Original Article

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A facile method for the synthesis of *N*-(α-aminoacyl) sulfonamides

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ABSTRACT: *N*-Acylsulfonamide derivatives have important applications in organic synthesis and drug discovery. It was found that many problems occurred preparing amino acid derived *N*-acylsulfonamides with the commonly used coupling approach in our previous studies. In this paper, we report an efficient approach to synthesize various amino acids derived *N*-acylsulfonamides in high yields without any racemization.

Keywords: Synthesis, amino acid-derived *N*-acyl-sulfonamides, the mixed anhydride method

1. Introduction

Currently, *N*-acylsulfonamide derivatives are used in various applications in organic chemistry and medicinal chemistry. According to the literature, *N*-acylsulfonamide derivatives can assist tandem C-H olefination for the synthesis of isoindolinones (*1*), and act as safety-catch linkers for the solid phase synthesis of peptide (*2*) and hyaluronic acid oligosaccharides (*3*). In addition, proline-derived *N*-sulfonylcarboxamides have been reported to be good chiral catalysts for asymmetric mannich reactions and anti-aldol reactions (*4-7*). For biological applications, *N*-acylsulfonamide derivatives not only can be used as therapeutic agents for Alzheimer's disease (*8*), but also can act as RNase A inhibitors (*9*), prostaglandin E receptor 3 (EP3) receptor antagonists (*10*), prostacyclin receptor agonists (*11*), HCV NS5B polymerase allosteric inhibitors (*12*), and HCV NS3 protease inhibitors. In a recent study, *N*-acylsulfonamide structures have been regarded as good moieties for Bcl-2 inhibitors. For example, ABT-737 has been confirmed as a potent Bcl-2 inhibitor for cancer treatment (*13*).

Recently, many efforts have been devoted to the synthesis of *N*-acylsulfonamides derivatives. Generally speaking, sulfonamide is the commonly used starting material which reacts with different acylating reagents, such as acyl chlorides (*3*), anhydrides (*14*), *N*-acyl benzotriazoles (*15*), and coupling reagents for peptide synthesis (*e.g.* 1-ethyl-3-(3-dimethyllaminopropyl)carbodiie hydrochlide (EDCI), dicyclohexylcarbodiimide (DCC), and carbonyl diimidazole) (*16,17*). On the other hand, *N*-acylsulfonamides can also be accessed through the reaction of amides and sulfonyl chlorides (*18*). All the methods mentioned above have their advantages, but some problems and inconveniences still occur during the process, such as long reaction time, and low product yield (*19*). Recently, a palladium-catalyzed amidocarbonylation protocol was disclosed producing *N*-acylsulfonamides in excellent yields when $Mo(CO)_6$ was employed as a carbon monoxide source (*20*). The reaction was efficient; however, the high-density microwave heating conditions necessary limit functional compatibility and potential substrate scope. Moreover, Williams documented that *N*-acylsulfonamides can be obtained from carboxylic acids through thio acid/azide amidation, which is highly compatible with acid- and base-sensitive amino acid protection (*21*). However, sulfonylazides are not easy to handle, and the method might have problems with large-scale manipulation. Therefore, development of a mild, simple, efficient and atom-economical method for synthesis of *N*-acylsulfonamides is still a worthwhile project.

In our recent studies, the phenylalanine derived *N*-acylsulfonamide lead compound, WL-276, was investigated as a Bcl-2 inhibitor to overcome drug resistance and suppress prostate tumor growth (*22,23*). However, low yield, a long reaction time (more than 48 h) and racemization give us problems when EDCI and related coupling reagents were used for synthesis of *N*-acylsulfonamides. To overcome these problems, we developed a convenient and facile method for preparing amino acids derived *N*-acylsulfonamides using a modified mixed anhydride method without product racemization.

2. Materials and Methods

2.1. *General methods*

Solvents were reagent grade and purified and dried using standard methods when necessary. All melting

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points were determined on a micromelting point apparatus (are uncorrected). ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Bruker Avance-300 in the indicated solvent. Chemical shifts are expressed in delta (δ) units with tetramethyl-silane (TMS) as the internal reference. Electrospray ionization-mass spectrometry (ESI-MS) was determined on an API 4000 spectrometer. All reactions were monitored using thin-layer chromatography (TLC) on 0.25 mm silica gel plates (60GF-254) and visualized with UV light. Flash column chromatography was performed on a column packed with silica gel 60 (200-300 mesh). Concentration of reaction solutions involved use of a rotary evaporator at reduced pressure. Specific rotation was determined on Modular Circular Polarimeter (MCP200). Enantiomeric excess analysis by HPLC used a Shimidazul LC-10Avp UV detector.

