STUDIES ON THE SYNTHESIS OF C-2 SUBSTITUTED CEPHALOSPORIN SULFONES : THE UNEXPECTED REACTIVITY OF THE C-2 CARBON

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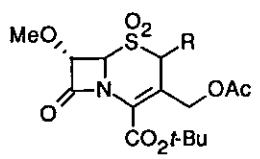
Abstract- An interesting route for the synthesis of C-2 substituted cephalosporin sulfones (**8**) has been described along with an unexpected reactivity on the C-2 carbon of C-2 substituted cephalosporin sulfoxides and sulfones.

C-2 Substituted cephalosporin dioxides of formula as **1** have been recently reported[1,2] to possess interesting human leukocyte elastase (HLE) inhibition properties. HLE is a serine protease that is implicated to be responsible for the tissue destruction associated with pulmonary emphysema.[3] Many of these cephalosporin sulfone esters bind well to the enzyme and some, like their antibiotic counterparts that are acylating inhibitors of bacterial transpeptidases and carboxypeptidases,[4] undergo ß-lactam ring opening to acylate the enzyme. Nevertheless, up today, no general route for the synthesis of analogs has been reported. With this motivation in mind we focused our attention to find out a general route to prepare such products also with the purpose of studying possible structure- activity relationships. This communication deals with the synthesis of 2-alkoxy- and 2-acetoxycephalosporin sulfones.



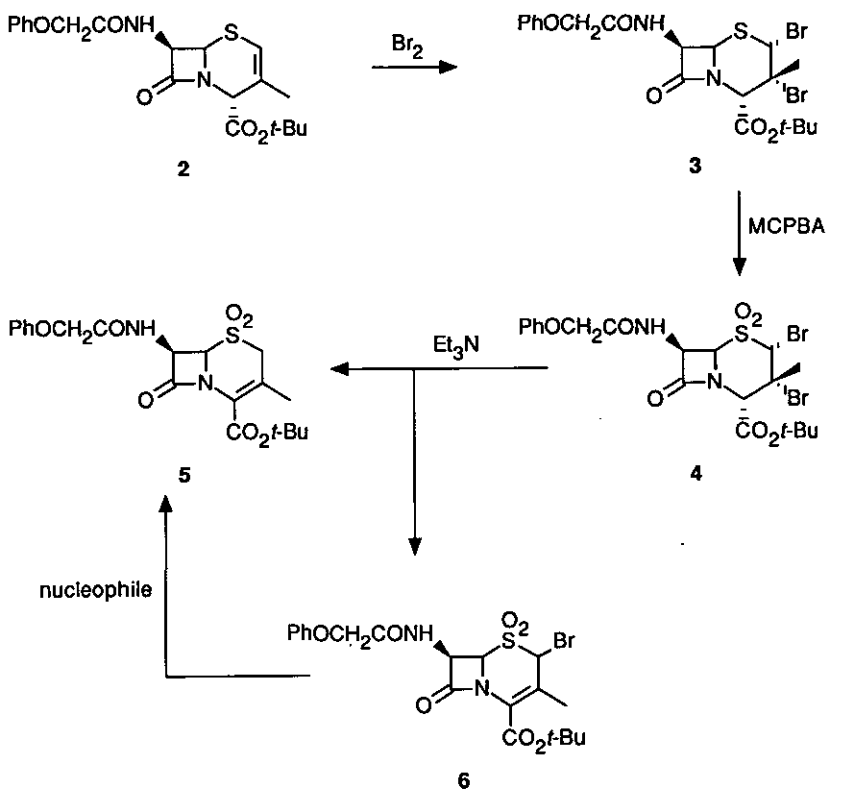
R : Me, OMe, CH_2=

1

The cephalosporin (**2**), obtained as reported from 7-ADCA,[5] was used as a starting material. Bromination of the double bond with bromine, as described by Macchia and

