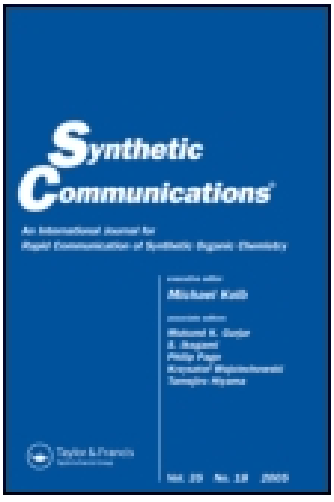

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

New Mild and Efficient Synthesis of Peptidosulfonamides

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Published online: 22 Feb 2008.

To cite this article: Giovanni Papandrea & Fabio Ponticelli (2008) New Mild and Efficient Synthesis of Peptidosulfonamides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:6, 858-865, DOI: 10.1080/00397910701845340

To link to this article: http://dx.doi.org/10.1080/00397910701845340

Synthetic Communications®, 38: 858–865, 2008

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701845340

New Mild and Efficient Synthesis of Peptidosulfonamides

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Abstract: This article describes a new route to peptidosulfonamide. Our study shows how sulfinamides were first obtained via nucleophilic cleavage of 3,6-dihydrothiazine-1-oxide system and how the products can be subjected to oxidation with *m*-chloroperbenzoic acid to give sulfonamides in good yield.

Keywords: 3,6-dihydrothiazine-1-oxide system, m-chloroperbenzoic acid, peptidomimetics, peptidosulfonamide, tripeptide

INTRODUCTION

Peptidomimetics are particularly interesting because they can be used to mimic biologically active peptides.[1] In the past, a wide variety of peptidomimetic building blocks has been developed, and one of the most important is the sulfonamide moiety. This functional group is ubiquitous in bioorganic and medicinal chemistry,[2] providing a key polar alternative to the amide group for which it is frequently used as a bioisosteric replacement.

In our previous communication we described the stereospecific synthesis of *cis*-4-aminocyclopent-2-ene-1-sulfonic acid.[3] As an extension to this work and to point out our interest in founding new routes for the formation of sulfonamides, herein we present a convenient synthetic route of a particular type of peptidomimetic building block including a β-aminocyclopentene sulfonic acid to be used for the preparation of peptidosulfonamides. This successively

Received in Poland July 3, 2007
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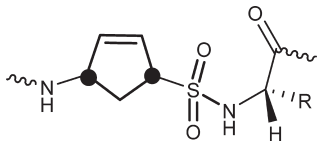


Figure 1. General structure of a peptidosulfonamide.

could be incorporated in a small peptide. The general structure of these compounds is shown in Fig. 1.

RESULTS AND DISCUSSION

Before employing amino acids, we began our study with several primary and secondary amines to obtain simple sulfonamide derivates.

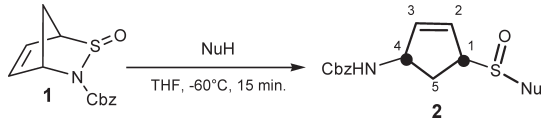
Initially, we investigated various standard methods for the synthesis of the target sulfonamides. The most frequently used procedure involves the reaction of a sulfonic acid with thionyl chloride, chlorosulfonic acid, or phosphorus pentachloride to give the corresponding chlorosulfonyl derivatives, followed by reaction of the chlorosulfonyl intermediate with the appropriate amine.[4] Although this method is usually efficient, this route failed under various reaction conditions when it was applied to our compound (*cis*-4-aminocyclopent-2-ene-1-sulfonic acid), and the expected sulfonamides could not be isolated.

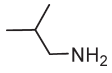
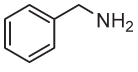
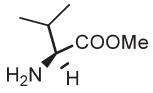
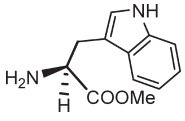
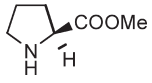
Hence, there was need to develop a mild, efficient, and, if possible, one-pot synthesis of sulfonamides that could avoid laborious purifications. We therefore tried to reinvestigate the preparation of our aminosulfonic acid,[3] which, as we previously reported, is obtained from the intermediate 3,6-dihydrothiazine-1-oxide system **1**, highly susceptible attack by several nucleophilic agents. As a consequence, we tested this reaction with a series of primary and secondary amines, obtaining several kinds of sulfinamide products (Table 1, entries a–d).

