BF₃-ÉTERATE PROMOTED ALKYLLATION OF AZIRIDINES WITH ORGANOCOPPER REAGENTS:
A NEW SYNTHESIS OF AMINES

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Summary: Boron trifluoride etherate promotes nucleophilic ring opening of a variety of substituted aziridines by diorganocopperlithium reagents leading to both primary and secondary amines.

Recent work by us¹ and Brown et al.² has elucidated the mechanism of BF₃-etherate promoted organolithium additions to epoxides, oxetanes and other oxygenated electrophiles. Extension of this methodology to appropriately protected aziridines would constitute overall a two-carbon aminooethylation of nucleophiles, thus complementing one and three-carbon aminoalkylations with tosyl cyanide³ and acrylonitrile, respectively. N-Acylated aziridines and aziridinecarbamates usually undergo only carbonyl addition reactions with organolithium and magnesium reagents.⁴-⁶ In 1975 the successful alkylation of a strained tricyclic N-acylaziridine was achieved by Aratani et al. using a cuprate, albeit in 15% yield.⁷ We now report that BF₃--etherate promotes the ring-opening addition of organocopper reagents to N-substituted aziridines in a general new synthesis of primary and secondary amines.

\[
\text{R}_2\text{CuLi} \quad + \quad \begin{array}{c} \text{N} \\ \text{R} \end{array} \quad \xrightarrow{\text{BF}_3-\text{Et}_2\text{O}} \quad \begin{array}{c} \text{RCH}_2\text{CH}_2\text{NHR}' \\ \text{or} \\ \text{RCH}_2\text{CH}_2\text{NH}_2 \end{array}
\]
The addition of trityllithium to aziridinecarbamates has been reported to afford the carbamate of 3,3,3-triphenylpropylamine in 35% yield. The same reaction in the presence of BF₃-Et₂O (5 min, -78°C) afforded a 74% yield of product. However, similar openings of N-methyl, N-benzyl or N-silylaziridines could not be achieved at -78°C, above which temperature mixtures of organolithiums and BF₃-Et₂O are not very stable. Only the addition of phenyllithium to N-(t-butyldimethylsilyl)aziridine in the presence of BF₃-Et₂O gave the desired β-phenethylamine in modest yield (19%). Alkylcopper(I) compounds, although more compatible with Lewis acids, manifested little improvement. Lithium diorganocuprates in THF, on the other hand, demonstrated just the right balance of stability to BF₃-Et₂O and nucleophilicity to a range of N-substituted aziridines. The Table summarizes our findings.

Most N-substituted aziridines were prepared either by N-alkylation or by the method of Wenker. Reaction with cuprates afforded N-methyl or N-benzylamines in good yield. Since ethylenemine itself could not be alkylated, an easily removed N-substituent was required to synthesize primary amines directly. Reactions of N-t-butyldimethylsilylaziridine with cuprates were only moderately successful (entries 5, 9). Ultimately the 4,4'-dimethoxybenzhydryl (DMB) group proved superior (entries 2, 10). Several attempts to alkylate DMB-substituted-2,2-dimethylaziridine failed, even using Ph₂CuCNLi₂, however the less hindered N-benzyl derivative did react (entries 6, 11) making it possible to prepare the N-benzyl analog of the appetite suppressant phenetermine. The methodology could not be extended to azetidines.

Preparation of N-(4,4'-Dimethoxybenzhydryl)aziridine — To a mixture of DMB chloride (3.8 mmol) and triethylamine (12.8 mmol) in THF (5 mL) at 0°C was added ethylenemine (3.3 mL). After stirring 5 min at 0°C and 8 h at rt, anhydrous ether (10 mL) was added and the precipitated solids filtered. The supernatant was dried over Na₂SO₄ and concentrated in vacuo to afford the crude product which crystallized after chromatography (silica, 4:1 hexane:ethyl acetate) in 67% yield, mp 58-61°C.

