Diazotization of S-Sulfonyl-cysteines

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Supporting Information

ABSTRACT: We report the preparation of enantiomerically enriched β-thio-α-hydroxy and α-chloro carboxylic acid and ester building blocks by diazotization of S-sulfonyl-cysteines. The thiosulfonate protecting group demonstrated resistance to oxidation and attenuation of sulfur’s nucleophilicity by the anomic effect. The key transformation was optimized by a 2² factorial design of experiment, highlighting the unique reactivity of cysteine derivatives in comparison with aliphatic amino acids.

Diazotization of naturally occurring α-amino acids yields enantiomerically enriched α-hydroxy or α-chloro acids, useful synthesis in medicinal chemistry, total synthesis of natural products, and polymer chemistry. Although α-hydroxy and α-chloro acids are commonly prepared by the diazotization of α-amino acids, cysteine remains an elusive substrate in this transformation because of the chemically sensitive sulfur atom. Cysteine derivatives offer many opportunities for synthesis and are prominently featured in the selective modification of polypeptides and in drug delivery. Herein we report that protection of the sulfur in cysteine as a thiosulfonate enables the preparation of enantiomerically enriched β-thio-α-hydroxy and α-chloro acids by diazotization (Figure 1a).

We were inspired to investigate the preparation of β-thio-α-hydroxy acids by diazotization of cysteine after the observation of Humber et al.’s use of α-hydroxy acid 1 as an intermediate in the synthesis of nucleoside reverse transcriptase inhibitor lamivudine (2) (Figure 1b). In this report, the enantiomerically enriched intermediate was prepared from racemic chlorohydrin, requiring chiral resolution with (−)-brucine. A similar β-thio-α-hydroxy acid derivative 3 was used by Biel et al. in the synthesis of acyl protein thioesterase inhibitor 4. We concluded from these examples that enabling the diazotization of cysteine could allow preparation of similar sulfur-containing enantiomerically enriched building blocks from the chiral pool.

In 2004, Deechongkit et al. demonstrated preparation of enantiomerically enriched α-hydroxy acids by diazotization of seven of the naturally occurring amino acids, describing cysteine as a limitation in the scope due to the acidic and oxidizing reaction conditions. Stuhr-Hansen et al. and Matthes et al. have reported diazotization of S-benzyl-cysteine derivatives with 8% and 57% yields; however, the enantiomeric ratio of the products was not reported in either case, and further elaboration of the side chain was not demonstrated. Given this precedent, we first investigated diazotization of cysteine using the common benzyl thioether protecting group, but we obtained less than 10% yield of the desired α-hydroxy product and observed a complex mixture of products, including debenzylated species (1H NMR). Thioester protecting groups were also not viable because of known S-to-N acyl migration pathways. We learned in the course of these investigations that disulfides are oxidized by nitrogen oxides to thiosulfonates by an established mechanism. We therefore hypothesized that an S-sulfonyl protecting group may prevent undesired oxidation of the substrate. S-Sulfonyl-cysteines S and 6 were prepared on multigram scale by slight modification of reported procedures (Figure 2).

Our initial investigations into the diazotization of 5 with 2 equiv of nitrite, 4 equiv of sulfuric acid, and 24 h reaction time produced the targeted α-hydroxy acid 7 in 33% yield, according to 1H NMR (Figure 2). This promising result demonstrated that the thiosulfonate was more stable to the acidic and oxidizing reaction conditions than the other thiol...
protecting groups tested. In the diazotization of 6, benzenesulfonyl acid was observed by ESI-MS as a side product, presumably by hydrolysis of the thiosulfonate. Derivatization of the products and separation of the enantiomers by HPLC using a column with a chiral stationary phase demonstrated that the reaction proceeds with >96:4 er (Figures S2−S4), despite the nucleophilic β-thio substituent. These results demonstrated that the sulfonyl protecting group provides resistance to oxidation and also controls the undesired nucleophilicity of the β-substituent.

Initial reaction optimization with 5 and 6 by a one-factor-at-a-time (OFAT) approach led to yields ranging from 19 to 54%, as determined by 1H NMR (see Tables S1 and S2). Reaction time of 4 h, higher dilution of starting material to 0.08 M, and use of acetone as cosolvent (with 6) gave improved yields while minimizing formation of impurities. We hypothesized that the molar ratio of acid and nitrite employed would affect the yield based on the reported mechanism for diazonium formation, which proceeds via generation of the reactive nitrosyl cation from nitrite and two acidic protons. To investigate this possible variable interaction effect, we performed a two-level, two-factor design of experiment (2^2 DoE) investigating the stoichiometry of acid and nitrite in the diazotization reaction of 6. To compare the results of this study with an amino acid less prone to oxidation, we performed the same DoE on the aliphatic amino acid valine. The results are summarized in Figure 2 (see also Tables S3−S8).