To assess efficiency of our approach, we extended the range of nucleophilic attack in coupling reaction by amino acids, and we were particularly encouraged by the observation that this reaction is not limited to simple amines but is applicable to the synthesis of dipeptidosulfinamides (Table 1, entries e–g).

Particularly remarkable is compound **2g**. This is the only product in which we recognize the presence of four diastereoisomers in high performance liquid chromatography (HPLC) analysis. This is possibly due to the presence of the chiral sulfur of the sulfinamide that shows its optical features. Finally, we found that the nucleophilic attack can be employed to acquire directly a tripeptide too. Indeed, when we reacted a dipeptide, previously synthesized, we obtained small peptidosulfinamides in good yield and in only one step (Table 1, entries h and i).

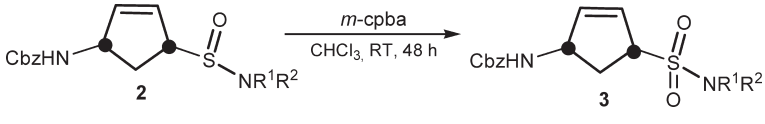
Table 1. Synthesis of sulfinamides derivates



Entry	NuH	Yield (%)[a]
a		94
b		86
c		70
d		62
e		72
f		70
g		74
h	NH_2Val-PheOCH$_3$	72
i	NH_2Arg(Mtr)-GlyO*t*-but	60

[a]Isolated yield of analytically pure ^{1}H sulfinamide.

Successively, sulfonamides can be smoothly obtained in good yeld, as shown for compound **3g**, by oxidation with a stoichiometric equivalent of *m*-chloroperbenzoic acid and purification by column chromatography (Scheme 1). The structures of all new compounds were unequivocally confirmed by one- and two-dimensional ^{1}H and ^{13}C NMR spectra.



Scheme 1. Oxidation of sulfinamides to sulfonamides.

We think that this method could be generally applicable to different 3,6-dihydrothiazine-1-oxide systems. Our approach offers several advantages over traditional methods for the synthesis of this particular type of sulfonamides. First, it avoids the use of sulfonyl chlorides (highly reactive, sometimes difficult to prepare, and often unstable species); second, it gives final products in very good yield. In addition, handling and purification are very easy, and the procedure shows broad applicability to a wide range of amines (including aminoacid). Finally, it is possible to get further chemical modification of the obtained compounds.

CONCLUSION

In summary, we have developed a mild, two-step method, which has shown its applicability as a building block for sulfonamide synthesis. Further investigations are under way to extend the applicability of this method.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 200 spectrometer at 200.13 and 50.33 MHz, respectively and a Bruker Avance 400 NMR instrument. ESI-MS spectra were obtained with a LCQ-DECA Thermo Finnigan instrument. All new compounds gave satisfactory (within 0.3%) analytical data.

General Procedure for the Synthesis of Peptidosulfinamides 2a–g

In a racemic solution of **1** (3.2 mmol) in toluene (3 mL) and THF (8 mL) at $-60^{\circ}C$ the corresponding amine or aminoacid previous protected as ester (3.2 mmol), solubilized in the minimal THF amount was added dropwise, and the mixture was stirred for 15 min. The solution was evaporated in vacuo, solubilized in 8 mL of chloroform, and submitted to an easy workup by extraction with water (2×6 mL). The organic solution was washed with a saturated $NaHCO_3$ solution (10 mL) and then dried over anhydrous $MgSO_4$. After removal of solvents under reduced pressure, a white solid or colorless oil was obtained.

Typical Procedure for the Synthesis of Tripeptidosulfinamides 2h and i

(a) The two amino acids (1 eq. each) were coupled using 4,6-dimethoxy-[1,3,5]-triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM) (3 eq.) in the presence of N-methylmorpholine (3 eq.) and $NaHCO_3$ (1.5 eq.) in

methanol solution at room temperature, followed by stirring for 12 h. After the reaction time, the solution was evaporated in vacuo, solubilized in EtOAc, extracted with 1 N HCl, and washed successively with water, saturated sodium bicarbonate, water, and brine. The organic layer was dried over $MgSO_4$. Concentration of the solution under reduced pressure yielded the dipeptide in good yield. Spectroscopic data are in agreement with previous publications.[5,6]

(b) To a racemic solution of **1** (2 mmol) in toluene (3 mL) and THF (8 mL) at $-30^{\circ}C$, the corresponding dipeptide, previously synthesized and protected as ester (2 mmol) and solubilized in the minimal THF amount, was added dropwise. The mixture was stirred for 15 min. After the reaction time, the solution was diluted with 6 mL of water, successively evaporated under reduced pressure, to give compounds **2h** and **i** as a colorless oil.

