Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5695-5698, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01195-1

Expedient Synthesis of 2-Chloroethylnitrososulfamides (CENS) *via* the Decarboxylative Reopening of Sulfamoyloxazolidinones

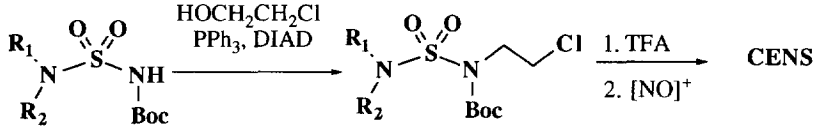
Mohamed Abdaoui, Georges Dewynter, and Jean-Louis Montero*

Laboratoire de Chimie Biomoléculaire, associé au CNRS
cc 073, Université de Montpellier-II, France

Key words: alkylating agent, carbamoylsulfamide, carboxylsulfamide, chloration, chloroethylnitrososulfamide, chlorosulfonyl isocyanate, decarboxylation, nitrosation, oncostatic, sulfamoyloxazolidinone.

abstract: The synthesis of chloroethylnitrososulfamides (CENS), was carried out starting from chlorosulfonyl isocyanate, amines and haloalcohols through heterocyclization and decarboxylative reopening of N-sulfamoyl-2-oxazolidinones. A total regioselectivity concerning CO_2 *versus* SO_2 site hydrolysis was observed. A related aminolysis of sulfamoyloxazolidinones gave N-carbamoylsulfamides. The specific nitrosation on the N-chloroalkyl moiety can be obtained after methylation of the sulfamoyloxazolidinones. Copyright © 1996 Elsevier Science Ltd

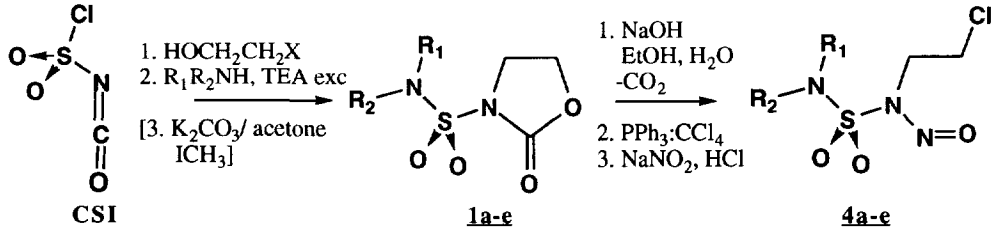
In a previous report [1] we have described the synthesis and the oncostatic properties of the entitled new compounds, building on the structural model of chloroethylnitrosoureas [2] (CENU). CENS are revealed as a new series of alkylating agents, which are devoid of any carbamoylating activity. The first approach for the preparation of CENS, named by us as a result of the *insertion of a sulfamoyl group* [3], was carried out in a 40-60 % overall yield, starting from chlorosulfonyl isocyanate (CSI) and primary or secondary amines R_1R_2NH (scheme 1):



Scheme 1

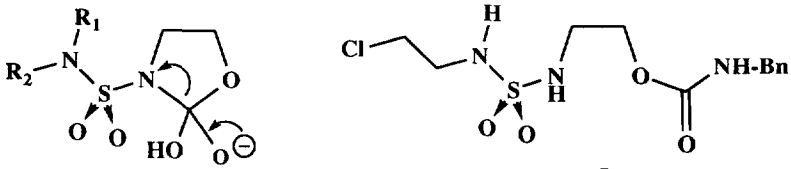
In this early route, the careful purification required after the Mitsunobu reaction on the Boc-sulfamides decreases the yield despite a total transformation of the four reactants. We present in this report an expedient alternative synthesis using a closure-methylation-reopening of N-sulfamoyl oxazolidinones [4] which avoids this main limitation and allows the regiospecific nitrosation on the N-chloroalkyl position. In this new approach, the NH-carbamic electronwithdrawing activation leads the introduction of the future alkylating group at the heterocyclic closure step (scheme 2).

