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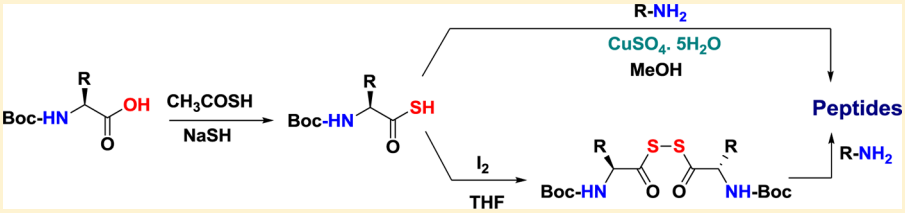
Thioacetic Acid/NaSH-Mediated Synthesis of *N*-Protected Amino Thioacids and Their Utility in Peptide Synthesis

Sachitanand M. Mali and Hosahudya N. Gopi*

Department of Chemistry, Indian Institute of Science Education and Research, Dr. Homi Bhabha Road, Pune 411 008, India

Supporting Information

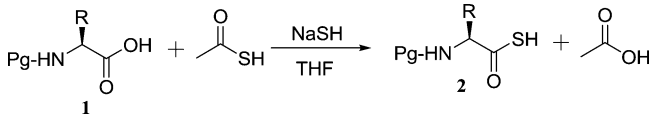


ABSTRACT: Thioacids are recently gaining momentum due to their versatile reactivity. The reactivity of thioacids has been widely explored in the selective amide/peptide bond formation. Thioacids are generally synthesized from the reaction between activated carboxylic acids such as acid chlorides, active esters, etc., and Na_2S, H_2S, or NaSH. We sought to investigate whether the versatile reactivity of the thioacids can be tuned for the conversion of carboxylic acids into corresponding thioacids in the presence of NaSH. Herein, we report that thioacetic acid- and NaSH-mediated synthesis of *N*-protected amino thioacids from the corresponding *N*-protected amino acids, oxidative dimerization of thioacids, crystal conformations of thioacid oxidative dimers, and the utility of thioacids and oxidative dimers in peptide synthesis. Our results suggest that peptides can be synthesized without using standard coupling agents.

INTRODUCTION

Sulfur in the form of thiols and thioacids plays a significant role in biology. The formation of covalent disulfide (R−S−S−R) bonds through the oxidation of thiols (R−SH) is a most distinctive property of sulfur, and these disulfide bonds are ubiquitous in nature. Further, the involvement of protein thioacids as "sulfide" donors in the biosynthesis of thiamin, thioquinolobactin, vitamin B1, and cysteine have been reported.[1−3] Wieland and colleagues in their preliminary investigation reported the potential of α-amino thioacids as acylating agents in the peptide synthesis as well as thioester strategy in the chemical ligation.[4] The versatile reactivity of thioacids (RCOSH) with various functional groups such as azides,[5−8] isonitriles,[9] sulfonamides,[10] nitroso derivatives,[11] isocyanates,[12] dinitrofluorobenzene,[13] aziridines,[14,15] and thiocarbamates[16] has been recently demonstrated in the amide bond formation. In addition, the affinity of the sulfur toward the metals has also been exploited in the synthesis of peptides using thioacids.[17−20] Danishefsky and colleagues showed the thioacid-mediated synthesis of peptides and glycopeptides in the presence of coupling additive HOBt.[21,22] Further, to support thioacids as possible precursors in the synthesis of polypeptides in primordial conditions, Orgel and colleagues demonstrated the *N*-acylation and polypeptide synthesis using thioacetic acid and α-amino thioacids, respectively, in the presence of oxidizing agents.[23,24] Due to the versatile chemistry of *N*-protected amino thioacids, various protocols have been developed for the synthesis of *N*-protected amino thioacids.[25−30] Most of these protocols involve the activation of carboxylic acid functional group followed by the nucleophilic substitution using sulfur reagents such as NaSH, Na_2S, Fm-SH [(9*H*-fluoren-9-yl)methanethiol], etc. For the activation of free carboxylic acids, various strategies including carbodiimides, active esters, acid chlorides, etc. have been utilized. All these activated carboxylic acid derivatives have also been practiced directly in the synthesis of peptides/amides. In addition, epimerization of the amino acids has been observed in the direct transformation of carboxylic acids to the thioacids using Lawesson's reagent.[30] Inspired by the versatile reactivity of thioacids, thioesters, and disulfide and persulfide (R−S−S−H) formation from sulfur, we anticipate that by tuning the reaction conditions it may be possible to synthesize the α-amino thioacids directly from α-amino acids in the presence of thioacetic acid and NaSH (Scheme 1), which can be further utilized for peptide synthesis either in the presence or absence of metal salts and coupling additives. Herein, we are reporting the thioacetic acid- and NaSH-mediated synthesis of *N*-protected amino thioacids, oxidation of thioacids to the

Scheme 1. Thioacetic Acid and NaSH-Mediated Synthesis of *N*-Protected α-Amino Thioacids Directly from the Corresponding *N*-Protected α-Amino Acids



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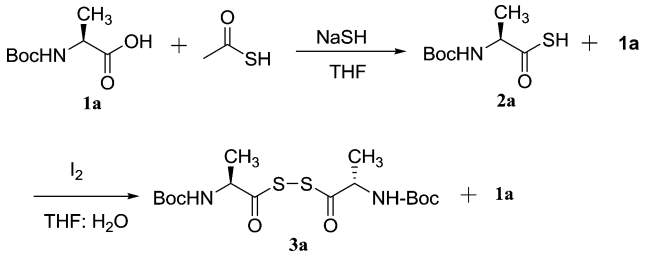
corresponding oxidative dimers, and their applications in peptide synthesis. Using *N*-protected amino thioacids as well as their oxidative dimers, various peptides were synthesized in moderate to good yields in the presence and absence of metals, respectively.

RESULTS AND DISCUSSION

To realize our hypothesis, the *N*-Boc-Ala (**1a**) was treated with thioacetic acid and NaSH in THF. The reaction mixture was subjected to the mass spectral analysis after stirring for ∼36 h at room temperature. Instructively, the mass spectral results (see the Supporting Inforamtion) suggested the partial conversion of *N*-Boc-Ala (**1a**) to corresponding *N*-Boc-Ala-SH (**2a**). The schematic representation of the reaction is shown in Scheme 2.

