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Citation	Synlett, 25(13), 1863-1868 https://doi.org/10.1055/s-0034-1378274
Issue Date	2014-08
Doc URL	https://hdl.handle.net/2115/59743
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Type	journal article
File Information	Synlett_25_1863-.pdf



Nucleophilic Addition Reactions of Nitriles to Nitrones under Mild Silylation Conditions

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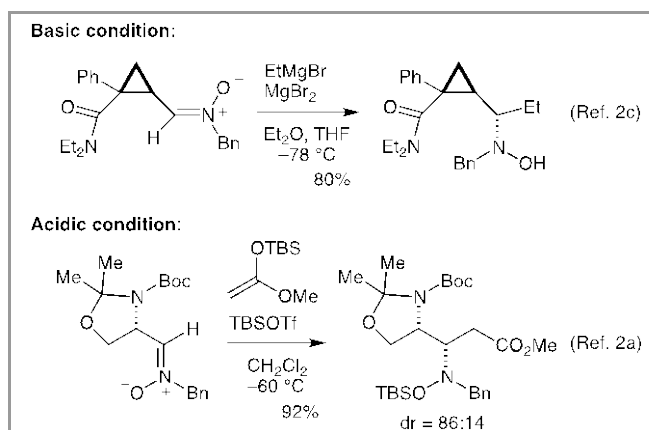
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Received: The date will be inserted once the manuscript is accepted.

Abstract: In the presence of triethylsilyl trifluoromethanesulfonate (TESOTf) and triethylamine (Et₃N), aliphatic nitriles undergo addition reactions with aldonitrones under non-basic mild conditions, providing *O*-triethylsilyl ethers of β -*N*-hydroxyamino nitriles with high yields. The reaction appears to proceed via in situ formation of an *N*-silyl ketene imine followed by the Mannich-type reaction.

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

The addition reaction of nucleophiles to nitrones is one of the 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 this type of reactions under basic (anionic) conditions (Scheme 1).^{1,2} Similarly 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 are scarcely explored under both basic and acidic conditions.³

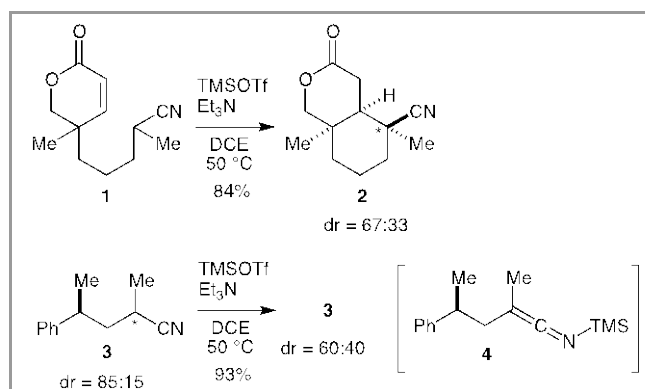


Scheme 1 Typical examples of the nucleophilic addition to nitrones

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 While 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*-aryldimines,⁵ giving rise to the corresponding α -substituted nitriles under mild conditions.

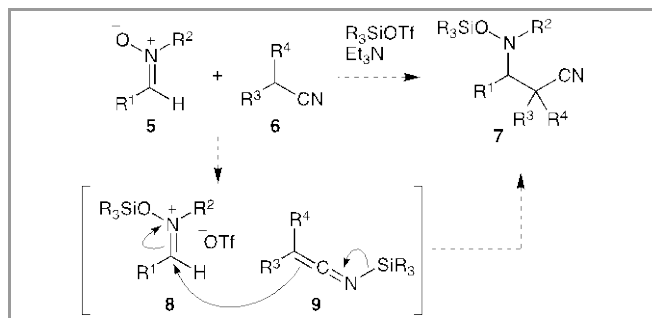
In the course of the studies on development of new synthetic reactions using α -cyano carbanions,⁶ we recently reported the intramolecular conjugate addition of α,β -unsaturated lactones having an alkanenitrile side chain promoted by TMSOTf and triethylamine (Et₃N) (Scheme 2, 1 $\rightarrow$ 2).⁷ The cyclization reaction was supposed to proceed through formation of the *N*-silyl ketene imine intermediate under the influence of TMSOTf and Et₃N. 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 a similar conditions.⁸ These results suggested that the combined use of TMSOTf and Et₃N shows promise for generating a *N*-silyl ketene imine from the corresponding nitrile without using a strong base such as LDA.⁹



