Convenient Syntheses of 2-Nitrophenylsulfen-(NPS-)imines by Oxidation of NPS-Protected Amines and Amino Acid Derivatives

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Received March 14, 1988

2-Nitrophenylsulfenimines **2** of large structural variety are easily available from 2-nitrophenylsulfenamides **1**, by direct and indirect electrochemical oxidation or by using stoichiometric amounts of a triarylamine radical cation salt. In most cases the direct electrochemical method is to be preferred, because of the convenient reaction procedure and the simple workup of the products. Inter- and intramolecular addition of nucleophiles to the C—N double bond is possible as shown by two examples.

Bequemer Zugang zu 2-Nitrophenylsulfen-(NPS-)iminen durch Oxidation von NPS-geschützten Aminen und Aminsäurederivaten

2-Nitrophenylsulfenimine **2** von großer Strukturvielfalt werden durch Oxidation von 2-Nitrophenylsulfenamiden **1** entweder auf direktem und indirektem elektrochemischen Wege oder durch Umsetzung mit stöchiometrischen Mengen eines Triarylamin-Radikalkation-Salzes leicht zugänglich. Wegen der bequemen Reaktionsführung und der einfachen Aufarbeitung ist der direkten elektrochemischen Methode meist der Vorzug zu geben. Die inter- und intramolekulare Addition von Nucleophilen an die C—N-Doppelbindung gelingt und wird an zwei Beispielen demonstriert.

Introduction and Basic Considerations

Sulfenimines are interesting building blocks, which have already found application in organic synthesis for several times. One example is the stereoselective synthesis of 7α-methoxycephalosporins and 6α-methoxypenicillines[1a,b] via a sulfenimine precursor. A second one is the formation of secondary and tertiary alkyl amines by alkylation or arylation of *N*-alkylarenesulfenimines[1c] followed by hydrolysis.

General application of these methods, however, is often restricted by the lack of convenient synthetic procedures leading to sulfenimines of large structural variety.

The formation of sulfenimines is mostly realized by the reaction of carbonyl compounds with ammonia and disulfides[2a], sulfenamides[2a–g] or for example arylthioiminophosphoranes[2h]. Only a few methods are described, in which the syntheses of sulfenimines are carried out by oxidation of the corresponding sulfenamides generated from amines.

These include oxidation of sulfenylcephalosporins and -penicillins with a large excess of manganese dioxide[1a], or the treatment of α-amino esters, cephalosporins and penicillins with three equivalents of sulfenyl chloride[3a,1b], and finally the electrochemical cross coupling of the same compounds with disulfides[3b]. To our knowledge, these last three oxidative methods have been applied to amino acid esters and amides, but not yet to *N*-alkyl- or *N*-benzylsulfenamides.

We now wish to report on a convenient synthetic procedure of *N*-alkylidene- and *N*-benzylidenesulfenamides as well as sulfenyliminoacid derivatives. For our investigations we used the *o*-nitrophenylsulfenyl group (NPS) for *N*-protection, which (besides the Z and the Boc group) is one of the most important protecting groups in peptide synthesis.

The substrates are easily available by reaction of NPS chloride with amines in the presence of a base in good to excellent yields (Table 1). We were able to perform the oxidation of the C—N bond either chemically (Method A), or electrochemically by using indirect (Method B) or direct (Method C) electrolysis (Scheme 1).

For the chemical conversion (Method A) we used stoichiometric amounts of the radical cation salt **4** of tris(4-bromophenyl)amine in acetonitrile in the presence of 2,6-dimethylpyridine as proton acceptor. We applied this method to four subtrates and were able to obtain sulfenimines in yields between 67 and 95%. These investigations were mainly considered as a test, whether organic radical cations, in general, would be suitable reagents for this type of oxidation. Our next aim was to substitute the use of stoichiometric amounts of this oxidizing reagent by electrochemical in-situ regeneration of the radical cation (indirect electrolysis, Method B). Such regeneration methods will minimize the necessary amount of oxidants, and thereby facilitate the problem of separation (often tedious, because of the high molecular weight of the applied salt).

But indirect electrolysis of a benzyl-substituted sulfenamide in the presence of tris(4-bromophenyl)amine at a controlled potential of 0.73 V vs. $Ag/AgNO_3$ failed, because cleavage of the substrate occurred. The oxidation worked well, however, when tetrakis(4-bromophenyl)-1,4-phenylendiamine (**5**) was used as redox catalyst (mediator) at a controlled potential of 0.39 V vs. $Ag/AgNO_3$ or even more positive potentials in 0.1 M tetrabutylammonium perchlorate (TBAP)/dichloromethane in the presence of 2,6-dimethylpyridine (Method B).

The formation of sulfenimines can also be performed in the same system without any redox catalyst present by direct electrolysis (Method C). Using the same reaction conditions as for the indirect process (potential, concentrations, tem-

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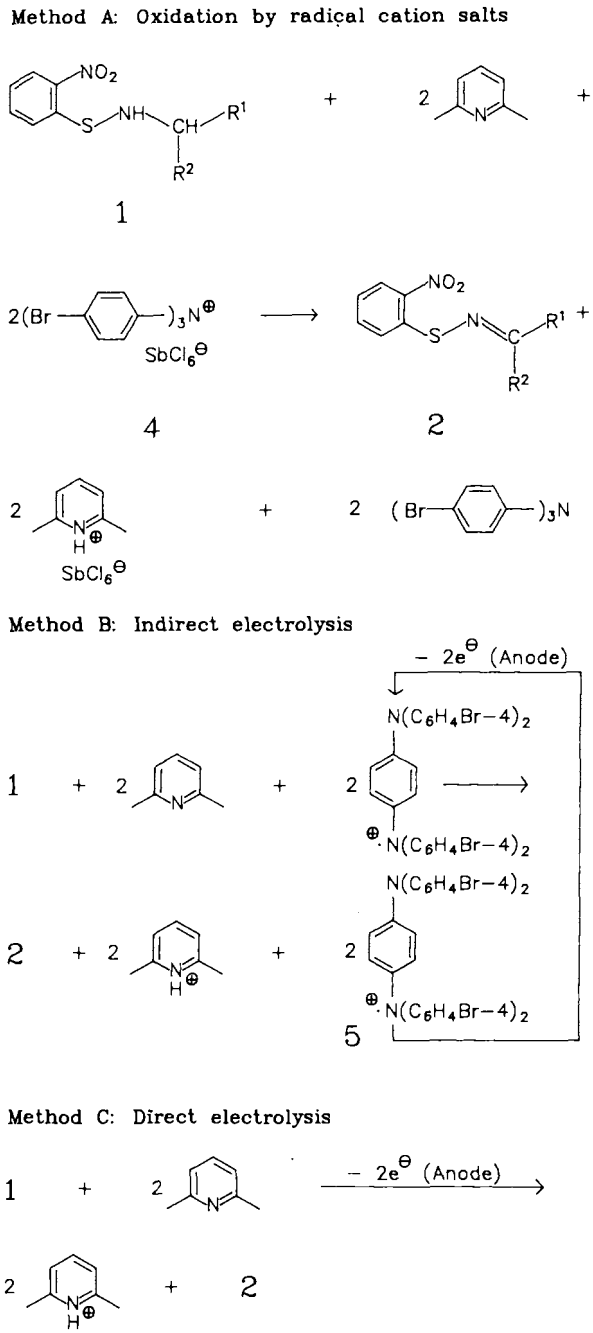
Scheme 1



perature etc.), the only consequence is a lower current density. This problem, however, may be overcome, because higher substrate concentrations are possible to apply (see below).

In both cases the applied potentials were up to 400 mV less positive than the cyclovoltammetrically determined first oxidation potentials of the substrates (Table 1). We conclude that 2,6-dimethylpyridine is responsible for this effect and suggest the mechanism outlined in Scheme 2 for the formation of sulfenimines.

A preceding deprotonation/protonation equilibrium generates a low concentration of a sulfenamide anion, an electron-rich species, which will undergo more facile oxidation than the sulfenamide itself.

