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A Unified Approach to Access *N*-Acyl Sulfonamide Tethered Peptide Conjugates

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Herein we demonstrate a chemoselective reaction of N^{β}-protected amino alkyl sulfonyl azides with in situ generated N^{α}-protected amino acid selenocarboxylates via step wise intramolecular cyclization followed by decomposition to obtain N-acyl sulfonamide tethered peptidyl conjugates. The protocol offers the synthesis of orthogonally protected N-acyl sulfonamide tethered peptidomimetics under simple and mild reaction conditions employing commercially available amino acids in presence of $NaBH_2Se_3$ as a selenating agent. Also, the synthesis of N-acyl sulfonamide tethered amino acid and aryl conjugates were accomplished as an extension of the above strategy.

Introduction

Over the last two decades, peptides, peptide conjugates and peptidomimetics have moved to the fore front of research in the areas of chemistry, biology and medicine.[1] Researchers are increasingly becoming curious in these molecules due to their inexhaustible potential to serve as molecules of choice for multiple applications. In particular, the study on peptidomimetic molecules which function by the imitation of the topological architecture of the peptide backbone but contain non-native linkages in lieu of native peptide bond or include tailor made amino acid like structures/amino acid derivatives has been receiving tremendous attention.[2] The study on peptide conjugates and peptide tethers are emerging as a vital area as a derivative of peptide chemistry. Several new types of peptide conjugates are being designed and assembled employing predominantly amino acids as starting compounds. In view of this, our group designed and synthesized various un-natural peptide tethers such as ureido,[3] thioureido,[4] selenoureido[5] and guanidine[6] subunits. We now delineate our studies on the synthesis of *N*-acylsulfonamide tethered peptide conjugates under simple and mild conditions employing *N*-protected amino acids as starting materials in few steps.

N-Acyl sulfonamides have significant importance in medicinal chemistry.[7] They find applications as linkers for anchoring the solid support and in chemoselective ligation and bioconjugation reactions.[8] Also, they constitute an important class of drugs such as therapeutic agents for Alzheimer's disease,[9] antibacterial inhibitors of tRNA synthetases,[10] antagonists for angiotensin[11] and leuko-triene D4 receptors.[12] Conventional approaches for *N*-acylation of sulfonamides rely on reaction of sulfonamide with carboxylic acid by commonly used coupling agents: 1,1′-carbonyldiimidazole (CDI)[13a] and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC).[13b] *N,N′*-Dicyclohexylcarbodiimide (DCC) has also been used as coupling agent to obtain *N*-acyl sulfonamide derived nucleosides.[13c] Alternatively, coupling of benzoyl chloride (acid chlorides)/ acid anhydrides with mesylaniline derivatives in presence of base resulted *N*-acyl-*N*-mesylaniline derivatives.[14] In addition, mixed anhydrides have also been used to make *N*-acyl sulphonamides by acylation of sulfonamides.[15] Katritzky employed *N*-acylbenzotriazoles for the acylation of acetazolamides.[16] Besides, synthesis of *N*-acyl sulfonamides was demonstrated by acylation of nitro pyridine sulfonamides using carboxylic acid anhydrides under acidic conditions.[17] Furthermore, metal catalysts were also employed to achieve *N*-acyl sulfonamides upon acylation of methane sulfonamides.[18] However, majority of the methods discussed above result in formation of diacylated byproducts which was the major disadvantage.[14] Also, the harsh reaction conditions, tedious work up procedures, long reaction times and usage of expensive reagents prompted us to look for an alternative strategy for the synthesis of the title molecules. In addition, very few reports describe the synthesis of *N*-acyl sulfonamide tethered peptide conjugates, which generally involve the reaction of thioacids as acid activator counterpart and sulfonyl azides as reacting partners.[19] Williams et. al have explored However, synthesis, handling, storage, purification and stability issues of thioacids lead the sulfo-click reaction less utilized and also base is required prior to amidation.[19a] Synthesis of only one example of *N*-acyl sulfonamide was reported by Wu and Hu by reacting selenocarboxylate derived from benzoic acid with *p*-tolylsulfonyl azide in one pot using LiAlHSeH as selenating agent.[20a] The in situ generated selenocarboxylate has been found as a potential precursor for diverse chemical reactions.[21a] Reich and Hondal reported the biological and chemical importance of selenolates as well as its

