molbank

MDPI

Short Note

(*R*)-*N*-Benzyl-*N*-(1-phenylethyl)cyclohexanamine

Ángel García-González, Leland Belda, Alejandro Manchado, Carlos T. Nieto and Narciso Martín Garrido *

Department of Organic Chemistry, Faculty of Chemical Sciences, University of Salamanca, Pl. Caídos, s/n, 37008 Salamanca, Spain

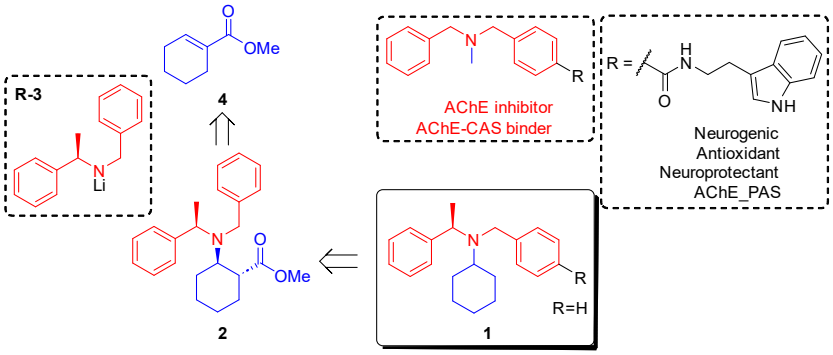
* Correspondence: nmg@usal.es

Abstract: The preparation and characterization of a new chiral tertiary dibenzylamine are described. These molecules are well known in the literature for their high neuropharmacological potential. The general synthetic pathway is based on asymmetric Aza–Michael addition of chiral (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to methyl cyclohex-1-en-carboxilate obtaining the β-amino ester, followed by carboxylic acid hydrolysis and subsequent Barton descarboxylation. Interestingly, it is a general synthetic procedure of a wide range of chiral amines by careful choice of insaturated esters and alkylation of the chiral enolate in the initial reaction. The new tertiary dibenzylamine molecule is fully characterized by NMR Spectroscopy (^{1}H and ^{13}C), as well by High-Resolution Mass Spectrometry and Infrared Spectroscopy.

Keywords: tertiary dibenzylamine; chiral lithium amide; neurodegenerative disorders; radical decarboxylation

1. Introduction

The favorable physiological properties of dibenzylamines and their capability to interfere with natural neurotransmission pathways make these structures attractive for the treatment of neurodegenerative disorders, such as Alzheimer's disease [1]. Several in silico studies and in vitro assays [2–4] have shown how these motifs are embedded in more complex molecular constructs with key drug-like properties (even hybrid molecules), such as neuronal regeneration and blocking neurodegeneration [5,6]. This represents a very powerful strategy to obtain drugs targeting complex pathologies [7]. *N*-methyl-dibenzylamine derivative (Scheme 1) is an important tertiary inhibitor of human AChE/BuChE (Acetylcholineristerase and Butylcholinestarase) and, in addition, acts as a pure competitive inhibitor, since it binds to the central active site (CAS) of the enzyme [8].



Scheme 1. Retrosynthetic scheme of **1** and dibenzylamine tertiary bioamine structure.

This paper describes the preparation and characterization of chiral tertiary dibenzylamine (*R*)-*N*-benzyl-*N*-(1-phenylethyl)cyclohexanamine (**1**), which features a cyclohexyl group replacing the methyl group in the AChE-CAS core group as a potential new ligand

check for updates

Citation: García-González, Á.; Belda, L.; Manchado, A.; Nieto, C.T.; Garrido, N.M. (*R*)-*N*-Benzyl-*N*-(1-phenylethyl)cyclohexanamine. *Molbank* **2023**, *2023*, M1561. https://doi.org/10.3390/M1561