Table 1. Results of the formation of NPS-amides **1** and electroanalytical data

	Sulfenamide **1** R¹	R²	First oxidation potentials of **1**[a]	Yields of **1** in.%
a[6b]	H	Ph	815	94[e]
b	H	n-C_7H_{15}	800	93[f]
c	H	CH=CH−Ph	820	89[e]
d[6c]	H	CH_3	775	72[f]
e	H	*t*Bu	785	96[f]
f	Ph	Ph	945	98[f]
g[6d]	H	COOMe	934	83[f]
h[b]	CH(Me)(Et)	COOMe	930	88[f]
i[c,d]	CH_2OH	COOMe	900	94[f]
j[b]	CH(Me)OH	COOMe	885	88[f]
k[c]	CH_2O*t*Bu	COO*t*Bu	970	96[g]
l[b]	CH(Me)O*t*Bu	COO*t*Bu	1005	52[g]
n[b]	NPS−NH−C_4H_8	COOMe	795	71[f]
o[b]	Bzl	CO−GlyO34DB[i]	820	63[h]

[a] Chemically irreversible peak potentials in mV vs. $Ag/AgNO_3$ determined by cyclic voltammetry at glassy carbon anodes. — [b] L-Amino acid derivative. — [c] DL-Amino acid derivative. — [d] L-Amino acid derivative, see ref.[6e]. — [e] Method 1. — [f] Method 2. — [g] Method 3. — [h] Method 4. — [i] 3,4-Dimethoxybenzyl ester.

Because of the low solubility of the mediator (2×10^{-3} mol/l in dichloromethane at room temp.) with a substrate concentration of 1×10^{-2} mol/l, only low current densities of ca. 3−5 mA/cm² at the beginning of a potential-controlled electrolysis can be obtained with indirect electrolysis. Therefore, long lasting electrolysis would have to be performed. This disadvantage may be avoided by applying the direct electrochemical method, because in this case a drastic increase of the substrate concentration (up to 30×10^{-2} mol/l) is possible. This leads to current densities of 30 mA/cm² at the beginning of the electrolysis.

Preparative Results

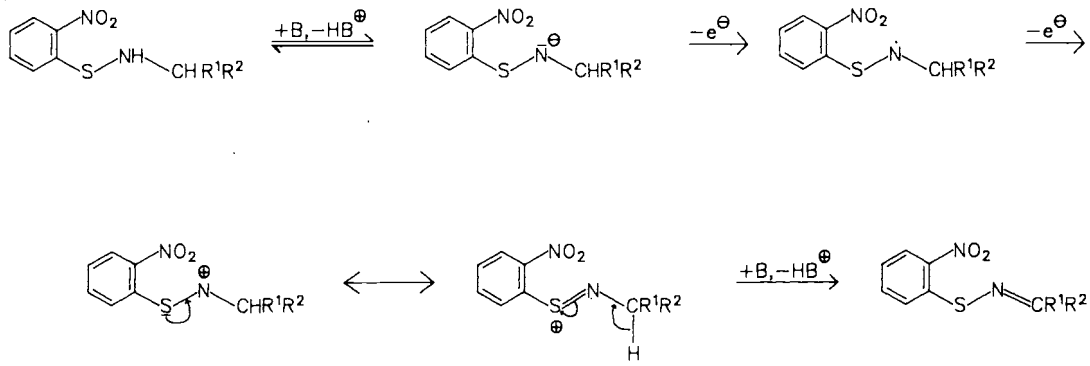
The results of the sulfenimine formation are reported in Table 2.

Table 2. Synthesis of NPS-imines **2** according to Scheme 1

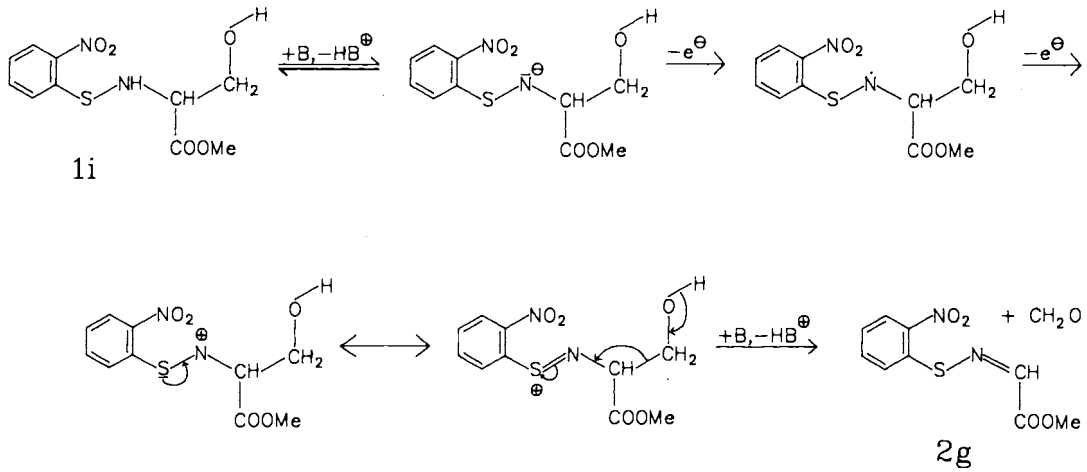
Substrate **1**	Yields of **2** (recovered **1**) in % Method A	Method B	Method C
a	95	77[c]	82[a]
b	79	56[c]	63[a]
c	81	56 (17)[a]	—
d	—	44[a]	48[b]
e	—	68 (10)[a]	57 (25)[a]
f	—	72 (10)[c]	65 (3)[b]
g	—	54 (18)[c]	82 (3)[c]
h	—	67[c]	66[b]
k	—	54[e]	54[d]
o	67	—	—

[a] At 390 mV vs. $Ag/AgNO_3$. — [b] At 530 mV vs. $Ag/AgNO_3$. — [c] At 650 mV vs. $Ag/AgNO_3$. — [d] At 730 mV vs. $Ag/AgNO_3$. — [e] At 900 mV vs. $Ag/AgNO_3$.

Scheme 2



Scheme 3



As expected, the products were mixtures of *E*/*Z* isomers. The *E* isomer is formed selectively only in the case of one bulky substituent attached to the α-carbon atom. The ratios were detected by ^{1}H- and ^{13}C-NMR spectra, see Experimental, Table 4.

In general, the formed sulfenimines are stable compounds and can be stored for months with exclusion of light in the cold. Two exceptions are the *N*-alkylsulfenimines **2b** and **2d**, which are relatively sensitive to hydrolysis and show partial cleavage under the conditions of liquid chromatography.

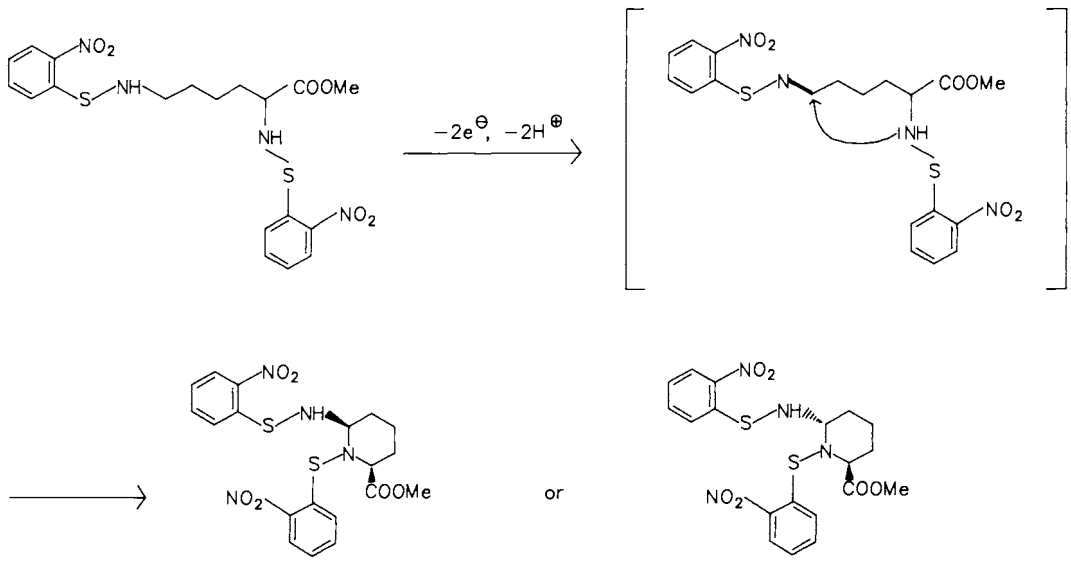
The electrochemical oxidation of NPS-serine (**1i**) and NPS-threonine methyl ester (**1j**) (Method B, 390 mV vs. Ag/$AgNO_3$) causes the loss of the side chain by fragmentation, leading to product **2g** (Scheme 3; the reaction was worked up only in the case of the oxidation of **1j** resulting in 35% isolated **2g** and 33% recovered **1j**). A similar reaction is known in biochemistry, where the CH_2OH group is transferred by hydroxymethylases from serine or threonine to glycine, carboxamide ribotide, etc.[4a].

