Nucleophilic Addition Reactions of Nitriles to Nitrones under Mild Silylation Conditions

Fumihiko Yoshimura,*[a] Taiki Abe,[b] Keiji Tanino*[a]

[a] Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan
Fax +81(11)7064920; E-mail: fumi@sci.hokudai.ac.jp; E-mail: ktanino@sci.hokudai.ac.jp

[b] Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo 060-0810, Japan

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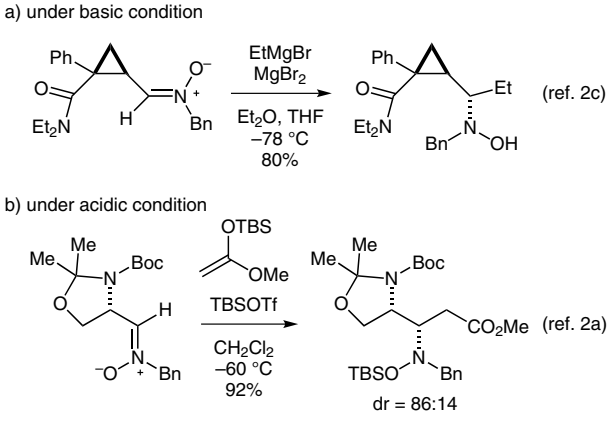
Abstract: In the presence of triethylsilyl trifluoromethanesulfonate and triethylamine, aliphatic nitriles undergo addition reactions with aldonitrones under non-basic, mild conditions, providing *O*-triethylsilyl ethers of β-*N*-hydroxyamino nitriles with high yield. The reaction appears to proceed through formation of an *N*-silyl ketene imine in situ followed by a Mannich-type reaction.

Key words: nucleophilic addition, nitriles, nitrones, amines, hydroxylamine

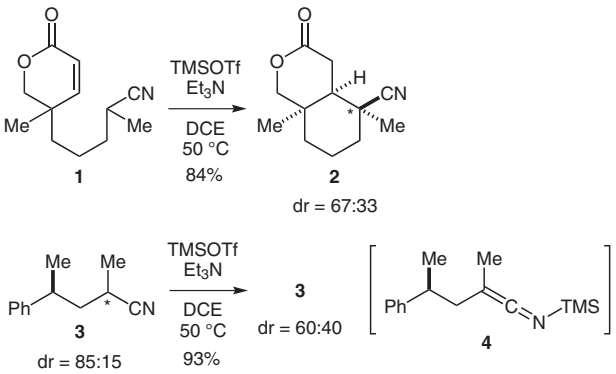
The addition reaction of nucleophiles to nitrones is one of the most powerful and reliable methods for the synthesis of α-branched *N*,*N*-disubstituted hydroxylamine derivatives.[1] Among various nucleophiles, organometallic reagents such as Grignard and organolithium reagents are frequently used in these types of reactions under basic (anionic) conditions (Scheme 1).[1,2] Similar to the Mukaiyama aldol reaction and the Hosomi–Sakurai allylation reactions, silyl enol ethers, silyl ketene acetals, and allylsilanes are also used in this process under acidic conditions (Scheme 1).[1,2] On the other hand, the addition reactions of nitrones with nitriles have rarely been explored under both basic and acidic conditions.[3]



Scheme 1 Typical examples of nucleophilic addition to nitrones

As a highly competent nitrile anion equivalent, *N*-silyl ketene imines, which are prepared by trapping of the anion with a bulky trialkylsilyl chloride, have been of much interest for the last decade.[4] Although a number of considerable drawbacks remain in their handling and storage due to the high tendency toward hydrolysis, *N*-silyl ketene imines react with a range of carbonyl electrophiles as well as *N*-acylhydrazones and *N*-arylaldimines,[5] giving rise to the corresponding α-substituted nitriles under mild conditions.