co-workers,[6] in CH_2Cl_2 using one mole equivalent of $NaHCO_3$ to prevent possible deprotection of the acid furnished **3** in good yield (the yield of the reaction increases up to 90% with the addition of $NaHCO_3$). According to the literature the α- isomer at C-2 has been obtained as the major product in these experimental conditions.
MCPBA oxidation, done with the worked up intermediate of the sulfoxide, gave the bromo sulfone (**4**) in good yield. Dehydrobromination with Et_3N gave unexpectedly[7] a mixture of the desired product (**6**) (10%) and the sulfone (**5**) (80%) (Scheme 1). Different bases were subsequently tried for this reaction, but only pyridine gave a little improvement in the yield of **6** (30%). The following displacement of the bromine of **6** by nucleophiles (MeOH, AcOK), that we expected to be very easy, afforded in quantitative yield the sulfone (**5**) as the sole product. Attempts to carry out the reaction under different experimental conditions afforded always the same reduced product (**5**).

Scheme 1



We tried to perform the C-2 bromine substitution directly on the dibromosulfone (**4**) using methanol in the presence of $AgNO_3$ and we obtained a mixture of C-2 methoxy

derivative (5%) and (**5**), while when AcOK was used as the nucleophile only **5** was present in the reaction mixture.

The unexpected reactivity of α-bromosulfones (**6**) and (**4**) on the C-2 carbon merits some comments.

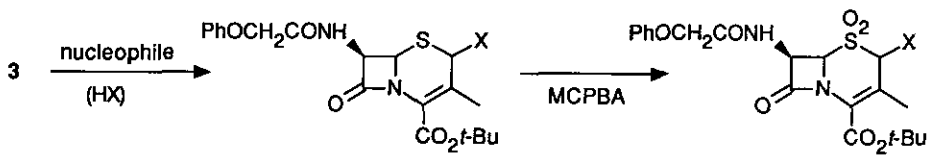
A single precedent of a similar behavior has been reported in the literature in the displacement of α-bromosulfones with thiophenols.[8]

The unusual behaviour of **6** may be explained taking into account both electronic and steric factors. C-2 Carbon can easily accomodate a negative charge through a stabilization operated by the sulfonyl and the α,ß-unsaturated ester function, but can not bear a positive one. On the other hand, there is a great steric hindrance to the approach of nucleophiles to the C-2 carbon to effect the displacement of bromine. The steric encumbering is due either to the presence of the neighboring sulfonyl group oxygen atoms and to the shape of the whole molecule that inhibits the attack from the ß-side. At the same time, the approach from the α-side of the molecule is prevented by the presence of bromine itself. In this situation the nucleophile prefers to interact with the bromine leaving a stabilized negative charge on the C-2 carbon, whose protonation gives the sulfone (**5**). In the case of compound (**4**) we can imagine that the base could be responsible of an initial dihydrobromination to give compound (**6**) that in turn undergoes the reduction as depicted above.

An alternative route to produce the C-2 bromosulfone, i.e. to carry out the same reactions in a different sequence (dehydrobromination of **3** followed by C-2 bromine substitution and then sulfur oxidation to sulfone) was unsuccessfull, since the dehydrobromination of **3** did not afford the expected product t-butyl 2-bromo-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate in a reasonable yield.

Ultimately the C-2 bromine was successfully substituted with different nucleophile (see Scheme 2) directly on the dibromosulfide (**3**) as reported for a similar compound with methanol as nucleophile in solvolytic conditions at room temperature.[6] When tert-butanol was used as nucleophile the reaction did not occur.

