Highly Symmetrical Amino Acid-Derived *N,N′*-Diacylated Sulfodiimines

Juan R. Dehli, Carsten Bolm*

Institut für Organische Chemie der RWTH Aachen, Professor-Pirlet-Str. 1, 52056 Aachen, Germany
Fax +49(241)8092391; E-mail: carsten.bolm@oc.rwth-aachen.de

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Abstract: A mild and efficient method for the coupling of sulfodiimines with *N*-protected amino acids has been developed, yielding the corresponding *N,N′*-diacylated sulfodiimines with up to 94% yield.

Key words: coupling, amino acids, acylations, peptides, sulfodiimines, asymmetric synthesis

During the last decades the chemistry of sulfoximines, **1**, has thoroughly been investigated.[1] As a consequence, a number of derivatives have found application in biological chemistry[2] and asymmetric catalysis.[3–5] In many of such systems the presence of a C_2 axis plays an important role for the effectiveness of the molecule.[5] Surprisingly, sulfodiimines **2** (Figure 1), the nitrogen analogues of sulfoximines, have been much less studied.[6] Despite their high stability towards hydrolysis and thermal decomposition, they have only found limited application in synthesis.[7] Furthermore, sulfodiimines with two unsubstituted nitrogen atoms are achiral rendering this particular building block inappropriate for asymmetric synthesis.[8]

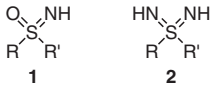
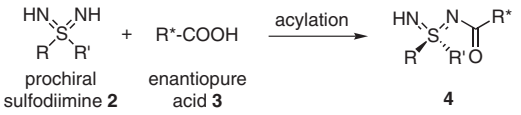


Figure 1 General structure of sulfoximines **1** and sulfodiimines **2**

Haake has shown that sulfodiimines can react with strong acylating agents, such as acyl chlorides and anhydrides, in the presence of triethylamine.[9] With only one equivalent of the acylating agent, the weakly nucleophilic sulfodiimines yield monoacyl derivatives, whereas with an excess of reagent the corresponding disubstituted compounds are obtained. We now wondered if upon using an enantiopure acylating agent such a process could be used for the stereodifferentiation of the two nitrogens of a prochiral sulfodiimine (**2** with R ≠ R′). As products diastereomeric *N*-acylated sulfodiimines **4** would result (Scheme 1), which we envisaged to be valuable intermediates for both building blocks for biologically interesting molecules and ligands for asymmetric catalysis.

For studying the stereoselective acylation reaction, the coupling between readily accessible *S*-benzyl-*S*-methylsulfodiimine (**2** with R = Bn, R′ = Me)[6] and enantiopure



Scheme 1 Concept for the stereodifferentiation of a prochiral sulfodiimine using an enantiopure carboxylic acid **3** as acylating agent

N-protected amino acids, which are available in high structural variability from the chiral pool, was initially investigated. Utilizing the mild carbodiimide-mediated protocol that we had previously applied for couplings between sulfoximines and *N*-protected amino acids,[10] we disappointingly noted that the reaction between **2a** and *N*-Boc-phenylalanine (**6a**) in the presence of *N,N′*-dicyclohexylcarbodiimide (DCC) as coupling reagent and 1-hydroxybenzotriazole (HOBt) as activator, did not lead to the expected product at all. Instead, compound **5** (Figure 2) was obtained in almost quantitative yield, most likely from direct nucleophilic attack of HOBt on the benzylic position of the starting sulfodiimine.

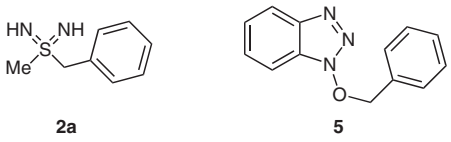


Figure 2 Product **5** from the attempted coupling of **2a** and *N*-Boc-phenylalanine in the presence of DCC and HOBt (for details see text)

HOBt is used in DCC-mediated coupling reactions of carboxylic acids with amines in order to avoid the racemization or epimerization of base-labile stereogenic centers.[11] Since the basicity of *N*-unsubstituted sulfodiimines is significantly lower than the one of amines, we wondered if a (stereochemistry-retaining) coupling could also be performed in the absence of HOBt. Gratifyingly we found that this was indeed the case. Thus, under these conditions, *N*-monoacyl sulfodiimine **7** was obtained in 98% yield (Scheme 2). Unfortunately, however, an almost equimolar mixture of diastereomers was formed, indicating that the chiral recognition between the two coupling partners during the acylation had been rather low. Moreover, we were unable to separate the diastereomers of **7** by conventional flash chromatography or preparative HPLC.

