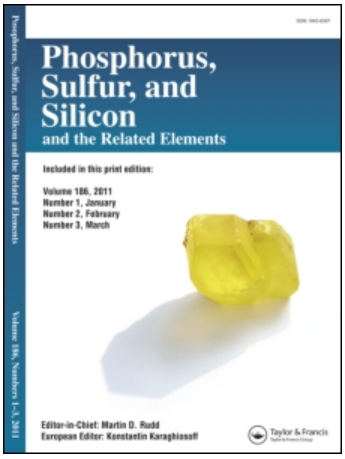

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SYNTHESIS OF 2-CHLOROETHYLNITROSOSULFAMIDES (CENS) VIA A TRANSSULFAMOYLATION REACTION

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SYNTHESIS OF 2-CHLOROETHYLNITROSOSULFAMIDES (CENS) VIA A *TRANSSULFAMOYLATION* REACTION

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In order to synthesize the series of 2-chloroethylnitrososulfamides (CENS), a procedure using the nucleophilic exchange of an activating group of both the sulfamoyl esters and amides by several amines was developed. The N-oxysuccinimide sulfamate ester was revealed as the most reactive sulfamoyl group donor. This transsulfamoylation procedure allows the preparation of title compounds, especially the derivatives of amino acid esters in two steps in a 75–80% yield.

Keywords: alkylating agent; carboxylsulfamides; chloroethylnitrososulfamides; chlorosulfonyl isocyanate; Mitsunobu reaction; nitrosation; nitrososulfamates; oncostatic; transsulfamoylation

In a previous report[1,2] we have described the synthesis and the oncostatic properties of the entitled new compounds. The four-step approach for the preparation of CENS[3], which proceeds by the insertion of a sulfamoyl group, was carried out in a 45–60% overall yield starting from chlorosulfonyl isocyanate[4] (CSI) and selected amines R_1R_2NH (scheme 1).

In the perspective of the synthesis of a larger series, required for the pharmacomodulation studies and to establish QSAR, we developed a *transsulfamoylation* alternative route, which would allow the direct access to the expected sulfamides through an one-step procedure (scheme 2). This reaction proceeds from a nucleophilic exchange (on the activated O- or N-sulfamates **3a–i** or **4a–i**) of a

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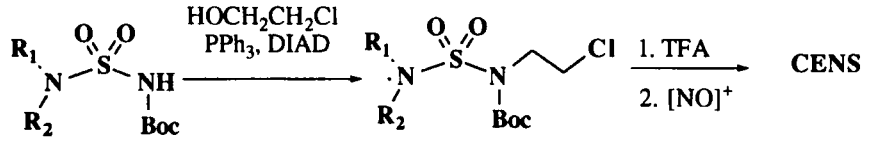
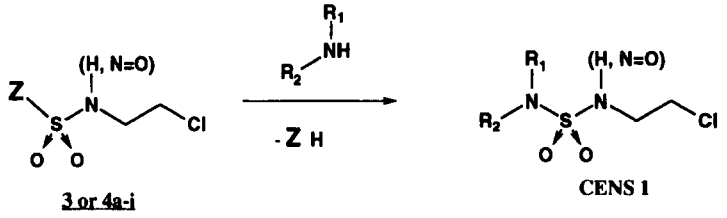


