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Simple and effective preparation of amino sulfonylureas from amino acids: application to the synthesis of amino sulfonylurea-containing peptidomimetics

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Dedicated to Professor Slavko Pečar on the occasion of his 60th birthday

Abstract

Several amino sulfonylureas have been synthesized, starting from amino acids. The synthetic procedure is simple affording high yields of products under mild conditions. Furthermore, it is shown that these compounds can be incorporated into a peptide sequence.

Keywords: Amino sulfonylurea; Peptidomimetic; Amino acid

Peptide backbone modification has developed into a powerful tool to introduce desired structural motifs and to enhance biological properties in peptidomimetics. Bioisosteric replacement of a peptide bond with various surrogates is a widespread strategy for improving the biological activity, physicochemical properties, and the stability of peptides.[1–3] In the past, a wide variety of modified peptides have been developed (e.g., azapeptides, depsipeptides, retro and retro-inverso peptides, phosphapeptides, ureidopeptides, and peptidosulfonamides).[4,5] By combining these classes of peptidomimetics, the diversity of compounds can be increased enormously to yield 'hybrid' peptidomimetics, which might be very useful for the development of lead compounds from peptides. The urea linkage is one of the most common types of peptide bond surrogate to be introduced into a peptide sequence.[6] On the other hand, peptidosulfonamides have been recognized as interesting building blocks for preparing peptidomimetics, especially transition state enzyme inhibitors, since sulfonamides possess a tetrahedral geometry similar to the tetrahedral intermediate formed in the process of amide bond cleavage and formation.[7]

In this context and as a part of our research on enzyme inhibitors, we have investigated the incorporation of amino sulfonylurea, which can be considered as a hybrid of a sulfonamide and a urea peptidomimetic, into a peptide backbone (Fig. 1).

Nonpeptidic amino sulfonylureas had been recognized previously as building blocks in hypoglycemic agents, ACAT inhibitors, and herbicides.[8] This scaffold possesses an acidic proton on the nitrogen atom situated between the carbonyl and sulfonyl groups that, in solution, can form salts which can be alkylated, and thus contributes the additional possibility for the introduction of diversity into this linkage.[9] In this Letter, the synthesis of amino sulf-

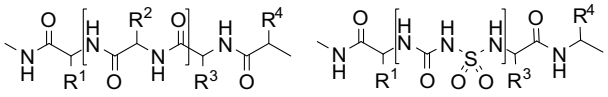

Fig. 1. Peptide backbone and a 'hybrid' amino sulfonylurea-containing peptide.

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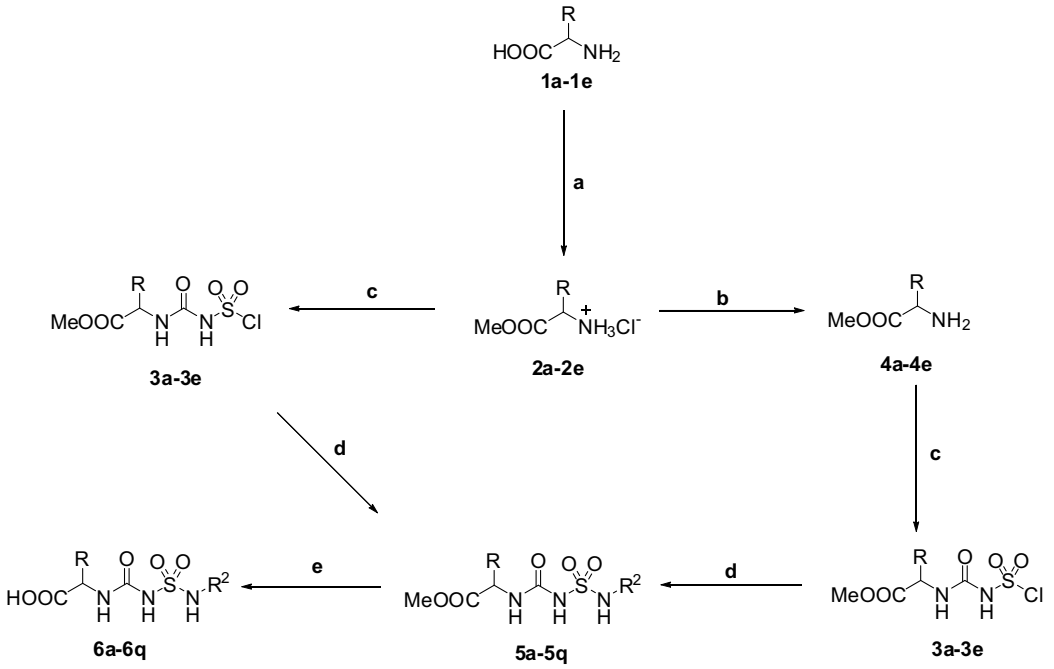


Scheme 1. Reagents and conditions. (a) MeOH, $SOCl_2$, 0 °C; (b) CH_2Cl_2, 0 °C, then washing with 0.5 M NaOH; (c) chlorosulfonyl isocyanate, CH_2Cl_2, −15 °C, 1 h; (d) R^2NH_2, dioxane, triethylamine, 5 °C, then rt 6–12 h; (e) NaOH/dioxane/water, 0 °C, 3 h.

onylurea-based peptidomimetics, starting from various amino acids, using mild conditions and affording high yields, is reported (Scheme 1).