At this stage, we began to consider the possibility of using the sulfodiimine sulfur not as stereogenic center, but as 'linker' between two chiral units. As described above, Haake had shown that treatment of sulfodiimines with

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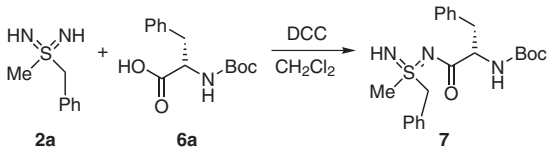
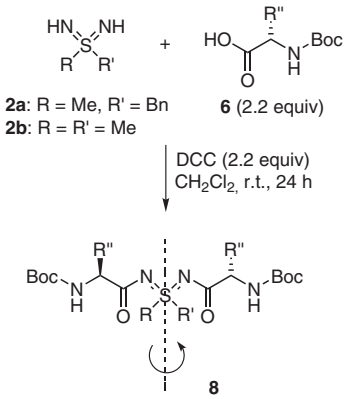


Scheme 2 Coupling between sulfodiimine **2a** and amino acid **6a**

strong acylating agents in excess led to N,N′-disubstituted derivatives. To our delight we found that this transformation also occurred in the DCC-mediated coupling with *N*-Boc-protected amino acids. Thus, using sulfodiimine **2a** and 2.2 equiv of *N*-Boc phenylalanine (**6a**) as starting materials and following the conditions shown in Scheme 3, diacylated product **8a** was obtained in 76% yield. Careful analysis of the ^{1}H NMR spectrum of **8a** confirmed that the reaction had proceeded without epimerization as indicated by the AB system for the benzylic methylene group at sulfur (consisting of two diastereotopic protons). This pattern also proved the pseudo-C_2 symmetry of the product, since a hypothetical epimerization at one of the amino acid-derived substituents would have led a *meso*-isomer, whose methylene group (with two enantiotopic protons) would appear as a singlet in the ^{1}H NMR spectrum.



Scheme 3 Synthesis of *N,N′*-diacylated sulfodiimines **8**

As revealed by the results summarized in Table 1, the DCC-mediated double coupling reaction was quite general. Other *N*-Boc-protected amino acids reacted with **2a** to give the corresponding *N,N′*-diacylated products **8** in up to 94% yield (entries 1–4). Complementary to this, using *S,S*-dimethylsulfodiimine (**2b**) as starting material afforded C_2-symmetric sulfodiimines in up to 48% yield (entries 5–8). In this case, the two methyl groups at sulfur appeared as a singlet in the ^{1}H NMR spectrum, which confirmed the stereochemical integrity of the product.[12]

As an extension of the substrate scope, *S*-benzyl-*S*-methyl sulfodiimine (**2a**) was coupled with two other chiral carboxylic acids. First, dipeptide *N*-Boc-Phe-Gly-OH and, second, non-proteinogenic carboxylic acid 2-(4-*iso*-butylphenyl)propionic acid (ibuprofen) were applied as a coupling partner. In both cases the corresponding products **9** and **10** were obtained in high yields (91 and 83% yield, respectively) (Figure 3) demonstrating the chemical flexibility of the developed approach.

Table 1 Synthesis of *N,N*-Diacylated Sulfodiimines **8** by DCC-Mediated Couplings with Chiral Carboxylic Acids

Entry	Substrate	Acid **6**	R″ in **6** and **8**	Product	Yield (%)
1	**2a**	Boc-Phe-OH	Bn	**8a**	76
2	**2a**	Boc-Ala-OH	Me	**8b**	93
3	**2a**	Boc-Val-OH	*i*-Pr	**8c**	75
4	**2a**	Boc-Leu-OH	*i*-Bu	**8d**	94
5	**2b**	Boc-Phe-OH	Bn	**8e**	39
6	**2b**	Boc-Ala-OH	Me	**8f**	48
7	**2b**	Boc-Val-OH	*i*-Pr	**8g**	41
8	**2b**	Boc-Leu-OH	*i*-Bu	**8h**	44

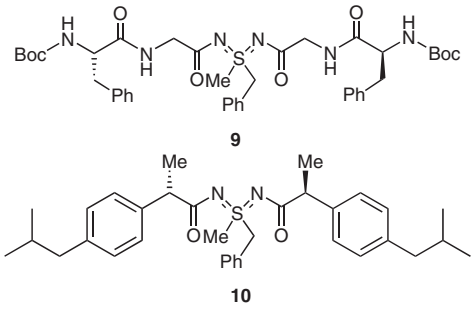


Figure 3 Sulfodiimines **9** and **10** stemming from couplings with a dipeptide and ibuprofen, respectively