* correspondence and reprints. e mail: dewynter@crit.univ-montp2.fr



Scheme 2

One-pot carbamoylation by bromoethanol followed by the sulfamoylation with the selected amines (piperidine [**a**], isopentylamine [**b**], and cysteamine ($H_2NCH_2CH_2S$-)$_2$ [**d**]) and a subsequent cyclization *in situ* by an excess of triethylamine (3 equiv.) gave the N-sulfamoyl oxazolidinones **1a,b,d** in 80-90% yield. Intermediate 2-bromoethoxycarbonyl sulfamides can however be isolated using controlled alkaline conditions. In order to prevent the formation of nitroso by-products, the precursors **1b** and **1d** 5 were methylated by methyl iodide in a solution of potassium carbonate in acetone to easily give **1c** and **1e** respectively. The crude *cyclocarbamates* were then saponified with a NaOH 2N hydroalcoholic solution, giving by a spontaneous decarboxylation the expected 2-hydroxyethylsulfamides **2a-c,e** with a total regioselectivity concerning CO_2 *vs* SO_2 hydrolysis 6. The reopening is furthered by the formation of intermediary sulfamide anion. In addition, a related aminolysis of N-sulfamoyl oxazolidinones gave carbamoylsulfamides such as **5** 7 in mild conditions (scheme 3). Hence further developments are in progress.



5

Scheme 3

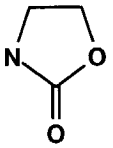
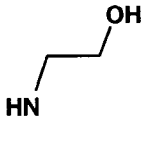
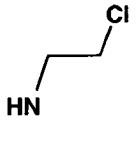
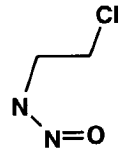
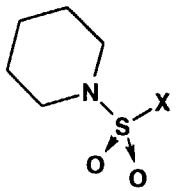
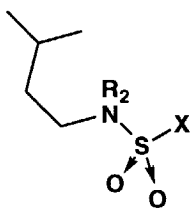
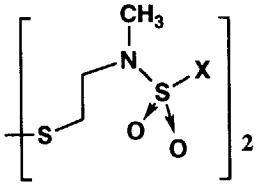
A subsequent chloration of 2-hydroxyethylsulfamides **2a-c,e** using CCl_4/PPh_3 in dichloromethane gave the 2-chloroethyl compounds **3a-c,e** in a quantitative yield. The nitrosation was *in fine* carried out using sodium nitrite/HCl in a biphasic system water:dichloromethane. In the case of isopentylamine, the desired CENS **4b** were accompanied by small amounts of the dinitrosated compound. The resulting 2-chloroethylnitrososulfamides **4a-c,e** were also obtained in a 70% overall yield. Derivatives of cystamine present a particulary potential interest because the CENU related compounds exhibit thiol/disulfide-like pharmacological properties 8.

Selected physicochemical (yield, Rf, mp °C) and ^{1}H NMR data are reported in the Table.

In conclusion, the described closure-methylation-reopening procedure constitutes a significant improvement for the CENS synthesis relating to the work-up and the overall yield. Moreover, sulfamoyloxazolidinones, as key-compounds in this approach, would be interesting templates for the preparation of new series of carbamate-sulfamide derivatives.

Acknowledgements

This work is partially supported by the franco-algerian academic agreement 93 MEN 234 (Ministère Français des Affaires Etrangères)

