1-Aza-2-siloxybutadiene: Structure and Synthetic Application as a Piperidinone Synthon

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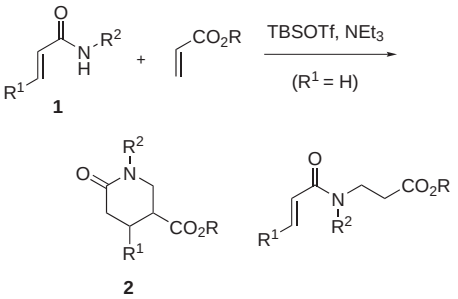
Abstract: Synthesis of 1-aza-2-siloxydienes and their structural analysis by multinuclear NMR are described. Moreover, the cycloaddition reaction of the isolated 1-aza-2-siloxydienes with dienophiles to synthesize piperidin-2-ones was explored.

Key words: silicon, amides, piperidines, cycloadditions, tandem reactions

Cycloaddition reactions of dienyl substrates and olefins by concerted pericyclic reactions or non-concerted stepwise cyclizations are one of the most useful methods to prepare 6-membered cyclic compounds in organic synthetic chemistry.[1] It is well known that the cycloaddition reactions extend to the synthesis of 6-membered heterocycles by employing heteroatom-containing dienes or olefins as substrates.[2] The reactions have attracted a great deal of interest to synthesize naturally occurring alkaloids, biologically active synthetic molecules, and organic fine chemicals.

α,β-Unsaturated amides are readily available from α,β-unsaturated acids, and are utilized as monomers in the preparation of polymers. However, they have been used less often as building blocks in the cycloaddition reaction leading to heterocyclic compounds.[3,4] Recently, we have demonstrated that α,β-unsaturated amides act as N-C(=O)-C-C synthons of piperidinones (Scheme 1).[5] The reaction of α,β-unsaturated amide **1** with acrylate is promoted by the assistance of silyl triflate and amine to give multi-substituted piperidin-2-one **2**. In our previous communication,[5] we have proposed the reaction proceeds through a stepwise double Michael addition, because an intermediacy of mono-Michael adduct has been obtained. During the further exploration of the cycloaddtion of α,β-unsaturated amide, the following problems are arising. First puzzle is the structure of an initial reaction intermediate. Treatment of α,β-unsaturated amide with silyl triflate and amine would cause either *N*- or *O*-silylation to give *N*-silyl amide **A** or *O*-silyl imidate (1-aza-2-siloxydiene) **B**, respectively (Figure 1). To best of our knowledge, only fragmental studies have been reported for the structural analysis of silylated α,β-unsaturated amide.[6,7] Second, acryl amide possessing no β-substituent does not react with acrylate but with another molecule of acryl amide to give cyclic acryl amide dimer. In this communication, we wish to report the structural determination of silylated α,β-unsaturated amide and their reactivity with acrylate to synthesize piperidinones from acrylamides.



Scheme 1

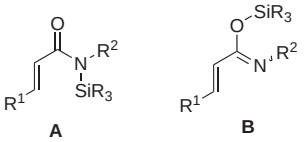
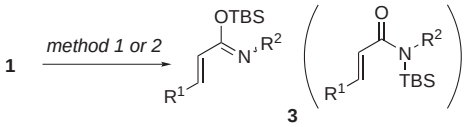


Figure 1 Structures of *N*-silyl amide (**A**) and *O*-silyl imidate (**B**)

We have attempted to isolate silylated intermediate **3** from α,β-unsaturated amide **1** by two different ways (Scheme 2); treatment of **1** with TBSOTf and NEt_3 in CH_2Cl_2 (method 1), and deprotonation of **1** with NaH followed by addition of TBSCl in THF (method 2). In spite of many efforts, no desired compound was obtained from *N*-alkyl acrylamides and cinnamamides because of their poor stability. On the other hands, *N*-phenyl acrylamide (**1a**) affords crude silylated product with reasonable stability under both methods. The ^1H and ^{13}C NMR spectra of the products, formed by both methods, are identical, but



a; R^1 = H, R^2 = Ph 69%
b; R^1 = Ph, R^2 = Ph 85%
c; R^1 = Ph, R^2 = Bn 0%
d; R^1 = H, R^2 = *p*-MeOPh 52%

Scheme 2 (method 1) TBSOTf (1.2 equiv), Et_3N (0.7–1.5 equiv), CH_2Cl_2, r.t.; (method 2) NaH (1.0 equiv), THF, r.t., then TBSCl (1.0 equiv). All chemical yields were based on method 2.

