Synthesis and Mass Spectral Study of New Phenylsulfonyl Substituted Isoxazolidines

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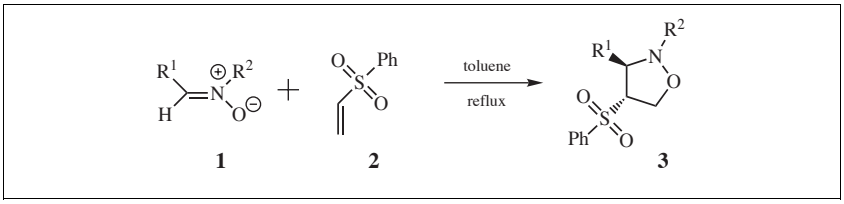

Ten 2,3-disubstituted 4-phenylsulfonyl isoxazolidines (**3a-j**) were prepared by 1,3-dipolar cycloaddition reaction of substituted nitrones (**1a-j**) with phenyl vinyl sulfone (**2**). The reaction products were identified by means of IR, NMR, and MS data. In addition, the factors influencing on the electron ionization induced mass spectral fragmentation of the title products are discussed in detail.

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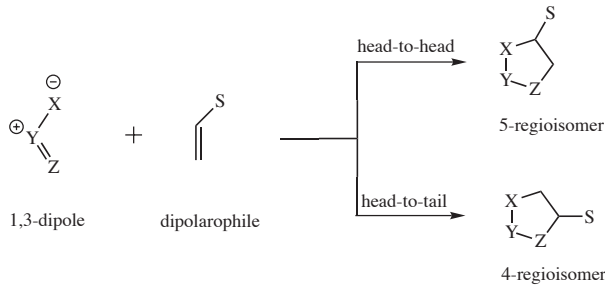
Introduction.

1,3-Dipolar cycloaddition (1,3-DC) reactions belong to the most important processes from both synthetic and mechanistic points of view. The usefulness of these cycloaddition reactions arises from their versatility and their remarkable stereochemistry. By varying the nature of the reagents many different types of carbocyclic and heterocyclic structures can be built up. The interaction between unsymmetrical reagents in a 1,3-DC reaction can give two isomeric adducts depending on the relative position of the substituent (S) in the cycloadduct, head-to-head, 5-regioisomer, or head-to-tail, 4-regioisomer (Scheme 1). High stereospecificity/stereoselectivity associated with these reactions makes them synthetically important. It has been found that 1,3-DC reactions proceed with a concerted mechanism. Among the large variety of strategies available for the synthesis of five-membered heterocycles, 1,3-DC reaction of nitrones with olefins is an extremely powerful one, which usually occurs under mild conditions. It can lead to as many as three new contiguous stereogenic centers in a single step and to yield efficiently the respective isoxazolidines with good regio- and stereoselectivity. Both inter- and intramolecular nitrone–alkene cycloaddition reactions have received much attention as useful methods for the formation of biologically interesting heterocycles [1].

1,3-Dipolar cycloaddition reactions of nitrones with a variety of unsaturated systems, including the multisubstituted ones, have been extensively exploited to synthesize isoxazolidine and isoxazoline heterocycles. Isoxazolidines, the saturated five-membered 1,2-O,N-heterocycles

Scheme 1



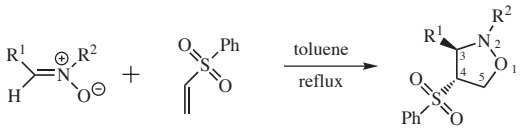
readily available from simple starting materials such as alkenes and nitrones, are useful intermediates in organic synthesis [2].

Literature survey reveals that isoxazolidine compounds have been synthesized to investigate their activities against various bacteria, fungi species and also viruses including HIV virus and tumor cells. In addition, they were assayed for transcriptional activation property and anxiolytic activity [3]. Multistep synthetic routes that involve isoxazolidine construction to the natural products, alkaloids like histrionicotoxin, have also been reported [4].