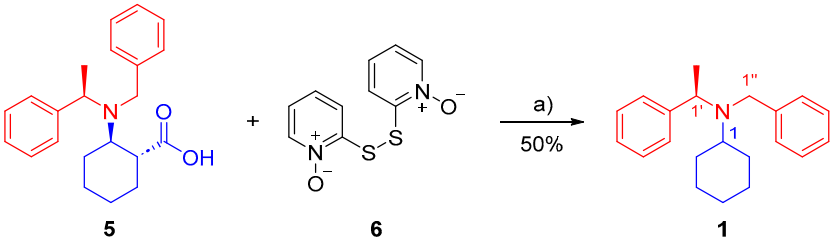
Academic Editor: Hideto Miyabe

Received: 21 December 2022
Revised: 16 January 2023
Accepted: 18 January 2023
Published: 20 January 2023

of AChE/BuChE. This paper also presents the characterization of this new potential ligand **1** by different analytical techniques, such as proton and carbon NMR, mass spectrometry and infrared spectroscopy.

2. Results and Discussion

The synthesis of (*R*)-*N*-benzyl-*N*-(1-phenylethyl)cyclohexanamine **1** was based on the general Barton decarboxylation reaction methodology [9,10]. In this way, **1** was synthesized from the reaction between β-amino acid **5** and 2,2′-dithiobis pyridine-*N*-oxide (**6**) dissolved in THF at 40 °C for 4 h. This reaction furnished the Barton thiohydroxamic ester [11,12], which under UV irradiation caused a "N-O" homolytic rupture bond and, after a thermodynamically favored decarboxylation, gave rise to the radical that reacted in the presence of *t*BuSH to form the decarboxylated product. The reaction mixture was worked up, and, after flash column chromatography purification, the desired product **1** was obtained in 50% yield (Scheme 2). The synthesis of β-amino acid **5** was based on the general Davies methodology of chiral amide Aza–Michael asymmetric addition [13–15] of methyl 1-cyclohexene-1-carboxylate (**4**) and lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide ***R*-3** at −78 °C for 2 h. Subsequent alkaline hydrolysis with KOH/MeOH in reflux for 24 h provided β-amino acid **5** [16,17].



Scheme 2. Reaction scheme of **1**; (a) 1: 2,2′-dithiobis pyridine-*N*-oxide (**6**), Ph_3P, THF; 2: *t*BuSH, hυ.

The molecular structure of compound **1** was confirmed by different analytical techniques (Supplementary Materials). First, the ^{1}H NMR spectrum exhibited characteristic peaks for Michael adduct compounds, such as the quartet at δ (ppm) = 3.99 (J = 6.8 Hz) for benzylic proton (H-1′); the doublets for SAB benzylic protons (H-1″a and H-1″b) at δ (ppm) = 3.81 and 3.71, respectively (J = 15.1 Hz), and the low-field doublet for α-Me at δ (ppm) = 1.33 (J = 6.8 Hz). Moreover, the signal triple triplet at δ (ppm) = 2.55 (J = 11.5, 3.3 Hz) corresponded to the H-1 hydrogen. The ^{13}C NMR spectrum accounted for peaks of the overall 21 C atoms of the molecule as expected, highlighting associated signals of the three C atoms bonded to N at δ (ppm) = 57.38, 57.28 (CH-N) and 50.21 (CH_2-N). The results of the ^{1}H-^{13}C heteronuclear correlation experiments (standard and long-range HSQC and HMBC; Supplementary Materials) allowed us to corroborate their structure and the full assignment of the ^{1}H and ^{13}C data. The infrared spectrum featured C-N stretching vibrations for alkyl-amine C-N at 1261 and 1026 cm^{-1}, and C-N stretch bands for benzylamines at 1371 cm^{-1}. Molecular composition was further confirmed by MS (ESI), indicating a measured m/z of 294.2214, which was coherent with the calculated mass for the molecular ion $[C_{21}H_{27}N + H]^+$ (m/z = 294.2216).