In the course of our studies on the development of new synthetic reactions using α-cyano carbanions,[6] we recently reported the intramolecular conjugate addition of α,β-unsaturated lactones having an alkanenitrile side chain promoted by TMSOTf and triethylamine (Et_3N) (Scheme 2, **1**→**2**).[7] The cyclization reaction is thought to proceed through formation of the *N*-silyl ketene imine intermediate under the influence of TMSOTf and Et_3N. Indeed, a 85:15 diastereomeric mixture of acyclic nitrile **3** was found to undergo isomerization to afford a 60:40 mixture of the diastereomers under similar conditions.[8] These results suggested that the combined use of TMSOTf and Et_3N shows promise for generating an *N*-silyl ketene imine from the corresponding nitrile without requiring a strong base such as lithium diisopropylamide (LDA).[9]



Scheme 2 TMSOTf–Et_3N promoted intramolecular conjugate addition and its mechanistic investigation

Based on these findings, we envisaged that the addition reaction between nitrones and nitriles would proceed under mild neutral conditions. Namely, treatment of a mixture of nitrones **5** and nitriles **6** with trialkylsilyl triflate and Et_3N would directly yield *O*-trialkylsilyl β-hydroxyamino nitrile **7** through the formation of *N*-siloxyiminium ion **8**[10] and *N*-silyl ketene imine **9** in situ (Scheme 3). This process would provide a simple and efficient synthetic

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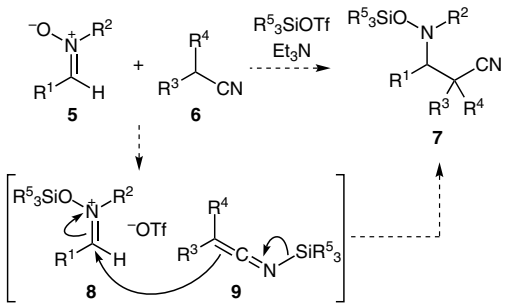
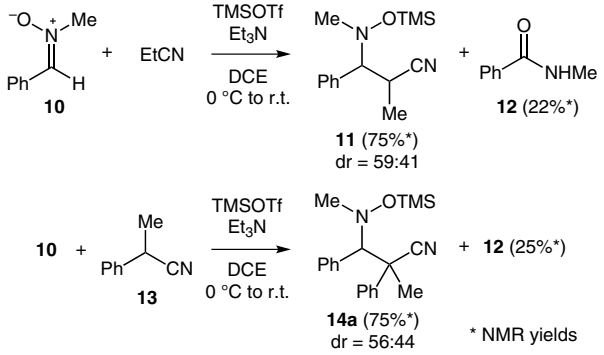
method for the generation of β-aminonitrile derivatives that are useful synthetic intermediates and important structural motifs in biologically active compounds, including β-amino acids and 1,3-diamines.[11]



Scheme 3 Proposal for addition reactions of nitriles to nitrones

To ascertain the feasibility of the expected addition reaction, we initially attempted the reaction of *N*-benzylideneemethanamine *N*-oxide (**10**) with propionitrile (Scheme 4). To our delight, the desired *O*-TMS β-hydroxyamino nitrile **11** was obtained in 75% yield as a 59:41 diastereomeric mixture when nitrone **10** (1 equiv) and propionitrile (1 equiv) were treated with TMSOTf (2 equiv) and Et_3N (2 equiv). However, a considerable amount of amide **12**, arising from **10** through a rearrangement pathway,[12,13] was formed in 22% yield. The reaction of **10** with 2-phenylpropanenitrile (**13**) gave similar results, and addition product **14a**, having a quaternary carbon atom, was obtained in 75% yield along with **12** (25% yield).

