Synthetic Approach toward Enantiopure Cyclic Sulfinamides
Glebs Jersovs, Matiss Bojars, Pavel A. Donets, and Edgars Suna

ABSTRACT: A synthetic approach toward densely substituted enantiopure cyclic sulfinamides possessing up to four consecutive stereogenic centers was developed based on a completely diastereoselective $S_N2'$ cyclization/tert-Bu cleavage sequence. Diastereospecific transformation of the obtained scaffold into chiral $S_{V1}$ derivatives such as sulfoximines and sulfonimidamides is demonstrated.

General utility of sulfinamides may be largely obscured by the amount and versatility of synthetic applications developed around Ellman’s and Davis’ chiral auxiliaries (Figure 1). Yet the sulfinamide moiety has also found use in asymmetric synthesis as an integral part of organocatalysts and ligands in metalallocatalysis. Although underappreciated as structural fragments in drug discovery, sulfinamides have been established as a convenient synthetic platform for more medicinally acknowledged sulfonamides and chiral $S_{V1}$-compounds. In particular, recently developed stereoselective methodologies toward increasingly more popular sulfoximes and sulfonimidamides rely on enantiopure sulfinamides as synthetic precursors. The fact that the general value of enantiopure sulfinamides has been long recognized is eloquently demonstrated by the sheer effort dedicated to their preparation over the years.

However, despite a considerably wide scope existing entries are generally inapplicable to cyclic structures. Hence the library of known enantiopure cyclic sulfinamides so far is limited to six- and five-membered congeners. Whereas the former have been approached via hetero Diels–Alder reaction of N-sulfinyl dienophiles, the latter have been obtained exclusively from Ellman’s sulfinamide derivatives (Scheme 1a) exploiting the lability of the tert-Bu-substituent. Thus, the susceptibility of the tert-Bu-group to radical scission was used in the synthesis of benzofused scaffolds. Radical $S_{V1}$ substitution at the S-atom directly delivers sulfinamides with configurational inversion at the S-
stereocenter (eq 1, Scheme 1a). The rest of the known methods are based on stereoretentive acid-induced cleavage of S-tert-butylation sulfoximines. The sulfoximines in turn have been synthesized via [3 + 2] cycloaddition of N-sulfinyl imines with benzenes (eq 2), AgNO$_3$-catalyzed cyclization (eq 3), and base-mediated cyclization of acetylenes (eq 4, Scheme 1a).

The common feature of the listed approaches consists of the limited capacity to introduce new stereocenters due to unsaturation dictated by the structure of the substrate. On the other hand, denser stereodefined substitution would be not only highly desirable by modern diversity-oriented synthesis but also rather realistic considering the richness of chemistry around Ellman’s auxiliary. Therefore, we envisioned a transformation starting with a novel S-exo-trig cyclization of sulfinamides 1 to sulfoximes 2 (Scheme 1b). The intended S-allylation via S$_2$N’ substitution would simultaneously install a new stereocenter and a synthetically useful vinyl handle. Subsequently, already well preceded t-Bu-removal would deliver sulfinamides 3 potentially accommodating up to four consecutive stereocenters. Previous success in S-alkylation of N-alkyl t-Bu-sulfinamides added soundness to the hypothesis and encouraged us to put it to practical scrutiny.

The investigation began with the cyclization of the iodide 1a-I (Table 1). Gratifyingly, deprotonation of 1a-I with non-nucleophilic NaH indeed led to the requisite sulfoxime 2a in moderate yield accompanied by the isomeric 4a (entry 1). More importantly 2a was formed as a single diastereomer, and its structure could be unambiguously determined by X-ray crystallographic analysis. Configuration of the S-atom in 2a was apparently retained with respect to the precursor 1a-I, while the newly installed vinyl opposed the t-Bu-group. On the other hand, independent conversion of 2a to 4a upon exposure to NaH ascertained that deprotonation at the allylic position should be responsible for the observed isomerization. While attempting chromatographic purification of 2a, we also determined that the intended t-Bu-cleavage leading to sulfinamide 3a is quite facile and can be accomplished with as weak an acid as silica gel. Therefore, the outcome of subsequent cyclization experiments was assessed by $^1$H NMR and sulfinamide 3a was isolated only in selected entries.

