Communication

Synthesis of (S)-4-Benzyl-3-Butyl-1-(2-Cycloheptylethyl)imidazolidine

Matevž Schweiger , Luka Ciber , Nejc Petek , Franc Požgan , Jurij Svete , Bogdan Štefane , Uroš Grošelj *

Posted Date: 25 March 2026

doi: 10.20944/preprints202603.1953.v1

Keywords: $LiAlH_4$; amide reduction; imidazolidine; β-elimination; cinnamamide

 doi:10.20944/preprints202603.1953.v1

Communication

Synthesis of (S)-4-Benzyl-3-Butyl-1-(2-Cycloheptylethyl)imidazolidine

Matevž Schweiger, Luka Ciber, Nejc Petek, Franc Požgan, Jurij Svete, Bogdan Štefane and Uroš Grošelj *

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, SI-1000 Ljubljana, Slovenia

* Correspondence: uros.groselj@fkkt.uni-lj.si; Tel.: +386 1 479 8565

Abstract

$LiAlH_4$ reduction of *tert*-butyl (*S*)-butyl(1-((2-cycloheptylethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**1**) gave imidazolidine **2**, while treatment with LDA furnished the β-elimination product, cinnamamide **3**. Both products were fully characterized. Reductive cyclization of *N*-alkylated-*N*-Boc-protected amino acid amides with $LiAlH_4$ may be a viable synthetic method for trisubstituted chiral imidazolidines.

Keywords: $LiAlH_4$; amide reduction; imidazolidine; β-elimination; cinnamamide

1. Introduction

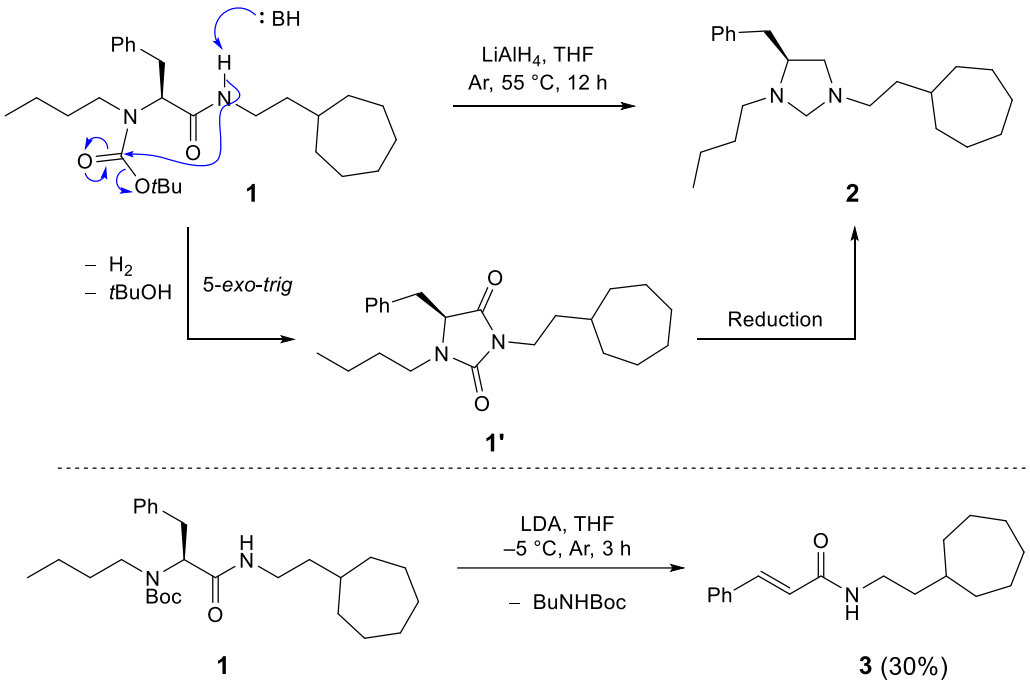
Five-membered cyclic aminals, imidazolidines, are structural motifs found in various natural products [1–5] and synthetic compounds, exhibiting diverse biological activities [6–9], including fungicidal, antiparasitic, antibacterial, antiamebic, antiviral, and anticancer effects [10]. Furthermore, imidazolidines, along with diarylprolinol silyl ethers [11], are workhorses of covalent enamine and iminium ion organocatalysis [12–16].