2.2. *General procedure for the preparation of amino acid-derived N-acylsulfonamides*

In our initial studies, the reaction of N^{α}-protected phenylalanine and benzenesulfonamide (1:1.1, molar ratios) was selected as the model to test the mixed anhydride method (*24*). However, no desired product was observed and all the starting materials were recovered. We believed that the possible reason for this phenomenon is the weak nucleophilicity of the sulfonamide. Therefore, different bases such as sodium hydroxide, sodium ethoxide and sodium hydride, were tested to depronate the sulfonamide so as to increase the nucleophilicity of the sulfonamide. The method is described as followed (Figure 1): First, to a solution of NaH or EtONa (2.5 eq) in anhydrous tetrahydrofuran (THF) (10 mL) benzenesulfonamide **3** was added at 0°C, and the mixture stirred at 0°C for 30 min and at room temperature for 3-4 h (with NaOH as base we needed 12 h) to give benzenesulfonamide sodium salt **3'**. Second, to a solution of N^{α}-protected phenylalanine 1(1 eq) in 10 mL anhydrous THF *N*-methyl morpholine (NMM) (1.1 eq) was added at −20°C. Ten min later, isobutylchloroformate (1.1 eq) was added. After another 45 min, the mixture was added to a solution of **3'**, the reaction was allowed to warm to room temperature gradually, and stirred for 5-8 h. After removal of the solvent, ethyl acetate was added and the mixture was washed successively with 1 M citric acid, then brine, and dried over $MgSO_4$. After removal of the solvent, the crude mixture was purified by recrystallization with ethanol or flash chromatography (petroleum ether/ethyl acetate, 5:1) to give the pure products **4**.

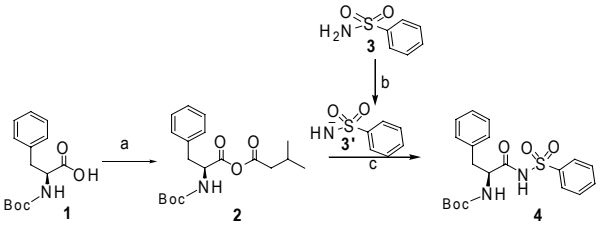


Figure 1. Synthesis of product 4. (a): i) 1, NMM, THF, -20ºC, 10 min; ii) isobutylchloroformate, 45 min. **(b)**: i) 3 (1 eq), base (2.5 eq), THF, 0ºC, 30 min; ii) rt, 3-4 h. **(c)**: 0ºC, 30 min, and then rose to room temperature, 5-8 h.

3. Results and Discussion

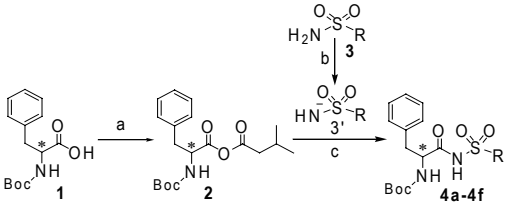
The results suggest that sodium hydride should be the best base to give excellent isolated yield (98%) and shortest time (Table 1). On the other hand, EtONa also afforded a good yield (87%), but the reaction time is over 16 h; sodium hydroxide did not work in this reaction. Therefore, sodium hydride was selected as the optimal base for further investigations.

The enantiomeric excess of (*S*)-**4** and (*R*)-**4** prepared with our modified mixed anhydride method (compound **4a** and **4b** in Table 2) were determined by HPLC on a Chiralpak IA column (Figure 2). Both of them gave a > 99% enantiomeric excess analysis, which demonstrated that our method could effectively overcome the problem of racemization when using EDCI and related coupling reagents.

Table 1. The reaction of N^{α}-protected phenylalanine with benzenesulfonamide

Entry	Base	Time (h)	Isolated yield (%) of **4**
1	None	16	0
2	NaOH	16	0
3	EtONa	16	87
4	NaH	6	98

Table 2. The reaction of N^{α}-protected phenylalanine with substituted benzenesulfonamides or alkylsulfonamide



Entry	Configuration of the amino acid 1	R	Base	Product	Isolated yield (%)
1	*S*	Phenyl	NaH	**4a**	98
2	*R*	Phenyl	NaH	**4b**	98
3	*S*	4-Nitrophenyl	NaH	**4c**	96
4	*S*	3-Chloro-4-nitro-phenyl	NaH	**4d**	97
5	*S*	4-Chloro-phenyl	NaH	**4e**	94
6	*S*	Methyl	NaH	**4f**	97