The fragmentation may be avoided, if the β-hydroxy group is protected. In the case of NPS-*O*-*tert*-butyl-DL-serine *tert*-butyl ester (**1k**) we were able to isolate the desired sulfenimine **2k**, while electrolysis (Method B, 900 mV vs. Ag/$AgNO_3$) of NPS-*O*-*tert*-butyl-L-threonine *tert*-butyl ester (**1l**) leads to a mixture of NPS-*O*-*tert*-butyl-L-threonine*tert*-butyl ester (**2l**, 7%) and NPS-glycinimine *tert*-butyl ester (**2m**, 73%).

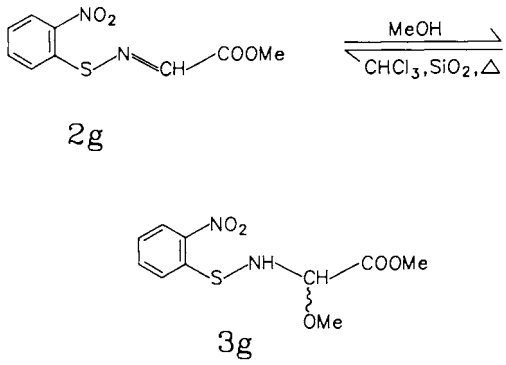
Direct electrolysis (Method C, 390 mV vs. Ag/$AgNO_3$) of *N*,*N*′-bis(2-nitrophenylsulfenyl)-L-lysine methyl ester (**1n**) causes the selective oxidation at the ε-sulfenamide function, because of its considerably lower oxidation potential as compared with that of the α-group (see Table 1). The formation of the C–N double bond is followed by an intramolecular nucleophilic attack of the protected α-amino group leading to *N*,*N*′-bis(2-nitrophenylsulfenyl)piperidine-2-carboxylic acid methyl ester (**2n**) (Scheme 4). The same reaction was carried out by Irie et al. using *N*,*N*′-bis(methoxycarbonyl)-L-lysine methyl ester[4b]. The product **2n** (19%, 69% recovered **1n**) is a relatively unstable compound and shows cleavage of the NPS group upon drying or recristallization. The configuration has not yet been determined, but only one set of signals is obtained in the ^{13}C-NMR spectrum. This fact may indicate, that only one of the two possible diastereomers is formed. Application of this compound as synthetic building block will be investigated.

By treating **2g** with an excess of methanol, α-methoxy-NPS-glycine methyl ester (**3g**) is formed quantitatively (Scheme 5). This reaction can be made reversible by dissolving **3g** in trichloromethane and refluxing it in the presence of silica gel. In this way **2g** is reformed quantitatively.

Scheme 4



Scheme 5



Direct formation of **3g** from **1g** in methanol/$LiClO_4$ is possible, but the preparative results are not as satisfactory as with the two-step reaction. Addition of other nucleophilic reagents to the formed sulfenimines is possible and is currently investigated. As conclusion, we can say that NPS-imines in general are preferably generated by direct electrochemical oxidation (Method C), because of the ease of the procedure and the simplicity of the workup. In comparison to other oxidative methods[1a,b,3a,b] the application to a large structural variety of the substrates and the possibility to avoid excessive amounts of oxidizing reagent are advantageous.

Financial support by the *Arbeitsgemeinschaft Industrieller Forschungsvereinigungen, Fonds der Chemischen Industrie,* and *BASF Aktiengesellschaft* is gratefully acknowledged.

Experimental

^{1}H-NMR spectra: Bruker WH-90 and Bruker AC-200 (δ values, TMS internal standard). – ^{13}C-NMR spectra: Bruker WH-90 and Bruker AC-200 (δ values, TMS internal standard). – Melting points (uncorrected): Kofler micro heating plate (Reichert). – Microanalyses: Perkin-Elmer CH-Analyser 240 and Heraeus CHN-O-Rapid. – The IR spectra of all compounds were in accordance with their structures; all mass spectra showed the M^+ peaks (except those of **1n** and **2n**).

Trichloromethane, dioxane, cyclohexane, ethyl acetate, triethylamine, and 2,6-dimethylpyridine were purified by distillation. $(n\text{-}Bu)_4N^{\oplus}$ $ClO_4^{\ominus}$ (TBAP; Fluka, parum), dichloromethane (Baker, p.a.), methanol (Merck, p.a.), *o*-nitrophenylsulfenyl chloride (Ega, Sigma) were used as obtained.

TLC Analyses: TLC aluminium sheets, silica gel 60 F_{254} (Merck, Riedel de Haën); mobile phases: mixtures of cyclohexane and ethyl acetate.

Preparative LC Separations: Silica gel for flash chromatography 30–60 μm (Baker) and silica gel 63–200 (Woelm).

Preparative HPLC Separations: Steel column, ∅ 16 mm, 0.5 m and ∅ 25 mm, 0.25 m, LiChrosorb Si 60 (Merck), 7 μm in combination with a Waters high pressure pump model 590 with UK 6 injection system, a Knauer UV photometer, a Gilson fraction collector model 201, and a Hewlett-Packard integrator model 3390 A.

Cyclic Voltammetry: An Amel potentiostat model 553 was used as current source in combination with a Kontron 20-MHz programmable function generator, a Hewlett-Packard 7045 A *X/Y*-recorder, a Metrohm EA 875-20 electrolysis cell equipped with a glassy carbon (Metrohm) anode with 3 mm ∅, a platinum wire cathode with 0.4 mm ∅, and a reference electrode, which was in contact with the electrolyte by a salt bridge. An $Ag/AgNO_3$ (0.1 M CH_3CN) reference electrode in combination with the electrolyte CH_2Cl_2 (0.2 M TBAP) was applied. The cyclic voltammetric data are reported in Table 1.

Preparative Electrolysis: A FUG potentiostat NTN 700 M-200 was used as current source in combination with a digital coulometer based on voltage-to-frequency conversion and the following cells.

Divided Beaker-Type Glass Cells: The divided beaker-type glass cells with cooling mantle and volumes of 150 cm^3 (cell 1) and 100 cm^3 (cell 2) were equipped with a graphite disk anode (8 cm^2 × 0.3 cm), an $Ag/AgNO_3$ (0.1 M CH_3CN) reference electrode, and a magnetic stirrer. The cathode compartment was formed by a glass cylinder closed by a G-4 glass frit and was equipped with a carbon felt cathode (6 cm^2 × 0.5 cm).

General Procedure for the Formation of Sulfenimines by Tris(4-bromophenyl)ammoniumyl Hexachloroantimonate (**4**) *(Method A):*

1 mmol of **1** and 0.40 g (3.74 mmol) of 2.6-dimethylpyridine are dissolved in 10 ml of CH_3CN. Then 1.63 g (2.00 mmol) of **4** is added in small portions. After decoloration to yellow or yellow-brown the solvent is evaporated at room temp. The residue is partially dissolved in CH_2Cl_2 or $CHCl_3$ and filtered. The filtrate is separated by LC. Also up to 95% of tris(4-bromophenyl)amine resulting from the reduction of the radical cation salt may be recovered by this workup procedure.

General Procedure for the Formation of Sulfenimines by Indirect Electrolysis (Method B): In cell 1 0.1 mmol of **5** is dissolved in 120 ml of CH_2Cl_2 (0.1 M TBAP) by stirring. After electrolysis has been started at the controlled potential given Table 2, 1 mmol of **1** and 1 ml (8.6 mmol) of 2,6-dimethylpyridine are added. After the theoretical amount of charge for the oxidation (193 As) has passed or the current had decreased to a value below 1 mA, the yellow or yellow-brown solution is worked up. For the separation of the conducting salt, the solvent is evaporated in presence of silica gel, and the residue is extracted with ether. After evaporation of the solvent, the crude product is purified by flash chromatography or HPLC. Up to 85% of the mediator may be recovered by this workup procedure.

