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N-Aminosulfamide Peptide Mimic Synthesis by Alkylation of Aza-sulfurylglycinyl Peptides

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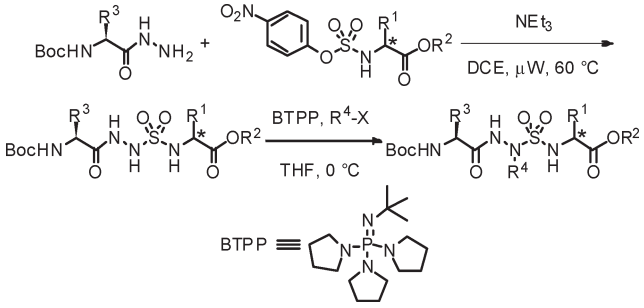
ABSTRACT



***N*-Aminosulfamides are peptidomimetics in which the $C_\alpha H$ and the carbonyl of an amino acid residue are both respectively replaced by a nitrogen atom and a sulfonyl group. Aza-sulfurylglycinyl tripeptide analogs were effectively synthesized from amino acid building blocks by condensations of *N*-protected amino hydrazides and *p*-nitrophenylsulfamidate esters. The installation of *N*-alkyl chains and access to other aza-sulfuryl amino acid residues were effectively achieved by chemoselective alkylation.**

The biological activity and physical properties of peptide structures are inherently contingent on backbone geometry and side chain functionality, such that attempts to modulate natural function are challenged to consider innate form. For example, replacement of a peptide amide by a phosphonamide[1] or a silanediol[2] may effectively mimic the tetrahedral transition states common in enzyme-catalyzed reactions and produce enzyme inhibitors. Although the respective amide to sulfonamide exchange may appear promising, the resulting α-sulfonamido peptides have been reported to be unstable.[3]

N-Aminosulfamido peptides **1** in which both the $C_\alpha H$ and the carbonyl of an amino acid residue are respectively replaced by a nitrogen atom and a sulfonyl group have proven to be more stable (Figure 1). Moreover,

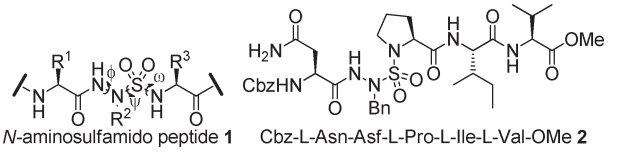


Figure 1. *N*-Aminosulfamido peptide **1** and proteinase inhibitor **2**.

aza-sulfurylphenylalaninyl (Asf) peptide **2** was reported to inhibit the human immunodeficiency virus-1 (HIV-1) proteinase, presumably by imitating the transition state for amide bond hydrolysis.[4]

Aza-sulfuryl peptide analogs combine the characteristics of aza- and α-sulfonamido peptides, thus offering interesting potential for modifying backbone geometry. The sulfonyl group possesses a tetrahedral sulfur, which adopts ω torsion angle values around ±60° and ±100° (instead of

(1) Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengeler, P. A.; Phillips, B. W.; Moore, W.; Smith, A. B., III *J. Am. Chem. Soc.* **1997**, *119*, 8177–8190 and refs 1–18 cited therein.

(2) Chen, C. A.; Sieburth, S. M. N.; Glekas, A.; Hewitt, G. W.; Trainor, G. L.; Erickson-Viitanen, S.; Garber, S. S.; Cordova, B.; Jeffry, S.; Klabe, R. M. *Chem. Biol.* **2001**, *8*, 1161–1166.

(3) Gilmore, W. F.; Lin, H. J. *J. Org. Chem.* **1978**, *43*, 4535–4537.

(4) Cheeseright, T. J.; Daenke, S.; Elmore, D. T.; Jones, J. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1953–1955.

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amide *cis*-(*E*) and *trans*-(*Z*) conformations at respectively 0° and ±180°) separated by a lower S−N rotational barrier ($\Delta G^{\ddagger} \approx 35$ kJ/mol), relative to the amide C−N ($\Delta G^{\ddagger} \approx 75$ kJ/mol).[5] Furthermore, the S−N bond length is longer than the C−N, due to lack of an amide bond resonance and greater sp^3 versus sp^2 character of the sulfonamide nitrogen (Figure 2).