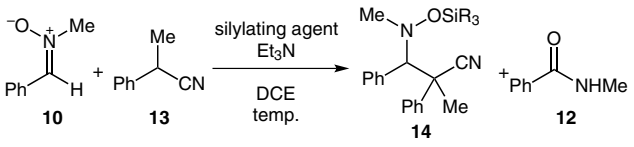


Scheme 4 Preliminary results

With a view to diminishing the competitive rearrangement pathway, the reactions of nitrile **13** and nitrone **10** with various silylating agents were explored as shown in Table 1. The use of TMSBr failed to promote the addition reaction, and amide **12** was obtained as the major product (entry 2). On the other hand, the reaction mediated by $TMSNTf_2$[14] afforded *O*-TMS β-hydroxyamino nitrile **14a** in excellent yield (93% by NMR spectroscopic analysis of the crude mixture; entry 3). However, purification of the crude product by silica gel column chromatography led to hydrolysis of the silyloxy group, which prompted us to employ the use of more bulky silylating reagents. Whereas the use of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) led to poor results (entry 4), triethylsilyl trifluoromethanesulfonate (TESOTf) gave promising results, with the stable *O*-TES β-hydroxyamino nitrile **14c** formed in 80% yield along with 12% yield of amide **12** (entry 5). After optimization of the reaction conditions, the best result was obtained at –30 °C, providing **14c** in 94% yield (*dr* 55:45) after purification (entry 6).

Note that the reaction with 1.1 equivalents of TESOTf and Et_3N at –30 °C resulted in the formation of **14c** only in 19% yield along with 49% of **12**, indicating that the use of two equivalents of both reagents, i.e., stoichiometric amounts, is of critical importance for this reaction. Unfortunately, although the reaction proceeded with excellent yield, diastereoselectivity was not induced, likely due to low level of stereodiscrimination in the addition step.

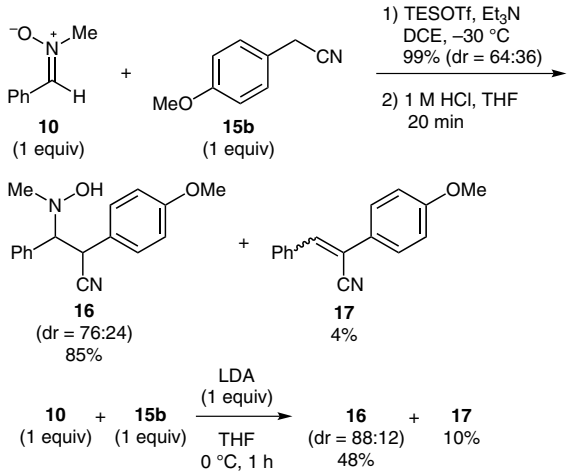
Table 1 Evaluation of Silylating Agents for the Addition Reaction of Nitrile **13** to Nitrone **10**[a]



Entry	Silylating agent	Temp. (°C)	Yield (%)[b]		
			14 (dr)[c]		**12**
1	TMSOTf	0 → r.t.	**14a**	75 (56:44)	25
2	TMSBr	0 → 80	**14a**	0	75
3	$TMSNTf_2$	0 → r.t.	**14a**	93 (59:41)	6
4	TBSOTf	0	**14b**	57 (51:49)	42
5	TESOTf	0	**14c**	80 (54:46)	12
6	TESOTf	–30	**14c**	94[d] (55:45)	0

[a] Reaction conditions: nitrone **10** (0.2 mmol), nitrile **13** (0.2 mmol), Et_3N (0.4 mmol), DCE (1 mL), silylating agent (0.4 mmol).
[b] Yield determined by ^1H NMR analysis of the crude product mixture using pyrazine as internal standard.
[c] Diastereomeric ratios of **14** given in parentheses. The relative configuration was not determined.
[d] Isolated yield after silica gel column chromatography on 0.4 mmol scale.

The synthetic advantage of our new method over the conventional method under anionic conditions[3] is demonstrated in Scheme 5. Thus, the addition reaction of 4-methoxyphenylacetonitrile (**15b**) to nitrone **10** under the influence of TESOTf and Et_3N gave base-sensitive β-hydroxyamino nitrile **16** in good yield after removal of the TES group under acidic conditions (85% yield for two steps). In contrast, the α-cyano carbanion generated from **15b** by LDA underwent the addition reaction with nitrone **10** to afford **16** only in 48% yield, along with the β-elimination product **17** (10% yield) and recovery of the substrates (**10**: 21%; **15b**: 35%).