Following disconnection at the aminal carbon of imidazolidines, the starting compounds are (substituted) 1,2-diamines and aldehydes or ketones, which is also the most frequently used method for their synthesis [17]. For a detailed account of synthetic methods for assembling imidazolidines, see the review by Abolfazl Olyaei and Mahdieh Sadeghpour and the references cited therein [10]. In this communication, we report the synthesis of an L-phenylalanine-derived imidazolidine **2** prepared from *N*-alkylated-*N*-Boc-protected amino acid amide **1** by reductive cyclization with $LiAlH_4$.

2. Results and Discussion

tert-Butyl (*S*)-butyl(1-((2-cycloheptylethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**1**), prepared in three steps from L-phenylalanine according to literature procedures [18,19], was treated with excess $LiAlH_4$ at 55 °C for 12 hours. Purification by column chromatography afforded (*S*)-4-benzyl-3-butyl-1-(2-cycloheptylethyl)imidazolidine (**2**) in 40% yield (Scheme 1). The formation of imidazolidine **2** can be tentatively explained by initial $LiAlH_4$-mediated deprotonation of amide **1**, followed by favorable 5-*exo*-*trig* cyclization to hydantoin derivative **1'**, which is then reduced to aminal **2**. Complete reduction of hydantoin derivatives to cyclic aminals with $LiAlH_4$ is documented in the literature [6,20]. An attempt to cyclize amide **1** to hydantoin **1'** using lithium diisopropylamide (LDA) as a strong base did not yield hydantoin **1'**; instead, the E2 elimination product **3** was isolated in 30% yield (Scheme 1). To better understand the sequence of events in the formation of cyclic aminal **2** (cyclization vs. reduction), further mechanistic investigation is required.

 doi:10.20944/preprints202603.1953.v1



Scheme 1. Synthesis of cyclic aminal **2** from *N*-alkylated-*N*-Boc-protected amino acid amide **1**, along with the proposed mechanism for its formation, and synthesis of cinnamamide **3** from **1** using LDA.

The structures of imidazolidine **2** and cinnamamide **3** were confirmed by ^{1}H and ^{13}C NMR, DEPT 135, HSQC, IR, and high-resolution mass spectrometry. The *trans* configuration around the C=C bond of cinnamamide **3** is supported by the coupling constant (^{3}J = 15.6 Hz) in the proton spectrum. Similarly, the proton and carbon spectra of imidazolidine **2** are consistent with those of the closely related imidazoline prepared from L-tryptophan [21]. The most prominent signals in the proton spectrum of **2** are the geminal aminal protons at 3.25 ppm and 3.73 ppm, with a ^{2}J coupling constant of 5.5 Hz, and the corresponding aminal carbon at 77.40 ppm in the ^{13}C NMR spectrum (Figure 1) [21,22].

