Construction of Tetrasubstituted Carbon by an Organocatalyst: Cyanation Reaction of Ketones and Ketimines Catalyzed by a Nucleophilic N-Heterocyclic Carbene

Yoshimasa Fukuda, Kazuhiro Kondo,* Toyohiko Aoyama*

Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan
Fax +81(52)8363439; E-mail: kazuk@phar.nagoya-cu.ac.jp; E-mail: aoyama@phar.nagoya-cu.ac.jp

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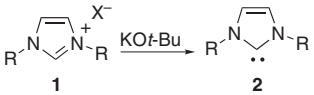
Abstract: A method for cyanation reaction of ketones and ketimines having lower reactivity than aldehydes and aldimines with TMSCN in the presence of N-heterocyclic carbene prepared from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride and potassium *tert*-butoxide, as a nucleophilic organocatalyst, is described. These cyanations of ketones and ketimines afford the corresponding products in good yields under mild reaction conditions.

Keywords: N-heterocyclic carbene, tetrasubstituted carbon, nucleophilic organocatalyst, cyanation, trimethylsilyl cyanide

Recently, the suitability of N-heterocyclic carbenes (NHCs) prepared from imidazolium salts and bases as nucleophilic organocatalysts has attracted considerable attention.[1] NHCs as nucleophilic organocatalysts have been used mainly in benzoin-type, trans-esterification reactions and so on, the key step of which involves the attack of NHCs to carbonyl groups.[1] Quite recently, we have reported the first example of NHC-**2a**-catalyzed cyanation reaction of aldehydes and aldimines with TMSCN.[2] We propose that the carbon–silicon bond in TMSCN is activated by a nucleophilic NHC catalyst for cyano-transfer in the reactions.[2c,3] In order to expand the scope of this cyanation, we decided to investigate the catalytic cyanation reaction of ketones and ketimines having lower reactivity than aldehydes and aldimines using NHC **2**.



1 **2**

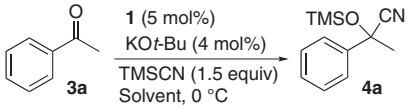
a: R = 2,4,6-$Me_3C_6H_2$, X = Cl^-
b: R = *i*-Pr, X = BF_4^-
c: R = *t*-Bu, X = BF_4^-
d: R = 1-adamantanyl, X = BF_4^-

Scheme 1

We first examined cyanosilylation of acetophenone (**3a**) with TMSCN in the presence of imidazolium salts **1a–d** as NHC precursors (Scheme 1). The results are shown in Table 1. The reaction with imidazolium salt **1a** in tetrahydrofuran resulted in no reaction (entry 1). On switching tetrahydrofuran to *N*,*N*-dimethylformamide, the reaction was dramatically accelerated, affording silylated cyanohydrin **4a** in 59% yield at 0 °C for 30 minutes (entry 2).[4] In the absence of NHC **2a**, no reaction occurred in *N*,*N*-dimethylformamide. NHCs **2b–d**, which were prepared from other imidazolium salts **1b–d** bearing a bulky alkyl group on the N atom (entries 2–4), were found to exhibit lower catalytic activity than **1a** under the identical conditions (0 °C, 30 min). During our search for cyanation, Boehringer Ingelheim Pharmaceuticals' group had independently reported[5a] the cyanosilylation of aldehydes[5b] and ketones using NHC, 1,3-di-*tert*-butylimidazol-2-ylidene (**2c**). The previous results with other organocatalysts[6] for cyanosilylation reaction of acetophenone (**3a**) with TMSCN, are as follows: 30 mol% of *N*-methylmorpholine *N*-oxide[6a] (8 h, r.t.), 2.5 mol% of quaternary ammonium salt and amine *N*-oxide[6b] (15 h, r.t.), 5 mol% of phenolic *N*-oxide[6c] (6 h, r.t.), 20 mol% of triethylamine[6d] (120 h, r.t.), 3 mol% of P[N(*i*-Pr)CH_2CH_2]$_3$N[6e] (1 h, r.t.).

