Synthesis of *cis*-Aminocyclobutanamide Compounds via Reductive Amination

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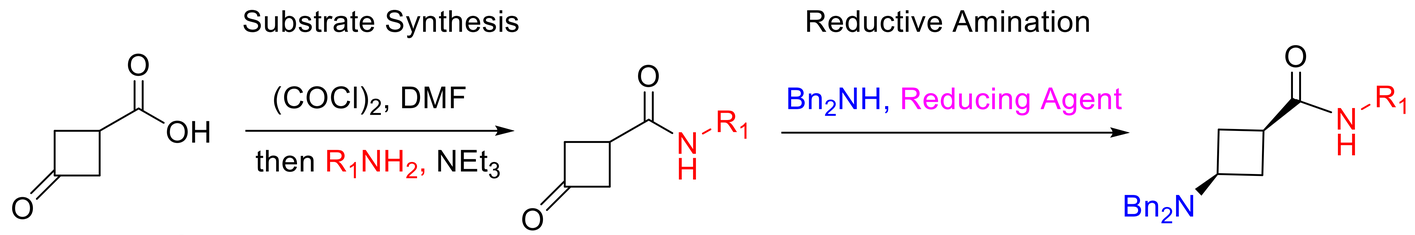
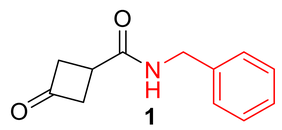
Abstract

In recent years, molecules containing cyclobutanes have shown potential in the medical field. Due to its strained, four-membered ring structure, it restricts the conformation of the molecule, which is useful in substituting a ligand that changes its conformation upon reacting with the target molecule and prevents isomerization of the molecule. In addition, the efficiency of the binding of two molecules increases because of its rigid structure (1). The purpose of this project was to synthesize stereochemically defined amino-substituted cyclobutyl amides to investigate their potential in drug discovery. Starting from 3-oxocyclobutane, two amides were synthesized by coupling with benzylamine and (2-methylthio)aniline, respectively. Reductive amination on N-benzyl-3oxocyclobutane-1-carboxamide was then investigated, where the goal was to experiment with varying reaction conditions to produce higher yields of our product than previous research done by students. To date, it has proven difficult to get clear results from reductive amination using dibenzylamine. Despite efforts to purify the final product with chromatography or debenzylate the mixture via hydrogenation, inconclusive results were obtained. As an alternate approach with more potential for success, reductive amination was attempted on N-(2-(methylthio)phenyl)-3-oxocyclobutane-1carboxamide. The reducing agents used on this amide were sodium triacetoxyborohydride (STAB) and sodium cyanoborohydride, to compare which produced a higher yield of the amine. The molecules in this research reacted in unpredictable ways that provided more insight into the field of reductive animation with molecules containing cyclobutanes, which will lead to the contribution of eventual breakthroughs in medicine.