In order to explore the counterion effect we switched to hexamethyldisilamid bases conveniently available as THF solutions (Table 1, entries 2–4). Reaction with LiHMDS reflected the usual propensity of sulfinamides for N-alkylation manifested in formation of azetidine 5a. While KHMSD produced a dramatically increased amount of isomerization, NaHMDS performed similarly to NaH. The degree of NaHMDS aggregation has been reported to depend significantly on the solvent. Therefore, we speculated that excessive basicity leading to poorly separable 4a could be mitigated by weaker coordinating media (entries 5–7). Although Et$_2$O failed to improve the situation, DCM and toluene performed equally well affording 2a with markedly improved yields without formation of 4a. Additional improvement was obtained by complete exclusion of THF from the reaction media utilizing NaHMDS in toluene (entry 8). Thus, the yield of the intermediate 2a was increased to 85% and subsequent t-Bu-cleavage delivered sulfinamide 3a with 80% yield. Finally, bromide 1a-Br was found to be an equally competent substrate in the cyclization (entry 9), while chloride 1a-Cl displayed slightly inferior behavior (entry 10). Interestingly, the selectivity of cyclization with 1a-Cl could be largely reversed in favor of N-alkylation (entry 11).

In view of the limited stability of allylic iodides, the scope of the transformation was explored using bromide substrates 1-Br (Scheme 2). Excellent reactivity was observed in the case of monoalkyl substituted 1a-d-Br. Aryl containing precursors 1e-g-Br were also efficiently converted to the corresponding sulfinamides 3e-g. The crystal structure obtained for 3e decisively confirmed the stereoretentive character of the t-Bu-cleavage. Notably, the developed standard conditions were successfully applied in a gram-scale synthesis of 3l. However, for reasons not fully understood heteroaryl-containing sulfinamides 3h,i were obtained with considerably lower yields. Quaternary centers in 3j,k and additional substitution at the double bond in 3l were found to be a small hurdle for the transformation. Importantly, no loss of enantiopurity could be detected in the corresponding conversion of 1k-Br to 3k. Furthermore, the crystal structure obtained for 3k mirrored syn S-O and vinyl alignment already established for 3e. Successful preparation of sulfinamide 3m conformed well to our declared aim at densely substituted structures.

Finally, transformation of epimers epi-1a-Br and epi-1d-Br addressed the influence of stereocenters next to the N-atom. The respective sulfinamides iso-3a and epi-3d were obtained with the anti arrangement of the vinyl and O-N-substituent contrary to 3a and 3d. Complementary to the case of 3k, this observation concludes that the new stereocenter must be controlled solely by the initial configuration at the S-atom placing the vinyl syn to S–O in an entirely stereospecific manner. Of additional note may be the attempt to expand the cyclization scope to the 6-exo-trig mode using homologous substrate 6. Despite favorable all equatorial positioning of substituents in the speculative S-alkylation product, only the five-membered N-alkylation 7 was obtained. This result suggests that the dominant S- instead of N-
alkylation in the case of substrates 1 is most likely determined by the typical kinetic preference for five-membered cycles.

Analysis of the acquired data allowed us to devise a stereochemical model accounting for the net stereochemical outcome of the transformation (Scheme 3). The envelope geometry of the transition state proposed for the cyclization step may be derived from the crystal structures obtained for sulfoximines 2a and 2g. Nucleophilic Si attack of the S-lone pair on the double bond of 1 leads to the favored TS1 and consequently to 2 with the vinyl opposed to the t-Bu-group. Subsequent stereoretentive removal of the latter affords sulfinamides 3 with the observed syn vinyl and S−O arrangement. Conversely, Re attack would result in congested TS2 featuring pronounced steric clash between the t-Bu-group and the halomethylene unit of 1. Hence, the corresponding anti vinyl and S−O alignment has not been detected in either sulfoximines 2 or sulfinamides 3.

