4	74
8	DBU (5)	25	2	0	79
9	DBU (10)	28	2	0	91
10	DBU (20)	25	2	0	94

[a] All reactions were carried out in CH_3CN.

[b] The yields of the products were the isolated yields after hydrolysis.

Keywords: Lewis base; α,β-unsaturated aldehyde; carboxylic acid.

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Table 2. Solvent effect in the reaction of (*E*)-cinnamaldehyde with Me_3SiCN[a]

Entry	Solvent	Conditions		Products (% yield)[b]	
		Temp (°C)	Time (h)	**2**	**3**
1	CH_3CN	29	3.5	0	90
2	THF	32	3	15	76
3	Toluene	32	3.5	14	74
4	CH_2Cl_2	32	3.5	42	51
5	DMF	20	3	74	14
6	EtOH	30	2	94	4
7	Et_2O	32	2	96	1

[a] All reactions were carried out in the presence of 20 mol% of TTMPP.

[b] The yields of the products were the isolated yields after hydrolysis.

(DBU) catalyze mild and direct conversion of α,β-unsaturated aldehydes to the corresponding saturated carboxylic acids, esters and amides.

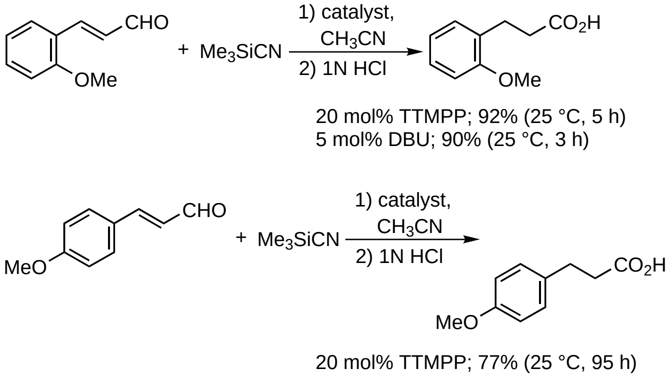
We first examined the effect of the nature of the Lewis base catalysts on the distribution of the products, that is, cyanohydrin trimethylsilyl ether and saturated carboxylic acid, in the reaction of (*E*)-cinnamaldehyde (**1**) with trimethylsilyl cyanide followed by hydrolysis (Table 1). Among the Lewis bases we examined, TTMPP and DBU worked most effectively for the conversion of (*E*)-cinnamaldehyde (**1**) to 3-phenylpropionic acid (**3**). That is, the reaction of **1** with trimethylsilyl cyanide in the presence of 20 mol% of TTMPP or 5 mol% of DBU in acetonitrile at room temperature for 2–3.5 h, then hydrolysis with 1 M HCl afforded **3** in 90% and 95% yield, respectively. In both cases, the trimethylsilyl ether of cyanohydrin was not obtained. DBU was found to be more effective than TTMPP for the above conversion. In the case of other Lewis bases such as triphenylphosphine, tris(4-methoxyphenyl)-phosphine (TMPP), and tris(2,6-dimethoxyphenyl)-phosphine (TDMPP), the products were only unsaturated cyanohydrin **2** or a mixture of cyanohydrin **2** and saturated carboxylic acid **3** (entries 1–3, 7). It should be mentioned that even in the reaction of TTMPP, use of a lesser amount of TTMPP led to the formation of a small amount of cyanohydrin (entries 4, 5). The tendency of the preferred formation of saturated acid **3** approximately correlates with the acidity of the conjugated acid of the bases used. The nature of the solvent also affected the distribution of cyanohydrin and acid (Table 2). The result of the reaction in acetonitrile was completely in contrast with that in ethanol and diethyl ether. That is, the reaction in ethanol and diethyl ether afforded cyanohydrin **2**, exclusively. The reactions in other solvents afforded mixtures of unsaturated cyanohydrin **2** and saturated acid **3**.

The reactions of α,β-unsaturated aldehydes other than (*E*)-cinnamaldehyde were also examined. 2- and 4-Methoxy-(*E*)-cinnamaldehyde were converted to the corresponding saturated acid in high yield by the aid of TTMPP and DBU (77–96% yield) (Scheme 1). On the other hand, the reactions of α-methyl-(*E*)-cinnamaldehyde, (*E*)-2-hexenal and (*E*)-2-nonenal with trimethylsilyl cyanide by in the presence of 20 mol% of TTMPP afforded trimethylsilyl ethers of cyanohydrin, exclusively.

