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Nucleophilic Addition of Alkanenitriles to Aldehydes via N-Silyl Ketene Imines Generated In Situ

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Abstract Upon treatment with triisopropylsilyl trifluoromethanesulfonate and 2,2,6,6-tetramethylpiperidine, alkanenitriles undergo direct addition to aldehydes under mild non-basic neutral conditions to provide triisopropylsilylethers of β-hydroxy nitriles in good yield. The reaction proceeds via in situ generation of an N-silyl ketene imine intermediate from the alkanenitrile followed by nucleophilic addition of the intermediate to the aldehyde.

Key words nitriles, nitrile aldol reaction, nucleophilic addition, N-silyl ketene imines, aldehydes

Nucleophilic addition of nitriles to carbonyl compounds (i.e., the nitrile aldol reaction) is a useful transformation in organic synthesis because of the high synthetic utility of β-hydroxy nitrile products owing to the versatile convertibility of the nitrile functionality. Traditionally, the reaction is carried out through deprotonation of nitriles followed by addition to carbonyl compounds. However, the generation of α-cyano carbamions from simple unactivated alkanenitriles (e.g., pKₐ 31.3 in dimethyl sulfoxide for acetonitrile) requires a stoichiometric amount of a strong base such as lithium diisopropylamide (LDA), which is incompatible with base-sensitive substrates. In addition, strongly basic conditions sometimes cause undesirable reactions, including β-elimination by dehydration to give the corresponding α,β-unsaturated nitriles and retro-additions. Recently, several types of catalytic activation of nitriles as nucleophiles have been established, which has led to successful metal-catalyzed nucleophilic additions of unactivated alkanenitriles to aldehydes. However, these catalytic reactions still have some drawbacks, for which excess amounts of nitrile (>5 equiv) are generally required. Thus, a new methodology that allows the nucleophilic addition of unactivated alkanenitriles to carbonyl compounds under mild reaction conditions without requiring excess substrates would be highly valuable.

N-Silyl ketene imines, which are typically prepared by lithiation of alkanenitriles with a strong base such as LDA followed by trapping with a bulky trialkylsilyl chloride, have recently attracted much attention as a competent α-cyano carbamion equivalent (Scheme 1). Although N-silyl ketene imines show synthetic potential, considerable drawbacks remain in their handling and storage instability because they are rapidly hydrolyzed with water. In this context, we reported that N-silyl ketene imines could be generated in equilibrium by treatment of alkanenitriles with trialkylsilyl triflate (R₃SiOTf) and a tertiary amine (Scheme 1). These mild and non-basic generation conditions allowed the development of several C-C bond forming reactions that do not require isolation of the labile N-silyl ketene imines.

Motivated by our interest in new reaction development by using in situ generated N-silyl ketene imines, we expected that treatment of a mixture of aldehydes 1 and alkanenitriles 2 with R₃SiOTf and tertiary amine would directly yield α-trialkylsilyl β-hydroxy nitriles 3 (Scheme 2). The reaction would proceed through in situ formation of the highly electrophilic silyloxonium intermediate 4 and N-silyl ketene imine 5, followed by addition of 5 to 4. We report herein trialkylsilyl triflate and alkylamine promoted novel nucleophilic addition reactions of nitriles to aldehydes, which offer an efficient synthetic method for β-hydroxy nitrile derivatives under non-basic mild conditions. This new method does not require preformation of the labile N-silyl ketene imine nucleophile or excess substrates. This is the nitrile analogue of a formal one-pot Mukaiyama aldol reaction.
To ascertain the feasibility of the proposed addition reaction, we initially tested the reaction of benzaldehyde (6) with phenylacetonitrile (7; Scheme 3). When 6 (1 equiv) and 7 (1 equiv) were treated with triethylsilyl trifluoromethanesulfonate (TESOTf; 2 equiv) and triethylamine (2 equiv) in 1,2-dichloroethane (DCE), the expected O-TES β-hydroxynitrile 8 was obtained in 41% yield as a 51:49 diastereomeric mixture; however, a considerable amount (52% yield) of the corresponding desilylated product 9 was also obtained due to the instability of the TES ether in the reaction medium. To suppress this desilylation side product, we next tested the ability of a more robust silyl group in the reaction. Happily, the use of trispropylysilyl trifluoromethanesulfonate (TIPSOTf) led to quantitative formation of O-TIPS β-hydroxynitrile 10. However, the reaction of 6 with the sterically hindered nitrile 11 gave inferior results with the TIPSOTf/Et3N system, and addition product 12 was obtained in 64% yield along with TIPS ether 13 (7% yield), which is derived from hydrosilylation of 6 as a side reaction product.11