Scheme 2

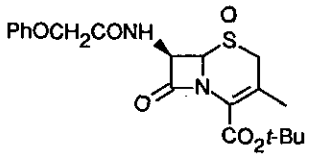


a : X = OMe; **b** : X = OEt; **c** : X = OPr; **d** : X = Oi-Pr; **e** : X = OBn; **f** : X = OAc

The substitution performed at reflux temperature gave a complex mixture of products. The C-2 substituted derivatives (**7 a-f**) were obtained in good yield (see Table 1). Probably, the dehydrobromination occurred during the purification. It is interesting to note that when we did not separate the dibromo derivative diastereoisomers, after the subsequent substitutions, we found out a presence of the ß-epimer at C-2 always less than 8%. The C-2 stereochemistry of the substituent in the major isomer in the case R=OMe was proved to be α in agreement with the literature[6] as shown by Overhauser effect (NOE, 6.4%) between C-3 methyl and the C-2ß protons, data in accordance also with Spry;[9] however we did not observe, in the nmr of our products (**6**) (α-epimer), the presence of the J long-range between H-2ß and H-7α reported in the same paper.

MCPBA (one mole equivalent) oxidation of **7 a,b,e,f** at room temperature afforded the corresponding sulfoxides which were in turn oxidized using an excess of MCPBA in $CHCl_3$ at reflux, the overall yield of the oxidation being good in the case of **7a**, **7b** and **7f** (Table 1), on the contrary to what reported for substrates lacking the C-7 acylamino side chain.[1,10] This result is probably due to the experimental procedure adopted. In fact, the one step oxidation of C-2 substituted sulfides directly to sulfones gave a poor yield in our case, too. We found out that the intermediate worked up at the sulfoxide stage always increases considerably the yields of the sulfones.

In the case of the oxidation (one mole equivalent of MCPBA) of **7c** and **7d** we obtained a single product in quantitative yield, at lower Rf on SiO_2 ($CHCl_3$: EtOAc - 8:2 as the solvent), which showed to be the sulfoxide (**9**). The correctness of the structure was chemically demonstrated by MCPBA oxidation of the sulfide (**2**) which occurs with concomitant double bond shift to the more substituted position. This product was always present in the reaction mixture, in traces during the oxidation of the sulfides (**7a**) and (**7b**) while in the case of **7e** it was present in 30% yield and 18% in the case of **7f**.



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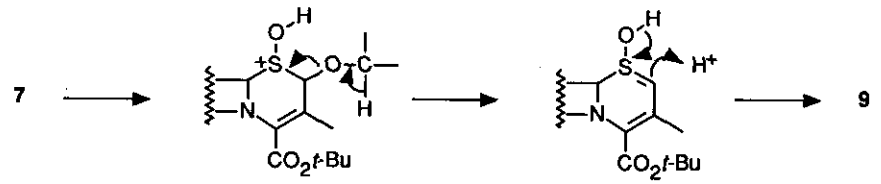
The very unusual complete reduction of substrates (**7c**) and (**7d**) during the MCPBA oxidation attracted our attention. Experiments in order to rationalize these unexpected findings were carried out. The possibility of an hydride transfer from the leaving side chain was ruled out by preparing the *tert*-butyl 2-heptadeuteroisopropoxy-7-phenoxyacetamido-3-cephem-4-carboxylate. This product

was prepared via C-2 bromine substitution with perdeuteroisopropyl alcohol under the same conditions reported for **7**. No deuterium incorporation at C-2 in the ^{1}H-nmr spectrum of the MCPBA (one mole equivalent) oxidation product was observed. This reaction occurred exactly in the same way as for the non-deuterated derivative (**7d**). When we performed the oxidation of the isopropoxy derivative (**7d**) in the presence of $NaHCO_3$ (one mole equivalent) we obtained the expected sulfoxide in a yield of 52%. Further oxidation at reflux temperature in the presence of the base, gave the sulfone (**8d**) indicating that the acidity of the medium plays an important role in the reaction course. Consequently, if we admit that the oxidation of the sulfur atom occurs prior to the loss of the side chain, we can imagine that the oxygen linked to the sulfur can be protonated by the acidic medium, and the resulting positive charge on the sulfur can be subsequently neutralized by the loss of the alcoholic residue as depicted in **10** (Scheme 3), giving rise to the possible intermediate (**11**) that evolves to the product (**9**). The extent of this reaction seems to be largely dependent on steric factors; in fact the yield of formation of product (**9**) raises with the increasing of the bulkiness of the C-2 substituents.