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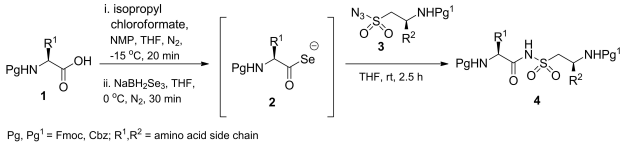
Table 1. Synthesis of orthogonally protected *N*-acyl sulfonamide tethered dipeptides



Pg, Pg^1 = Fmoc, Cbz; R^1,R^2 = amino acid side chain

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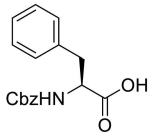
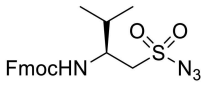
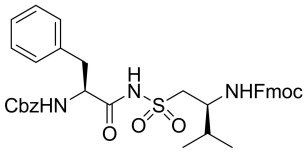
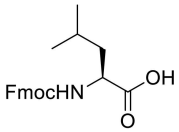
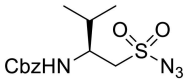
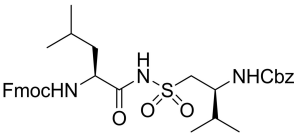
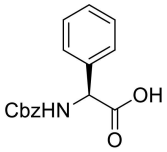
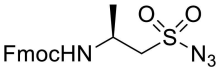
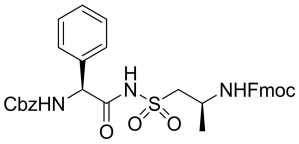
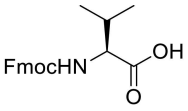
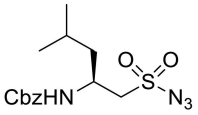
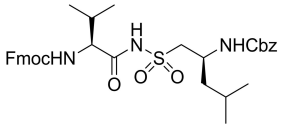
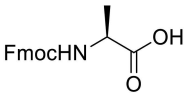
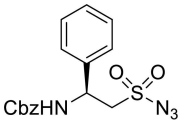
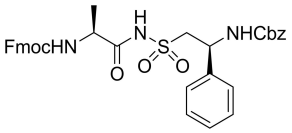
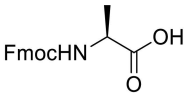
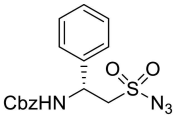
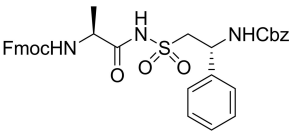
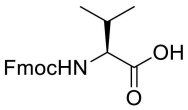
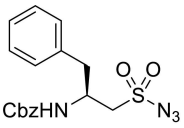
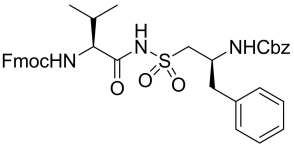
a				91
b				86
c				93
d				89
e				93
e*				92
f				90

[a]Isolated yield after column chromatography

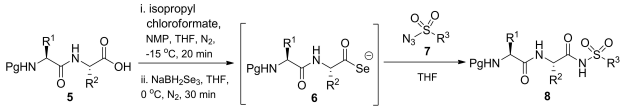
comparision with sulfur analogues.[21b] Apart from medicinal chemistry application, *N*-acyl sulfonamide moiety introduces additional tetrahedral-type geometry at the peptide backbone and such modification would favour the disruption of amyloidogenic aggregation.

In continuation of our interest in the design and synthesis of novel molecules, as an extension of our previous work imides,[22] we tried to explore the synthesis of yet another new class of urethane protected *N*-acyl sulfonamide tethered aryl as well as peptidyl conjugates as an improved alternative protocol. This was achieved by employing commercially available amino acids and sulfonyl azides in presence of $NaBH_2Se_3$ as selenating agent without the isolation of *in situ* generated seleninate intermediate, which otherwise acts as an activated acid counterpart.