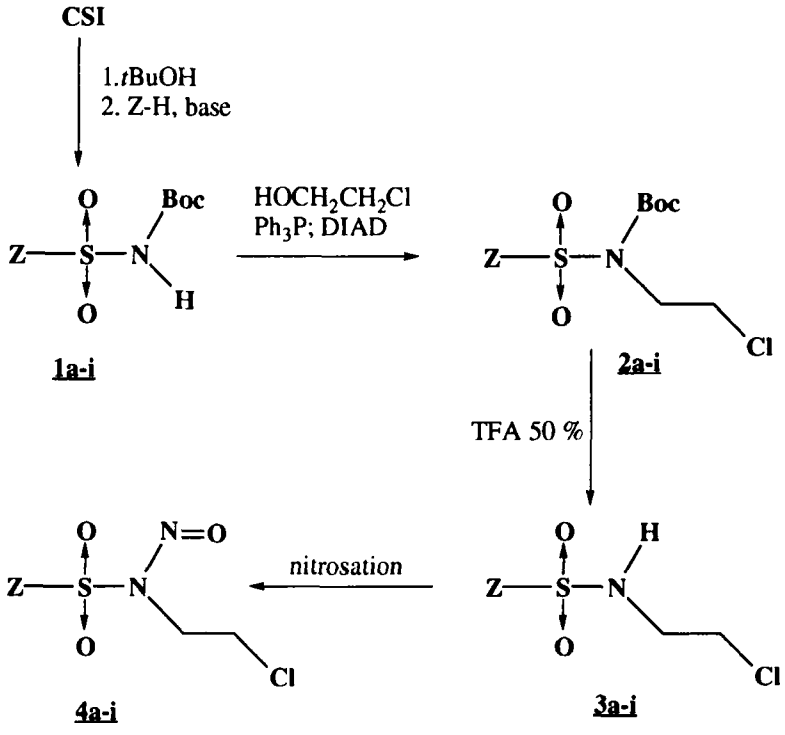
SCHEME 1

leaving group such as phenol, aniline, imidazole or hydroxysuccinimide by the required primary or secondary amine. This approach by the displacement of an activated group is commonly used in acyl, carbamoyl and even N-nitrosocarbamoyl[5,6] transfer reactions, but few examples were described in the sulfamoylated derivatives chemistry: thus were only reported a related aminolysis of arylsulfamides[7], and sulfamates esters of catechol[8,9,10].



SCHEME 2

The preparation of such activated synthons was carried out starting from CSI and several ZH series according to scheme 3. The first one-pot carbamoylation-sulfamoylation step is carried out in presence of pyridine as buffer in a 60–80% yield. The N-chloroalkylation is then achieved under the Mitsunobu conditions[11,12]. Starting from the 4-nitrophenyl carboxylsulfamide, the expected derivative **2b** is accompanied by the dialkylated compound in the 4:1 ratio, relating to the acidity enhancement in the Ar-NH-SO_2 group. The BOC cleavage is realized in acidic medium (50% trifluoroacetic acid in dichloromethane solution) in a quantitative yield. The nitrosation reaction was easily carried out in acidic or alkaline media according to the nature of Z group: ,starting from the N-sulfamates **3a–e**, the reaction is achieved by addition of sodium nitrite in a heterogeneous medium CH_2Cl_2/HCl; concerning the O-derivatives **3f–i** the nitrosation is performed by addition of nitrosyl tetrafluoroborate, nitrosyl chloride or nitrosylsulfuric acid in a biphasic medium of CH_2Cl_2 and aqueous LiOH. However the resulting N-nitroso **4a–h** derivatives are not stable and the starting material was recovered by spontaneous denitrosation about 12 h to 2 days later. No nitrosation was observed with the N-oxysuccinimide derivative **3i**.



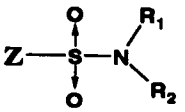
SCHEME 3

Selected data concerning the obtained sulfamides **1-4a–e** and sulfamates **1-4f–h** are reported in the Tables I and II.

Transsulfamoylation assays were carried out with freshly prepared nitrososulfamides **4a–h** and benzylamine, in dichloromethane as solvent. The results are erratic and disappointing, due to the lability of activated compounds. In contrast, the nucleophilic exchange starting from the 2-chloroethylsulfamides precursors **3a–i** and several amines (primary, secondary, aminoester) can be achieved under the conditions reported in the following entries:

	activated sulfamoyl compounds		
	3a–c	**3e–h**	**3i**
primary amines	benzene reflux 2H	MeCN reflux	MeCN RT
(*benzylamine*,	amine 1.5 equiv	30 min	15 min
pentylamine)	TEA 1 equiv	amine 1.5 equiv	amine 1.5 equiv
	yield 30-40%	TEA 1.5 equiv	TEA 1.1 equiv
		Yield 70%	Yield 90%

TABLE I Physicochemical and IR data of the series of O- and N-sulfamoyl derivatives: Analysis (C,H,N), Yield %, mp °C, Rf (a: CH_2Cl_2; b: CH_2Cl_2/MeOH 95/5).
IR (KBr; νcm^{-1}) (NH, CO, NO, SO_2, miscell.)