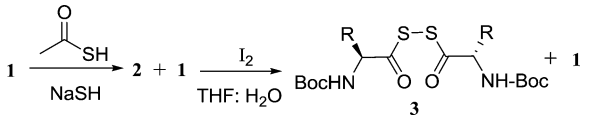
Scheme 2. Synthesis of Boc-Ala-SH from the Thioacetic Acid and NaSH and Subsequent Oxidative Dimerization of *N*-Boc-Ala-SH



Although the results were quite encouraging, we found it difficult to separate the pure *N*-Boc-Ala-SH from the reaction mixture as it is contaminated with unreacted Boc-Ala. We anticipate that thioacids can be selectively separated from the reaction mixture through the oxidative dimerization. In this regard, the excess thioacetic acid was removed from the reaction mixture through the evaporation under reduced pressure. The crude reaction mixture containing both **1a** and **2a**, after the aqueous workup, was subjected to the iodine mediated oxidation reaction[31] in THF and water in a ratio of 4:1 (Scheme 2). The pure Boc-Ala thioacid dimer (**3a**) was isolated after the aqueous workup and column purification with 40% yield. To further understand the necessity of thioacetic acid and NaSH in the conversion of *N*-protected amino acids to the corresponding thioacids, we performed two control reactions, one without thioacetic acid and the other without NaSH. The mass spectral analysis reveals that there is no formation of *N*-protected amino thioacids in both the control reactions, suggesting the requirement of thioacetic acid and NaSH for the formation of *N*-protected amino thioacids. In order to understand the role of solvents in the conversion of carboxylic acids to corresponding thioacids, we carried out the same experiment in DCM, EtOAc, MeOH, DMF, and THF; however, we found better yields of thioacids in THF compared to other solvents.

With these encouraging results, we subjected various other Boc-amino acids (Table 1) including the sterically hindered Boc-Aib (α-amino isobutyric acid) to the synthesis of corresponding thioacids mediated by the thioacetic acid and NaSH and subsequent oxidative dimerization. The list of *N*-Boc-amino thioacid oxidative dimers synthesized using the above protocol is given in Table 1. All *N*-Boc-thioacid oxidative dimers (**3a**−**e**) were isolated after the column purification in 25−40% overall yield. The compatibility of the reaction with

Table 1. Synthesis of *N*-Protected Amino Thioacid Oxidative Dimers Starting from the Corresponding Amino Acids



	Boc-AA (1)	Boc-AA-SH (2)	Boc-AA-S-S-AA-Boc (3)	yield (%)
a	Boc-Ala	Boc-Ala-SH	Boc-Ala-S-S-Ala-Boc	40
b	Boc-Leu	Boc-Lue-SH	Boc-Leu-S-S-Leu-Boc	35
c	Boc-Phe	Boc-Phe-SH	Boc-Phe-S-S-Phe-Boc	31
d	Boc-Val	Boc-Val-SH	Boc-Val-S-S-Val-Boc	33
e	Boc-Aib	Boc-Aib-SH	Boc-Aib-S-S-Aib-Boc	25
f	Fmoc-Leu	Fmoc-Leu-SH	Fmoc-Leu-S-S-Leu-Fmoc	26

Fmoc-protected amino acids was studied using Fmoc-Leu. The thioacid oxidative dimer of Fmoc-Leu (**3f**) was isolated in similar yields as that of Boc-amino acids. The results suggest that this method is compatible for both *N*-Fmoc and *N*-Boc protecting groups. We anticipate that the lower yields of the oxidative dimers are probably due to the dissociation/hydrolysis of thioacid disulfides during the aqueous workup and column chromatography. To validate our assumption, the solution of pure thioacid dimer **3d** in THF was treated with 10% Na_2CO_3 solution. The TLC and mass spectral analyses suggests (see Supporting Information) that dissociation of thioacid dimer into corresponding *N*-protected amino acids and thioacids, indicating the instability of thioacid oxidative dimers in the aqueous solution.

However, out of all the thioacid oxidative dimers in the Table 1, we were able to get the single crystals for **3a** and **3e**, and their X-ray structures are shown in Figure 1. Analysis of the crystal structures reveals that the disulfides adopted the *gauche* conformation ($g \approx \pm 60°$) with a S−S bond distance of 2.03 Å.

The remarkable results of the thioacetic acid- and NaSH-mediated conversion of a variety of *N*-protected amino acids to the corresponding amino thioacids enable us to propose the possible mechanism of the reaction. The schematic representation is shown in Scheme 3. Both Orgel[23,24] and Danishefsky[21,22] in their pioneering work proposed that diacyl disulfide and thioacid persulfide are the probable intermediates in the thioacid-mediated amide bond synthesis. We speculate that the treatment of NaSH with the thioacetic acid may lead to the formation of activated thioacetic acid persulfide **A**. The persulfide formation may be facilitated by the open air oxidation as the reactions were performed in the open flasks and hydrated NaSH. The reaction between **A** and the *N*-Boc-amino acid (**1**) leads to the formation of a mixed anhydride, **C**. The in situ generated reactive mixed anhydride (**C**) further reacted with NaSH to give thioacid **2**. In addition, persulfide **A** can also be expected from the reaction between oxidative dimer (**B**) and NaSH. To confirm whether the mixed anhydride **C** will undergo thionation reaction, we synthesized the mixed anhydride by reacting Boc-Ala with acetic anhydride in the presence of DIPEA (Scheme 4). The in situ generated mixed anhydride was further treated with NaSH. After the aqueous workup, the Boc-Ala-SH was isolated in 95% yield, suggesting that mixed anhydride **C** is a competent intermediate in the formation of *N*-protected amino thioacids. In a control reaction under inert argon atmosphere, we observed drastic decrease in the yield of *N*-protected thioacid (**2a**), indicating the requirement of open air to facilitate the formation of **A**.