Scheme 5 Comparison with a conventional method

We next applied the optimized reaction conditions using TESOTf to the reactions of nitrone **10** with a series of nitriles (Table 2). Gratifyingly, simple alkanenitrile **15a**, α-aryl acetonitriles **15b**–**d**, and α-heteroaryl acetonitriles **15e**–**g** afforded the corresponding *O*-TES β-hydroxyamino nitriles **18** in good to excellent yields (entries 1–7), although the diastereomeric ratios of **18** were rather low (74:26 to 58:42). In the case of the reaction of 2-pyridylacetonitrile (**15e**), TESOTf–Et_3N reagent triggered the elimination reaction of *O*-TES hydroxylamine from the desired product **18e**, giving (*Z*)-3-phenyl-2-(pyridin-2-yl)acrylonitrile (**19**; Figure 1) in 38% yield along with **18e** (entry 5). α,α-Disubstituted nitriles, including isobutyronitrile (**15h**) and diphenylacetonitrile (**15i**), gave addition products having the newly formed quaternary carbon atom in good yields (entries 8 and 9), although two equivalents of nitrile **15h** were required because of its low reactivity (entry 8). Note that the neutral reaction conditions using TESOTf–Et_3N allows the use of nitriles with various functional groups, and chloroacetonitirile (**15j**) and *N*-(diphenylmethylene)aminoacetonitrile (**15k**) afforded the desired products in excellent yields (entries 10 and 11).

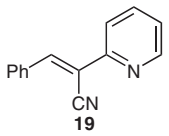
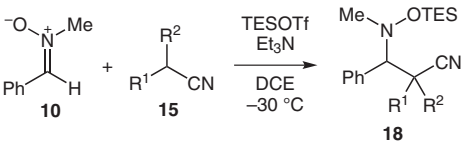
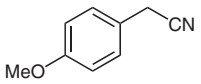
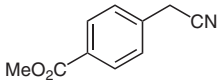
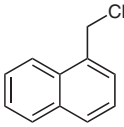
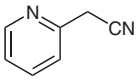
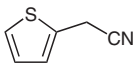
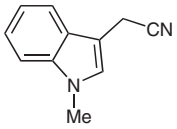
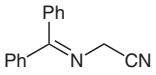


Figure 1 Structure of **19**

The scope of the reaction with respect to nitrones was then examined by using nitrile **15b** as a nucleophile (Table 3). Addition of **15b** to aromatic nitrones **20a**–**c** proceeded smoothly to furnish the corresponding *O*-TES β-hydroxyamino nitriles in good to excellent yields (entries 1–3). Chemoselective addition to the nitrone moiety was achieved in the reaction of **20c**, keeping the ester group intact (entry 3). The reaction of endocyclic nitrone **20d** provided tetrahydroisoquinoline derivative **21d** as a single diastereomer (entry 4).[15,16] Addition to α,β-unsaturated nitrone **20e** occurred exclusively in a 1,2-fasion (entry 5). Whereas the addition reaction was applicable to an α,α-disubstituted aliphatic nitrone (entry 6), aliphatic nitrone **20g**, bearing an acidic α-proton, failed to react with nitrile **15b**, resulting in decomposition under the reaction conditions (entry 7).[17]

Table 2 Reactions of Nitrone **10** with Nitriles **15**[a]