In this study, a set of new isoxazolidines (**3a-j**) were obtained by 1,3-DC reaction of *N*-substituted 4-(substituted)benzylidineamine *N*-oxides (**1a-j**) with phenyl vinyl sulfone (**2**) (Scheme 2). The reaction products were identified by means of IR, NMR, and MS data. Due to the limited amount of mass spectrometric information avail-

able [5-7] the mass spectral fragmentations of the synthesized products (**3a–j**) under electron ionization were discussed in detail to clarify the effect of the phenylsulfonyl substitution.

Scheme 2



1 **2** **3**

	R^1	R^2
3a	4-NMe_2-C_6H_4	Me
3b	4-NMe_2-C_6H_4	Ph
3c	4-OMe-C_6H_4	Me
3d	4-OMe-C_6H_4	Ph
3e	(3-OMe-4-OCH_2Ph)-C_6H_3	Me
3f	2-OH-C_6H_4	Ph
3g	2-pyridyl	Me
3h	2-furyl	Me
3i	2-thienyl	Me
3j	2-(3-methyl)-thienyl	Me

Results and Discussion.

NMR Spectroscopy.

Structures of all substances were determined by NMR spectra measured in $CDCl_3$. Chemical shifts were assigned, in addition to the information from basic proton and carbon spectra, using gradient-selected DQF-COSY, NOESY, HSQC and HMBC (see Experimental). Proton and carbon NMR results are presented in Tables 1, 2 and 3, respectively.

The assignment of the signals from the isoxazolidine ring was easy. The methylene C-5 was first identified being only CH_2 type carbon. All the proton and carbon signals in isoxazolidine ring were assigned with the aid of HSQC and COSY. The *ortho* protons from the benzene sulfonyl group were identified by the NOESY correlation with protons H-4 and H-5b. The remaining signals from the SO_2-phenyl moiety were revealed by the COSY, HSQC and HMBC correlations. The signals from the substituent R^1 were assigned first based on the long-range correlations with H-3 or C-3. Thereafter the whole assignment of R^1 was done by, again, by the combination of COSY, HSQC and HMBC. In a similar way, the signals of the R^2 substituent were identified resulting into the unambiguous assignment of the whole structure. The ^{1}H NMR results, *i.e.* proton chemical shifts and proton-proton coupling constants, are in accordance with the ones for 4-phenylsulfonyl-2-methyl-3-phenyl-isoxazolidine reported by Caddick and Bush [8].

NOE measurements were used in order to assign the orientations of the substituents of isoxazolidine ring, since the values of the coupling constants did not allow conclusions with certainty about the configuration of substituents [2n,9]. The phenylsulfonyl group and the substituent R^1 can be deduced to be in the *trans* position from the NOESY spectra. If they were *cis*, there should be an intensive NOE correlation between H-3 and H-4, but this NOE signal is not observed. H-5 protons can be assigned from their coupling constants and NOE results. H-5a (Table 1 and 2) was found to be close to H-4 by NOESY, and therefore to have a *cis* relationship to H-4. The large coupling constant (approximately 8 Hz) is in agreement with *cis* orientation, because the torsion angle between H-4 and H-5a is relatively close to 0° and thus coupling constant fairly large (Karplus equation). H-5b has not NOE correlation with H-4 and the coupling constant is medium size, which fits well for the envelope type conformation of isoxazolidine ring in which oxygen atom is out of plane.

It was noted that, in the case of N-Me substituted compounds, the signals H-3, H-4 and N-Me, as well as the corresponding carbon signals, were considerably broadened, whereas N-Ph substituted compounds gave very sharp signals. This is most likely due to the nitrogen inversion, which can happen with the methyl group being slow in NMR timescale, and which is inhibited by the sterically large phenyl group. Systematic differences were observed in the ^{1}H-^{1}H coupling constants between N-Me and N-Ph structures (Table 1 and 2). For example, the *J*(H-3, H-4) was approximately 7 and 5 Hz with N-Me and N-Ph compounds, respectively. This refers to the slightly different torsion angles, *i.e.* conformations of the isoxazolidine ring.