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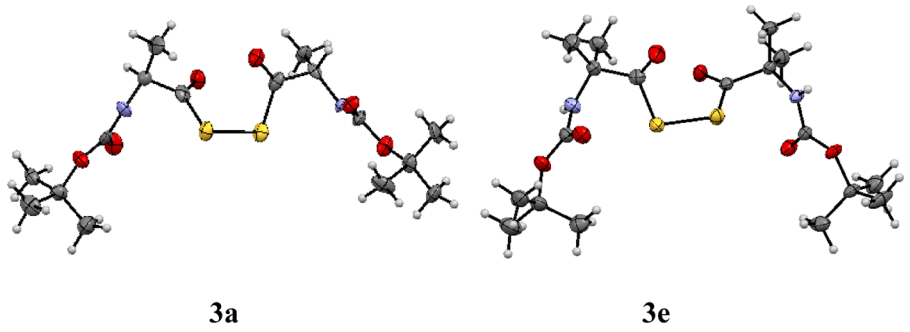
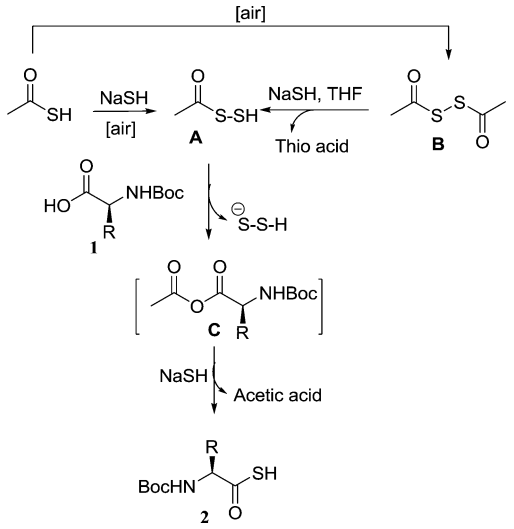


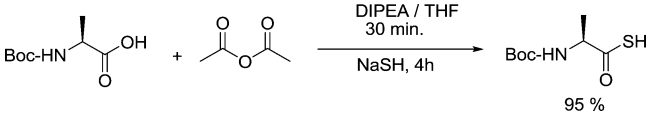
3a 3e

Figure 1. X-ray structures of **3a** [$(Boc\text{-}Ala\text{-}S)_2$] and **3e** [$(Boc\text{-}Aib\text{-}S)_2$].

Scheme 3. Mechanism of the Synthesis of α-Amino Thioacid from α-Amino Acids Mediated by Thioacetic Acid and NaSH



Scheme 4. Synthesis of Thioacids from in Situ Generated Mixed Anhydrides



In order to understand whether these *N*-protected-thioacid oxidative dimers can undergo coupling reactions with free amino acid esters and peptides, we subjected them for the coupling reactions with various amino esters in THF. The schematic representation of the peptide synthesis is shown in Scheme 5. Results reveal that all thioacid oxidative dimers undergo coupling reactions with amines and peptides without any additives. The coupling reactions were found to be rapid, and the products were isolated within 30 min. The list of peptides synthesized using *N*-protected diacyl disulfides is given in Table 2. Further, these coupling reactions also suggest that

Scheme 5. Synthesis of Peptides from Diacyl Disulfides

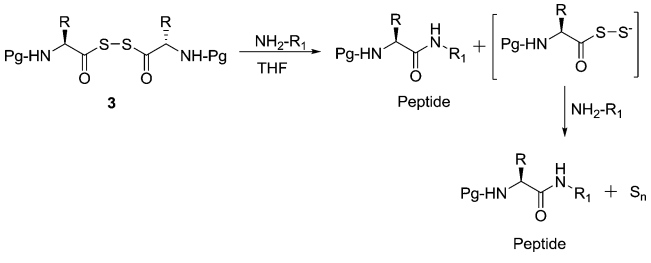


Table 2. Peptides Synthesized from Diacyl Disulfides

no.	3	NH_2-R1	peptides	yield (%)
P1	**3a**	H-Val-OMe	Boc-Ala-Val-OMe	75
P2	**3a**	H-Trp-OMe	Boc-Ala-Trp-OMe	86
P3	**3b**	H-Phe-Ala-OBn	Boc-Leu-Phe-Ala-OBn	84
P4	**3b**	H-Trp-Val-OMe	Boc-Leu-Trp-Val-OMe	70
P5	**3c**	H-Val-OMe	Boc-Phe-Val-OMe	74
P6	**3c**	H-D-Val-OMe	Boc-Phe-D-Val-OMe	76
P7	**3c**	H-Ala-OMe	Boc-Phe-Ala-OMe	81
P8	**3d**	H-Ala-Trp-OMe	Boc-Val-Ala-Trp-OMe	73
P9	**3e**	H-Val-OMe	Boc-Aib-Val-OMe	65
P10	**3e**	H-Trp-OMe	Boc-Aib-Trp-OMe	74
P11	**3f**	H-Ala-Leu-OMe	Fmoc-Leu-Ala-Leu-OMe	84

thioacid persulfide, a reactive intermediate after the first coupling reaction, can undergo a coupling reaction with free amines as postulated by Danishefsky and colleagues.[21,22] As both acyl groups in the diacyl disulfides are involved in the acylation reactions, it requires 2 equiv of free amine to complete the reaction. The dipeptides **P1** and **P2** were synthesized by reacting **3a** with methyl esters of valine and tryptophan, respectively. The tripeptides **P3** and **P4** were synthesized from **3b** by reacting with benzyl and methyl esters of the dipeptides Phe-Ala and Trp-Val, respectively. Further, **3c** was coupled with methyl esters of L-Val, D-Val, and Ala to give dipeptides **P5**, **P6**, and **P7**, respectively. Similarly, tripeptide **P8** was isolated from the reaction between **3d** and the methyl ester of dipeptide Ala-Trp. To ensure whether the sterically hindered thioacid dimers can undergo peptide coupling reactions, we subjected *N*-Boc-Aib thioacid dimer (**3e**) to the coupling reaction with the methyl ester of valine as well as the methyl ester of Trp to give dipeptides **P9** and **P10**, respectively. Peptide **P11** was synthesized from the reaction between **3f** and the free dipeptide Ala-Leu methyl ester. All peptides (**P1**−**P11**) were isolated in moderate to good yields and are given in Table 2. The only byproduct that we observed in the coupling reaction is S_n (poly sulfur, n = 1, 2, 3, etc). Overall, these findings signify that peptides can be synthesized without using coupling reagents, additives and the activated carboxylic acids of *N*-protected amino acids. Further, to understand the racemization during the peptides synthesis, we coupled **3c** with the methyl ester of racemic mixture of (±)-Val and subjected it to chiral HPLC analysis along with diastereomeric dipeptides **P5** and **P6**. The HPLC profiles of these peptides are

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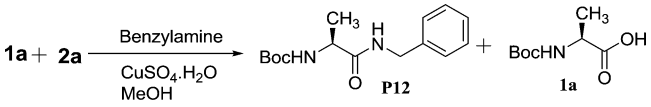
given in the Supporting Information. Single peaks were observed for peptides **P5** and **P6** at t_R 12.15 and 13.23 min respectively, whereas the diastereomeric mixture obtained after the coupling of **3c** with (±) Val methyl ester showed two peaks at t_R 12.20 and 13.28 min, corresponding to the individual **P5** and **P6**, respectively. Analysis suggests that no racemization during the synthesis of these dipeptides and it was further supported by the ^{1}H NMR.