3. Materials and Methods

All reagents were purchased from commercial suppliers and used as received without further purification, except for solvents used for flash chromatography. The (1*R*,2*R*)-2-(benzyl((*R*)-1-phenylethyl)amino)cyclohexane-1-carboxylic acid (**5**) was prepared by a method adapted from the literature (Supplementary Material). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance Neo at 400 MHz using $CDCl_3$ as a solvent. Infrared spectrum was recorded on a Shimazdu IR Affinity-1 spectrophotometer, using capillary film on KCl crystals. Specific rotation measurements were carried out on a Perkin–Elmer 241 digital polarimeter in 1 dm optical step cuvettes and in chloroform solution. Mass spectra were recorded at a quadruple-time-of-flight (QTOF) spectrometer from Applied

Biosystems QSTAR XL, under conditions of ionization by electrospray (ESI), APCI and photospray. Column chromatographies (CC) were performed on glass columns, packed with Merck-60 silica gel (particle size 0.063–0.200 mm) and the initial eluent. Eluents were prepared with solvent mixtures of increasing polarity (usually Hexane/AcOEt mixtures), which changed as the chromatography progressed and were followed by TLC on 0.2 mm thick Merck silica gel plates (60 F254). Fluorescent substances were directly visualized by illumination with ultraviolet light of λ = 254 nm.

(*R*)-*N*-Benzyl-*N*-(1-phenylethyl)cyclohexanamine (**1**)*:* 0.07 g of **5** (0.21 mmol), 0.06 g of 2,2′-dithiobis(pyridine-*N*-oxide) (**6**) (0.23 mmol), 0.06 g of PPh_3 (0.23 mmol) and 5.00 mL of THF in stirring at 40 °C, reflux under Ar atmosphere for 2 h. Then, 0.10 mL of *t*BuSH (0.63 mmol) was added, and the mixture was irradiated with a 220 V lamp for 1 h. The crude reaction mixture was chromatographed on a silica gel column and by increasing the eluent (Hex/AcOEt 99/1 to 95/5) to isolate **1** as a pale yellow solid (0.018 g, 50%). Rf = 0.67, Hex/AcOEt 8/2; ^{1}H NMR ($CDCl_3$, 400 MHz,) δ (ppm): 7.47–7.11 (m, 10H, H-Ar), 3.99 (q, *J* = 6.8 Hz, 1H, H-1′), 3.81 (d, *J* = 15.1 Hz, 1H, H-1″a), 3.71 (d, *J* = 15.1 Hz, 1H, H-1″b), 2.55 (tt, *J* = 11.5, 3.3 Hz, 1H, H-1), 1.91–1.47 (m, 4H, H-2. H-6), 1.33 (d, *J* = 6.8 Hz, 3H, α-CH_3), 1.14–1.02 (m, 4H, H-5, H-3), 1.06–0.95 (m, 2H, H-4). ^{13}C NMR ($CDCl_3$, 100 MHz,) δ (ppm): 145.71, 143.13, 128.04–126.16, 57.38, 57.27, 50.21, 31.59, 30.45, 26.37, 18.56; MS (ESI): calc. for $[C_{21}H_{27}N + H]^+$ 294.2216, found 294.2214; IR (KBr): νmax (cm^{-1}): 1026.13, 1261.45, 1371.39 cm^{-1}; $[\alpha]_D^{20}$ = + 19.8 (c = 0.21 g/100 mL, $CHCl_3$).

4. Conclusions

A useful method for the enantioselective synthesis of (*R*)-*N*-benzyl-*N*-(1-phenylethyl) cyclohexanamine (**1**) is described. By applying the Barton descarboxylation described protocol to (1*R*,2*R*)-2-(benzyl((*R*)-1-phenylethyl)amino)cyclohexane-1-carboxylic acid **5,** the chiral tertiary dibenzylamine **1** was obtained in 50% yield. It is important to note that this β-amino acid **5** was obtained in 90% overall yield from affordable methylcyclohexene carboxylate **4**. The methodology is applicable to the synthesis of a wide range of tertiary dibenzyl amines. Current extension to other substrates is in progress and the results will be published in due course.