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removal of the impurity was rather difficult in the case of method 1. Accordingly, silylated compounds **3** were prepared by method 2 in the following synthesis.

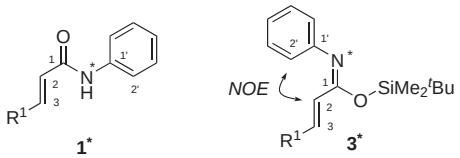
For the NMR study, we have prepared ^{15}N-labelled (98% enriched) α,β-unsaturated amides **1a***, **1b*** and their silylated derivatives **3a***, **3b***. Their spectral data of selected atoms (^{1}H, ^{13}C, ^{15}N and ^{29}Si) are summarized in Table 1.[8] When the spectra of amides **1*** are compared with the ones of silylated **3***, the chemical shifts are significantly changed. Especially, chemical shifts of aromatic carbon at *ipso* position [C(1′)] and the nitrogen atom move to ca 10 ppm and ca 130 ppm downfield, respectively. Although the isolation of pure silylated derivative **3c** from *N*-benzyl cinnamamide (**1c**) (unlabeled) was unsuccessful, ^{15}N NMR of in situ generated **3c** by the method 1 resulted in ca 90 ppm downfield shift (δ_N 115.7 ppm for **1c**, 204.2 ppm for **3c**). The phenomenon would indicate the conjugation system of **3*** is elongated by silylation of **1***. No ^{29}Si-^{15}N spin-spin coupling of **3*** is observed, which indicates that there exists no covalent bonding between nitrogen and silicon atoms. Moreover, a single peak in the ^{29}Si NMR is detected at 23.5 ppm for **3***. The expected ^{29}Si chemical shifts for an *O*-silyl imidate and *N*-silyl amide are 19.6 ppm and 8.7 ppm, respectively.[9] Judging from whole NMR studies, the structure of silylated species **3*** is concluded to be *O*-silyl imidate, 1-aza-2-siloxydiene. Observation of a bathochromic (blue shift) effect in the UV spectrum of **3** compared to **1** also supports the *O*-silyl imidate structure (λ_{max} = 268.5 nm for **1a**, 297.0 nm for **3a**). In addition, the geometry of **3a** and **3b** could be determined as (*E*)-imidate by NOE observation.

Next, the cycloaddition reaction of 1-aza-2-siloxydiene **3** was explored. When an equimolar of **3a** and methyl acrylate is treated with TBSOTf (1.0 equiv) in dichloroethane at room temperature, the desired 2-piperidinone **2a** (cyclic hetero-dimmer) was obtained in 37% yield (Table 2, entry 1). Under the conditions cyclic homo-dimer **4a**, acyclic hetero-dimer **5a** and acyclic homo-dimer **6a** were produced as by-products. The formation of acyclic **5** and **6** suggests that the cycloaddition reaction takes place through a sequential pathway. We have found the reactions performed using of 3 equivalents of TBSOTf or under neat conditions result in better chemical yield of desired **2a** (entries 2 and 3). Piperidinone **2d** was also obtained in the reaction with *p*-methoxyphenyl substrate **3d** in 50% yield, but cinnamamide derivative **3b** resulted in no reaction (entries 4 and 5).

Next, we surveyed another Lewis acids [$MgCl_2$, $MeAlCl_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Sn(OTf)_2$, $Yb(OTf)_3$, $Ti(OiPr)_4$, $FeCl_3$] in the reaction of **3a** and **3d** with methyl acrylate. Among them, only $FeCl_3$ afforded the desired **2a** and **2d** in a medium yield (entries 6 and 7). No reaction proceeded without catalyst even at higher temperature, but **3a** was recovered (entries 8 and 9). Cycloaddition of **3a** promoted by TBSOTf with α,β-unsaturated ketone, such as methyl vinyl ketone, give cyclic hetero-dimer **2e** (entry 10), but only homo-dimers **4a** and **5a** were produced with maleic anhydride or styrene (entries 11 and 12).

