Georgia Southern University

Digital Commons@Georgia Southern

Honors College Theses

2024

Synthesis of Chiral Amino Acids via Direct Amination of Diazo Ester with a Rhodium-Based Catalyst

Steven J. Boyles
Georgia Southern University

Follow this and additional works at: https://digitalcommons.georgiasouthern.edu/honors-theses

 Part of the Organic Chemistry Commons

Recommended Citation

Boyles, Steven J., "Synthesis of Chiral Amino Acids via Direct Amination of Diazo Ester with a Rhodium-Based Catalyst" (2024). *Honors College Theses*. 975.
https://digitalcommons.georgiasouthern.edu/honors-theses/975

This thesis (open access) is brought to you for free and open access by Digital Commons@Georgia Southern. It has been accepted for inclusion in Honors College Theses by an authorized administrator of Digital Commons@Georgia Southern. For more information, please contact digitalcommons@georgiasouthern.edu.

Synthesis of Chiral Amino Acids *via* Direct Amination of Diazo Ester with a Rhodium-Based Catalyst

An Honors Thesis submitted in partial fulfillment of the requirements for Honors in the Department of Biochemistry, Chemistry, and Physics

By
Steven J. Boyles

Under the mentorship of Dr. Abid Shaikh

ABSTRACT

Amino acids are critical molecules within living organisms as they are the building blocks of proteins. In organisms, proteins serve as regulators of necessary processes, structural components in tissue, hormones, and neurotransmitters. Amino acid therapy is an emerging treatment in the medical field used to treat symptoms of diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Amino acid therapies have also shown promising effects when it comes to treating mood disorders and weight management. In order to increase the number of amino acids available and increase the potential treatments for other ailments, there is a drive to increase the availability of synthetic methods of amino acid synthesis. Previous research has shown that these methods are best aided by the use of a rhodium, ruthenium, or copper catalyst. This paper proposes a synthetic path utilizing these catalysts to accomplish this task. The proposed reaction strategy was successful, and it is determined to be an effective means to synthesize chiral amino acids.

Thesis Mentor: Dr. Abid Shaikh

_____

Honors Dean: Dr. Steven Engel

_____

April 2024
Department of Biochemistry, Chemistry, and Physics
Honors College
Georgia Southern University

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

The dedicated and most understanding Dr. Abid Shaikh

The supportive and tenacious Dr. Shainaz Landge

The Honors College

The Department of Biochemistry, Chemistry, and Physics

The College of Science and Mathematics

The College Office of Undergraduate Research

Introduction

Amino acids are crucial to all living organisms and without them, living organisms would not be able to function. The most important function of amino acids is serving as the constituent parts of proteins in the body[1]. Proteins are critical in the human body contributing to everything from the structure and function of cells to the regulation of various processes. These proteins then go one to serve as enzymes[2], hormones[1], antibodies[2], neurotransmitters[1], and structural components in tissues[2].

Amino acids are essentially molecules that contain an amino group and a carboxylic acid group within the same molecule[1]. These two functional groups give these amino acids unique polar and intermolecular properties[2]. All amino acids also have other functional groups within their structure that determine other important structural and functional properties of the amino acid. The human body uses 20 standard amino acids to serve as the building blocks of proteins. These 20 amino acids are more specifically alpha amino acids. This means that the amino group and the carboxylic acid group are one central carbon away from each other in the molecule.[1] This arrangement determines a lot of the functional properties of these amino acids and makes them crucial molecules when building proteins[3]. Of these 20 amino acids, nine are considered "essential" amino acids because they are crucial in protein synthesis, but the body cannot synthesize them on its own. These nine amino acids must be obtained from other sources, typically from the diet[1].

