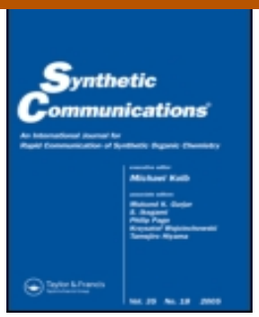


Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Simple Preparation of N-Protected Chiral β-Amino Alkyl Thiols from Corresponding Iodides Employing Sodium Trithiocarbonate

Chilakapati Madhu , H. P. Hemantha , T. M. Vishwanatha & V. V. Sureshbabu

To cite this article: Chilakapati Madhu , H. P. Hemantha , T. M. Vishwanatha & V. V. Sureshbabu (2013) Simple Preparation of N-Protected Chiral β-Amino Alkyl Thiols from Corresponding Iodides Employing Sodium Trithiocarbonate, Synthetic Communications, 43:2, 228-235, DOI: 10.1080/00397911.2011.595522

To link to this article: http://dx.doi.org/10.1080/00397911.2011.595522

Accepted author version posted online: 01 Feb 2012.
Published online: 01 Feb 2012.

Synthetic Communications®, 43: 228–235, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.595522

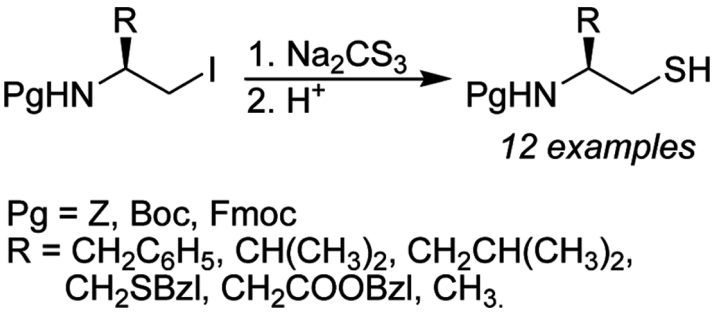
Taylor & Francis
Taylor & Francis Group

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

Chilakapati Madhu, H. P. Hemantha, T. M. Vishwanatha, and V. V. Sureshbabu

Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Bangalore University, Bangalore, India

GRAPHICAL ABSTRACT



Abstract *A simple protocol for the preparation of N-protected amino alkyl thiols is reported that employs a reaction of sodium trithiocarbonate (Na_2CS_3) with N-protected amino alkyl iodides. Na_2CS_3 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.*

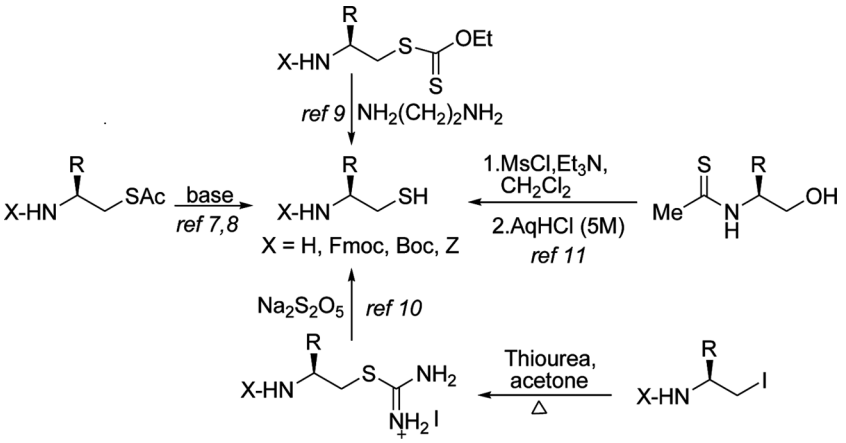
Keywords Alkyl iodide; chiral β-amino alkyl thiol; sodium trithiocarbonate

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

Received May 2, 2011.

Address correspondence to V. V. Sureshbabu, Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Bangalore University, Dr. B. R. Ambedkar Veedhi, Bangalore 560 001, India. E-mail: sureshbabuvommina@rediffmail.com, hariccb@gmail.com, hariccb@hotmail.com



Scheme 1. Various approaches reported for the synthesis of β-amino alkyl thiols.

asymmetric reactions and have been found to be better substituents than amino alcohols in several asymmetric syntheses.[5] They are useful components for various thio derivatives such as thiocarbamates, taurins, and *S*-heterocycles.[6] 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 K_2CO_3.[7,8] Ethylenediamine-mediated hydrolysis of *O*-ethyl thiocarbonate was employed for the preparation of Boc-Leu-ψ[CH_2SH].[9] 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.[10] Various protocols employed to access β-amino alkyl thiols are summarized in Scheme 1.