In conclusion, we describe here the structural analysis of 1-aza-2-siloxydienes by multinuclear NMR analysis. Furthermore, their synthetic application towards 5-substituted piperidin-2-ones was reported. Although it will be required to improve the chemical yield, this study is, to

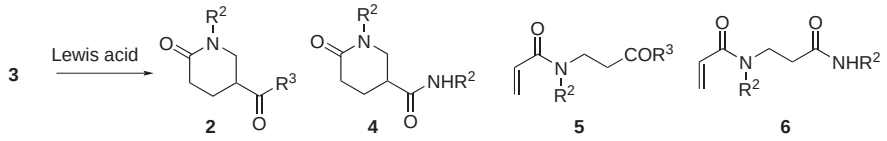
Table 1 NMR Spectral Data of Selected Atoms of **1*** and **3***[a]



Atom	**1a***	**3a***	**1b***	**3b***
C(1)	163.9 (d, J_{C-N} = 14.5 Hz)	156.3 (d, J_{C-N} = 12.9 Hz)	164.1 (br s)	156.7 (d, J_{C-N} = 12.9 Hz)
C(2)	131.3 (d, J_{C-N} = 10.1 Hz)	125.4 (s)	120.9 (s)	N.A.[b]
C(3)	127.5 (s)	125.2 (s)	142.4 (s)	N.A.[b]
C(1′)	137.8 (d, J_{C-N} = 15.8 Hz)	148.0 (d, J_{C-N} = 2.9 Hz)	138.0 (d, J_{C-N} = 14.5 Hz)	148.2 (s)
H(2)	6.36 (dd, *J* = 16.8, 10.5 Hz)	6.09 (dd, *J* = 15.0, 8.4 Hz)	6.59 (d, *J* = 15.6 Hz)	6.43 (d, *J* = 15.3 Hz)
H(3_{trans})	5.69 (dd, *J* = 10.5, 2.4 Hz)	5.53 (dd, *J* = 8.4, 4.0 Hz)	–	–
H(3_{cis})	6.39 (dd, *J* = 16.8, 2.4 Hz)	6.10 (dd, *J* = 15.0, 4.0 Hz)	7.5 (d, *J* = 115.6 Hz)	7.42 (d, *J* = 15.3 Hz)
H(2′)	7.60 (d, *J* = 6.6 Hz)	6.76 (d, *J* = 7.7 Hz)	7.64 (br d)	6.84 (d, *J* = 7.7 Hz)
N	133.9 (d, J_{N-H} = 90.0 Hz)	265.5 (s)	133.8 (d, J_{N-H} = 90.0 Hz)	259.0 (s)
Si	–	23.5 (s)	–	23.5 (s)

[a] ^{13}C, ^{1}H and ^{29}Si chemical shifts: relative to TMS (δ = 0 ppm); ^{15}N chemical shifts: relative to CH_3NO_2 (δ = 379.6 ppm).
[b] N.A. means not assigned.

Table 2 Lewis Acid-Mediated Cycloaddition of **3** with Dienophile



Entry	Substrate	Dienophile (R^3)[a]	Lewis acid (equiv)	Solvent[a]	Temp.	Yield (%)[a]			
						2	**4**	**5**	**6**
1	**3a**	MA (OMe)	TBSOTf (1 equiv)	DCE	r.t.	37	18	trace	6
2	**3a**	MA (OMe)	TBSOTf (3 equiv)	DCE	r.t.	48	nd	3	nd
3	**3a**	MA (OMe)	TBSOTf (1 equiv)	neat	r.t.	47	10	0	0
4	**3b**	MA (OMe)	TBSOTf (1 equiv)	DCE	r.t.–60 °C	0	0	0	0
5	**3d**	MA (OMe)	TBSOTf (1 equiv)	DCE	r.t.	50	nd	nd	nd
6	**3a**	MA (OMe)	$FeCl_3$ (1 equiv)	DCE	r.t.	38	21	trace	trace
7	**3d**	MA (OMe)	$FeCl_3$ (1 equiv)	DCE	r.t.	45	17	trace	8
8	**3a**	MA (OMe)	none	DCE	r.t.	0	0	0	0
9	**3a**	MA (OMe)	none	toluene	110 °C	0	0	0	0
10	**3a**	MVK (Me)	TBSOTf (1 equiv)	DCE	r.t.	30	nd	nd	nd
11	**3a**	maleic anhydride	TBSOTf (1 equiv)	DCE	r.t.	0	ca 20	0	ca 10
12	**3a**	styrene	TBSOTf (1 equiv)	DCE	r.t.–60 °C	0	ca 20	0	ca 10

