

Synthesis of N^β -Protected Amino Sulfenyl Methyl Formamides and Sulfonyl Methyl Formamides: A Simple Protocol

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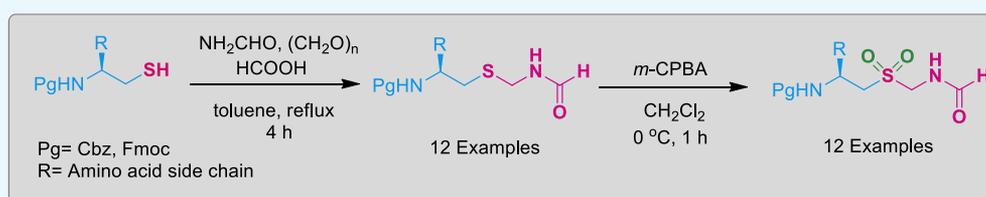
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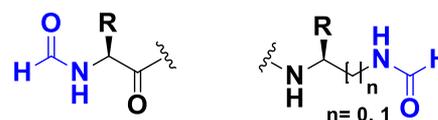
ABSTRACT: Chiral amino acid-derived formamides represent one of the most versatile components in multicomponent reactions. Herein, we describe a facile synthesis of N^β -protected amino sulfenyl methyl formamides and sulfonyl methyl formamides *via* the Mannich reaction of N^α -protected amino alkyl thiols followed by oxidation using 3-chloroperbenzoic acid (*m*-CPBA). This protocol is applicable to a wide range of Fmoc- and Cbz-protected amino acids. Notably, the reaction provides high yield and retains the stereochemistry of the chiral center of the starting component.

INTRODUCTION

The formamide group has been considered as an important synthon for the synthesis of isocyanides,¹ which has shown diverse applications in isocyanide-based multicomponent reactions (IMCRs).² A massive variety of formamides and their corresponding isocyanides³ have been investigated, thereby greatly expanding the capacity of molecular diversity through IMCRs.⁴ Some isocyanides are less stable and possess a foul smell compared to formamides, and therefore, the ability to perform one-pot dehydration/MCR would significantly widen the versatility and scope of formamides.⁵ This protocol proved to be particularly valuable when the desired isocyanides were inaccessible. In this context, several groups have made a significant contribution for one-pot dehydration/MCR without the isolation of isocyanides or sensitive aldehydes.⁶ It is important to note that amino acid- and peptide-derived formamides and its isocyanides have gained attention in MCRs for medicinal chemistry and drug discovery applications.⁷ We also explored the C-terminal modification of amino acids to prepare formamides and isocyanides (Figure 1) and employed in MCRs for the construction of a new class of peptidomimetics.⁸ With a view toward enabling a new class of formamides as well as isocyanides, we considered that sulfonyl formamides derived from chiral amino acids (Figure 1b) might be useful for generating a novel class of peptidomimetics. In this context, impressive applications of *para*-tosylmethylisocyanide (TosMIC)⁹ inspired us.

TosMIC serves as a precursor for the synthesis of several drug intermediates and pharmacologically active compounds.¹⁰ Its utility in the synthesis of nitriles, aldehydes, ketones, alkanes,

a) Reported amino acid - derived formamides



b) Present work

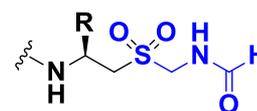


Figure 1. Variations of amino acid-derived formamides.

cyclophanes, and a large number of natural products is known.¹¹ The solid-phase version of TosMIC has also been utilized for the synthesis of various heterocycles.¹² More importantly, chiral TosMIC analogues have been synthesized and employed for the synthesis of optically active compounds.¹³ In addition, the incorporation of sulfur into a given biomolecule can dramatically modify its physical and biological properties, thereby resulting in the enhancement of the stability against proteolysis and improve

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bioavailability.¹⁴ Certain other properties, such as receptor selectivity or potency, often can be substantially improved. As a result, the development of novel sulfur-based unnatural amino acids and peptidomimetics within a peptide framework constitutes a prime goal of interest in the drug discovery space.