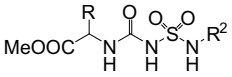
Amino acids were used as starting compounds. First, conversion of the amino acid carboxyl group to a methyl ester using methanol and thionyl chloride (95–98% yields) was performed. For the next step, the reaction between the amino group and the isocyanate group of chlorosulfonyl isocyanate, different synthetic approaches have been described.[8–13] However, in our hands, for the reaction between the amino group of a protected amino acid and the isocyanate group of chlorosulfonyl isocyanate, these procedures gave yields that were too low, and not reproducible enough to be used in the early steps of complex syntheses of enzyme inhibitors.

We therefore sought an improved synthetic route that would be generally applicable to the preparation of amino sulfonylurea-based peptidomimetics.

The reaction of the amino group of the protected amino acid with chlorosulfonyl isocyanate was performed with and without the conversion of the hydrochloride salt of the amine to the free primary amino group, however, there was no significant difference in yields. The reaction was optimized with respect to solvent, reaction time and temperature. Given the reaction type and solubility problems, it was not surprising that only a few solvents were found to be appropriate, however, the use of dichloromethane at low temperature led to high yields of the desired products (Table 1).[14]

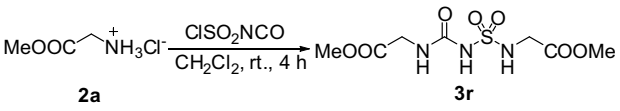
If the temperature was raised, or the reaction time was prolonged, the predominant product **3r** shown in Scheme 2 was obtained and characterized.[15]

Table 1
R and R^2 in synthesized compounds **6a**–**q** and the overall yields



	R	R^2	Overall yield (%)
6a	H	Benzyl	80
6b	H	Phenyl	82
6c	H	Cyclopentyl	79
6d	H	Benzothiazol-2-yl	63
6e	H	Thiazol-2-yl	57
6f	CH_3	Benzyl	83
6g	CH_3	Phenyl	77
6h	CH_3	Cyclopentyl	80
6i	CH_2CH_2COOH	Benzyl	79
6j	CH_2CH_2COOH	Phenyl	76
6k	CH_2CH_2COOH	Cyclopentyl	86
6l	CH_2Ph	Benzyl	73
6m	CH_2Ph	Phenyl	72
6n	CH_2Ph	Cyclopentyl	81
6o	$CH(CH_3)_2$	Benzyl	83
6p	$CH(CH_3)_2$	Phenyl	76
6q	$CH(CH_3)_2$	Cyclopentyl	76

Isolation of the chlorosulfonylurea derivatives turned out to be very difficult because these compounds are very



Scheme 2. An undesired product of the synthesis.

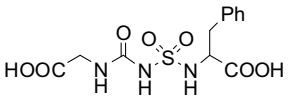


Fig. 2. Amino sulfonylurea-linked pseudodipeptide.

unstable in the presence of moisture. Therefore it was decided in the next step, the reaction between the chlorosulfonylurea and an amine or amino acid in the presence of triethylamine,[16] to use the crude product, after vacuum filtration.

Finally, saponification of the methyl ester was carried out to obtain the free carboxylic group.[17]

The products were fully characterized by IR, MS, and ^{1}H NMR spectroscopy.[15–17]

In order to test the general applicability of this almost one-pot procedure, a series of compounds **6a–q** were synthesized from various amino acids **1a–e**. Products **6a–q** and the total yields of the synthesis are listed in Table 1. The procedure can be used with different amino acid esters and aliphatic or aromatic amines, since the yields were satisfactory regardless of the type of amino acid or amine used.

Finally, the applicability of the reported protocol for the insertion of an amino sulfonylurea linkage into a peptide backbone was demonstrated. The amino sulfonylurea-linked pseudodipeptide presented in Figure 2 was synthesized as shown in Scheme 1 in 73% yield.

In conclusion, a convenient route for the synthesis of interesting novel peptidomimetic building blocks is presented for the preparation of amino sulfonylurea-based peptidomimetics. The applicability was illustrated by incorporating an amino sulfonylurea moiety into a small peptide.