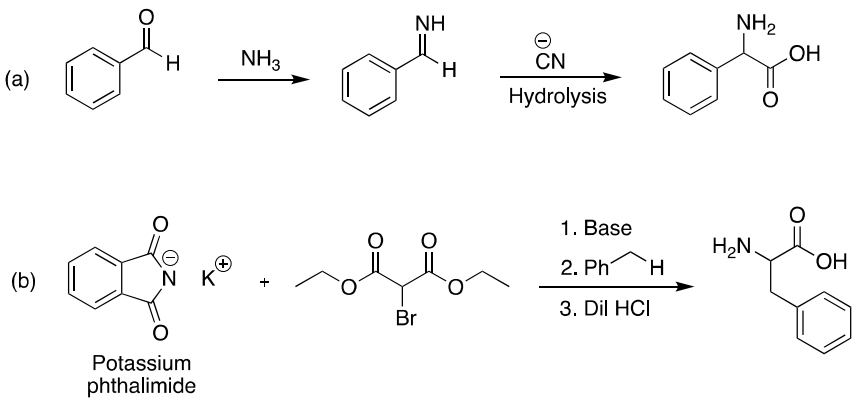
Due to the importance of amino acids in the body, other amino acids different from the 20 standard ones used by the body have been used to address various health conditions or imbalances within the body[4]. Amino acid therapies have currently been used to treat mood disorders[5], metabolic disorders[6], and tissue damage[7]. Amino acid therapy is also

showing promising results when it comes to treating neurological conditions, such as Alzheimer's disease[8], Parkinson's disease[9], multiple sclerosis[10], and epilepsy[11]; weight management and control[12]; and detoxification[12]. Amino acids are important precursors in processes that help mitigate the symptoms of these diseases.

Due to the emerging importance of amino acid therapy, there is a drive to expand the number of amino acids available for these therapies[13]. Additionally, there is also a drive to find efficient reactions to synthesize these novel amino acids[14]. There is extensive research into what the standard set of 20 amino acids do in the body[1]. Expanding the library of amino acids available for therapies is important in order to drive further research into what these nonstandard amino acids can offer medical professionals and scientists[14]. Current research has proposed reactions under the presence of catalytic metals such as copper, ruthenium, rhodium, and palladium to yield non-standard amino acids[15]. Furthermore, reactions that yield enantiomerically pure amino acids are the most promising due to their ability to yield the highest quality products[10].

Literature Overview

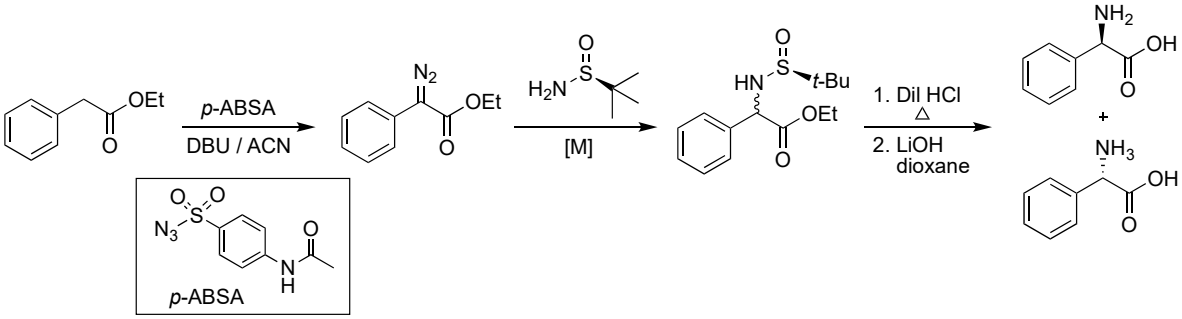
Amino acid synthesis can be achieved via various chemical methods that typically involve the reaction of appropriate starting material to form the desired amino acid. Traditionally, Strecker synthesis is a common method that involves the reaction of an aldehyde or ketone with ammonia and cyanide followed by the hydrolysis of the cyanide to a carboxylic acid to provide an amino acid (Scheme 1a).[16] Another method is the Gabriel synthesis, which involves the reaction of phthalimide with an alkyl halide to form an *N*-alkyl phthalimide, which can then undergo hydrolysis and decarboxylation to yield an amino acid (Scheme 1b).[17]



Scheme 1. Literature methods for the synthesis of amino acids.

Research Hypothesis and Objective

This work involves the functionalization of diazo esters with *tert*-butanesulfinamide using a metal-catalyzed carbenoid insertion strategy. The use of *tert*-butanesulfinamide for amination of diazo esters has not been pursued in the literature. We anticipate the use of chiral *tert*-butanesulfinamide is a viable approach for the synthesis of diastereoselective *N*-sulfinyl amino esters, which on further removal of *tert*-butanesulfonyl group and successive ester hydrolysis would provide pure amino acids (Scheme 2). In comparison with the previous methods, the work highlighted in this paper was performed at room temperature, safely on a common benchtop, and using commercially available starting materials.