In this regard, we report a novel class of amino acid-derived sulfonyl methyl formamides from the corresponding thiol through acid-catalyzed three-component Mannich type reaction followed by oxidation under mild conditions in a two-step process.

RESULTS AND DISCUSSION

We had described an efficient protocol for the synthesis of N-protected amino alkyl thiols and demonstrated their multiple applications for the construction of sulfur-containing peptidomimetics.¹⁵ In the proposed protocol, the sulfonyl methyl formamides were synthesized from corresponding N-protected amino alkyl thiols, which were prepared from our previously reported protocol.^{15a} All the N-protected amino alkyl thiols could be stored for a long time under an inert atmosphere.

Initially, the reaction was commenced using Cbz-Phe- ψ [CH₂SH] as a model substrate for optimizing the reaction conditions. Cbz-Phe- ψ [CH₂SH] was treated with formamide (1.0 equiv) and para formaldehyde (1.0 equiv) in tetrahydrofuran (THF) and stirred at rt. The reaction failed to proceed even after 4 h of stirring, leaving behind the reactant as it is. Further, the investigation of the use of acid catalysts was carried out. Initially, the reaction was performed using PhCOOH and turned to be unproductive, although liquid chromatography–mass spectrometry data provided the formation of **2a** in trace amounts. As shown in Table 1, when 20 mol % of CF₃COOH was used, a low conversion (12%) of **2a** was observed. Next, without varying the equivalents of formamide and paraformaldehyde, PhSO₃H was used wherein a 28% yield of **2a** was observed. Thereafter, the reaction was carried out at 90 °C in THF and the equivalents of formamide and paraformaldehyde when increased; the progressive yield of **2a** was noticed (Table

1, entry 7). The preliminary optimization indicated the influence of temperature on reaction; in other words, no increase in yield was recorded when the reaction was carried at rt to 60 °C (Table 1, entries 2–6). These observations also inferred that the increase in the acidic strength of a catalyst led to a gradual improvement in the yield, as reflected in Table 1 until entry 7. When none of the above acid catalysts was found efficient in conversion to **2a**, we turned out to use 98% HCOOH. Using 30 mol % of HCOOH, stoichiometric amounts of both formamide and paraformaldehyde were increased to 4.0 equiv, and the reaction was carried out at reflux in toluene till the completion. The reaction proceeded well to afford **2a** in moderate to good yield. Among the reactions carried out with HCOOH, the optimized condition for the efficient conversion was found when 5.0 equiv of formamide and 4.0 equiv of paraformaldehyde were used which led to the highest yield (90%) of **2a** without any formation of noticeable impurities (Table 1, entry 10). Further, when the reaction was carried out with increased equivalents of formamide and formic acid, no improvement in the yield was observed. Alongside, different commonly used solvents, such as dichloromethane, CH₂Cl₂, THF, CH₃CN, and toluene, were examined; however, toluene was found beneficial to the reaction to furnish the target molecule **2a** in good yield by a one-pot manner and allowing complete solubility of N^α-protected alkyl thiol.

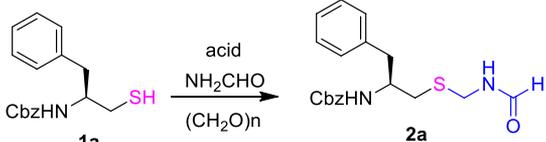
This protocol could be used for the gram-scale synthesis, as the desired compound **2a** was isolated in 84% yield (1.29 g) for 1.3 g of the starting material. All the title compounds were obtained as stable solids and could be stored at room temperature for several months.

To represent the generality and scope of the optimized protocol, various Fmoc- and Cbz-protected amino alkyl thiols were investigated. As shown in Scheme 1, all the thiols were valid substrates and smoothly proceeded to afford corresponding sulfonyl methyl formamide (**2**) in good to excellent yields. Even sterically constrained residues such as Phe, Phg, Val, and Ile were well tolerated without demanding additional time for the completion of the reaction.