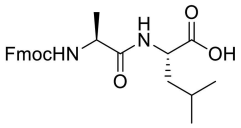
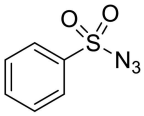
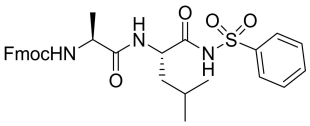
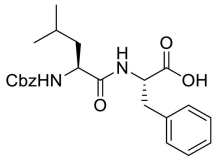
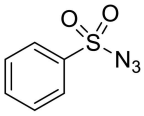
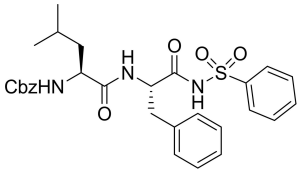
Results and Discussion

Williams et al. have explored the stoichiometric coupling, reactivity and mechanism of thio acid/ azide amidation in detail. Having referred the reactivity of azides,[19b,19c][24] in our initial part of the study, as a representative reaction Cbz-Phe-OH was converted to corresponding selenocarboxylate by treating it with freshly prepared $NaBH_2Se_3$.[22] The *in situ* generated selenocarboxylate was then reacted with Fmoc-Val-$CH_2SO_2N_3$ (3a, 1.0 mmol) at room temperature. 3a was synthesized as reported earlier by our group.[23] The reaction was monitored by TLC till the consumption of sulfonylazide and was found to complete in 2.5 h to afford the corresponding *N*-acyl sulfonamide (4a) in 91% yield after column purification.

Table 2. Synthesis of N^{α}-protected dipeptide acid derived *N*-acyl sulfonamides.



Pg = Fmoc, Cbz; R^1, R^2 = amino acid side chain; R^3 = C_6H_5

Entry	Peptide **5**	Sulfonyl azide **7**	Product **8**	Yield [a] [%]
a				82
b				85

[a]Isolated yield after column chromatography

In one of the reports, to obtain *N*-acyl sulfonamide, DMF was chosen over DCM as an alternative solvent by reasoning partial solubility of sulfonyl azide.[8n] However, high boiling point solvents are onerous to remove from reaction mixture and so is DMF. Since THF was preused to obtain selenocarboxylates, other solvents seemed redundant for further coupling with sulfonyl azide. This prompted us to prefer THF as a solvent as various sulfonyl azides were completely soluble.

Interestingly, orthogonally protected *N*-acyl sulfonamide tethered dipeptides was obtained from the coupling of N^{β}-protected amino alkyl sulfonyl azides with in situ generated amino acid selenocarboxylate in almost quantitative yield (Table 1). The generality of protocol was demonstrated by employing a series of simple and sterically hindered alkyl and aryl side chains with urethane protectors Fmoc and Cbz.

The above strategy was further extended to peptides, where in N^{α}-protected dipeptide acids were used as starting materials to generate dipeptide derived selenocarboxylates under established procedure. This *in situ* generated intermediate was made to react with benzene sulfonyl azide to form N^{α}-protected dipeptide derived *N*-acyl sulfonamides in good yields (Table 2).

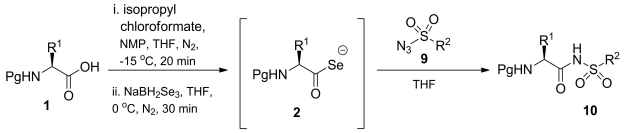
The methodology was also extended to prepare a few examples of *N*-acyl sulfonamide tethered amino acid and aryl conjugates by treating N^{α}-protected amino acids with phenyl-, tolyl- dansyl-, difluorobenzyl sulfonyl azides in presence of $NaBH_2Se_3$ under the optimized conditions. Barlett et al have explored NAS peptide conjugates in good yield.[24] However, employed strategy is not suitable for acid sensitive functional groups. To overcome this problem, we have synthesized ^{t}Bu-side chain protected serine and tyrosine based *N*-acyl sulfonamide wherein protector, tertiary butyl group was found tolerant under the present reaction conditions. The respective products were obtained in good yields (Table 3).

In additon, N^{β}-protected amino alkyl sulfonyl azides was treated with selenocarboxylates derived from coumarin-3- and 2-thiophene carboxylic acids to form corresponding *N*-acyl sulfonamides with aryl ring at one end and N^{α}-protected amino acid skeleton at the other end (Table 4).