Using the best imidazolium salt **1a** in *N*,*N*-dimethylformamide, cyanosilylation of several ketones **3b–g** was exam-

Table 1 Effects of NHCs and Solvents[a]



3a **4a**

Entry	Compound **1**	Solvent	Time	Yield of **4a** (%)
1	**1a**	THF	24 h	trace[b]
2	**1a**	DMF	30 min	59[b]
3	**1b**	DMF	30 min	42[b]
4	**1c**	DMF	30 min	54[b]
5	**1d**	DMF	30 min	43[b]
6[c]	**1a**	DMF	15 min	89
7[c,d]	**1a**	DMF	1 h	91

[a] The reactions were performed using acetophenone (**3a**), imidazolium salt **1** (5 mol%), *t*-BuOK (4 mol%), and TMSCN (1.5 mol equiv) in the shown solvent at 0 °C.
[b] Remainder of mass balance was the unreacted acetophenone (**3a**).
[c] The reactions were performed at r.t.
[d] Imidazolium salt **1a** (2.5 mol%) and *t*-BuOK (2 mol%) were used.

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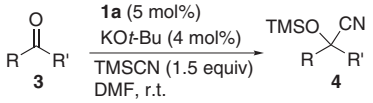
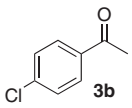
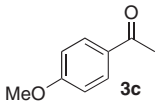
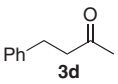
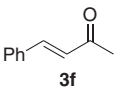
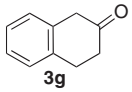
ined (Table 2). The presence of a chloro group or a methoxy group on the phenyl ring in the acetophenone derivative respectively enhanced or reduced the reaction rate due to electronic effects (entries 1 and 2). Acyclic, sterically hindered, and cyclic aliphatic ketones **3d**,**e**,**g** were converted to the corresponding silylated cyanohydrins in good yields (entries 3, 4, and 6). α,β-Unsaturated ketone **3f** was cyanated in only the 1,2-mode, and no 1,4-addition product was observed (entry 5).

Table 2 Cyanosilylation of Several Ketones[a]

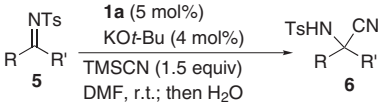


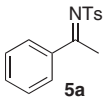
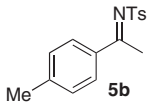
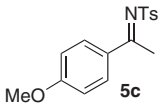
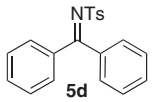
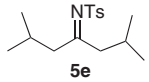
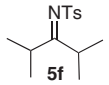
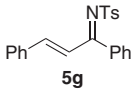
Entry	Ketone **3**	Time	Yield of **4** (%)
1	 **3b**	10 min	91 (**4b**)
2[b]	 **3c**	1 h	90 (**4c**)
3	 **3d**	5 min	94 (**4d**)
4	 **3e**	1 h	89 (**4e**)
5	 **3f**	20 min	87 (**4f**)
6	 **3g**	5 min	90 (**4g**)

[a] For detailed reaction conditions, see experimental section.
[b] TMSCN (3 mol equiv) was used.

Encouraged by the results obtained for ketones, the cyanation of ketimines was then examined. There is, to our knowledge, no example of the application of NHC as a nucleophilic organocatalyst for cyanation of ketimines.[7] The results with several ketimines **5a**–**g** are shown in Table 3. The yield of isolated products **6** is good in each case; the scope of the process includes not only a range of aromatic ketimines **5a**,**b**,**d** except for electron-rich ketimine **5c** but also sterically hindered aliphatic and α,β-unsaturated ketimines **5e**,**f**,**g**. Because of the difficulty in purifying the Ts-ketimines bearing a electron-withdrawing group, such as *N*-[1-(4-cyanophenyl)ethylidene]-4-methylbenzenesulfonamide and 4-methyl-*N*-[1-(4-nitrophenyl)ethylidene]benzenesulfonamide, the cyanation reactions with their ketimines were not performed.