Typical Procedure for the Preparation of Sulfonamides from Sulfinamides

Sulfinamide (2 mmol) was added to a solution of *m*-chloroperbenzoic acid (2.2 mmol) in chloroform, and the reaction mixture was stirred for 48 h at room temperature. After the reaction time, the solution was evaporated in vacuo, solubilized in 10 mL of chloroform, and submitted to an easy workup by extraction with a saturated Na_2CO_3 solution (2×8 mL). The organic solution was dried over anhydrous $MgSO_4$. After solvents were removed under reduced pressure, the residue was purified by silica-gel chromatography, eluting with a 3:1 solution of benzine/diethylether to afford a colorless oil in near quantitative yield.

Analytical and Spectroscopic Data of Compounds

(Z) Pirrolidinsulfinamoyl-cyclopent-2-enyl-4-carbamic acid benzyl ester 2a: ^{1}H NMR (200 MHz $CDCl_3$) δ: 1.90 (m, 4H, $\underline{CH_2}CH_2N$), 2.25 (dt, 1H, $J = 14.9$, 2.5 Hz, *cis* H_5), 2.55 (dt, 1H, $J = 14.9$, 8.5 Hz, *trans* H_5), 3.25 (m, 4H, CH_2N), 3.76 (m, 1H, H_1), 4.75 (m, 1H, H_4), 5.05 (s, 2H, $PhCH_2O$), 5.78 (m, 2H, H2,H3), 7.25 (s, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ: 25.5 ($\underline{CH_2}CH_2N$), 33.3 (C_5), 46.4 (CH_2N), 55.6 (C_4), 66.5 (OCH_2Ph), 66.6, 66.8* (C_1), 127.9 (Ph), 128.3 (Ph), 128.9 (C_3), 129.2 (Ph), 137.1 (C_2), 137.5 (Ph), 155.4 (NCOO); MS (ESI), m/z: 335 $(M + H)^+$.

(Z) Morpholinsulfinamoyl-cyclopent-2-enyl-4-carbamic acid benzyl ester 2b: ^{1}H NMR (200 MHz $CDCl_3$) δ: 1.59 (dt, 1H, $J = 14.9$, 4.6 Hz, *cis* H_5), 2.45 (dt, 1H, $J = 14.9$, 6.7 Hz *trans* H_5), 3.05 (m, 4H, CH_2N), 3.65 (m, 4H, CH_2O), 3.68 (m, 1H, H_1), 4.32 (m, 1H, H_4), 5.08 (s, 2H, $PhCH_2O$), 5.82 (m, 2H, H_2,

*Double signals due to the presence of diastereoisomers.

H_3), 7.25 (s, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ: 32.6 (C_5), 45.9 (CH_2N), 51.6 (C_4), 62.6 (OCH_2Ph), 64.1 (CH_2O), 66.3, 66.4* (C_1), 127.7 (Ph), 128.2 (C_3), 128.4 (Ph), 129.2 (Ph), 137.4 (C_2), 138.1 (Ph), 156.0 (NCOO); MS (ESI), m/z: 351 $(M + H)^+$.

(Z) Isobutylsulfinamoyl-cyclopent-2-enyl-4-carbamic acid benzyl ester 2c: ^{1}H NMR (200 MHz $CDCl_3$) δ: 0.92 (d, 6H, $J = 6.8$ Hz, $\underline{CH_3}CH$), 1.68 (m, 1H, $CH_3\underline{CH}$), 1.81 (dt, 1H, $J = 14.9$, 1.7 Hz, *cis* H_5), 2.5 (dt, 1H, $J = 14.9$, 7.9 Hz, *trans* H_5), 2.90 (m, 2H, CH_2N), 3.94 (m, 1H, H_1), 4.80 (m, 1H, H_4), 5.08 (s, 2H, OCH_2Ph), 6.05 (m, 2H, H_2-H_3), 7.28 (s, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ: 19.8 (CH_3CH), 30.0 ($CH_3\underline{CH}$) 33.1 (C_5), 52.1 (C_4), 55.3 (CH_2N), 66.6 (OCH_2Ph), 68.0 (C_1), 127.8 (Ph), 127.9 (Ph), 128.3 (C_3), 128.4 (Ph), 133.1 (Ph), 136.2 (C_2), 156.9 (NCOO); MS (ESI), m/z: 337 $(M + H)^+$, 359 $(M + Na)^+$, 695 $(2M + Na)^+$.