The results of the DoE indicated that the stoichiometry of both reagents must be considered in combination to maximize the yield. For cysteine, the yield was maximized when equimolar amounts of the two reagents were employed, while lower yields were observed with an excess of either reagent (Figure 2). For valine, an inverse trend was observed and the yield was maximized when an excess of nitrite was used (Figure 2). This demonstrated that the optimal conditions for diazotization of cysteine derivatives are not obvious based on results for other amino acids. Further optimization confirmed that 4 equiv of nitrite and sulfuric acid produced the highest yield (Figure S1).

To demonstrate the utility of this method on preparative scale, the diazotization was performed on 1 mmol scale, and the resulting products were isolated and characterized (Figure 3).
We observed an approximate 10% improvement in mass balance when saturated sodium sulfate solution was added to the reaction mixture before workup to provide a salting-out effect. The S-mesyl derivative 7 was sufficiently pure after aqueous workup, requiring no further purification. The S-phenylsulfonyl derivative 9 was prepared by a two-step procedure after esterification to form the methyl ester, which was purified by column chromatography. The allyl ester derivatives 10 and 11 were prepared by Fischer esterification; yields were limited by heat-sensitivity of 7 and 8. By replacing sulfuric acid with hydrochloric acid in the diazotization of 6, we found that α-chloro acid 12 is prepared; the methyl ester 13 was isolated by column chromatography after a two-step procedure involving methylation of 12 with trimethylsilyldiazomethane (see Safety Considerations). Furthermore, by reaction of the thiosulfonate 9 with a thiol and triethylamine, mixed disulfide product 14 is prepared in a single step. Preparation of 14 demonstrates a new synthetic route to medicinally relevant building block 3 from chiral pool precursor l-cysteine.

The stereochanical fidelity of this transformation is notable when compared with the diazotization of other β-substituted amino acids such as O-benzyl-l-serine, for which the hydroxy-acid derivative has been prepared previously with 80:20 er.12 In the course of exploratory investigations with the disulfide cysteine, we observed formation of thirane carboxylic acid and acrylic acid in 51% and 19% yields after diazotization. We believe that the thirane forms by nucleophilic displacement of the diazonium by sulfur. The observed thirane product provides indirect evidence of the problematic nucleophilicity of the β-thio substituent. We propose that the successful diazotization of S-sulfonyl-cysteines results from minimization of this undesired substitution pathway.

We obtained a crystal structure of allyl ester derivative 11 and observed the thiosulfonate in a gauche conformation with a C−S−S−C dihedral angle of 64.33° (Figure 4). Existing theoretical and spectroscopic studies of dimethylthiosulfonate derivatives also demonstrate a preference for the gauche conformation.27,28 The anomeric effect explains this observation; the conformation is stabilized by delocalization of a sulfonyl lone pair into the antibonding orbital of the adjacent S−C bond.

Figure 4. Crystal structure of 11 showing a gauche conformation about the thiosulfonate S−S bond.

Figure 5 illustrates how the anomeric effect in thiosulfonates could contribute to the stereochanical fidelity of this transformation by minimizing undesired substitution pathways. After diazotization, an episulfonium may form competitively with the α-lactone by substitution at the α-position. Any variation in the sequence of substitution events could lead to erosion in the er. Likewise, preventing epilsulfonium formation should improve the er (blue pathway). We propose that the anomeric effect decreases the nucleophilicity of the sulfonyl sulfur, destabilizing the undesired episulfonium and favoring the α-lactone pathway.

The anomeric effect can help rationalize the higher enantiomeric ratio of the products observed in preparation of the α-chloro derivative 13; hydrochloric acid likely protonates the thiosulfonate oxygens to a greater extent than sulfuric acid, increasing the anomeric effect. Alternatively, the steric bulk of the thiosulfonate may also contribute to the stereochanical fidelity of this transformation. Repulsive interactions between the sulfonyl oxygens and the carbonyl oxygen could minimize undesired nucleophilic substitution at the α-position after diazonium formation (Figure 5a).