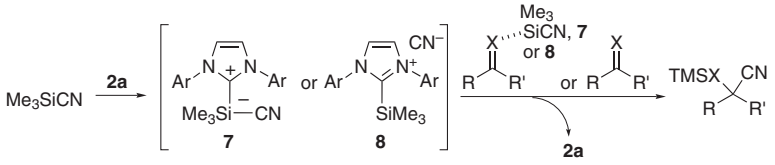
Table 3 Cyanation of Various Ketimines[a]



Entry	Ketimine **5**	Time (h)	Yield of **6** (%)
1	 **5a**	3 h	93 (**6a**)
2	 **5b**	3 h	99 (**6b**)
3	 **5c**	1 h	59[b] (**6c**)
4	 **5d**	4 h	88 (**6d**)
5	 **5e**	5 min	94 (**6e**)
6	 **5f**	5 min	84 (**6f**)
7	 **5g**	2 h	98 (**6g**)

[a] For detailed reaction conditions, see experimental section.
[b] Remainder of mass balance was the unknown product, which was decomposed by silica gel column.

We propose that this NHC **2a**-catalyzed cyanation follows a pathway involving activation of the carbon–silicon bond in TMSCN by a nucleophilic NHC catalyst, as shown in Scheme 2. NHC **2a** reacts with TMSCN to form hypervalent silicate **7** or TMS-imidazolium **8**.[2c] Subsequently, cyano-transfer occurs to afford the corresponding product, while regenerating NHC **2a**.



Scheme 2

In summary, N-heterocyclic carbene **2a** was found to function as a good catalyst in cyanation reaction of ketones and ketimines with TMSCN. This contribution should provide a new synthetic strategy for the construction of tetrasubstituted carbon by organocatalyst under mild reaction conditions. Ongoing efforts are focused on developing an asymmetric version[8] of this reaction with a chiral N-heterocyclic carbene.

IR spectra were measured on a JASCO IR Report-100 diffraction grating IR spectrophotometer. ^{1}H NMR (270 MHz) and ^{13}C NMR (68 MHz) spectra were measured on a JEOL JNM-EX-270 NMR spectrometer. EI–MS, HRMS, and FAB–MS spectra were measured on a JEOL JMS-SX-102A instrument. Commercially available imidazolium salts, TMSCN and *t*-BuOK were used without any purification. Tetrahydrofuran was distilled from Na/benzophenone ketyl under a nitrogen atmosphere. *N*,*N*-Dimethylformamide was distilled from CaH_2 under reduced pressure. Silica gel column chromatography was performed on Fuji silysia PSQ 60B.

Cyanosilylation of Ketone; Typical Procedure

To a stirred solution of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (**1a**; 5.1 mg, 15 μmol) in DMF (1.0 mL) was added *t*-BuOK (1.4 mg, 13 μmol) and the mixture was stirred for 15 min at r.t. After dissolving the imidazolium chloride **1a** completely, acetophenone (**3a**; 35 μL, 0.30 mmol) and TMSCN (56.5 μL, 0.45 mmol) were added to this mixture. The reaction mixture was stirred for 15 min at r.t., quenched with water and extracted with EtOAc. The organic extracts were successively washed with H_2O and brine, dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (hexane–EtOAc, 10:1; the silica gel was pretreated with 1% Et_3N in hexane) gave 2-phenyl-2-(trimethylsilanyloxy)propionitrile (**4a**; 58.6 mg, 89%) as a colorless oil. The physical data were comparable to those reported.[6a]

The physical data of the known silylated cyanohydrins shown below were comparable to those of the corresponding literature: 2-(4-chlorophenyl)-2-(trimethylsilanyloxy)propionitrile (**4b**),[6a] 2-(4-methoxyphenyl)-2-(trimethylsilanyloxy)propionitrile (**4c**),[6a] 2-methyl-4-phenyl-2-(trimethylsilanyloxy)butyronitrile (**4d**),[9] (3*E*)-2-methyl-4-phenyl-2-(trimethylsilanyloxy)but-3-enenitrile (**4f**).[6a]

3-Methyl-2-phenyl-2-(trimethylsilanyloxy)butyronitrile (4e)

Colorless oil.