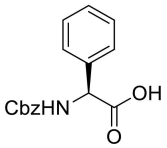
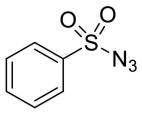
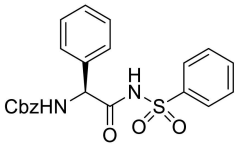
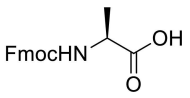
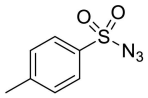
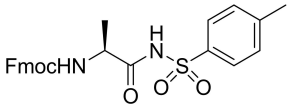
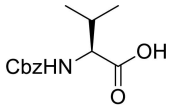
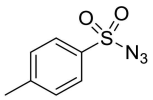
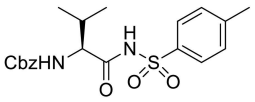
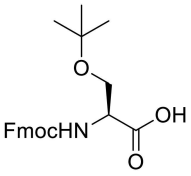
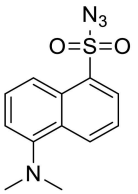
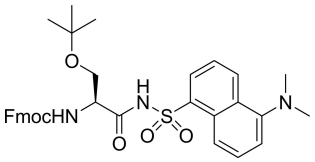
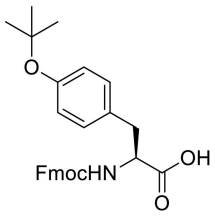
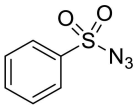
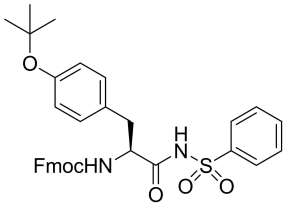
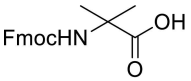
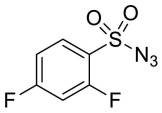
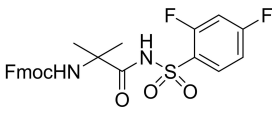
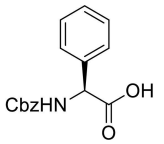
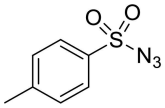
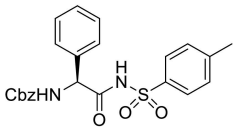
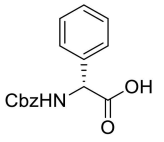
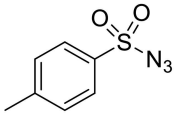
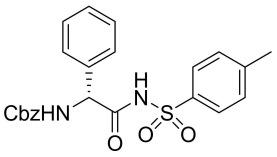
To check the possible epimerization during the course of the reaction, Fmoc-Ala-Ψ[$NHSO_2CH_2$]-Phg-(L)-Cbz (**4e**) and Fmoc-Ala-Ψ[$NHSO_2CH_2$]-Phg-(D)-Cbz (**4e***) were subjected to racemization studies. The HPLC analyses of the diastereomeric *N*-acyl sulfonamides **4e** and **4e***, when injected separately, showed the retention times of 23.35 min and 21.42 min, respectively. However, intentionally mixed two compounds showed distinct retention times of 23.00 min and 21.72 min respectively. Also, optically pure Cbz-(L)-Phg-OH and Cbz-(D)-Phg-OH was employed as substrates for the synthesis of corresponding *N*-acyl sulfonamides through in situ generated selenocarboxylates. In both these cases, *p*-tolylsulfonyl azide was used as a standard reaction partner. HPLC analyses of **10g** and **10g*** when injected separately, showed the retention times of 15.72 min and 13.05 min, respectively. However purposely mixed two compounds showed distinct retention times of 15.59 min and 12.91 min respectively. Thus this study infers that the present protocol is free from observable racemization.