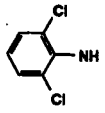
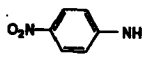
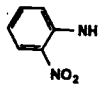
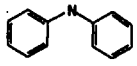
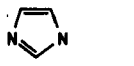
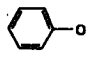
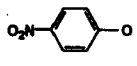
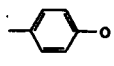
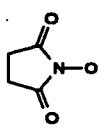
Z group	R_1 = *Boc* R_2 = *H*	R_1 = *Boc* R_2 = CH_2CH_2Cl	R_1 = *H* R_2 = CH_2CH_2Cl	R_1 = *NO* R_2 = CH_2CH_2Cl
	**1a** $C_{11}H_{14}N_2O_4SCl_2$ 60%; 149°C; 0.65[b] 3300; 3200; 1710 1355; 1150.	**2a** $C_{13}H_{17}N_2O_4SCl_3$ 62%; °C; 0.73[b] 3300; 1725; 1350; 1160.	**3a** $C_8H_9N_2O_2SCl_3$ 98%; °C; 0.66[b] 3330; 1340; 1150	**4a** $C_8H_8N_3O_3SCl_3$ 51%; foam; 0.70[a] 3250; 1560; 1340; 1150.
	**1b** $C_{11}H_{15}N_3O_6S$ 68%; 136°C; 0.40[b] 3325; 1710; 1340; 1140.	**2b** $C_{13}H_{18}N_3O_6SCl$ 51%; 140°C; 0.51[a] 3270; 1710; 1350; 1145.	**3b** $C_8H_{10}N_3O_4SCl$ 88%; 134°C; 0.56[b] 3230; 1595; 1345; 1130.	**4b** $C_8H_9N_4O_5SCl$ 48%; foam; 0.75[a] 3300; 1625; 1570 1350; 1140.
	**1c** $C_{11}H_{15}N_3O_6S$ 63%; 111°C; 0.68[a] 3375; 3175; 1710; 1610; 1345; 1135.	**2c** $C_{13}H_{18}N_3O_6SCl$ 61%; 90°C; 0.74[a] 3300; 1730; 1620; 1360; 1140.	**3c** $C_8H_{10}N_3O_4SCl$ 83%; 77°C; 0.56[a] 3300; 1610; 1360; 1140.	**4c** $C_8H_9N_4O_5SCl$ 55%; foam; 0.71[a] 3300; 1615; 1580 1360; 1140.
	**1d** $C_{17}H_{20}N_2O_4S$ 63%; 61°C; 0.41[a] 3400; 1700; 1320; 1150.	**2d** $C_{19}H_{23}N_2O_4SCl$ 73%; foam; 0.85[a] 1730; 1370; 1140.	**3d** $C_{14}H_{15}N_2O_2SCl$ 86%; foam; 0.52[a] 3300; 1360; 1140.	**4d** $C_{14}H_{14}N_3O_3SCl$ 73%; 56°C; 0.77[a] 1550; 1365; 1150.
	**1e** $C_8H_{13}N_3O_4S$ 80%; 125°C; 0.69[b] 3105; 1680; 1355; 1140; 1570.	**2e** $C_{10}H_{16}N_3O_4SCl$ 65%; foam; 0.64[a] 1670; 1360; 1155 1540.	**3e** $C_5H_8N_3O_2SCl$ 85%; <50°C; 0.60[b] 3250; 1370; 1170 1585.	**4e** $C_5H_7N_4O_3SCl$ 60%; foam; 0.60[a] 1580; 1360; 1150; 1570.
	**1f** $C_{11}H_{15}NO_5S$ 75%; foam; 0.64[a] 3250; 1740; 1365; 1140.	**2f** $C_{13}H_{18}NO_5SCl$ 88%; foam; 0.69[a] 1755; 1340; 1140.	**3f** $C_8H_{10}NO_3SCl$ 93%; 67°C; 0.70[a] 3250; 1350; 1140.	**4f** $C_8H_9N_2O_4SCl$ 93%; dec; 0.70[a] 1580; 1360; 1145.
	**1g** $C_{11}H_{14}N_2O_7S$ 65%; 130°C; 0.90[b] 3270; 1715; 1360; 1160; 1605.	**2g** $C_{13}H_{17}N_2O_7SCl$ 81%; foam; 0.74[a] 1730; 1370; 1150 1600.	**3g** $C_8H_9N_2O_5SCl$ 94%; 84°C; 0.60[a] 3270; 1345; 1160 1615.	**4g** $C_8H_8N_3O_5SCl$ 83%; dec; 0.60[a] 1615; 1580; 1360; 1150.
	**1h** $C_{12}H_{17}NO_5S$ 72%; foam; 0.70[a] 3250; 1740; 1365; 1140.	**2h** $C_{14}H_{20}NO_5SCl$ 90%; foam; 0.77[a] 1735; 1340; 1140.	**3h** $C_9H_{12}NO_3SCl$ 97%; 55°C; 0.50[a] 3250; 1350; 1140.	**4h** $C_9H_{11}N_2O_4SCl$ 75%; dec; 0.75[a] 1585; 1365; 1145.
	**1i** $C_9H_{14}N_2O_7S$ 72%; 120°C; 0.30[b] 3350; 1860; 1730; 1365; 1150.	**2i** $C_{11}H_{17}N_2O_7SCl$ 82%; 106°C; 0.87[b] 3300; 1770; 1735 1375; 1160.	**3i** $C_6H_{17}N_2O_7SCl$ 82%; 106°C; 0.87[b] 3300; 1740; 1375; 1185.	**4i** no reaction