Next, we set out to carry out the oxidation of sulfonyl methyl formamide to sulfone using *m*-CPBA as an oxidizing agent. Thus, a reaction of sulfonyl methyl formamides **2** with 2.0 equiv of *m*-CPBA in dry CH₂Cl₂ at 0 °C afforded the corresponding formamides **3** in excellent yield in an hour (Scheme 2).

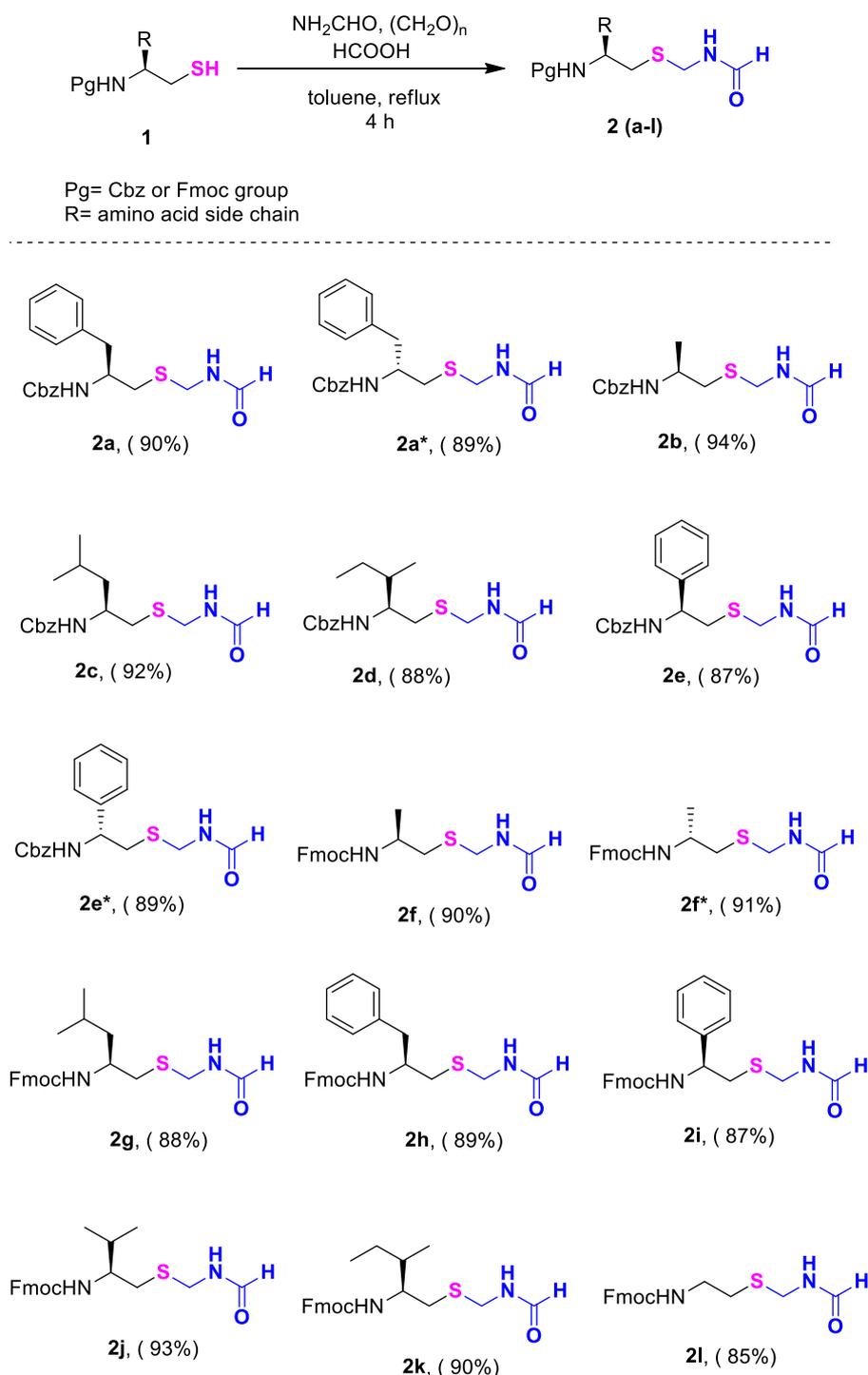
To check the potential loss of chiral integrity during the transformation of the title compounds, chiral reversed-phase high-performance liquid chromatography (RP-HPLC) analysis was carried out employing the Phe residue. Initially, the racemization study was carried out using an enantiomeric mixture of **2a** and **2a***, which showed well-separated twin peaks at 23.25 and 28.12 min, respectively (Figure 2, ii). This indicated the presence of two enantiomers and used the same as the reference racemate. The sample **2a** gives a single peak at retention time 24.29 min (Figure 2, i), which revealed the retention of the stereochemistry of sample **2a** with respect to Figure 2, ii. These results indicated that the protocol was devoid of racemization. Further, the oxidized product sulfonyl methyl formamide was also screened. A single peak appeared for **3a** at retention time 19.42 min (Figure 2, iii), and a mixture of **3a** and **3a*** showed two distinct peaks with a significant difference at 19.12 and 19.86 min, respectively (Figure 2, iv). These data inferred that optical homogeneity is maintained throughout the protocol (Figure 2).