General Procedure for the Formation of Sulfenimines by Direct Electrolysis (Method C): Same procedure as for Method B, using, however, cell 2, 40 ml of CH_2Cl_2 (0.1 M TBAP), no **5**. The system allows also to apply larger amounts of the substrate, if the concentration of the base is increased accordingly. [In the case of formation of **2n**, electrolysis was stopped after 61 As (32% of the theoretical amount of charge needed for the oxidation of one C–N bond) had passed].

Purification of the Formed Sulfenimines: The compounds **2b** and **2d** were purified by HPLC, **2a**–**2c** and **2e**–**m** by LC and flash chromatography using mixtures of cyclohexane/ethyl acetate as eluent; **2n** was purified by flash chromatography on Al_2O_3 (ICN Biomedicals, 32–63 μm, 7% H_2O), with cyclohexane/ethyl acetate (8:2) as eluent. **2o** was purified by LC using ether/dichloromethane (1:1). Yields and analytical data are summarized in Tables 2–4.

Preparation of α-Methoxyglycine Methyl Ester (**3g**): 73 mg (0.3 mmol) of **2g** was dissolved in 10 ml of methanol and stirred for 2 d at room temp. The solvent was removed and the product dried in vacuo. No further purification was necessary.

Preparation of **2g** *from* **3g** *(Retro Reaction):* 22 mg (0.08 mmol) of **3g** is dissolved in 5 ml of trichloromethane and 1 g of silica gel (30–60 μm) is added. After refluxing for 1 h, the silica gel is filtered off. The pure product can be obtained by removal of the solvent and drying in vacuo.

Preparation of Tris(4-bromophenyl)ammoniumyl Hexachloroantimonate (**4**) *and N,N,N′,N′-Tetrakis(4-bromophenyl)-1,4-phenylenediamine* (**5**): **4**[5a] was prepared according to the literature. **5**[5b] was obtained as a gift or was prepared as follows: 3.00 g (7.3 mmol) of *N,N,N′,N′*-tetraphenyl-*p*-phenylendiamine[5c] is dissolved in 150 ml of trichloromethane. After addition of 2.33 g (14.6 mmol) of bromine the solution is heated until boiling and, still hot, filtered off from the unsoluble residue. The residue is washed with hot trichloromethane. The filtrates are combined and the solvent is partially removed. While the solution cools to room temp. the product crystallizes (yield: 57% m.p. 280–284°C).

Preparation of the NPS-Protected Amines, Amino Acid Esters and the Dipeptide: 2-Nitrobenzenesulfenamides **1** and NPS-amino acid esters were prepared according to a literature procedure[6a], which up to now was only applied to the formation of NPS-protected amino acids and esters.

Method 1: For the synthesis of **1a** and **1c**, 1 equivalent of amine and 1 equivalent of NPS-Cl are treated with 1 equivalent of 2 N NaOH in dioxane as solvent.

Method 2: For the synthesis of **1b** and **1d**–**f**, 1 equivalent of amine and 1 equivalent of NPS-Cl are treated with 1 equivalent of

Table 3. Melting points, elemental analysis, and high resolution MS data of educts **1** and the products **2** and **3**

No.	Melting points (Lit.)[°C]	Elemental analyses
1a	57–58	$C_{13}H_{12}N_2O_2S$ (260.3)
	(59.5–60)[6b]	Calcd. C 59.98 H 4.65 N 10.76
		Found C 60.13 H 4.67 N 10.67
1b	48–49	$C_{14}H_{22}N_2O_2S$ (282.4)
		Calcd. C 59.54 H 7.85 N 9.92
		Found C 59.56 H 7.99 N 10.07
1c	50–52	$C_{15}H_{14}N_2O_2S$ (286.4)
		Calcd. C 62.92 H 4.93 N 9.78
		Found. C 63.19 H 4.97 N 9.55
1d	32–33	$C_8H_{10}N_2O_2S$ (198.2)
	(32.5–33)[6c]	Calcd. C 48.47 H 5.08 N 14.13
		Found C 48.71 H 5.33 N 14.04
1e	oil	$C_{11}H_{16}N_2O_2S$ (240.3)
		Calcd. C 54.98 H 6.71 N 11.66
		Found C 55.09 H 6.62 N 11.53
1f	118	$C_{19}H_{16}N_2O_2S$ (336.4)
		Calcd. C 67.84 H 4.79 N 8.33
		Found C 67.65 H 4.85 N 8.11
1g	80	$C_9H_{10}N_2O_4S$ (242.3)
	(80)[6d]	Calcd. C 44.62 H 4.16 N 11.56
		Found C 44.47 H 4.18 N 11.33
1h	65–66	$C_{13}H_{18}N_2O_4S$ (298.4)
		Calcd. C 52.33 H 6.08 N 9.39
		Found C 52.44 H 6.23 N 9.32
1i	83–85	$C_{10}H_{12}N_2O_5S$ (272.3)
		Calcd. C 44.11 H 4.44 N 10.29
		Found C 44.16 H 4.50 N 10.13
1j	62–63	$C_{11}H_{14}N_2O_5S$ (286.3)
		Calcd. C 46.15 H 4.93 N 9.78
		Found C 46.31 H 4.91 N 9.68
1k	52–55	$C_{17}H_{26}N_2O_5S$ (370.5)
		Calcd. C 55.12 H 7.07 N 7.56
		Found C 54.94 H 6.97 N 7.57
1l	77–80	$C_{18}H_{28}N_2O_5S$ (384.5)
		Calcd. C 56.23 H 7.34 N 7.57
		Found C 56.05 H 7.32 N 7.25
1n	oil	$C_{19}H_{22}N_4O_6S_2$ (466.5)
		Calcd. C 48.92 H 4.75 N 12.01
		Found C 49.02 H 5.09 N 11.70
1o	45–50	$C_{26}H_{27}N_3O_7S$ (525.6)
		Calcd. C 59.42 H 5.18 N 7.99
		Found C 59.32 H 5.41 N 8.10

No.	Melting points (Lit.)[°C]	Elemental analyses or high resolution MS data
2a	162–164	$C_{13}H_{10}N_2O_2S$ (258.3)
	(159)[2b]	Calcd. C 60.45 H 3.90 N 10.85
		Found C 60.16 H 3.87 N 10.90
2b	oil	$C_{14}H_{20}N_2O_2S$ (280.4)
		Calcd. 280.1246
		Found 280.1242
2c	160–162	$C_{15}H_{12}N_2O_2S$ (284.3)
		Calcd. C 63.36 H 4.25 N 9.85
		Found C 63.24 H 4.19 N 9.77
2d	68–79	$C_8H_8N_2O_2S$ (196.2)
		Calcd. C 48.97 H 4.11 N 14.28
		Found C 48.76 H 4.13 N 13.98
2e	43–45	$C_{11}H_{14}N_2O_2S$ (238.3)
		Calcd. C 55.44 H 5.92 N 11.76
		Found C 55.69 H 6.12 N 11.42
2f	160	$C_{19}H_{14}N_2O_2S$ (334.4)
		Calcd. C 68.24 H 4.22 N 8.38
		Found C 68.29 H 4.39 N 8.31
2g	120	$C_8H_8N_2O_4S$ (240.2)
		Calcd. C 45.00 H 3.36 N 11.66
		Found C 45.08 H 3.42 N 11.94
2h	39–42	$C_{13}H_{16}N_2O_4S$ (296.3)
		Calcd. C 52.69 H 5.44 N 9.45
		Found C 52.75 H 5.57 N 9.21
2k	oil	$C_{17}H_{24}N_2O_5S$ (368.5)
		Calcd. C 55.42 H 6.57 N 7.60
		Found C 55.52 H 6.61 N 7.57
2l	56	$C_{18}H_{26}N_2O_5S$ (382.5)
		Calcd. C 56.53 H 6.85 N 7.32
		Found C 58.29 H 6.55 N 6.95
2m	85–86	$C_{12}H_{14}N_2O_4S$ (282.3)
		Calcd. C 51.05 H 5.00 N 9.92
		Found C 51.40 H 5.12 N 9.82
2n	137–140.5	$C_{19}H_{20}N_4O_6S_2$(464.5)
		M- COOMe (405.5)
		Calcd. 405.0692
		Found 405.0702
2o	141–143	$C_{26}H_{25}N_3O_7S$ (523.6)
		Calcd. C 59.65 H 4.81 N 8.03
		Found C 59.41 H 4.86 N 7.98
3g	91	$C_{10}H_{12}N_2O_5S$ (272.3)
		Calcd. C 44.11 H 4.44 N 10.29
		Found C 44.30 H 4.74 N 10.09

triethylamine in trichloromethane as solvent. For the synthesis of **1g – 1h**, 1 equivalent of amino acid ester hydrochloride and 1 equivalent of NPS-Cl are treated with 2 equivalents of triethylamine in trichloromethane as solvent. For the synthesis of **1n**, 1 equivalent of amino acid ester dihydrochloride and 2 equivalents of NPS-Cl