TABLE II ^{1}H NMR data of compounds **1-4(a–i)**

Cp	*^{1}H NMR (250MHz)*
1a	8.25 (s, 1H, Ar-NH), 7.40-7.20 (m, 4H, NH Boc + ArH), 1.40 (s, 9H, *t*Bu).
1b	10.10 (s, 1H, NH Boc), 8.35 (d, 2H, o-ArH), 8.15 (d, 2H, m-ArH), 7.3 (s, 1H, Ar-NH), 1.40 (s, 9H, *t*Bu).
1c	10.05 (s, 1H, NH Boc), 8.15-7.20 (m, 4H, ArH), 5.10 (s, 1H, Ar-NH), 1.35 (s, 9H, *t*Bu).
1d	7.5-7.30 (m, 10H, 2ArH), 7.00 (t, 1H, NH Boc), 1.40 (s, 9H, *t*Bu).
1e	9.10 (s, 1H, *imid*), 8.80 (s, 1H, NH-Boc), 7.75 (s, 2H, *imid*), 1.35 (s, 9H, *t*Bu).
1f	7.40-7.25 (m, 6H, ArH + NH), 1.47 (s, 9H, *t*Bu).
1g	8.35, 7.55 (2d, 4H, ArH), 1.55 (s, 9H, *t*Bu).
1h	7.16 (m, 5H, ArH + NH), 2.33 (s, 3H, CH_3), 1.40 (s, 9H, *t*Bu).
1i	NH ?? 2.74 (s, 4H, CH_2), 1.47 (s, 9H, *t*Bu).
2a	8.25 (s, 1H, Ar-NH), 7.40-7.20 (m, 3H, ArH), 4.15 (t, 2H, CH_2N), 3.70 (t, 2H, CH_2Cl), 1.45 (s, 9H, *t*Bu).
2b	8.15 (d, 2H, o ArH), 7.3 (d, 2H, m ArH), 3.85 (t, 2H, CH_2N), 3.30 (t, 2H, CH_2Cl), 1.40 (s, 9H, *t*Bu).
2c	10.0 (s, 1H, NH), 8.15-7.30 (m, 4H, ArH), 3.95 (t, 2H, N-CH_2), 3.50 (t, 2H, CH_2Cl), 1.50 (s, 9H, *t*Bu).
2d	7.50-7.30 (m, 10H, 2ArH), 3.70 (t, 2H, N-CH_2), 3.25 (t, 2H, CH_2Cl), 1.50 (s, 9H, *t*Bu).
2e	8.05, 7.35, 7.05 (3s, 3H, *imid*), 4.15 (t, 2H, N-CH_2), 3.75 (t, 2H, CH_2Cl), 1.45 (s, 9H, *t*Bu).
2f	7.45, 7.32 (m, 6H, ArH + NH), 4.36 (t, 2H, CH_2N), 3.90 (t, 2H, CH_2Cl), 1.55 (s, 9H, *t*Bu).
2g	8.30, 8.50 (2d, 4H, ArH), 4.00 (t, 2H, CH_2N), 3.55 (t, 2H, CH_2Cl), 1.55 (s, 9H, *t*Bu).
2h	7.27-7.16 (m, 4H, ArH), 3.85 (t, 2H, CH_2N), 3.35 (t, 2H, CH_2Cl), 2.40 (s, 3H, CH_3), 1.59 (s, 9H, *t*Bu).
