Addition of Nitro Compounds to N-Acyliminium Ions and Coupling with Aldehydes Performed by N-Heterocyclic Carbenes.

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Abstract

Aiming the synthesis of the fragment pyrrolo[1,2-a]azepino present in Stemona alkaloids, a different method of synthesis was studied. In this method, the addition of nitro compounds to N-acyliminium ions using Lewis acid or Bronsted acid as catalysts was tried.

Key words:
N-Acyliminium Ions, Nitro compounds, Stemona alkaloids

Introduction

Herbal extracts have been used in folk medicine in East Asia for thousands of years. The Stemonaceae family was used in herbal extracts because it was claimed to present antituberculosis, antibacterial, antifungal and antihelminic properties. A representative of this family of alkaloids is depicted below (Figure 1).

Image 1. Structure of Stenine (the atoms in blue are the pyrrolo[1,2-a]azepino fragment)

This work aims to synthesize the fragment pyrrolo[1,2-a]azepino present in the Stemona alkaloids exploring the addition of nitro compounds to N-acyliminium ions derived from pyrrolidines. With this aduct in hand, we would be able to proceed with the synthesis of the Stemona alkaloids in order to support biological studies and structural validation/determination.

Results and Discussion

The synthesis of fragment 3 started with protection of pyrrolidone 1 to produce carbamate 2 in 60% yield. Reduction with disobutyaluminium hydride (DIBAL-H) in THF, followed by the treatment with ethanol under acidic conditions provided hemiinal 3 in 70% yield.

Image 2. Synthesis of intermediate 3

Fragment 3 was used as a substrate for the reaction with nitro compounds. At first, we started using nitromethane 4a as a model nucleophile due to its commercial availability which allowed us to use it as the reaction solvent. To improve the chances of success, we tested three different Lewis acids (indium chloride, boron trifluoride etherate and zinc trifluoromethanesulfonate) and a Bronsted acid (p-toluenesulfonic acid) as catalyst and varied the reaction temperature. Unfortunately, we didn’t observe any sign of product 5a by 1H NMR spectroscopy or IR spectroscopy of the crude reaction mixture.

Despite of the failure of the reaction with nitromethane, we used methyl 4-nitrobutyrate in presence of InCl₃ or DBU but TLC revealed that no reaction occurred.

Aiming a stronger nucleophile, we generated in situ the silyl nitronate corresponding to methyl 4-nitrobutyrate 4b, in the presence of 1,8-diazobicycloundec-7-ene (DBU) and trimethylsilyl chloride (TMSCl) in dichloromethane. After that, we added 3 and InCl₃. Despite the increase in the nucleophility of our nitro compound, we didn’t observe any sign of product 5b by 1H NMR spectroscopy or IR spectroscopy after the purification by column chromatography.

Conclusions

In this work, we have examined the addition of nitro compounds to N-acyliminium ions derived from N-Cbz pyrrolidin-2-one. Under the reaction conditions investigated, we weren’t able to isolate the desired adduct. We are now exploring the addition of Grignard reagents to Weinreb amide prepared form L-proline in order to obtain the pyrrolo[1,2-a]azepino fragment of Stemona alkaloids.

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References


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