Table 4. ^{1}H- and ^{13}C-NMR data of **1**, **2** and **3**

No.	^{1}H-NMR δ[ppm] =	^{13}C-NMR δ [ppm] =
1a	(90 MHz, $CDCl_3$) 8.2 (CH,ddd 8.1 Hz, 1.5 Hz, ≈ 0.3 Hz, 1H) 7.9 (CH, ddd 8.1 Hz, 1.5 Hz, ≈ 0.3 Hz, 1H) 7.6 (CH,ddd 8.1 Hz, 7.2 Hz, ≈ 1.5 Hz, 1H) 7.1 - 7.0 (m 6H) 4.0 (CH_2,d 7 Hz ,2H) 2.9 (NH,t broad,1H)	(90 MHz, $CDCl_3$) 145.6 (1C) 142.8 (1C) 139.7 (1C) 133.8 (1CH) 128.8 (2CH) 128.2 (2CH) 127.9 (1CH) 126.0 (1CH) 124.7 (1CH) 124.4 (1CH) 56.0 ($1CH_2$)
1b	(200 MHz, $CDCl_3$) 8.25 (CH,dd 8.3 Hz, 1.5 Hz, 1H) 7.95 (CH,dd 8.3 Hz, 1.5 Hz,1H) 7.62 (CH,ddd 8.3 Hz, 6.8 Hz, 1.5 Hz, 1H) 7.22 (CH,ddd 8.3 Hz, 6.8 Hz, 1.5 Hz, 1H) 2.87 (CH_2,dt 2H) 2.70 (NH,t broad 6.5 Hz,1H) 1.60 (m, 2H) 1.4-1.2 (m, 10H) 0.85 (CH_3,t 6.5 Hz,3H)	(200 MHz, $CDCl_3$) 146.3 (1C) 142.7 (1C) 133.6 (1CH) 125.8 (1CH) 124.4 (1CH) 124.4 (1CH) 51.8 ($1CH_2$) 31.8 ($1CH_2$) 30.8 ($1CH_2$) 29.4 ($1CH_2$) 29.3 ($1CH_2$) 26.9 ($1CH_2$) 22.7 ($1CH_2$) 14.1 ($1CH_3$)
1c	(90 MHz, acetone) 8.3 (CH,dd 8Hz,≈1.5 Hz, 1H) 8.1 (CH,dd 8 Hz,≈1.5 Hz, 1H) 7.8 (CH,ddd 8 Hz, 7 Hz,≈1.5 Hz ,1H) 7.5-7.2 (m,6H) 6.6 (CH olef.,d 15 Hz , 1H) 6.4 (CH olef.,dt 15 Hz,5 Hz, 1H) 4.3 (NH, t broad, 1H) 3.8 (CH_2, t 5 Hz, 2H)	(90 MHz, $CDCl_3$) 145.8 (1C) 142.6 (1C) 136.6 (1C) 133.8 (1CH) 132.5 (1CH) 128.6 (2CH) 127.8 (1CH) 126.8 (1CH) 126.4 (2CH) 125.8 (1CH) 124.6 (1CH) 124.4 (1CH) 53.8 ($1CH_2$)
1d	(90 MHz, $CDCl_3$) 8.3 (CH,ddd 8.1 Hz, 1.35 Hz, ≈ 0.3 Hz, 1H) 8.0 (CH, ddd 8.25 Hz, 1.35 Hz, ≈0.3 Hz, 1H) 7.7 (CH,ddd 8.25 Hz, 6.8 Hz,1.35 Hz, 1H) 7.2 (CH,ddd 8.1 Hz, 6.8 Hz, 1.35 Hz, 1H) 3.1 (CH_2,dq 5.0 Hz, 6.0 Hz, 2H) 2.7 (NH,broad, 1H) 1.2 (CH_3,t 6.0 Hz, 3H)	(90 MHz, $CDCl_3$) 146.2 (1C) 142.8 (1C) 133.7 (1CH) 125.9 (1CH) 124.5 (1CH) 124.4 (1CH) 46.1 ($1CH_2$) 15.9 ($1CH_3$)
1e	(200 MHz, $CDCl_3$) 8.28 (CH,ddd 8.25 Hz, 1.25 Hz, ≈0.3 Hz, 1H) 7.88 (CH,ddd 8.25 Hz, 1.25 Hz,≈0.3 Hz, 1H) 7.63 (CH,ddd 8.25 Hz, 7.00 Hz,1.25 Hz, 1H) 7.25 (CH,ddd 8.25 Hz, 7.00 Hz,1.25 Hz, 1H) 2.83 (CH_2,d 6 Hz, 2H) 2.67 (NH,t 6 Hz, 1H) 0.99 (CH_3,s, 9H)	(90 MHz, $CDCl_3$) 147.1 (1C) 142.6 (1C) 133.6 (1CH) 125.9 (1CH) 124.5 (1CH) 124.3 (1CH) 64.7 ($1CH_2$) 32.7 (1C) 27.3 ($3CH_3$)
1f	(200 MHz, $CDCl_3$) 8.25 (CH,d 8 Hz, 1H) 8.03 (CH,d 8 Hz,1H) 7.65 (CH,dd 8 Hz, 7 Hz, 1H) 7.50 - 7.15 (m,11H) 5.15 (CH,d 6 Hz,1H) 3.46 (NH,d 6 Hz,1H)	(200 MHz, $CDCl_3$) 145.2 (1C) 142.9 (1C) 142.5 (2C) 133.7 (1CH) 128.8 (4CH) 127.7 (2CH) 127.4 (1CH) 125.9 (1CH) 124.7 (2CH)
1g	(90 MHz, $CDCl_3$) 8.2 (CH,ddd 8.4 Hz, 1.4 Hz, ≈ 0.3 Hz,1H) 8.0 (CH,ddd 8.4 Hz, 1.4 Hz, ≈ 0.3 Hz,1H) 7.6 (CH,ddd 8.4 Hz, 6.8 Hz, 1.4 Hz,1H) 7.2 (CH,ddd 8.4 Hz, 6.8 Hz, 1.4 Hz,1H) 3.8 - 3.6 (m,5H) 3.2 (NH,t broad, 1H)	(90 MHz, $CDCl_3$) 172.0 (1C) 144.9 (1C) 142.7 (1C) 134.0 (1CH) 125.9 (1CH) 124.9 (1CH) 124.3 (1CH) 52.8 ($1CH_2$) 52.4 ($1CH_3$)
1h	(90 MHz, $CDCl_3$) 8.2 (CH,dd 8.1 Hz, 1.5 Hz,1H) 8.1 (CH,dd 8.1 Hz, 1.5 Hz,1H) 7.6 (CH,ddd 8.1 Hz, 7.2 Hz, 1.5 Hz,1H) 7.2 (CH,ddd 8.1 Hz, 7.2 Hz, 1.5 Hz, 1H) 3.7 (OCH_3 s,3H) 3.5 - 3.1 (m, 2H) 2.0 - 1.7 (m,1H) 1.6 - 1.1 (m,2H) 1.0 - 0.7 (m,6H)	(90 MHz, $CDCl_3$) 174.1 (1C) 145.4 (1C) 133.8 (1CH) 125.8 (1CH) 124.8 (1CH) 124.6 (1CH) 69.2 (1CH) 52.1 ($1CH_3$) 39.1 (1CH) 25.4 ($1CH_2$) 15.7 ($1CH_3$) 11.7 ($1CH_3$)
1i	(90 MHz, $CDCl_3$) 8.3 (CH,dd 8 Hz,≈ 1.5 Hz,1H) 8.0 (CH,dd 8 Hz,≈ 1.5 Hz,1H) 7.7 (CH,ddd 8 Hz, 7 Hz, ≈1.5 Hz,1H) 7.3 (CH, ddd 8 Hz, 7 Hz, ≈ 1.5 Hz, 1H) 4.0 (CH_2,s breit, 2H) 3.8 (OCH_3 s, 3H) 3.7 - 3.5 (m, 2H) 2.1 (OH, broad,1H)	(90 MHz, $CDCl_3$) 172.4 (1C) 144.7 (1C) 142.8 (1C) 134.1 (1CH) 126.0 (1CH) 125.1 (1CH) 124.3 (1CH) 64.8 (1CH) 63.1 ($1CH_2$) 52.9 ($1CH_3$)
1j	(200 MHz, $CDCl_3$) 8.15 (CH,dd 8,5 Hz, ≈ 1.5 Hz, 1H) 8.05 (CH, dd 8.5 Hz, ≈1.5 Hz, 1H) 7.58 (CH, ddd 8.5 Hz, 7 Hz, ≈1.5 Hz, 1H) 7.18 (CH, ddd 8.5 Hz, 7 Hz, ≈1,5 Hz, 1H) 4.28 - 4.12 (CHOH, m broad, 1H) 3.78 -3.67 (OCH_3, NH,m, 4H) 3.42 (NH-CH,dd 9 Hz, 4 Hz, 1H) 2.95 (OH, s broad, 1H) 1.36 (CH_3, d 6 Hz, 3H)	(200 MHz, $CDCl_3$) 173.2 (1C) 145.1 (1C) 142.4 (1C) 133.9 (1CH) 125.6 (1CH) 124.8 (1CH) 124.4 (1CH) 69.7 (1CH) 88.1 (1CH) 52.5 ($1CH_3$) 20.2 ($1CH_3$)
1k	(90 MHz, $CDCl_3$) 8.3 - 8.1 (CH, m, 2H) 7.6 (CH, ddd 8 Hz, 7 Hz, ≈1.5 Hz, 1H) 7.2 (CH, ddd 8 Hz, 7 Hz, ≈1.5 Hz, 1H) 3.7 -3.3 (m, 4H) 1.4 (CH_3,s, 9H) 1.2 (CH_3,s, 9H)	(200 MHz, $CDCl_3$) 170.9 (1C) 146.0 (1C) 142.5 (1C) 133.7 (1CH) 125.6 (1CH) 125.1 (1CH) 124.7 (1CH) 82.0 (1C) 73.3 (1C) 65.1 ($1CH_3$) 62.8 ($1CH_2$) 28.1 ($3CH_3$) 27.4 ($3CH_3$)