To understand better the dynamic behavior of N-Me compounds, low temperature measurements were also utilized. For this purpose, compound **3g** was selected since it gave the most broadened signals at room temperature. As the temperature was decreased, the signals began first to sharpen. The sharpest signals were observed approximately at –20 °C. So, in this temperature, the nitrogen inversion seems to be inhibited. However, the value of *J*(H-3, H-4) was 7.0 Hz; the same as for the N-Me compounds at room temperature, and only one set of signals was observed. Thus, there is only one isomeric form all the time; only the dynamical process at room temperature broadens the signals. As the temperature was further decreased, the signals began to broaden again. At –60 °C, the proton signals for isoxazolidine and pyridyl (**3g**) protons were very broad. This indicates the restricted rotation of the pyridyl substituent.

Table 1

The proton chemical shifts in ppm (and coupling constants for stereochemically essential oxazolidine ring protons in Hz) for compounds **3a-e** in $CDCl_3$ at 298 K referenced internally to TMS (0.00 ppm).

	3a	**3b**	**3c**	**3d**	**3e**[a]
H-3	3.75 br. d	4.79 d	3.81 br. d	4.85 d	3.80 br. d
J	*6.0*	*4.9*	*7.0*	*5.0*	*7.1*
H-4	4.04 ddd	4.11 ddd	4.03 ddd	4.12 ddd	4.03 ddd
J	*3.2; 6.0; 8.2*	*4.5; 4.9; 7.5*	*3.5; 7.0; 8.2*	*4.8; 5.0; 7.5*	*3.4; 7.1; 8.3*
H-5[a]	4.26 dd	4.38 dd	4.26 dd	4.37 dd	4.25 dd
J	*8.2; 10.0*	*7.5; 10.0*	*8.2; 10.0*	*7.5; 10.0*	*8.3; 10.0*
H-5b	4.48 dd	4.54 dd	4.48 dd	4.53 dd	4.48 dd
J	*3.2; 10.0*	*4.5; 10.0*	*3.5; 10.0*	*4.8; 10.0*	*3.4; 10.0*
H-2'/H-6'	7.83	7.83	7.81	7.83	7.80
H-3'/H-5'	7.45	7.48	7.48	7.49	7.44
H-4'	7.55	7.61	7.60	7.62	7.54
R^1: H-2	7.00	7.16	7.09	7.26	6.75
R^1: H-3	6.55	6.62	6.75	6.82	-
R^1: H-4	-	-	-	-	-
R^1: H-5	$=R^1$: H-3	$=R^1$: H-3	$=R^1$: H-3	$=R^1$: H-3	6.68
R^1: H-6	$=R^1$: H-2	$=R^1$: H-2	$=R^1$: H-2	$=R^1$: H-2	6.59
R^1: C*H*$_3$	2.91	2.94	3.77	3.79	3.83
R^2: H-2/H-6	-	6.85	-	6.84	-
R^2: H-3/H-5	-	7.16	-	7.17	-
R^2: H-4	-	6.95	-	6.97	-
R^2: NC*H*$_3$	2.58	-	2.58	-	2.60

[a] For R^1: 5.10 and 5.13 (C*H*$_2$), 7.42 (H-2'/H-6'), 7.38 (H-3'/H-5'), 7.32 (H-4').

Mass Spectrometry.

The electron ionization mass spectra of **3a–j** were also studied in detail since very limited and mostly very old information has been available on the mass spectra of isoxazolidines [5-7]. An early report [5] proved that a typical primary fragmentation for substituted isoxazolidines (not having the $PhS(O)_2$ substituent) is the loss of R^2NOH where the hydrogen transfer occurs from C-4 (*cf.* Scheme 3). In the other report [6], it has been shown that a typical primary fragmentation is also the formation of an enamine (B^+ in Scheme 3). The most recent report [7] deals with the fast atom bombardment mass spectra of isoxalidinyl nucleosides. It is interesting that even here the $[M+H]^+$ ion lost NH_2OH (protonation occurred on

Table 2

The proton chemical shifts in ppm (and coupling constants for stereochemically essential oxazolidine ring protons in Hz) for compounds **3f-j** in $CDCl_3$ at 298 K referenced internally to TMS (0.00 ppm).