| Table 1 Optimization of Amines for Addition of Nitrile 11 to Benzaldehyde (6) |
|---------------------------------|-----------------|----------------|
| Entry  | Amine  | Temp. (°C) | Yield (%)* |
| 1      | DIPEA  | 50 to 80   | 6 (55:45)   | 35 |
| 2      | PMP    | 50 to 80   | 0            | 70 |
| 3      | DABCO  | 50 to 80   | 0            | 0  |
| 4      | 2,6-lutidine | 50 to 80  | trace        | 0  |
| 5      | TMP    | r.t.       | 85 (55:45)* | 0  |
| 6      | HMDS   | 50 to 80   | 0            | trace |

* Reaction conditions: aldehyde 6 (0.4 mmol), nitrile 11 (0.4 mmol), TIPSOTf (0.8 mmol), amine (0.8 mmol), DCE (2 ml), 80 min-21 h.
11 Yield determined by 'H NMR spectroscopic analysis of the crude product mixture by using pyrazine as an internal standard.
12 Diastereomeric ratios of 12 are given in parentheses. The relative configuration was not assigned.
13 Yield of isolated product after purification by silica gel column chromatography.

With the optimized reaction conditions using the TIPSOTf/TMP system in hand, we next investigated the reactions of benzaldehyde (6) with a series of nitriles (Table 2). The results show that the reaction has broad applicability to nitriles including simple unactivated alkenanitrides (i.e., 14a, 14b, and 14e). The α-alkyl nitriles 14a,b, α-aryl nitriles 7 and 14c,d, acetonitrile (14e), and α-halo nitrile 14f afforded the corresponding O-TIPS β-hydroxy nitriles in good to excellent yields (entries 1–7). Note that the reactions of unactivated nitriles 14a and 14b with 6 under the TIPSOTf/Et3N system provided no addition products 15a,b, which clearly indicated the unique and remarkable reactivity of TMP as an amine base.14 α,α-Disubstituted nitriles including isobutyronitrile (14b), 2-phenylpropanenitrile (14c), and diphenylacetonitrile (14d)
gave addition products with a newly formed quaternary carbon atom in good yields, indicating the advantage of the sterically unhindered nitrile group (entries 3–5). When an equimolar amount of acetonitrile was used in this addition, an inseparable mixture of the desired product 15e, the double aldol type addition product (not shown), and the C-silylation product, i.e., 2-(trisopropylsilyl)acetonitrile, was obtained. Thus, excess amounts of nitrile were used in the case of acetonitrile (14e) to prevent these side reactions (entry 6). Although chloroacetonitrile (14f) produced the desired product in good yield (entry 7),\(^*\) fluoroacetonitrile (14g) remained unreactive (entry 8). The diastereomeric ratio of addition products 15, however, remained low (68:32–50:50).

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\(^a\) Reaction conditions: aldehyde 6 (0.4 mmol), nitrile 14 or 7 (0.4 mmol), TIPSOTI (0.8 mmol), TMP (0.8 mmol), DCE (2.0 mL), r.t., 30 min–140 min.  
\(^b\) Yield of isolated product after purification by silica gel column chromatography.  
\(^c\) Determined by \(^1\)H-NMR spectroscopic analysis of the crude product; relative stereochemistry not assigned.  
\(^d\) Acetonitrile was used as the solvent (0.2 M). Two equivalents of TIPSOTI and TMP were used.  
\(^e\) Toluene was used as the solvent. Reaction temperature was 100 °C.  
\(^f\) Reaction temperature was 80 °C.