1l	(90 MHz, $CDCl_3$) 8.4 - 8.2 (CH, m, 2H) 7.6 (CH, ddd 8 Hz, 7 Hz, ≈1.5 Hz, 1H) 7.2 (CH, ddd 8 Hz, 7 Hz, ≈1.5 Hz, 1H) 4.1 (CH-O,m, 1H) 3.5 (NH,d 10 Hz, 1H) 3.2 (CH, dd 10 Hz, 4 Hz, 1H) 1.5 (CH_3, s, 9H) 1.3 (CH_3, d 6 Hz, 3H) 1.2 (CH_3, s, 9H)	(200 MHz, $CDCl_3$) 171.8 (1C) 146.2 (1C) 142.5 (1C) 133.6 (1CH) 125.6 (1CH) 125.1 (1CH) 124.5 (1CH) 82.0 (1C) 74.0 (1C) 71.2 (1CH) 68.5 (1CH) 28.8 ($3CH_3$) 26.9 ($3CH_3$) 21.2 ($1CH_3$)
1n	(200 MHz, $CDCl_3$) 8.25 - 8.17 (CH, m ,2H) 8.00 (CH, dd 8 Hz, ≈1.5 Hz, 1H) 7.88 (CH, dd 8 Hz, ≈ 1.5 Hz, 1 H) 7.63 - 7.56 (CH, m, 2H) 7.26 - 7.16 (CH,m, 2H) 3.75 (OCH_3, s, 3H) 3.58 - 3.45 (CH-NH), m, 1H) 3.32 (NH-CH, d 9 Hz, 1H) 2.98 (CH_2-NH,q 7 Hz, 2H) 2.80 (NH-CH_2, t 7 Hz, 1H) 1.60 (CH_2-CH, quint 7 Hz, 2H) 1.7-1.4 (CH_2, m, 4H)	(200 MHz, $CDCl_3$) 174.2 (1C) 146.0 (1C) 144.9 (1C) 142.6 (1C) 142.5 (1C) 133.9 (1CH) 133.7 (1CH) 125.7 (1CH) 125.7 (1CH) 124.6 (1CH) 124.4 (1CH) 124.2 (1CH) 63.8 (1CH) 52.4 ($1CH_3$) 51.2 ($1CH_2$) 33.2 ($1CH_2$) 30.2 ($1CH_2$) 22.8 (1 CH_2)
1o	(200 MHz, $CDCl_3$) 8.02 (CH, dd 8 Hz, 1.6 Hz, 1H) 7.39 - 7.02 (CH, m,7H) 6.98 (NH, t 5 Hz, 1H) 6.27 - 5.72 (CH, m, 4H) 5.06 (OCH_2, s ,2H) 4.06 (NH-CH_2), t 5 Hz, 2H) 3.82 (OCH_3, s, 3H) 3.80 (OCH_3, s, 3H) 3.58 - 3.46 (NH-CH-CH_2, m, 1H) 3.42 (NH, d 5 Hz, 1H) 3.18 + 2.86 (CH_2-NH, dd 14 Hz, 4 Hz + dd 14 Hz, 9 Hz, 2H)	(90 MHz, $CDCl_3$) 173.0 (1C) 169.6 (1C) 149.4 (1C) 149.1 (1C) 143.9 (1C) 142.6 (1C) 136.9 (1C) 134.0 (1CH) 129.6 (2CH) 129.0 (1CH) 127.6 (1C) 127.4 (1CH) 125.8 (1CH) 124.8 (1CH) 124.0 (1CH) 121.6 (1CH) 112.0 (1CH) 111.1 (1CH) 67.5 ($1CH_2$) 66.3 (1CH) 55.9 ($2CH_3$) 41.5 ($1CH_2$) 40.3 ($1CH_2$)
2a	(90 MHz, acetone,DMSO) 9.0 (CH,s, 1H) 8.7 (CH, ddd, 8.1 Hz, 1.35 Hz, ≈ 0.3 Hz, 1H) 8.4 (CH, ddd 8.25 Hz, 1.5 Hz, ≈ 0.3 Hz, 1H) 8.1 - 7.8 (CH,m , 3H) 7.7 - 7.4 (CH, m, 4H)	(200 MHz, $CDCl_3$) 160.1 (1CH) 141.3 (1C) 139.8 (1C) 135.3 (1C) 133.8 (1CH) 130.8 (1CH) 128.3 (2CH) 127.4 (2CH) 125.3 (1CH) 124.9 (1CH) 124.7 (1CH)
2b	(90 MHz, $CDCl_3$) 8.6 -8.2 + 7.9 - 7.5 (CH,m,m, 4H) 7.4 - 7.1 (CH, m, 1H) 2.6 (CH_2-N, m, 2H) 1.9 - 1.6 (CH_2, m, 10H) 1.0 - 0.6 (CH_3, m, 3H)	(200 MHz,$CDCl_3$) *E* : 167.2 (1CH) 142.9 (1C) 141.9 (1C) 134.0 (1CH) 125.8 (1CH) 125.4 (1CH) 124.6 (1CH) 37.9 ($1CH_2$) 31.7 ($1CH_2$) 29.2 ($1CH_2$) 29.1 ($1CH_2$) 25.6 ($1CH_2$) 22.6 ($1CH_2$) 14.1 ($1CH_3$) *Z* : 166.7 (1CH) 142.7 (1C) 138.8 (1C) 134.0 (1CH) 126.2 (1CH) 125.4 (1CH) 125.0 (1CH) 34.8 (CH_2) 31.7 ($1CH_2$) 29.3 ($1CH_2$) 29.0 ($1CH_2$) 25.7 ($1CH_2$) 22.6 ($1CH_2$) 14.1 ($1CH_3$) ratio *E/Z*: 7 : 3
2c	(90 MHz, acetone) 8.6 (CH dd 4.5 Hz, 4 Hz, 1H) 8.4 (CH, dd 8.4 Hz, 1.6 Hz, 1H) 8.2 (CH, dd 8.4 Hz, 1.6 Hz, 1H) 7.9 -7.1 (CH, m, 9H)	(90 MHz, $CDCl_3$) *E* : 162.1 (1CH) 142.3 (1C) 140.7 (1C) 135.5 (1C) 134.1 (1CH) 129.9 (1CH) 129.1 (1CH) 127.8 (1CH) 127.6 (2CH) 126.0 (1CH) 125.6 (1CH) 125.0 (1CH) ratio *E/Z* : 9 : 1
2d	(90 MHz, $CDCl_3$) 8.5 - 8.1 (CH, m, 2H) 7.9 (CH, q 5Hz, 1H) 7.8 - 7.4 (CH, m, 1H) 7.4 - 7.1 (CH, m, 1H) 2.2 (CH_3,2 d 5 Hz, 3H)	(200 MHz, $CDCl_3$) *E* : 163.1 (1CH) 140.9 (1C) 134.0 (1CH) 125.8 (1CH) 125.5 (1CH) 124.8 (1CH) 24.3 ($1CH_3$) *Z* : 161.6 (1CH) 139.6 (1C) 134.0 (1CH) 126.2 (1CH) 125.5 (1CH) 125.1 (1CH) 21.2 ($1CH_3$) ratio *E/Z* : 6 : 4
2e	(200 MHz, $CDCl_3$) 8.43 (CH, ddd 8.5 Hz, 1.5 Hz, ≈ 0.3 Hz, 1H) 8.30 (CH, ddd 8.5 Hz, 1.5 Hz, ≈ 0.3 Hz, 1H) 8.20 (CH, s, 1H) 7.67 (CH, ddd 8.5 Hz, 7.0 Hz, 1.5 Hz, 1H) 7.27 (CH, ddd 8.5 Hz, 7.0 Hz, 1.5 Hz, 1H) 1.19 (CH_3, s, 9H)	(200 MHz, $CDCl_3$) 173.1 (1CH) 141.9 (1C) 141.4 (1C) 134.0 (1CH) 125.8 (1CH) 125.4 (1CH) 124.7 (1CH) 39.4 (1C) 26.7 ($3CH_3$)
2f	(200 MHz, $CDCl_3$) 8.78 (CH, dd 8.5 Hz, 1.5 Hz, 1H) 8.28 (CH,dd 8.5 Hz, 1.5 Hz, 1H) 7.82 - 7.25 (CH, m, 12H)	(200 MHz, $CDCl_3$) 167.0 (1CH) 142.8 (1C) 141.3 (1C) 139.1 (1C) 137.2 (1C) 134.0 (1CH) 130.4 (1CH) 129.7 (1CH) 129.1 (2CH) 128.4 (2CH) 128.3 (2CH) 127.6 (2CH) 126.4 (1CH) 125.5 (1CH) 125.0 (1CH)
2g	(200 MHz, $CDCl_3$) 8.46 (CH, dd 8.4 Hz, 1.2 Hz, 1H) 8.30 (CH, dd 8.4 Hz, 1.2 Hz, 1H) 8.25 + 7.97 (CH=N, *E* + *Z*, s + s, 1H) 7.73 (CH, ddd 8.4 Hz , 7.0 Hz , 1.2 Hz, 1H) 7.40 (CH, ddd 8.4 Hz, 7.0 Hz, 1.2 Hz, 1H) 3.91 (OCH_3, s, 1H)	(200 MHz, $CDCl_3$) *E* : 161.6 (1C) 149.3 (1CH) 142.6 (1C) 137.8 (1C) 134.6 (1CH) 126.4 (1CH) 126.3 (1CH) 125.4 (1CH) 52.8 ($1CH_3$) ratio *E/Z* : 8 : 2