2i	3.96 (t, 2H, CH_2N), 3.65 (t, 2H, CH_2Cl), 2.79 (s, 4H, CH_2), 1.51 (s, 9H, *t*Bu).
3a	7.35 (d, 2H, ArH), 7.25 (t, 1H, ArH), 5.00 (s Broad, 2H, 2 NH), 3.80 (t, 2H, CH_2Cl), 3.70 (q, 2H, CH_2NH).
3b	8.15; 7.20 (2d, 4H, ArH), 6.95 (s, 1H, ArNH), 5.05 (t, 1H, CH_2NH), 3.55 (t, 2H, CH_2Cl), 3.35 (q, 2H, CH_2N).
3c	9.70 (s, 1H, ArNH), 8.35 (t, 1H, CH_2NH), 8.05-7.40 (m, 4H, ArH), 3.80 (t, 2H, CH_2Cl), 3.30 (q, 2H, CH_2N)
3d	7.50-7.20 (m, 10H, 2ArH), 4.95 (t, 1H, NH), 3.60 (t, 2H, CH_2Cl), 3.45 (q, 2H, CH_2N).
3e	8.85 (s, 2H, *imid*), 7.65 (s, 1H, *imid*), 4.75 (t, 1H, NH), 3.75 (t, 2H, CH_2Cl), 3.25 (q, 2H, CH_2N).
3f	7.43-7.25 (m, 5H, ArH), 5.19 (t, 1H, NH), 3.65 (t, 2H, CH_2Cl), 3.55 (q, 2H, CH_2N).
3g	8.35 and 7.55 (2d, 4H, ArH(, 5.36 (t, 1H, NH), 3.79 (t, 2H, CH_2Cl), 3.70 (q, 2H, CH_2N).
3h	7.17 (s, 4H, ArH), 5.10 (t, 1H, NH), 3.68 (t, 2H, CH_2Cl), 3.56 (q, 2H, CH_2N), 2.35 (s, 3H, CH_3).
3i	9.45 (t, 1H, NH), 3.65 (t, 2H, CH_2Cl), 3.45 (q, 2H, CH_2), 2.70 (s, 4H, CH_2).
4a	7.40-7.20 (m, 3H, ArH), 4.85 (t, 2H, CH_2N), 4.20 (t, 2H, CH_2Cl).
4b	8.20 and 7.45 (2d, 4H, ArH), 4.65 (t, 2H, N-CH_2), 3.65 (t, 2H, CH_2Cl).
4c	8.15 (s, 1H, ArNH), 8.00-7.40 (m, 4H, ArH), 4.50 (t, 2H, CH_2N), 3.45 (t, 2H, CH_2Cl).
4d	7.50-7.30 (m, 10H, 2ArH), 4.00 (t, 2H, CH_2N), 3.15 (t, 2H, CH_2Cl).
4f	7.50-7.20 (m, 5H, ArH), 4.10 (t, 2H, CH_2N), 3.45 (t, 2H, CH_2Cl).
4g	7.25 and 7.00 (2d, 4H, ArH), 4.35 (t, 2H, CH_2N), 3.90 (t, 2H, CH_2Cl).
4h	7.20 (m, 4H, ArH), 4.05 (t, 2H, CH_2N), 3.40 (t, 2H, CH_2Cl), 2.40 (s, 3H, CH_3).