RESULTS AND DISCUSSION

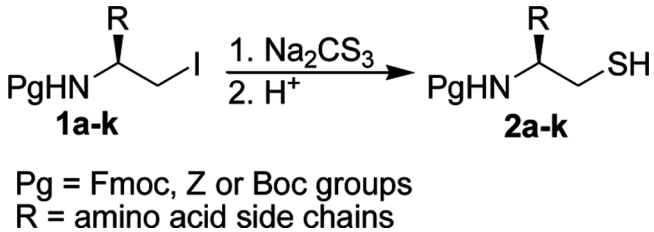
Presently, our group is exploring further synthetic applications of these chiral thiol intermediates for assembling novel peptidomimetics. For example, the synthesis of selenothiocarbamates and dithiocarbamate-linked peptidomimetics is in progress. Thus, owing to the extensive application of N-protected 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 (Na_2CS_3),[12] which was employed to transfer alkyl halides into mercaptans via a SN_2 displacement.[13] 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 CS_2 in water according to the reported protocol.[12] 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 (PPh_3/imidazole/I_2).[14] For the preparation of N-protected β-amino thiols, in a typical reaction Z-Phe-ψ[CH_2-I] **1a** was treated with the stock solution of Na_2CS_3 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.

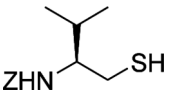
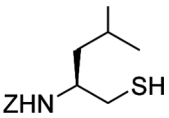
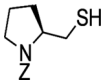
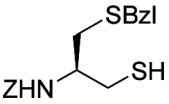
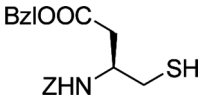
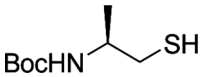
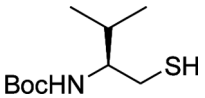
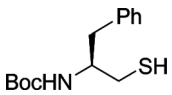
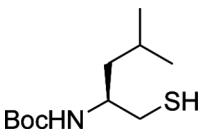
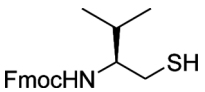
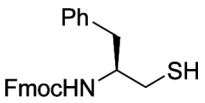
The reproducibility and efficacy of the protocol was then demonstrated by preparing a series of β-amino alkyl thiols from Z- as well as Boc-protected amino alkyl iodides in affordable yields and purities (Table 1). However, the mild basic nature of the reagent caused cleavage of the Fmoc group to an 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[CH_2-SH] and Z-D-Leu-ψ[CH_2-SH] were analyzed through HPLC (HPLC particulars: Agilent 1100 series having G1311A VWD at $\lambda = 254$ 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 t_R values (16 min and 23 min respectively), which evidenced the presence of a single isomer in each sample. Further, ^{1}H 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, CS_2 released at the end of the reaction was recovered, which provides direct evidence for the proposed mechanism.[12]

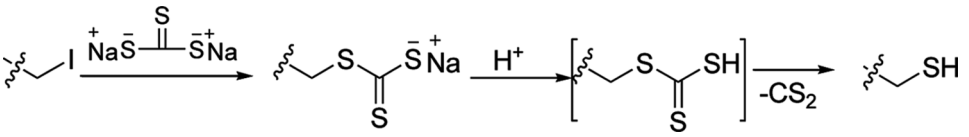


Scheme 2. Conversion of *N*-protected β-amino alkyl iodides to thiols.

Table 1. List of N-protected β-amino alkyl thiols **2**

Entry	Thiol **2**	Yield (%)	$[\alpha]^{[25]}$ ($c = 0.1$, $CHCl_3$)	HRMS $[M + Na]^+$ Calcd.	HRMS $[M + Na]^+$ Observed
a		85	−21.5	276.1034	276.1042
b		86	−15.7	290.1191	290.2136
c		78	−9.6	274.0878	274.1443
d		75	+8.1	370.0911	370.1152
e		62	−10.75	382.1089	382.1135
f		76	−26.65	214.0878	214.0251
g		67	−5.7	242.1191	241.9774
h		70	−23.85	290.1191	290.0598
i		65	−4.05	256.1347	256.1256
j		48	−13.9	380.1087[a]	380.0922
k		55	−12.4	412.1347	412.1355

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



Scheme 3. Mechanism of transformation of alkyl iodide into thiol.

CONCLUSION

We have employed sodium trithiocarbonate (Na_2CS_3) 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 ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively, with tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on HRMS.

Preparation of Na_2CS_3

CS_2 (4.25 mL, 1.1 eq) was added to a solution of Na_2S (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[CH_2SH] (2a). ^1H NMR (300 MHz, $CDCl_3$): 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); ^{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, 22.8l. HRMS (m/z) calc. for $C_{13}H_{19}NO_2S$ 276.1034; found 276.1042 $[M + Na]^+$.