Although the coupling reactions of thioacid oxidative dimers were found to be mild and clean and required no additional coupling agents, base, or additives; however, the major remaining issue is the dissociation of thioacid dimers during the aqueous workup. We hypothesized that instead of the isolation of thioacid oxidative dimers we can selectively couple the *N*-protected amino thioacids from the reaction mixture (Scheme 1) containing carboxylic acids with free amines in the presence of 30 mol % copper sulfate ($CuSO_4{\cdot}5H_2O$). To validate, we subjected the crude mixture containing unreacted **1a** and thioacid **2a** for the coupling reaction with benzylamine in the presence of 30 mol % copper sulfate in methanol as reported earlier (Scheme 6).[19,20] The *N*-acylated product **P12**

Scheme 6. Selective Amide Bond Formation from the Crude Reaction Mixture Containing Unreacted Boc-Ala and Boc-Ala-SH



was isolated in 78% yield. The unreacted *N*-protected amino acid was removed through aqueous workup. Motivated by this result, we extend the same methodology for the synthesis of peptides. Using this methodology, peptides **P1**, **P2**, **P5**, and **P7** were synthesized and isolated in good yields. Along with these peptides, we also synthesized dipeptides **P13** and **P14** and isolated them in good yields after the column purification (Table 3).

In comparison of thioacid dimers versus copper sulfate mediated thioacid peptide coupling reactions, better yields were observed in the case of thioacid dimer mediated coupling reactions. Overall, these results indicate that peptides can be synthesized through selective coupling of *N*-protected thioacids in the presence of *N*-protected carboxylic acids.

CONCLUSION

In conclusion, we have demonstrated the potential of thioacetic acid and NaSH in the synthesis of *N*-protected α-amino thioacids and their utility in peptide synthesis. The *N*-protected thioacids were selectively oxidized to the corresponding thioacid oxidative dimers in the presence of unreacted *N*-protected amino acids and showed their utility in peptide synthesis. Though yields of these diacyl disulfides are low, however, their coupling reactions were found to be very neat, fast and high yielding in comparison with the copper sulfate mediated synthesis of peptides from the corresponding thioacids. We are presently investigating how to improve the yields of the thioacid oxidative dimers and their utility in the solid-phase peptide synthesis. The results presented here suggest that peptides can be synthesized without using standard coupling reagents. The involvement of the thioacetic acid in the conversion of amino acids to the corresponding thioacids in the presence of NaSH and the peptides coupling reactions from the both thioacid oxidative dimers as well as thioacids indicate the significant role of thioacids in the synthesis of polypeptide in prebiotic era. Overall, the chemistry reported here may open new opportunities to rethink the amide bond formation[32] in both chemistry and biology.

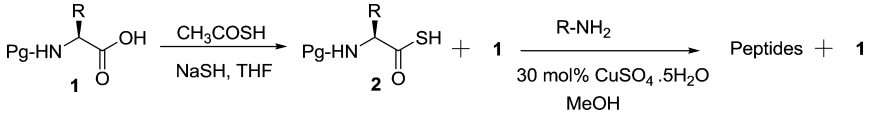
EXPERIMENTAL SECTION

General Information. All amino acids, thioacetic acid, *N*-hydroxysuccinamide, di-*tert*-butyl dicarbonate, $CuSO_4{\cdot}5H_2O$, NaSH, and THF were used as commercially available. Column chromatography was performed on silica gel (100−200 mesh). ^{1}H and ^{13}C NMR were recorded on a 400 MHz instrument (100 MHz for ^{13}C) using the residual solvent signals as an internal reference. The chemical shifts (δ) are reported in ppm, and coupling constants (J) are given in hertz. IR spectra were recorded on an FT-IR spectrophotometer using KBr pellets. High-resolution mass spectra were obtained from an ESI-TOF MS spectrometer.

General Procedure for the Synthesis of *N*-Protected Amino Thioacid Oxidative Dimers. In a 50 mL round-bottom (RB) flask was dissolved *N*-protected amino acid (10 mmol) in 15 mL of dry THF. This solution was then treated with NaSH (20 mmol) and thioacetic acid (10 mmol) at room temperature. After the reaction mixture was stirred for about 36 h in open air, the solvent was evaporated under reduced pressure. The residue was diluted with water (50 mL) and acidified with 5% HCl (pH ∼ 2). This aqueous solution was extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give *N*-protected amino thioacid which was used for oxidative dimerization without further purification.

The *N*-protected amino thioacid obtained from the above procedure was dissolved in a THF/H_2O (4:1, 20 mL/5 mL) solvent mixture at room temperature. To this solution was added iodine (10 mmol). The reaction mixture was stirred for about 12 h. The solvent was evaporated under reduced pressure. The residue was diluted with water (40 mL) and extracted with ethyl acetate (30 mL × 3). The

Table 3. List of the Thioacid and Peptides Synthesized by Using NaSH and Thioacetic Acid



entry	thioacid	amine	peptide	yield (%)
1	Boc-Ala-SH	H_2N-Val-OMe	P1	67
2	Boc-Ala-SH	H_2N-Trp-OMe	P2	63
3	Boc-Phe-SH	H_2N-Val-OMe	P5	65
4	Boc-Phe-SH	H_2N-Ala-OMe	P7	69
5	Boc-Ser(O^tBu)-SH	H_2N-Trp-OMe	Boc-Ser(O^tBu)-Trp-OMe (P13)	65
6	Cbz-Leu-SH	H_2N-Ala-OMe	Cbz-Leu-Ala-OMe (P14)	60

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combined organic layer was washed with 10% aq Na_2CO_3 and brine and dried over anhydrous Na_2SO_4. The combined organic layer was evaporated under reduced pressure to give *N*-protected amino thioacid dimer. The pure thioacid oxidative dimer was obtained after the silica gel column purification using ethyl acetate and petroleum ether.

