DIRECTED LITHIATION OF 1-TRIISOPROPYLSILYLGRAMINE. A SHORT ACCESS TO 3,4-DISUBSTITUTED INDOLES

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Abstract- 1-Triisopropylsilylgramine was lithiated regioselectively at C-4 by treatment with t-BuLi in ether at 0 °C for 1 h. The lithiated species was trapped with a variety of electrophiles to furnish 4-functionalized gramine derivatives in good yields. Replacement of the triisopropylsilyl protecting group by a methyl group resulted in C-2 selective lithiation under the similar reaction conditions.

Due to the pronounced pharmacological activities of ergot alkaloids,¹ the practical syntheses of 4-substituted indoles have been long desired as the starting points for these compounds.² The direct functionalization of indole derivatives at C-4, however, is relatively difficult due to high reactivity of pyrrole moiety. The commercially available gramine³ [3-(dimethylaminomethyl)indole] has been widely used for functionalization of indole at C-3 side chain by nucleophilic substitution of dimethylamino group.⁴ Therefore, if gramine could be functionalized at C-4, this compound should serve as an ideal starting material for the preparation of 3,4-disubstituted indoles related to ergot alkaloids. In this communication, we wish to report the C-4 selective functionalization of gramine via the directed lithiation⁵ of 1-triisopropylsilylgramine (1) in which the dimethylaminomethyl group promotes the lithiation and the bulky triisopropylsilyl group prevents undesirable C-2 lithiation.⁶

The compound (1) was prepared from gramine by metalation with n-BuLi (1.05 equiv. / THF / -78°C / 1 h) followed by silylation with triisopropylsilyl chloride (1.1 equiv. / -78°C / 4 h) in 96% yield after Kugelrohr distillation (bp 140°C / 0.1 mmHg). Treatment of an ethereal solution of 1 with 1.2 equiv. of t-BuLi (15 min at -78°C and then 1 h at 0°C) followed by quenching with MeOD at -78°C recovered the deuterated gramine (3a) in
88% yield after chromatographic purification. The 400 MHz $^1$H nmr spectrum of this product showed >95% deuterium incorporation at C-4 and no evidence of C-2 deuteration. In this reaction, however, 2-triisopropylsilylgramine (4) was isolated as a by-product in 10% yield. This compound must be formed via C-2 lithiation of 1 followed by rapid N to C migration of triisopropylsilyl group under the lithiation conditions. When 1 was lithiated at -78°C (1.2 equiv. of t-BuLi / ether / 2 h), 4 was not formed (MeOD quenching). However, deuterium incorporation in the recovered 1 was only 10% at C-4. Thus the lithiation at 0°C is essential for the efficient generation of the lithiated species (2). Using the lithiation conditions thus established, 2 was then reacted with a variety of electrophiles. The results were summarized in Table 1. In all cases, the expected 4-substituted gramine derivatives (3) were obtained in good yields. 

Table 1. Synthesis of 4-Substituted Gramines via Directed Lithiation of 1-Triisopropylsilylgramine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Product</th>
<th>E</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOD</td>
<td>3a</td>
<td>D</td>
<td>88</td>
<td>oil</td>
</tr>
<tr>
<td>2</td>
<td>Me$_3$SiCl</td>
<td>3b</td>
<td>Me$_3$Si</td>
<td>82</td>
<td>oil</td>
</tr>
<tr>
<td>3</td>
<td>Bu$_3$SnCl</td>
<td>3c</td>
<td>Bu$_3$Sn</td>
<td>78</td>
<td>oil</td>
</tr>
<tr>
<td>4</td>
<td>PhSSPh</td>
<td>3d</td>
<td>PhS</td>
<td>70</td>
<td>85-86</td>
</tr>
<tr>
<td>5</td>
<td>I$_2$</td>
<td>3e</td>
<td>I</td>
<td>58</td>
<td>oil</td>
</tr>
<tr>
<td>6</td>
<td>BrCH$_2$CH$_2$Br</td>
<td>3f</td>
<td>Br</td>
<td>68</td>
<td>oil</td>
</tr>
<tr>
<td>7</td>
<td>Cl$_3$CCC$_3$</td>
<td>3g</td>
<td>Cl</td>
<td>65</td>
<td>oil</td>
</tr>
<tr>
<td>8</td>
<td>N$_3$CH$_2$SiMe$_3$</td>
<td>3h</td>
<td>NH$_2$</td>
<td>80</td>
<td>97-97.5</td>
</tr>
<tr>
<td>9</td>
<td>DMF</td>
<td>3i</td>
<td>CHO</td>
<td>57</td>
<td>oil</td>
</tr>
<tr>
<td>10</td>
<td>Me$_2$C=CHCHO</td>
<td>3j</td>
<td>Me$_2$C=CHCHO(OH)</td>
<td>82</td>
<td>oil</td>
</tr>
</tbody>
</table>

