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$\mathrm{Bu^tMe_2SiOTf}$-promoted cyanosilylation of six-membered cyclic nitronates with trialkylsilyl cyanides or *tert*-butyl isocyanide[†]

Andrey A. Mikhaylov,*[a] Yuliya A. Khomutova,[a] Dmitry E. Arkhipov,[b]
Alexander A. Korlyukov[b] and Sema L. Ioffe*[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: iof@ioc.ac.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

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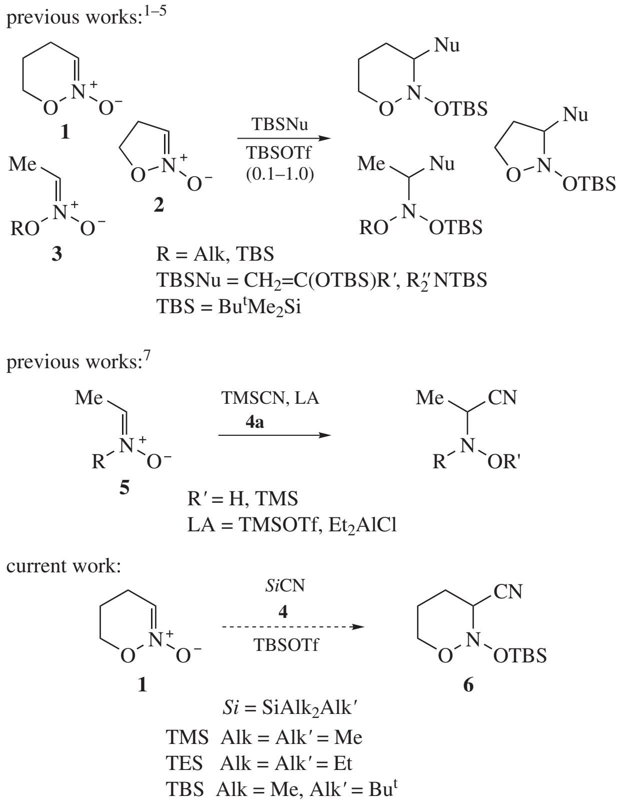
Six-membered cyclic nitronates smoothly react with trialkylsilyl cyanide/$\mathrm{Bu^tMe_2SiOTf}$ or *tert*-butyl isocyanide/$\mathrm{Bu^tMe_2SiOTf}$ systems to afford 2-trialkylsilyloxy-3-cyanotetrahydro-[4*H*]-1,2-oxazines or δ-oxo-α-trialkylsilyloximinonitriles depending on the ring-substitution pattern.

The recently discovered nucleophile addition to nitronate function under silyl Lewis acid (LA) catalysis significantly extends synthetic potential of nitro compounds and their derivatives.[1] Thus, we previously reported C,C- and C,N-couplings for six-membered cyclic nitronates **1** with silyl ketene acetal or related species[2] and N–Si and N–H amines,[3] respectively, as well as silyl ketene acetal addition to five-membered cyclic nitronates **2**[4] and their acyclic analogues **3** (Scheme 1).[5] Noteworthy, six-membered nitronates **1** are usually considered as model compounds in such investigations due to their availability in diastereo- and entantiopure forms.[1]



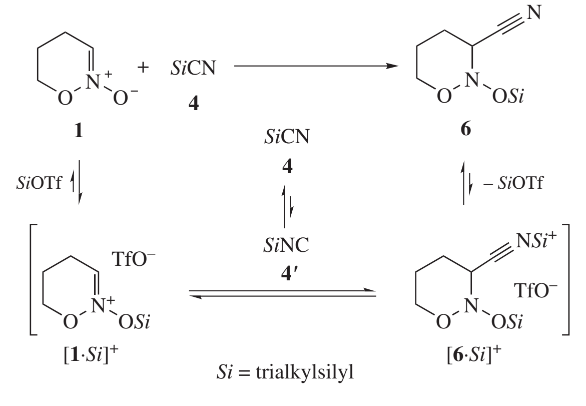
Scheme 1

The extension of the nucleophiles range is the priority task. In this context ability of silyl cyanides **4** to act as nucleophilic agents under LA catalysis is of special interest (for recent progress, see, *e.g.*, ref. 6). In particular, the reaction of structural analogues of nitronates – nitrones **5** – with these reagents is widely employed in synthesis either with or without electrophilic activation (Scheme 1).[7]

According to considered above, the detailed investigation of C,C-coupling of six-membered cyclic nitronates **1** with silyl cyanides **4** is the topic of this manuscript (Scheme 1).[‡]

Starting from general considerations, cyanosilylation of nitronates **1** could be analyzed with recently developed by H. Mayr and co-workers[9] scale nucleophilicity – electrophilicity.