In summary, the previously developed methodology for the coupling of sulfoximines with *N*-protected amino acids and peptides has been adapted for the case of sulfodiimines. Under appropriate conditions a nucleophilic attack at the labile C–S bond leading to a destruction of the sulfodiimine unit can be avoided. Although the coupling itself is non-stereoselective, it can be used for the preparation of highly symmetrical compounds with sulfur-based bidirectional core units. For such C_2- and pseudo-C_2-symmetric compounds we foresee a wide variety of applications in asymmetric synthesis and catalysis.

All reactions were carried out under argon using standard Schlenk techniques. CH_2Cl_2 (free of alcohols as stabilizing agents) was distilled over calcium hydride and stored under argon. *NH*-sulfodiimines were prepared according to the literature.[6] All other starting materials were obtained from commercial suppliers and used without further purification. NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Varian Gemini 300 spectrometer (300 and 75 MHz for ^{1}H and ^{13}C NMR spectra, respectively), FTIR spectra on a Perkin-Elmer PE-1760 FT apparatus and MS spectra on a Varian MAT 212 using a chemical ionization technique.

Representative Procedure

To a well stirred solution of the sulfodiimine (1.0 mmol) and the *N*-Boc-protected amino acid (2.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C, a

solution of DCC in CH_2Cl_2 (1 M; 2.2 mL, 2.2 mmol) was slowly added. The suspension was allowed to warm up to r.t. and after 24 h of stirring the CH_2Cl_2 was removed under reduced pressure. The precipitate was then suspended in EtOAc and filtered through Celite. After column chromatography on silica gel (pentane–EtOAc gradient) the product was obtained as a white solid.

(*S*,*S*)-*S*-Benzyl-*S*-methyl-*N*,*N*′-bis[2-(*N*-*tert*-butoxycarbonylamino)-3-phenylpropanoyl]sulfodiimine (8a)
Yield: 76%.

IR: 3431, 1709, 1640 cm^{-1}.

^1H NMR: δ = 1.42 (s, 18 H), 3.0–3.3 (m, 7 H), 4.55 (m, 2 H), 4.97/5.07 (AB system, *J* = 13.1 Hz, 2 H), 5.14 (br s, 2 H), 7.1–7.5 (m, 15 H).

^{13}C NMR: δ = 28.4 (CH_3), 35.6 (CH_3S), 38.7 (CH_2), 57.5 (CH_2S), 57.7 (CH), 79.5 (C), 125.4 (C), 126.7 (CH), 128.3 (CH), 129.3 (CH), 129.7 (CH), 130.3 (CH), 131.7 (CH), 137.0 (C), 155.2 (CO), 180.5 (CO).

MS: *m*/*z* (%) = 663 [(M + H)$^+$, 1], 255 (52), 91 (100).

Anal. Calcd for $C_{36}H_{46}N_4O_6S$: C, 65.23; H, 6.99; N, 8.45. Found: C, 64.91; H, 7.14; N, 8.33.

(*S*,*S*)-*S*,*S*-Dimethyl-*N*,*N*′-bis[2-(*N*-*tert*-butoxycarbonylamino)-3-phenylpropanoyl]sulfodiimine (8e)
Yield: 39%.

IR: 3431, 1705, 1640 cm^{-1}.

^1H NMR: δ = 1.34 (s, 18 H), 2.95–3.20 (m, 4 H), 3.30 (s, 6 H), 4.40–4.55 (m, 2 H), 5.09 (d, *J* = 6.7 Hz, 2 H), 7.05–7.25 (m, 10 H).

^{13}C NMR: δ = 28.4 (CH_3), 38.7 (CH_2), 39.2 (CH_3S), 57.5 (CH), 79.6 (C), 126.8 (CH), 128.3 (CH), 129.7 (CH), 136.9 (C), 155.2 (CO), 180.4 (CO).

MS: *m*/*z* (%) = 587 [(M + H)$^+$, 2], 487 (18), 255 (93), 120 (100).

Anal. Calcd for $C_{30}H_{42}N_4O_6S$: C, 61.41; H, 7.21; N, 9.55. Found: C, 61.07; H, 7.35; N, 9.30.

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(12) In this case, the *meso*-product resulting from an epimerization would possess two diastereotopic methyl groups. Those would be in rather different chemical and electronic environments and, therefore, two different chemical shifts would be likely to occur in the ^1H NMR spectrum.