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SIMPLE PREPARATION OF N-PROTECTED CHIRAL β-AMINO ALKYL THIOLS FROM CORRESPONDING IODIDES EMPLOYING SODIUM TRITHIOCARBONATE

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GRAPHICAL ABSTRACT

Abstract A simple protocol for the preparation of N-protected amino alkyl thiols is reported that employs a reaction of sodium trithiocarbonate (Na₂CS₃) with N-protected amino alkyl iodides. Na₂CS₃ is easy to prepare and the protocol circumvents the use of strong bases and multiple steps. All the thiol compounds made were obtained as enantiopure samples and were characterized employing NMR and mass spectrometry.

Keywords Alkyl iodide; chiral β-amino alkyl thiol; sodium trithiocarbonate

INTRODUCTION

There is growing interest in the preparation of chiral β-amino alkyl thiols, which have a marked existence in medicinal and synthetic chemistry.[1,2] Naturally occurring amino thiols such as cysteine, homocysteine, and penicillamine are involved in several biological processes.[3] Mercapto derivatives possess useful physicochemical and pharmacokinetic properties by virtue of their acidity and metal affinity.[4] Furthermore, amino alkyl thiols serve as precursors for chiral sources in...
asymmetric reactions and have been found to be better substituents than amino alcohols in several asymmetric syntheses. They are useful components for various thio derivatives such as thiocarbamates, taurins, and S-heterocycles. Because of their synthetic applications in the construction of a diverse class of thia-peptidomimetics, development of protocols for the preparation of β-amino thiols is of considerable interest. One of the most frequently employed protocols for the preparation of 2-amino thiols is the hydrolysis of corresponding thioacetates using strong bases NaOH, KOH, NaOMe, or K₂CO₃. Ethylenediamine-mediated hydrolysis of O-ethyl thiocarbonate was employed for the preparation of Boc-Leu-ψ(CH₂SH). Recently, we reported a facile synthesis of N-protected chiral β-amino alkyl thiols by reaction of corresponding iodides with thiourea at reflux followed by the hydrolysis of the resulting isothiouronium salt with sodium pyrosulfite in a two-step protocol. Various protocols employed to access β-amino alkyl thiols are summarized in Scheme 1.

RESULTS AND DISCUSSION

Presently, our group is exploring further synthetic applications of these chiral thiol intermediates for assembling novel peptidomimetics. For example, the synthesis of selenothiocarbamates and dithiocarbamate-linked peptidomimetics is in progress. Thus, owing to the extensive application of N-protected amino alkyl thiols, we became interested in establishing simpler routes to prepare chiral-β-amino alkyl thiols from amino acids. During this quest, we came across sodium trithiocarbonate (Na₂CS₃), which was employed to transfer alkyl halides into mercaptans via a SN₂ displacement. Surprisingly, this potential reagent has received only scant attention. The mild reaction conditions, simplicity of reagent preparation, and reaction efficacy prompted us to explore its applicability for the preparation of N-protected amino alkyl thiols from their iodo precursors.

The reagent was prepared by mixing a known quantity of sodium sulfide with slight excess of CS₂ in water according to the reported protocol. The resulting
brick-red solution was stored at rt. On the other hand, N-protected amino acid was reduced to alcohol and then converted to its iodide under Mitsunobu conditions (PPh₃/imidazole/I₂). For the preparation of N-protected β-amino thiols, in a typical reaction Z-Phe-ψ(CH₂-I) 1a was treated with the stock solution of Na₂CS₃ in dioxane at 50 °C (Scheme 2). About 1.5 h was sufficient for complete consumption of the starting material (thin-layer chromatographic TLC, analysis), after which the thiol product 2a was isolated by an acidic workup followed by column chromatography in 88% yield. The product was identified by comparing its TLC and high-performance liquid chromatographic (HPLC) data with the authentic sample and later confirmed through mass and NMR spectroscopy.

