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Nitration of Silyl Allenes To Form Functionalized Nitroalkenes

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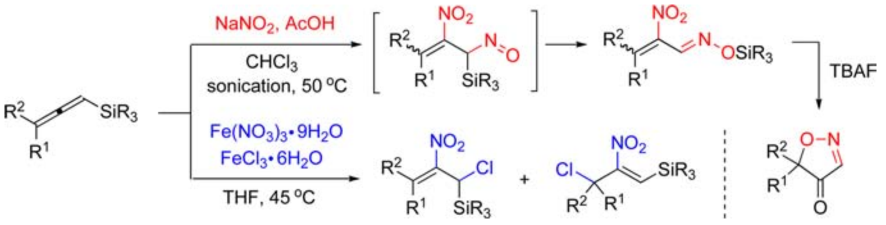
ABSTRACT

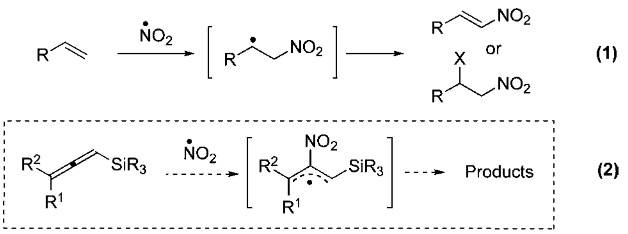


An efficient nitration of silyl allenes with nitrogen dioxide radical, generated from $NaNO_2$ and AcOH, to form α-nitro-α,β-unsaturated silyl oximes has been developed. A similar nitration could be achieved by using $Fe(NO_3)_3 \cdot 9H_2O$ and $FeCl_3 \cdot 6H_2O$, but different from the regioselective oxime formation, two regioisomeric chloride-trapped products were isolated with varying ratios depending on the steric bulk of the silyl group. A novel ring-closure reaction of α-nitro-α,β-unsaturated silyl oximes upon treating with TBAF to form isooxazolidinone derivatives was also developed.

The strong electron-withdrawing nature of the nitro group and its facile conversion to other functional groups makes nitro compounds versatile building blocks in chemical synthesis.[1] Nitro compounds are also widely used as medicine, fuel, solvent, and raw material in the chemical industry. Therefore, developing methods that can efficiently introduce a nitro group onto saturated and unsaturated hydrocarbons is highly sought after.

One of the most representative nitration methods is based on the addition of nitrogen dioxide with an alkene starting material (Scheme 1, eq 1).[2] To generate structurally more elaborate nitro compounds, we envisioned the corresponding nitration of silyl allenes, which so far has not been reported in the literature (eq 2).[3] Compared to the addition of a nitrogen dioxyl with alkene, we expected that the addition of a radical species with silyl allenes should be more favorable due to the formation of a relatively more stable allylic radical intermediate. The resulting radical intermediate will be directly captured by another radical species or be oxidized to the corresponding allylic cation, which then reacts with a nucleophile. Herein we report the result of our investigation for the nitration of silyl allenes under two different conditions, and facile 5-*endo-dig*

Scheme 1. Nitration of Simple Alkene versus Silyl Allene



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(3) For an example of N_2O_4 addition with sterically hindered trialkyl allene, see: Wieser, K.; Berndt, A. *Angew. Chem., Int. Ed.* **1975**, *14*, 69.

10.1021/ol401735v

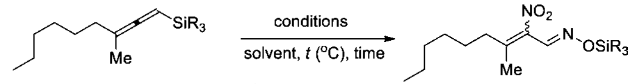
cyclization of the products of nitroso-nitration of silyl allenes, α-nitro-α,β-unsaturated silyl oximes, upon treatment with TBAF to form isooxazolidinone derivatives.

