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Short Note

2-((3*R*,9b*S*)-5,5-Dioxido-2,3-dihydro-9b*H*-benzo[4,5]isothiazolo[3,2-*b*]oxazol-3-yl)-1-phenylethan-1-one

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Abstract: A highly efficient method has been developed for preparing 2-((3*R*,9b*S*)-5,5-dioxido-2,3-dihydro-9b*H*-benzo[4,5]isothiazolo[3,2-*b*]oxazol-3-yl)-1-phenylethan-1-one. This enantioenriched title compound was obtained via an organocatalytic asymmetric [3+2]-cycloaddition of benzo[*d*]isothiazole 1,1-dioxide with (*E*)-4-hydroxy-1-phenylbut-2-en-1-one, using a bifunctional squaramide-based chiral catalyst. The reaction yielded 99% of the product with high enantioselectivity and diastereoselectivity (89:11 er and >20:1 dr). The structure of the newly synthesized compound was confirmed by ^{1}H-, ^{13}C-NMR, IR and mass spectral data.

Keywords: cycloaddition; asymmetric synthesis; organocatalysis; benzosultam; oxazolidine

1. Introduction

Benzosultam derivatives, *N*-heterocycles featuring sulfonamide functionality within their ring structure, are highly valued due to their wide-ranging bioactivities [1–6]. These frameworks are frequently encountered in a variety of biologically active natural products, pharmaceuticals, and agrochemicals, making them important for drug discovery (Figure 1). In addition to their bioactive potential, benzosultams are versatile tools in organic chemistry, functioning as chiral auxiliaries in asymmetric synthesis, protecting groups, and directed metalation groups [7]. As a result, benzosultams are not only promising targets for new drug development but also serve as crucial intermediates in synthetic methodologies. In addition, oxazolidine *N*,*O*-heterocycles are notable as crucial building blocks in natural products, displaying a wide range of important biological activities [8–12]. Building on our research interest in the stereoselective synthesis of *N*,*O*-heterocycles using γ-hydroxy-α,β-unsaturated carbonyl compounds [13,14], we considered that cyclic *N*-sulfonyl ketimine and γ-hydroxy-α,β-unsaturated phenyl ketone would be suitable substrates for a cycloaddition reaction, potentially leading to the synthesis of enantioenriched benzosultam-fused oxazolidine derivatives.

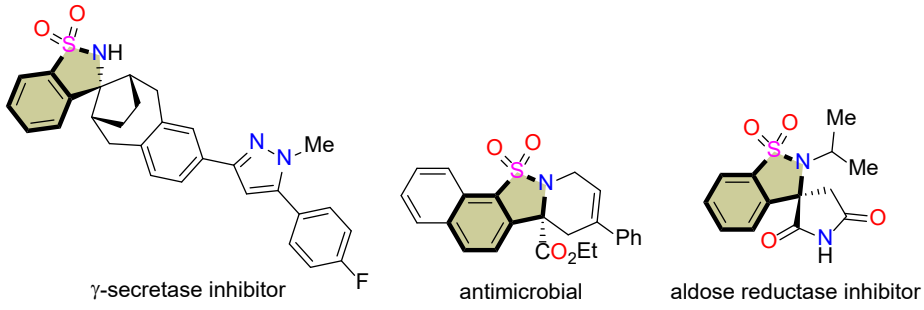

Figure 1. Representative examples of bioactive benzosultam scaffolds.