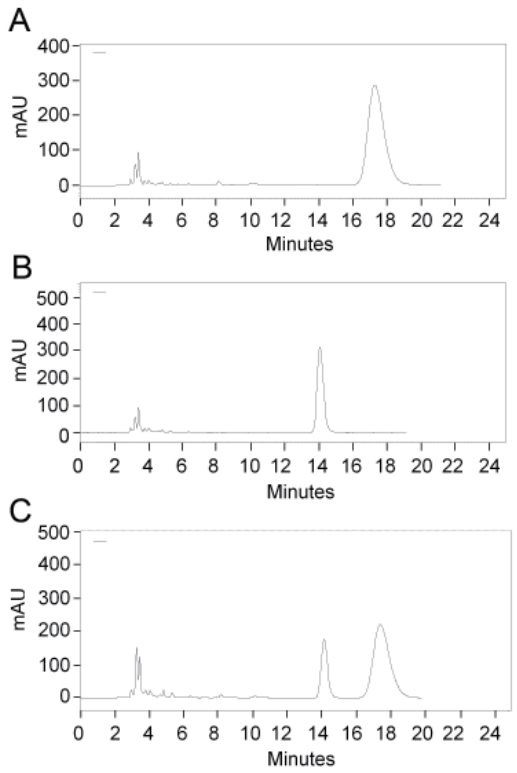
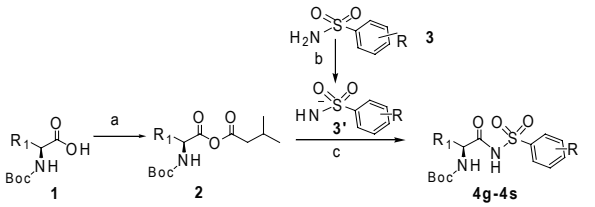


Figure 2. HPLC trace of 4a and 4b. Condition: Chiralpak IA 4.6 × 150 mm; mobile phase: 100/30 hexane/isopropyl alcohol (containing 0.05% trifluoroacetic acid) detection at 230 nm, flow rate: 1.0 mL/min. **(A)**: Compound **4a** with *S* configuration; **(B)**: Compound **4b** with *R* configuration; **(C)**: mixture of compound **4a** and **4b**.

Various benzenesulfonamides and alkylsulfonamide were further examined to react with different N^{α}-protected phenylalanine, and the results are summarized in Table 2. Generally speaking, excellent yields (94-98%) were obtained. Our improved mixed anhydride method shows many advantages such as cheap reagents, easy and safe operation, and is suitable for amino acid substrates.

To demonstrate the generality of this approach, a broad range of N^{α}-protected amino acids were chosen to explore the scope of this reaction (Table 3). In general, good to excellent (73-98%) yields were obtained not only for the selected N^{α}-protected amino acids substrates, but also for substituted benzenesulfonamides. According to the results, the electron withdraw group (EWG) substitutents on the phenyl ring of benzenesulfonamides also gave good isolated yields (*e.g.* entries 2, 3, 5, and 6). On the other hand, Boc-protected gama-aminobutanoic acid was used to react with different substituted benzensulonamides in our studies. The results demonstrate that good isolated yield can be achieved through our procedures (Table 4).

Table 3. Synthesis of *N*-(N^{α}-protected aminoacyl) sulfonamides



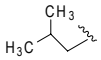
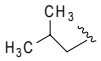
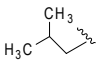
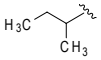
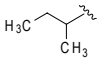
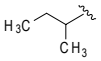
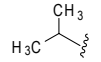
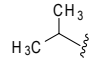
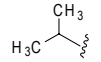
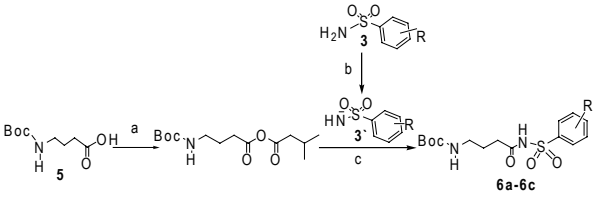
Entry	R	R_1	Products	Isolated Yield %
1	H		**4g**	90
2	4-Nitro		**4h**	96
3	3-Chloro-4-nitro		**4i**	85
4	H		**4j**	97
5	4-Nitro		**4k**	87
6	3-Chloro-4-nitro		**4l**	98
7	H		**4m**	91
8	4-Nitro		**4n**	88
9	3-Chloro-4-nitro		**4o**	84
10	H	H	**4p**	92
11	4-Nitro	H	**4q**	90
12	3-Chloro-4-nitro	H	**4r**	81
13	H	CH_3-	**4s**	73