The reproducibility and efficacy of the protocol was then demonstrated by preparing a series of β-amino alkyl thiols from Z- as well as Boc-protected amino alkyl iodides in affordable yields and purities (Table 1). However, the mild basic nature of the reagent caused cleavage of the Fmoc group to an extent of 20–30% (TLC) during the reaction, because of which N-Fmoc-amino alkyl thiols (2j and 2k) were obtained in fairly poor yields. All the compounds were characterized by mass and NMR techniques. Importantly, during these preparations, no sulfide formation was detected that otherwise would arise by the reaction of thiols with unreacted alkyl iodides in the reaction mixture (LC-MS analysis). The HPLC analysis of crude samples showed that the compounds are enantiomerically pure. To check the enantiomeric purity of the thiols, in a case study, crude samples of Z-L-Leu-ψ(CH₂-SH) and Z-D-Leu-ψ(CH₂-SH) were analyzed through HPLC (HPLC particulars: Agilent 1100 series having G1311A VWD at λ = 254 nm, flow 0.5 mL/min, column: Chiralcell OD-H, pore size 5 μm, diameter ∗ length = 4.6 ∗ 250 mm; method: gradient n-hexane–ethanol in 45 min). Major peaks corresponded to thiol compound eluted at distinct tᵣ values (16 min and 23 min respectively), which evidenced the presence of a single isomer in each sample. Further, ¹H NMR spectra of a pair of isomeric thiols prepared starting from Boc-L-Ala-OH and its D-isomer had distinct methyl doublets, thus confirming the presence of a single isomer in each sample.

In the reaction, the alkyl iodide first reacts with sodium trithiocarbonate to afford monoalkyl trithiocarbamic acid salt, which upon acidification yields monoalkyl trithiocarbonate. This is unstable and undergoes spontaneous decomposition into the desired thiol (Scheme 3). In one report, CS₂ released at the end of the reaction was recovered, which provides direct evidence for the proposed mechanism. 

![Scheme 2](image)

**Scheme 2.** Conversion of N-protected β-amino alkyl iodides to thiols.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Thiol 2</th>
<th>Yield (%)</th>
<th>$\lambda^{[25]}$ ($c = 0.1$, CHCl$_3$)</th>
<th>Calcd.</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td><img src="image1.png" alt="Thiol a" /></td>
<td>85</td>
<td>-21.5</td>
<td>276.1034</td>
<td>276.1042</td>
</tr>
<tr>
<td>b</td>
<td><img src="image2.png" alt="Thiol b" /></td>
<td>86</td>
<td>-15.7</td>
<td>290.1191</td>
<td>290.2136</td>
</tr>
<tr>
<td>c</td>
<td><img src="image3.png" alt="Thiol c" /></td>
<td>78</td>
<td>-9.6</td>
<td>274.0878</td>
<td>274.1443</td>
</tr>
<tr>
<td>d</td>
<td><img src="image4.png" alt="Thiol d" /></td>
<td>75</td>
<td>+8.1</td>
<td>370.0911</td>
<td>370.1152</td>
</tr>
<tr>
<td>e</td>
<td><img src="image5.png" alt="Thiol e" /></td>
<td>62</td>
<td>-10.75</td>
<td>382.1089</td>
<td>382.1135</td>
</tr>
<tr>
<td>f</td>
<td><img src="image6.png" alt="Thiol f" /></td>
<td>76</td>
<td>-26.65</td>
<td>214.0878</td>
<td>214.0251</td>
</tr>
<tr>
<td>g</td>
<td><img src="image7.png" alt="Thiol g" /></td>
<td>67</td>
<td>-5.7</td>
<td>242.1191</td>
<td>241.9774</td>
</tr>
<tr>
<td>h</td>
<td><img src="image8.png" alt="Thiol h" /></td>
<td>70</td>
<td>-23.85</td>
<td>290.1191</td>
<td>290.0598</td>
</tr>
<tr>
<td>i</td>
<td><img src="image9.png" alt="Thiol i" /></td>
<td>65</td>
<td>-4.05</td>
<td>256.1347</td>
<td>256.1256</td>
</tr>
<tr>
<td>j</td>
<td><img src="image10.png" alt="Thiol j" /></td>
<td>48</td>
<td>-13.9</td>
<td>380.1087</td>
<td>380.0922</td>
</tr>
<tr>
<td>k</td>
<td><img src="image11.png" alt="Thiol k" /></td>
<td>55</td>
<td>-12.4</td>
<td>412.1347</td>
<td>412.1355</td>
</tr>
</tbody>
</table>

$^[M + K]^+$. 
CONCLUSION

We have employed sodium trithiocarbonate (Na₂CS₃) as a useful reagent for the one-step conversion of N-protected amino alkyl iodides into corresponding thiols. The reaction is simple, and the reagent is easy to prepare and handle. Unlike most of the earlier protocols, which require either multiple steps, strong bases, or isolation of intermediates, the present approach delivers the product in a simple and economic way. We hope that the protocol attracts considerable attention as a method of choice for fulfilling the increasing demand for chiral β-amino alkyl thiols in synthetic and biomedical applications.