secondary amines (*piperidine, dibenzylamine*)	benzene as solvent amine 1.5 equiv TEA 1 equi reflux 5H yield 10%	MeCN reflux 30 min amine 1.5 equiv TEA 1.5 equiv Yield 50–60%	MeCN RT 30 min amine 1.5 equiv TEA 1.1 equiv Yield 75%
amino acid esters *H-Pro-OMe* *H-Sarc-OMe*	benzene as solvent amine 1.5 equiv TEA 1 equiv reflux 5H yield 5%	MeCN reflux 30 min amine 1.5 equiv TEA 1.5 equiv Yield 65%	MeCN RT 30 min amine 1.5 equiv TEA 1.1 equiv Yield 80%

O-sulfamoylated compounds, and especially N-oxysuccinimide derivative also appeared as the best donor of sulfamoyl group in the transsulfamoylation procedure. With benzylamine, pentylamine, piperidine and dibenzylamine, the resulting 2-chloroethylsulfamides are easily identified with original compounds and the subsequent nitrosation can be carried out by the protocol previously described[1]. The best results are obtained for the synthesis of prolinate **7** and sarcosinate **8** CENS-derivatives. Relating to the pharmacomodulation described in the CENU's series, the association of the pharmacophore CENS with the amino acids is potentially interesting for an eventual vectorization[6,13,14]. In conclusion, the above preparation allows an efficient two-step synthesis of CENS starting from a common precursor with appropriate reactivity.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a thermotechnal apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer. Microanalysis were performed in the microanalysis laboratory of ENSCM (Montpellier). Proton Magnetic Resonance were determined with a AC 250 Bruker spectrometer. Thin-layer chromatography (TLC) was performed on silica gel $60F_{254}$ (Merck). Column chromatography was performed with silica gel 60. All solvents used for the reactions were anhydrous.

1. Carbamoylation-Sulfamoylation. A solution of 0.05 mol of N-chlorosulfonyl *tert*butylcarbamate was prepared by addition of *tert*-butanol (4.8 mL in 25 mL of dried dichloromethane) into a solution of CSI (7.1 g in the

same solvent). This reagent was slowly added at 0°C into of a solution containing, phenol, aniline, imidazole or hydroxysuccinimide (0.05 mol in 100 mL dichloromethane) and 1.1 equiv of pyridin. The reaction was achieved in 45 minutes. The medium was diluted with 100 mL dichloromethane, washed by two fractions of HCl 0.1 N, dried and concentrated *in vacuo*. The crude residue was then purified by column chromatography. **1a–i** are obtained in a 85–95% yield.

2. N-chloroalkylation. A solution of N-*t* butyloxycarbonyl, O- or N-sulfamates (0.03 mol), triphenylphosphine (7.6 g) and chloroethanol (2.4 g; 2 mL) in THF (25mL) was added dropwise (20min, 5°C) to a solution of equimolar quantities of diethyl (di*iso*propyl) azodicarboxylate (0.03 mol; 5.22 g or 6.06 g) in THF (25 mL). The reaction medium was stirred under an atmosphere of dry nitrogen for about 45 min. TLC reveals the formation of a substituted compound (UV, ninhydrine) less polar than its precursor. Oxydoreduction compounds were removed by filtration after precipitation into diethylether. The filtrate was concentrated and the crude residue was purified by column chromatography eluted with dichloromethane. Chloroalkylated sulfamides **2a–i** were recovered in 70–80% yield.

3. Deprotection. A solution of trifluoroacetic acid (50% in dried dichloromethane; 3 equiv) was dropwise added into a stirred solution of substituted N-Boc, N-chloroethylsulfamide (0.02 mol) in dried dichloromethane (15 mL) at 0°C. The reaction medium was stirred during two hours, concentrated under reduced pressure and coevaporared with diethyl ether. The residue was recrystallized in a AcOEt:hexane mixture. **1a–i** are obtained in a 85–95% yield.