General Procedure for the Synthesis of Peptides Using *N*-Protected Amino Thioacid Oxidative Dimers. The *N*-protected amino thioacid oxidative dimer (0.5 mmol) was dissolved in dry THF at room temperature. To this solution was added the methyl ester of amino acid or *N*-terminal free peptide (1.5 mmol in ∼2 mL ethyl acetate). The reaction mixture was stirred for about 30 min. After completion of the reaction (as monitored by TLC), the reaction mixture was diluted with ethyl acetate (50 mL) and washed with 5% aq HCl, 10% Na_2CO_3, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude peptide, which was purified by column chromatography using ethyl acetate and petroleum ether.

Synthesis of Boc-Ala-SH by Using Boc-Ala-OH, NaSH, and Acetic Anhydride. In a 50 mL RB flask, Boc-Ala-OH (0.945 g, 0.5 mmol) was dissolved in 7 mL of dry THF. To this solution was added diisopropylethylamine (1 mmol). This reaction mixture was then cooled to 0 °C prior to addition of acetic anhydride (0.510 g, 0.5 mmol) and stirred for another 30 min. The reaction mixture was treated NaSH (0.308 g, 0.55 mmol) and stirred for another 4 h. After completion of the reaction (indicated by mass spectra), the solvent THF was evaporated and residue was treated with water (25 mL) and acidified with 5% HCl to reach pH ∼ 2. This aqueous layer was then extracted with ethyl acetate (20 mL × 3), washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to get Boc-Ala-SH in 95% (0.974 g).

General Procedure for the Synthesis of Di/Tripeptides by Using *N*-Protected Amino Thioacids and Copper Sulfate. The *N*-protected amino thioacid (10 mmol) obtained by the above procedure was dissolved in distilled methanol (10 mL). To this solution was added the methyl ester of amino acid or *N*-terminal free peptide (12 mmol) with stirring. This reaction mixture was treated with 30 mol % of $CuSO_4{\cdot}5H_2O$. After 5 min, the clean reaction mixture was converted to a dark brown turbid solution indicating the completion of the reaction (also monitored by TLC). The reaction mixture was centrifuged, and the residue was further washed with methanol. The combined methanol solution was evaporated under reduced pressure. The residue was then dissolved in ethyl acetate (80 mL), washed with 10% aq Na_2CO_3, 5% aq HCl, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The product was purified by column chromatography using ethyl acetate and petroleum ether.

*(S)-2-((tert-Butoxycarbonyl)amino)propanoic dithioperoxyanhydride [(Boc-Ala-S)$_2$] (**3a**):* white powder (0.82 g, 40%); mp = 123−125 °C; $[\alpha]^{25}_D$ +20 (*c* 0.1, MeOH); UV (λ_{max}) = 231 nm; IR ν (cm^{-1}) 3379, 2972, 1705, 1507, 1367, 1271, 1241, 1164, 1048, 1031, 965, 912; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.07 (d, *J* = 8 Hz, 2H), 4.54 (t, *J* = 6 Hz, 2H), 1.48 (s, 18H), 1.45 (d, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 199.6, 154.8, 80.9, 56.3, 28.2, 18.7; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{28}N_2NaO_6S_2$ $[M + Na]^+$ = 431.1286, obsd $[M + Na]^+$ = 431.1287.

*(S)-2-((tert-Butoxycarbonyl)amino)-4-methylpentanoic dithioperoxyanhydride [(Boc-Leu-S)$_2$] (**3b**):* white powder (0.87 g, 35%); mp = 106−108 °C; $[\alpha]^{25}_D$ +2 (*c* 0.1, MeOH); UV (λ_{max}) = 231 nm; IR ν (cm^{-1}) 3395, 2973, 1719, 1701, 1495, 1393, 1366, 1235, 1162, 1052, 870; ^{1}H NMR (400 MHz; $CDCl_3$); δ 4.97 (d, *J* = 8, 2H), 4.51 (br, 2H), 1.74 (t, *J* = 6 Hz, 4H), 1.60−1.57 (m, 2H), 1.47 (s, 18H), 0.96 (dd, *J* = 8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$); 196.7, 155.0, 80.8, 59.2, 41.0, 28.2, 24.6, 22.9, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{40}N_2NaO_6S_2$ $[M + Na]^+$ = 515.2225, obsd $[M + Na]^+$ = 515.2228.

*(S)-2-((tert-Butoxycarbonyl)amino)-3-phenylpropanoic dithioperoxyanhydride [(Boc-Phe-S-)$_2$] (**3c**):* white powder (0.868 g, 31%); mp = 137−139 °C; $[\alpha]^{25}_D$ −14 (*c* 0.1, MeOH); UV (λ_{max}) = 209 and 252 nm; IR ν (cm^{-1}) 3337, 2972, 2928, 1733, 1502, 1449, 1368, 1224, 1163,1053, 849, 750, 701; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.37−7.23 (m, 10H), 5.01 (br, 2H, 4.81 (br, 2H), 3.27−3.14 (m, 4H), 1.44 (s, 18H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 196.1, 154.9, 135.0, 129.3, 128.8, 127.3, 80.9, 81.0, 61.0, 37.8, 28.1 HRMS (ESI) *m*/*z* calcd for $C_{28}H_{36}N_2NaO_6S_2$ $[M + Na]^+$ = 583.1912, obsd $[M + Na]^+$ = 583.1919.

*(S)-2-((tert-Butoxycarbonyl)amino)-3-methylbutanoic dithioperoxyanhydride [(Boc-Val-S)$_2$] (**3d**):* white powder (0.8 g, 33%); mp = 127−129 °C; $[\alpha]^{25}_D$ +18 (*c* 0.1, MeOH); UV (λ_{max}) = 231 nm; IR ν (cm^{-1}) 3383, 2961, 1721, 1705, 1504, 1368, 1250, 1167, 1057, 1019; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.09 (d, *J* = 8 Hz, 2H), 4.42 (q, *J* = 4 Hz, 2H), 2.38−2.34 (m, 2H), 1.48 (s, 18H), 1.0 (dd, *J* = 8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 195.9, 155.3, 80.8, 65.3, 31, 28.2, 19.1, 16.8; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{36}N_2NaO_6S_2$ $[M + Na]^+$ = 487.1912, obsd $[M + Na]^+$ = 487.1925.