Scheme 3



10 **11**

In conclusion the lack of the displacement of the C-2 bromine in the cephalosporin sulfoxide and sulfones, along with the results of this last reaction, shows the very unusual behavior of this carbon atom to undergo a facile reduction instead of substitution. This fact probably justifies the scarce chemistry present in the literature at the moment on these biologically important substrates. What proposed here is a general procedure to overpass such a problem in the synthesis of C-2 substituted cephalosporin sulfones.

EXPERIMENTAL

^{1}H Nmr spectra were recorded with either Varian EM 360 or XL 300 instrument using $CDCl_3$ the solvent and TMS as an internal standard. ^{13}C-Nmr spectra were carried out with a Varian XL 300 spectrometer, ir spectra with a Perkin Elmer 257 spectrometer and mass spectra by means of a Kratos MS-80 instrument. Dry sodium sulfate was always used in drying organic extracts. Microanalyses were performed on a Carlo-Erba Model 1106 analyzer.

Table 1. Physical and chemical data for the new compounds

Compd	Yield %	Formula	Elemental Analysis Calcd/Found			ms m/z (M^++1)
			C	H	N	
7a	70	$C_{21}H_{26}N_2O_6S$	58.05/58.30	6.03/6.10	6.45/6.30	435
7b	75	$C_{22}H_{28}N_2O_6S$	58.91/58.70	6.29/6.15	6.24/6.15	449
7c	68	$C_{23}H_{30}N_2O_6S$	59.72/59.60	6.54/6.40	6.05/6.15	463
7d	65	$C_{23}H_{30}N_2O_6S$	59.72/59.62	6.54/6.50	6.05/6.18	463
7e	33	$C_{27}H_{30}N_2O_6S$	63.52/63.43	5.92/5.90	5.49/5.53	511
7f	55	$C_{22}H_{26}N_2O_7S$	57.13/59.10	5.67/5.70	6.06/6.15	463
8a	90	$C_{21}H_{26}N_2O_8S$	54.07/54.00	5.56/5.40	6.00/6.10	467
8b	60	$C_{22}H_{28}N_2O_8S$	54.99/54.80	5.87/5.70	5.83/5.90	481
8d	48	$C_{23}H_{30}N_2O_8S$	55.84/55.70	6.12/6.10	5.70/5.79	495
8e	52	$C_{27}H_{30}N_2O_8S$	59.75/59.78	5.58/5.40	5.16/5.20	543
8f	58	$C_{22}H_{26}N_2O_9S$	53.41/53.37	5.30/5.28	5.71/5.50	496

Thin-layer chromatography (tlc) was performed on 0.25 mm and 2 mm layers of silica gel Merck 60F-254 and column chromatography was done on Merck-Kiesegel 60 (70-400 and 230-400 mesh). All chemicals and solvents were reagent grade unless otherwise specified. Attempted recrystallizations gave only decomposed products.

t-Butyl 2,3-Dibromo-3-methyl-7-phenoxyacetamido-4-carboxylate **3**

In a 50-ml flask 200 mg (0.25 mmol) of t-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate **2** , 2.5 ml of bromine (1% solution in CH_2Cl_2) , 10 mg of Na_2CO_3 in 8 ml of dry CH_2Cl_2 were stirred for 5 min at room temperature.The solution was washed with $Na_2S_2O_3$ (10% solution) , H_2O, brine and dried (Na_2SO_4). The solvent was removed *under vacuum* and subsequent purification by tlc (n-hexane/EtOAc=70/30) gave 250 mg (75%) of the mixture of α and ß epimer at C-2 (ratio a/ß=90/10 by ^1H nmr): foam; ir (ν, cm-1) ($CHCl_3$): 3420, 1790, 1750, 1700, 1490 ^1H nmr ($CDCl_3$) δ (ppm) : 1.51 (s, 9H), 2.30 (s, 3H), 4.52(s, 2H), 4.80 (s,1H), 5.41 (s, 1H), 5.54 (d, J=4 Hz ,1H), 5.78 (m, 1H), 6.81-7.50 (m, 6H); ms FAB (m/z, MH^+-Br_2) 405.Anal. Calcd for $C_{20}H_{24}N_2O_5Br_2S$: C, 42.57; H, 4.29; N, 4.96. Found: C, 42.60; H, 4.10; N, 4.91.