Table 4 (*Continued*)

2h	(200 MHz, $CDCl_3$) 8.51 - 8.41 (CH, m, 1H) 8.29 - 7.99 (CH, m, 1H) 7.75 - 7.62 (CH, m, 1H) 7.37 - 7.23 (CH, m, 1H) 3.92 + 3.85 (OCH_3, *E* + *Z*, s + s, 3H) 3.20 - 2.95 (CH, m, 1H) 2.01 - 1.37 (CH_2, m, 2H) 1.32 + 1.20 (CH_3, *E* + *Z*, d + d 6Hz + 6Hz, 3H)	(200 MHz, $CDCl_3$) *E* or *Z* : 164.6 (1C) 159.4 (1C) 143.4 (1C) 141.7 (1C) 133.9 (1CH) 125.9 (1CH) 125.6 (1CH) 125.3 (1CH) 52.7 ($1CH_3$) 41.8 (1CH) 27.6 ($1CH_2$) 17.8 ($1CH_3$) 11.6 ($1CH_3$) *Z* or *E* : 162.6 (1C) 161.4 (1C) 143.0 (1C) 138.6 (1C) 134.3 (1CH) 126.4 (1CH) 125.8 (1CH) 125.4 (1CH) 52.5 ($1CH_3$) 42.2 (1CH) 26.8 ($1CH_2$) 16.0 ($1CH_3$) 12.3 ($1CH_3$) ratio *E/Z* or *Z/E* : 6 : 4
2k	(90 MHz, $CDCl_3$) 8.7 - 8.5 (CH, m, 1H) 8.4 - 8.2 (CH, m, 1H) 7.9 - 7.6 (CH, m, 1H) 7.5 - 7.2 (CH, m, 1H) 4.6 + 4.4 (CH_2, *E* + *Z*, s + s, 2H) 1.6 (CH_3, *E* + *Z*, s + s, 9H) 1.4 (CH_3, *E* + *Z*,s + s, 9H)	(200 MHz, $CDCl_3$) *E* or *Z*: 160.9 (1C) 156.6 (1C) 143.3 (1C) 140.7 (1C) 134.5 (1CH) 126.3 (1CH) 125.6 (1CH) 125.3 (1CH) 82.6 (1C) 75.4 (1C) 61.3 ($1CH_2$) 28.1 ($3CH_3$) 27.3 ($3CH_3$) *Z* or *E* : 159.5 (1C) 154.3 (1C) 141.4 (1C) 134.1 (1CH) 126.3 (1CH) 125.7 (1CH) 125.3 (1CH) 84.3 (1C) 74.2 (1C) 65.0 ($1CH_2$) 28.2 ($3CH_3$) 27.7 ($3CH_3$) ratio *Z/E* or *E/Z*: 6.5 : 3.5
2l	(200 MHz, $CDCl_3$) 8.65 - 8.52 (CH, m, 1H) 8.31 - 8.23 (CH, m, 1H) 7.74 (CH, m, 1H) 7.37 - 7.27 (CH, m, 1H) 4.94 + 4.72 (CH, *E* + *Z*, q + q, 7 Hz + 7 Hz, 1H) 1.63 + 1.57 (CH_3, *E* + *Z*, s + s, 9H) 1.42 + 1.37 (CH_3, *E* + *Z*, d + d, 7 Hz + 7 Hz, 3H) 1.23 + 1.20 (CH_3, *E* + *Z*, s + s, 9H)	(200 MHz, $CDCl_3$) *E* or *Z* : 162.1 (1C) 160.3 (1C) 143.5 (1C) 141.0 (1C) 134.1 (1CH) 126.1 (1CH) 125.6 (1CH) 125.4 (1CH) 82.6 (1CH) 75.6 (1C) 68.2 (1CH) 28.1 ($3CH_3$) 27.4 ($3CH_3$) 18.7 ($1CH_3$) *Z* or *E* : 161.3 (1C) 141.3 (1C) 134.1 (1CH) 126,1 (1CH) 125.6 (1CH) 125.4 (1CH) 84.6 (1C) 74.7 (1C) 71.3 (1CH) 28.3 ($3CH_3$) 28.5 ($3CH_3$) 21.9 ($1CH_3$) ratio *E/Z* or *Z/E* : 6.5 : 3.5
2m	(90 MHz, $CDCl_3$) 8.5 (CH, dd 8 Hz, ≈ 1.5 Hz, 1H) 8.3 (CH, dd, 8 Hz, ≈ 1.5 Hz, 1H) 8.1 + 7.8 (CH, *E* + *Z*, s + s, 1H) 7,7 (CH, ddd 8 Hz, 7 Hz, ≈ 1.5 Hz, 1H) 7.4 (CH, ddd 8 Hz, 7 Hz, ≈ 1,5 Hz, 1H) 1.5 (CH_3, s, 9H)	(90 MHz, $CDCl_3$) *E* : 160.3 (1C) 151.3 (1CH) 142.3 (1C) 138.6 (1C) 134.6 (1CH) 126.4 (1CH) 126.2 (1CH) 125.7 (1CH) 28.1 ($3CH_3$) ratio *E/Z* : 7 : 3
2n	(200 MHz, $CDCl_3$) 8.30 -8.20 (CH, m, 2H) 8.14 (CH, dd, 8.2 Hz, 1.5 Hz, 1H) 8.07 (CH, dd 8.2 Hz, 1.5 Hz, 1H) 7.73 (CH, ddd 8.2 Hz, 7.0 Hz 1.5 Hz, 1H) 7.52 (CH, ddd 8.2 Hz, 7.0 Hz, 1.5 Hz, 1H) 7.28 (CH, ddd 8.2 Hz, 7.0 Hz, 1.5 Hz, 1H) 7.15 (CH, ddd 8.2 Hz, 7.0 Hz, 1.5 Hz, 1H) 4.78 -4.63 (CH, m, 1H) 4.07 (CH, t, 4.5 Hz, 1H) 3.84 (NH, d, 5 Hz, 1H) 3.73 (OCH_3, s, 3H) 2.20 - 1.33 (CH_2, m, 6H)	(200 MHz, $CDCl_3$) 173.2 (1C) 145.8 (1C) 142.7 (1C) 142.6 (1C) 142.4 (1C) 134.2 (1CH) 133.6 (1CH) 125.8 (1CH) 125.6 (1CH) 125.4 (1CH) 125.2 (2CH) 124.6 (1CH) 73.4 (1CH) 66.2 (1CH) 52.2 ($1CH_3$) 30.4 ($1CH_2$) 29.2 ($1CH_2$) 20.2 ($1CH_2$)
2o	(200 MHz, $CDCl_3$) 8.33 - 8.24 (CH, m, 2H) 7.70 (CH, ddd 8.2 Hz, 7.0 Hz, 1.5 Hz, 1H) 7.51 (NH, t broad, 5 Hz, 1H) 7.45 - 7.15 (CH, m, 6H) 6.99 - 6.61 (CH, m, 3H) 5.15 (OCH_2, s, 2H) 4.26 (CH_2-Ph, s, 2H) 4.19 (CH_2-NH,d 5Hz, 2H) 3.87 (OCH_3, s, 6H)	(90 MHz, $CDCl_3$) 169.6 (1C) 162.2 (1C) 161.6 (1C) 149.9 (1C) 149.2 (1C) 143.6 (1C) (1C) 138.0 (1C) 134.4 (1CH) 133.9 (1C) 129.9 (2CH) 128.9 (2CH) 127.5 (1C) 127.1 (1CH) 126.2 (1CH) 126.1 (1CH) 125.7 (1CH) 121.6 (1CH) 111.9 (1CH) 67.6 ($1CH_2$) 55.9 ($2CH_3$) 41.8 ($1CH_2$) 37.2 ($1CH_2$)