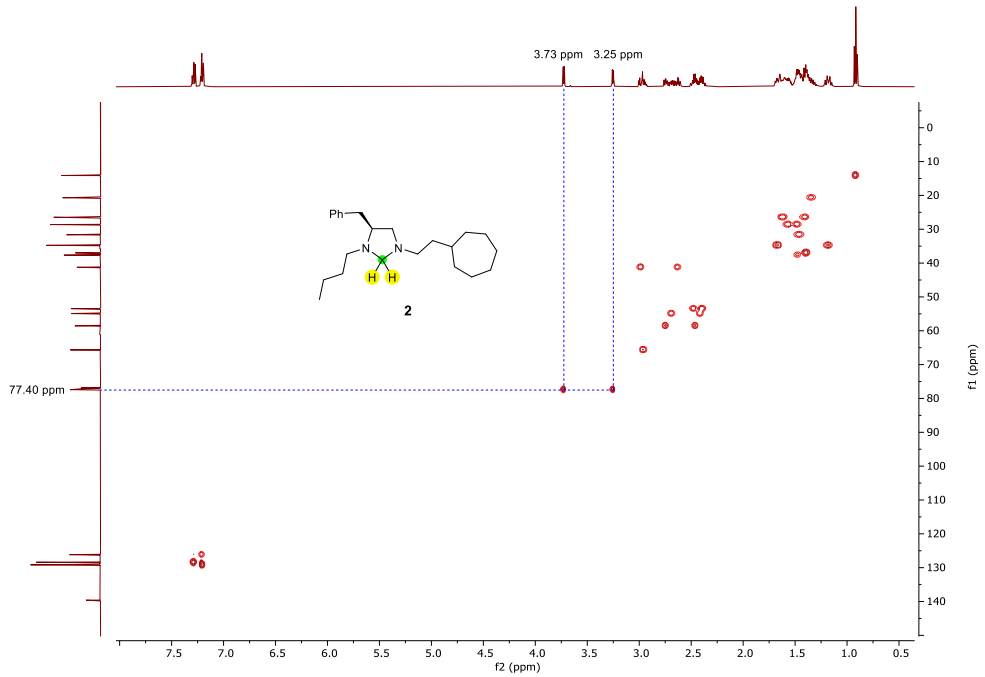


Figure 1. HSQC spectrum of imidazolidine **2** in $CDCl_3$.

 doi:10.20944/preprints202603.1953.v1

3. Materials and Methods

Solvents for extractions and chromatography were technical grade and distilled before use. Extracts were dried over technical grade anhydrous Na_2SO_4. Melting points were determined with an SRS OptiMelt MPA100 Automated Melting Point System (Stanford Research Systems, Sunnyvale, CA, USA). NMR spectra were recorded on a Bruker UltraShield 500 Plus spectrometer (Bruker, Billerica, MA, USA) at 500 MHz for ^{1}H and 126 MHz for ^{13}C, using $CDCl_3$ as the solvent and TMS as the internal standard. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS (Agilent Technologies, Santa Clara, CA, USA), and IR spectra were recorded on a PerkinElmer Spectrum BX FTIR spectrophotometer (PerkinElmer, Waltham, MA, USA). Column chromatography was performed on silica gel (Silica gel 60, particle size 0.035–0.070 mm; Sigma-Aldrich, St. Louis, MI, USA). All commercially available chemicals were purchased from Sigma-Aldrich (St. Louis, MI, USA). The starting compound, *tert*-butyl (*S*)-butyl(1-((2-cycloheptylethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**1**), was prepared according to literature procedures [19].

3.1. Synthesis of (S)-4-benzyl-3-butyl-1-(2-cycloheptylethyl)imidazolidine (2)

To *tert*-butyl (*S*)-butyl(1-((2-cycloheptylethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**1**) (294 mg, 0.660 mmol) under argon, $LiAlH_4$ (3 mL, 2.4 M in THF, 7.20 mmol) was added. The reaction mixture was stirred under argon at 55 °C for 12 h. The mixture was cooled in an ice bath and quenched by careful addition of saturated aqueous NaCl. The resulting semi-solid was extracted with Et_2O (5×30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the volatile components were evaporated *in vacuo*. The residue was purified by column chromatography (Silica gel 60, CH_2Cl_2/MeOH = 50:1). Fractions containing pure product **2** were combined, and the volatile components were evaporated *in vacuo*. Yield: 92 mg (0.269 mmol, 40%) of colorless oil. $[\alpha]_D^{r.t.}$ = +58.5 (0.93 mg/mL, CH_2Cl_2). EI-HRMS: *m*/*z* = 343.3101 (MH^+); $C_{23}H_{39}N_2$ requires: *m*/*z* = 343.3108 (MH^+); ν_{max} 3062, 3026, 2919, 2853, 2798, 1603, 1495, 1454, 1356, 1237, 1186, 1081, 1031, 902, 742, 698 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 0.92 (*t*, *J*=7.3, 3H), 1.12 – 1.24 (*m*, 2H), 1.28 – 1.73 (*m*, 17H), 2.34 – 2.52 (*m*, 4H), 2.58 – 2.79 (*m*, 3H), 2.91 – 3.02 (*m*, 2H), 3.25 (*d*, *J*=5.5 Hz, 1H), 3.73 (*d*, *J*=5.5 Hz, 1H), 7.16 – 7.25 (*m*, 3H), 7.25 – 7.32 (*m*, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (ppm) 14.12, 20.69, 26.46, 26.47, 28.60, 31.63, 34.76, 36.97, 37.66, 41.24, 53.46, 54.92, 58.53, 65.65, 77.40, 126.15, 128.39, 129.16, 139.61.