The mechanism involving in this reaction seems to operate in a similar fashion as we observed in our previous work on preparation of thioureidopeptidomimetics by reacting azides and dithiocarbamates.[20b] Also, the similar reaction pathway was illustrated by Manetsch and coworkers for sulfo-click reaction of thioacids and sulfonyl azides.[19a] In the possible mechanism, selenocarboxylate formed in situ by the selenation of corresponding acid in presence of selenating agent reacts with azide via stepwise linear coupling to form an intermediate **I**. This later undergoes intramolecular cyclization to form a five membered ring with 4-heteroatoms including three N-atoms and one selenium atom. This on further decomposition through retro-[3 + 2] reaction result in the expulsion of N_2 and Se to give desired *N*-acyl sulfonamide.

Table 3. Synthesis of *N*-acyl sulfonamide tethered amino acid and aryl conjugates.



Pg = Fmoc, Cbz; R^1 = amino acid side chain, R^2 = phenyl, tolyl, dansyl, difluorobenzyl

Entry	Amino acid **1**	Sulfonyl azide **9**	Product **10**	Yield[a] [%]
a				94
b				90
c				92
d				88
e				86
f				90
g				95
g*				94

[a]Isolated yield after column chromatography

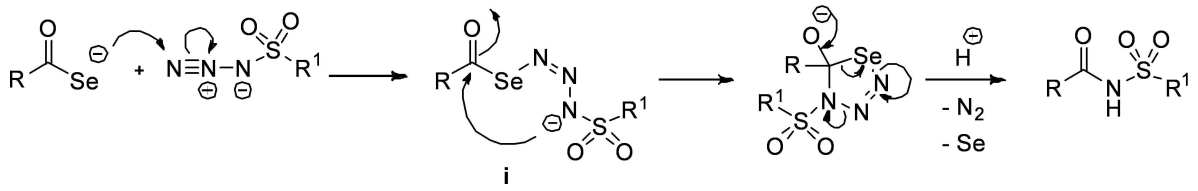
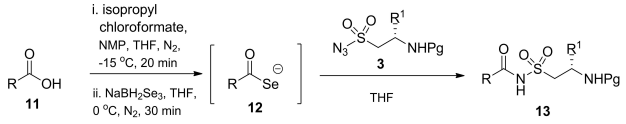
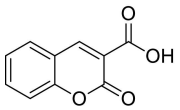
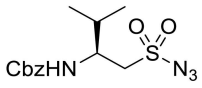
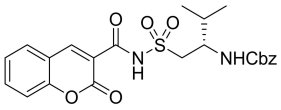
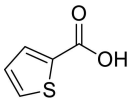
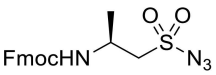
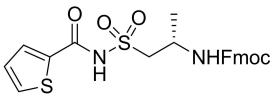


Figure 1. Possible mechanism for *N*-acyl sulfonamide formation.

Table 4. Synthesis of *N*-acyl sulfonamide derived from coumaric- and thiophene acid selenocarboxylates.



Pg = Fmoc, Cbz; R= coumaryl, thiophenyl moiety; R^1 = amino acid side chain

Entry	Acid **11**	Sulfonyl azide **3**	Product **13**	Yield[a] [%]
a				82
b				85

[a]Isolated yield after column chromatography

Conclusions

We have demonstrated a straight forward approach for the synthesis of orthogonally protected *N*-acyl sulfonamide tethered dipeptides under mild reaction conditions employing commercially available amino acids and sulfonyl azides mediated by selenating agent without the isolation of active intermediate, selenocarboxylate. The protocol was also extended to synthesize N^{α}-protected dipeptide acid derived acyl sulfonamides bearing amide and *N*-acyl sulfonamide hybrid tethers in the back bone. In addition, synthesis of *N*-acyl sulfonamide tethered amino acid and aryl conjugates was also accomplished. All the products were obtained in good yields irrespective of nature of side chains including simple as well as sterically hindered ones.

Supporting information summary

General procedure for the synthesis of *N*-acyl sulfonamides, HRMS, ^{1}H, ^{13}CNMR spectra, and characterization data of all the synthesized compounds (4a–4f, 8a,8b, 10a–10 g* and 13a,13b), and RP-HPLC chromatograms with data are appended in the supporting information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: *N*-Acyl sulfonamide · N^{α}-protected amino selenocarboxylate · N^{β}-protected amino alkyl sulfonyl azides · peptide conjugates

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