*2-((tert-Butoxycarbonyl)amino)-2-methylpropanoic dithioperoxyanhydride [(Boc-Aib-S)$_2$] (**3e**):* white powder (0.54 g, 25%); mp = 167−169 °C; UV (λ_{max}) = 231 nm; IR ν (cm^{-1}) 3368, 2980, 2929, 1712, 1507, 1386, 1366, 1274, 1253, 1159, 970, 878, 828; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.09 (br, 2H), 1.55 (s, 12H), 1.46 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) 198.3, 153.9, 80.6, 62.5, 28.2, 25.5; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{32}N_2NaO_6S_2$ $[M + Na]^+$ = 459.1599, obsd $[M + Na]^+$ = 459.1592.

*2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-4-methylpentanoic dithioperoxyanhydride [(Fmoc-Leu-S-)$_2$] (**3f**):* white powder (0.95 g, 26%); mp = 154−156 °C; $[\alpha]^{25}_D$ −14 (*c* 0.1, MeOH); UV (λ_{max}) = 212, 265, 289, 300 nm; IR ν (cm^{-1}) = 3387, 2956, 2922, 2861, 1703, 1522, 1447, 1381, 1323, 1246, 1122, 1045, 738, 547; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8 Hz, 4H), 7.62 (t, *J* = 6 Hz, 4H), 7.44−7.31 (m, 8H), 5.21 (d, *J* = 8 Hz, 1H), 5.05 (d, *J* = 8 Hz, 1H), 4.67−4.42 (m, 6H), 4.25 (t, *J* = 6 Hz, 2H), 0.93 (dd, *J* = 6, 6 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 196.1, 155.6, 143.6, 141.3, 127.7, 127.1, 124.9, 120.0, 67.1, 60.4, 59.7, 59.4, 47.2, 41.0, 24.6, 23.0, 21.3; HRMS (ESI) *m*/*z* calcd for $C_{42}H_{44}N_2O_6S_2$ $[M + Na]^+$ = 759.2538, obsd $[M + Na]^+$ = 759.2536.

*Boc-Ala-Val-OMe (**P1**):*[33] white powder (0.226g, 75%); $[\alpha]^{25}_D$ −44 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.76 (d, *J* = 4, 1H), 5.09 (d, *J* = 8 Hz, 1H), 4.51 (dd, *J* = 8 Hz, 1H), 4.18 (br, 1H), 3.72 (s, 3H), 2.20−2.21 (m, 1H), 1.43 (s, 9H), 1.34 (d, *J* = 8 Hz, 3H), 0.90 (dd, *J* = 4 Hz, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 172.2, 155.5, 80.0, 56.9, 52.0, 49.9, 31.1, 28.1, 18.8, 17.6; MALDI TOF/TOF *m*/*z* calcd for $C_{14}H_{26}N_2NaO_5$ (M + Na) is 325.1739 obsd 325.1589.

*Boc-Ala-Trp-OMe (**P2**):* white powder (0.334 g, 86%); $[\alpha]^{25}_D$ −12 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.35 (d, *J* = 8 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H), 7.35 (d, *J* = 8 Hz, 1H), 7.18 (t, *J* = 8 Hz, 1H), 7.11 (t, *J* = 8 Hz, 1H), 7.01 (br, 1H), 6.63 (d, *J* = 8 Hz, 1H), 5.01 (br, 1H), 4.92−4.87 (m, 1H), 4.16−4.14 (m, 1H), 3.66 (s, 3H), 3.32 (d, *J* = 8 Hz, 2H), 1.41 (s, 9H), 1.29 (d, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.3, 172.0, 136.0, 127.5, 123.0, 122.1, 119.5, 118.4, 111.2, 109.6, 80.0, 52.9, 52.3, 28.2, 27.5, 18.3; MALDI TOF/TOF *m*/*z* calcd for $C_{20}H_{27}N_3NaO_5$ (M + Na) is 412.1848, obsd 412.1998.

*Boc-Leu-Phe-Ala-OBn (**P3**):* white powder (0.452 g, 84%); $[\alpha]^{25}_D$ −36 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.38−7.32 (m, 5H), 7.25−7.17 (m, 5H), 6.71−6.69 and 6.67−6.65 (d, *J* = 8 Hz, 1H) and (d, *J* = 8 Hz, 1H), 5.15 (s, 2H), 4.83 (d, *J* = 8 Hz, 1H), 4.69 (q, *J* = 8 Hz, *J* = 4 Hz, 1H), 4.56−4.49 (m, *J* = 8 Hz, 1H), 4.05 (br, 1H), 3.14−3.02 (m, 2H), 1.62−1.55 (m, 2H), 1.4 (s, 9H), 1.34 (d, *J* = 8 Hz, 3H), 0.90 (t, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.3, 172.0, 170.1, 155.6, 136.3, 135.3, 129.2, 128.5, 128.3, 128.1, 126.9, 80.2, 67.0, 53.8, 48.2, 40.9, 37.8, 29.6, 28.2, 24.6, 22.9, 21.7, 17.9; MALDI TOF/TOF *m*/*z* calcd for $C_{30}H_{41}N_3NaO_6$ (M + Na) 562.2893, obsd 562.3182.

*Boc-Leu-Trp-Val-OMe (**P4**):*[34] white powder (0.371 g, 70%); $[\alpha]^{25}_D$ −28 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.23 (br, 1H), 7.71 (d, *J* = 8 Hz, 1H), 7.35 (d, *J* = 8 Hz, 1H), 7.20−7.11 (m, 3H), 6.88 (d, *J* = 8 Hz, 1H), 6.34 (d, *J* = 8 Hz, 1H), 4.83 (d, *J* = 8 Hz, 1H), 4.76 (br, 1H), 4.13 (q, *J* = 4 Hz, 1H), 4.13 (q, *J* = 8 Hz, 1H), 3.63 (s, 3H), 3.33 (dd, *J* = 8 Hz, *J* = 4 Hz, 1H), 3.15 (dd, *J* = 8 Hz, *J* = 4 Hz, 1H), 2.03−1.97 (m, 1H), 1.63 (t, *J* = 6 Hz, 2H), 1.39 (s, 9H), 0.91 (d, *J* = 4 Hz, 6H), 0.77 (dd, *J* = 8 Hz, *J* = 8 Hz 6H); ^{13}C NMR (100 MHz,

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$CDCl_3$) 171.9, 171.7, 171,2, 156.0, 136.0, 127.4, 123.3, 122.0, 119.4, 118.3, 111.3, 109.3, 80.2, 52.6, 52.3, 51.4,, 30.4, 28.2, 27.4, 24.5, 22.8, 17.3; MALDI TOF/TOF *m*/*z* calcd for $C_{28}H_{42}N_4NaO_6$ (M + Na) is 553.3002, obsd 553.3280.