While developing a method for the synthesis of differently substituted allenes and exploring their reactivities,[4] we prepared a series of trisubstituted silyl allenes via a three-component coupling reaction involving ketone, lithium trimethylsilyldiazomethane, and free trimethylsilyldiazomethane.[4b] Occasionally in this study, we observed the instability of some of these silyl allenes under air.[5] Unaware of any reported instabilty of the corresponding alkyl-substituted allenes, we inferred that the instability of silyl allenes should be caused by the silyl substituent. This property, we envisioned, can be exploited in developing new chemical processes such as nitration, which has been extensively studied with alkenes under conditions that generate nitrogen dioxyl, and most representative conditions are: $NaNO_2$/AcOH/cerium ammonium nitrate (CAN),[6a] $AgNO_2$/TEMPO,[6b,c] $Fe(NO_3)_3\cdot 9H_2O/FeCl_3$,[6d] and ^{t}BuONO/TEMPO.[6e]

Not knowing which conditions are most suitable for silyl allenes, we decided to screen these systems to find the optimal conditions (Table 1). When trimethylsilyl allene **1a** was used as the substrate under $NaNO_2$/AcOH/CAN-(cerium ammonium nitrate) in $CHCl_3$ or CH_3CN, only decomposition of the substrate was observed (entry 1 and 2). Changing the conditions to $AgNO_2$/TEMPO in $CHCl_3$ or $ClCH_2CH_2Cl$ resulted in the same negative outcome (entry 3 and 4). Then, we changed the substrate from **1a** to **1b** where the trimethyl silyl group is replaced with a *tert*-butyldimethylsilyl group since we believed that substrate **1a** containing a trimethylsilyl group might not be compatible with the acidic conditions that cause protodesilylation.[7]

Gratifyingly, *tert*-butyldimethylsilyl allene **1b** smoothly participated in the addition reaction under $NaNO_2$/AcOH/CAN in $CHCl_3$ at room temperature to deliver the product α-nitro-α,β-unsaturated silyl oxime **2b** in 81% yield with a 1:1 ratio of *E*/*Z* isomers (entry 5). Running the reaction at higher temperature (50 °C) considerably shortened the reaction time and further improved the yield to 89% (entry 6). Reactions without AcOH or $NaNO_2$ did not proceed at all and returned the starting material intact (entry 7 and 8). On the other hand, the same reaction without CAN showed a similar reaction profile as that with CAN, providing product **2b** in 85% yield (entry 9). When another reagent combination of $AgNO_2$/TEMPO was tried, product **2b** was produced but only in 45% yield (entry 10).

Table 1. Optimization of Reaction Conditions



1a SiR_3= $SiMe_3$, **1b** SiR_3 = $SiMe_2{}^tBu$ **2a, 2b**

entry	allene	conditions	solvent	temp (°C)	time (h)	product	yield[a] (%)
1	**1a**	$NANO_2$/ AcOH/CAN	$CHCl_3$	25	2	dec	
2	**1a**	$NANO_2$/ AcOH/CAN	$CHCl_3$	25	2	dec	
3	**1a**	$AgNO_2$/TEMPO	$ClCH_2CH_2Cl$	25	8	dec	
4	**1a**	$AgNO_2$/TEMPO	$CHCl_3$	25	8	dec	
5	**1b**	$NANO_2$/ AcOH/CAN	$CHCl_3$	25	24	**2b**	81 (1:1)[b]
6	**1b**	$NANO_2$/ AcOH/CAN	$CHCl_3$	50	3	**2b**	89 (1:1)[b]
7	**1b**	$NANO_2$/CAN	$CHCl_3$	50	3	no rxn[c]	
8	**1b**	AcOH/CAN	$CHCl_3$	50	3	no rxn[c]	
9	**1b**	$NANO_2$/AcOH	$CHCl_3$	50	3	**2b**	85 (1:1)[b]
10[d]	**1b**	$AgNO_2$/TEMPO	$ClCH_2CH_2Cl$	60	10	**2b**	45 (1:1)[b]

[a] Isolated yields after purification by flash chromatography. [b] *E*/*Z* ratio were determined by ^1H NMR. [c] Most starting material was recovered. [d] Similar yield in $CHCl_3$.

