

Synthesis of fused bicyclic Pyridones

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Introduction

The objective of this summer project was to investigate the synthesis of fused bicyclic pyridones. These compounds show a range of biological activity such as antifungal, antibiotic, antiviral and protein tyrosine kinase inhibition properties. These compounds display potential for forming hydrogen bonds, hence these are potential drug candidates as anticancer agents. Molecules of this general topology (fused pyridones, acylpyridone) have also been shown to have agrochemical potential e.g. as herbicides.

Step 1

Commercially available ethyl acetoacetate was reacted with pyrrolidine in toluene to form the **enamine 1** precursor for the cycloaddition.

Step 2

An alternative approach was followed for the esterification step. Commercially available β -alanine ethyl ester was used instead of using the diaminopropanoic acid. The amine was protected with a Boc group (di-*tert*-butyl dicarbonate (BOC)₂) to afford the BOC protected methyl ester **2**

Step 3

The BOC protected methyl ester **2** was treated with diisobutylaluminium hydride (DIBAL-H) in toluene at -78°C to afford the aldehyde **3**.

Step 4

This is a key step in the reaction, the formation of the isoxazolopyridone via **1,3 dipolar cycloaddition**. Dry oxime **3** was reacted with N-chlorosuccinimide (NCS) followed by the addition of triethylamine.

Step 5

This is a simple deprotection of the BOC group by the addition of trifluoroacetic acid to the isoxazole **4**, followed by HCL 2M, this activates the amine to form the cyclisation.

Step 6

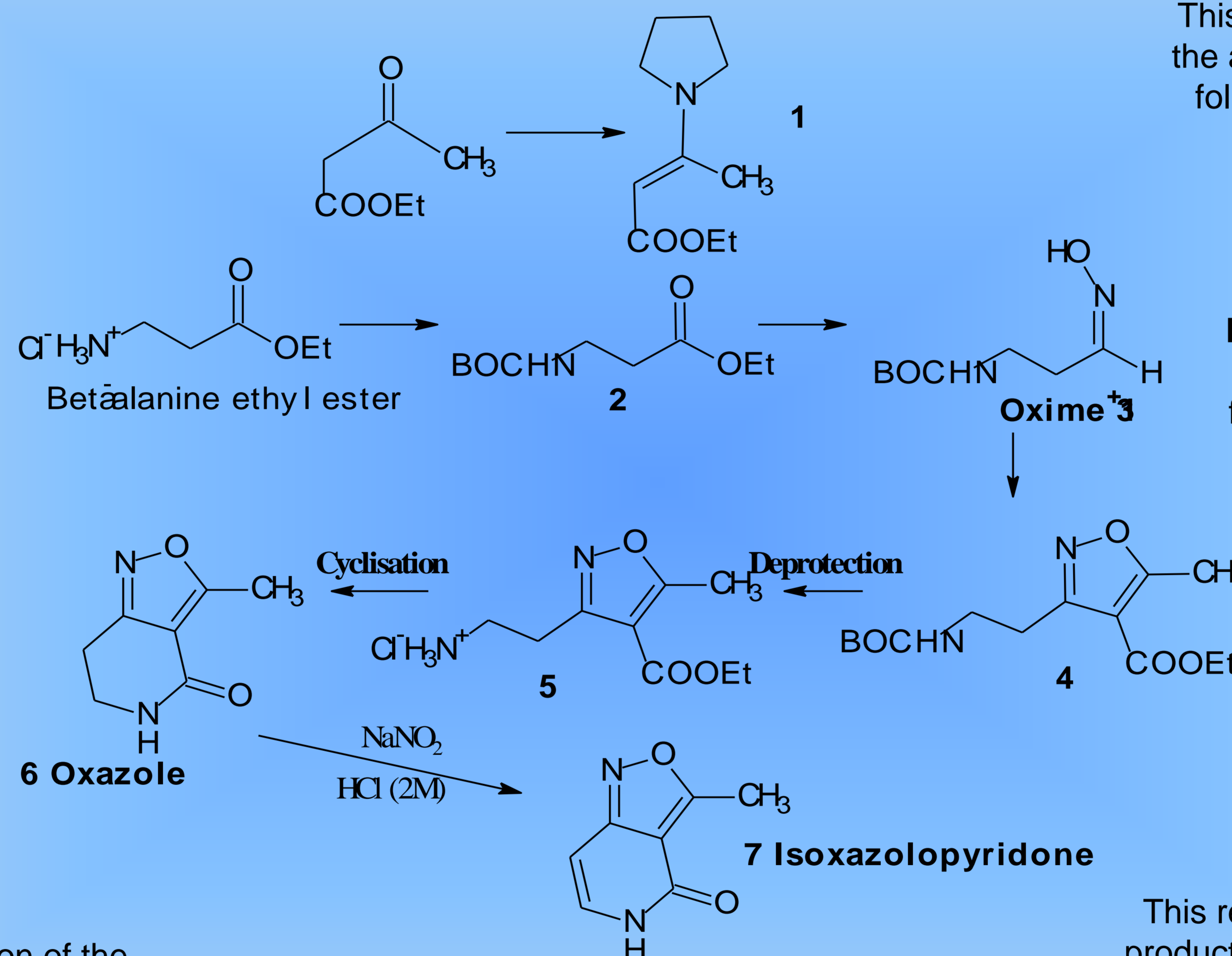
Formation of the isoxazolopyridone. The **hydrochloride salt 5** was treated with sodium carbonate solution to release the amines and forms hydrochloride salts. Which subsequently activates the cyclisation.

Step 7

The unsaturated bond is introduced with the treatment of sodium nitrite and 2M HCl in water.

Conclusion

This reaction involves 7 steps to form the final desired product, the Isoxazolopyridone. This decreases the yield significantly as the yield is lost in each step. Future work could involve investigating different approaches to yield the desired product, this could involve using different commercially available reagents to optimise the yield.



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