EXPERIMENTAL

All solvents were freshly distilled before use. Amino acids were used as received from Sigma-Aldrich Company. TLC analysis was carried out using precoated silica-gel G254 plates. The reaction mixture was purified by column chromatography over silica gel (200–300). ¹H and ¹³C NMR spectra were recorded at 300 and 75 MHz respectively, with tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on HRMS.

Preparation of Na₂CS₃

CS₂ (4.25 mL, 1.1 eq) was added to a solution of Na₂S (5 g, 64 mmol) in water (30 mL), and the reaction mixture was maintained at 40 °C for 1 h. The resulting brick-red solution was stored at rt.

Preparation of N-Protected Chiral β-Amino Alkyl Thiols 2a–j: General Procedure

N-Protected alkyl iodide (1.26 mmol) was dissolved in dioxane (5 mL), and sodium trithiocarbonate solution (1.5 eq, 0.95 mL) was added. The homogeneous solution was heated to 50 °C (Scheme 2). About 1.5 h was sufficient for complete consumption of the starting material (TLC analysis). The reaction mixture was acidified with 5% diluted HCl extracted into EtOAc (10 mL × 2). The organic phase was washed with water and brine and concentrated in vacuo. The residue was purified via column chromatography.

Z-Val-ψ[CH₂SH] (2a). ¹H NMR (300 MHz, CDCl₃): δ 7.13 (br, 1H), 6.94–7.1 (m, 5H), 5.17 (s, 2H), 3.7 (m, 1H), 2.85 (m, 2H), 2.43 (br, 1H), 2.34 (m, 1H), 1.05 (d, 6H, J = 4.1 Hz); ¹³C NMR (75 MHz, CDCl₃): 155.5, 141.3 128.8, 127.6, 127.3, 65.1,
Z-Leu-\(\psi(\text{CH}_2\text{SH})\) (2b). \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 6.8 (br, 1H), 6.98–7.2 (m, 5H), 5.2 (s, 2H), 3.85 (m, 1H), 2.79 (m, 2H), 2.4 (br, 1H), 1.89 (m, 1H), 1.65 (m, 2H), 0.9 (d, 6H, \(J = 2.3\) Hz); \(^{13}^C\) NMR (75 MHz, CDCl\(_3\)): 155.5, 141.3, 128.8, 127.6, 127.3, 65.1, 51.3, 44.0, 32.4, 28.9, 22.8. HRMS (\(m/z\)) calc. for C\(_{13}\)H\(_{19}\)NO\(_2\)S 276.1034; found 276.1042 [M + Na].

Z-Pro-\(\psi(\text{CH}_2\text{SH})\) (2c). \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 6.98–7.21 (m, 5H), 5.11 (s, 2H), 3.51 (m, 1H), 3.3 (t, 3H, \(J = 3.9\) Hz), 2.83 (m, 2H), 2.47 (br, 1H), 1.71 (m, 2H) 1.59 (m, 2H); \(^{13}^C\) NMR (75 MHz, CDCl\(_3\)): 156.9, 141.3, 128.9, 127.7, 127.0, 65.7, 56.1, 47.6, 31.0, 28.9, 21.8. HRMS (\(m/z\)) calc. for C\(_{13}\)H\(_{17}\)NO\(_2\)S 290.1191; found 290.2136 [M + Na].

Z-Cys(S-BzI)-\(\psi(\text{CH}_2\text{SH})\) (2d). \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 6.94–7.2 (m, 10), 6.83 (br, 1H), 5.2 (s, 2H), 3.9 (m, 1H), 3.51 (s, 2H), 2.81 (m, 2H), 2.65(d, 2H, \(J = 4.3\) Hz), 2.23 (br, 1H); \(^{13}^C\) NMR (75 MHz, CDCl\(_3\)): 154.9, 142.1, 136.3, 129.5, 129.0, 128.8, 127.4, 127.3, 66.3, 57.2, 39.5, 37.2, 31.0. HRMS calc. for C\(_{18}\)H\(_{21}\)NO\(_2\)S \(_2\) 370.0911; found 370.1152 [M + Na].