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Citation: Kim, Y.; Kim, S.-G. 2-((3*R*,9b*S*)-5,5-Dioxido-2,3-dihydro-9b*H*-benzo[4,5]isothiazolo[3,2-*b*]oxazol-3-yl)-1-phenylethan-1-one. *Molbank* **2024**, *2024*, M1931. https://doi.org/10.3390/M1931

Academic Editor: Alberto Marra

Received: 19 November 2024
Revised: 3 December 2024
Accepted: 3 December 2024
Published: 5 December 2024

2. Results and Discussion

In our previous study [15], bifunctional cinchona-squaramide has proven to be an efficient catalyst for asymmetric [3+2]- and [4+2]-cycloaddition reactions involving cyclic *N*-sulfimines. Building on this, we anticipated that the cinchona-squaramide-catalyzed [3+2]-cycloaddition of cyclic *N*-sulfonyl ketimine with γ-hydroxy-α,β-unsaturated phenyl ketone would yield an enantioenriched benzosultam-fused oxazolidine. And we carried out an asymmetric [3+2]-cycloaddition between benzo[*d*]isothiazole 1,1-dioxide (**1**) and (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**2**) using the quinine-derived squaramide I (Figure 2) as a catalyst in $ClCH_2CH_2Cl$ at room temperature. This reaction successfully produced the desired enantioenriched benzosultam-fused oxazolidine **3** with an excellent yield (99%) and high diastereoselectivity and enantioselectivity (>20:1 dr and 89:11 er) (Scheme 1). The structure of compound **3** was confirmed by ^{1}H- and ^{13}C-NMR, IR, and mass spectral data, all of which were consistent with the proposed structure.

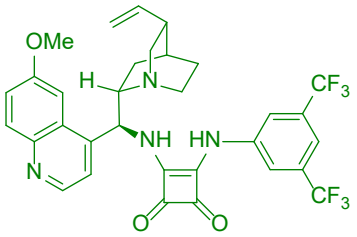
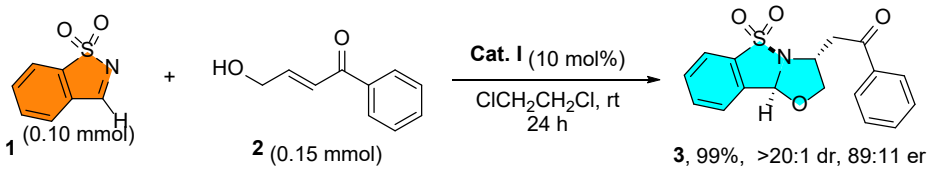


Figure 2. Cinchona-squaramide catalyst **I**.



Scheme 1. Synthesis of 2-((3*R*,9b*S*)-5,5-dioxido-2,3-dihydro-9b*H*-benzo[4,5]isothiazolo[3,2-*b*]oxazol-3-yl)-1-phenylethan-1-one (**3**).

The structure of compound **3** was confirmed by ^{1}H- and ^{13}C-NMR, IR, and mass spectral data, all of which were consistent with the proposed structure. The diastereoselective ratio value was determined by ^{1}H NMR analysis and the enantioselective ratio value was determined by chiral HPLC of the major diastereomer. All data are available in the Supplementary Materials File (Figures S1–S4 and Table S1).

3. Materials and Methods

3.1. General

All reagents were used as received without further purification. Chromatographic purification of title compound **3** was accomplished using forced-flow chromatography on ICN 60 32–64 mesh silica gel 63 (Merck, Darmstadt, Germany). Thin-layer chromatography (TLC) (Merck, Darmstadt, Germany) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Developed chromatograms were visualized by fluorescence quenching and anisaldehyde stain. ^{1}H- and ^{13}C-NMR spectra were recorded on 400 MHz instrument (Bruker BioSpin GmbH, Karlsruhe, Germany) as noted, and are internally referenced to residual proton solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C-NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrometer (Bruker Optics GmbH, Ettlingen, Germany), and reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectrometry data were recorded on a JEOL JMS-700 M

Station mass spectrometer (JEOL, Tokyo, Japan). Enantiomeric excesses were determined using an HPLC instrument with Chiralpak columns, as indicated.