t-Butyl 2,3-Dibromo-3-methyl-7-phenoxyacetamido-4-carboxylate 1,1-Dioxide **4**

In a 50-ml flask 150 mg of **3** (0.266 mmol) , 54 mg (0.266 mmol) of MCPBA in 5 ml of dry CH_2Cl_2 were stirred at room temperature for 4 h. The solution was washed with $Na_2S_2O_3$ (10% solution) , $NaHCO_3$ (saturated solution), brine, dried (Na_2SO_4) , and the solvent was removed *under vacuum*. The crude residue without purification was dissolved in 5 ml of dry CH_2Cl_2 , 124 mg (0.61 mmol) of MCPBA was added and the mixture was heated at reflux for 5 h. After work-up (same procedure of the first oxidation) the crude product was purified by tlc ($CHCl_3$ /EtOAc=80/20) to give the pure product (**4**) as a foam (75%): ir (ν, cm^{-1})($CHCl_3$) 3420 ,1820, 1730, 1705, 1495, 1350, 1140;^{1}H nmr ($CDCl_3$) δ (ppm) : 1.53 (s, 9H), 2.17 (s, 3H), 4.55 (s, 1H), 4.57 (s, 2H), 4.92 (s, 1H), 5.46 (d, J=4 Hz,1H), 6.17-6.25 (m, 1H), 6.88-7.34 (m, 5H); ms FAB (m/z, MH^+) 597. Anal. Calcd for $C_{20}H_{24}N_2O_7Br_2S$: C, 40.29; H, 4.06; N, 4.70. Found: C, 40.10; H, 4.10; N, 4.73.

t-Butyl 3-Methyl-7-phenoxyacetamido-2-bromo-3-cephem-4-carboxylate 1,1-Dioxide **6.**

A mixture of 84 mg (0.14 mmol) of **4** and 2.5 ml (0.28 mmol) of pyridine in 5 ml of dry CH_2Cl_2 was stirred in a 50-ml flask at room temperature overnight. The solution was washed with 2N HCl, H_2O, brine, dried (Na_2SO_4), and the solvent was removed *under vacuum*. Purification by tlc (n-hexane/EtOAc=70/30) gave the pure product (**6**), 21.6 mg (30%) and the sulfone (**5**), 31.8 mg (52%).

6:ir (ν, cm^{-1}) ($CHCl_3$): 3415, 1820, 1705, 1490, 1350, 1141; ^{1}H nmr ($CDCl_3$) δ (ppm): 1.55 (s, 9H), 2.21 (s, 3H), 4.55 (s, 2H), 4.95 (s, 1H), 5.51 (d, J=4 Hz, 1H), 6.00-6.35 (m, 1H), 6.81-7.50 (m, 5H), 7.93-8.10 (m, 1H); ms FAB (m/z, MH^+) 516. Anal. Calcd for $C_{20}H_{23}N_2O_7BrS$: C, 46.50; H, 4.50; N 5.42. Found C, 46.70; H, 4.58; N, 5.50.