Scheme 2 TMSOTf–Et₃N promoted intramolecular conjugate addition and its mechanistic investigation

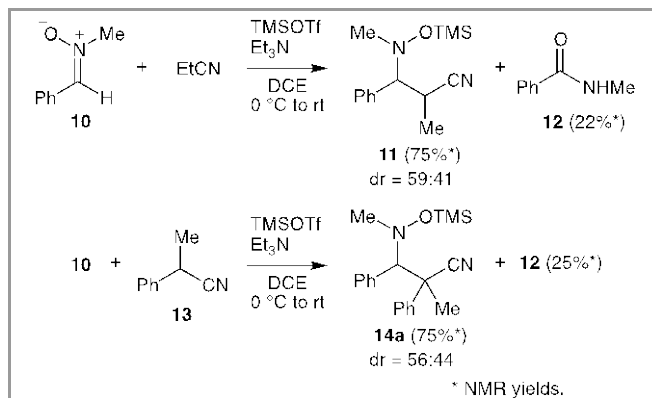
With these findings, we envisaged that the addition reaction between nitrones and nitriles would proceed under mild neutral conditions. Namely, treatment of a mixture of nitrones 5 and nitriles 6 with trialkylsilyl triflate and Et₃N would directly yield *O*-trialkylsilyl β -hydroxyamino nitrile 7 through the in situ formation of *N*-siloxyiminium ion 8¹⁰ and *N*-silyl ketene imine 9 (Scheme 3). This process would provide a simple and efficient synthetic method for 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*-benzylidenemethanamine *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 Et₃N (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 TMSNTf₂¹⁴ afforded *O*-TMS β -hydroxyamino nitrile **14a** in excellent yield (93% by crude NMR) (entry 3). However, purification of the crude product by silica gel column chromatography suffered from hydrolysis of the silyloxy group, which prompted us to employ more bulky silylating reagents. While the use of *tert*-butyldimethylsilyl

(TBSOTf) led to poor results (entry 4), triethylsilyl trifluoromethanesulfonate (TESOTf) gave promising results with the stable *O*-TES β -hydroxyamino nitrile **14c** 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 Et₃N 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, despite the reaction proceeds with an 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	Yields (%) ^b	
		14 (dr) ^c	12
1	TMSOTf	14a : 75 (56:44)	25
2	TMSBr ^d	14a : 0	75
3	TMSNTf ₂	14a : 93 (59:41)	6
4	TBSOTf ^e	14b : 57 (51:49)	42
5	TESOTf ^e	14c : 80 (54:46)	12
6	TESOTf ^f	14c : 94 ^g (55:45)	0

^a A mixture of nitrone **10** (0.2 mmol), nitrile **13** (0.2 mmol) and Et₃N (0.4 mmol) in DCE (1 mL) was treated with a silylating agent (0.4 mmol) at 0 °C to rt.

^b Yields determined by ¹H NMR analysis of the crude product mixture using pyrazine as an internal standard.

^c Diastereomeric ratios of **14** are in parenthesis. The relative configuration was not determined.

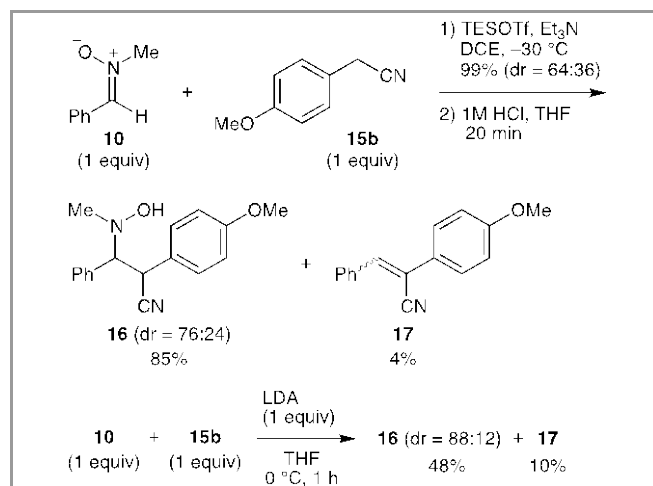
^d Reaction at 0 to 80 °C.

^e Reaction at 0 °C.

^f Reaction at -30 °C.

