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Direct Synthesis of α -Thio Aromatic Acids from Aromatic Amino Acids

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Abstract

Modified amino acids are useful synthetic components in both chemistry and biology. Here we describe a simple, scalable two-step procedure to generate α -thio aromatic acids from aromatic amino acids with yields of up to 96%. Diazotization and α -lactone mediated bromination efficiently form the α -bromo acid with retention of configuration. Thiol substitution with mild reagents such as sodium hydrosulfide or sodium trithiocarbonate provides the inverted, free α -thio acid. The mildly acidic soft nucleophile can then be utilized in many synthetic applications.

Graphical Abstract

Keywords

thiol synthesis; α -thio acid; diazonium compound; α -bromo acid; aromatic amino acids

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Supporting Information:

Experimental details, optical rotation data, and ¹H NMR, ¹³C NMR, and HRMS spectra are provided in the supporting information.

Introduction

Modified amino acids are valuable synthetic tools in numerous fields from total synthesis, chemical and synthetic biology, and medicinal chemistry. One such method of modification involves transformation of the α -amine to bromine, which can be utilized as an electrophile in a range of synthetic applications^{1,2}. Notwithstanding, little has been reported on the direct synthesis of free α -thio acids, particularly from α -bromo acids.

In general, free thiols are useful moieties involved in an assortment of reactions from conjugate addition to polymer cross-linking. The soft, reactive nucleophile is frequently involved in click chemistry, bioconjugation, and materials chemistry^{3,4}. Moreover, α -thio acids can be utilized in a variety of proteomic techniques beyond cysteine conjugation and even peptidomimetic chemistry. For our purposes, α -thio aromatic acids are useful backbone thioether intermediates in the synthesis of ritonavir like CYP3A4 inhibitors⁵.

Previous synthetic methods to generate free α -thio acids from α -bromo acids typically involve protected thiol nucleophiles, such as 1,1-diphenylmethanethiol, which must be subsequently deprotected⁶. Here we describe a simple and effective two-step synthesis of free α -thio aromatic acids through diazotization, bromination, and nucleophilic substitution that has been optimized accordingly.

α -Bromination of amino acids was initially reported by Izumiya and Nagamatsu, who diazotized the α -amine with sodium nitrite and brominated with KBr in the presence of H_2SO_4 ⁷. The resulting α -bromo acids maintained retention of configuration. Since then several adjustments have been reported to generate a variety of α -bromo acids^{1,2,8,9}. We discovered that HBr alone was a sufficient bromine source for phenylalanine, whereas KBr was required for bromination of tryptophan and 1-naphthylalanine. α -Bromo phenylalanine was easily converted into α -thio phenylalanine in the presence of aqueous sodium hydrosulfide¹⁰. However, the more nucleophilic sodium trithiocarbonate was necessary to thiolate tryptophan and 1-naphthylalanine (Scheme 1). Conveniently, both reagents were able to form the free thio acid in a one-pot manner. Due to the retentive nature of α -bromination, thiolation resulted in an inversion of configuration. Therefore, an opposite aromatic amino acid enantiomer should be utilized to produce the desired α -thio aromatic amino acid.

The optimized syntheses of the aforementioned α -bromo and α -thio acids were found to be not only straightforward, but also highly robust. Aside from α -bromo tryptophan and naphthylalanine, liquid-liquid extraction was sufficient to obtain the pure α -bromo or α -thio acid in excellent yields. Another advantage is that all reagents - with the exception of sodium trithiocarbonate, which needs to be freshly prepared - are commonly found in most organic chemistry laboratories.

Results and Discussion

Diazotization of aromatic amines commonly occurs through a radical $\text{S}_{\text{RN}}1$ or standard $\text{S}_{\text{N}}1$ fashion, with a free radical or aryl cation intermediate respectively^{11,12,13}. However, few mechanical examples of diazotization of aliphatic amines exist. Previous studies with amino

acids have shown that halide substitution of a formed alpha diazonium compound results in retention of configuration. Despite this, little has been postulated regarding the mechanism. We presume that the reaction occurs via a double inversion, with an alpha lactone intermediate (Scheme 2). The mechanism is comparable to that of γ -butyrolactone- γ -carboxylic acid synthesis from glutamic acid^{14,15}. Following diazotization, the carboxylic acid displaces the nitrogen to form an alpha lactone with an inversion of configuration. The second inversion occurs when aqueous hydrogen halide (with or without a metal halide) protonates the lactone while halogenating the alpha carbon in a SN2 fashion. Lactone formation is presumably more stable than tertiary carbocation or alpha radical formation - as with other diazonium compounds - because the product retains stereochemistry, rather than forming a racemic mixture.

D- or L-phenylalanine were the only amino acids in the series that a) effectively brominated with HBr alone, and b) substituted more efficiently with NaSH than sodium trithiocarbonate. For bromination, addition of KBr did produce the desired product, however, higher yields were obtained with salt-free, aqueous HBr⁹. The resulting α -bromo-acid was then treated with aqueous NaSH, heated, and acidified¹⁰ to produce the thiol with typical yields of around 75%. Interestingly, large-scale synthesis (40 mmol) of D- α -thio-phenylalanine produced the highest yield, 92% overall, denoting that the synthesis is highly efficient.

Reactions with unprotected L-tryptophan were unsuccessful, presumably due to the semi-reactive indole ring. Boc protection of the indole however, allowed for synthesis of the bromide and subsequent thiol. As reported previously, a mixture of KBr with aqueous HBr was more effective than HBr alone or with NaBr¹. This was also the case for DL-1-naphthylalanine, despite the similarity to phenylalanine. Likewise, NaSH failed to produce the final thiol of tryptophan and naphthylalanine, so the more sensitive sodium trithiocarbante was prepared as described previously, and used as the thiol nucleophile^{16,17}. The synthesis was highly robust, with yields 90% achieved in both small and large scale.

For tryptophan, the thiol product was expediently a mixture of Boc protected and free amine. In an effort to deprotect the Boc product in one pot, longer exposure to H₂SO₄ during wash was attempted. However, protected product still remained. Lingering Boc product was simply deprotected with HCl in dioxane to form the unprotected D- α -thio-tryptophan.

In summary, a simple and effective method for the production of α -thio acids from several aromatic amino acids has been developed. For other aromatic amino acids with different R-functionalities, i.e. tyrosine and histidine, the bromination and thiolation process developed for tryptophan could be applicable, but Boc protection of the histidine imidazole would be necessary. The final thiol can be used in numerous applications: as a starting material in thioether/thioester synthesis, to conjugate addition in click chemistry. Moreover, an alternate soft nucleophile at the α -carbon can be very useful in the synthesis of new peptide-like pharmaceuticals, or humbly as a modified amino acid in chemical/synthetic biology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Two-step procedure to produce α -thio aromatic acids from aromatic amino acids.
- Stereospecific synthesis that results in free thiols, with yields above 90%.
- The free thiol can be used in numerous applications.

Scheme 1.
Synthesis of α -thio acids from aromatic amino acids

Scheme 2.

Proposed mechanism of α-halogenation of amino acids via α-lactone intermediate