Scheme 2. Our new method for the synthesis of amino acids.

Results and Discussion

We envisioned the most straightforward route for the synthesis of an amino acid would involve the acquisition of diazo ester which will serve as a reactant further in the reaction sequence. As a next step, we tried the amine insertion to diazo ester as the most important transformation. Multiple metal catalysts were utilized in this experiment to yield the desired product. Rhodium trifluoroacetate dimer and dichloro(*p*-cymene)ruthenium(II) dimer catalysts both yielded a dimeric product of diazo ester. Later trials with rhodium(II) octanoate dimer yielded the correct product from reaction. After successful execution of step 2 of this synthesis, *tert*-butyl sulfoxide was removed using dilute hydrochloric acid and further treatment with lithium hydroxide resulted in the required amino acid as final product. All the products and intermediates were isolated in high analytical purity and were fully characterized using ^{1}H NMR and ^{13}C NMR spectroscopy. It is worth mentioning that the final amino acid product was isolated as a racemic mixture. We did not carry out analysis for enantioselectivity determination, however, we anticipate to develop a chiral HPLC method in order perform this analysis.

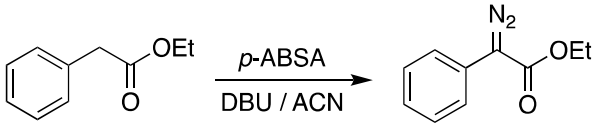
Conclusion

In conclusion, we plan to develop a simple and efficient synthesis to both enantiomers of amino acids. We anticipate obtaining high yields and enantioselectivities of intermediates and products. The major advantages of the process are the use the commercially available chiral auxiliaries and catalyst, which can provide both enantiomers of the products.

Experimental Section

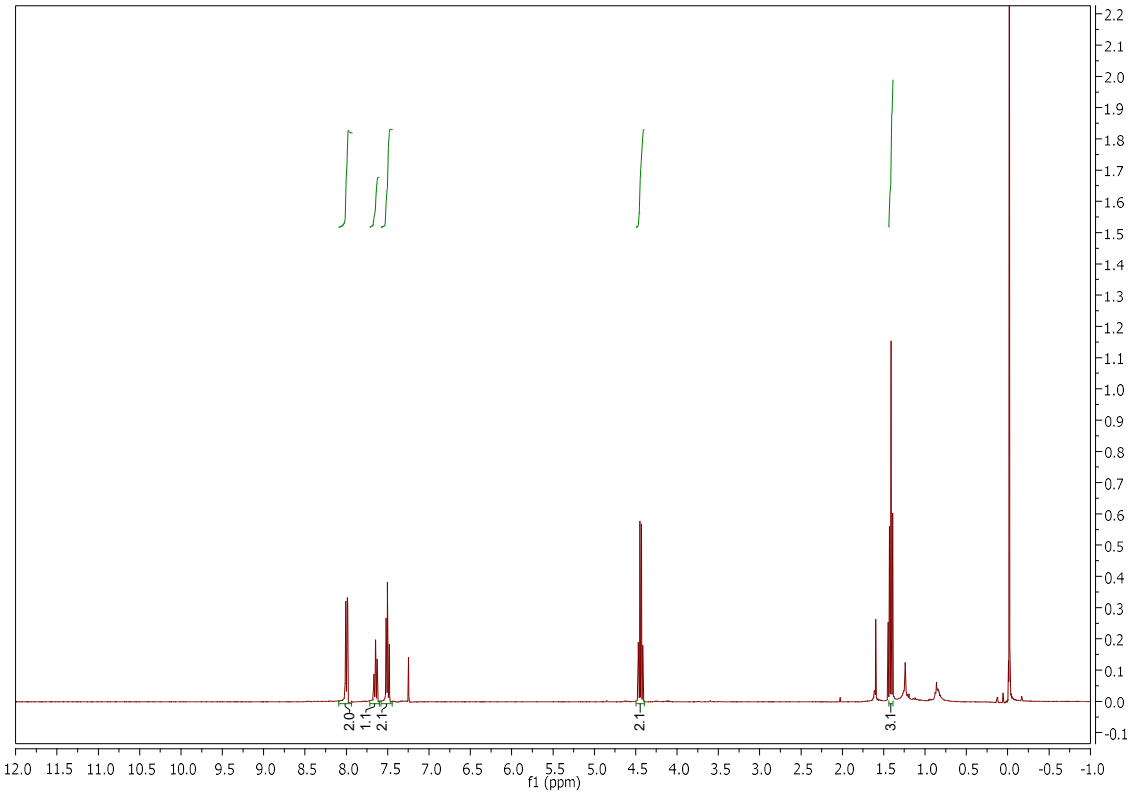
General experimental considerations: All the starting materials such as were purchased from Aldrich and used without further purification. Thin layer chromatography (TLC) was performed using Merck silica gel 60 F_{250} aluminum coated plates and were visualized by exposure to short-wave ultraviolet light or by exposure to iodine sealed in a bottle. Organic solutions were concentrated by rotary evaporation and flash column chromatography was performed with silica gel 60 Å. Methaol-D4 and $CDCl_3$ were used as a solvent (99.8%) for the NMR studies was purchased from Aldrich. The ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz JEOL NMR spectrometer and chemical shifts are reported relative to internal tetramethylsilane TMS or the residual solvent signal.