Table 4. The reaction of *N*-protected γ-aminoacid with benzenesulfonamide



Entry	R	Products	Isolated yield(%) of **4**
1	H	**6a**	80
2	4-Nitro	**6b**	85
3	3-Chloro-4-nitro	**6c**	79

4. Conclusion

In summary, a modified mixed anhydride method was developed for preparation of amino acids derived *N*-(α-aminoacyl) sulfonamides. This method shows the advantages of efficiency, convenience and economics, which could overcome problems of low yields, long reaction time and racemization when using common coupling methodology. This would greatly help the organic chemists and medicinal chemists to prepare more bioactive compounds in the future.

Acknowledgements

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Appendix

*Synthesis of N-acylsulfonamide derivatives **4a-4s**, **6a-6c***

*(S)-Tert-butyl (1-oxo-3-phenyl-1-(phenylsulfonamido) propan-2-yl) carbamate (**4a**)*

Yield: 98%. $[\alpha]_D^{20}$ = 8.6 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.34 (s, 1H), 8.04-8.06 (d, *J* = 7.5 Hz, 2H), 7.57-7.66 (tt, 1H), 7.52-7.57 (dt, 2H), 7.04-7.23 (3H), 7.02-7.04 (2H), 4.90 (s, 1H), 4.31 (s, 1H), 3.02-3.08 (dd, *J* = 14.1 Hz, 6.3 Hz, 1H), 2.89-2.97 (dd, 1H), 1.38 (s, 9H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 169.5, 155.7, 138.4, 135.3, 134.0, 129.2, 128.9, 128.5, 127.3, 81.5, 55.9, 36.9, 28.1. HRMS (ESI): calcd. for $C_{20}H_{23}N_2O_5S^-$ 403.1333, found 403.1311[M − H]$^-$. Melting point: 133-135°C.

*(R)-Tert-butyl (1-oxo-3-phenyl-1-(phenylsulfonamido) propan-2-yl) carbamate (**4b**)*

Yield: 98%. $[\alpha]_D^{20}$ = −8.6 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.23 (s, 1H), 8.04-8.06 (d, *J* = 7.5 Hz, 2H), 7.64-7.69 (tt, 1H), 7.53-7.61 (dt, 2H), 7.22-7.24 (3H), 7.03-7.06 (2H), 4.83-1.85 (d, 1H), 4.29 (s, 1H), 3.02-3.09 (dd, *J* = 14.1 Hz, 6.3 Hz, 1H), 2.91-2.98 (dd, *J* = 14.1 Hz, 7.5 Hz, 1H), 1.38 (s, 9H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 169.5, 155.8, 138.5, 135.3, 133.9, 129.2, 128.9, 128.5, 127.3, 81.5, 56.1, 36.9, 28.1. HRMS (ESI): calcd. for $C_{20}H_{23}N_2O_5S^-$ 403.1333, found 403.1311 [M − H]$^-$. Melting point: 133-135°C.

*(S)-Ttert-butyl(1-(4-nitrophenylsulfonamido)-1-oxo-3-phenylpropan-2-yl) carbamate (**4c**)*

Yield: 96%. $[\alpha]_D^{20}$ = 8.2 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.57 (s, 1H), 8.35-8.38 (d, *J* = 8.7 Hz, 1H), 8.22-8.24 (d, *J* = 8.7 Hz, 1H), 7.25-7.26 (3H), 7.06-7.07 (2H), 4.84-4.86 (d, *J* = 6.9 Hz, 1H), 4.24-4.26 (q, 1H), 3.04-3.108 (dd, *J* = 14.1 Hz, 6.3 Hz, 1H), 2.93-2.99 (dd, *J* = 14.1 Hz, 7.8 Hz, 1H), 1.40 (s, 9H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 169.6, 156.1, 150.8, 143.9, 135.0, 129.9, 129.1, 128.9, 127.46, 124.0, 82.0, 56.2, 36.5, 28.1. HRMS (ESI): calcd. for $C_{20}H_{22}N_3O_7S^-$ 4483.1184, found 448.1314 [M − H]$^-$. Melting point: 244-245°C.