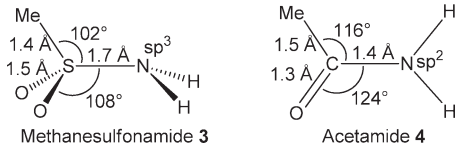
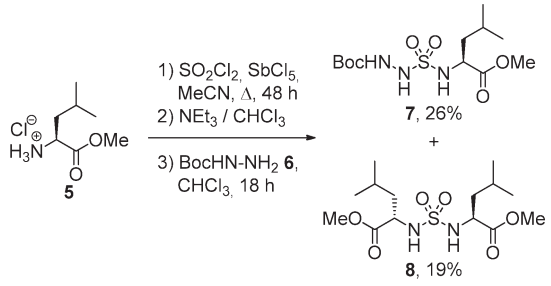


Figure 2. Sulfonamide[6] and amide[7] bond lengths and angles.

In light of their interesting conformational and biological properties, the synthesis of *N*-aminosulfamides has apparently restricted their application in peptide mimicry.[4] To the best of our knowledge, only one method has been reported for constructing acyclic *N*-aminosulfamides and employs sulfuryl chloride (SO_2Cl_2) to combine hydrazide and amine components (Scheme 1).[8]

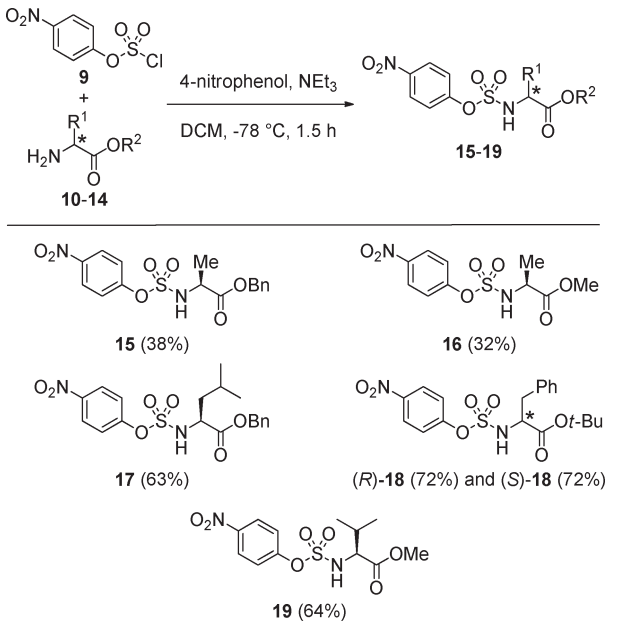
Scheme 1. Reported Synthesis of *N*-Aminosulfamides



Coupling was relatively sluggish, in spite of the addition of catalytic amounts of toxic antimony pentachloride ($SbCl_5$), such that, in the synthesis of *N*-aminosulfamide **7**, reaction of 2 equiv of the amine component with sulfuryl chloride competed to produce symmetric sulfamide **8** as a major side product. In addition, introduction of side chains onto the *N*-aminosulfamide residue required synthesis of *N*-alkyl protected hydrazide precursors.[8]

Inspired by our past applications of sulfamidates as synthetic intermediates,[9] as well as the application of aza-glycine alkylation in the submonomer synthesis of azapeptides,[10] we have pursued an approach to *N*-aminosulfamide peptides featuring convergent synthesis of an aza-sulfurylglycine intermediate and subsequent chemoselective alkylation. 4-Nitrophenyl chlorosulfate **9** has been used effectively in the synthesis of sulfamides[11] and was thus studied for the selective synthesis of *N*-aminosulfamides.