*3.2. Synthesis of 2-((3R,9bS)-5,5-Dioxido-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazol-3-yl)-1-phenylethan-1-one (**3**)*

A solution of benzo[*d*]isothiazole 1,1-dioxide (**1**, 0.15 mmol, 1.5 equiv) and catalyst **I** (0.01 mmol, 0.1 equiv) in $ClCH_2CH_2Cl$ (1.0 mL, 0.1 M) was stirred for 10 min at 0 °C and then added (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**2**, 0.10 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 24 h. Then, the resulting mixture was concentrated in vacuo and was purified by flash column chromatography with EtOAc/CH_2Cl_2/hexanes (1/5:4) as eluent to afford desired product **3** (99%, 45 mg). The enantiomeric excess was determined using HPLC analysis. >20:1 dr, $[\alpha]_D^{24} = -72.0$ (c = 1.32, $CHCl_3$); 78% ee; white solid; m.p. 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.95 (m, 2H), 7.85–7.77 (m, 1H), 7.74–7.65 (m, 2H), 7.65–7.58 (m, 2H), 7.49 (dd, J = 8.3, 7.0 Hz, 2H), 6.15 (s, 1H), 4.89–4.73 (m, 1H), 4.38 (dd, J = 9.0, 6.2 Hz, 1H), 3.91 (dd, J = 9.1, 5.2 Hz, 1H), 3.71 (dd, J = 18.0, 4.5 Hz, 1H), 3.39 (dd, J = 18.0, 9.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.1, 136.1, 134.3, 133.8, 133.6, 131.6, 128.7(two peaks overlapping), 128.0, 125.5, 121.6, 91.7, 73.0, 55.6, 42.9; IR (neat) 2934, 2895, 2850, 1681, 1597, 1450, 1371, 1306, 1207, 1167, 1073 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{15}NO_4S$: 329.0722 found the following: 329.0721; Chiralpak OJ-H column and OJ-H guard column (50% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); minor-isomer t_r = 37.9 min and major-isomer t_r = 46.4 min.

Supplementary Materials: Figure S1: ^{1}H NMR spectrum of compound **3**; Figure S2: ^{13}C NMR spectrum of compound **3**; Figure S3: HPLC chromatogram of compound **3**; Figure S4: IR spectra of compound **3**; Table S1: high mass data of compound **3**.

Author Contributions: Conceptualization, resources, writing—original draft preparation, writing—review and editing, visualization, supervision, project administration, and funding acquisition, S.-G.K.; methodology, validation, formal analysis, and investigation, Y.K. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by Kyonggi University's Graduate Research Assistantship 2024.

Data Availability Statement: Data are contained within the article and Supplementary Materials.