3.2. Synthesis of N-(2-cycloheptylethyl)cinnamamide (3)

To a solution of *tert*-butyl (*S*)-butyl(1-((2-cycloheptylethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**1**) (338 mg, 0.760 mmol) in anhydrous THF (3 mL) under argon at –5 °C, LDA (1.0 mL, 2 M in THF, 2.0 mmol) was added over 10 minutes. The reaction mixture was stirred under argon at –5 °C for 3 hours. The mixture was quenched by addition of saturated aqueous NaCl (5 mL). The resulting mixture was extracted with EtOAc (3×15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the volatile components were evaporated *in vacuo*. The residue was purified by column chromatography (Silica gel 60, EtOAc/petroleum ether 1:2). Fractions containing pure product **3** were combined, and the volatile components were evaporated *in vacuo*. Yield: 63 mg (0.232 mmol, 30%) of white solid; m.p. = 86–89 °C. EI-HRMS: *m*/*z* = 272.2009 (MH^+); $C_{18}H_{26}NO$ requires: *m*/*z* = 272.2009 (MH^+); ν_{max} 3253, 3083, 2918, 2851, 1666, 1651, 1607, 1552, 1495, 1450, 1344, 1284, 1223, 1174, 1070, 981, 871, 842, 762, 679 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 1.12 – 1.27 (*m*, 2H), 1.36 – 1.66 (*m*, 11H), 1.67 – 1.75 (*m*, 2H), 3.39 (*dt*, *J*=5.7, 7.5 Hz, 2H), 5.86 (*t*, *J*=5.8 Hz, 1H), 6.42 (*d*, *J*=15.6 Hz, 1H), 7.29 – 7.38 (*m*, 3H), 7.44 – 7.51 (*m*, 2H), 7.62 (*d*, *J*=15.6 Hz, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (ppm) 26.42, 28.58, 34.54, 37.02, 37.84, 38.21, 121.00, 127.86, 128.89, 129.67, 135.02, 140.83, 166.02.

4. Conclusions

Reduction of *tert*-butyl (*S*)-butyl(1-((2-cycloheptylethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**1**) with excess $LiAlH_4$ yielded imidazolidine **2**. Treatment of **1** with LDA gave the β-

 doi:10.20944/preprints202603.1953.v1

elimination product, cinnamamide **3**, rather than the hydantoin cyclization product. The formation of imidazolidine **2** and its previously reported tryptophan analogue [21] suggests that reductive cyclization of *N*-alkylated-*N*-Boc-protected amino acid amides with $LiAlH_4$ may be a viable synthetic method for trisubstituted chiral imidazolidines. Further studies of the reaction scope and mechanism of the reported transformation are necessary.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org: copies of ^{1}H- and ^{13}C-NMR spectra; copies of DEPT 135 and HSQC spectra, copies of IR and HRMS spectra.