Scheme 2. Synthesis of the *p*-Nitrophenylsulfamidate Esters **15**–**19**



Initial attempts to prepare sulfamidates from hydrazones and chlorosulfate **9** gave however azines. In contrast, the corresponding sulfamidates were prepared successfully from various amino esters, i.e., L-Ala-OBn (**10**), L-Ala-OMe (**11**), L-Leu-OBn (**12**), D- and L-Phe-O*t*-Bu [(*R*)- and (*S*)-**13**], and L-Val-OMe (**14**) (Scheme 2).

A 2 equiv amount of 4-nitrophenol was necessary as an additive to avoid formation of symmetric sulfamide. Additionally, 2 equiv of chlorosulfate **9** were also crucial for sulfamidate formation. Lower yields of **15** and **16** were incurred during purification on silica gel and using aq. $NaHCO_3$ washings to remove 4-nitrophenol (Supporting Information). Relative to sulfuryl chloride, which needs to be distilled prior to use, chlorosulfate **9** was a convenient solid. Similarly, except for sulfamidate **18**, the *p*-nitrophenylsulfamidates were solids, which could be stored for several months without decomposition.

(5) Baldauf, C.; Gunther, R.; Hofmann, H. J. *THEOCHEM* **2004**, *675*, 19–28.
(6) Bharatam, P. V.; Gupta, A.; Kaur, D. *Tetrahedron* **2002**, *58*, 1759–1764.
(7) Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 866–870.
(8) Cheeseright, T. J.; Edwards, A. J.; Elmore, D. T.; Jones, J. H.; Raissi, M.; Lewis, E. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1595–1600.
(9) (a) Wei, L.; Lubell, W. D. *Can. J. Chem.* **2001**, *79*, 94–104. (b) Atfani, M.; Wei, L.; Lubell, W. D. *Org. Lett.* **2001**, *3*, 2965–2968. (c) Jamieson, A. G.; Boutard, N.; Beauregard, K.; Bodas, M. S.; Ong, H.; Quiniou, C.; Chemtob, S.; Lubell, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 7917–7927. (d) Boutard, N.; Turcotte, S.; Beauregard, K.; Quiniou, C.; Chemtob, S.; Lubell, W. D. *J. Pept. Sci.* **2011**, *17*, 288–296. (e) Meléndez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581–2616.
(10) (a) Sabatino, D.; Proulx, C.; Klocek, S.; Bourguet, C. B.; Boeglin, D.; Ong, H.; Lubell, W. D. *Org. Lett.* **2009**, *11*, 3650–3653. (b) Bourguet, C. B.; Proulx, C.; Klocek, S.; Sabatino, D.; Lubell, W. D. *J. Pept. Sci.* **2010**, *16*, 284–296. (c) Sabatino, D.; Proulx, C.; Pohankova, P.; Ong, H.; Lubell, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 12493–12506.

To further examine conformational properties, sulfamidate **19** was crystallized from EtOAc on diffusion of hexane vapors (Figure 3 and Supporting Information). The crystal structure shows that the sulfamidate (−N−$S(O_2)$−O−) adopts a distorted tetrahedral structure and that the N−S bond length (1.593 Å) is longer than an amide bond (Figure 2). Furthermore, the ω torsion angle (62.2°) was close to the ideal theoretical value (60°) for sulfonamides.[5]

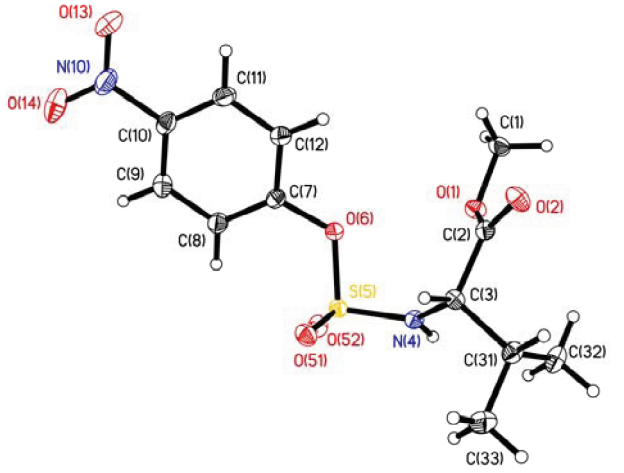


Figure 3. Crystal structure of sulfamidate **19**, showing the atomic numbering system employed.