Experimental procedure for the synthesis of diazo ester.

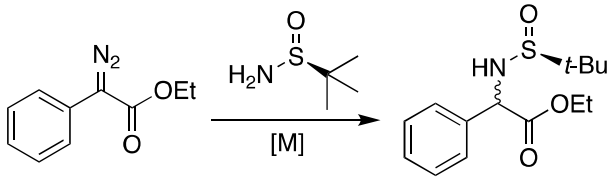


Ethyl phenylacetate (1 mL) and 2.25 g of *p*-ABSA were mixed in 20 mL of acetonitrile in a 100 mL round bottom flask. A mixture of 4 mL 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 4 mL acetonitrile was added dropwise to the stirring round bottom flask that had been cooled in an ice bath. This was allowed to stir for 24-48 hours. Upon confirmation of the production of the diazo ester via thin layer chromatography (TLC), the reaction mixture was quenched with water (15 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, wash with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting crude residue was purified by flash chromatography on silica gel and 10% ethyl acetate in hexanes as an eluting solvent to

afford the desired product. The product formation was confirmed by ^{1}H NMR spectroscopy, a scan of product is provided below.

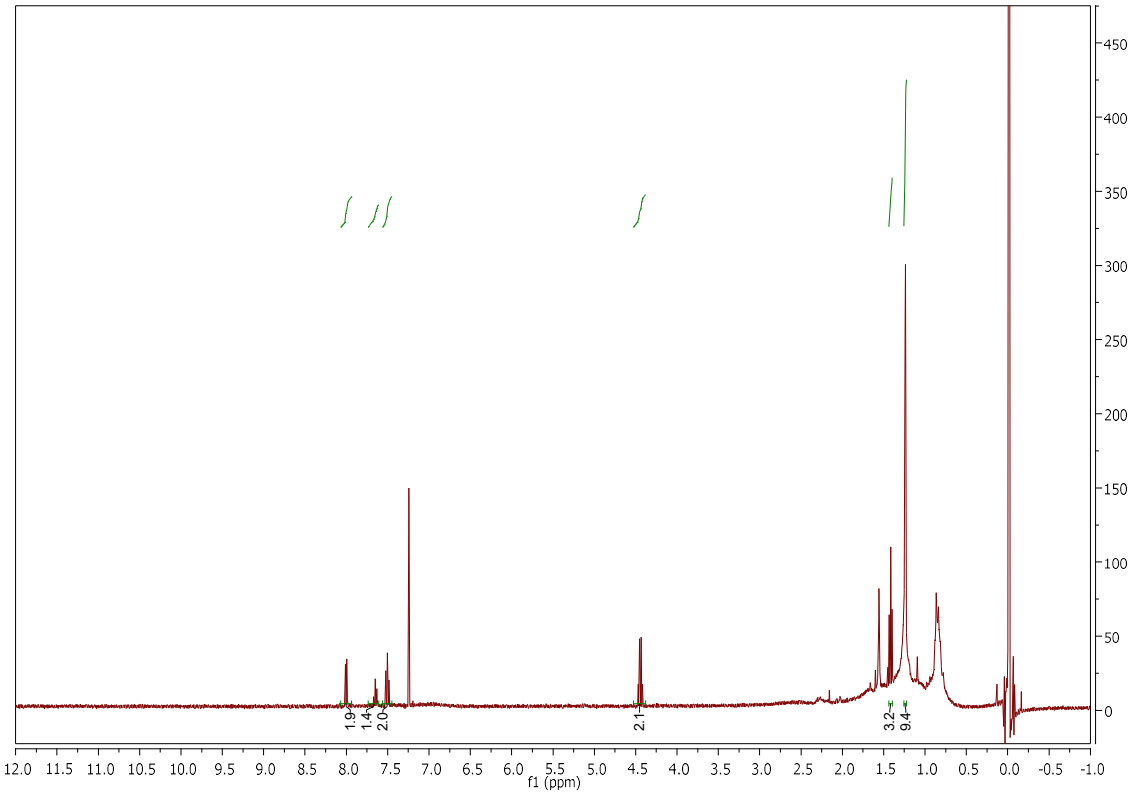


Experimental procedure for the amination of diazo ester.

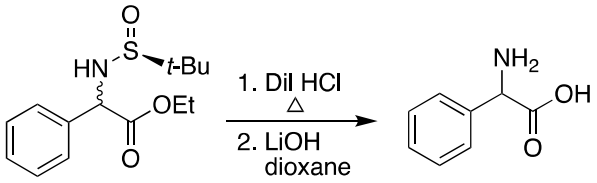


Diazo ester 11 mg was placed in a 20 mL scintillation vial, along with 9 mg *tert*-butanesulfinamide and were dissolved in 2 mL acetonitrile. 1 mg of a metal catalyst (rhodium(II)octanoate) was then added and the resulting reaction mixture was allowed to stir for 24 hours. The reaction progress was monitored by TLC to confirm the desired product formation. Upon this confirmation, the reaction mixture was separated via column

chromatography. The desired product was then further confirmed by ^{1}H NMR spectroscopy.