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

References

1. Wells, G.J.; Tao, M.; Josef, K.A.; Bihovsky, R. 1,2-Benzothiazine 1,1-Dioxide P2-P3 Peptide Mimetic Aldehyde Calpain IInhibitors Bihovsky. *J. Med. Chem.* **2001**, *44*, 3488–3503. [CrossRef] [PubMed]
2. Cherney, R.J.; Mo, R.; Meyer, D.T.; Hardman, K.D.; Liu, R.-Q.; Covington, M.B.; Qian, M.; Wasserman, Z.R.; Christ, D.D.; Trzaskos, J.M.; et al. Sultam Hydroxamates as Novel Matrix Metalloproteinase Inhibitors. *J. Med. Chem.* **2004**, *47*, 2981–2983. [CrossRef] [PubMed]
3. Bag, S.; Tulsan, R.; Sood, A.; Cho, H.; Redjeb, H.; Zhou, W.H.; LeVine, H., III; Török, B.; Török, M. Sulfonamides as multifunctional agents for alzheimer's disease. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 626–630. [CrossRef] [PubMed]
4. Chen, Y.; Aurell, C.J.; Pettersen, A.; Lewis, R.J.; Hayes, M.A.; Lepistö, M.; Jonson, A.C.; Leek, H.; Thunberg, L. Saccharin Aza Bioisosteres—Synthesis and Preclinical Property Comparisons. *ACS Med. Chem. Lett.* **2017**, *8*, 672–677. [CrossRef] [PubMed]
5. Akgül, O.; Lucarini, E.; Lorenzo, D.C.M.; Ghelardini, C.; D'Ambrosio, K.; Buonanno, M.; Monti, S.M.; Simone, G.D.; Angeli, A.; Supuran, C.T.; et al. Sultam based Carbonic Anhydrase VII inhibitors for the management of neuropathic pain. *Eur. J. Med. Chem.* **2022**, *227*, 113956. [CrossRef] [PubMed]
6. Yu, Y.; Yang, F.; Yu, Q.; Liu, S.; Wu, C.; Su, K.; Yang, L.; Bao, X.; Li, Z.; Li, X.; et al. Discovery of a Potent and Orally Bioavailable Hypoxia-Inducible Factor 2α (HIF-2α) Agonist and Its Synergistic Therapy with Prolyl Hydroxylase Inhibitors for the Treatment of Renal Anemia. *J. Med. Chem.* **2021**, *64*, 17384–17402. [CrossRef] [PubMed]
7. Zhao, Q.-Q.; Hu, X.Q. Recent Advances in Catalytic Synthesis of Benzosultams. *Molecules* **2020**, *25*, 4367. [CrossRef] [PubMed]
8. Kamal, A.; Swapna, P.; Shetti, R.V.C.R.N.C.; Shaik, A.B.; Rao, M.P.N.; Gupta, S. Synthesis, biological evaluation of new oxazolidino-sulfonamides as potential antimicrobial agents. *Eur. J. Med. Chem.* **2013**, *62*, 661–669. [CrossRef] [PubMed]
9. Foti, C.; Piperno, A.; Scala, A.; Giuffrè, O. Oxazolidinone Antibiotics: Chemical, Biological and Analytical Aspects. *Molecules* **2021**, *26*, 4280. [CrossRef] [PubMed]

10. Jin, B.; Chen, J.-y.; Sheng, Z.-l.; Sun, M.-q.; Yang, H.-l. Synthesis, Antibacterial and Anthelmintic Activity of Novel 3-(3-Pyridyl)-oxazolidinone-5-methyl Ester Derivatives. *Molecules* **2022**, *27*, 1103. [CrossRef] [PubMed]
11. Liu, Y.; Esser, L.; Bai, H.; Fu, B.; Xia, D.; Zhou, Y.; Hong, S.; Yang, S.; Xiao, Y.; Qin, Z.J. Synthesis and antiphytopathogenic activity of novel oxazolidine-2, 4-diones bearing phenoxypyridine moiety. *Agric. Food Chem.* **2023**, *71*, 14199–14210. [CrossRef] [PubMed]
12. Yuan, S.; Shen, D.-D.; Bai, Y.-R.; Zhang, M.; Zhou, T.; Sun, C.; Zhou, L.; Wang, S.-Q.; Liu, H.-M. Oxazolidinone: A promising scaffold for the development of antibacterial drugs. *Eur. J. Med. Chem.* **2023**, *250*, 115239. [CrossRef] [PubMed]
13. Kim, H.; Kim, S.-G. [4+2]-Annulation of δ-Hydroxy/δ-Sulfonamido-α,β-Unsaturated Ketones with Azlactones for Diastereoselective Synthesis of Highly Substituted 3-Amino-δ-Lactones and 3-Amino-δ-Lactams. *J. Org. Chem.* **2023**, *88*, 3830–3844. [CrossRef] [PubMed]
14. Kim, Y.; Kim, Y.; Kim, S.-G. [4+2]-Cycloaddition of 2-Aminophenyl Enones with Cyclic *N*-Sulfimines to Access Enantioenriched Ring-Fused Aminals. *Chem. Asian. J.* **2024**, *19*, e202301011. [CrossRef] [PubMed]
15. Yang, J.; Kim, S.-G. Catalytic enantioselective [3+2] and [4+2]-annulation of cyclic *N*-sulfonyl ketimines with γ- or δ-hydroxy-α,β-unsaturated ketones. *Chem. Commun.* **2024**, *60*, 7954–7957. [CrossRef] [PubMed]