Since the chemistry of cyclic sulfinamides like 3 is scarcely presented in literature, we decided to screen the behavior of the obtained scaffold in relevant synthetic transformations using 3g as a typical representative (Scheme 4). Thus, chemoselective S-oxidation delivered sulfonamide 8, which belongs to the class...
of medicinally privileged γ-sultams. Another modification at the S-atom resulted in sulfinimine in the course of a Pummerer-like reaction. The reactivity of the double bond was probed in reductive ozonolysis cleanly affording . In spite of the previously noted base-induced isomerization of , N-alkylation of leading to could be accomplished with a synthetically useful yield. As an alternative option to utilize the double bond in we considered Simmons–Smith cyclopropanation. Surprisingly, the respective fairly standard conditions delivered sulfoximine as the major product rather than the expected cyclopropane. The single comparable example of such atypical reactivity was reported by Zercher et al. and regarded primarily as an undesirable synthetic obstacle. Furthermore, the transformation in greater detail. Further modifications of included diimide reduction to , which in turn was smoothly converted to the tertiary sulfinamide. Finally, electrophilic NH transfer under reported conditions resulted in stereospecific formation of sulfinimidamide with anticipated configurational retention at S-atom as confirmed by X-ray crystallographic analysis. In summary, the transformation presented herein opens access to enantiopure sulfinamide scaffold via a facile cyclization–deprotection sequence. The cyclization proceeds with retention of configuration at the S-atom and stereospecific introduction of the additional vinyl substituent, while subsequent mild deprotection completely preserves the installed stereocchemical arrangement. These features enable synthesis of densely substituted structures accommodating up to four consecutive centers. Complementary to the existing methods our methodology considerably enriches the library of yet underexplored cyclic sulfinamides. Moreover, disclosed additional modifications at S- and N-atoms as well as at the vinyl handle suggest the promising potential of the obtained scaffold in synthetic and medicinal chemistry. Specific relevance for the latter is demonstrated by preparation of γ-sultam, sulfoximine, and sulfinimidamide.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01738.

Experimental procedures, analytical and spectroscopic data for new compounds, copies of NMR spectra, and X-ray crystallographic data for 2a, 2g, 3e, 3k, and 15 (PDF)

Accession Codes

CCDC 2173342—2173346 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Edgars Suna — Latvian Institute of Organic Synthesis, Riga LV-1006, Latvia; Department of Chemistry, University of Latvia, Riga LV-1004, Latvia; orcid.org/0000-0002-3078-0576; Email: edgars@osi.lv

Authors

Glebs Jersovs — Latvian Institute of Organic Synthesis, Riga LV-1006, Latvia; Department of Chemistry, University of Latvia, Riga LV-1004, Latvia
Matiss Bojars — Latvian Institute of Organic Synthesis, Riga LV-1006, Latvia; Department of Chemistry, University of Latvia, Riga LV-1004, Latvia
Pavel A. Donets — Latvian Institute of Organic Synthesis, Riga LV-1006, Latvia

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.2c01738

Notes

The authors declare no competing financial interest. During the preparation of this manuscript, a complementary methodology toward cyclic sulfinamides via radical cyclization was reported by Chen, Y.; Wu, X.; Yang, S.; Zhu, C. Asymmetric Radical Cyclization of Alkenes by Stereospecific Homolytic Substitution of Sulfinamides. Angew. Chem., Int. Ed. 2022, Just Accepted: anie.202201027.

ACKNOWLEDGMENTS

This work was financially supported by Latvian Science Council Grant LZP-2021-1/0578. The authors thank Dr. Sergey Belyakov from the Latvian Institute of Organic Synthesis for X-ray crystallographic analysis.