X=				
	**1a** $C_8H_{14}N_2O_4S$ Yld 88% mp=103-105°C; Rf: 0.85[b]; NMR[d]: 4.45 (t, J= 7.43 Hz, 2H, CH_2O) 4.05 (t, 2H, CH_2N), 3.45 (t, 4H, 2 CH_2N pip), 1.75-1.55 (m, 6H, 3 CH_2N pip).	**2a** $C_7H_{16}N_2O_3S$ Yld 92% foam; Rf: 0.43[a]; NMR[d]: 3.75 (t, J= 5.02 Hz, 2H, CH_2O), 3.20 (m, 6H, CH_2N and 2 CH_2NH), 2.15 (s, 1H, OH), 1.7-1.5 (m, 6H, 3 CH_2 pip).	**3a** $C_7H_{15}ClN_2O_2S$ Yld 95% mp: 52°C; Rf: 0.72[b]; NMR[d]: 4.62 (t,1H,NH), 3.64 (t, J= 5.77 Hz, 2H, CH_2Cl), 3.40 (q, 2H, CH_2N), 3.32 (t, 4H, 2 CH_2N pip), 1.62-1.50 (m, 6H, 3 CH_2 pip).	**4a** $C_7H_{14}ClN_3O_3S$ Yld 86% mp: 52-53°C; Rf: 0.82[a]; NMR[d]: 4.50 (t, J= 7.06 Hz, 2H, CH_2NNO), 4.10 (t, 2H, CH_2Cl), 3.52 (t, 4H, 2 CH_2N pip), 1.62-1.50 (m, 6H, 3 CH_2 pip).
 **1-4b R_2= H** **1-4c R_2= Me**	**1b** $C_8H_{16}N_2O_4S$ Yld 80% mp: 135°C; Rf: 0.46[b]; NMR[d]: 5.35 (t, 1H, NH), 4.45 (t, J= 7.78 Hz, 2H, CH_2O), 4.05 (t, 2H, CH_2N het), 3.17 (t, 2H, CH_2NH), 1.65 (m, 1H, CH), 1.45 (q, 2H, CH_2), 0.85 (d, 6H, 2 CH_3). **1c** $C_9H_{18}N_2O_4S$ Yld 88% foam; Rf: 0.79[b]; NMR[d]: 4.40 (t, J= 7.78 Hz, 2H, CH_2O), 4.0 (t, 2H, CH_2N het), 3.30 (t, 2H, CH_2NMe), 2.95 (s, 3H, NMe), 1.60 (m, 1H, CH), 1.45 (q, 2H, CH_2), 1.35 (d, 6H, 2 CH_3).	**2b** $C_7H_{18}N_2O_3S$ Yld 88% mp: 60°C; Rf: 0.74[c]; NMR[d]: 4.70, 4.22 (2t, 2H, 2NH), 3.75 (q, J= 4.88 Hz, 2H, CH_2O), 3.15, 3.05 (2q, 4H, 2 CH_2NH), 2.1 (sb, 1H, OH), 1.60 (m, 1H, CH), 1.40 (q, 2H, CH_2), 0.9 (d, 6H, 2 CH_3). **2c** $C_8H_{20}N_2O_3S$ Yld 95% foam; Rf: 0.45[b]; NMR[d]: 4.55, (t, 1H, NH), 3.75 (q, J= 4.98 Hz,2H, CH_2O) 3.15, (2t, 4H, CH_2NH and CH_2NMe), 2.75 (s,3H; NMe) 2.0 (t, 1H, OH), 1.55 (m, 1H, CH), 1.45 (q, 2H, CH_2) 0.85 (d, 6H, 2 CH_3)	**3b** $C_7H_{17}ClN_2O_2S$ Yld 82% mp: 69-70°C; Rf: 0.87[b]; NMR[d]: 4.65, 3.95 (2 t, 2H, NH), 3.55 (t, J= 5.80 Hz, 2H, CH_2Cl), 3.25 (q, 2H CH_2NH), 2.95 (t, 2H, CH_2N), 1.55 (m, 1H, CH), 1.30 (q, 2H, CH_2), 0.77 (d, 6H, 2 CH_3). **3c** $C_8H_{19}ClN_2O_2S$ Yld 85% foam; Rf: 0.74[b]; NMR[d]: 4.55, (t, 1H, NH), 3.62 (t, J= 5.77 Hz, 2H, CH_2Cl), 3.30, (q, 2H, CH_2NH), 3.12 (t, 2H; CH_2NMe) 2.75 (s, 3H, NMe), 1.60 (m, 1H, CH), 1.42 (q, 2H, CH_2) 0.85 (d, 6H, 2 CH_3).	**4b** $C_7H_{16}ClN_3O_3S$ Yld 80% foam; Rf: 0.83[b]; NMR[d]: 4.55 (sb, 1H, NH), 4.00 (t, J= 7.12 Hz, 2H, CH_2N-NO), 3.55 (t, 2H, CH_2Cl) 2.45 (t, 2H, CH_2N), 1.55 (m, 1 H, CH), 1.30 (m, 2H, CH_2), 0.77 (d, 6H, 2 CH_3). **4c** $C_8H_{18}ClN_3O_3S$ Yld 88% foam; Rf: 0.91[b]; NMR[d]: 4.10 (t, J= 7.12 Hz, 2H, CH_2N-NO), 3.55 (t, 2H, CH_2Cl), 3.38 (t, 2H, CH_2NMe), 3.05(s, 3H, NMe), 1.66 (m, 1H, CH), 1,55 (q, 2H, CH_2), 0.95 (d, 6H, 2 CH_3).
	**1e** $C_{12}H_{22}N_4O_8S_4$ Yld 80% mp: 89-91°C; Rf: 0.68[b]; NMR[d]: 4.40 (t, J= 7.84 Hz, 4H, CH_2O), 4.05 (t, 4H, CH_2N het), 3.65 (t, 4H, CH_2NMe), 3.0 (s, 6H, NMe), 2.85 (t, J= 7.23 Hz, 4H, CH_2S).	**2e** $C_{10}H_{26}N_4O_6S_4$ Yld 77% foam; Rf: 0.43[c]; NMR[e]: 7.15 (t,2H, NH), 4.65 (t, 2H,OH) 3.40 (q, J= 6.12 Hz,4H, CH_2O), 3.28 (q, 4H, CH_2NMe), 2.85 (m, 8H, CH_2S J= 6.19 Hz, CH_2NH) 2.68 (s, 6H, NMe).	**3e** $C_{10}H_{24}Cl_2N_4O_4S_4$ Yld 82% mp: 73-74; Rf: 0.89[b]; NMR[d]: 4.80 (t, 2H, NH), 3.65 (t, J= 5.79 Hz,4H, CH_2Cl), 3.45 (t, 4H, CH_2NMe), 3.35 (q, 4H, CH_2NH), 2.88 (m, J= 7.25 Hz, 4H, CH_2S) 2.82 (s, 6H, NMe).	**4e** $C_{10}H_{22}Cl_2N_6O_6S_4$ Yld 80% foam; Rf: 0.68[a]; NMR[d]: 4.15 (t, J= 6.96 Hz, 4H, CH_2NNO), 3.70 (t, 4H, CH_2Cl), 3.55 (t, 4H, CH_2NMe), 3.10 (s, 6H, NMe), 2.95 (m, J= 6.72 Hz, 4H, CH_2S).