^g 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 conditions³ was demonstrated in Scheme 5. Thus, the addition reaction of 4-methoxyphenylacetonitrile (**15b**) to nitrone **10** under the influence of TESOTf and Et₃N gave base-sensitive β -hydroxyamino nitrile **16** in good yield after removal of the TES group under acidic conditions (85% yield for 2 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 nitron **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 ratio of **18** was rather low (74:26~58:42). In the case of the reaction of 2-pyridylacetonitrile (**15e**), TESOTf–Et₃N reagent triggered the elimination reaction of *O*-TES hydroxylamine from the desired product **18e**, giving rise to (*Z*)-3-phenyl-2-(pyridin-2-yl)acrylonitrile (**19**) 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), while two equivalents of nitrile **15h** was required in entry 8 because of its low reactivity. Note that the neutral reaction condition using TESOTf–Et₃N allows the use of nitriles with various functional groups, and chloroacetonitrile (**15j**) and *N*-(diphenylmethylene)aminoacetonitrile (**15k**) afforded the desired products in excellent yields, respectively (entries 10 and 11).

Table 2 Reactions of nitron **10** with various nitriles **15**^a

Entry	Nitrile	Yield (%) ^b	dr ^c
1	CH ₃ CH ₂ CN (15a)	18a : 94	60:40
2		18b : 99	64:36
3		18c : 96	58:42

4		18d : 95	74:26
5		18e : 58 ^d	69:31
6		18f : 95	59:41
7		18g : 100	68:32
8	(CH ₃) ₂ CHCN (15h) ^e	18h : 79 ^f	–
9	Ph ₂ CHCN (15i) ^g	18i : 84 ^h	–
10	ClCH ₂ CN (15j)	18j : 99	79:21
11		18k : 98	73:27

^a Reaction conditions: nitron **10** (0.4 mmol), nitrile **15** (0.4 mmol), TESOTf (0.8 mmol), Et₃N (0.8 mmol), DCE (2 mL), –30 °C, 0.5–1.5 h.

^b Isolated yield after purification.

^c Determined by ¹H NMR analysis of the crude product, relative stereochemistry not assigned.

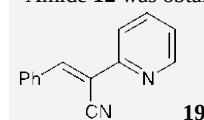
^d (*Z*)-3-Phenyl-2-(pyridin-2-yl)acrylonitrile (**19**) was obtained in 38% yield.

^e Two equivalents of nitrile were used.

^f Yield is based on **10**. Amide **12** was obtained in 13% yield.

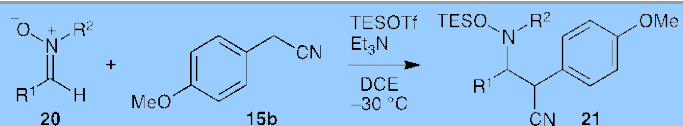
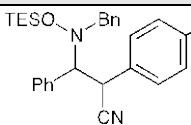
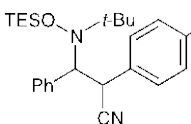
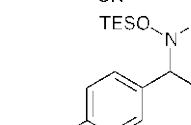
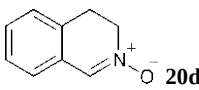
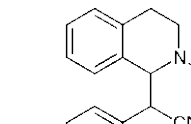
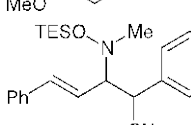
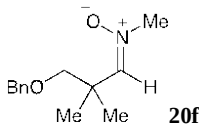
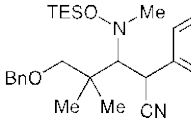
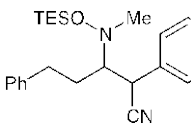
^g –30 to 0 °C, 1.5 h.

^h Amide **12** was obtained in 6% yield.



The scope of nitrones was then examined by using nitrile **15b** as a nucleophile (Table 3). Additions 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). The chemoselective addition to nitron moiety was achieved in the reaction of **20c** keeping the ester group intact (entry 3). The reaction of endocyclic nitron **20d** provided tetrahydroisoquinoline derivative **21d** as a single diastereomer (entry 4).^{15,16} Addition to α,β -unsaturated nitron **20e** occurred exclusively in a 1,2-fashion (entry 5). While the addition reaction was applicable to an α,α -disubstituted aliphatic nitron (entry 6), aliphatic nitron **20g** bearing an acidic α -proton failed to react with nitrile **15b**, resulting in decomposition under the reaction conditions (entry 7).¹⁷