(Z) Benzylsulfinamoyl-cyclopent-2-enyl-4-carbamic acid benzyl ester 2d: ^{1}H NMR (200 MHz $CDCl_3$) δ: 1.90, (dt, 1H, $J = 14.1$, 5.05 Hz, *cis* H_5), 2.81 (dt, 1H, $J = 14.1$, 7.7 Hz, *trans* H_5), 3.24 (m, 1H, H_1), 4.05 (s, 2H, NCH_2Ph), 4.60 (m, 1H, H_4), 4.95 (s, 2H, OCH_2Ph), 5.90 (m, 2H, H_2-H_3), 7.2 (m, 10H, Ph); MS (ESI), m/z: 393 $(M + Na)^+$, 763 $(2M + Na)^+$.

(±)-Cis-4-amino-benzyloxycarbonil-cyclopent-2-ene-1-sulfinamoyl-(S)-valine methyl ester 2e: ^{1}H NMR (400 MHz CD_3OD) δ: 0.97, 1.03* (2d, 12H, $J = 2.45$ Hz, CH_3CH), 1.75, 2.00* (2dt, 2H, $J = 14.9$, 4.2 Hz, *cis* H_5), 2.25 (m, 2H, $CH_3\underline{CH}$), 2.48 (m, 2H, *trans*, H_5), 3.64 (m, 2H, H_1), 3.75 (s, 6H, OCH_3), 4.05 (m, 2H, α-CH), 4.68 (m, 2H, H_4), 4.98, 5.02* (2s, 4H, OCH_2Ph), 5.94 (m, 4H, H2,3), 7.22 (s, 10H, Ph); ^{13}C NMR (CD_3OD) δ: 18.1, 18.3* ($\underline{CH_3}CH$), 30.0 ($CH_3\underline{CH}$), 30.9, 31.6* (C_5), 55.7, 55.8* (OCH_3), 56.7, 57.1* (C_4), 59.3, 59.7* (α-CH), 64.4, 65.7* (C_1), 67.1, 67.4* (OCH_2Ph), 128.9, 129.3* (C_3), 127.8, 127.9*, 128.1, 128.5*, 128.7, 129.3*, 138.5, 138.7* (Ph), 139, 139.6* (C_4), 157.6 (NCOO), 170.3 ($COOCH_3$). MS (ESI), m/z: 395 $(M + H)^+$.

(±)-cis-4-amino-benzyloxycarbonyl-cyclopent-2-ene-1-sulfinamoyl-(S)-triptophane methyl ester 2f: ^{1}H NMR (200 MHz CD_3OD) δ: 1.75, 2.02* (2dt, 2H, $J = 14.6$, 3.8 Hz, *cis* H_5), 2.48 (m, 2H, *trans* H_5), 3.31 (m, 4H, CH_2–Ind), 3.60 (s, 6H, OCH_3), 3.71 (m, 2H, H_1), 4.25 (m, 2H, α-CH), 4.72 (m, 2H, H_4), 5.03, 5.05* (2s, 2H, OCH_2Ph), 5.89 (m, 4H, H_2,H_3), 7.00–7.65 (m, 20H, Ph, Ind); MS (ESI), m/z: 482 $(M + H)^+$.

(±)-Cis-4-amino-benzyloxycarbonyl-cyclopent-2-ene-1-sulfinamoyl-(S)-proline methyl ester 2g: ^{1}H NMR (200 MHz $CDCl_3$) δ: 1.50–1.78 (m, 10H, $NCH_2\underline{CH_2CH_2}$; *cis* H_5), 1.90–2.11 (m, 2H, *trans* H_5), 2.60–2.95 (m, 4H,

*Double signals due to the presence of diastereoisomers.

NCH_2-$\underline{CH_2}$), 3.42 (m, 2H, H_1), 3.48 (s, 6H, OCH_3), 3.66 (m, 2H, H_1), 3.72 (m, 2H, α-CH), 4.68 (m, 2H, H_4), 4.82 (s, 4H, OCH_2), 5.50 (m, 4H, H_2,H_3), 7.05 (s, 10H, Ph); MS (ESI), m/z: 415 $(M + Na)^+$, 807 $(2M + Na)^+$. The HPLC-ESI-MS analyses were performed on a LCQ-DECA Thermo Finnigan instrument coupled with P4000 spectra System HPLC pump. The column used was a 250 × 4.6 mm i.d., 5 μm C_{18} LiChroCART® 250–4 Merck. Elution was with a binary solution of 70% H_2O (1% HCOOH) and 30% AcCN. Injection volume was 80 μL. Retention times were 34.1, 36.3, 38.3, and 44.6 min.