*(S)-Tert-butyl(1-(4-chloro-3-nitrophenylsulfonamido)-1-oxo-3-phenylpropan-2-yl)carbonate (**4d**)*

Yield: 97%. $[\alpha]_D^{20}$ = 12.8 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.50 (s, 1H),8.48-8.49 (d, *J* = 2.1 Hz, 1H), 8.18-8.21 (dd, *J* = 8.4 Hz, 2.1 Hz,) 7.72-7.75 (d, *J* = 8.4 Hz, 1H), 7.26 (3H), 7.07-7.10 (2H), 4.80-4.82 (d, *J* = 6.6 Hz, 1H), 4.20-4.27 (q, 1H), 3.04-3.11 (dd, *J* = 14.1 Hz, 6.3 Hz, 1H), 2.93-2.99 (dd, *J* = 14.1 Hz, 7.8 Hz, 1H), 1.40 (s, 9H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 169.5, 156, 147.7, 138.3, 135.0, 133.1, 132.7, 129.1, 129.0, 127.5, 125.8, 82.2, 56.4, 36.3, 28.1. HRMS (ESI): calcd. for $C_{20}H_{21}ClN_3O_7S^-$ 482.0794, found 482.0977 [M − H]$^-$. Melting point: 147-150°C.

*(S)-Tert-butyl(1-(4-chlorophenylsulfonamido)-1-oxo-3-phenylpropan-2-yl) carbamate (**4e**)*

Yield: 94%. $[\alpha]_D^{20}$ = 6.8 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$: δ (ppm) = 9.55 (s, 1H), 7.95-7.98 (d, *J* = 8.7 Hz, 2H), 7.49-7.52 (d, *J* = 8.7 Hz, 2H), 7.22-7.23 (3H), 7.02-7.04 (2H), 4.96 (s, 1H), 4.32 (1H), 3.01-3.08 (dd, *J* = 14.1 Hz, 6.3 Hz, 1H), 2.88-2.95 (dd, *J* = 14.1 Hz, 7.8 Hz, 1H), 1.38 (s, 9H). ^{13}C-NMR (300 MHz, CDCl3): δ = 169.8, 155.9, 140.7, 136.8, 135.2, 130.0, 129.2, 129.2, 128.8, 127.3, 81.5, 55.9, 37.1, 28.2. HRMS (ESI): calcd. for $C_{20}H_{22}ClN_2O_5S^-$ 437.0943, found 437.0950 [M − H]$^-$. Melting point: 132-134°C.

*(S)-Tert-butyl (1-(methylsulfonamido)-1-oxo-3-phenylpropan-2-yl)carbamate (**4f**)*

Yield: 98%. $[\alpha]_D^{20}$ = 17.6 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.05 (s, 1H), 7.30-7.36 (m, 3H), 7.19-7.21 (dd, 2H), 4.94-4.97 (d, 1H), 4.38 (s, 1H), 3.24 (s, 3H), 3.16-3.24 (dd, *J* = 14.1 Hz, 6 Hz, 1H), 2.99-3.07 (dd, *J* = 14.1 Hz, 8.1 Hz, 1H), 1.41 (s, 9H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 170.9, 155.9, 135.4, 129.3, 128.93, 127.4, 81.6, 56.2, 41.4, 37.1, 28.2. HRMS (ESI): calcd. for $C_{15}H_{21}N_2O_5S^-$ 341.1177, found 347.1192 [M − H]$^-$. Melting point: 145-147°C.

*(S)-Tert-butyl(4-methyl-1-oxo-1-(phenylsulfonamido) pentan-2-yl) carbamate (**4g**)*

Yield: 90%. $[\alpha]_D^{20}$ = −9.4 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) =9. 54 (s, 1H), 8.049 -8.074 (d, *J* = 7.5 Hz, 2H), 7.61-7.66 (tt, 1H), 7.51-7.56 (td, 2H), 4.76 (s, 1H), 4.04 (S, 1H), 1.56-1.66 (m, 2H), 1.43 (s, 9H), 1.26 (1H), 0.85-0.91 (dd, 6H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 170.4, 156.3, 138.6, 133.9, 128.9, 128.4, 81.4, 53.5, 39.3, 28.2, 24.5, 22.8, 21.7. HRMS (ESI): calcd. for $C_{17}H_{25}N_2O_5S^-$ 369.1490, found 369.1501 [M − H]$^-$. Melting point: 152-155°C.