Tertiary dibenzyl amines have proven appealing neuropharmacological properties. With the present description, we propose a novel, accessible transformation to elaborate a great variety of similar analogues by careful choice of starting materials and alkylation of the initial enolate.

Supplementary Materials: The following supporting information can be downloaded online. Synthetic protocol for the preparation of β-amino acid **5**; ^{1}H, ^{13}C, Bidimensional NMR spectra (HMBC, HSQC and COSY), IR spectra and MS-ESI report of tertiary dibenzylamine **1**.

Author Contributions: Conceptualization, N.M.G. and C.T.N.; investigation, Á.G.-G., L.B. and A.M.; writing—original draft preparation, Á.G.-G.; writing—review and editing, Á.G.-G., L.B., N.M.G. and C.T.N.; supervision, N.M.G., C.T.N. and A.M. All authors have read and agreed to the published version of the manuscript.

Funding: We are indebted to the European Regional Development Fund (FEDER), Spanish Ministerio de Ciencia e Innovación (PID2020-118303GB-I00/MCIN/AEI/10.13039/501100011033) and Junta de Castilla y León (SA076P20).

Data Availability Statement: The data from this study are available in this paper and in its Supplementary Materials.

Acknowledgments: The authors also acknowledge support from Servicios de la Universidad de Salamanca (Nucleus): A.M. Lithgow for the NMR and César Raposo for the mass spectra.

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

Sample Availability: Samples of the compounds are available from the authors.