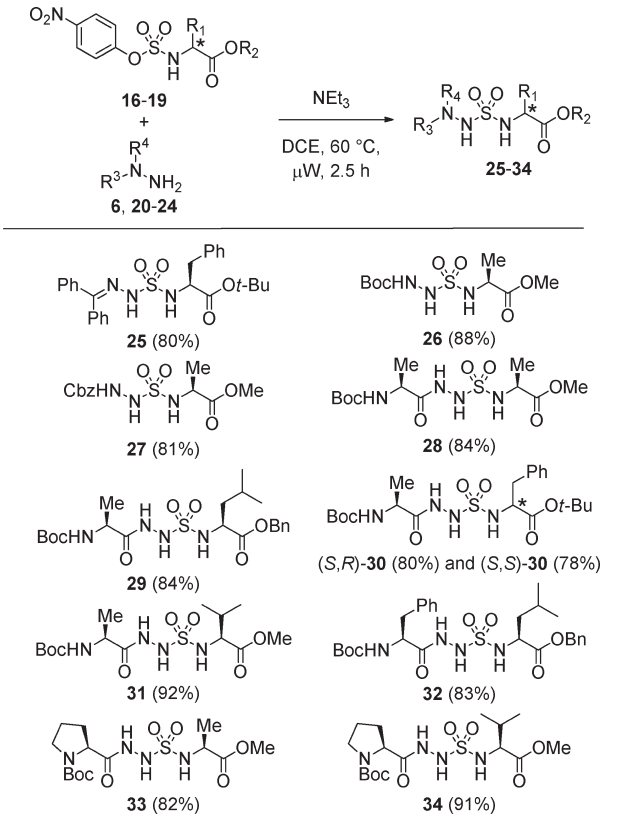
N-Aminosulfamides **25**−**34** were synthesized by reaction of sulfamidates **16**−**19** respectively with benzophenone hydrazone (**20**), *tert*-butyl and benzyl carbazates (**6** and **21**), and *N*-(Boc)-L-Ala, L-Phe, and L-Pro hydrazides (**22**−**24**) (Scheme 3).

Microwave irradiation proved important in the formation of the *N*-aminosulfamides and favored coupling between the two precursors. In contrast to the 80% yield using microwave heating, synthesis of *N*-aminosulfamide **25** in DCM using conventional heating at reflux for 24 h gave only a 36% yield and recovered starting material.

Although side chains may in principle be introduced onto the *N*-aminosulfamide moiety by employing *N*′-alkylhydrazides, inspired by our submonomer approach to azapeptides,[10] chemoselective alkylation was pursued to provide a combinatorial approach to aza-sulfuryl amino acid residues. Initially, attempts to employ hydrazone and carbazate derivatives **25**−**27** in chemoselective alkylation/deprotection sequences failed, likely due to sulfonyl hydrazide decomposition.[12]

Chemoselective alkylation of aza-sulfurylglycinyl (Asg) peptides **28**−**30** and **32** proved effective for preparing orthogonally protected building blocks **35**−**41** for incorporation into longer peptides (Scheme 4). Initially, *N*-Boc-Ala-Asg-Ala-OMe (**28**) was treated with potassium *tert*-butoxide and propargylbromide to provide azasulfuryl tripeptide **35**, albeit in 20% yield with recovered starting material. By switching to the phosphazene base, *tert*-butylimino-tri(pyrrolidino)-phosphorane (BTPP), the alkylation yield was improved to 73%. Subsequent reactions were performed with BTPP. *Bis*-alkylation was minimized by employing stoichiometric amounts of base and alkylating reagent.