In conclusion, we have enabled preparation of enantiomerically enriched sulfur-containing α-hydroxy and α-chloro acid building blocks by diazotization of S-sulfonyl-cysteines. Key to the success of this investigation was the use of a thiosulfonate protecting group and optimization of the reaction conditions by a 2² factorial DoE. We posit that the thiosulfonate protecting group enables this transformation by rendering the sulfur in cysteine resistant to the oxidizing reaction conditions and by attenuating sulfur’s nucleophilicity by the anomeric effect.

### EXPERIMENTAL SECTION

**General Remarks.** Reagents were used as supplied commercially without further purification. Solvents were dried and sparged with Argon using a solvent purification system prior to use. Reactions were run under inert atmosphere except where otherwise noted. Thin-layer chromatography (TLC) was performed using 0.2 mm coated glass silica gel plates and visualized using either ultraviolet light or staining with KMnO₄ solution. Purification by column chromatography over silica gel was performed on a Biotage Isolera flash chromatography system using SNAP KP-Sil or RediSep Rf Gold normal-phase columns. All NMR spectra were collected on Bruker instruments. Spectra reported with field strength of 400 MHz were collecting using a two-channel Bruker Avance-III HD Nanobay spectrometer.
operating at 400.09 MHz. Spectra reported with field strength of 500 MHz were collected using a three-channel Bruker Avance Neo spectrometer operating at 500.34 MHz. Both spectrometers were equipped with a 5 mm liquid-nitrogen-cooled Prodigy broad band observe (BBO) cryoprobe. Chemical shifts (δ) are reported in units of ppm, relative to the residual solvent peak, which was adjusted to match reported values. Individual peaks are assigned multiplicity with the following definitions: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Reported NMR data follow the general format: Nuclei NMR (resonance frequency, reference solvent) chemical shift (multiplicity, coupling constants, integration). High-resolution mass spectroscopy data was recorded using an Agilent Technologies 6545 Q-TOF LC/MS. Samples were directly injected using a mobile phase of 0.1% formic acid in acetonitrile. Infrared (IR) resonances were observed using an Agilent Cary 630 FTIR spectrometer. IR samples were prepared as solutions in dichloromethane then loaded onto a diamond surface, with the exception of compounds 5 and 6 which were observed in solid form. Enantiomeric ratio was assessed by HPLC using an Agilent 1290 Infinity II series instrument equipped with a chiral column. For each compound, a racemic standard was prepared to identify retention times for each enantiomer. Method details are described separately for each compound. Optical rotation was measured using a Jasco Model 2010 Polarimeter configured with a standard 589 nm Sodium D line to determine the specific rotation of compounds. Method details are described separately for each compound.

### General Screening Procedure for Amino Acid Diazo sensitization

All optimization data (OFAT and DoE data) reported for amino acid diazo sensitization of cysteine derivatives and valine was collected according to the following general procedure: amino acid starting material (0.25 mmol) was dissolved in aqueous acid (0.5−2 M stock solution, stoichiometry as indicated) and added to a 2 dram glass vial equipped with a magnetic stirrer. Cosolvent and/or additional DI water was added to achieve indicated cosolvent mixture and starting material concentration, and the mixture was cooled in an ice−water bath for 5 min. A 1 M aqueous solution of sodium nitrite (as indicated) was added with stirring. The vial was not capped but left open to ambient atmosphere. The reaction was allowed to warm slowly to room temperature and stirred for the indicated reaction time (1−24 h). Ethyl acetate (1.5 mL) was added directly to the vial. The vial was shaken vigorously, then the layers were allowed to separate. The organic layer was separated, and this extraction procedure was repeated 4 times. The combined organic fractions were dried (MgSO4) then filtered through cotton. Benzyl benzoate (0.25 mmol) was added, and then the solvent was removed under reduced pressure. The resulting mixture was analyzed by 1H NMR with a 25 s relaxation delay in (CD3)2SO to calculate an assay yield for the transformation. The results of OFAT and DoE optimization experiments are tabulated and summarized in the Supporting Information.
Preparation of (R)-1-Methoxy-3-((methylsulfonyl)thio)-1-oxopropan-2-yl Benzoate (7b). The hydroxy acid 7 was derivatized as described for chiral HPLC analysis: 7 (50 mg, 0.25 mmol) was dissolved in dry methanol (1 mL), heated to 60 °C, and stirred overnight. The crude residue was diluted with ethyl acetate, washed with dilute sodium bicarbonate, and then dried (MgSO₄). The solvent was removed under reduced pressure. The resulting oil (ca. 0.23 mmol) was dissolved in dry ethyl acetate (3 mL) and purified using a silica gel column chromatography (7–40% EtOAc/hexanes, Rf = 0.14, 25% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃): δ 8.54–8.05 (m, 2H), 7.68–7.56 (m, 1H), 7.48 (dd, J = 8.5, 7.1 Hz, 2H), 5.65 (dd, J = 7.0, 4.1 Hz, 1H), 3.86 (dd, J = 14.8, 4.1 Hz, 1H), 3.82 (s, 3H), 3.74 (dd, J = 14.8, 7.1 Hz, 1H), 3.37 (s, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 168.2, 165.5, 134.0, 130.1, 128.7, 128.7, 71.2, 51.2, 37.2. HRMS (ESI-QTOF) m/z: [M + Na]⁺ calc'd for C₁₂H₁₀O₅S₂Na, 325.0175; found, 325.0177. IR 3482, 3065, 2955, 1718, 1700, 1600, 1500, 1295, 1279, 1199, 1067, 1031, 1013, 937, 897, 847, 775, 716, 685 cm⁻¹. Specific rotation [α]D²⁰ = +28.9 (c 1.7, CHCl₃). Enantiomeric ratio 96:4. HPLC chromatograms and method information for assessment of enantiomeric ratio are included in the Supporting Information.