For iminium cations $[\mathbf{1}\cdot Si]^+$ (Scheme 2) derived from C-3 unsubstituted nitronates **1**, electrophilicity parameter *E* belongs to –4 ... –6 interval.[2(b),§] According to these data, nitronates **1** are supposed to react at low temperature with nucleophiles with *N* parameter higher than 4.[2(b)] Unfortunately, there are no *N* parameters in literature given for silyl cyanides (as though for any other organic cyanides); however, from general considerations their nucleophilicities should be lower than those for cor-



Scheme 2

[†] In memory of Dr. Ilya M. Lyapkalo.

[‡] The only example of interaction **1** + **4** is reported in our recent paper,[8] though a detailed investigation of the process as well as the optimization of the synthesis are not discussed.

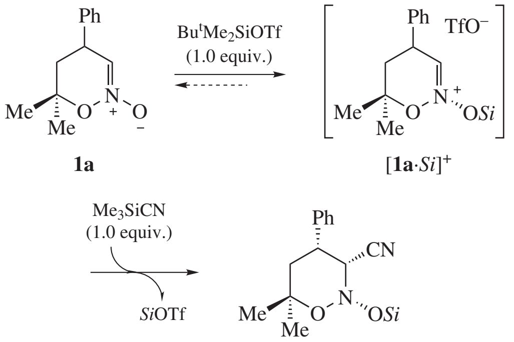
[§] The C-3 substituted nitronates evidently have electrophilicity parameter *E* 5–6 points lower.[2(b)] responding isocyanides. In fact, structurally similar to *Si*NC *tert*-butyl isocyanide has $N = 5.47$.[10]

With rather fast equilibrium

$$\mathit{Si}\mathrm{CN} + \mathit{Si}\mathrm{OTf} \rightleftarrows [\mathit{Si}\mathrm{CN}\mathit{Si}]^{+}\mathrm{TfO}^{-} \rightleftarrows \mathit{Si}\mathrm{OTf} + \mathit{Si}\mathrm{NC}$$

given,[11] one may suggest that the coupling partners in the reaction **1** + **4** are more nucleophilic silyl isocyanide **4′** species and the iminium cations [**1**·SiAlk$_2$Alk′]$^+$ (Scheme 2).

Nitronate **1a** was chosen as a model object for cyanosilylation in the current work.[2(*a*)] We started with investigation of interaction at –78 °C between its pregenerated *in situ* salt [**1a**·Bu^{t}Me$_2$Si]$^+$TfO$^-$ [2(*b*)] and available inexpensive Me$_3$SiCN **4a**. We took into account that earlier silyl group *Si* in products of the reactions of nitronates **1** with π-nucleophiles was introduced only by *Si*OTf promoter (taken in stoichiometric amount) but not from nucleophile.[2(*b*)] However, in our case only equimolar mixture of Bu^{t}Me$_2$Si- and Me$_3$Si-nitroso acetals (**6a** and **6a′**, respectively) was obtained in 89% yield (Scheme 3). Moreover, nitroso acetal **6a′** with trimethylsilyl group turned out to be unstable during isolation on silica. For this reason, in the next studies we focused on *tert*-butyldimethylsilyl-substituted nitroso acetals **6**.

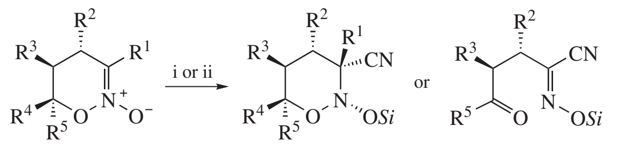


6a *Si* = SiMe$_2$Bu^t, 45%
6a′ *Si* = SiMe$_3$, 44%

Scheme 3 *Conditions*: CH$_2$Cl$_2$, –78 °C, 3 h.

When nitronate **1a** was reacted with Bu^{t}Me$_2$SiCN **4b** under reduced to substechiometric amounts (20 mol%) of Bu^{t}Me$_2$SiOTf, its conversion into nitroso acetal **6a** reached only 19%. Only the use of full equivalent of Bu^{t}Me$_2$SiOTf succeeded in 88% yield of **6a**. Obviously, it could be associated with final nitroso acetal **6a** reversibly forming complex with Bu^{t}Me$_2$SiOTf and drawing out of the reaction a large amount of catalyst. However, the discussed procedure opened access for a presentative series of 3-cyano nitroso acetals **6** (procedure A in Table 1).[¶]

Table 1 Cyanosilylation of nitronate **1** series.