*(S)-Tert-butyl(4-methyl-1-(4-nitrophenylsulfonamido)-1-oxopentan-2-yl)carbamate (**4h**)*

Yield: 96%. $[\alpha]_D^{20}$ = 4.6 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.85 (s, 1H), 8.35 -8.39 (d, 2H), 8.23-8.28 (d, 2H), 4.75 (s, 1H), 4.00 (S, 1H), 1.63-1.65 (m, 3H), 1.45 (s, 9H), 0.86-0.93 (dd, 6H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 170.6, 156.6, 150.8, 144.0, 129.9, 124.1, 81.8, 53.4, 39.0, 28.2, 24.5, 22.8, 21.6. HRMS (ESI): calcd. for $C_{17}H_{24}N_3O_7S^-$ 414.1340, found 414.1360 [M − H]$^-$. Melting point: 121-123°C.

*(S)-Tert-butyl(1-(4-chloro-3-nitrophenylsulfonamido)-4-methyl-1-oxopentan-2-yl)carbamate (**4i**)*

Yield: 85%. $[\alpha]_D^{20}$ = 23.2 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.91 (s, 1H), 8.5-8.52 (d, *J* = 2.1 Hz, 2H), 8.20-8.23 (dd, *J* = 8.4 Hz, 2.1 Hz, 2H), 7.72-7.75 (d, *J* = 8.7 Hz, 2H), 4.78 (s, 1H), 4.02 (S, 1H), 1.61-1.65 (m, 2H), 1.43-1.51 (m, 10H), 0.87-0.96 (dd, 6H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 170.9, 156.6, 152.5, 147.6, 138.5, 132.9, 132.7, 125.8, 82.0, 53.4, 39.2, 28.1, 24. 6, 22.8, 21.6. HRMS (ESI): calcd. for $C_{17}H_{23}ClN_3O_7S^-$ 448.0951, found 448.0924 [M − H]$^-$. Melting point: 142-144°C.

*Tert-butyl((2S)-3-methyl-1-oxo-1-(phenylsulfonamido) pentan-2-yl)carbamate (**4j**)*

Yield: 97%. $[\alpha]_D^{20}$ = −11.8 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.34 (s, 1H), 8.05-8.08 (d, *J* = 7.5 Hz, 2H), 7.61-7.66 (tt, *J* = 7.5 Hz, 1H), 7.51-7.56 (dt, *J* = 7.5 Hz, 2H), 4.9 (s, 1H), 3.89 (s, 1H), 1.85 (m, 1H), 1.67 (m, 2H), 1.42 (s, 9H), 1.06-1.13 (m, 1H), 0.82-0.88 (m, 6H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 170.0, 156.1, 138.5, 133.9, 128.9, 128.4, 81.1, 59.6, 36.4, 28.2, 24.6, 15.4, 11.1. HRMS (ESI): calcd. for $C_{17}H_{25}N_2O_5S^-$ 369.1490, found 369.1592 [M − H]$^-$. Melting point: 152-154°C.

*Tert-butyl((2S)-3-methyl-1-(4-nitrophenylsulfonamido)-1-oxopentan-2-yl)carbamate (**4k**)*

Yield: 87%. $[\alpha]_D^{20}$ = 3.2 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.99 (s, 1H), 8.353-8.39 (d, *J* = 9.0 Hz, 2H), 8.25-8.28 (d, *J* = 9.0 Hz, 2H), 5.02 (s, 1H), 3.94 (s, 1H), 1.79-1.81 (m, 1H), 1.43-1.49 (10H), 1.04-1.18 (m, 1H), 0.83-0.88 (m, 6H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 170.7, 156.5, 150.8, 144.0, 129.9, 124.1, 81.6, 59.5, 36.5, 28.2, 24.7, 15.4, 10.9 HRMS (ESI): calcd. for $C_{17}H_{24}N_3O_7S^-$ 414.1340, found 414.1359 [M − H]$^-$. Melting point: 119-120°C.

*Tert-butyl((2S)-1-(4-chloro-3-nitrophenylsulfonamido)-3-methyl-1-oxopentan-2-yl)carbamate (**4l**)*

Yield: 98%. $[\alpha]_D^{20}$ = 6.8 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) =10.17 (s, 1H), 8.53-8.54 (d, *J* = 8.4 Hz, 1H), 8.22-8.24 (d, *J* = 8.4 Hz, 1H), 7.74-7.76 (d, *J* = 8.7 Hz, 2H), 5.07 (s, 1H), 3.90-3.96 (s, 1H), 1.81 (1H), 1.43 (10H), 1.10-1.14 (m, 1H), 0.84-0.89 (m, 6H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 170.8, 156.0, 147.6, 138.5, 132.9, 132.8, 132.7, 125.9, 81.7, 59.5, 36.6, 28.2, 24.69, 15.4, 10.9. HRMS (ESI): calcd. for $C_{17}H_{23}ClN_3O_7S^-$ 448.0951, found 448.0967 [M − H]$^-$. Melting point: 125-127°C.