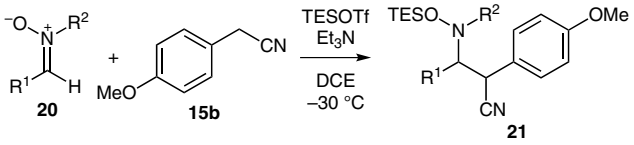


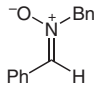
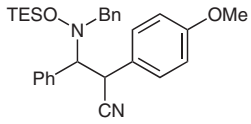
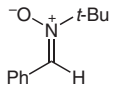
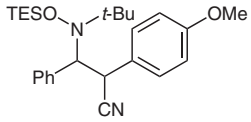
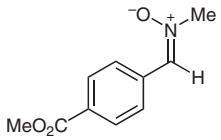
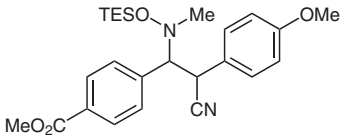
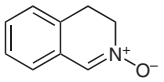
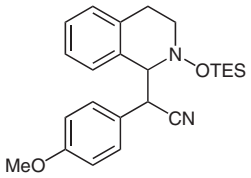
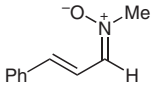
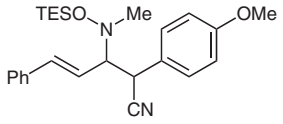
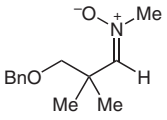
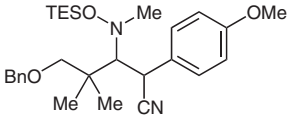
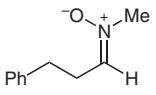
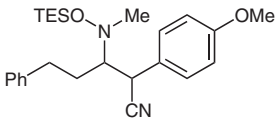
Entry	Nitrile **15**		**18**	Yield (%)[b]	*dr*[c]
1	**15a**	EtCN	**18a**	94	60:40
2	**15b**		**18b**	99	64:36
3	**15c**		**18c**	96	58:42
4	**15d**		**18d**	95	74:26
5	**15e**		**18e**	58[d]	69:31
6	**15f**		**18f**	95	59:41
7	**15g**		**18g**	100	68:32
8	**15h**	*i*-PrCN[e]	**18h**	79[f]	–
9	**15i**	Ph_2CHCN[g]	**18i**	84[h]	–
10	**15j**	$ClCH_2CN$	**18j**	99	79:21
11	**15k**		**18k**	98	73:27

[a] Reaction conditions: nitrone **10** (0.4 mmol), nitrile **15** (0.4 mmol), TESOTf (0.8 mmol), Et_3N (0.8 mmol), DCE (2 mL), –30 °C, 0.5 to 1.5 h.
[b] Isolated yield after purification.
[c] Determined by ^1H NMR analysis of the crude product; relative stereochemistry not assigned.
[d] (*Z*)-3-Phenyl-2-(pyridin-2-yl)acrylonitrile (**19**; Figure 1) was obtained in 38% yield.
[e] Nitrile (2 equiv.) was used.
[f] Yield based on **10**. Amide **12** was obtained in 13% yield.
[g] Reaction conditions: –30 to 0 °C, 1.5 h.
[h] Amide **12** was obtained in 6% yield.

Finally, transformations of the *O*-TES β-hydroxyamino nitriles were briefly examined to evaluate the synthetic utility and versatility of the addition products (Scheme 6). Nitrile **18h** was converted into the corresponding amine **22** by treatment with Zn/H_2SO_4, whereas the reaction of **18h** with Zn/TFA in MeOH at 60 °C afforded amide **23**. In addition, nitrile **18h** was converted into β-amino acid **25** through isoxazolidin-5-one formation followed by N–O cleavage under hydrogenation. Furthermore, 1,3-diamine derivative **26** was obtained by reduction of the cyano group using $LiAlH_4$. Conversely, upon treatment with LDA at 0 °C, nitrile **18a** underwent a 3-*exo*-tet ring-

Table 3 Reactions of Nitrones **20** with Nitrile **15b**[a]