With the optimized protocol for silyl allene nitration in hand, we examined the substrate scope by using a variety of silyl allenes (Table 2). Although CAN additive did not play any major role for the reaction of **1b**, we ran additional reactions with other substrates with and without CAN in parallel (entries 1, 2, 4, 5, and 8). From these data, we conclude that not only with **1b** but also with most of other silyl allenes examined in general the CAN additive was unnecessary.

First, we probed the influence of the steric bulk of the silyl group by comparing the reactivity between triethyl- and triisopropylsilyl allenes **1c** and **1d**. Both substrates reacted smoothly to provide silyl oxime products **2c** and **2d** in 91 and 85% yield, respectively, both with 1:1 ratio of *E*/*Z* isomers (entries 1 and 2). The slightly inferior yield of the latter implies that the steric bulk of the silyl group plays a certain role but only to a minor extent. On the other hand, *tert*-butyl-substituted allene **1e** decomposed when treated under identical conditions (entry 3), which clearly indicates the important role of the silyl group to promote the current nitration reaction.

Next, we examined the effect of extra π-systems on the allene containing benzyl/phenethyl (**1f**), phenyl (**1g**), 4-pentenyl (**1g′**), and 3-adamentylidene (**1h**) groups (entries 4–6). Other than a slight difference in yields, no byproducts involving these extra π-systems were observed. While benzyl-substituted substrate **1f** provided product **2f** in 83% yield (entry 4), phenyl and 4-pentenyl group-substituted substrate **1g** and **1g′** afforded **2g** and **2g′** in 88 and 86% yield, respectively (entry 5). The differences in *E*/*Z* ratio for the products should be the consequence of the steric bias of these substituents. Allene **1h** containing a 3-adamantylidene moiety provided product **2h** in 67% yield without complication by the trisubstituted alkenyl functionality (entry 6). Based on these results, we concluded that the silyl allene moiety is much

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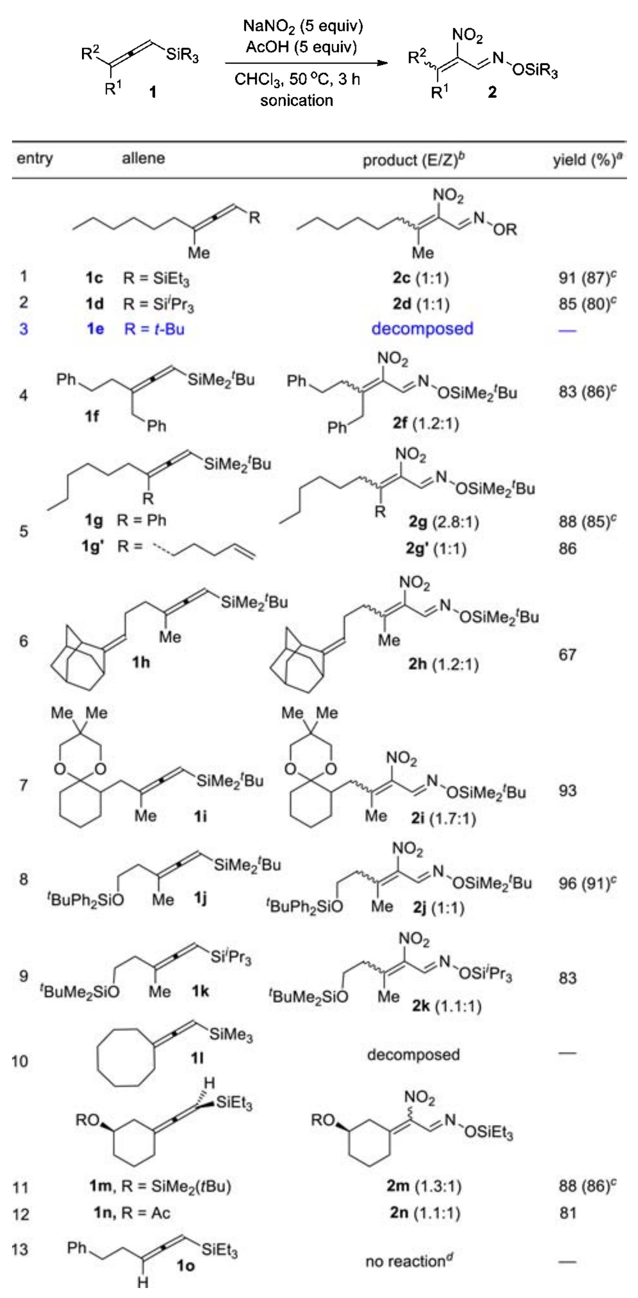
Table 2. Scope of the Reaction with $NaNO_2$/AcOH with and without CAN