Author Contributions: Conceptualization, L.C., U.G., J.S., and B.Š.; methodology, L.C. and U.G.; software, L.C., M.S., U.G., J.S., and B.Š.; validation, L.C., N.P., M.S., U.G., J.S., F.P., and B.Š.; formal analysis, U.G., M.S., and L.C.; investigation, M.S., L.C, and U.G.; resources, L.C., U.G., and J.S.; data curation, L.C., N.P., M.S., U.G., J.S., and B.Š.; writing—original draft preparation, L.C., U.G., J.S., and B.Š.; writing—review and editing, L.C., N.P., U.G., J.S., F.P., and B.Š.; visualization, L.C., M.S., U.G., B.Š., and J.S.; supervision, U.G.; project administration, U.G. and J.S.; funding acquisition, U.G. and J.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Slovenian Research and Innovation Agency (ARIS), research core funding No. P1-0179, and infrastructure program No. I0-0022.

Data Availability Statement: The original contributions presented in this study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Acknowledgments: We thank the EN-FIST Centre of Excellence, Dunajska 156, 1000 Ljubljana, Slovenia, for the use of their BX FTIR spectrophotometer.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Jiao, R. H.; Xu, S.; Liu, J. Y.; Ge, H. M.; Ding, H.; Xu, C.; Zhu, H. L.; Tan, R. X., Chaetominine, a Cytotoxic Alkaloid Produced by Endophytic Chaetomium sp. IFB-E015. *Org. Lett.* **2006**, *8*, 5709–5712. https://doi.org/10.1021/ol062257t
2. Malgesini, B.; Forte, B.; Borghi, D.; Quartieri, F.; Gennari, C.; Papeo, G., A Straightforward Total Synthesis of (−)-Chaetominine. *Chem. Eur. J.* **2009**, *15*, 7922–7929. https://doi.org/10.1002/chem.200900793
3. Nakao, Y.; Kuo, J.; Yoshida, W. Y.; Kelly, M.; Scheuer, P. J., More Kapakahines from the Marine Sponge Cribrochalina olemda. *Org. Lett.* **2003**, *5*, 1387–1390. https://doi.org/10.1021/ol026830u
4. Mao, Z.-Y.; Geng, H.; Zhang, T.-T.; Ruan, Y.-P.; Ye, J.-L.; Huang, P.-Q., Stereodivergent and enantioselective total syntheses of isochaetominines A–C and four pairs of isochaetominine C enantiomers: a six-step approach. *Org. Chem. Front.* **2016**, *3*, 24–37. https://doi.org/10.1039/C5QO00298B
5. Yu, G.; Zhou, G.; Zhu, M.; Wang, W.; Zhu, T.; Gu, Q.; Li, D., Neosartoryadins A and B, Fumiquinazoline Alkaloids from a Mangrove-Derived Fungus *Neosartorya udagawae* HDN13-313. *Org. Lett.* **2016**, *18*, 244–247. https://doi.org/10.1021/acs.orglett.5b02964
6. Charton, J.; Gassiot, A. C.; Girault-Mizzi, S.; Debreu-Fontaine, M.-A.; Melnyk, P.; Sergheraert, C., Synthesis and pharmacological evaluation of Tic-hydantoin derivatives as selective σ1 ligands. Part 1. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4833–4837. https://doi.org/10.1016/j.bmcl.2005.07.040
7. Caterina, M. C.; Perillo, I. A.; Boiani, L.; Pezaroglo, H.; Cerecetto, H.; González, M.; Salerno, A., Imidazolidines as new anti-Trypanosoma cruzi agents: Biological evaluation and structure–activity relationships. *Bioorg. Med. Chem.* **2008**, *16*, 2226–2234. https://doi.org/10.1016/j.bmc.2007.11.077
8. Sharma, V.; Khan, M. S. Y., Synthesis of novel tetrahydroimidazole derivatives and studies for their biological properties. *Eur. J. Med. Chem.* **2001**, *36*, 651–658. https://doi.org/10.1016/S0223-5234(01)01256-9
9. Shalo, R. R.; Karthiga, A. R.; Divyabharathi, S.; Rajeswari, K.; Vidhyasagar, T., Novel highly unsymmetrical Imidazolidines as potential anticancer agents: Design, synthesis, crystal structure, in silico & in vitro evaluation. *J. Mol. Struct.* **2026**, *1353*, 144804. https://doi.org/10.1016/j.molstruc.2025.144804