Methodology

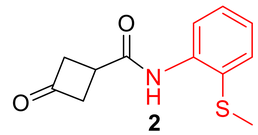




1

N-benzyl-3-oxocyclobutane-1-carboxamide

37% Yield



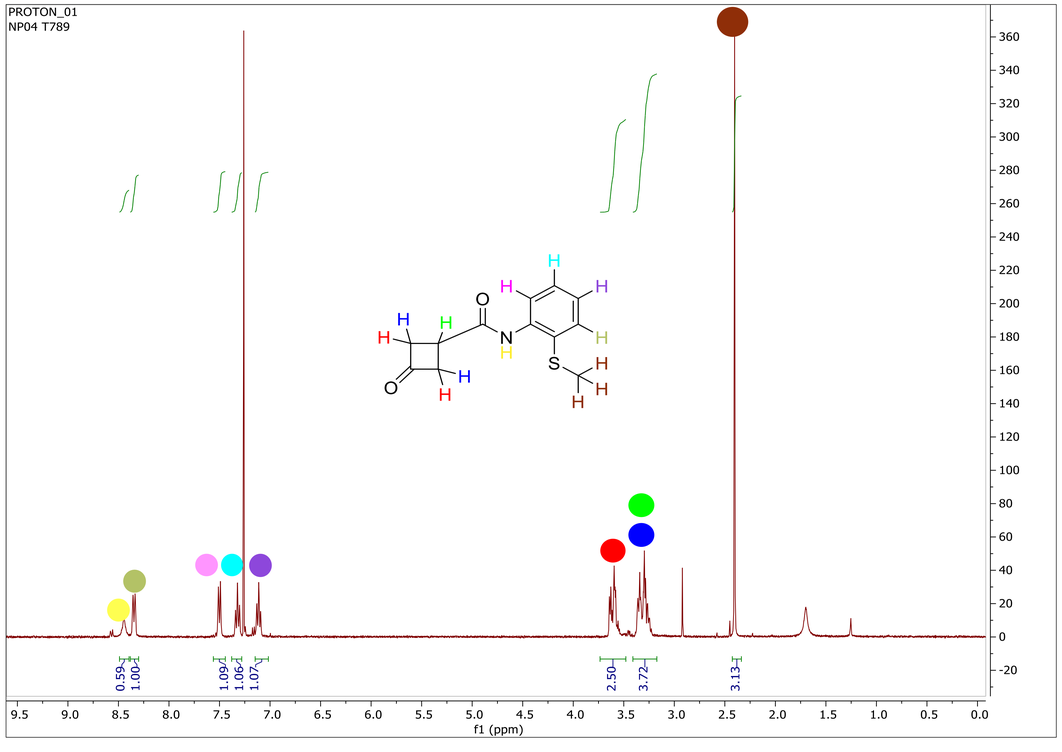
2

N-(2-(methylthio)phenyl)-3-oxocyclobutane-1-carboxamide

66% Yield

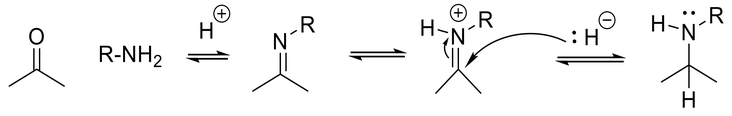
Substrate	Reductant	Conditions	Observations/Results
1	STAB	At room temp., mixed 0.127mL Acetic acid, 0.247mL Dibenzylamine, and 3.2mL DCE	We had inconclusive NMR results after washing and doing a column chromatography. Possibly have lost the product in running the column.
1	STAB	Same conditions as above- Prepared a hand column and performed hydrogenation. Redid the reductive amination, used hand column instead. Ran it in 100% DCM at first, then to 5% MeOH/DCM, and finally 10%.	The NMR from attempting to debenzylate the compound was difficult to interpret and led to the conclusion that a different substrate should be used to better identify the product. The NMR was inconclusive because the benzyl from the amide was indistinguishable from the benzyls attached to the amine.
2	STAB	Same conditions- Prepared a hand column. First ran it in 25% EtOAc/Hex and with ~0.5% NEt_3 Second run was 50% EtOAc/Hex with ~0.5% NEt_3 Third run was 100% EtOAc with ~0.5% NEt_3	After running the hand column and obtaining the tubes in which we predicted contained the product through TLC analysis, the NMR showed that the product contained impurities
2	$NaCNBH_3$	At 50°C, mixed 0.032mL Acetic acid, 0.063mL Dibenzylamine, and 2mL THF	-Currently in Progress-

Results

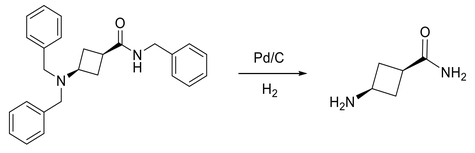


Discussion

Reductive Amination Mechanism



Hydrogenation Scheme



- Key Challenges
  - Unable to distinguish all aspects of our molecule that underwent reductive amination
  - Characterization of reaction mixture
    - Isolation of polar compound has proven to be difficult

Future Directions

- Explore using primary amines in the process of Reductive Amination
  - Benzylamine
- Possibly change the amount of acetic acid
- Change the amount of reducing agent
- Change TLC and chromatography method after work up
  - Use alumina instead of silica gel

References

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