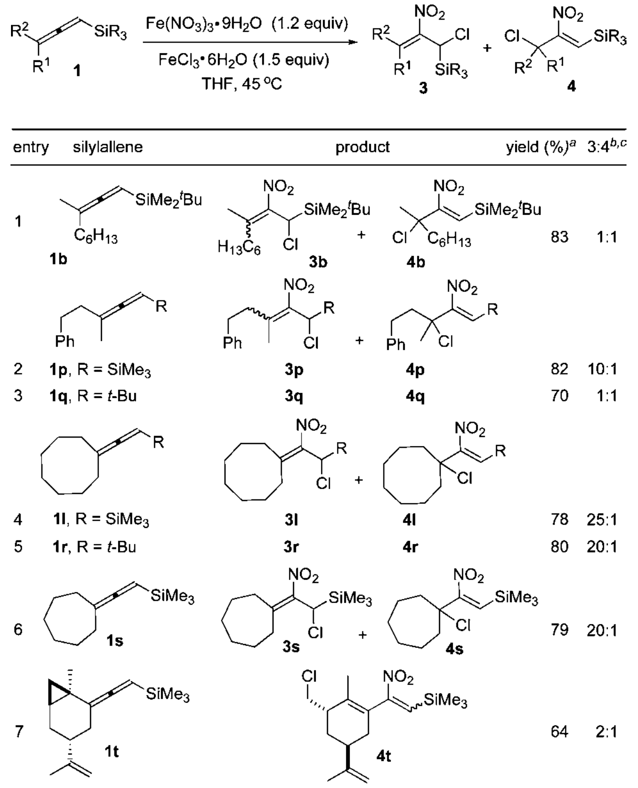


$NaNO_2$ (5 equiv), AcOH (5 equiv), $CHCl_3$, 50 °C, 3 h, sonication

entry	allene	product (E/Z)[b]	yield (%)[a]
1	**1c** R = $SiEt_3$	**2c** (1:1)	91 (87)[c]
2	**1d** R = Si^iPr_3	**2d** (1:1)	85 (80)[c]
3	**1e** R = *t*-Bu	decomposed	—
4	**1f**	**2f** (1.2:1)	83 (86)[c]
5	**1g** R = Ph	**2g** (2.8:1)	88 (85)[c]
	1g' R =	**2g'** (1:1)	86
6	**1h**	**2h** (1.2:1)	67
7	**1i**	**2i** (1.7:1)	93
8	**1j**	**2j** (1:1)	96 (91)[c]
9	**1k**	**2k** (1.1:1)	83
10	**1l**	decomposed	—
11	**1m**, R = $SiMe_2(tBu)$	**2m** (1.3:1)	88 (86)[c]
12	**1n**, R = Ac	**2n** (1.1:1)	81
13	**1o**	no reaction[d]	—

[a] Isolated yields. [b] *E*/*Z* ratios were determined by ^1H NMR. [c] The yields in the parentheses are for the reactions with CAN. [d] Starting material was recovered even after heating to 70 °C.

