Efforts Towards the Synthesis of β- and γ-Amino Acids Containing N-Alkyl Pyridones

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Introduction

N-Alkyl-2-pyridones are of interest to scientists, as they are found in a variety of naturally occurring molecules and pharmaceutically active compounds.1

![Figure 1: N-Alkyl Pyridones and N-Alkyl Pyridone-Containing Natural Product](image)

The Anderson research group has developed a method of converting N-substituted O-propargyloxypyridones to β-ido-N-alkenyl pyridones using LiI.2 These compounds have a dense core of orthogonal functionality and are expected to allow access to a broad range of targets, including unnatural amino acids.

Di-Boc Protected Amine

Beginning with propargyl amine, treatment with Boc anhydride provided di-boc protected amine 3 in excellent yield. Di-Boc propargyl amine 5 is then deprotected with nBuLi and quenched with paraformaldehyde to afford the amino-alcohol 6 in moderate yields.

![Scheme 2: Synthesis of Di-Boc Protected Amino-Alcohol 6](image)

Alcohol-Pyridine Coupling

While coupling the amino-alcohol 6 with 2-fluoropyridine (7) was attempted, none of the desired product was isolated. Rather, mono-Boc propargyloxypyridine 8 was recovered in low yields. After further optimization, mono-boc propargyl amine 9 was observed as a major byproduct.

![Scheme 3: Observation of Mono-Boc Propargyl Amine 9](image)

Mono-Boc Alternative

Although the original target was di-boc amine 6, mono-boc protection is expected to retain the electron poor quality of the amine while providing a more stable alternative to di-Boc protection.

Formaldehyde Homologation

Deprotonation of mono-boc amine 9 with two equivalents of nBuLi, followed by quenching with two equivalents of paraformaldehyde lead to the formation of a mixture of products 10 and 11.

![Scheme 4: Formation of Mono-Boc Amino-Alcohol 10 and di-Homologated Product 11](image)

Due to the instability of compound 11, it was shown that it could be converted to the desired amino-alcohol 10 in good yields upon treatment with NaOH, followed by NHCl.

![Scheme 5: Conversion of Di-Homologated Product 11 into Mono-Boc Amino Alcohol 10](image)

Rearrangement

The mono-Boc amino alcohol 10 can be coupled to 2-fluoropyridine (7) under the conditions shown in scheme 6.

![Scheme 6: Synthesis of Mono-Boc Propargyloxypyridine 12](image)

Mono-Boc protected N-alkenyl pyridine 12 was afforded from the corresponding propargyloxypyridine 13 upon treatment with Li and SiO2 under an O2 atmosphere.

![Scheme 7: Formation of Mono-Boc Protected N-Alkenyl Pyridine 13](image)

Efforts to optimize the formation of β-ido N-alkenyl pyridine 14 are currently underway and will be extended to the generation of additional N-alkenyl pyridines in due course.

PMB-Boc Protected Amine

Although the original target was di-boc amine 6, mono-boc protection is expected to retain the electron poor quality of the amine while providing a more stable alternative to di-Boc protection.

Formaldehyde Homologation

Deprotonation of amine 15 with nBuLi, followed by a formaldehyde quench, results in the formation of the desired amino alcohol 16.

![Scheme 8: Synthesis of PMB-Boc Protected Amino-Alcohol 16](image)

Coupling

Amino alcohol 16 can be coupled to halopyridine 7 under optimized conditions to give a N-substituted-O-propargyloxypyridine 17.

![Scheme 9: Synthesis of PMB-Boc Protected Amino-Alcohol 16](image)

![Scheme 10: Synthesis of PMB-Boc Propargyloxypyridine 17](image)

Rearrangement

Upon treatment with Li and SiO2, the nitrogen-containing O-propargyloxypyridine 17 is converted into PMB-Boc protected N-alkenyl pyridine in 48% yield. This rearrangement is undergoing further optimization.

![Scheme 11: Formation of PMB-Boc Protected N-Alkenyl Pyridine 18](image)

Summary

- Di-Boc amino alcohol 6 proved to be unstable under various reaction conditions.
- Mono-Boc amino alcohol 10 appears to be a more viable alternative.
- Synthesis of the mono-Boc N-alkenyl pyridine 13 is currently being evaluated.
- Boc-PMB propargyloxypyridine 17 has been converted to the N-alkenyl pyridine 18 in moderate yields.

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References