Generation and Cycloaddition of Heteroatom-Substituted 2-Azaallyl Anions with Alkenes and Alkynes. Synthesis of 1-Pyrrolines and Pyrroles

William H. Pearson* and Roland P. Stevens

Department of Chemistry, The University of Michigan, Ann Arbor, MI 48109-1055

Abstract: Imidates and thioimidates 1 bearing an N-(1-tri-n-butyllithium)alkyl group (e.g., 7-9) were transesterified with n-BuLi to generate heteroatom-substituted 2-azaallyl anions 2. These anions underwent [π4s + π2s] cycloadditions with alkenes to produce 1-pyrrolines 4 after loss of alkoxide or thiolate. The pyrrolines were further deprotonated in situ with n-BuLi to generate 1-metalloenamines 5, which could be quenched with water or CH2I2 to produce 1-syrrolines 4 or 6. The use of diphenylacetylene in the cycloaddition resulted in the formation of a pyrrole.

We have previously described the synthesis of pyrrolidines by the [π4s + π2s] cycloaddition of non-stabilized 2-azaallyl anions with electron-rich alkenes.1,2 The anions were generated by tin-lithium exchange of 2-azaallyl stannanes. The 2-azaallyl anion method is complementary to azomethine ylide cycloaddition chemistry, since the latter species generally require electron-poor dipolarophiles.3 We now wish to describe the generation and cycloaddition chemistry of heteroatom-substituted 2-azaallyl anions 2, which allow access to 1-pyrrolines 4 and 6 (Scheme 1).

The archetype for the conversion of an alkene to a 1-pyrrolone involves the cycloaddition of a nitrile ylide.4 The cycloaddition of aryl-substituted nitrile ylides ArCN(=N)C(=N)HR with electron-poor dipolarophiles has been widely studied. Nitrile ylides without aromatic substitution are rare.5,6 Heteroatom-substituted azomethine ylides have been used frequently as synthetic equivalents of a nitrile ylide in cycloadditions with electron poor dipolarophiles.7,12 The reactions of certain stabilized heteroatom-substituted 2-azaallyl
anions$^{13,10c}$ or N-metalloazomethine ylides$^5$ with carbonyl compounds or electron-poor alkenes have also been studied. In order to complement the approach to 1-pyrrolines based on heteroatom-substituted 1,3-dipoles, we felt that the higher reactivity of 2-azaallyl anions would allow cycloaddition with less reactive alkenes. We wish to report that non-stabilized heteroatom-substituted 2-azaallyl anions 2 may be generated by tin-lithium exchange on stannyl imidates and thioimidates 1. These anions undergo cycloadditions with relatively electron-rich alkenes, producing intermediate N-lithiopyrrolidines 3, which undergo loss of alkoxide or thiolate to give 1-pyrrolines 4. Under the basic reaction conditions, 4 is deprotonated to give the metalloenamine 5. This may be quenched with water to regenerate 4, or may be alkylated to give a different 1-pyrrole 6.

The tin-substituted imidates and thioimidates 7-9$^{14}$ were mixed with various anionophiles (1 equiv.) and added to n-BuLi (ca. 5 equiv.) in THF at -78 °C. After about 30 minutes, workup with aqueous NH$_4$Cl and column chromatography (SiO$_2$) afforded good to excellent isolated yields of the pyrrolines 10-18 (Table 1).$^{15}$ The use of an acetylenic anionophile provided the pyrrole 19 in modest yield. Particularly noteworthy is the opposite regioselectivity observed in entries 1 and 2, where the only difference is the heteroatom substituent (oxygen versus sulfur) on the 2-azaallyl anion. The generality of this regioselectivity is currently under investigation. The shift in regioselectivity observed in entries 1 and 3 is also notable. In both cases, the most crowded regioisomer is formed selectively. Complete regiocontrol was observed in the cycloaddition with a vinyl silane (entry 4). Entries 5 and 6 produce the same products 15-18, even though the geometry of the anionophile is different. Normally, we observe stereospecificity with respect to the alkene geometry.$^1$ However, imines with adjacent aromatic substituents are capable of undergoing imine-enamine tautomerization,$^{16,17}$ which allows scrambling of the stereochemistry of these cycloadducts. The formation of oxidized products, tentatively assigned as 17 and 18, presumably occurs by air oxidation upon purification. Norbornene and ethyl acrylate were unsuccessful in attempted cycloadditions using 9.