1 **6** **8**

Reagents and conditions: i, Bu^{t}Me$_2$SiCN (1.2 equiv.), Bu^{t}Me$_2$SiOTf (1.0 equiv.), CH$_2$Cl$_2$, –78 °C, 24 h; ii, *Si*OTf (1.05 equiv.), CH$_2$Cl$_2$, –78 °C, then Bu^{t}NC (1.05 equiv.), –78 °C, 15 min, then Et$_3$N (1.2 equiv.).

Entry	Nitronate	R^1	R^2	R^3	R^4	R^5	*Si*	Product	Yield (%)	Procedure
1	**1a**	H	Ph	H	Me	Me	Bu^{t}Me$_2$Si	**6a**	88	A
2	**1a**	H	Ph	H	Me	Me	Bu^{t}Me$_2$Si	**6a**	56	B
3	**1a**	H	Ph	H	Me	Me	Et$_3$Si	**6a′**	55	B
4	**1b**	H	(CH$_2$)$_2$Ph	H	Me	Me	Bu^{t}Me$_2$Si	**6b**	91	A
5	**1c**	H	OBz	H	Me	Me	Bu^{t}Me$_2$Si	**6c**[a]	88	A
6	**1d**	H	Ph	–(CH$_2$)$_4$–		H	Bu^{t}Me$_2$Si	**6d**	84	A
7	**1e**	Me	Ph	H	Me	Me	Bu^{t}Me$_2$Si	**6e**	60	A[b]
8	**1f**	H	Ph	H	Me	OMe	Bu^{t}Me$_2$Si	**8a**	71	A
9	**1f**	H	Ph	H	Me	OMe	Bu^{t}Me$_2$Si	**8a**	54	B

[a] Mixture of four diastereomers, *dr* 1.0 : 4.8 : 0.2 : 2.1. [b] Reaction time 48 h.

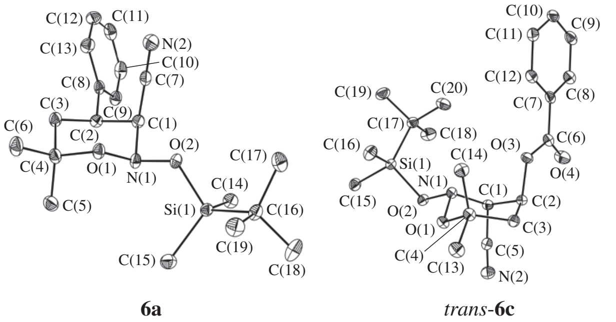


Figure 1 Molecular structures of **6a** and the major *trans*-**6c** diastereomer. Thermal ellipsoids are shown at 50% probability level. Hydrogen atoms are omitted for clarity.

The other method employed stable Bu^{t}NC **7** instead of **4** (procedure B, Table 1).[¶] Compound **7** is known to react with acylnitronates giving rise to α-oximino amides,[12] as well to serve cyanide equivalent under basic conditions.[10]

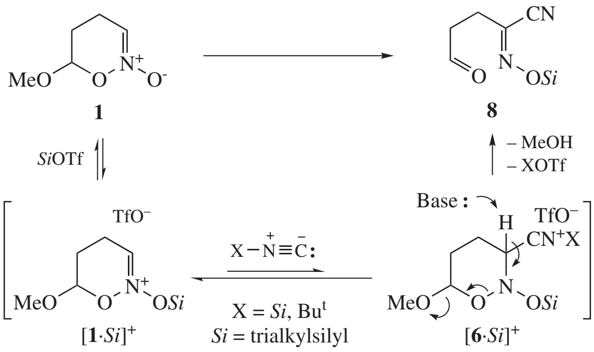
[¶] *Procedure A*: Bu^{t}Me$_2$SiOTf (23 μl, 264 mg, 1 mmol) was added at –78 °C to a stirred solution of nitronate **1** (1 mmol), 2,6-lutidine (30 μl, 27 mg, 0.25 mmol) and Bu^{t}Me$_2$SiCN (169 mg, 1.2 mmol) in CH$_2$Cl$_2$ (5 ml). The reaction mixture was kept for 24 h at –78 °C, then poured into mixture of hexane (12 ml) and saturated aqueous solution of NaHCO$_3$ (15 ml). The organic layer was separated and the aqueous one was extracted with hexane (2×4 ml). The combined organic layers were washed successively with H$_2$O (10 ml), brine (15 ml) and dried over Na$_2$SO$_4$. The solvents were evaporated *in vacuo*. The residue was subjected to column chromatography (hexane–EtOAc, 10 : 1 → 5 : 1) either recrystallized from hexane (1–3 ml) to give pure nitroso acetal **6** or γ-oxocyanoxime **8a**.