Z-Leu-ψ[CH_2SH] (2b). ^1H NMR (300 MHz, $CDCl_3$): δ 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, 22.5. HRMS (m/z) calc. for C_{14} $H_{21}NO_2S$ 290.1191; found 290.2136 $[M^+ + Na]$.

Z-Pro-ψ[CH_2SH] (2c). ^1H NMR (300 MHz, $CDCl_3$): δ 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 $C_{13}H_{17}NO_2S$ 274.0878; found 274.1443 $[M^+ + Na]$.

Z-Cys(S-Bzl)-ψ[CH_2SH] (2d). ^1H NMR (300 MHz, $CDCl_3$): δ 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 $C_{18}H_{21}NO_2S_2$ 370.0911; found 370.1152 $[M^+ + Na]$.

Z-Asp(OBzl)-ψ[CH_2SH] (2e). ^1H NMR (300 MHz, $CDCl_3$): δ 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, 127.8, 127.6, 127.4, 127.1, 126.5, 60.2, 57.3, 54.7, 39.2, 32.1. HRMS (m/z) calc. for $C_{19}H_{21}NO_4S$ 382.1089; found 382.1135 $[M^+ + Na]$.

Boc-Ala-ψ[CH_2SH] (2f). ^1H NMR (300 MHz, $CDCl_3$): δ 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 $C_8H_{17}NO_2S$ 214.0878; found 214.0251 $[M^+ + Na]$.

Boc-Val-ψ[CH_2SH] (2g). ^1H NMR (300 MHz, $CDCl_3$): δ 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, 76.9, 643, 32.7, 29.9, 28.5, 17.2. HRMS (m/z) calc. for $C_{10}H_{21}NO_2S$ 242.1191; found 241.9774 $[M^+ + Na]$.

Boc-Phe-ψ[CH_2SH] (2h). ^1H NMR (300 MHz, $CDCl_3$): δ 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, 128.2, 126.1, 77.7, 54.4, 37.6, 28.3. HRMS (m/z) calc. for $C_{14}H_{21}NO_2S$ 290.1191; found 290.0598 $[M^+ + Na]$.

Fmoc-Val-ψ[CH_2SH] (2i). ^1H NMR (300 MHz, $CDCl_3$): δ 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, $J = 4.28$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 156.1, 143.8, 142.1, 128.9, 128.5, 126.5, 66.1, 63.4, 46.8, 32.6, 30.1, 17.2 HRMS calc. for $C_{20}H_{23}NO_2S$ 380.1087; found 380.0922 $[M^+ + K]$.

Fmoc-Phe-ψ[CH_2SH] (2j). ^1H NMR (300 MHz, CDCl3): δ 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 $C_{24}H_{23}NO_2S$ 412.1347; found 412.1355 [$M^+ + Na$].

ACKNOWLEDGMENTS

The authors thank the University Grants Commission, New Delhi (UGC), for financial support [F. No. 37-79/2009 (SR)]. The departments of Inorganic and Physical Chemistry (IPC) and Organic Chemistry at IISc, Bangalore, are thanked for the compound characterization data. Timely help from H. N. Gopi, IISER, Pune, during the preparation of the manuscript is gratefully acknowledged.