Table 1. Optimization of Reaction Conditions for the Synthesis of Sulfonyl Methyl Formamide^a



s. no	catalyst (mol %)	NH ₂ CHO (equiv)	(CH ₂ O) _n (equiv)	yield (%) ^b
1		1.0	1.0	
2	PhCOOH (10)	1.0	1.0	trace
3	PhCOOH (20)	1.0	1.0	trace
4	CF ₃ COOH (20)	1.0	1.0	12
5	PhSO ₃ H (20)	1.0	1.0	28
6	PhSO ₃ H (20)	2.0	2.0	36
7	PhSO ₃ H (30)	3.0	3.0	54
8	HCOOH (30)	3.0	3.0	74
9	HCOOH (30)	4.0	4.0	82
10	HCOOH (30)	5.0	4.0	90
11	HCOOH (30)	6.0	4.0	89
12	HCOOH (40)	5.0	4.0	88

^aEntries 2–6 = reaction carried out at 60 °C. Entries 7–12 = reaction carried out at 90 °C. ^bYield obtained after column chromatography.

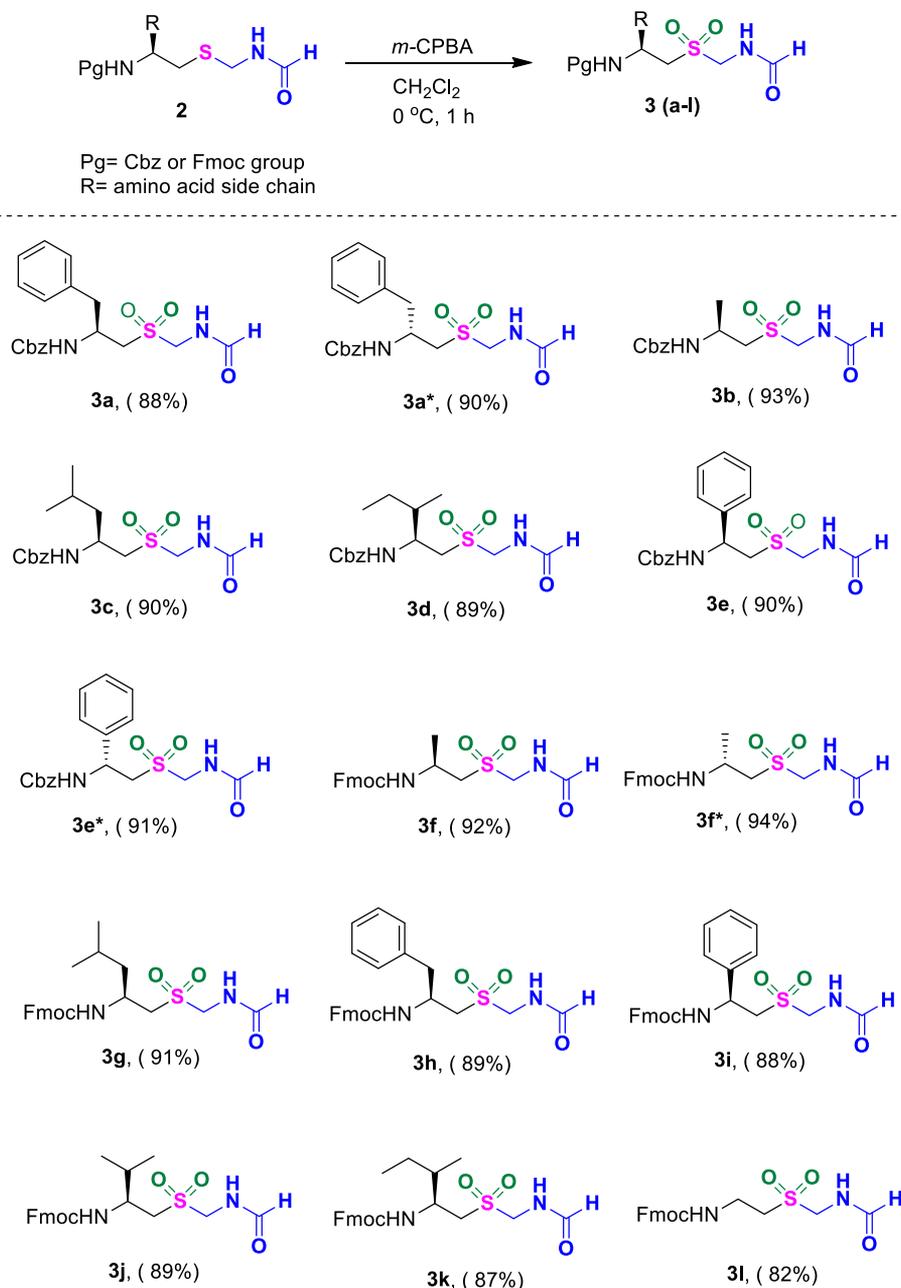
Scheme 1. List of N^β-Protected Amino Sulfenyl Methyl Formamides Synthesized

A plausible mechanism based on the experimental results obtained during the reaction is depicted in Scheme 3. The proposed mechanism occurs *via* a Mannich-type three-component acid-catalyzed fashion. The reaction proceeds through the formation of key intermediate protonated imino formamide (I) by the reaction of paraformaldehyde and formamide in the presence of formic acid. Further, thiol as a Mannich donor attacks the imino carbon of the intermediate (I) to furnish sulfenyl methyl formamide (II). In the next step, sulfonyl methyl formamide (III) forms by the oxidation of

sulfenyl methyl formamide by a well-known oxidizing agent *m*-CPBA.

CONCLUSIONS

In conclusion, a straightforward procedure has been described for the preparation of a series of N^β-protected amino sulfonyl methyl formamides by a two-step protocol. The present procedure can afford N^β-protected amino sulfonyl methyl formamides and N^β-protected amino sulfonyl methyl formamides in good to excellent yields. These formamides could be