Acknowledgments

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14. *Typical procedure for compound* **3e**: Methyl 2-amino-3-methyl butanoate (1.5 mmol; 200 mg) or methyl 2-amino-3-methyl butanoate hydrochloride (1.5 mmol; 250 mg) was dissolved or suspended in dry dichloromethane (25 ml), cooled to −15 °C, then chlorosulfonyl isocyanate (1.55 mmol; 0.13 ml) was added dropwise. The reaction mixture was stirred at −15 °C for 1 h, then 40 ml of hexane was added and warmed to room temperature. The crude product, methyl 2-(3-(chlorosulfonyl)ureido)-3-methylbutanoate (390 mg; 96% yield) (**3e**) was isolated by vacuum filtration, and then used immediately in the next step.
15. *Characterization of compound* **3r**: Methyl 2-{[({[(2-methoxy-2-oxoethyl)amino]carbonyl}amino)sulfonyl]amino}acetate: white solid; mp: 114–115 °C; IR (KBr, cm^{-1}): 3389, 3294, 2961, 2917, 2364, 1752, 1676, 1534, 1485, 1436, 1373, 1345, 1246, 1216, 1171, 1121, 1062, 985, 898, 603; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 3.64 (6H), 3.80–3.85 (m, 4H), 6.60 (t, 1H, J = 5.7 Hz), 7.97 (t, 1H, J = 6 Hz), 10.26 (s, 1H); MS (ESI) m/z: 316 (MH$^+$); HRMS calcd for $C_7H_{14}N_3O_7S$ m/z: (MH$^+$) 284.0552, found 284.0554.
16. *Typical procedure and selected data for* compound **5l**: Benzylamine (1 mmol; 0.1 ml) was dissolved in dry dioxane (15 ml), cooled to 5 °C, then triethylamine was added (3 mmol; 0.4 ml) followed by slow dropwise addition of methyl 2-(3-(chlorosulfonyl)ureido)-3-phenylpropanoate (1 mmol; 320 mg). The mixture was allowed to warm to room temperature and stirred for 8 h. On completion of the reaction, the reaction mixture was poured into 1 M hydrochloric acid (20 ml), cooled to 0 °C and extracted with ethyl acetate (3 × 10 ml), then dried (Na_2SO_4) and concentrated in vacuo to afford methyl 2-(3-(*N*-benzylsulfamoyl)ureido)-3-phenylpropanoate as a solid product (347 mg; 89% yield). Mp: 85–87 °C; IR (KBr, cm^{-1}): 3343, 3064, 2887, 1739, 1663, 1557, 1454, 1334, 1217, 1047, 915, 739, 697; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 2.97–3.04 (m, 2H), 3.65 (s, 3H), 4.04 (m, 2H), 4.44–4.50 (m, 1H), 6.52 (d, 1H, J = 7.2 Hz), 7.18–7.34 (m, 10H), 7.98 (t, 1H, J = 6.3 Hz), 10.01 (s, 1H); MS (ESI) m/z: 392 (MH$^+$); HRMS calcd for $C_{18}H_{22}N_3O_5S$ m/z: (MH$^+$) 392.1280, found 392.1276.
17. *A typical procedure and selected data for* compound **6f**: Methyl 2-(3-(*N*-benzylsulfamoyl)ureido)propanoate (**5f**) (0.5 mmol; 157 mg) was dissolved in dioxane/water (5 ml), cooled to 0 °C, then 1 M NaOH (2 ml) was added and the reaction mixture stirred for 3 h. On completion of the reaction, the mixture was allowed to warm to room temperature and dioxane was removed under reduced pressure. The solution was washed with ethyl acetate (3 × 10 ml), then acidified to pH 2 with 2 M HCl and extracted with ethyl acetate (3 × 10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 2-(3-(*N*-benzylsulfamoyl)ureido)propanoic acid as a solid product (143 mg; 95% yield). Mp: 103–106 °C; IR (KBr, cm^{-1}): 3368, 3105, 2922, 1721, 1657, 1557, 1480, 1346, 1261, 1164, 1059, 906, 700; ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 1.27 (d, 3H, J = 7.2 Hz), 4.11 (dd, 2H, J_1 = 6.0 Hz, J_2 = 3.9 Hz), 4.15–4.17 (m, 1H), 6.53 (d, 1H, J = 7.2 Hz), 7.31–7.33 (m, 5H), 8.02 (t, 1H, J = 6.3 Hz), 9.91 (s, 1H), 12.8 (s, 1H); MS (ESI) m/z: 302 (MH$^+$); HRMS calcd for $C_{11}H_{16}N_3O_5S$ m/z: (MH$^+$) 302.0743, found 302.0745.