The synthetic advantage of our new method over the standard method under anionic conditions\(^3\) is clearly demonstrated in Scheme 4. Namely, our addition reaction of base-sensitive 3-(benzyloxy)propanenitrile (14b) to benzaldehyde (6) with TIPSOTI and TMP gave addition product 15b in 81% yield. By contrast, \(\beta\)-hydroxy nitrile 16 was not obtained under the conventional anionic conditions with LDA as a base because competitive \(\beta\)-elimination of the benzyloxy group from the resulting \(\alpha\)-cyano carbanion occurred even at –78 °C.

<table>
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\(^a\) Reaction conditions: aldehyde 17 (0.4 mmol), nitrile 7 or 14 (0.4 mmol), TIPSOTI (0.8 mmol), TMP (0.8 mmol), DCE (2.0 mL), r.t., 30 min–140 min.  
\(^b\) Yield of isolated product after purification by silica gel column chromatography.  
\(^c\) Determined by \(^1\)H-NMR spectroscopic analysis of the crude product; relative stereochemistry not assigned.  
\(^d\) Acetonitrile was used as the solvent (0.2 M). Two equivalents of TIPSOTI and TMP were used.  
\(^e\) Toluene was used as the solvent. Reaction temperature was 100 °C.  
\(^f\) Reaction temperature was 80 °C.
Finally, nucleophilic addition to a ketone was briefly examined to evaluate the synthetic potential of this reaction (Scheme 5). Thus, upon treatment with TIPSOTf and TMP at room temperature, nitrile 7 underwent an efficient addition reaction with benzophenone (22) to afford adduct 23 in 97% yield.

In conclusion, we have developed a novel method for nucleophilic addition reactions of alkanonitriles, including simple unactivated nitriles, to aldehydes promoted by TIPSOTf and TMP under mild silylation conditions.15 The reaction appears to proceed via in situ N-silyl ketene imine formation followed by a Mukaiyama aldol-type reaction.16 The synthetic benefits of the reaction include the avoidance of preformation and isolation of labile N-silyl ketene imines. The non-basic mild reaction conditions mean that the present method tolerates many functional groups and provides β-hydroxy nitrile products with a high yield without β-elimination and retro-additions, which sometimes occur with conventional anionic conditions. The new method does not require excess substrates and will offer an efficient route to β-hydroxy nitrile derivatives, which serve as useful intermediates in the synthesis of natural products and biologically active substrates. Further studies will focus on the reaction of in situ generated N-silyl ketene imines to other classes of electrophiles.

Acknowledgment

We acknowledge Dr. Eri Fukushi and Mr. Yusuke Takata (GC-MS & NMR Laboratory, Faculty of Agriculture, Hokkaido University) for performing mass spectral measurements. This work was supported by a Grant for Basic Science Research Projects from The Sumitomo Foundation (to Y.F.) and JSPS KAKENHI Grant Numbers JP15K01795 (to Y.F.), JP15H05842 (to K.T.), and JP15H05842 in Middle-Molecular Strategy (to K.T.).

References and Notes


8 Emde, H.; Simchen, G. Synthesis 1977, 636.

9 It has been reported that N-(trimethylsilyl)diphénylketene imine undergoes nucleophilic addition to several benzaldehyde derivatives under solvent-free conditions; see: Cazeau, P.; Lomisch, J.-P.; Simonin-Dabescat, F.; Frainet, E. J. Organomet. Chem. 1976, 105, 145.


12 The combination of TIPSOTf and PMP smoothly promoted hydrosilylation of benzaldehyde (6) to afford TIPS ether 13 in 82% yield (Scheme 6).