5:ir (ν, cm^{-1}) (CHCl3) 3415, 1820, 1705, 1480. ^{1}H nmr ($CDCl_3$) δ (ppm): 1.55 (s, 9H), 2.20 (s, 3H), 3.75 (m, 1H), 4.50 (s, 2H), 4.85 (m, 1H), 6.25 (m, 1H), 6.80-7.45 (m, 5H), 8.00 (m, 1H); ms FAB (m/z, MH^+) 437. Anal. Calcd for $C_{20}H_{24}N_2O_7S$: C, 55.04 ; H, 5.54; N, 6;42. Found C, 55.10; H, 5.51; N, 6.48.

t-Butyl 3-Methyl-7-phenoxyacetamido-2-alkoxy-3-cephem-4-carboxylate **7(a-e)**: General procedure.

In a 100 ml flask **3** (1 mmol) and 0.50 ml (3.9 mmol) of N,N-dimethylaniline in 30 ml of dry ethanol were stirred for 4 days at room temperature. The solvent was removed and the residue was diluted with CH_2Cl_2.The solution obtained was washed with 2N HCl, $NaHCO_3$ (saturated solution), brine, and dried (Na_2SO_4). Solvent was removed *under vacuum* and purification by tlc (n-hexane/EtOAc=70/30) gave the products. Yields, elemental analyses and spectroscopic data are reported in Tables 1 and 2.

Table 2. Ir and 1H nmr spectral data for the new compounds

Compd	ν (cm^{-1}) ($CHCl_3$)	δ (ppm) ($CDCl_3$)
7a	3420, 1780, 1745, 1700, 1490	1.50 (s, 9H), 2.12 (s, 3H), 3.51 (s, 3H), 4.50 (s, 2H), 4.61 (s, 1H), 5.42 (d, J=4 Hz, 1H), 5.59 (m, 1H), 6.71-7.50 (m, 6H)
7b	3420, 1780, 1740, 1700, 1480	1.21 (t, J=6.5 Hz, 3H), 1.50 (s, 9H), 2.10 (s, 3H), 3.60 (m, 2H), 4.41 (s, 2H), 4.61 (s, 1H), 5.40 (d, J=4 Hz, 1H), 5.65 (m, 1H), 6.70-7.50 (m, 6H)
7c	3420, 1770, 1745, 1700, 1490	0.91 (t, J=6.5 Hz, 3H), 1.45 (s, 9H), 1.58 (m, 2H), 2.14 (s, 3H), 3.32-3.85 (m, 2H), 4.55 (s, 2H), 4.64 (s, 1H), 5.40 (d, J=4 Hz, 1H), 5.64 (m, 1H), 6.78-7.54 (m, 6H)
7d	3420, 1780, 1745, 1700, 1490	1.20 (s, 6H), 1.50 (s, 9H), 2.11(s, 3H), 3.80-4.31 (m, 1H), 4.52 (s, 2H), 4.71 (s, 1H), 5.42 (d, J=4 Hz, 1H), 5.65 (m, 1H), 6.70-7.51 (m, 6H)
7e	3420, 1780, 1745, 1700, 1490	1.49 (s, 9H), 1.90 (s, 3H), 4.18 (m, 2H), 4.56 (m, 2H), 4.68 (s, 1H), 5.81 (d, J=4 Hz, 1H), 5.72 (m,1H), 5.80-7.41 (m, 11H)
7f	3420, 1790, 1730 1700, 1490	1.51 (s, 9H), 2.00 (s, 3H), 2.11 (s, 3H), 4.50 (s, 2H), 5.11 (d, J=4 Hz, 1H), 5.85 (m, 1H), 6.30 (s, 1H), 6.70-7.51 (m, 6H)
8a	3420, 1790, 1745, 1700, 1490, 1335, 1140	1.51 (s, 9H), 2.10 (s, 3H), 3.82 (s, 3H), 4.60 (s, 2H), 4.71 (s, 1H), 5.40 (d, J=4 Hz, 1H), 6.25 (m, 1H), 6.70-7.53 (m, 6H)
8b	3420, 1790, 1745, 1700, 1490, 1335, 1140	1.21 (t, J=6.5 Hz, 3H), 1.47 (s, 9H), 2.10 (s, 3H), 3.68-4.38 (m, 2H), 4.53 (s, 2H), 4.72 (s, 1H), 5.46 (d, J=4 Hz, 1H), 6.18 (m, 1H), 6.70-7.40 (m, 5H), 8.35 (m, 1H)
8d	3420, 1790, 1745, 1700, 1490, 1335, 1140	1.10-1.21 (m, 6H), 1.45 (s, 9H), 2.04 (s, 3H), 4.31 (m, 1H), 4.49 (s, 2H), 4.68 (s, 1H), 5.45 (d, J=4 Hz, 1H), 6.18 (m, 1H), 6.87-7.24 (m, 5H), 8.25 (m, 1H)
8e	3420, 1790, 1745, 1700, 1490, 1335 1140	1.53 (s, 9H), 2.10 (s, 3H), 3.70 (m, 2H), 4.53 (s, 1H), 4.57 (s, 2H), 4.82 (d, J=4 Hz, 1H), 6.22 (m, 1H), 6.87-7.24 (m, 10H), 7.98 (m, 1H)
8f	3420, 1790, 1745, 1700, 1490, 1335 1140	1.48 (s, 9H), 2.97 (s, 3H), 2.18 (s, 3H), 4.49 (s, 2H), 4.83 (d, J=4 Hz, 1H), 5.76 (s, 1H), 6.18 (m, 1H), 6.72-7.48 (m, 5H), 7.83 (m, 1H)