(±)-Cis-4-amino-benzyloxycarbonyl-cyclopent-2-ene-1-sulfinamoyl-(S)-valine-(S)-phenylalanine methyl ester 2h: ^{1}H NMR (400 MHz CD_3OD) δ: 0.68, 0.85* (2d, 12H, $J = 7.2$ Hz, $\underline{CH_3}CH$), 1.80–1.98 (m, 4H, $CH_3\underline{CH}$; *cis*-H_5), 2.34 (dt, 2H, $J = 13.8$, 8.9 Hz, *trans*-H_5), 2.95, 3.21* (2 m, 4H, CH_2Ph), 3.29 (m, 2H, H_1), 3.32 (s, 6H, OCH_3), 3.58 (m, 2H, α-CHval), 4.51 (m, 2H, α-CHphe), 4.67 (m, 2H, H_4), 5.03 (s, 4H, OCH_2Ph), 5.84–5.98 (bs, 4H, H2, H3), 7.03–7.41 (m, 20H, Ph); ^{13}C NMR (CD_3OD) δ: 17.9, 19.2* (CH_3CH), 30.6 ($CH_3\underline{CH}$), 32.7 (C_5), 39.5 (CH_2Ph), 52.9 (α-CHphe), 56.8 (C_4), 58.2, 58.7* (C_1), 61.8 (OCH_3), 67.3 (α-CHval), 74.7 (OCH_2Ph), 135.5, 139.6 (C_2/C_3), 127.2, 128.7, 128.8, 129.1, 129.4, 130.4, 131.1, 136.0 (Ph), 176.2 (NCOO), 179.3 ($COOCH_3$); MS (ESI), m/z: 540 $(M\text{-}H)^-$.

(±)-Cis-4-amino-benzyloxycarbonyl-cyclopent-2-ene-1-sulfinamoyl-(S)-arginine(Mtr)-(S)-glycine-t-butyl ester 2i: ^{1}H NMR (200 MHz $CDCl_3$) δ: 1.45 (s, 9H, *t*-but), 1.52 (m, 4H, α-$\underline{CH_2CH_2}CH_2N$), 1.82 (dt, 1H, J = 14.9, 3.3 Hz, *cis* H_5), 2.16 (s, 9H, CH_3Ph), 2.52 (m,1H, *trans*-H_5), 2.63 (m, 2H, $NCH_2\underline{CH_2}CH_2$), 3.31 (m, 1H, H_1), 3.48 (m, 1H, α-CHarg), 3.64 (s, 3H, OCH_3), 4.02 (s, 2H, α-CH_2gly), 4.72 (m, 1H, H_4), 5.02 (s, 2H, OCH_2Ph), 5.94 (m, 2H, H_2-H_3), 6.65 (s, 1H, H-Ar), 7.25 (s, 5H, Ph); MS (ESI), m/z: 763 $(M + H)^+$.

(±)-Cis-4-amino-benzyloxycarbonyl-cyclopent-2-ene-1-sulfonamoyl-(S)-proline methyl ester 3g: ^{1}H NMR (200 Mhz CD_3OD) δ: 1.85, 2.12* (2 m, 10H, $NCH_2\underline{CH_2CH_2}$; *cis* H_5), 2.18, 2.38* (2 m, 2H, *trans* H_5), 2.59, 2.82* (2 m, 4H, $NCH_2\underline{CH_2}$), 3.55 (m, 2H, α-CH), 3.69 (s, 6H, OCH_3), 3.75 (m, 2H, H_1), 4.48 (m, 2H, H_4), 5.02 (s, 4H, OCH_2), 5.92, 6.08* (2 m, 4H, H_2/H_3), 7.31 (s, 10 H, Ph); MS (ESI), m/z: 431 $(M + H)^+$.

ACKNOWLEDGMENTS

The authors thank Laura Salvini (Centro di Analisi e Determinazioni Strutturali, University of Siena) for recording ESI-MS spectra. This work was financially supported by the University of Siena (Piano di Ateneo per la Ricerce (PAR) Project 2006) and by Ministero Istruzione, Università e Ricerca (MIUR) (Piano di Ricerca di Interesse Nazionale (PRIN) project.

*Double signals due to the presence of diastereoisomers.

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