Boc-Phe-Val-OMe (**P5**):[35] white powder (0.279 g, 74%); $[\alpha]^{25}_D$ −18 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.35−7.26 (m, 5H), 6.45 (d, *J* = 8 Hz, 1H), 5.10 (br, 1H), 4.51 (q, *J* = 4 Hz, 1H), 4.4 (br, 1H), 3.74 (s, 3H), 3.12 (d, *J* = 8 Hz, 2H), 2.18−2.12 (m, 1H), 1.46 (s, 9H), 0.90 (dd, *J* =4 Hz, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.7, 171.1, 155.3, 136.5, 129.2, 128.5, 126.8, 80.1, 57.1, 55.7, 52.0, 37.9, 31.2, 28.1, 18.7, 17.6; MALDI TOF/TOF *m*/*z* calcd for $C_{20}H_{30}N_2O_5$ (M + Na) 401.2052, obsd (M + Na) 401.2318.

Boc-Phe-^{D}*Val-OMe* (**P6**):[36] white powder (0.287 g, 76%); $[\alpha]^{25}_D$ +6 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.35−7.25 (m, 5H), 6.45 (d, *J* = 4 Hz, 1H), 5.06 (br, 1H), 4.51 (br, 1H), 4.45 (br, 1H), 3.75 (s, 3H), 3.12 (d, *J* = 8 Hz, 2H), 2.13−2.06 (m,, 1H), 1.46 (s, 9H), 0.83 (dd, *J* = 8 Hz, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.9, 171.1, 155.3, 136.5, 129.2, 128.7, 126.9, 80.2, 57.0, 55.8, 52.1, 38.2, 31.0, 28.2, 18.7, 17.5; MALDI TOF/TOF *m*/*z* calcd for $C_{20}H_{30}N_2O_5$ (M + Na) 401.2052, obsd (M + Na) 401.2291.

Boc-Phe-Ala-OMe (**P7**): white powder (0.283 g, 81%); $[\alpha]^{25}_D$ −22 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.32−7.20 (m, 5H), 6.47 (d, *J* = 4 Hz, 1H), 5.03 (d, *J* = 8 Hz, 1H), 4.56−4.49 (m, 1H), 4.38−4.37 (m, 1H), 3.72 (s, 3H), 3.08 (t, *J* = 6 Hz, 2H), 1.41 (s, 9H), 1.35 (d, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.8, 170.7, 155.3, 136.4, 129.3, 128.6, 126.9, 80.2, 55.5, 52.4, 48.0, 38.3, 28.2, 18.3; MALDI TOF/TOF *m*/*z* calcd for $C_{18}H_{26}N_2O_5$ (M + Na) = 373.1739, obsd (M + Na) 373.1906.

Boc-Val-Ala-Trp-OMe (**P8**): white powder (0.356 g, 73%); $[\alpha]^{25}_D$ −34 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.56 (br, 1H), 7.48 (d, *J* = 8 Hz, 1H), 7.33 (d, *J* = 8 Hz, 1H), 7.16 (t, *J* = 8 Hz, 1H), 7.09 (t, *J* = 8 Hz, 1H), 7.00 (br, 1H), 6.78 (d, *J* = 8 Hz, 1H), 6.69 (d, *J* = 8 Hz, 1H), 5.12 (d, *J* = 8 Hz, 1H), 4.90−4.85 (m, 1H), 4.53−4.45 (m,1H), 3.94 (t, *J* = 8 Hz, 1H), 3.67 (s, 3H), 3.30 (d, *J* = 8 Hz, 2H), 2.06−2.00 (m, 1H), 1.45 (s, 9H), 1.32 (d, *J* = 8 Hz, 3H), 0.86 (dd, *J* = 8 Hz, *J* = 16 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$); 171.9, 171.8, 171.5, 136.0, 127.4, 123.3, 122.0, 119.4, 118.3, 111.3, 109.3, 80.2, 59.8, 52.8, 52.4, 48.6, 30.7, 29.6, 28.7, 19.1, 17.2; MALDI TOF/TOF *m*/*z* calcd for $C_{25}H_{36}N_4NaO_6$ (M + Na) 511.2532, obsd 511.2528.

Boc-Aib-Val-OMe (**P9**): white powder (0.205 g, 65%); $[\alpha]^{25}_D$ −6 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.02 (br, 1H), 4.94 (br, 1H), 4.52 (q, *J* = 4 Hz, 1H), 3.71 (s, 3H), 2.19−2.13 (m, 1H), 1.51 and 1.47 (s, 6H), 1.43 (s, 9H), 0.92 (dd, *J* = 8 Hz, *J* = 4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.4, 172.4, 154.5, 80.1, 57.0, 56.8, 52.0, 31.1, 28.3, 28.2, 26.0, 18.9, 17.5; MALDI TOF/TOF *m*/*z* calcd for $C_{15}H_{28}N_2NaO_5$ (M + Na) 339.1896, obsd 339.1841.

Boc-Aib-Trp-OMe (**P10**): white powder (0.298 g, 74%); $[\alpha]^{25}_D$ +2 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.43 (br, 1H), 7.54 (d, *J* = 8 Hz, 1H), 7.34 (d, *J* = 4 Hz, 1H), 7.18−7.03 (m, 3H), 6.89 (br, 1H), 5.02 (d, *J* = 4 Hz, 1H), 4.91−4.85 (m, 1H), 3.63 (s, 3H), 3.36−3.25 (m, 2H), 1.43 and 1.39 (s, 6H) and (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.4, 172.4, 154.5, 136.0, 127.4, 122.9, 121.9, 119.3, 118.4, 111.2, 109.7, 79.9, 56.6, 53.0, 52.2, 28.1, 27.6, 24.4; MALDI TOF/TOF *m*/*z* calcd for $C_{21}H_{29}N_3NaO_5$ (M + Na) is 426.2005, obsd 426.1302.