Table 3. Nitration Reaction with Iron(III) Nitrate



$Fe(NO_3)_3 \cdot 9H_2O$ (1.2 equiv), $FeCl_3 \cdot 6H_2O$ (1.5 equiv), THF, 45 °C

entry	silylallene	product		yield (%)[a]	3:4[b,c]
1	**1b**	**3b**	**4b**	83	1:1
2	**1p**, R = $SiMe_3$	**3p**	**4p**	82	10:1
3	**1q**, R = *t*-Bu	**3q**	**4q**	70	1:1
4	**1l**, R = $SiMe_3$	**3l**	**4l**	78	25:1
5	**1r**, R = *t*-Bu	**3r**	**4r**	80	20:1
6	**1s**	**3s**	**4s**	79	20:1
7	**1t**		**4t**	64	2:1

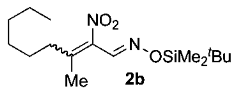
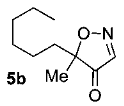
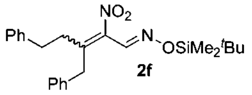
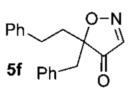
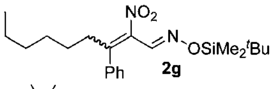
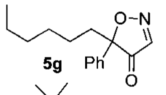
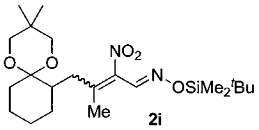
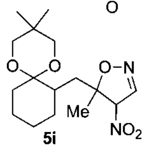
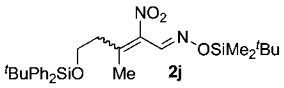
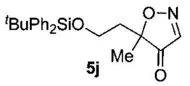
[a] Combined yields after purification. [b] The ratios of **3** and **4** were determined by ^1H NMR analysis. [c] The double-bond geometry of **4** was determined by NOE experiments.

more reactive than simple alkene functionality toward nitrogen dioxyl. Other silyl allenes **1i**–**k** containing oxygen-based functional groups such as ketal or silyl ether moiety afforded expected products **2i**–**k** in 93, 96, and 83% yield (entries 7–9). Only when two alkyl substituents on the allene are substantially different in size did the *E*/*Z* ratio increase to around 1.7–2:1 (entries 5 and 7) compared to 1:1, otherwise.

Even though cyclooctanylidene allene **1l** containing trimethylsilyl substituent decomposed (entry 10), cyclohexanylidene allene **1m** and **1n** substituted with triethysilyl group smoothly afforded nitration products **2m** and **2n** in 88% and 81% yield, respectively (entries 11 and 12). Unexpectedly, disubstituted silyl allene **1o** was recovered intact under identical reaction conditions (entry 12), which is probably due to the difficulty in forming a relatively unstable secondary carbon-centered radical intermediate form **1n** as opposed to the tertiary from trisubstituted silyl allenes.

Having silyl allenes successfully engaged in nitration with metal nitrites, we next examined their nitration using $Fe(NO_3)_3 \cdot 9H_2O$ as the source of nitrite under oxidative conditions (Table 3). Even though silyl allene **1b** decomposed when exposed to $Fe(NO_3)_3 \cdot 9H_2O$ alone, by adding an oxidant such $FeCl_3 \cdot 6H_2O$ to the reaction, chlorinated nitroalkenes **3b** and **4b** were obtained in 83% yield with a 1:1 ratio (entry 1). Gratifyingly, silyl allene **1p** containing a sterically less encumbered trimethylsilyl group, not a viable substituent in the previous reaction, is not only compatible with the conditions but also controlled the regioselectivity, affording products **3p** and **4p** in 82% yield with a 10:1 ratio (entry 2). The reaction of *tert*-butyl allene **1q** afforded **3q** and **4q** in 70% combined yield without regioselectivity (entry 3). A related pair of cyclooctanylidene allenes **1l** and **1r** showed similar behaviors where both trimethylsilyl and *tert*-butyl groups efficiently controlled the regioselectivity, providing **3l**/**4l** and **3r**/**4r** in 78 and 80% yield with 25:1 and

Table 4. Conversion of α-Nitro α,*β*-Unsaturated Silyl Oximes to Isooxazolidinones