3g	(200 MHz, $CDCl_3$) 8.25 (CH, ddd 8.2 Hz, 1.5 Hz, ≈ 0.3 Hz, 1H) 8.02 (CH, ddd 8.2 Hz, 1.5 Hz, ≈1,5 Hz, 1H) 7.65 (CH, ddd 8.2 Hz, 7.0 Hz, 1.5 Hz, 1H) 7.26 (CH, ddd 8.2 Hz, 7.0 Hz ,1.5 Hz, 1H) 4.52 (CH, d, 9.0 Hz, 1H) 3.95 (NH, d 9.0 Hz, 1H) 3.82 (OCH_3, s, 3H) 3.46 (OCH_3, s, 3H)	(90 MHz, $CDCl_3$) 168.8 (1C) 144.8 (1C) 142.5 (1C) 134.1 (1CH) 125.7 (1CH) 125.2 (1CH) 124.6 (1CH) 91.3 (1CH) 65.2 ($1CH_3$) 52.8 ($1CH_3$)

are treated with 4 equivalents of triethylamine in trichloromethane as solvent.

Method 3: DL-serine and L-threonine can be converted to the *O-tert*-butyl protected amino acid *tert*-butyl esters according to the method of Taschner et al.[6f] for the formation of amino acid *tert*-butyl esters. The crude products were used for the formation of the NPS compounds **1k** and **1l**. The yields for these compounds given in Table 1 are calculated on both steps.

Method 4[6g]: 4.99 g (10 mmol) of NPS-phenylalaninedicyclohexylammonium salt and glycine 3,4-dimethoxybenzyl ester hydrochloride[6h] are suspended in 80 ml of trichoromethane and stirred until the solution becomes clear. Then 1.70 g (13 mmol) of 1-HOBt and 2.26 (11 mmol) of DCC are added at 0°C. After 10 h the solution is worked up and the crude product is purified by filtration through a short path column [dichloromethane/petroleum ether (1:1)]. The pure product **1o** remains on the column and can be eluted with ethyl acetate.

The compounds **1a**–**n** were purified by flash chromatography using mixtures of cyclohexane/ethyl acetate or cyclohexane/ethyl acetate/dichloromethane as eluent. Yields and analytical data of all NPS-sulfenamides formed are summarized in Tables 1, 3, and 4.

CAS Registry Numbers

1a: 7257-63-8 / **1b**: 114691-68-8 / **1c**: 114675-73-9 / **1d**: 24398-42-3 / **1e**: 114675-74-0 / **1f**: 114675-75-1 / **1g**: 14608-72-1 / **1h**: 114675-76-2 / **1i**: 114675-77-3 / **1j**: 114675-78-4 / **1k**: 114675-79-5 / **1l**: 114691-69-9 / **1n**: 114675-80-8 / **1o**: 114675-81-9 / **2a**: 110793-23-2 / (*E*)-**2b**: 114675-82-0 / (*Z*)-**2b**: 114675-83-1 / (*E*)-**2c**: 114675-84-2 / (*Z*)-**2c**: 114675-85-3 / (*E*)-**2d**: 114675-86-4 / (*Z*)-**2d**: 114675-87-5 / **2e**: 111017-24-4 / **2f**: 111017-28-8 / (*E*)-**2g**: 114675-88-6 / (*Z*)-**2g**: 114675-89-7 / (*E*)-**2h**: 114675-90-0 / (*Z*)-**2h**: 114675-91-1 / (*E*)-**2k**: 114675-92-2 / (*Z*)-**2k**: 114691-70-2 / (*E*)-**2l**: 114675-93-3 / (*Z*)-**2l**: 114675-94-4 / (*E*)-**2m**: 114675-95-5 / (*Z*)-**2m**: 114675-96-6 / **2n**: 114675-97-7 / **2o**: 114675-98-8 / **3g**: 114675-99-9 / **4**: 24964-91-8 / **5**: 111017-60-8 / NPS-Cl: 7669-54-7 / NPS-Lys-OMe · 2 HCl: 114676-00-5 / $PhCH_2NH_2$: 100-46-9 / $PhCH{=}CHCH_2NH_2$: 4360-51-4 / *n*-$C_8H_{17}NH_2$: 111-86-4 / $CH_3CH_2NH_2$: 75-04-7 / *t*-$BuCH_2NH_2$: 5813-64-9 / Ph_2CHNH_2: 91-00-9 / H-Gly-OMe: 6000-43-7 / H-Ile-OMe · HCl: 18598-74-8 / NPS-phenylalaninedicyclohexylammonium salt: 80971-72-8 / 2,6-dimethylpyridine: 108-48-5 / *N,N,N',N'*-tetraphenyl-*p*-phenylenediamine: 14118-16-2 / DL-serine: 302-84-1 / L-threonine: 72-19-5 / glycine 3,4-dimethoxybenzyl ester: 85134-09-4

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