REFERENCES

(1) Zhang, Q.; Xi, J.; Ze, H.; Qingle, Z. Syntheses and Transformations of Sulfinamides. Synthesis 2021, 53, 2570–2582.
(2) (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. Synthesis and Applications of Tert-Butanesulfinamide. Chem. Rev. 2010, 110, 3600–3740. (b) Davis, F. A. Adventures in Sulfur–Nitrogen Chemistry. J. Org. Chem. 2006, 71 (24), 8993–9003.
(3) For a comprehensive review, see: (a) Otocka, S.; Kwiatkowska, M.; Madalińska, L.; Kiełbasinski, P. Chiral Organosulfur Ligands/Catalysts with a Stereogenic Sulfur Atom: Applications in Asymmetric Synthesis. Chem. Rev. 2017, 117, 4147–4181. (b) Zhou, W.; Su, X.; Tao, M.; Zhu, C.; Zhao, Q.; Zhang, J. Chiral Sulfinamide Bisphosphine Organosulfur Catalysts in Asymmetric Dihalogenation Reactions. J. Org. Chem. 2010, 75 (21), 9443–9451.
Catalysts: Design, Synthesis, and Application in Highly Enantioselective Intramolecular Cross-Rauber—Currier Reactions. Angew. Chem., Int. Ed. 2015, 54, 14853–14857.

(4) (a) Borrego, L. G.; Recio, R.; Álvarez, E.; Sánchez-Coronilla, A.; Khiar, N.; Fernández, I. Steric Taming of Sulfinamide/Sulfoxides as Chiral Ligands with C2, Pseudo- Meso, and Pseudo-C2 Symmetries: Applications in Rhodium(1)-Mediated Arylation. Org. Lett. 2019, 21, 6513–6518. (b) Wan, Q.; Zhang, L.; Xiong; J.; Zeng, Q. A New Type of Chiral Cyclic Sulfinamide–Olefin Ligands for Rhodium-Catalyzed Asymmetric Addition. Eur. J. Org. Chem. 2016, 2016, S360–S364.

(5) Single example of biological activity: Finn, P.; Charlton, M.; Edmund, G.; Jirgensons, A.; Loza, E. WO201806511A1, 2018.

(6) Wojcieszyska, E.; Wojczyński, J. Modern Stereoselective Synthesis of Chiral Sulfinyl Compounds. Chem. Rev. 2020, 120, 4575–4611.

(7) For the utility of sulfoximines and sulfonimidamides in medicinal and agricultural chemistry, see: (a) Mader, P.; Kattner, L. Sulfoximines as Rising Stars in Modern Drug Discovery? Current Status and Perspective on an Emerging Functional Group in Medicinal Chemistry. J. Med. Chem. 2020, 63, 14243–14275. (b) Han, Y.; Xing, K.; Zhang, J.; Tong, T.; Shi, Y.; Cao, H.; Yu, H.; Zhang, Y.; Liu, D.; Zhao, L. Application of Sulfoximines in Medicinal Chemistry from 2013 to 2020. Eur. J. Med. Chem. 2021, 209, 112885. (c) Frings, M.; Bolm, C.; Blum, A.; Gnamm, C. Sulfoximines from a Medicinal Chemist’s Perspective: Physicochemical and in Vitro Parameters Relevant for Drug Discovery. Eur. J. Med. Chem. 2017, 126, 225–245. (d) Chinthakindi, K. P.; Naicker, T.; Thota, N.; Govender, T.; Kruger, H. G.; Arvidsson, P. I. Sulfinamides in Medicinal and Agricultural Chemistry. Angew. Chem., Int. Ed. 2017, 56, 4100–4109.