Scheme 2. List of N^β -Protected Amino Sulfonyl Methyl Formamides Synthesized

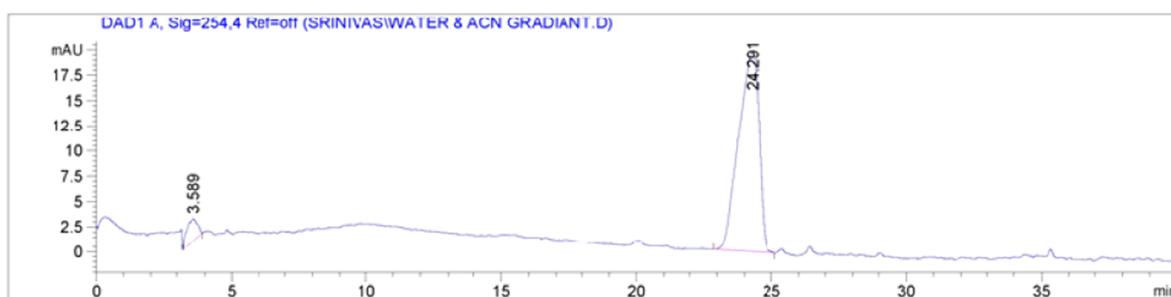
employed for MCR for the construction of novel peptidomimetic molecules.

EXPERIMENTAL SECTION

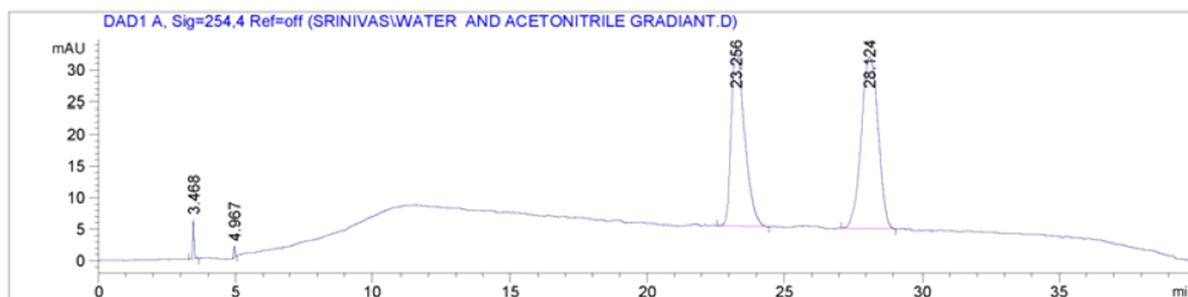
General Information. All reagents were obtained from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) experiments were carried out using precoated silica gel 60F254. HRMS spectra were recorded on a micromass Q-TOF spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 MHz and 100 MHz spectrometer, respectively, in $\text{DMSO}-d_6$ and analyzed using MestriNova software and reported as chemical shifts (δ) in parts per million (ppm). The coupling constants were reported in hertz (Hz). Column chromatography for purification of products was performed on silica gel (100–200 mesh). The RP-HPLC experiments were carried out on a Agilent 1260

instrument (chiral column: amylose-2 and cellulose-1, pore size: $5\ \mu\text{m}$, diameter \times length: $4.6 \times 250\ \text{mm}$). The melting points of the compounds were determined on a VEEGO (model: VMP-DS) melting point apparatus.

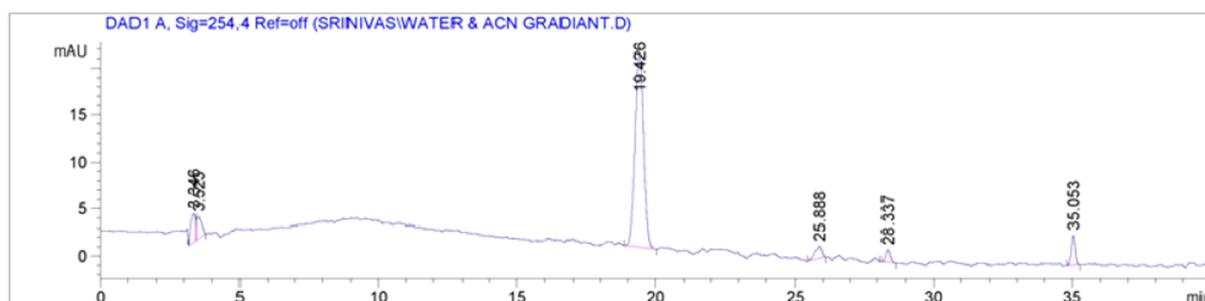
General Procedure for N^β -Protected Amino Sulfonyl Methyl Formamide. To a stirred solution of N^β -protected amino thiol (1.0 equiv) in toluene (10 mL), formamide (5.0 equiv), para formaldehyde (4.0 equiv), and formic acid (30 %) were added, and the solution was refluxed for 4 h. After the completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, and the solvent was vacuum evaporated and diluted with EtOAc, washed with water ($2 \times 10\ \text{mL}$) and brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 100–200 mesh) with 4:6