Preparation of Allyl (R)-2-Hydroxy-3-(phenylsulfonyl)thio)propanoate (9). Amino acid 6 (261.3 mg, 1.0 mmol) was dissolved in 4 mL of 1 M sulfuric acid in a 50 mL round-bottom flask equipped with a magnetic stirrer. The reaction was run open to the atmosphere. The mixture was cooled in an ice–water bath; 4 mL of acetone was then added. Sodium nitrite (276 mg, 4.0 mmol) was dissolved in DI water (3 mL) and then added dropwise, using additional DI water for rinsing (1 mL). The solution was warmed to room temperature gradually over 4 h. The reaction mixture was transferred to a separatory funnel. Saturated sodium chloride was added and then the aqueous layer was washed with ethyl acetate (4 mL) and cooled in an ice–water bath; 4 mL of acetone was then added. Sodium nitrite (276 mg, 4.0 mmol) was dissolved in DI water (3 mL) and then added dropwise, using additional DI water for rinsing (1 mL). The solution was warmed to room temperature gradually over 4 h. The reaction mixture was transferred to a separatory funnel. Saturated sodium chloride was added and then the aqueous layer was washed with ethyl acetate (4 mL) and cooled in an ice–water bath; 4 mL of acetone was then added. Sodium nitrite (276 mg, 4.0 mmol) was dissolved in DI water (3 mL) and then added dropwise, using additional DI water for rinsing (1 mL). The solution was warmed to room temperature gradually over 4 h. The reaction mixture was transferred to a separatory funnel. Saturated sodium chloride was added and then the aqueous layer was washed with ethyl acetate (4 mL) and cooled in an ice–water bath; 4 mL of acetone was then added. Sodium nitrite (276 mg, 4.0 mmol) was dissolved in DI water (3 mL) and then added dropwise, using additional DI water for rinsing (1 mL). The solution was warmed to room temperature gradually over 4 h. The reaction mixture was transferred to a separatory funnel. Saturated sodium chloride was added and then the aqueous layer was washed with ethyl acetate (4 mL) and cooled in an ice–water bath; 4 mL of acetone was then added. Sodium nitrite (276 mg, 4.0 mmol) was dissolved in DI water (3 mL) and then added dropwise, using additional DI water for rinsing (1 mL). The solution was warmed to room temperature gradually over 4 h. The reaction mixture was transferred to a separatory funnel. Saturated sodium chloride was added and then the aqueous layer was washed with ethyl acetate (4 mL) and cooled in an ice–water bath; 4 mL of acetone was then added. Sodium nitrite (276 mg, 4.0 mmol) was dissolved in DI water (3 mL) and then added dropwise, using additional DI water for rinsing (1 mL). The solution was warmed to room temperature gradually over 4 h. The reaction mixture was transferred to a separatory funnel. Saturated sodium chloride was added and then the aqueous layer was washed with ethyl acetate (4 mL) and cooled in an ice–water bath; 4 mL of acetone was then added. Sodium nitrite (276 mg, 4.0 mmol) was dissolved in DI water (3 mL) and then added dropwise, using additional DI water for rinsing (1 mL).
Supplementary graphs and tables; crystallographic data; and copies of $^1$H, $^13$C NMR spectra and HPLC chromatograms for relevant compounds (PDF)

Crystallographic data for 11 (CIF)

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**Notes**

Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Science Foundation.

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CCDC 1949213 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre

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