Synthesis of β-phenethylamine — A 50 mL roundbottom flask charged with CuI (1.5 mmol) and THF (6 mL) was cooled under Ar to -40°C and treated with phenyllithium (3 mmol in 7:3 cyclohexane:ether). The resulting black mixture was stirred 15 min, then cooled to -78°C. To it was rapidly added the DMB-protected aziridine (1.5 mmol) in THF (1.5 mL) followed by BF₃-Et₂O (1.5 mmol). After warming the mixture to rt, 15% NH₄OH (15 mL) was added along with ether (10 mL) and solid NH₄Cl (1g). The resulting dark blue aqueous layer was extracted three times with 1:1 hexane:ether. The combined extracts dried (K₂CO₃), filtered and concentrated to afford the N-DMB derivative of β-phenethylamine in 95% after flash chromatography (4:1 hexane:ethyl acetate).

This sample was deprotected according to the procedure of Trost by stirring in 88% formic acid (5 mL) at 80-85°C for 90 min. After removing the solvent as described, the amine was partitioned between 5% aqueous HCl and ether to furnish pure β-phenethylamine (44 mg, 80%).
## Table

**Alkylation of Aziridines with Organocuprates**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile&lt;sup&gt;a&lt;/sup&gt;</th>
<th>R'&lt;&lt;sup&gt;b&lt;/sup&gt; R'&lt;&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product&lt;sup&gt;b&lt;/sup&gt; (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CuLi</td>
<td>R=Bn, R'=H</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;NHBn (80%)</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>R=DMB, R'=H</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;NHDMB (97%)</td>
</tr>
<tr>
<td>3</td>
<td>(Bu)&lt;sub&gt;2&lt;/sub&gt;CuLi</td>
<td>R=CH&lt;sub&gt;3&lt;/sub&gt;, R'=H</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;NHCH&lt;sub&gt;3&lt;/sub&gt; (94%)</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>R=Bn, R'=H</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;NHBn (75%)</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>R=TBDMS, R'=H</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;NH&lt;sub&gt;2&lt;/sub&gt; (30%)</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>R=CH&lt;sub&gt;3&lt;/sub&gt;, R'=CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;C(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;NHBn (92%)</td>
</tr>
<tr>
<td>7</td>
<td>(Ph)&lt;sub&gt;2&lt;/sub&gt;CuLi</td>
<td>R=CH&lt;sub&gt;3&lt;/sub&gt;, R'=H</td>
<td>Ph(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;NHCH&lt;sub&gt;3&lt;/sub&gt; (56%)</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>R=Bn, R'=H</td>
<td>Ph(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;NHBn (92%)</td>
</tr>
<tr>
<td>9</td>
<td>&quot;</td>
<td>R=TBDMS, R'=H</td>
<td>Ph(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;NH&lt;sub&gt;2&lt;/sub&gt; (45%)</td>
</tr>
<tr>
<td>10</td>
<td>&quot;</td>
<td>R=DMB, R'=H</td>
<td>Ph(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;NH&lt;sub&gt;2&lt;/sub&gt; (80%)</td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td>R=Bn, R'-'CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;C(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;NHBn (50%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>(Ph)&lt;sub&gt;3&lt;/sub&gt;CuLi</td>
<td>R=t-BOC, R'=H</td>
<td>(Ph)&lt;sub&gt;3&lt;/sub&gt;C(C(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;NHBOC (74%)</td>
</tr>
</tbody>
</table>

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(a) Except as noted, all alkylations were carried out using a 3:3:1 ratio of cuprate:BF<sub>3</sub>-Et<sub>2</sub>O: aziridine. THF was preferred as solvent over ether. Lesser quantities of BF<sub>3</sub> or cuprate resulted in 10-35% recovered starting material.

(b) All products were isolated as described in the representative procedures and characterized by comparison with authentic samples.

(c) A 7:7:1 ratio of reactants was used in this experiment.
REFERENCES AND FOOTNOTES

10. Even forcing hydrogenolysis conditions with a variety of catalysts failed to reduce N-benzyl secondary amines.
14. We thank the National Institutes of Health for a predoctoral traineeship to M.J.E. on Grant GM 97273, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous financial assistance. Support of the Cornell Nuclear Magnetic Resonance Facility by NSF (CHE 7904825, PCM 8018643) and NIH (RR02002) is gratefully acknowledged.

(Received in USA 14 November 1984)