Table 3 Reactions of various nitrones **20** with nitrile **15b**^a

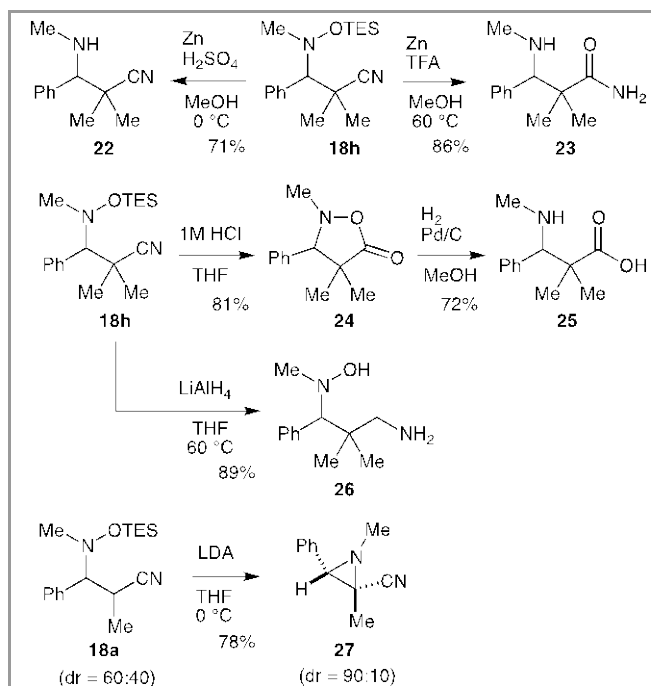
				
Entry	Nitrone	Product	Yield (%) ^b	dr ^c
1	20a	 21a	100	74:26
2	20b	 21b	85	91:9
3	20c	 21c	96	56:44
4	 20d	 21d	81	100:0
5	20e	 21e	77	50:50
6	 20f	 21f	83	58:42
7	20g	 21g	0	–

^a Reaction conditions: nitrone **20** (1 equiv), nitrile **15b** (1 equiv), TESOTf (2 equiv), Et₃N (2 equiv), DCE (0.2 M), –30 to 0 °C, 0.5–3 h.^b Isolated yield after purification.^c Determined by ¹H NMR analysis of the crude product, relative stereochemistry not assigned.

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** can be converted to the corresponding amine **22** by treating with Zn/H₂SO₄, whereas treatment of **18h** with Zn/TFA in MeOH at 60 °C afforded amide **23**. In addition, nitrile **18h** can be converted to 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 LiAlH₄. Conversely, upon treatment with LDA at 0 °C, nitrile **18a** underwent 3-exo-tet ring closure reaction,¹⁸ giving rise to *N*-methylaziridine **27** with high diastereoselectivity.

In conclusion, we developed a novel method for nucleophilic addition reactions of nitriles to nitrones

promoted by TESOTf and Et₃N under mild conditions.¹⁹ The reaction appears to proceed via in situ *N*-silyl ketene imine formation followed by the Mannich-type addition reaction. In contrast with the conventional addition reactions using strong bases, the non-basic 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 will 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

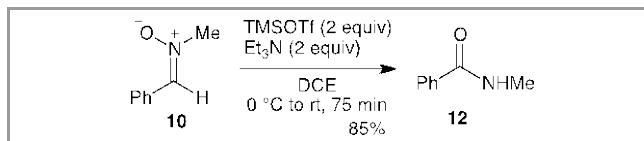
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Acknowledgment

We acknowledge Dr. Eri Fukushima and Mr. Yusuke Takata (GC-MS & NMR Laboratory, Faculty of Agriculture, Hokkaido University) for their mass spectral measurements. This work was supported by JSPS KAKENHI Grant Number 24510290 and the Mitsubishi Tanabe Pharma Award in Synthetic Organic Chemistry, Japan.