t-Butyl 3-Methyl-7-phenoxyacetamido-2-acetoxy-3-cephem-4-carboxylate **7f.**
A mixture of 480 mg (0.85 mmol) of **3**, and 420 mg (4.26 mmol) of CH_3COOK in dry MeCN (20 ml) was stirred for 12 h at room temperature. The solution was filtered off and the organic layer was washed with H_2O, followed by brine, dried (Na_2SO_4), and the solvent was removed *under vacuum*. Purification by tlc (n-hexane/EtOAc=70/30) gave the product. Yield, elemental analysis and spectroscopic data are reported in Tables 1 and 2.

Oxidation of compound **7 (a-f) :** General procedure.

In a 100-ml flask 1 mmol of **7** (**a-f**) and 203 mg (1 mmol) of MCPBA in 8 ml of dry CH_2Cl_2 were stirred for 3 h at room temperature. The solution was then washed with $Na_2S_2O_5$ (10% solution), $NaHCO_3$ (saturated solution), brine, dried (Na_2SO_4), and the solvent was removed *under vacuum.* The mixture obtained, without purification, was treated with MCPBA (203 mg, 1 mmol) in dry CH_2Cl_2 (10 ml) at reflux for 6 h. The reaction mixture was worked up using the same procedure of the first oxidation. Purification by tlc ($CHCl_3$/EtOAc=80/20) gave the sulfones (**7 a, b, e, f**) in the yields reported in Table 1. Spectroscopic data are reported in Table 2.

Oxidation of **7 c** and **7d** gave the sulfoxide **9** (70%) as a single product.
Data of compound **9** : ir (v, cm^{-1}) ($CHCl_3$) 3420, 1820, 1730, 1705, 1495, 1350; ^1H nmr ($CDCl_3$) δ (ppm) : 1.50 (s, 9H), 2.15 (s, 3H), 3.50 (m, 2H), 4.45 (m, 1H), 4.60 (s, 2H), 6.31 (m, 1H), 6.90-7.55 (m, 5H); ms FAB (m/z, MH^+) 421. Anal. Calcd for $C_{20}H_{24}N_2O_6S$: C, 57.13, H, 5.75, N, 6.64. Found C, 57.21, H, 5.60, N, 6.62.

When the oxidation of **7d** was performed using the experimental procedure described above but in the presence $NaHCO_3$ (1 mmol), the sulfone (**8d**) was obtained. Yield, elemental analysis and spectroscopic data are reported in Tables 1 and 2.

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