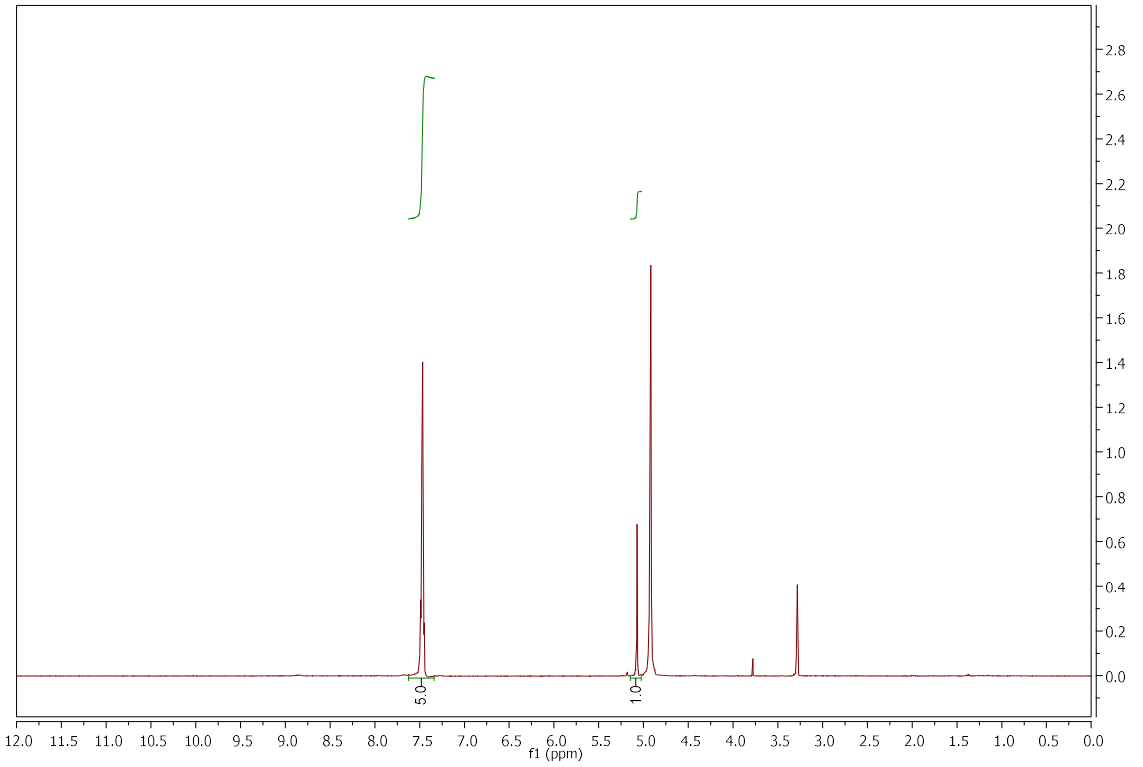


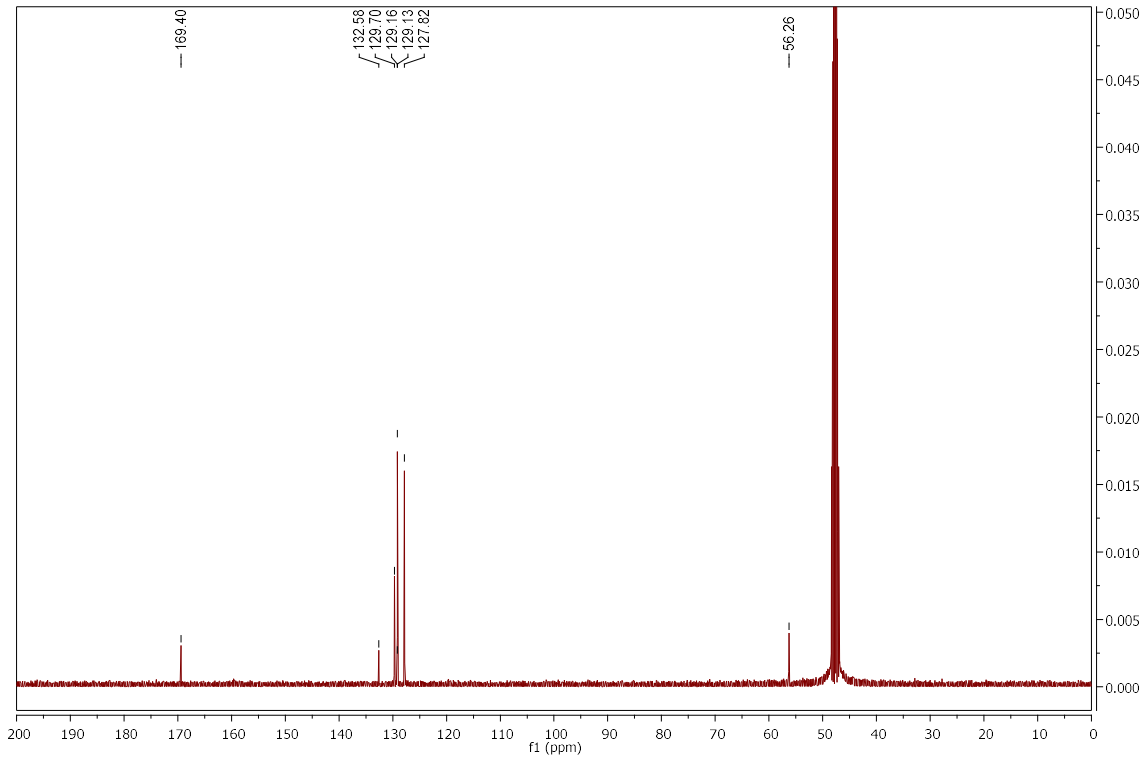
Experimental procedure for the removal tert-butylsulfoxide and hydrolysis of ester.