Z-Asp(OBzl)-\(\psi(\text{CH}_2\text{SH})\) (2e). \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.24–7.28 (m, 10H) 5.34 (br, 1H), 5.1.4 (s, 2H), 5.04 (s, 2H), 4.08 (m, 1H), 2.70 (m,2H), 2.61 (d, 2H, \(J = 2.3\) Hz), 1.55 (br, 1H); \(^{13}^C\) NMR (75 MHz, CDCl\(_3\)): 171.2, 154.1, 139.2, 138.3, 128.1, 129.5, 129.0, 128.8, 129.4, 126.5, 130.2, 57.3, 39.2, 32.1. HRMS (\(m/z\)) calc. for C\(_{19}\)H\(_{21}\)NO\(_4\)S 382.1089; found 382.1135 [M + Na].

Boc-Ala-\(\psi(\text{CH}_2\text{SH})\) (2f). \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 6.9 (br, 1H), 4.9 (m, 1H), 2.8 (m, 2H), 2.59 (br, 1H), 1.6 (d, 3H, \(J = 6.9\) Hz), 1.38 (s, 9H); \(^{13}^C\) NMR (75 MHz, CDCl\(_3\)): 155.9, 77.3, 51.2, 33.8, 28.3, 19.3. HRMS calc. for C\(_8\)H\(_{17}\)NO\(_2\)S 214.0878; found 214.0251 [M + Na].

Boc-Val-\(\psi(\text{CH}_2\text{SH})\) (2g). \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.1 (br, 1H), 3.9 (m, 1H), 2.78 (m, 2H), 2.45 (br, 1H), 2.36 (m, 1H), 1.4 (s, 9H), 1.1 (d, 6H, \(J = 4.2\) Hz); \(^{13}^C\) NMR (75 MHz, CDCl\(_3\)): 155.7, 138.9, 129.2, 126.1, 77.7, 54.4, 37.6, 28.3. HRMS (\(m/z\)) calc. for C\(_{10}\)H\(_{21}\)NO\(_2\)S 242.1191; found 241.9774 [M + Na].

Boc-Phe-\(\psi(\text{CH}_2\text{SH})\) (2h). \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.11–7.25 (m, 5H), 4.64 (br, 5H), 4.11 (m, 1H), 2.86 (d, 2H, \(J = 4.5\) Hz), 2.52 (m, 2H), 2.02 (br, 1H), 1.33 (s, 9H); \(^{13}^C\) NMR (75 MHz, CDCl\(_3\)): 155.3, 138.9, 129.2, 128.1, 126.1, 77.7, 54.4, 37.6, 28.3. HRMS (\(m/z\)) calc. for C\(_{14}\)H\(_{21}\)NO\(_2\)S 290.1191; found 290.0598 [M + Na].

Fmoc-Val-\(\psi(\text{CH}_2\text{SH})\) (2i). \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.3–7.8 (m, 8H), 6.9 (br, 1H), 4.68 (d, 2H, \(J = 6.5\) Hz), 4.39 (t, 1H, \(J = 3.7\) Hz), 3.7 (m, 1H), 2.72 (m, 2H), 2.34 (br, 1H), 2.34 (m, 1H), 1.1 (d, 6H, \(J = 4.2\) Hz); \(^{13}^C\) NMR (75 MHz, CDCl\(_3\)): 156.1, 143.8, 142.1, 128.9, 128.5, 126.5, 66.1, 64.3, 46.8, 32.6, 30.1, 17.2 HRMS calc. for C\(_{20}\)H\(_{23}\)NO\(_2\)S 380.1087; found 380.0922 [M + K].

Fmoc-Phe-\(\psi(\text{CH}_2\text{SH})\) (2j). \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 6.95–7.9 (m, 13H), 6.83 (br, 1H), 4.6 (m, 1H), 4.59 (d, 2H, \(J = 6.2\) Hz), 4.35 (t, 1H, \(J = 3.3\) Hz), 2.83 (m, 2H), 2.75 (d, 2H, \(J = 4.2\) Hz), 2.39 (br, 1H); \(^{13}^C\) NMR (75 MHz, CDCl\(_3\)): 143.5,
141.1, 139.0, 128.5, 128.3, 128.1, 127.9, 126.3, 125.8, 66.8, 56.7, 48.5, 40.9, 31.2. HRMS (m/z) calc. for C$_{24}$H$_{23}$NO$_2$S 412.1347; found 412.1355 [M$^+$ + Na].

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