IR (neat): 2232, 1254, 1099 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.10 (s, 9 H), 0.82 (d, *J* = 6.8 Hz, 3 H), 1.09 (d, *J* = 6.8 Hz, 3 H), 2.11 (sept, *J* = 6.8 Hz, 1 H), 7.29–7.41 (m, 3 H), 7.45–7.51 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 0.92, 17.25, 17.38, 41.54, 80.08, 119.80, 125.63, 128.14, 128.41, 140.07.

EI–MS: *m*/*z* = 247 [M$^+$], 204, 105.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{21}NOSi$: 247.1392; found: 247.1383.

2-(Trimethylsilanyloxy)-1,2,3,4-tetrahydronaphthalene-2-carbonitrile (4g)

Colorless oil.

IR (neat): 2232, 1254, 1127, 1103 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.26 (s, 9 H), 2.00–2.30 (m, 2 H), 2.95–3.05 (m, 2 H), 3.09 (d, *J* = 16.4 Hz, 1 H), 3.31 (d, *J* = 16.4 Hz, 1 H), 6.90–7.60 (m, 1 H), 7.07–7.17 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ = 1.45, 26.20, 35.69, 42.95, 68.45, 121.46, 126.15, 126.61, 128.49, 129.00, 131.13, 133.73.

EI–MS: *m*/*z* = 245 [M$^+$], 155, 104.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{19}NOSi$: 245.1236; found: 245.1232.

Cyanation of Ketimine: Representative Procedure

To a stirred solution of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (**1a**; 5.1 mg, 15 μmol) in DMF (1.0 mL) was added *t*-BuOK (1.4 mg,13 μmol) and the mixture was stirred for 15 min at r.t. After dissolving the imidazolium chloride **1a** completely, 4-methyl-*N*-(1-phenylethylidene)benzenesulfonamide (**5a**; 82.0 mg, 0.30 mmol) and TMSCN (56.5 μL, 0.45 mmol) were added to this mixture. The reaction mixture was stirred for 3 h at r.t., then quenched with H_2O at 0 °C and extracted with EtOAc. The organic extracts were successively washed with H_2O and brine, dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (hexane–EtOAc, 4:1) gave *N*-(1-cyano-1-phenylethyl)-4-methylbenzenesulfonamide (**6a**; 83.7 mg, 93%) as a white solid; colorless needles; mp 130–132 °C ($CHCl_3$–hexane).

IR (nujol): 3255, 2250, 1339, 1155 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.93 (s, 3 H), 2.41 (s, 3 H), 5.85 (s, 1 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.20–7.34 (m, 3 H), 7.41–7.51 (m, 2 H), 7.57 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 21.66, 30.33, 56.59, 118.92, 125.50, 127.29, 128.72, 129.05, 129.42, 136.96, 137.00, 143.86.

FAB–MS: *m*/*z* = 301 [M$^+$ + 1].

Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.74; H, 5.38; N, 9.16.

***N*-(1-Cyano-1-*p*-tolylethyl)-4-methylbenzenesulfonamide (6b)**

Colorless crystals; mp 129–130 °C ($CHCl_3$–hexane).

IR (nujol): 3258, 2248, 1335, 1151cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.90 (s, 3 H), 2.30 (s, 3 H), 2.40 (s, 3 H), 6.09 (s, 1 H), 7.03 (d, *J* = 8.1 Hz, 2 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 21.03, 21.59, 30.23, 56.29, 119.09, 125.40, 127.21, 129.16, 129.23, 133.90, 137.02, 138.91, 143.59.

FAB–MS: *m*/*z* = 315 [M$^+$ + 1].

Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91. Found: C, 64.95; H, 5.96; N, 8.83.

***N*-(1-Cyano-1-*p*-methoxyphenylethyl)-4-methylbenzenesulfonamide (6c)**

Colorless crystals; mp 152–154 °C ($CHCl_3$–hexane).