(8) (a) Aota, Y.; Kano, T.; Maruoka, K. Asymmetric Synthesis of Chiral Sulfoximines through the S-Alkylation of Sulfinamides. Angew. Chem., Int. Ed. 2019, 58, 17661–17665. (b) Greed, S.; Briggs, E. L.; Idiris, F. I. M.; White, A. J. J.; Lücking, U.; Bull, J. A. Synthesis of Highly Enantioenriched Sulfinimidoyl Fluorides and Sulfinimidamides by Stereospecific Sulfur–Fluorine Exchange (SuFEx) Reaction. Chem.—Eur. J. 2020, 26, 12533–12538. (c) Feng, J.; Liu, H.; Yao, Y.; Lu, C.-D. Synthesis of Enantiopure Benzo Fused Cyclic Sulfinimine: (b) Zhang, X.; Ang, E. C. X.; Yang, Z.; Kee, C. W.; Tan, S.-C.; Ng, B. J.; Lu, C.-D. Mannich-Type Reaction of o-Sulfanyl N-Tert-Butanesulfinylimidates: Diastereoselective Access to o-Mercapto-β-Amino Acid Derivatives. J. Org. Chem. 2021, 86, 3049–3058. (g) Hsung, R. P.; Wang, X.-N.; Fox, S. K.; Qi, R.; Lu, M.-C. Synthesis of Novo Chiral γ-Amino-Ynamides Using Lithiated Ynamides. Observation of a Unique S-Endo-Dig Cyclization with an Inversion of S-Center. Heterocycles 2014, 88, 1233–1254.

(13) Galloway, W. R. J. D.; Isidro-Lloret, A.; Spring, D. R. Diversity-Oriented Synthesis as a Tool for the Discovery of Novel Biologically Active Small Molecules. Nat. Commun. 2010, 1, 80.

(14) (a) Martjuga, M.; Belyakov, S.; Liepinsh, E.; Suna, E. Asymmetric Synthesis of 1,3-Dianimes. II: Diastereoselective Reduction of Atropisomeric N-Tert-Butanesulfinyliminates. J. Org. Chem. 2011, 76, 2635–2647. (b) Kazak, M.; Priede, M.; Shubin, K.; Bartrum, H. E.; Poisson, J.-F.; Suna, E. Stereodivergent Synthesis of Pseudoatobenzonitrile Alkylides. Org. Lett. 2017, 19, 5529–5532.

(15) Mendes, J. A.; Costa, P. R. R.; Yus, M.; Foubelo, F.; Buarque, C. D. N-Tert-Butanesulfinyl Imines in the Asymmetric Synthesis of Nitrogen-Containing Heterocycles. Beilstein J. Org. Chem. 2021, 17, 1096–1160.

(17) Thermal displacement ellipsoids are drawn at the 50% probability level and hydrogen atoms are omitted for clarity in X-ray crystal structures for 2a (Table 1), 2g (Scheme 3), and 3e (Scheme 2).

(20) García Ruano, J.; Parra, A.; Yuste, F.; Mastranzo, V. Mild and General Method for the Synthesis of Sulfinamides. Synthesis 2008, 2008, 311–319.

(21) Okwuchukwu, P. M.; Bandyopadhyay, D. Medicinally Privileged Sultams: Synthesis and Mechanism of Action. MRMC 2021, 20, 2193–2206.

(22) Isola, M.; Ciufrain, E.; Sagamora, L.; Nicolai, C. Pummerer-like Reaction of Sulfinamides. Tetrahedron Lett. 1982, 23, 1381–1384.

(23) Charette, A. B.; Beauchemin, A. Simmons–Smith Cyclopropanation Reaction. In Organic Reactions; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2001; pp 1–415.

(24) Aota, Y.; Parra, A.; Yuste, F.; Mastranzo, V. Mild and General Method for the Synthesis of Sulfinamides. Synthesis 2008, 2008, 311–319.

(25) Marsh, B. J.; Carbery, D. R. One-Pot α-Nitrobenzenesulfonylhydrazide (NBSH) Formation—Diimide Alkene Reduction Protocol. J. Org. Chem. 2009, 74 (8), 3186–3189.

(26) Izzo, F.; Schäfer, M.; Stockman, R.; Lücking, U. A New, Practical One-Pot Synthesis of Unprotected Sulfinimidamides by Transfer of Electrophilic NH to Sulfonimides. Chem.—Eur. J. 2017, 23, 15189–15193.