*(S)-Tert-butyl(3-methyl-1-oxo-1-(phenylsulfonamido) butan-2-yl)carbamate (**4m**)*

Yield: 91%. $[\alpha]_D^{20}$ = −13.4 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.61 (s, 1H), 8.06 -8.09 (d, *J* =7.5 Hz, 2H), 7.61-7.66 (tt, *J* = 7.2 Hz, 1H), 7.51-7.56 (dt, 2H), 5.02 (s, 2H), 3.95 (s, 1H), 2.06-2.08 (m, 1H), 1.42 (s, 9H), 0.84-0.90 (dd, 6H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 170.4, 156.2, 138.6, 133.9, 128.9, 128.4, 80.8, 59.9, 30.4, 28.2, 19.0, 17.6. HRMS (ESI): calcd. for $C_{16}H_{23}N_2O_5S^-$ 355.1333, found 355.1320 [M − H]$^-$. Melting point: 165-167°C.

*(S)-Tert-butyl(3-methyl-1-(4-nitrophenylsulfonamido)-1-oxobutan-2-yl)carbamate (**4n**)*

Yield: 88%. $[\alpha]_D^{20}$ = 2.2 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.85 (s, 1H), 8.35-8.42 (d, *J* = 9 Hz, 2H), 7.25-7.28 (d, *J* = 9 Hz, 2H), 4.97 (s, 1H), 3.83-3.90 (t, 1H), 2.03-2.14 (m, 1H), 1.43 (s, 9H), 0.89-0.93 (dd, 6H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 170.6, 156.3, 150.8, 144.0, 129.9, 124.1, 81.6, 60.3, 30.2, 28.2, 19.0, 17.9. HRMS (ESI): calcd. for $C_{16}H_{22}N_3O_7S^-$ 400.1184, found 400.1193 [M − H]$^-$. Melting point: 155-157°C.

*(S)-Tert-butyl(1-(4-chloro-3-nitrophenylsulfonamido)-3-methyl-1-oxobutan-2-yl)carbamate (**4o**)*

Yield: 84%. $[\alpha]_D^{20}$ = 26.6 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.89 (s, 1H), 8.53-8.54 (d, *J* = 2.1 Hz, 1H), 8.2-8.24 (dd, *J* = 8.4 Hz , *J* = 2.1 Hz, 1H), 7.73-7.76 (d, *J* = 8.4 Hz, 1H), 4.98 (s, 2H), 3.82-3.87 (t, 1H), 2.04-2.15 (m, 1H), 1.43 (s, 9H), 0.91-0.955 (dd, 6H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 170.6, 156.6, 147.6, 138.5, 133.0, 132.8, 132.7, 125.9, 81.7, 60.3, 30.2, 28.3, 19.1, 17.9. HRMS (ESI): calcd. for $C_{16}H_{22}ClN_3O_7S^-$ 434.0794, found 434.0806 [M − H]$^-$. Melting point: 127-130°C.

*Tert-butyl (2-oxo-2-(phenylsulfonamido)ethyl) carbamate (**4p**)*

Yield: 92%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.60 (s, 1H), 8.06-8.08 (d, *J* = 7.5 Hz, 2H), 7.61-7.67 (tt, *J* = 8.7 Hz, 1H), 7.52-7.57 (td, 2H), 5.242 (s, 1H), 3.823 (s, 2H), 1.44 (s, 9H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 168.0, 156.3, 138.5, 134.0, 129.0, 128.3, 81.1, 44.8, 28.2. HRMS (ESI): calcd. for $C_{13}H_{17}N_2O_5S^-$ 313.0864, found 313.0866 [M − H]$^-$. Melting point: 116-120°C.

*Tert-butyl(2-(4-nitrophenylsulfonamido)-2-oxoethyl) carbamate (**4q**)*

Yield: 90%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.80 (s, 1H), 8.37-8.40 (d, *J* = 8.7 Hz, 2H), 8.26-8.29 (d, *J* = 8.7 Hz, 2H), 5.21 (s, 1H), 3.81-3.83 (d, *J* = 5.7 Hz, 2H), 1.46 (s, 9H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 167.7, 156.7, 150.9, 143.9, 129.9, 124.2, 82.0, 45.4, 28.2. HRMS (ESI): calcd. for $C_{13}H_{16}N_3O_7S^-$ 358.0714, found 358.0697 [M − H]$^-$. Melting point: 144-147°C.