Fmoc-Leu-Ala-Leu-OMe (**P11**): white powder (0.460 g, 84%); $[\alpha]^{25}_D$ −50 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8 Hz, 2H), 7.58 (d, *J* = 8 Hz, 2H), 7.39 (t, *J* = 6 Hz, 2H), 7.30 (t, *J* = 8 Hz, 2H), 6.77 (d, *J* = 16 Hz, 2H), 7.30 (t, *J* = 8 Hz, 2H), 6.77 (d, *J* = 16 Hz, 2H), 5.43 (d, *J* = 8 Hz, 1H), 4.56 (br, 2H), 4.47−4.34 (m, 2H), 4.20 (t, *J* = 6 Hz, 2H), 3.71 (s, 3H), 1.62−154 (m, 6H), 1.37 (d, *J* = 8 Hz, 3H), 0.92 (t, *J* = 6 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.1, 172.2, 171.7, 156.2, 143.7, 141.3, 127.7, 127.0, 125.0, 120.0, 67.0, 54.0, 52.3, 50.8, 48.7, 47.1, 41.7, 42.3, 29.7, 24.7, 24.6, 23.0, 21.8, 18.0; MALDI TOF/TOF *m*/*z* calcd for $C_{31}H_{41}N_3NaO_6$ [M + Na] 574.2893, obsd 574.3691.

Boc-Ala-NHBn (**P12**):[19] white solid (1.5 g, 78%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.32−7.22 (m, 5H), 6.821 (br, 1H), 5.201 (br, 1H), 4.412 (br, 2H), 4.226 (br, 1H), 1.395 (s, 9H), 1.376−1.357 (d, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) 172.7, 155.6, 138.1, 128.7, 127.4, 80.1, 50.2, 43.4, 28.3, 18.5; MALDI TOF/TOF *m*/*z* calcd for $C_{15}H_{22}N_2O_3$ (M + Na) is 301.1528, obsd 301.1804.

Boc-Ser(OtBu)-Trp-OMe (**P13**): gummy (1.94 g, 65%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.331 (br, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.34 (d, *J* = 8 Hz, 1H), 7.31 (br, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 6.8 Hz, 1H), 7.01 (d, *J* = 1 Hz, 1H), 5.42 (d, *J* = 5.2 Hz, 1H), 4.5 (m, 1H), 4.18 (br, 1H), 3.75 and 3.37 (dd, 2H), 3.30 (br, 2H), 3.63 (s, 3H), 1.42 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.0, 170.3, 155.5, 136.1, 127.6, 123.0, 122.2, 119.6, 118.7, 111.3, 109.9, 80.0, 74.0, 61.8, 60.5, 54.2, 53.1, 52.3, 28.3, 27.3, 21.1, 14.3. MALDI TOF/TOF *m*/*z* calcd for $C_{24}H_{35}N_3O_6$ (M + Na) 484.2424, obsd 484.2915.

Cbz-Leu-Ala-OMe (**P14**):[37] white powder (1.26 g, 60%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.35 (m, 5H), 6.62 (d, *J* = 5.6 Hz, 1H), 5.30 (d, *J* = 8.4 Hz, 1H), 5.10 (s, 2H), 4.59−4.54 (m,1H), 4.26−4.20 (m,1H), 3.74 (s, 3H), 1.73−1.60 (m, 2H), 1.55−1.48 (m, 1H), 1.39 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz; $CDCl_3$) 173.1, 171.7, 156.1, 136.1, 128.5, 128.1, 128.0, 67.0, 53.3, 52,5, 48.0, 41.5, 24.6, 22.9, 22.0, 18.2; MALDI TOF/TOF *m*/*z* calcd for $C_{18}H_{26}N_2O_5$ (M + Na) 373.1739, obsd 373.2563.

Crystal Structure Analysis of (Boc-Ala-S-)$_2$ (**3a**). Crystals of (Boc-Ala-CO-S-)$_2$ were grown by slow evaporation of ethyl acetate/*n*-hexane (40/60). A single crystal (0.12 × 0.07 × 0.04 mm) was mounted in a loop with a small amount of the mother liquor. The X-ray data were collected at 100 K using Mo Kα radiation (λ = 0.71073 Å), ω-scans (2θ = 56.56°) for a total number of 3080 independent reflections. Space group *P*2(1),2(1),2(1) *a* = 10.322(3) Å, *b* = 11.312(4) Å, *c* = 18.663(6) Å, α = 90.00°, β = 90°, γ = 90.00°, *V* = 2179.1(12) Å^3, orthorhombic *P*, *Z* = 4 for chemical formula $C_{16}H_{28}N_2O_6S_2$, with one molecule in asymmetric unit; ρ_{calcd} =1.245 g cm^{-3}, μ = 0.275 mm^{-1}, *F*(000) = 872, R_{int} = 0.1890. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. The final *R* value was 0.0684 (wR2 = 0.1170) for 3080 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 243 variables, *S* = 0.943. The largest difference peak and hole were 0.284 and −0.341 e Å^3, respectively.

Crystal Structure Analysis of (Boc-Aib-S-)$_2$ (**3e**). Crystals of (Boc-Aib-CO-S-)$_2$ were grown by slow evaporation of ethyl acetate/*n*-hexane (40/60). A single crystal (0.1 × 0.06 × 0.03 mm) was mounted in a loop with a small amount of the mother liquor. The X-ray data were collected at 100 K temperature using Mo Kα radiation (λ = 0.71073 Å), ω-scans (2θ = 56.56°) for a total number of 6601 independent reflections. Space group *Pca*2(1), *a* = 23.375(11) Å, *b* = 9.575(4) Å, *c* = 10.580(5) Å, α = 90.00°, β = 90°, γ = 90.00°, *V* = 2368.1(19) Å^3, orthorhombic *P*, *Z* = 4 for chemical formula $C_{18}H_{32}N_2O_6S_2$, with one molecule in asymmetric unit; ρ_{calcd} = 1.225 g cm^{-3}, μ = 0.258 mm^{-1}, *F*(000) = 936, R_{int} = 0.0806. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. The final *R* value was 0.0386 (wR2 = 0.0680) for 6601 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 263 variables, *S* = 0.766. The largest difference peak and hole were 0.205and −0.249 e Å^3, respectively.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR, ^{13}C NMR, and mass spectra of all compounds (**3a**−**f**, and **P1**−**P14**) and crystallographic information for compounds **3a** and **3e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hn.gopi@iiserpune.ac.in.

Notes

The authors declare no competing financial interest.

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