tlc; a: dichloromethane; b: dichloromethane/methanol 95/5;c: dichloromethane/methanol 90/10; **NMR 250 MHz**; d: $CDCl_3$; e: DMSO d6.

References and notes

[1] Abdaoui, M.; Dewynter, G.; Aouf, N.; Favre, G.; Morere, A.; Montero, J-L. *Biorg. Med. Chem.* **1996**, in press. Related papers concerning N-nitrososulfamates and Diazald® see White, E. H.; Min Li and Shanzheng Lu.*J. Org. Chem.* **1992**,*57*, 1252-1258. de Boer, Th. J.; Backer, H. J. *Rec. Trav. Chim. Pays-Bas* **1954**, *73*, 229-233. de Boer Th. J.; Backer, H. J. *Org. Synth. Coll.* **1963**, *4*, 250-255. (c). Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377-5378. For a review see: *Sulfamic Acid and its N-substituted Derivatives*. Benson, G. A.; Spillane, W. J. *Chem. Rev.* **1980**, *80*, 151-186.

[2] For a general reviews concerning the clinical use and the pharmacological properties of CENU see Mc Cormick, J.E.; Mc Elhinney, R.S. *Eur. J. Cancer* **1990**, *26*, 207-221 (and ref. cit. therein). Carter, S. K.; Bakowski, M. T.; Hellman, K. *Chemotherapy of Cancer* 3rd ed.; Churchill Livingston: New York, **1987**. Calabresi, P.; Schein, P. S.; Rosenberg, S.A. Eds. *Medical Oncology* Macmillan: New York. **1985**. Eisenbrand, G. in *Relevance of N-Nitroso Compounds to Human Cancer: exposure and Mechanisms* Bartsch, H.; O'Neill, I. K.; Schulte-Herman, R. Eds; International Agency for Research on Cancer, Lyon, France, **1984**.

[3] Dewynter, G.; Montero, J-L. *C-r. Acad. Sci. Paris. Ser II.* **1992**, *315*, 1675-1682.

[4] Montero, J-L.; Dewynter,G.; Agoh, B.; Delaunay, B.; Imbach, J-L. *Tetrahedron Lett,* **1983**, *24*, 3091-3094. Bonnaud, B.; Viani, R.; Agoh, B.; Delaunay, B.; Dewynter, G.; Montero, J-L. *Acta cryst.* **1987**, *C-43*, 2466-2468. Agoh, B.; Dewynter, G.; Montero, J-L.; Leydet, A.; Imbach, J-L. *Bull. Soc Chim. Fr.* **1987**, *5*, 867-872.