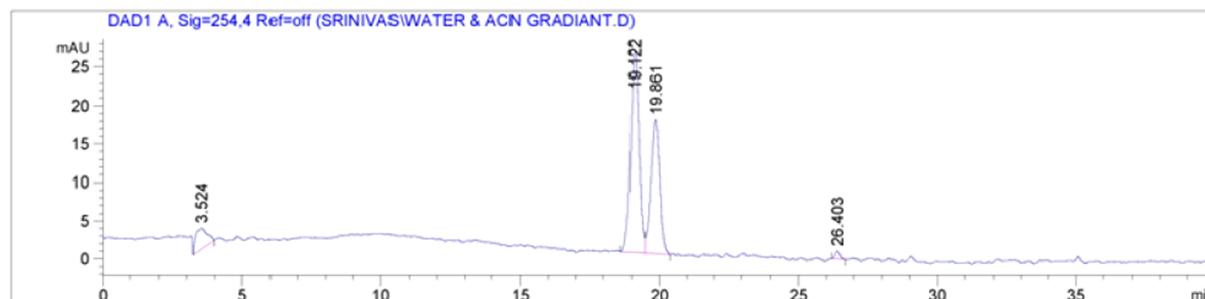
i. Compound 2a



ii. Mixture of compounds 2a & 2a*



iii. Compound 3a



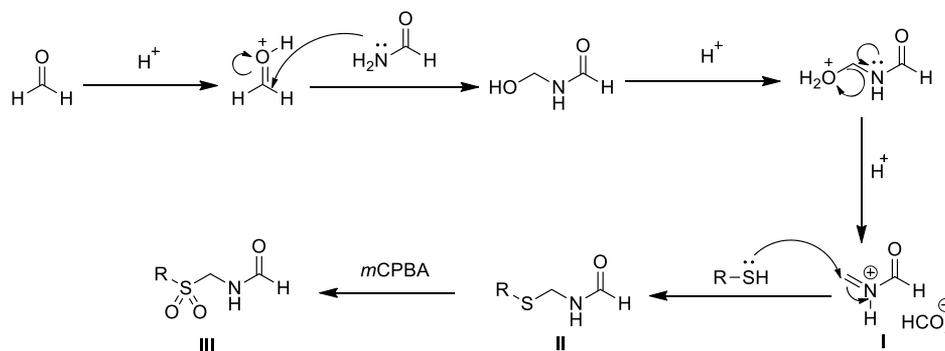
iv. Mixture of compounds 3a & 3a*

Figure 2. RP-HPLC profiles of DL & L Cbz-Phe residue sulfenyl and sulfonyl methyl formamides.

ethyl acetate and hexane to afford the corresponding sulfenyl methyl formamide.

General Procedure for N^β -Protected Amino Sulfonyl Methyl Formamide. To a stirred solution of N^β -protected

Scheme 3. Proposed Reaction Pathway



amino sulfenyl methyl formamide (1.0 equiv) in CH_2Cl_2 , *m*-CPBA (2.0 equiv) was added at $0\text{ }^\circ\text{C}$, and the solution was stirred for 1 h at $0\text{ }^\circ\text{C}$. After completion of the reaction (monitored by TLC), the solvent was vacuum evaporated and diluted with EtOAc, washed with water ($2 \times 10\text{ mL}$) and brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 100–200 mesh) with 5:5 ethyl acetate and hexane to afford the corresponding title compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.0c05419>.

Copies of the HPLC profiles of racemization study and characterization spectra (^1H , ^{13}C and HRMS) for all the synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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