Amino ester 50 mg was placed in a 20 mL scintillation and 10 mL of dilute hydrochloric acid was added slowly. The reaction mixture was stirred for 30 min and then extracted with ethyl acetate. The crude product was further dissolved in dioxane and a dilute solution of lithium hydroxide was added dropwise. The reaction mixture was allowed to stir at room temp. for 4 hours and then water. Slow removal of water under reduced pressure provided

translucent crystals of pure amino acid. The product formation was confirmed using ^{1}H and ^{13}C NMR spectroscopy.





References

1. Lopez MJ, Mohiuddin SS. Biochemistry, Essential Amino Acids. [Updated 2023 Mar 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557845/

2. LaPelusa A, Kaushik R. Physiology, Proteins. [Updated 2022 Nov 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555990/

3. Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002. The Shape and Structure of Proteins. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26830.

4. Jin X, Park OJ, Hong SH. Incorporation of non-standard amino acids into proteins: challenges, recent achievements, and emerging applications. Appl Microbiol Biotechnol. 2019 Apr;103(7):2947-2958. doi: 10.1007/s00253-019-09690-6. Epub 2019 Feb 21. PMID: 30790000; PMCID: PMC6449208.

5. Lakhan SE, Vieira KF. Nutritional therapies for mental disorders. Nutr J. 2008 Jan 21;7:2. doi: 10.1186/1475-2891-7-2. PMID: 18208598; PMCID: PMC2248201.

6. Simonson M, Boirie Y, Guillet C. Protein, amino acids and obesity treatment. Rev Endocr Metab Disord. 2020 Sep;21(3):341-353. doi: 10.1007/s11154-020-09574-5. PMID: 32827096; PMCID: PMC7455583.

7. Arribas-López E, Zand N, Ojo O, Snowden MJ, Kochhar T. The Effect of Amino Acids on Wound Healing: A Systematic Review and Meta-Analysis on Arginine and Glutamine. Nutrients. 2021 Jul 22;13(8):2498. doi: 10.3390/nu13082498. PMID: 34444657; PMCID: PMC8399682.

8. Larsson, S.C., Markus, H.S. Branched-chain amino acids and Alzheimer's disease: a Mendelian randomization analysis. Sci Rep 7, 13604 (2017). https://doi.org/10.1038/s41598-017-12931-1

9. Wang W, Jiang S, Xu C, Tang L, Liang Y, Zhao Y and Zhu G (2022) Interactions between gut microbiota and Parkinson's disease: The role of microbiota-derived amino acid metabolism. Front. Aging Neurosci. 14:976316. doi: 10.3389/fnagi.2022.976316

10. Laura Negrotto, Jorge Correale; Amino Acid Catabolism in Multiple Sclerosis Affects Immune Homeostasis. J Immunol 1 March 2017; 198 (5): 1900–1909.

11. Ebrahimi HA, Ebrahimi S. Evaluation of the Effects of Charged Amino Acids on Uncontrolled Seizures. Neurol Res Int. 2015;2015:124507. doi: 10.1155/2015/124507. Epub 2015 Jul 9. PMID: 26240759; PMCID: PMC4512581.

12. Simonson M, Boirie Y, Guillet C. Protein, amino acids and obesity treatment. Rev Endocr Metab Disord. 2020 Sep;21(3):341-353. doi: 10.1007/s11154-020-09574-5. PMID: 32827096; PMCID: PMC7455583.

13. (a) Wu, G. Amino Acids, 2009, 37, 1-17. (b) Ikeda, M. Adv. Biochem. Eng. Biotechnol., 2003, 79, 1–35. (c) Augeri, et al. J. Med. Chem., 2005, 48, 5025-5037.

14. Qvit, N., Rubin, S. J. S., Urban, T. J., Mochly-Rosen, D., Gross, E. R. Drug Discov. Today., 2017, 2, 454-462.

15. (a) Yang, J., Ruan, P., Yang, W., Feng, X., Liu, X. Chem. Sci., 2019, 10, 10305-10309. (b) Liu, G. et al. Org. Biomol. Chem., 2013, 11, 5998-6002. (b) Kankanala, R., Chinnappan, S. J. Organomet. Chem., 2016, 805, 122-129.

16. Petr Vachal and and Eric N. Jacobsen, *Organic Letters* **2000,** *2* (6), 867-870

17. Gibson, M. S.; Bradshaw R. W. *Chem. Int. Ed.* **1968,** *7* (12), 919-930