*a Isolated yield after alumina column chromatography. b See reference 8.
In order to assess the steric requirement of triisopropylsilyl group,\textsuperscript{6b-c,9} lithiation of 1-methylgramine (5)\textsuperscript{10} was conducted. Treatment of an ethereal solution of 5 with 1.2 equiv. of \textit{t}-BuLi at -78°C for 1 h followed by MeOD quenching provided C-2 deuterated compound (7a) in 93% yield (deuterium incorporation > 95%). This result clearly indicates that the methyl group is not large enough to prevent the preferential C-2 lithiation of the indole ring and the protection of indole nitrogen with bulky triisopropylsilyl group is essential for the success of C-4 lithiation. The lithiated species (6) reacted with Me\textsubscript{3}SiCl and PhSSPh to give the corresponding C-2 substituted compounds (7b) (oil) and (7c) (mp 65-65.5°C) in 80% and 99% yields, respectively.\textsuperscript{7}

\begin{equation}
\text{Me} \quad \text{NMe}_2 \quad \text{Me} \quad \text{NMe}_2 \quad \text{Me} \quad \text{E}
\end{equation}

In conclusion, we have devised a convenient procedure for C-4 functionalization of gramine \textit{via} directed lithiation strategy. Most of the C-4 substituted gramines prepared in this work will be used as useful intermediates for the synthesis of more complex 3,4-disubstituted indole derivatives.\textsuperscript{11} Application of this reaction for the short synthesis of ergot alkaloids is in progress in this laboratory.

\textit{Typical experimental procedure for the synthesis of 4-substituted gramines (3):} Under an argon atmosphere, \textit{t}-BuLi (1.5 M in pentane, 1.6 ml, 2.4 mmol) was added dropwise to a stirred solution of 1 (661 mg, 2.0 mmol) in dry ether (10 ml) at -78°C. After 15 min, dry ice-acetone bath was removed and the mixture was allowed to warm to 0°C (ca. 10 min). The reaction flask was then immersed in an ice-water bath and kept for 1 h. After cooling to -78°C, a solution of the appropriate electrophile (3.0 mmol) in dry ether (2 ml) was added. The solution was stirred for 1 h at -78°C and then allowed to warm to ambient temperature and quenched with water. After usual extractive workup (ether), the crude product was purified by alumina column chromatography using a mixture of hexane and ethyl acetate as an eluent.

\textbf{REFERENCES AND NOTES}


7. All new compounds were fully characterized by $^1$H nmr (400 MHz), ir, and HRms.


11. The triisopropylsilyl group can be readily removed from the indole ring with tetrabutylammonium fluoride (TBAF). For example, compound (3g) was converted (1.2 equiv. of TBAF, THF, ambient temperature, 10 min) to 4-chlorogramine in 78% yield. This compound has been prepared in multiple steps as an intermediate for a plant growth hormone, 4-chloroindole-3-acetic acid, see: a) F. C. Uhle, *J. Am. Chem. Soc.*, 1949, 71, 761; b) C. Hansch and J. C. Godfrey, *J. Am. Chem. Soc.*, 1951, 73, 3518; c) M. Somei and M. Tsuchiya, *Chem. Pharm. Bull.*, 1981, 29, 3145.

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