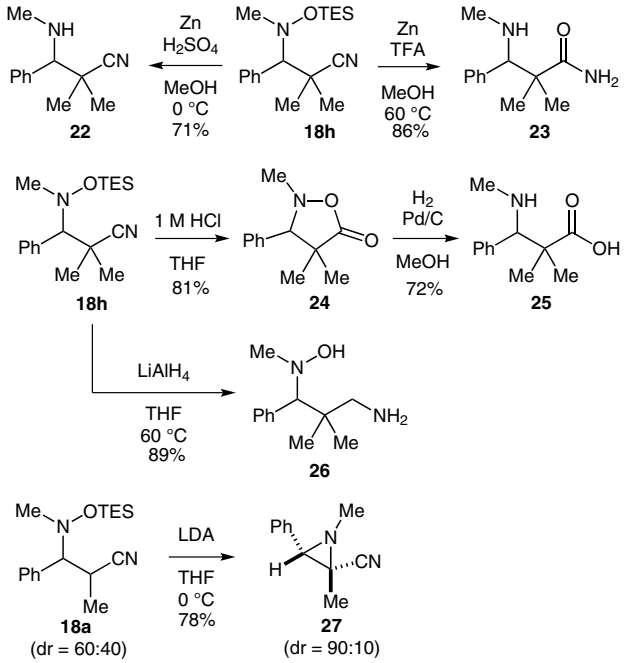


Entry	Nitrone	Product	Yield (%)[b]	*dr*[c]
1	 **20a**	 **21a**	100	74:26
2	 **20b**	 **21b**	85	91:9
3	 **20c**	 **21c**	96	56:44
4	 **20d**	 **21d**	81	100:0
5	 **20e**	 **21e**	77	50:50
6	 **20f**	 **21f**	83	58:42
7	 **20g**	 **21g**	0	–

[a] Reaction conditions: nitrone **20** (1 equiv), nitrile **15b** (1 equiv), TESOTf (2 equiv), Et_3N (2 equiv), DCE (0.2 M), –30 to 0 °C, 0.5 to 3 h.
[b] Isolated yield after purification.
[c] Determined by ^1H NMR analysis of the crude product; relative stereochemistry not assigned.

closure reaction,[18] giving rise to *N*-methylaziridine **27** with high diastereoselectivity.

In conclusion, we have developed a novel method for nucleophilic addition reaction of nitriles to nitrones promoted by TESOTf and Et_3N under mild conditions.[19] The reaction appears to proceed through *N*-silyl ketene imine formation in situ followed by a Mannich type addition reaction. In contrast to the conventional addition reactions using strong bases, the nonbasic, mild reaction conditions of the present method tolerates various functional groups and usually provides the β-aminonitrile derivatives in high yields without causing β-elimination reactions or retro-addition reactions. The new method is expected to offer an efficient route to base-sensitive β-aminonitrile derivatives, which serve as useful intermediates in the synthesis of biologically important compounds, including β-amino acids and 1,3-diamines.



Scheme 6 Transformations of the addition products

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(8) We could not detect *N*-silyl ketene imine **4** when monitoring the reaction by ^1H and ^{13}C NMR spectroscopy. The isomerization of **3** did not proceed in the absence of either TMSOTf or Et_3N. Accordingly, very reactive intermediate **4** was immediately protonated by triethylamine salt of triflic acid generated in situ as a proton source, providing the isomerized product **3**.

(9) In this connection, Emde and Simchen reported that silylation of acetonitrile with excess TMSOTf and Et_3N in ether gave a mixture of $(Me_3Si)_2C{=}C{=}N(SiMe_3)$ (44%) and $(Me_3Si)_3CCN$ (56%), see: Emde, H.; Simchen, G. *Synthesis* **1977**, 6363.

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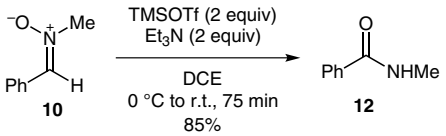
(12) Interestingly, the combination of TMSOTf and Et_3N smoothly promoted rearrangement of an aromatic aldonitrone to the isomeric amide (Scheme 7).



Scheme 7

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(15) All attempts to determine the relative stereochemistry of nitrile **21d** were unsuccessful.

(16) The reason for the high stereoselectivity observed in the formation of nitrile **21d** is not yet clear.

(17) It is assumed that aliphatic nitrone **20g** decomposed through formation of the corresponding *N*-triethylsiloxyenamine derivative and subsequent self-condensation or polymerization.
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(19) **General Procedure (Table 1, entry 6):** To a mixture of nitrone **10** (0.4 mmol), nitrile **13** (0.4 mmol), and Et_3N (0.8 mmol) in DCE (2 mL), was added TESOTf (0.8 mmol) at –30 °C, and the reaction mixture was stirred at this temperature for 30 min. Sat. aq sodium bicarbonate (1 mL) was added to the mixture, and the product was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; hexane–Et_2O, 15:1) afforded *O*-TES β-hydroxyamino nitrile **14c** (0.377 mmol, 94%).