References

1. de Freitas Silva, M.; Dias, K.S.T.; Gontijo, V.S.; Ortiz, C.J.C.; Viegas, C., Jr. Multi-Target Directed Drugs as a Modern Approach for Drug Design Towards Alzheimer's Disease: An Update. *Curr. Med. Chem.* **2018**, *25*, 3491–3525. [CrossRef] [PubMed]
2. Buendia, I.; Egea, J.; Parada, E.; Navarro, E.; León, R.; Rodríguez-Franco, M.I.; López, M.G. The Melatonin- N,N-Dibenzyl(N-Methyl)Amine Hybrid ITH91/IQM157 Affords Neuroprotection in an in Vitro Alzheimer's Model via Hemo-Oxygenase-1 Induction. *ACS Chem. Neurosci.* **2015**, *6*, 288–296. [CrossRef] [PubMed]
3. Estrada, M.; Herrera-Arozamena, C.; Pérez, C.; Viña, D.; Romero, A.; Morales-García, J.A.; Pérez-Castillo, A.; Rodríguez-Franco, M.I. New Cinnamic—N-Benzylpiperidine and Cinnamic—N,N-Dibenzyl(N-Methyl)Amine Hybrids as Alzheimer-Directed Multitarget Drugs with Antioxidant, Cholinergic, Neuroprotective and Neurogenic Properties. *Eur. J. Med. Chem.* **2016**, *121*, 376–386. [CrossRef] [PubMed]
4. López-Iglesias, B.; Pérez, C.; Morales-García, J.A.; Alonso-Gil, S.; Pérez-Castillo, A.; Romero, A.; López, M.G.; Villarroya, M.; Conde, S.; Rodríguez-Franco, M.I. New Melatonin- N, N -Dibenzyl(N -Methyl)Amine Hybrids: Potent Neurogenic Agents with Antioxidant, Cholinergic, and Neuroprotective Properties as Innovative Drugs for Alzheimers Disease. *J. Med. Chem.* **2014**, *57*, 3773–3785. [CrossRef] [PubMed]
5. Silva Gontijo, V.; Dias Viegas, F.P.; Juliet Cristancho Ortiz, C.; de Freitas Silva, M.; Miranda Damasio, C.; Chagas Rosa, M.; Gaspar Campos, T.; Souza Couto, D.; Simone Tranches Dias, K.; Viegas, C., Jr. Molecular Hybridization as a Tool in the Design of Multi-Target Directed Drug Candidates for Neurodegenerative Diseases. *Curr. Neuropharmacol.* **2020**, *18*, 348–407. [CrossRef] [PubMed]
6. Mesiti, F.; Chavarria, D.; Gaspar, A.; Alcaro, S.; Borges, F. The Chemistry Toolbox of Multitarget-Directed Ligands for Alzheimer's Disease. *Eur. J. Med. Chem.* **2019**, *181*, 111572. [CrossRef] [PubMed]
7. Sang, Z.; Wang, K.; Dong, J.; Tang, L. Alzheimer's Disease: Updated Multi-Targets Therapeutics Are in Clinical and in Progress. *Eur. J. Med. Chem.* **2022**, *238*, 114464. [CrossRef]
8. Estrada-Valencia, M.; Herrera-Arozamena, C.; Pérez, C.; Viña, D.; Morales-García, J.A.; Pérez-Castillo, A.; Ramos, E.; Romero, A.; Laurini, E.; Pricl, S.; et al. New Flavonoid–N,N-Dibenzyl(N-Methyl)Amine Hybrids: Multi-Target-Directed Agents for Alzheimer´s Disease Endowed with Neurogenic Properties. *J. Enzyme. Inhib. Med. Chem.* **2019**, *34*, 712–727. [CrossRef] [PubMed]
9. Manchado, A.; García, M.; Salgado, M.M.; Díez, D.; Garrido, N.M. A Novel Barton Decarboxylation Produces a 1,4-Phenyl Radical Rearrangement Domino Reaction. *Tetrahedron* **2018**, *74*, 5240–5247. [CrossRef]
10. Barton, D.H.R. The Use of Photochemical Reactions in Organic Synthesis. *Pure Appl. Chem.* **1968**, *16*, 1–16. [CrossRef]
11. Barton, D.H.R.; Crich, D.; Motherwell, W.B. The Invention of New Radical Chain Reactions. Part VIII. Radical Chemistry of Thiohydroxamic Esters; A New Method for the Generation of Carbon Radicals from Carboxylic Acids. *Tetrahedron* **1985**, *41*, 3901–3924. [CrossRef]
12. Barton, D.H.R.; Bridon, D.; Fernandaz-Picot, I.; Zard, S.Z. The Invention of Radical Reactions: Part XV. Some Mechanistic Aspects of the Decarboxylative Rearrangement of Thiohydroxamic Esters. *Tetrahedron* **1987**, *43*, 2733–2740. [CrossRef]
13. Davies, S.G.; Smith, A.D.; Price, P.D. The Conjugate Addition of Enantiomerically Pure Lithium Amides as Homochiral Ammonia Equivalents: Scope, Limitations and Synthetic Applications. *Tetrahedron Asymmetry* **2005**, *16*, 2833–2891. [CrossRef]
14. Davies, S.G.; Fletcher, A.M.; Roberts, P.M.; Thomson, J.E. The Conjugate Addition of Enantiomerically Pure Lithium Amides as Chiral Ammonia Equivalents Part II: 2005–2011. *Tetrahedron Asymmetry* **2012**, *23*, 1111–1153. [CrossRef]
15. Davies, S.G.; Fletcher, A.M.; Roberts, P.M.; Thomson, J.E. The Conjugate Addition of Enantiomerically Pure Lithium Amides as Chiral Ammonia Equivalents Part III: 2012–2017. *Tetrahedron Asymmetry* **2017**, *28*, 1842–1868. [CrossRef]
16. Salgado, M.M.; Manchado, A.; Nieto, C.T.; Díez, D.; Garrido, N.M. Asymmetric Synthesis of 2,3,6-Trisubstituted Piperidines via Baylis–Hillman Adducts and Lithium Amide through Domino Reaction. *Synlett* **2019**, *31*, 600–604. [CrossRef]
17. Manchado, A.; Ramos, V.E.; Díez, D.; Garrido, N.M. Multicomponent Domino Reaction in the Asymmetric Synthesis of Cyclopentan[c]Pyran Core of Iridoid Natural Products. *Molecules* **2020**, *25*, 1308. [CrossRef]