Cyanosilylation of Ketones Catalyzed by Quaternary Ammonium Salt and *N***-Oxide**

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Abstract: Dibenzyldimethyl ammonium bromide and triethanolamine *N*-oxide catalyze the formation of cyanohydrin trimethylsilyl ethers of ketones in 80–99% yield.

Key words: cyanohydrins, ketones, *N*-oxides, quaternary ammonium salts, organocatalysis

Cyanation reaction of carbonyl compounds is one of the most powerful procedures for the synthesis of polyfunctionalized molecules.¹ Among various cyanating reagents such as KCN or NaCN and HCN, trimethylsilyl cyanide (TMSCN) is a safe and more effective cyanide source for nucleophilic addition to carbonyl compounds under mild conditions.² Its addition to keto compounds affords cyanohydrin trimethylsiyl ethers, which are useful intermediates for the synthesis of cyanohydrins and related compounds. Various catalysts including Lewis acids and Lewis bases have been used to promote this transformation.^{3,4} Among them, the catalysts usually contain metals. Although the metal derivatives offer tremendous benefits, they are also the source of increasing problems.⁵ Therefore, new catalytic methods based on metal-free organic molecules have been developed in the last few years.^{6,7} However, there are few examples of the cyanosilylation of ketones employing organocatalysts.8 Herein, we reported the use of quaternary ammonium salt and N-oxide as combinatorial catalysts for cyanosilylation of ketones.

In the preliminary study, we investigated the addition of TMSCN to acetophenone in the presence of the easily prepared dibenzyldimethyl ammonium bromide (1) (20 mol%) and *N*,*N*-dimethylaniline *N*-oxide (4) (20 mol%). Fortunately, the product was obtained in 68% yield after 24 h at room temperature (Table 1, entry 3), while neither 1 nor 4 (Figure 1) was enough to promote the addition of TMSCN to acetophenone (Table 1, entries 1 and 2). Additionally, this reaction was found to be insensitive to air and moisture. Hence, there was no need for an inert atmosphere.

Subsequently, a series of bases have been examined. The results are summarized in Table 2. The highest yield is obtained in the presence of triethanolamine *N*-oxide, while

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Table 1 The Addition of TMSCN to Acetophenone^a

R^1 R^2 +	TMSCN quaternary ammo	onium salt de R ¹ R ²
Entry	Catalyst(s)	Yield (%) ^b
1	20 mol% 1	0
2	20 mol% 4	0
3	20 mol% 1 + 20 mol%	4 68

 $^{\rm a}$ Conditions: 23 °C, 24 h, concentration of acetophenone, 0.13 M in CH_2Cl_2.

^b Isolated yields.

the *N*-oxides that contain one or two ethylol groups have relatively lower catalytic activity (Table 2, entries 3–5). The catalytic activities of aromatic amine *N*-oxide and heterocyclic amine *N*-oxide are moderate (Table 2, entries 1, 7). The aliphatic amine *N*-oxide without the ethylol group gives the lower yield (Table 2, entry 2). The examined phosphine oxides do not show any catalytic activity as well as pyridine *N*-oxide (Table 2, entries 6, 8 and 9).

And then, we investigated the use of a reduced catalyst loading. When the catalysts 1 and 2 were employed, the catalyst loading could be reduced to 2.5 mol% without affecting the reaction rate and the yield (Table 3). It was found that excellent yield could be obtained by increasing



Figure 1

Table 2 Catalytic Addition of TMSCN to Acetophenone^a

Entry	Lewis base	Yield (%) ^b
1	4	68
2	TMNO	46
3	2	82
4	BDENO	64
5	DBENO	64
6	PyNO	0
7	NMNO	60
8	P(O)Ph ₃	0
9	HMPA	0

^a All the reactions were carried out with 2 equiv. TMSCN in CH_2Cl_2 at 23 °C with the quaternary ammonium salt 1 (20 mol%) and the bases (20 mol%) along with 0.13 M of acetophenone during 24 h. ^b Isolated yields after flash column chromatography.