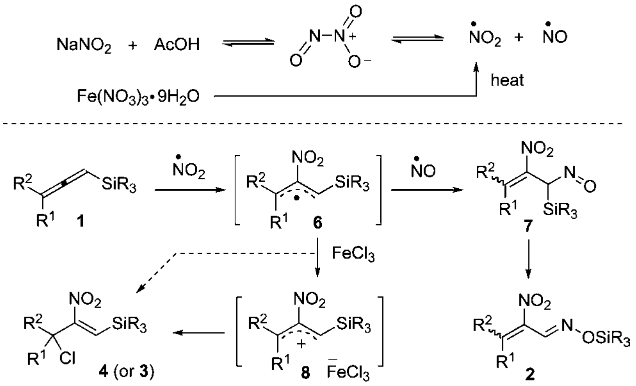
entry	substrate 2	product	yield(%)[a]
1	 2b	 5b	54
2	 2f	 5f	58
3	 2g	 5g	35[b]
4	 2i	 5i	68
5	 2j	 5j	52

[a] Isolated yields. [b] A 1:1 mixture with 1-phenylheptan-1-one.

20:1 ratio, respectively (entries 4 and 5). Cycloheptanylidene allene **1s** also afforded a mixture of **3s** and **4s** in 79% yield with 20:1 selectivity (entry 6). Carvone-derived cyclopropane-containing silyl allene **1t** resulted in 64% yield of only the cyclopropane ring-opened product **4t** in a 2:1 ratio (entry 8).

Next, we examined the behavior of functionalized nitroalkenes **2** by treating them with desilylating agent (Table 4). Upon treatment of **2** with TBAF, novel isooxazolidinone derivatives **5** were obtained in moderate yields, which is the consequence of a spontaneous Nef reaction initiated by 5-*endo*-*dig* Michael addition of the oxime oxygen onto the electron-deficient nitroalkene moiety.[8] In the case of **5i** (dr = 1.7:1), the nitronate intermediate, however, was not hydrolyzed, preserving the nitro group. The desilylation of **2j** was chemoselective such that even a primary silyl ether moiety in **2j** was untouched while the silyl ether of oxime moiety was desilylated and participated in subsequent Michael reaction (entry 5).

Scheme 2. Plausible Mechanism for the Formation of α-Nitro α,*β*-Unsaturated Silyl Oximes



A plausible reaction mechanism for the formation of **2** and **3**/**4** are depicted in Scheme 2.[9−11] The given reagents combinations would generate nitrogen dioxyl, which then react with silyl allene **1** to generate allylic radical **6**.[12] In the case with $NaNO_2$/AcOH, **6** reacts with nitroxyl, resulting in the formation of **7**,[13] which then undergoes tautomerization to provide observed product **2**. On the other hand, under the conditions with $Fe(NO_3)_3\cdot 9H_2O/FeCl_3$, intermediate radical **6** would react with ferric chloride either directly or indirectly via an electron-transfer process to form ion pair **8** followed by chloride transfer to give **4** or **3** depending on the substituents on **8**.

In summary, we have developed efficient nitration of of trisubstituted silyl allenes: with $NaNO_2$/AcOH, a new class of nitroalkene, α-nitro-α,*β*-unsaturated silyl oximes were synthesized, and with $Fe(NO_3)_3\cdot 9H_2O/FeCl_3$, allylic chloro-substituted nitroalkene were generated. Another novel class of compound isooxazolidinones were obtained upon treating the initially formed α-nitro-α,*β*-unsaturated silyl oximes with TBAF. This unprecedented nitration of silyl allenes clearly demonstrated their unusual reactivity toward radicals, which might be further exploited in other types of radical-based transformations.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(13) The proposed sequence of events are assumed to be controlled by electronic factors of the reacting counterparts; the electro-rich silyl allene reacts faster with more electron-deficient nitrogen dioxyl over nitroxyl, which is further supported by the lack of reactivity of electron-deficient allene **1e′**.