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# Selective reduction of acyl aziridines to Mannich bases using silyllithium reagents

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### ARTICLE INFO

## ABSTRACT

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# Introduction

The regioselective  $\alpha$ -reduction of acyl aziridines is a synthetically useful transformation, providing an alternative to the Mannich reaction for the formation of  $\beta$ -aminoketones. The few reducing agents that have been reported to effect this transformation include samarium iodide,<sup>1</sup> magnesium metal,<sup>2</sup> tributyltinhydride,<sup>3</sup> and titanium tetraiodide.<sup>4</sup> A ruthenium catalyzed photoreduction using the Hantzsch ester has also been developed.<sup>5</sup>

Based on our success with the selective  $\alpha$ -reduction of acyloins<sup>6</sup> and  $\alpha$ , $\beta$ -epoxyketones,<sup>7</sup> we envisioned that the preparation of Mannich bases from acyl aziridines using silyllithium reagents could be similarly achieved (Scheme 1). A key step in this process is a Brook rearrangement, which has found recent synthetic utility,<sup>8</sup> particularly in the anion relay chemistry (ARC) of Smith.<sup>9</sup>

The reaction proceeds via an initial nucleophilic attack of the silyllithium reagent on the carbonyl of **1**, triggering a Brook rearrangement on **2**. Concomitant  $\pi$ -bond formation and aziridine ring opening would then give silyl enol ether intermediate **4**. Desilylation of **4** by a second equivalent of silyllithium reagent<sup>10</sup> would form dianion **5**, providing Mannich base **6** upon acidic aqueous work-up.

We began with the two representative substrates, shown in Table 1. The benzoyl aziridine (entry 1) was treated with 2.5 equiv of dimethylphenylsilyllithium in THF at -50 °C, which provided the corresponding Mannich base with a modest yield of 56%. Similar reaction with an acyl aziridine (entry 2) resulted in only a 28% yield

of the desired Mannich base. The lower yield is attributed to an inability to stabilize the developing negative charge on carbon (**3** in Scheme 1). By contrast, the phenyl substituent of the benzoyl aziridine allows for the formation of a resonance-stabilized benzylic anion, thus promoting the necessary Brook rearrangement.

Mannich bases are prepared from the selective  $\alpha$ -reduction of acyl aziridines using silyllithium reagents.

The reaction proceeds via an aziridine ring-opening assisted Brook rearrangement.

Believing that the disappointing yield from the reaction of the acyl aziridine was due at least in part to a slower Brook rearrangement, we next explored the use of methyldiphenylsilyllithium in place of dimethylphenylsilyllithium. The methyldiphenylsilyl group has been reported to promote Brook rearrangement relative to the dimethylphenylsilyl group, <sup>10b</sup> and its use has improved yields in similar reactions.<sup>6,7</sup> Thus, treatment of the acyl aziridine (entry 2) with 2.5 equiv of methyldiphenylsilyllithium in THF at  $-50 \,^{\circ}$ C gave the desired Mannich base with a greatly improved yield of 64%. We were pleased to find that similar treatment of the benzoyl aziridine (entry 1) with methyldiphenylsilyllithium provided the corresponding Mannich base with an improved yield of 70%.

A number of acyl aziridines were then subjected to reduction with methyldiphenylsilyllithium in order to determine the scope of the reaction. These results are summarized in Table 2. An unprotected aziridine (entry 1) gave none of the desired Mannich base, resulting in recovery of starting material. This is likely due to the acidity of the aziridine hydrogen, resulting in deprotonation by the silyllithium reagent and preventing any further reaction. An alkyl protected aziridine (entry 2) gave only a trace of the expected Mannich base, likely due to the poor stabilization of the developing negative charge on nitrogen. Substrates with electron withdrawing protecting groups were more successful. An acetyl protected aziridine (entry 3) gave good results, but the electrophilic nature of this





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#### Table 1

Reduction of acyl aziridines with dimethylphenyl- and methyldiphenylsilyllithium (2.5–3.0 equiv) in THF at -50 °C



 $^{\rm a}$  Yields determined by  $^1{\rm H}$  NMR using hexamethylbenzene as an internal standard.

#### Table 2

Reduction of acyl aziridines with methyldiphenylsilyllithium (2.5–3.0 equiv) in THF at  $-50\ ^{\circ}\mathrm{C}$ 



<sup>a</sup> Yields determined by <sup>1</sup>H NMR using hexamethylbenzene as an internal standard due to decomposition during purification via chromatography.

group resulted in some deprotection by the silyllithium reagent. More robust protecting groups (entries 4 and 5) gave excellent yields of Mannich base and no deprotection was observed. The reaction of enolizable acyl aziridines often resulted in the recovery of some amount of starting material. This is attributed to the partial enolization of the substrate by the powerfully basic silyllithium reagent, and subsequent reprotonation upon workup.

In conclusion, a new method for the selective reduction of acyl aziridines to Mannich bases using silyllithium reducing agents has been developed. Use of methyldiphenylsilyllithium provided significantly higher yields than the more common dimethylphenylsilyllithium.

*Typical procedure:* A solution of acyl aziridine (1.0 mmol) in 5 mL of dry THF was cooled to -50 °C under argon. A solution of methyldiphenylsilyllithium (~0.7 M, 2.5–3.0 equiv) in THF was added drop-wise with stirring. The reaction was quenched after 10 min with saturated aqueous NH<sub>4</sub>Cl and warmed to room temperature. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL) and the combined organic layers dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The dried solution was concentrated in vacuo and the residue purified by flash chromatography (silica gel, ethyl acetate/petroleum ether) to give the Mannich base.

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## Supplementary data

Supplementary data associated (experimental procedures and spectral data for products) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.005.

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