13 A deuterium-labeling experiment proved that PMP acts as the hydride source (Scheme 7).

Supporting Information

YES

Primary Data

NO
PhCHO $+\text{Me}_2\text{TIPSOTf (2.0 equiv)}$

$\text{Me}_2\text{DCE (0.2 M)}$

$80^\circ\text{C}, 9\text{ h}$

87%

$\text{Me}_2\text{Ph OTIPS}$

$>99\text{D}$

$\text{CD}_3\text{N Me}$

$\text{Me}_2\text{D}$

$\text{Ph H}$

$\text{O}$

$\text{Si(\text{i-Pr})}_3$

$\text{D N D}$

$\text{Me}_2\text{Me}$

Scheme 7

(14) The reason for the superior reactivity of TMP is not clear yet. Very low solubility of 2,2,6,6-tetramethylpiperidinium triflate (TfOH·TMP) in DCE might cause the equilibrium shifts slightly toward the $N$-silyl ketene imine.

(15) When DCE was used as the solvent, a significant amount of inseparable double aldol type addition product accompanied 15f. Solvent screening revealed that toluene could suppress such side reactions, although it required heating of the reaction mixture to 100°C.

(16) General Procedure (Table 1, Entry 5): To a mixture of benzaldehyde (6; 40.8 µL, 0.400 mmol), 2-methoxy-2-phenylacetonitrile (11; 55.5 µL, 0.400 mmol), and 2,2,6,6-tetramethylpiperidine (136 µL, 0.800 mmol) in DCE (2.0 mL) was added TIPSOTf (215 µL, 0.800 mmol), and the mixture was stirred at room temperature for 22 h, at which point the consumption of starting materials 6 and 11 was complete (as determined by TLC analysis, hexane:EtOAc = 4:1). After cooling to 0 °C, the reaction was quenched by slow addition of saturated aqueous NaHCO$_3$ (1 mL), and the resulting mixture was filtered through a cotton plug to remove the precipitate (risen with CH$_2$Cl$_2$). The filtrate was extracted with CH$_2$Cl$_2$ (1 mL×3). The combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO$_2$, hexane:EtOAc = 50:1) to give nitrile 12 (139.6 mg, 0.341 mmol, 85% yield) as an inseparable 55:45 mixture of diastereomers.

Compound 12: Colorless oil; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.53–7.51 (1H, m), 7.40–7.36 (3H, m), 7.31–7.27 (2H, m), 7.22 (1H, t, $J$ = 7.4 Hz), 7.13–7.04 (2H, m), 6.92 (1H, m), 4.98 (0.55H, s), 4.97 (0.45H, s), 3.34 (0.45×3H, s), 3.18 (0.55×3H, d, $J$ = 1.15–1.09 (0.45×3H, m), 1.06 (0.45×9H, d, $J$ = 6.9 Hz), 1.00 (0.45×9H, d, $J$ = 7.5 Hz), 0.81–0.74 (0.55×21H, m); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 139.08, 137.95, 134.79, 133.93, 129.21, 128.99, 128.51, 128.45, 128.18, 128.09, 127.96, 127.86, 127.76, 127.41, 127.20, 127.07, 117.15, 116.89, 88.12, 86.64, 81.44, 81.06, 54.03, 53.97, 17.87, 17.82, 17.70, 17.63, 12.44, 12.40; IR (ATR) ν 2943, 2867, 2365, 1122, 1069 cm$^{-1}$; HRMS (FD) calcld for C$_{25}$H$_{36}$NO$_2$Si ([M+H]$^+$): 410.2515, found: 410.2484.

(17) Attempts to detect $N$-silyl ketene imine intermediates by $^1$H- or $^{13}$C-NMR were unsuccessful, suggesting that these reactive species in equilibration with the corresponding nitriles are existing only in low concentration. The reaction of 6 with 11 did not proceed in the absence of either TIPSOTf or TMP. The alkanenitrile underwent isomerization at the $\alpha$-position of the cyano group by treatment with TIPSOTf/TMP (i.e., nitrile 28 in Scheme S2). These results support that the nucleophilic addition should proceed via the $N$-silyl ketene imine intermediate. For details, see Scheme S2 in the Supporting Information.