^c TMNO = trimethylamine *N*-oxide; BDENO = *N*-benzyl-*N*,*N*-diethanolamine *N*-oxide; DBENO = *N*,*N*-dibenzylethanolamine *N*-oxide; PyNO = Pyridine *N*-oxide; NMNO = *N*-methylmorpholine *N*-oxide; P(O)Ph₃ = triphenyl phosphine oxide; HMPA = hexamethyl phosphorous triamide.

the substrate concentration (Table 3, entries 3 and 4). This is in agreement with our previous report.^{3a} In addition, the *N*-oxide **2** alone can catalyze this transformation although the yield is low (Table 3, entry 1).

Under the optimized conditions (2.5 mol% of 1, 2.5 mol% of 2), the cyanosilylation of a wide range of ketones was investigated with results shown in Table 4. Most of aromatic, conjugated and aliphatic ketones afforded the corresponding products in excellent yields within 11-16 hours (Table 4, entries 1-13) with three exceptions (Table 4, entries 3, 5 and 11). It is a pity that the problem of low reaction rate of cyanosilylation of heterocyclic ketone is still not solved (Table 4, entry 14).

Table 3 Catalytic Addition of TMSCN to Acetophenone Mediated by 1 and $2^{\rm a}$

Entry	Catalysts load- ing (mol%) 1:2	Concentration of acetophenone (M)	Time (h)	Yield (%) ^b
1	0:20	0.13	24	23
2	20:20	0.13	24	82
3	2.5:2.5	1.1	24	95
4	2.5:2.5	2.2	15	95

 $^{\rm a}$ All the reactions were carried out with 2 equiv. TMSCN in $\rm CH_2Cl_2$ at 23 °C.

^b Isolated yields.

Table 4 Catalytic Addition of TMSCN to Ketones using 1 and 2 a

Entry	Ketone	Time (h)	Yield (%) ^b
1	C ₆ H ₅ COCH ₃	15	95
2	4-FC ₆ H ₄ COCH ₃	11	92
3	4-MeC ₆ H ₄ COCH ₃	22	93
4	C ₆ H ₅ COCH ₂ CH ₃	12	99
5	4-O ₂ NC ₆ H ₄ COCH ₃	46	98
6	2-Acetonaphthone	16	99
7	(E)-C ₆ H ₅ CH=CHCOCH ₃	14	99
8	C ₆ H ₅ CH ₂ CH ₂ COCH ₃	12	99
9	2-Octanone	11	99
10	Cyclohexanone	16	99
11	α-Tetralone	36	93
12	β-Tetralone	12	80
13	4-Phenylcyclohexanone	12	99
14	2-Acetylthiophene	72	99

^a Conditions: 2.5 mol% of **1**, 2.5 mol% of **2**, substrate concentration 2.2 M in CH_2Cl_2 , 23 °C. For typical procedure, see ref.⁹

^b Isolated yields.

Moreover, we also made an attempt to investigate the enantioselective cyanosilylation of ketones by chiral quaternary ammonium salt. In CH_2Cl_2 solvent and at 0 °C, the use of 20 mol% chiral quaternary ammonium salt **3** and *N*-oxide **4** as catalysts for cyanosilylation of acetophenone gave 2-trimethylsilyloxy-2-phenylpropanenitrile in 10% isolated yield with 20% ee after 80 hours.

At present the mechanistic detail of this conversion remains obscure. As one explanation, we speculate that the role of *N*-oxide may be a Lewis base to activate the TMSCN,^{3a-c,4a-e,4h-j} and the positively charged N atom of quaternary ammonium salt attracts the O atom of carbonyl group and thus activates the carbonyl group.

In summary, the use of dibenzyldimethyl ammonium bromide and triethanolamine *N*-oxide as catalysts for cyanosilylation of ketones has been described. This method is effective for the cyanation of aliphatic ketones and aromatic ketones in low catalyst loading and mild conditions. In addition, the catalysts are inexpensive and easily prepared. Further mechanistic study and the enantioselective version of this transformation are underway in our laboratory.

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- (9) Typical Procedure: To a mixture of ketone (1.1 mmol), dibenzyldimethyl ammonium bromide (0.027 mmol) and triethanolamine *N*-oxide (0.027 mmol) in CH_2Cl_2 (0.5 mL) was added trimethylsilyl cyanide (2.2 mmol, 2 equiv.) at r.t. The reaction was monitored by TLC, and after the reaction period described in Table 4, the reaction mixture was concentrated under reduced pressure and purified by silica gel column to give the pure product with Et_2O -petroleum ether (1:100) as the eluent.