REFERENCES

1. (a) Park, J. D.; Kim, D. H. Cysteine derivatives as inhibitors for carboxypeptidase A: synthesis and structure–activity relationships. *J. Med. Chem.* **2002**, *45*, 911–918; (b) Ocain, T. D.; Rich, D. H. L-Lysinethiol: A subnanomolar inhibitor of aminopeptidase B. *Biochem. Biophys.* **1987**, *145*, 1038–1042.
2. Chiotellis, E.; Stassinopoulou, C. I.; Varvarigou, A.; Vavouraki, H. Structure–activity relationships of some technetium-99 m labeled [(thioethyl)amino] carboxylates. *J. Med. Chem.* **1982**, *25*, 1370–1374.
3. Bienvenue, D. L.; Bennett, B.; Holz, R. C. J. Inhibition of the aminopeptidase from *Aeromonas proteolytica* by L-leucinethiol: Kinetic and spectroscopic characterization of a slow, tight-binding inhibitor–enzyme complex. *Inorg. Biochem.* **2000**, *78*, 43–54.
4. (a) Procter, D. J. The synthesis of thiols, selenols, sulfides, selenides, sulfoxides, selenoxides, sulfones and selenones. *J. Chem. Soc., Perkin Trans. 1* **1999**, 641–667; (b) Penning, T. D.; Akonas, L. J.; Djuric, S. W.; Haack, R. A.; Yu, S. S.; Michener, M. L.; Krivi, G. G.; Pyla, E. Y. Kelatorphan and related analogs: Potent and selective inhibitors of leukotriene A_4 hydrolase. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2517–2522.
5. (a) Tseng, S.-L.; Yang, T.-K. New β-amino thiols as efficient catalysts for highly enantioselective alkenylzinc addition to aldehydes. *Tetrahedron: Asymmetry* **2005**, *16*, 773–782; (b) Procter, D. J. The synthesis of thiols, selenols, sulfides, selenides, sulfoxides, selenoxides, sulfones, and selenones. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335–354.
6. (a) Brouwer, A. J.; Monnee, M. C. F.; Liskamp, R. M. J. An efficient synthesis of ***N***-protected β-aminoethanesulfonyl chlorides: Versatile building blocks for the synthesis of oligopeptidosulfonamides. *Synthesis* **2000**, 1579–1584; (b) Narendra, N.; Lalithamba, H. S.; Sureshbabu, V. V. An efficient one-pot access to trithiocarbonate-tethered peptidomimetics. *Tetrahedron Lett.* **2010**, *51*, 6169–6173; (c) Dehmel, F.; Weinbrenner, S.; Julius, H.; Ciossek, T.; Maier, T.; Stengel, T.; Fettis, K.; Burkhardt, C.; Weiland, H.; Beckers, T. Trithiocarbonates as a novel class of HDAC inhibitors: SAR studies, isoenzyme selectivity, and pharmacological profiles. *J. Med. Chem.* **2008**, *51*, 3985–3995.
7. Myllymaki, V. T.; Lindvall, M. K.; Koskinen, A. M. P. Computer-assisted discovery of novel amino acid derived sulfides for enantioselective epoxidation of aldehydes. *Tetrahedron* **2001**, *57*, 4629–4635.
8. (a) Kondo, M.; Uchida, H.; Kodama, H.; Kitajima, H.; Shimohigashi, Y. Synthesis of enkephalin analog with leucinthiol at C-terminus as probe for thiol group in opiate receptors. *Chem. Lett.* **1987**, 997–100; (b) Fournie-Zaluski, M.-C.; Coric, P.; Turcaud, S.; Lucas, E.; Noble, F.; Maldonado, R.; Roques, B. P. Mixed-inhibitor-prodrug as a new approach toward systemically active inhibitors of enkephalin-degrading enzymes. *J. Med. Chem.* **1992**, *35*, 2473–2481; (c) Han, M. S.; Oh, D. J.; Kim, D. H. Inhibition

of α-chymotrypsin with thiol-bearing substrate analogues in the presence of zinc ion. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 701–705.
9. Dutta, A. S.; Giles, M. B.; Gormley, J. J. Inhibitors of human leucocyte elastase: Peptides incorporating an α -azanorvaline residue or a thiomethylene linkage in place of a peptide bond. *J. Chem. Soc., Perkin Trans. 1* **1987**, 111–120.
10. (a) Sureshbabu, V. V.; Vishwanatha, T. M.; Vasantha, B. A simple synthesis of N^{β}-Fmoc/Z-amino alkyl Thiols and their use in the synthesis of N^{β}-Fmoc/Z-amino alkyl sulfonic acids. *Synlett* **2010**, *7*, 1037–1042; (b) Meinzer, A.; Breckel, A.; Thaher, B. A.; Manicone, N. Properties and reactions of substituted 1,2-thiazetidine 1,1-dioxide: Chiral mono- and bicyclic 1,2-thiazetidine 1,1-dioxide from α-amino acids. *Helv. Chim. Acta* **2004**, *87*, 90–105.
11. Mercey, G.; Bregeon, D.; Gaumont, A.-C.; Levillain, J.; Gulea, M. Efficient synthesis of primary 2-aminothiols from 2-aminoalcohols and methyldithioacetate. *Tetrahedron Lett.* **2008**, *49*, 6553–6555.
12. Martin, D. J.; Greco, C. C. Thiol synthesis. *J. Org. Chem.* **1968**, *33*, 1275–1276.
13. (a) Kurth, M. J.; Tahir, S. H.; Olmstead, M. M. A thioxanone-based chiral template: Asymmetric induction in the [2,3]-sigmatropic rearrangement of sulfur ylides: Enantioselective preparation of Cβ-chiral pent-4-enoic acids. *J. Org. Chem.* **1990**, *55*, 2286–2288; (b) Yankeelov, J. A.; Fok, Jr. K.-F.; Carothers, D. J. Peptide-gap inhibitors. Stereoselective synthesis of enantiomeric dipeptide analogs of glycylleucine which contain methylene thioether groups substituted for peptide linkages. *J. Org. Chem.* **1978**, *43*, 1623–1624.
14. Sureshbabu, V. V.; Naik, S. A.; Hemantha, H. P.; Narendra, N.; Das, U.; Row, T. N. G. N-Urethane-protected amino alkyl isothiocyanates: Synthesis, isolation, characterization, and application to the synthesis of thioureidopeptides. *J. Org. Chem.* **2009**, *74*, 5260–5266.