[a] Abbreviations; MA = methyl acrylate, MVK = methylvinylketone, DCE = 1,2-dichloroethane, nd = not determined.

our best knowledge, the first demonstration for the cycloaddition of the isolated 1-aza-2-siloxydienes. Piperidin-2-ones, which would be obtained by the above reaction, would be useful as synthetic building blocks for a variety of biologically active substances. We suppose further investigation would reveal the possibility of 1-aza-2-siloxydiene as a new synthon of various heterocyclic compounds.

All reactions were carried out under an inert atmosphere. Anhydrous dichloroethane and toluene were distilled from CaH_2 under atmospheric or reduced pressure. ^{15}N-enriched aniline was purchased from Aldrich Chemical Co., Inc. ^1H, ^{13}C, ^{15}N and ^{29}Si NMR spectra were recorded on a JEOL ECP 600 (600 MHz, 150 MHz, 60 MHz and 120 MHz for ^1H, ^{13}C, ^{15}N and ^{29}Si, respectively) or JEOL AL400 (400 MHz and 100 MHz for ^1H and ^{13}C) apparatus in $CDCl_3$. Chemical shifts were reported in ppm downfield from TMS ($\delta = 0$) for the ^1H and ^{29}Si NMR, $MeNO_2$ ($\delta = 379.60$) for the ^{15}N NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.00$) for the ^{13}C NMR measurements.

Cycloaddition Reaction of 3; Typical procedure

To a solution of methyl acrylate (0.1 mmol) and TBSOTf (0.3 mmol) in dichloroethane (0.4 mL) was added a solution of **3** (0.1 mmol) in dichloroethane (0.1 mL) at 0 °C. After being stirred for 24 h at ambient temperature, the resulting mixture was quenched with sat. $NaHCO_3$. The resultant was extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography.

Compound 2a

Colorless oil.

IR (neat): 1709, 1651 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.41–7.37$ (m, 2 H), 7.28–7.24 (m, 3 H), 3.88 (dd, $J = 12.4$, 9.0 Hz, 1 H), 3.70 (dd, $J = 12.4$, 5.1 Hz, 1 H), 3.06–2.99 (m, 1 H), 2.65–2.60 (m, 2 H), 2.30–2.03 (m, 2 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.4$, 169.5, 142.5, 129.2, 127.0, 126.2, 52.3, 52.2, 39.1, 30.8, 23.8.

HRMS: *m*/*z* [M^+] calcd for $C_{13}H_{15}NO_3$: 233.1052; found: 233.1045.

Compound 4a

Colorless oil.

IR (neat): 1632, 1605 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.94$ (br s, 1 H), 7.45 (d, $J = 7.8$ Hz, 2 H), 7.38 (t, $J = 7.8$ Hz, 2 H), 7.31–7.24 (m, 5 H), 7.11 (t, $J = 7.3$ Hz, 1 H), 4.01 (dd, $J = 12.3$, 9.9 Hz, 1 H), 3.74 (dd, $J = 12.3$, 4.1 Hz, 1 H), 2.89–2.85 (m, 1 H), 2.76–2.68 (m, 1 H), 2.60–2.51 (m, 1 H), 2.26–2.12 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.9$, 169.1, 142.2, 137.5, 134.2, 129.2, 129.0, 127.1, 126.1, 124.5, 119.8, 53.0, 42.2, 31.6, 25.1.

HRMS: *m*/*z* [M^+] calcd for $C_{18}H_{18}N_2O_2$: 294.1368; found: 294.1364.

Compound 6a

Colorless oil.