[5] **1d**: starting from CSI (2 equiv.), bromoethanol (2 equiv.), cystamine dihydrochloride (1 equiv.) and triethylamine (5.5 equiv.). Yield 88%; Rf 0.76 (CH_2Cl_2/methanol 95/5); mp: 150°C. ^1H NMR (DMSO, 250 MHz): 8.25 (t, 2H, NH), 4.45 (t, 4H, CH_2O), 4.00 (t, 4H, CH_2N), 3.38 (t, 4H, CH_2NH), 2.88 (t, 4H, CH_2S).

[6] Hydrolysis of N-acyloxazolidinones is carried out in oxidative conditions (*i.e.* $LiOH:H_2O_2$) in Evans-like reactions [Evans, D.A.; Ellman, J.A. *J. Amer. Chem. Soc.* **1989**, *111*, 1063-1072. Beckett, R.P.; Crimmin, M.J.; Davis, M.H.; Spavold, Z. *Synlett*, **1993**, *2*, 137-138. Chan, P.C.-M; Chong, J.M.; Kousha, K. *Tetrahedron*, **1994**, *50*, 2703-2714]. The formation of 1,2-aminoalcohols by oxazolidinones opening is usually carried out in alkaline conditions [*i.e.* NaOH/EtOH: Yuasa, Y.; Ando, J.; Shibuya, S.J.; *J. Chem. Soc., Chem. Commun.* **1994**, *4*, 455-456. Cs_2CO_3: Hassner, A.; Falb, E.; Nudelman, A.; Albeck, H.E.; Tetrahedron Lett. **1994**, *35*, 2394-2397. $Ba(OH)_2$: Scam, H.L.; Wideburg, N.E.; Spanton, S.G.; Kolhbrenner, W.E.; Betebenner, D.ZA.; Kempf, D.J.; Norbeck, D.W.; Plattner, J.J.; Erickson, J.W. *J. Chem. Soc., Chem. Commun.* **1991**, *2*, 110-112. Neutral hydrolysis: Monsanto *USA Pat.* 4810426, **1989**]. The N-sulfonyloxazolidinone cleavage can be obtained under irradiation conditions [Li, C.; Fuchs, P.L. *Tetrahedron Lett.* **1993**, *34*, 1855-1858]; a related radical approach to N-desulfonylation was recently reported [Parsons, A.F.; Pettifer, R.M. *Tetrahedron Lett.* **1996**, *37*, 1667-1670] .

[7] **5**: starting from N(2-chloroethylsulfamoyl)-2-oxazolidinone (ref4c) (1 equiv.), benzylamine (1 equiv.) in acetonitrile-triethylamine. Yield 73%; Rf: 0.55 (diethylether); mp: 99-100°C. IR (KBr, νcm^{-1}): 3300, 3200 (NH), 1745 (C=O), 1350, 1150 (SO_2). ^1H NMR ($CDCl_3$, 250 MHz): 7.35 (m, 5H, Ar**H**), 5.20 (s, 1H, **NH**CO), 4.87 (t, 1H, N**H** ester), 4.79 (t, 1H, $NHCH_2Cl$), 4.40 (d, 2H, CH_2Ph), 4.30 (t, 2H, CH_2O), 3.70 (t, 2H, CH_2Cl), 3.35 (m, 4H, $2CH_2NH$). MS (FAB>0; thioglycerol): 336 $(M+H]^+)$, 300 $(M-Cl]^+)$, 203 (carbamoyl cleavage), 106 $(PhCH_2NH]^+)$.

[8] Oiry, J.; Imbach, J-L. *Eur. J. Med. Chem.*; **1984**, *19*, 305-310. Oiry, J.; Pompon, A.; Madelmont, J-C.; Imbach, J-L. *ibid,* p 311-314. Maral, R.; Bourrut, C.; Chenut, E.; Mathé, G.; Imbach, J-L. *ibid,* p 315-319. Maral, R.; Mathé, G.; Schein, P.S.; Bourrut, C.; Chenut, E.; Oiry, J.; Imbach, J-L. *Exptl. Clin. Res.* **1984**, *12*, 883-886. Oiry, J.; Imbach, J-L. *Eur pat.* 834 010 795 **1983** and *US pat.*499 130 **1983**.

(*Received in France* 21 *May* 1996; *accepted* 16 *June* 1996)