IR (nujol): 3234, 2245, 1336, 1151 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.91 (s, 3 H), 2.40 (s, 3 H), 3.77 (s, 3 H), 5.95 (s, 1 H), 6.74 (d, *J* = 8.8 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.8 Hz, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 21.60, 30.17, 55.34, 56.04, 113.85, 119.19, 126.97, 127.25, 128.74, 129.30, 137.09, 143.63, 159.84.

FAB–MS: *m*/*z* = 331 [M$^+$ + 1].

Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.51; H, 5.50; N, 8.43.

***N*-(Cyanodiphenylmethyl)-4-methylbenzenesulfonamide (6d)**

Colorless plates; mp 150–156 °C ($CHCl_3$–hexane).

IR (nujol): 3264, 2244, 1335, 1166 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3 H), 5.88 (s, 1 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 7.21–7.34 (m, 6 H), 7.36–7.47 (m, 4 H), 7.53 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 21.62, 63.59, 118.36, 126.60, 127.32, 128.71, 129.03, 129.25, 137.09, 137.34, 143.71.

FAB–MS: *m*/*z* = 363 [M$^+$ + 1].

Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.59; H, 5.01; N, 7.73. Found: C, 69.35; H, 5.02; N, 7.74.

_N_-(1-Cyano-1-isobutyl-3-methylbutyl)-4-methylbenzenesulfonamide (6e)
Colorless oil.

IR (neat): 3264, 2241, 1318, 1159 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.65–1.08 (m, 14 H), 1.78–1.85 (m, 4 H), 2.44 (br s, 3 H), 5.33 (br s, 1 H), 7.32 (br d, *J* = 8.2 Hz, 2 H), 7.85 (br d, *J* = 8.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 21.61, 21.67, 23.80, 23.85, 24.62, 47.87, 55.99, 118.54, 126.84, 127.36, 129.23, 129.44, 137.53, 143.11, 143.83.

FAB–MS: *m*/*z* = 323 [M^+ + 1].

EI–MS: *m*/*z* = 265 (M^+ – *i*-Bu), 155, 91.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{17}N_2O_2S$ (M^+ – *i*-Bu): 265.1011; found: 265.1010.

_N_-(1-Cyano-1-isopropyl-2-methylpropyl)-4-methylbenzenesulfonamide (6f)
Colorless crystals; mp 183–185 °C ($CHCl_3$–hexane).

IR (nujol): 3307, 2242, 1348, 1162, 1149 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.90 (d, *J* = 6.8 Hz, 6 H), 1.03 (d, *J* = 6.8 Hz, 6 H), 2.07 (sept, *J* = 6.8 Hz, 2 H), 2.43 (s, 3 H), 5.21 (s, 1 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 7.90 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 16.76, 18.35, 21.65, 35.44, 66.12, 116.27, 127.70, 129.37, 137.56, 143.60.

FAB–MS: *m*/*z* = 295 [M^+ + 1].

Anal. Calcd for $C_{15}H_{22}N_2O_2S$: C, 61.19; H, 7.53; N, 9.52. Found: C, 61.25; H, 7.49; N, 9.50.

(2*E*)-*N*-(1-Cyano-1,3-diphenyl-2-propenyl)-4-methylbenzenesulfonamide (6g)
Colorless crystals; mp 149–151 °C ($CHCl_3$–hexane).

IR (nujol): 3259, 2243, 1342, 1161 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.38 (s, 3 H), 5.81 (s, 1 H), 6.08 (d, *J* = 15.8 Hz, 1 H), 6.85 (d, *J* = 15.8 Hz, 1 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 7.20–7.38 (m, 8 H), 7.50–7.58 (m, 2 H), 7.62 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 21.62, 62.09, 116.99, 125.36, 125.76, 126.99, 127.76, 128.49, 128.79, 129.02, 129.33, 129.40, 132.65, 134.41, 136.44, 136.87, 143.97.

FAB–MS: *m*/*z* = 389 [M^+ + 1].

Anal. Calcd for $C_{23}H_{20}N_2O_2S$: C, 71.11; H, 5.19; N, 7.21. Found: C, 71.17; H, 5.33; N, 7.18.

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