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 dienes or olefins 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 step-wise 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,3 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 cycloaddition 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.

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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 \( 15N \)-labelled (98% enriched) \( \alpha,\beta \)-unsaturated amides \( 1a^* \), \( 1b^* \) and their silylated derivatives \( 3a^* \), \( 3b^* \). Their spectral data of selected atoms (\( ^1H, ^13C, ^15N \) and \( ^29Si \)) are summarized in Table 1.\(^8\)

<table>
<thead>
<tr>
<th>Atom</th>
<th>( 1a^* )</th>
<th>( 3a^* )</th>
<th>( 1b^* )</th>
<th>( 3b^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>163.9 (d, ( J_{CN} = 14.5 ) Hz)</td>
<td>156.3 (d, ( J_{CN} = 12.9 ) Hz)</td>
<td>164.1 (br s)</td>
<td>156.7 (d, ( J_{CN} = 12.9 ) Hz)</td>
</tr>
<tr>
<td>C(2)</td>
<td>131.3 (d, ( J_{CN} = 10.1 ) Hz)</td>
<td>125.4 (s)</td>
<td>120.9 (s)</td>
<td>N.A.(^b)</td>
</tr>
<tr>
<td>C(3)</td>
<td>127.5 (s)</td>
<td>125.2 (s)</td>
<td>142.4 (s)</td>
<td>N.A.(^b)</td>
</tr>
<tr>
<td>C(1')</td>
<td>137.8 (d, ( J_{CN} = 15.8 ) Hz)</td>
<td>148.0 (d, ( J_{CN} = 2.9 ) Hz)</td>
<td>138.0 (d, ( J_{CN} = 14.5 ) Hz)</td>
<td>148.2 (s)</td>
</tr>
<tr>
<td>H(2)</td>
<td>6.36 (dd, ( J = 16.8, 10.5 ) Hz)</td>
<td>6.09 (dd, ( J = 15.0, 8.4 ) Hz)</td>
<td>6.59 (d, ( J = 15.6 ) Hz)</td>
<td>6.43 (d, ( J = 15.3 ) Hz)</td>
</tr>
<tr>
<td>H(2')</td>
<td>5.69 (dd, ( J = 10.5, 2.4 ) Hz)</td>
<td>5.53 (dd, ( J = 8.4, 4.0 ) Hz)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>H(3')</td>
<td>6.39 (dd, ( J = 16.8, 2.4 ) Hz)</td>
<td>6.10 (dd, ( J = 15.0, 4.0 ) Hz)</td>
<td>7.5 (d, ( J = 115.6 ) Hz)</td>
<td>7.42 (d, ( J = 15.3 ) Hz)</td>
</tr>
<tr>
<td>N</td>
<td>133.9 (d, ( J_{NH} = 90.0 ) Hz)</td>
<td>265.5 (s)</td>
<td>133.8 (d, ( J_{NH} = 90.0 ) Hz)</td>
<td>259.0 (s)</td>
</tr>
<tr>
<td>Si</td>
<td>–</td>
<td>23.5 (s)</td>
<td>–</td>
<td>23.5 (s)</td>
</tr>
</tbody>
</table>

\(^8\) C, \(^1H\) and \(^29Si\) chemical shifts: relative to TMS (\( \delta = 0 \) ppm); \(^15N\) chemical shifts: relative to \( CH_3NO_2 (\delta = 379.6 \) ppm).

\(^b\) N.A. means not assigned.

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-dimer) 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 \([\text{MgCl}_2, \text{MeAlCl}_2, \text{Zn(OTf)}_2, \text{Cu(OTf)}_2, \text{Sn(OTf)}_2, \text{Yb(OTf)}_3, \text{Ti(OiPr)}_4, \text{FeCl}_3] \) 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 \( \alpha,\beta\)-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
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-siloxydienes as a new synthon of various heterocyclic compounds.