Scheme 3. Synthesis of the *N*-Aminosulfamides **25**−**34**



The position of alkylation was ascertained by NMR experiments on tripeptide **35** (Supporting Information). In the 2D COSY spectrum, through-bond correlations were observed between the alanine N−H and C_α−H protons. In the 2D HMBC spectrum, through-bond correlation was observed between the hydrazide NH and carbonyl carbon. The position of alkylation was assigned for analogs **36**−**41** based on analogy to **35**, because of the relatively similar chemical shifts for the N−H signals in the ^{1}H NMR spectra.

In order to ascertain if epimerization had occurred during the alkylation of aza-sulfurylglycine, (*S*,*R*)- and (*S*,*S*)-diastereoisomers of aza-sulfurylallylglycinyl

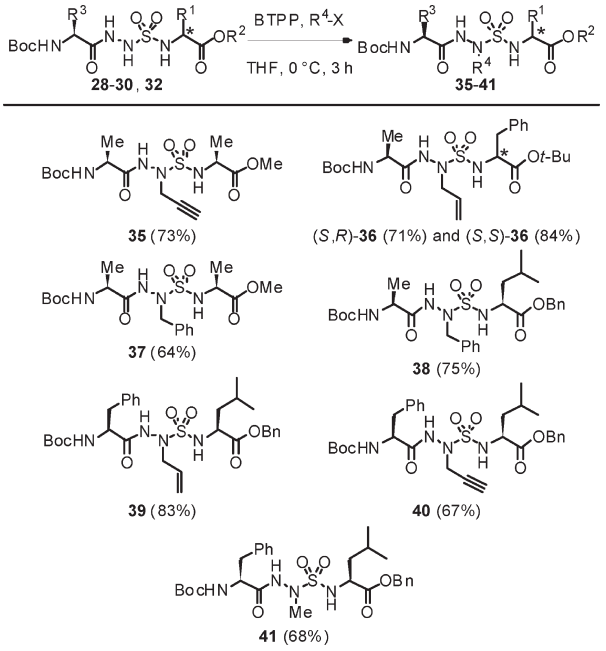
(11) Fettes, K. J.; Howard, N.; Hickman, D. T.; Adah, S.; Player, M. R.; Torrence, P. F.; Micklefield, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 485–495.

(12) Movassaghi, M.; Ahmad, O. K. *J. Org. Chem.* **2007**, *72*, 1838–1841.

(13) The presence of < 10% diastereomeric aza-sulfurylglycinyl tripeptide **30** may likely be caused by racemization during formation of the *N*-(Boc)-L-Ala hydrazide. See: Benoiton, N.; Kuroda, K.; Chen, F. M. F. *Int. J. Pept. Protein Res.* **1982**, *20*, 81–86.

tripeptide **36** were synthesized and analyzed by ^{1}H NMR spectroscopy. The diastereoisomeric ratio observed for the alkylated product **36** was consistent with the starting aza-sulfurylglycinyl tripeptide diastereomers **30**, indicating no epimerization.[13] Furthermore, treatment of aza-sulfurylallylglycinyl tripeptide (*S*,*R*)-**36** with 1 equiv of BTPP at room temperature for 3 h failed to cause epimerization.

Scheme 4. Chemoselective Alkylation of Aza-sulfurylglycinyl Peptides



In conclusion, a new method for the synthesis of *N*-aminosulfamides has been developed featuring the coupling of *p*-nitrophenylsulfamidates and *N*-(Boc)-amino acid hydrazides under microwave irradiation. Chemoselective alkylation of the aza-sulfurylglycinyl peptides was used to add side-chain diversity and prepare other aza-sulfuryl amino acid residues. This method avoids symmetric sulfamide formation as well as the use of *N*′-alkyl hydrazides in the synthesis of the *N*-aminosulfamide peptides. The crystallization of sulfamidate **19** confirmed the tetrahedral nature of the sulfur and the 60° ω-torsion angle. We are currently working on crystallizing the *N*-aminosulfamides to validate the potential for mimicry of the transition state of amide bond hydrolysis. In addition, insertion of the *N*-aminosulfamide tripeptide building blocks into biologically active peptides is being pursued to study structure–activity relationships.

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Supporting Information Available. Experimental procedures, NMR data for all compounds, and cif file for compound **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.