IR (neat): 3310, 1651cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (br s, 1 H), 7.60–7.07 (m, 10 H), 6.41 (dd, *J* = 16.6, 1.7 Hz, 1 H), 6.00 (dd, *J* = 16.6, 10.2 Hz, 1 H), 5.57 (dd, *J* = 10.2, 1.7 Hz, 1 H), 4.19 (t, *J* = 6.7 Hz, 2 H), 2.73 (t, *J* = 6.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 166.5, 140.9, 138.1, 129.8, 128.8, 128.6, 128.3, 128.2, 128.0, 124.0, 119.8, 46.0, 36.6.

HRMS: *m*/*z* [M^+] calcd for $C_{18}H_{18}N_2O_2$: 294.1368; found: 294.1367.

Compound 3a* (98% ^{15}N-enriched)
IR (neat): 2939, 1652, 1598 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.7 Hz, 2 H), 7.03 (t, *J* = 7.7 Hz, 1 H), 6.76 (d, *J* = 7.7 Hz, 2 H), 6.09 (d, *J* = 4.0 Hz, 1 H), 6.08 (d, *J* = 8.4 Hz, 1 H), 5.53 (dd, *J* = 8.4, 4.0 Hz, 1 H), 1.01 (s, 9 H), 0.35 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.3 (d, $J_{C\text{-}N}$ = 12.9 Hz), 148.0 (d, $J_{C\text{-}N}$ = 2.9 Hz), 128.8, 125.4, 125.2, 122.9, 121.3, 25.9, 18.1, –4.6.

^{15}N NMR (60 MHz, $CDCl_3$): δ = 258.1.

^{29}Si NMR (120 MHz): δ = 23.5.

UV–Vis (CH_3CN): λ_{max} = 297 nm.

Compound 3b* (98% ^{15}N-enriched)
IR (KBr): 1661, 1626, 1595 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 15.3 Hz, 1 H), 7.36–7.30 (m, 7 H), 7.08 (t, *J* = 7.8 Hz, 1 H), 6.84 (t, *J* = 7.7 Hz, 2 H), 6.43 (d, *J* = 15.3 Hz, 1 H), 1.07 (s, 9 H), 0.41 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.7 (d, $J_{C\text{-}N}$ = 13.0 Hz), 148.2, 139.4, 135.5, 129.0, 128.8, 128.6, 127.7, 122.9, 121.6, 115.7, 26.0, –4.5.

^{15}N NMR (60 MHz, $CDCl_3$): δ = 259.0.

^{29}Si NMR (120 MHz, $CDCl_3$): δ = 23.6.

UV–Vis (CH_3CN): λ_{max} = 326 nm.

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References

(1) (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, **1990**.
(b) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S.; Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, **2002**.
(2) (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, **1987**. (b) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379.
(3) Synthesis of piperidines by intermolecular cyclodimerization of acrylamide equivalents: (a) Lorente, A.; Navio, J. L. G.; Perez, J. C. L.; Soto, J. L. *Synthesis* **1985**, 89. (b) Elliott, M. C.; Galea, N. M.; Long, M. S.; Willock, D. J. *Tetrahedron Lett.* **2001**, *42*, 4937.
(4) Synthesis of piperidines by intramolecular cycloaddition of α,β-unsaturated amides: (a) Ihara, M.; Ishida, Y.; Tokunaga, Y.; Kabuto, C.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2085. (b) Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 7110. (c) Mekouar, K.; Genisson, Y.; Leue, S.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 5212.
(5) Takasu, K.; Nishida, N.; Ihara, M. *Tetrahedron Lett.* **2003**, *44*, 7429.
(6) Jones, K.; Wilkinson, J.; Ewin, R. *Tetrahedron Lett.* **1994**, *35*, 7673.
(7) For comparable examples, structural analysis of silylated benzamides: (a) Klebe, J. F. *Acc. Chem. Res.* **1970**, *3*, 299. (b) Misaki, T.; Kurihara, M.; Tanabe, Y. *Chem. Commun.* **2001**, 2478.
(8) Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; John Wiley & Sons: New York, **1979**.
(9) Jancke, H.; Engelhardt, G.; Wagner, S.; Dirnens, W.; Herzog, G.; Tieme, E.; Rühlmann, K. *J. Organomet. Chem.* **1977**, *134*, 21.