References and Notes

- For reviews, see: (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407; (b) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442; (c) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759; (d) Merino, P.; Tejero, T. *Synlett* **2011**, 1965.
- For typical examples, see: (a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **2000**, *65*, 5575; (b) Murahashi, S.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc.* **2002**, *124*, 2888; (c) Kazuta, Y.; Abe, H.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2004**, *69*, 9143; (d) Fu, Y.; Liu, Y.; Chen, Y.; Hügel, H. M.; Wang, M.; Huang, D.; Hu, Y. *Org. Biomol. Chem.* **2012**, *10*, 7669.
- (a) Aurich, H. G.; Schmidt, M.; Schwerzel, T. *Chem. Ber.* **1985**, *118*, 1086; (b) Babu, Y. S.; Chand, P.; Ghosh, A. K.; Kotian, P. L.; Kumar, S. Y. *PCT Int. Appl. WO* 2006002231, **2006**; (c) Behr, J.; Chavarria, D.; Plantier-Royon, R. *J. Org. Chem.* **2013**, *78*, 11477.
- For an excellent review of *N*-silyl ketene imines, see: Denmark, S. E.; Wilson, T. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 9980.
- (a) Notte, G. T.; Baxter Vu, J. M.; Leighton, J. L. *Org. Lett.* **2011**, *13*, 816; (b) Zhao, J.; Liu, X.; Luo, W.; Xie, M.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 3473.
- (a) Tanino, K.; Tomata, Y.; Shiina, Y.; Miyashita, M. *Eur. J. Org. Chem.* **2006**, 328; (b) Yamada, T.; Yoshimura, F.; Tanino, K. *Tetrahedron Lett.* **2013**, *54*, 522.
- Yoshimura, F.; Torizuka, M.; Mori, G.; Tanino, K. *Synlett* **2012**, 23, 251.
- We could not detect *N*-silyl ketene imine **4** when monitoring the reaction by ^1H and ^{13}C NMR. 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**.
- In this connection, Emde and Simchen reported that silylation of acetonitrile with excess TMSOTf and Et_3N in ether gave a mixture of $(\text{Me}_3\text{Si})_2\text{C}=\text{C}=\text{N}(\text{SiMe}_3)$ (44%) and $(\text{Me}_3\text{Si})_3\text{CCN}$ (56%), see: Emde, H.; Simchen, G. *Synthesis* **1977**, 6363.
- It is reported that the reactions of aldinitrones with TMSOTf afford the corresponding *N*-trimethylsiloxyiminium ions which can be identified by NMR spectroscopy, see: Camiletti, C.; Dhavale, D. D.; Gentilucci, L.; Trombini, C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3157.
- (a) Muller, G. W.; Shire, M. G.; Wong, L. M.; Corral, L. G.; Patterson, R. T.; Chen, Y.; Stirling, D. I. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2669; (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991; (c) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.
- Interestingly, the combination of TMSOTf and Et_3N smoothly promoted rearrangement of an aromatic aldinitrone to the isomeric amide (Scheme 7).



Scheme 7

- Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.
- (a) Mathieu, B.; Ghosez, L. *Tetrahedron Lett.* **1997**, *38*, 5497; (b) Ishii, A.; Kotera, O.; Saeki, T.; Mikami, K. *Synlett* **1997**, 1145.
- All attempts at determination of the relative stereochemistry of nitrile **21d** were unsuccessful.
- The high stereoselectivity in the formation of nitrile **21d** is not well understood.
- It is assumed that aliphatic nitron **20g** was decomposed through the formation of the corresponding *N*-triethylsiloxyenamine derivative and subsequent self-condensation or polymerization.
- For related aziridinations, see: (a) Tsuge, O.; Sone, K.; Urano, S.; Matsuda, K. *J. Org. Chem.* **1982**, *47*, 5171; (b) Bew, S. P.; Hughes, D. L.; Savic, V.; Soapi, K. M.; Wilson, M. A. *Chem. Commun.* **2006**, 3513.
- General procedure (Table 1, entry 6):** To a mixture of nitron **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 $-30\text{ }^\circ\text{C}$, and the reaction mixture was stirred at this temperature for 30 min. Saturated aqueous 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%).

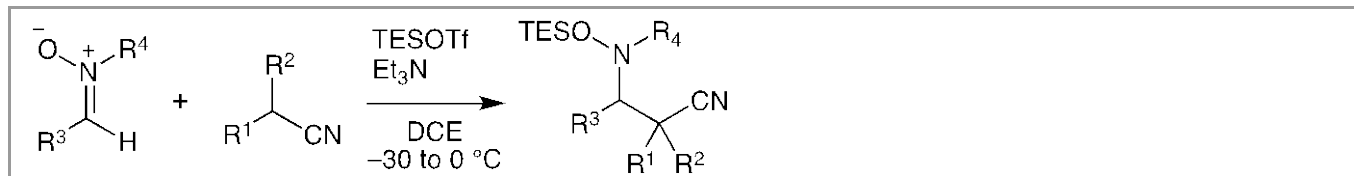
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Nucleophilic Addition Reactions of Nitriles to Nitrones

Graphical abstract

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