The use of at least 2 equivalents of n-BuLi was found to be necessary because of in situ deprotonation of the initial pyrrole products 4 to form metalloenamines 5. The presence of 5 was shown by workup of the cycloadditions with methyl iodide, which led to the formation of the 2-ethyl pyrrolines 20 and 21 in good yield (eq. 1,2).

\[
\begin{align*}
\text{CH}_3O\text{SnBu}_3N & \xrightarrow{1) \text{Et}_3\text{Si} \xrightarrow{n-\text{BuLi}} \xrightarrow{2) \text{CH}_3\text{I}} 65\%} \\
\text{CH}_3O\text{SnBu}_3N & \xrightarrow{1) \text{Ph} \xrightarrow{n-\text{BuLi}} \xrightarrow{2) \text{CH}_3\text{I}} 51\% + 26\%}
\end{align*}
\]

In conclusion, the cycloaddition of oxygen- and sulfur-substituted 2-azaallyl anions with alkenes is complementary to 1,3-dipolar methods for making 1-pyrrolines. These anions are far more reactive (i.e., cycloaddition occurs at -78 °C), allowing the use of relatively electron-rich alkenes. Metalloenamines are formed, which are known to be useful synthetic intermediates for further functionalization. Finally, a striking difference in the regioselectivity of oxygen- versus sulfur-substituted 2-azaallyl anions was observed. We are currently exploring this interesting selectivity, as well as nitrogen-substituted 2-azaallyl anions and particularly anions bearing a chiral heteroatom-linked auxiliary for asymmetric cycloadditions.
Table I. Generation and Cycloaddition of Heteroatom-Substituted 2-Azaallyl Anions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Stannane</th>
<th>Anionophile</th>
<th>Product(s)</th>
<th>Yield, Ratio(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(<em>3)O(\text{SnBu}</em>{3})</td>
<td>Ph</td>
<td>10, 11</td>
<td>86% (10:1)(^b)</td>
</tr>
<tr>
<td>2</td>
<td>CH(<em>3)S(\text{SnBu}</em>{3})</td>
<td>Ph</td>
<td>10, 11</td>
<td>65% (1:4.5)(^b)</td>
</tr>
<tr>
<td>3</td>
<td>CH(<em>3)O(\text{SnBu}</em>{3})</td>
<td>Ph</td>
<td>12, 13</td>
<td>80% + 13%</td>
</tr>
<tr>
<td>4</td>
<td>CH(<em>3)O(\text{SnBu}</em>{3})</td>
<td>Et(_3)Si(\text{Allyl})</td>
<td>14</td>
<td>97%</td>
</tr>
<tr>
<td>5</td>
<td>CH(<em>3)O(\text{SnBu}</em>{3})</td>
<td>Ph(\text{Allyl})</td>
<td>15, 16, 17, 18</td>
<td>85% (6.8:1.2:5.2:1)(^c)</td>
</tr>
<tr>
<td>6</td>
<td>CH(<em>3)O(\text{SnBu}</em>{3})</td>
<td>Ph(\text{Allyl})</td>
<td>15, 16, 17, 18</td>
<td>93% (1:3.0:3.6:2.8)(^d)</td>
</tr>
<tr>
<td>7</td>
<td>CH(<em>3)O(\text{SnBu}</em>{3})</td>
<td>Ph(\text{Allyl})</td>
<td>19</td>
<td>33%</td>
</tr>
</tbody>
</table>

\(^a\) isolated, chromatographed yields. \(^b\) isomers not separated. \(^c\) isolated yield of three chromatographic fractions: 41% of 15, 22% of a 1:2 mixture of 16 and 17, and 22% of a 3:1 mixture of 17 and 18. \(^d\) isolated yield of three chromatographic fractions: 9% of 15, 59% of a 1:1:2 mixture of 16 and 17, and 25% of 18.
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NOTES AND REFERENCES


(14) **Imidate 7**: Treatment of Bu3SnCH2I with acetamide (5 equiv.) and NaH (1 equiv.) in THF/DMF at 0 °C gave AcNHCH2SnBu3 (65%). Heating this material with neat Me2SO4 (1 equiv.) at 60 °C gave 7 (61%, Kugelrohr distillation).

**Thioimidate 8**: Treatment of AcNHCH2SnBu3 with Lawesson's reagent in THF using ultrasound gave CH2C(S)NHCH2SnBu3 (49%) which was alkylated with Me2SO4 (1 equiv., neat, 23 °C) to produce 8 (85%, Kugelrohr distillation).

**Imidate 9**: Prepared from AcNH(Br)CH2Me2 (Karatzyk, A. R.; Drewniak, M.; Le, P. J. *Org. Chem.* 1988, 53, 5854-5856, Bt = benzotriazolyl) by the following sequence: (1) 2 eq. Bu3SnLi, THF, 0 °C (86%); (2) Me2SO4 (1 equiv.), neat, 60 °C (74%, Kugelrohr distillation). See: Pearson, W. H.; Stevens, E. P. *Synthesis* 1994, 0000.

The stereochemical assignments of the cycloadducts 12-14 were based on NOE studies.


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