4. Nitrosation.

I. To a stirred solution of N-(2-chloroethyl)sulfamide (0.01 mol) **3(a–e)** in 25 mL of dichloromethane and 3 mL of hydrochloric acid was added in fractions dried sodium nitrite (2 equiv) at 0°C during 30 min. After filtering the suspension, the solution was washed, dried and evaporated under reduced pressure (yield = 50–70%).

II. To a stirred solution of N-(2-chloroethyl)sulfamate (0.01 mol) **3(f–h)** in 25 mL of dichloromethane and 2 equiv. of lithium hydroxide in 5 mL of water at 0°C was added with stirring 2.5 equiv. of nitrosyl chloride in the same solvent. Nitrosyl tetrafluoroborate or nitrosylsulfuric acid can be use under the same conditions. Then the reaction medium was separated and the organic phase was washed by HCl 0.1 N, dried and evaporated under reduced pressure. The recrystallization (petroleum ether) affords CENS in a 80–93% yield.

5. Preparation of CENS aminoacid esters by transsulfamoylation A solution of methyl prolinate (sarcosinate) hydrochloride (0.005 mol) was stirred with 1.1 equiv of triethylamine in acetonitrile (10 mL) during 10 min at r.t.. Sulfamate **3i** (0.0035 mol) was then added and the reaction stirred for 30 min. The medium was successively washed by fractions of HCl 0.1 N, water and hydrogenocarbonate solution, dried and evaporated. The crude residue was recrystallized in AcOEt:hexane mixture. N-2-chloroethylsulfamoyl prolinate (sarcosinate) **5** (**6**) were then nitrosated in the above 4-I conditions, affording the expected aminoacid esters-CENS **7** and **8**, respectively.

Methyl N-(N-2-chloroethylsulfamoyl)prolinate **5**
Yield 88%. F = 69–71°C. Rf = 0.84 (CH_2Cl_2:MeOH 98:2). Anal. $C_8H_{15}N_2O_4SCl$ (270–272). IR (KBr, ν cm^{-1}): 3380 (NH), 1745 (C=O), 1340, 1130 (SO_2).
^1H NMR ($CDCl_3$): 4.97 (t, 1H, NH); 4.38 (m, 1H, *CH); 3.66 (t, 2H, CH_2Cl); 3.52 (s, 3H, OMe); 3.44 (q + m, 4H, CH_2NH + CH_2N); 2.20–1.90 (m, 4H, βCH_2 γCH_2 Pro).

Methyl N-(N-2-chloroethylsulfamoyl)sarcosinate **6**
Yield 84%. foam. Rf = 0.79 (CH_2Cl_2:MeOH 95:5). Anal. $C_6H_{13}N_2O_4SCl$ (244–246)
IR (neat, ν cm^{-1}): 3400 (NH), 1740 (C=O), 1335, 1120 (SO_2).
^1H NMR ($CDCl_3$): 5.15 (t, 1H, NH); 4.0 (s, 2H, CH_2NMe); 3.72 (s, 3H, OMe); 3.64 (t, 2H, CH_2Cl); 3.45 (t, 2H, CH_2NH); 2.88 (s, N-CH_3).

Methyl N-(N-2-chloroethylsulfamoyl)prolinate **7**
Yield 91%. Foam. Rf = 0.80 (CH_2Cl_2). Anal. $C_8H_{14}N_3O_5SCl$ (299–301).
^1H NMR ($CDCl_3$): 4.55 (dd, 1H, *CH); 3.75 (t, 2H, CH_2NNO); 3.54 (m, 4H, CH_2Cl + CH_2NPro); 3.53 (s, 3H, OMe); 2.30–2.00 (m, 4H, βCH_2 γCH_2 Pro)

Methyl N-(N-2-chloroethylsulfamoyl)sarcosinate **8**
Yield 95%. foam. Rf = 0.90 (CH_2Cl_2). Anal. $C_6H_{12}N_3O_5SCl$ (273–275)
^1H NMR ($CDCl_3$): 4.15 (s, 2H, CH_2NMe); 4.05 (t, 2H, CH_2NNO); 3.72 (s, 3H, OMe); 3.47 (t, 2H, CH_2Cl); 3.10 (s, N-CH_3).

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