All reactions were carried out under an inert atmosphere. Anhydrous dichloroethane and toluene were distilled from CaH₂ under atmospheric or reduced pressure. 15N-enriched aniline was purchased from Aldrich Chemical Co., Inc. 1H, 13C, 15N and 29Si NMR spectra were recorded on a JEOL ECP 600 (600 MHz, 150 MHz, 60 MHz and 120 MHz for 1H, 13C, 15N and 29Si, respectively) or JEOL AL400 (400 MHz and 100 MHz for 1H and 13C) apparatus in CDCl₃. Chemical shifts were reported in ppm downfield from TMS (δ = 0) for the 1H and 29Si NMR, MeNO₂ (δ = 379.60) for the 15N NMR and relative to the central CDCl₃ resonance (δ = 77.00) for the 13C 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. NaHCO₃. The resultant was extracted with EtOAc, washed with brine, dried over MgSO₄, and concentrated. The residue was purified by flash column chromatography.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Dienophile (R³)</th>
<th>Lewis acid (equiv)</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>MA (OMe)</td>
<td>TBSOTf (1 equiv)</td>
<td>DCE</td>
<td>r.t.</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>MA (OMe)</td>
<td>TBSOTf (3 equiv)</td>
<td>DCE</td>
<td>r.t.</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>MA (OMe)</td>
<td>TBSOTf (1 equiv)</td>
<td>neat</td>
<td>r.t.</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>3b</td>
<td>MA (OMe)</td>
<td>TBSOTf (1 equiv)</td>
<td>neat</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>3d</td>
<td>MA (OMe)</td>
<td>TBSOTf (1 equiv)</td>
<td>DCE</td>
<td>r.t.</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>3a</td>
<td>MA (OMe)</td>
<td>FeCl₃ (1 equiv)</td>
<td>DCE</td>
<td>r.t.</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>3d</td>
<td>MA (OMe)</td>
<td>FeCl₃ (1 equiv)</td>
<td>DCE</td>
<td>r.t.</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>3a</td>
<td>MA (OMe)</td>
<td>none</td>
<td>DCE</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>3a</td>
<td>MA (OMe)</td>
<td>none</td>
<td>toluene</td>
<td>110 °C</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>3a</td>
<td>MVK (Me)</td>
<td>TBSOTf (1 equiv)</td>
<td>DCE</td>
<td>r.t.</td>
<td>30</td>
</tr>
<tr>
<td>11</td>
<td>3a</td>
<td>maleic anhydride</td>
<td>TBSOTf (1 equiv)</td>
<td>DCE</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>3a</td>
<td>styrene</td>
<td>TBSOTf (1 equiv)</td>
<td>DCE</td>
<td>r.t.</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: MA = methyl acrylate, MVK = methylvinylketone, DCE = 1,2-dichloroethane, nd = not determined.

**Compound 2a**
Colorless oil.
IR (neat): 1709, 1651 cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 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).
13C NMR (100 MHz, CDCl₃): δ = 172.4, 169.5, 142.5, 129.2, 127.0, 126.2, 52.3, 52.2, 39.1, 30.8, 23.8.

**Compound 4a**
Colorless oil.
IR (neat): 1632, 1605 cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 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).
13C NMR (100 MHz, CDCl₃): δ = 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.

**Compound 6a**
Colorless oil.
IR (neat): 3310, 1651 cm⁻¹.
1H NMR (400 MHz, CDCl3): 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).

13C NMR (100 MHz, CDCl3): δ = 168.4, 166.5, 140.9, 138.1, 129.8, 128.8, 128.6, 128.2, 128.0, 124.0, 119.8, 46.0, 36.6.


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

1H NMR (600 MHz, CDCl3): 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).

13C NMR (150 MHz, CDCl3): δ = 156.3 (d, J_C-N = 12.9 Hz), 148.0 (d, J_C-N = 2.9 Hz), 128.8, 125.4, 125.2, 122.9, 121.6, 26.0, –4.6.

15N NMR (60 MHz, CDCl3): δ = 257.5.

29Si NMR (120 MHz, CDCl3): δ = 25.4.

UV–Vis (CH3CN): λ_max = 297 nm.

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

1H NMR (600 MHz, CDCl3): 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).

13C NMR (150 MHz, CDCl3): δ = 156.7 (d, J_C-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.

15N NMR (60 MHz, CDCl3): δ = 259.0.

29Si NMR (120 MHz, CDCl3): δ = 236.3.

UV–Vis (CH3CN): λ_max = 326 nm.

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References