The reaction would be initiated by trimethylsilylcyanation of aldehydes affording trimethylsilyl ether of cyanohydrin, which was followed by base-catalyzed isomerization to produce saturated acids after hydrolysis. Actually, trimethylsilyl ether of cyanohydrin can be used as a substrate. Furthermore, before hydrolysis, the generation of the intermediate α-trimethylsiloxy vinyl cyanide, which was the isomerization product of cyanohydrin trimethylsilyl ether, was confirmed by ^1H NMR and mass spectral analyses of the reaction mixture. At this stage, the formation of acyl cyanide was not observed.

As for the direct conversion of (*E*)-cinnamaldehyde (**1**) to 3-phenylpropionic acid (**3**), Vries et al. reported a reaction catalyzed by $RuCl_3 \cdot H_2O/PCy_3$ system; however, this reaction needed high temperature (180°C), and the yield was only moderate (46% yield).[5] Our present method is superior to the ruthenium-catalyzed method from the viewpoint of yield of the product and mildness of the reaction conditions.

Methanolysis instead of hydrolysis afforded saturated methyl esters in high yield. That is, the reaction of (*E*)-cinnamaldehyde (**1**) with trimethylsilyl cyanide by the aid of 20 mol% of TTMPP or 5 mol% of DBU

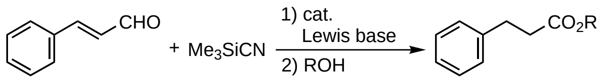


20 mol% TTMPP; 92% (25 °C, 5 h)
5 mol% DBU; 90% (25 °C, 3 h)

20 mol% TTMPP; 77% (25 °C, 95 h)
5 mol% DBU; 96% (25 °C, 4 h)

Scheme 1.

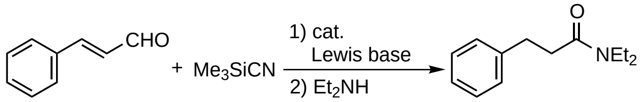
followed by addition of methanol gave methyl 3-phenylpropionate (**4**) in 63% and 67%, respectively (28°C, 3.5–6 h) (Eq. (1)). Ethyl 3-phenylpropionate (**5**) and *i*-propyl 3-phenylpropionate (**6**) were also obtained by treatment with ethanol or isopropyl alcohol (Eq. (1)). Furthermore, quenching by 1.2 equiv. of diethylamine or piperidine afforded the corresponding amides (**7** and **8**) in 77–81% and 95–97%, respectively (Eqs. (2) and (3)).



1

R = Me (**4**), 20 mol% TTMPP; 63% (28 °C, 6 h)
5 mol% DBU; 67% (28 °C, 3.5 h)
R = Et (**5**), 20 mol% TTMPP; 69% (25 °C, 4.5 h)
5 mol% DBU; 77% (25 °C, 4.5 h)
R = *i*-Pr (**6**), 20 mol% TTMPP; 46% (25 °C, 22 h)
5 mol% DBU; 49% (25 °C, 2.5 h)

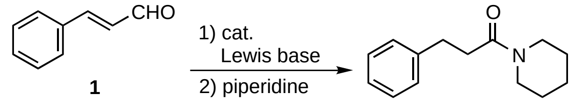
(1)



1 **7**

20 mol% TTMPP; 77% (25 °C, 4.5 h)
5 mol% DBU; 81% (25 °C, 4.5 h)

(2)



1
+
Me_3SiCN

8

20 mol% TTMPP; 95% (25 °C, 7 h)
5 mol% DBU; 97% (25 °C, 7 h)

(3)

Typical experimental procedure is as follows: In a flask were placed (*E*)-cinnamaldehyde (**1**) (1.06 g, 8.0 mmol) and CH_3CN (7 mL). To this mixture were added trimethylsilyl cyanide (1.3 mL, 9.75 mmol) and TTMPP (855 mg, 1.6 mmol). The whole was stirred at 29°C for 3.5 h. After confirmation of the consumption of aldehyde and then cyanohydrin trimethylsilyl ether by TLC analysis, the mixture was poured into a mixture of 1 M HCl solution (10 mL) and diethyl ether (10 mL), and stirred vigorously for 3 h at room temperature. Usual extractive work-up, then silica gel column chromatography using hexane–ethyl acetate (3/1) as an eluent gave 3-phenylpropionic acid (**3**) (1.08 g, 90%), mp 47–49°C.

In conclusion, some Lewis bases such as TTMPP and DBU promote novel and efficient transformation of α,β-unsaturated aldehydes into saturated carboxylic acids and the corresponding esters and amides. Study of the detailed reaction mechanism and synthetic applications of the method are now in progress in our laboratory.

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