 doi:10.20944/preprints202603.1953.v1

10. Olyaei, A.; Sadeghpour, M., Recent advances in the synthesis of highly substituted imidazolidines. *RSC Adv.* **2024,** *14*, 30758–30806. https://doi.org/10.1039/D4RA06010E
11. Marcantonio, E.; Bitsch, R. S.; Jørgensen, K. A., The Diarylprolinol Silyl Ethers: After 20 Years Still Opening New Doors in Asymmetric Catalysis. *Angew. Chem. Int. Ed.* **2026**, *65*, e26146. https://doi.org/10.1002/anie.202526146
12. Raimondi, L.; Faverio, C.; Boselli, M. F., Chiral imidazolidinones: A class of priviliged organocatalysts in stereoselective organic synthesis. *Physical Sciences Reviews*, vol. 5, no. 5, **2020**, pp. 20180087. https://doi.org/10.1515/psr-2018-0087
13. Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C., New Strategies for Organic Catalysis: The First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition. *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875. https://doi.org/10.1021/ja005517p
14. Erkkilä, A.; Majander, I.; Pihko, P. M., Iminium Catalysis. *Chem. Rev.* **2007**, *107*, 5416–5470. https://doi.org/10.1021/cr068388p
15. Grošelj, U.; Schweizer, W. B.; Ebert, M.-O.; Seebach, D., 5-Benzyl-3-methylimidazolidin-4-one-Derived Reactive Intermediates of Organocatalysis – A Comforting Resemblance of X-Ray, NMR, and DFT Solid-Phase, Liquid-Phase, and Gas-Phase Structures. *Helv. Chim. Acta* **2009**, *92*, 1–13. https://doi.org/10.1002/hlca.200800432
16. Hayashi, Y., ASYMMETRIC ENAMINE AND IMINIUM ION CATALYSIS. In *Catalytic Asymmetric Synthesis*, eds Akiyama, T. and Ojima, I., 2022 John Wiley & Sons, Inc., pp 1–28. https://doi.org/10.1002/9781119736424.ch1
17. Ferm, R. J.; Riebsomer, J. L., The Chemistry of the 2-Imidazolines and Imidazolidines. *Chem. Rev.* **1954**, *54*, 593–613. https://doi.org/10.1021/cr60170a002
18. Verardo, G.; Geatti, P.; Pol, E.; Giumanini, A. G., Sodium borohydride: A versatile reagent in the reductive N-monoalkylation of α-amino acids and α-amino methyl esters. *Can. J. Chem.* **2002**, *80*, 779–788. https://doi.org/10.1139/v02-083
19. Meden, A.; Knez, D.; Malikowska-Racia, N.; Brazzolotto, X.; Nachon, F.; Svete, J.; Sałat, K.; Grošelj, U.; Gobec, S., Structure-activity relationship study of tryptophan-based butyrylcholinesterase inhibitors. *Eur. J. Med. Chem.* **2020**, *208*, 112766.
20. Aryal, S.; Hone, C. A.; Polson, M. I. J.; Foley, D. J., Enantioselective synthesis of hydantoins by chiral acid-catalysed condensation of glyoxals and ureas. *Chem. Sci.* **2023**, *14*, 7905–7912. https://doi.org/10.1039/D3SC01656K
21. Meden, A.; Knez, D.; Brazzolotto, X.; Nachon, F.; Dias, J.; Svete, J.; Stojan, J.; Grošelj, U.; Gobec, S., From tryptophan-based amides to tertiary amines: Optimization of a butyrylcholinesterase inhibitor series. *Eur. J. Med. Chem.* **2022**, *234*, 114248. https://doi.org/10.1016/j.ejmech.2022.114248
22. Cortes, S.; Kohn, H., Selective reductions of 3-substituted hydantoins to 4-hydroxy-2-imidazolidinones and vicinal diamines. *J. Org. Chem.* **1983**, *48*, 2246–2254. https://doi.org/10.1021/jo00161a021