Procedure B: Bu^{t}Me$_2$SiOTf or Et$_3$SiOTf (277 mg, 1.05 mmol) was added at –78 °C to a stirred solution of nitronate **1** (1 mmol) in CH$_2$Cl$_2$ (5 ml). The resulting clear solution was kept for 5 min at –78 °C, and then Bu^{t}NC (119 μl, 87 mg, 1.05 mmol) was added. After additional 15 min Et$_3$N (170 μl, 121 mg, 1.2 mmol) was added. The resulting orange reaction mixture was stirred at –78 °C for 2 h and poured into mixture of hexane (12 ml)/H$_2$O (15 ml). The organic layer was separated and aqueous one was extracted with hexane (2×4 ml). The combined organic layers were washed successively with H$_2$O (10 ml), brine (15 ml) and dried over Na$_2$SO$_4$. The solvents were evaporated *in vacuo*. The residue was subjected to column chromatography (hexane–EtOAc, 10 : 1 → 5 : 1) to give nitroso acetal **6** or δ-oxo-α-oximino nitrile **8a**. Products **6** and **8** yields, their spectral and analytical data are described in Online Supplementary Materials.

[††] *Crystal data for* **6a**: colorless crystals, C$_{19}$H$_{30}$N$_2$O$_2$Si (M = 346.54), monoclinic, space group $C2/c$, at 100 K: a = 25.561(2), b = 6.1744(5) and c = 27.689(2) Å, β = 114.841(2)°, V = 3965.8(6) Å^3, Z = 8, d_{calc} = 1.161 g cm^{-3}, μ(MoKα) = 0.131 mm^{-1}, F(000) = 1504. Bruker Smart Apex II CCD diffractometer, 23 501 reflections collected, 5777 independent reflections (R_{int} = 0.1014), 3448 observed reflections with $I > 2\sigma(I)$, R_1 = 0.0527 [$I > 2\sigma(I)$], wR_2 = 0.1222 (all reflections), 224 refined parameters, GOOF = 0.991 (all reflections).

Crystal data for trans-**6c**: colorless crystals, C$_{20}$H$_{30}$N$_2$O$_4$Si (M = 390.55), monoclinic, space group $C2/c$, at 120 K: a = 32.602(2), b = 7.9334(5) and c = 21.8174(14) Å, β = 130.862(1)°, V = 4267.7(5) Å^3, Z = 8, d_{calc} = 1.216 g cm^{-3}, μ(MoKα) = 0.136 mm^{-1}, F(000) = 1680. Bruker Smart Apex II CCD diffractometer, 17 805 reflections collected, 6291 independent reflections (R_{int} = 0.0475), 4808 observed reflections with $I > 2\sigma(I)$, R_1 = 0.0561 [$I > 2\sigma(I)$], wR_2 = 0.1260 (all reflections), 251 refined parameters, GOOF = = 1.077 (all reflections).

CCDC 973921 and 973922 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2014.



Scheme 4

Indeed, when pregenerated cation [**1a**·SiMe$_2$Bu^t]$^+$ was treated with **7** and Et$_3$N successively, nitroso acetal **6a** was obtained in 56% yield (Table 1, entry 2). This seemed to be a simple procedure for the preparation of nitroso acetals **6** with various silyl groups, for example, triethylsilyl derivative **6a′** (Table 1, entry 3), although providing lower yields compared to the procedure A.

Cyanosilylation of nitronates **1b–e** with various ring-substituents afforded cyanides **6b–e** in 60–84% yields (Table 1, entries 4–7), though long reaction time (~48 h) was necessary for full conversion of substituted at C^3 nitronate **1e**.

The stereochemistry of products **6** and substituents positions were assigned with NMR (based on spin-spin coupling constants and NOESY) and X-ray analysis (Figure 1).[††] The nitroso acetals **6a**,**b**,**d**,**e** were obtained as single 3,4-*cis* diastereomers. Product **6c** was a mixture of four diastereomers (*dr* 1.0 : 4.8 : 0.2 : 2.1) with preferred formation of 3,4-*trans* diastereomers (*trans* : *cis* ~ 5.8 : 1).

These data are in a good agreement with mechanistic model, previously proposed for coupling of nitronates **1** with π-nucleophiles, which was also based on stereochemistry of final products.[2(*a*)]

Reaction between 6-methoxy substituted nitronate **1f** and silyl cyanide **4** either *tert*-butyl isocyanide **7** proceeded in a different way and gave cyanoxime *O*-silyl ether **8a** as the only product (Table 1, entries 8 and 9). Apparently, it could be associated with increased acidity of proton at C^3 position in cationic intermediate [**6**·*Si*]$^+$ which in case of methoxy group at C^6 can undergo methanol elimination (Scheme 4).

In summary, two procedures for cyanosilylation of six-membered cyclic nitronates **1** were developed to provide an access to new promising compounds. The cyanosilylations of 5-membered cyclic and acyclic nitronates are in near progress.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.11.023.

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