*Tert-butyl(2-(4-chloro-3-nitrophenylsulfonamido)-2-oxoethyl)carbamate (**4r**)*

Yield: 81%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.720 (s, 1H), 8.53-8,54 (d, *J* = 2.1 Hz, 1H), 8.21-8.25 (dd, *J* = 2.1 Hz , *J* = 8.4 Hz, 1H), 7.74-7.77 (d, *J* = 8.4 Hz, 1H), 5.11-5.15 (t, 1H), 3.79-3.81 (d, 2H), 1.47 (s, 9H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 167.7, 156.9, 147.8, 138.4, 133.2, 132.7, 132.6, 125.8, 82.2, 45.6, 28.2. HRMS (ESI): calcd. for $C_{13}H_{15}ClN_3O_7S^-$ 392.0325, found 392.0331 $[M-H]^-$. Melting point: 142-145°C.

*(S)-Tert-butyl(1-oxo-1-(phenylsulfonamido)propan-2-yl)carbamate (**4s**)*

Yield: 73%. $[\alpha]_D^{20}$ = −23.4 (c = 0.50, CH_3OH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.76 (s, 1H), 8.05-8.08 (d, *J* = 7.8Hz, 2H), 7.62-7.67 (tt, 1H), 7.51-7.56 (dt, 2H), 4.89 (s, 1H), 4.11 (s, 1H), 1.44 (s, 9H), 1.29-1.46 (d, 3H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 170.6, 156.2, 138.6, 133.9, 128.9, 128.3, 81.4, 50.4, 28.2, 16.7. HRMS (ESI): calcd. for $C_{14}H_{19}N_2O_5S^-$ 327.1020, found 327.1101 $[M-H]^-$. Melting point: 142-145°C.

*Tert-butyl (4-oxo-4-(phenylsulfonamido)butyl) carbamate (**6a**)*

Yield: 80%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.19 (s, 1H), 8.07-8.09 (d, *J* = 14.1 Hz, 1H), 7.61-7.66 (tt, 1H), 7.51-7.56 (td, 2H), 4.76 (s, 1H), 3.07-3.13 (q, 2H), 2.27-2.31 (t, *J* = 12.9 Hz, 2H), 1.66-1.77 (m, 2H), 1.46 (s, 9H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 171.2, 157.2, 139.0, 133.7, 128. 9, 128.3, 80.1, 39.1, 33.44, 28.4, 26.1. HRMS (ESI): calcd. for $C_{15}H_{21}N_2O_5S^-$ 341.1177, found 341.1188 $[M-H]^-$. Melting point: 139-141°C.

*Tert-butyl(4-(4-nitrophenylsulfonamido)-4-oxobutyl) carbamate (**6b**)*

Yield: 85%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 12.4 (s, 1H), 8.41-8.46 (d, 2H), 8.14-8.19 (d, 2H), 6.74-6.78 (t, 1H), 2.77-2.84 (q, 2H), 2.21-2.26 (t, 2H), 1.45-1.54 (m, 2H), 1.35 (s, 9H). ^{13}C-NMR (300 MHz, DMSO): δ = 171.6, 155.5, 150.2, 144.5, 129.1, 124.1, 77.5, 56.0, 32.7, 28.2, 24.2. HRMS (ESI): calcd. for $C_{15}H_{20}N_3O_7S^-$ 386.1027, found 386.1040 $[M-H]^-$. Melting point: 163-165°C.

*Tert-butyl (4-(4-chloro-3-nitrophenylsulfonamido)-4-oxobutyl)carbamate (**6c**)*

Yield: 79%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.93 (s, 1H), 8.56 (s, 1H), 8.25-8.28 (dd, *J* = 8.4 Hz, *J* = 2.1 Hz, 1H), 7.72-7.75 (d, *J* = 8.4 Hz, 1H), 4.84 (s, 1H), 3.10-3.17 (q, 2H), 2.285-2.328 (t, 2H), 1.714-1.80 (m, 2H), 1.47 (s, 9H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 171.6, 157.6, 147.6, 139.0, 132.7, 125.7, 80.6, 39.0, 33.5, 28.3, 26.3. HRMS (ESI): calcd. for $C_{15}H_{19}ClN_3O_7S^-$ 420.0638, found 420.0643 $[M-H]^-$. Melting point: 92-95°C.