	3f	**3g**	**3h**	**3i**	**3j**
H-3	4.82 d	4.06	3.91	4.21	4.28
J	*6.1*	very br.	very br.	very br.	very br.
H-4	4.25 ddd	4.79	4.37 ddd	4.03 ddd	4.11 ddd
J	*3.2; 6.1; 7.6*	very br.	*3.3; 7.5; 8.6*	*3.3; 7.0; 8.2*	*3.3; 7.0; 8.3*
H-5a	4.47 dd	4.33 dd	4.29 dd	4.26 dd	4.26 dd
J	*7.6; 10.1*	*8.2; 9.8*	*8.6; 9.9*	*8.2; 10.0*	*8.3; 10.0*
H-5b	4.68 dd	4.55 dd	4.54 dd	4.50 dd	4.43 dd
J	*3.2; 10.1*	*4.0; 9.8*	*3.3; 9.9*	*3.3; 10.0*	*3.3; 10.0*
H-2'/H-6'	7.86	7.83	7.83	7.86	7.84
H-3'/H-5'	7.53	7.45	7.49	7.52	7.49
H-4'	7.66	7.55	7.60	7.64	7.61
R^1: H-2	-	-	-	-	-
R^1: H-3	6.90	8.50	7.25	7.20	7.14
R^1: H-4	7.19	7.16	6.17	6.81	6.68
R^1: H-5	6.70	7.56	6.06	6.66	-
R^1: H-6	6.75	7.16	-	-	-
R^1: C*H*$_3$	8.98 (O*H*)	-	-	-	2.19
R^2: H-2/H-6	7.06	-	-	-	-
R^2: H-3/H-5	7.24	-	-	-	-
R^2: H-4	7.12	-	-	-	-
R^2: NC*H*$_3$	-	2.69	2.66	2.68	2.62

Table 3

The carbon chemical shifts in ppm for compounds **3a-j** in $CDCl_3$ at 298 K referenced internally to TMS (0.00 ppm).

	3a	**3b**	**3c**	**3d**	**3e**[a]	**3f**	**3g**	**3h**	**3i**	**3j**
C-3	73.47	70.26	73.15	70.02	73.27	71.87	74.44	67.41	69.14	67.01
C-4	75.15	76.96	75.38	77.01	75.32	74.49	73.18	71.33	75.61	75.35
C-5	66.09	66.51	66.11	66.66	66.06	67.34	66.23	65.80	65.93	66.25
C-1'	138.13	137.80	138.06	137.70	138.05	137.39	138.21	137.86	137.89	137.96
C-2'/C-6'	*128.60*	128.82	128.55	*128.75*	*128.51*	128.78	128.48	128.42	128.63	128.32
C-3'/C-5'	129.26	129.37	129.34	129.44	129.30	129.61	129.22	129.31	129.44	129.31
C-4'	133.89	134.10	134.01	134.23	134.02	134.46	133.90	134.07	134.20	134.05
R^1: C-1	123.48	126.57	128.50	131.36	129.52	121.61	154.92	147.68	139.59	132.37
R^1: C-2	*128.58*	127.73	128.97	128.12	110.62	155.41	-	-	-	-
R^1: C-3	112.38	112.61	114.09	114.32	149.69	117.94	149.96	143.23	126.12	125.06
R^1: C-4	150.51	150.30	159.60	159.43	148.10	130.20	123.30	110.51	126.88	130.05
R^1: C-5	=R^1: C-3	=R^1: C-3	=R^1: C-3	=R^1: C-3	113.65	120.56	136.73	110.00	126.67	137.13
R^1: C-6	=R^1: C-2	=R^1: C-2	=R^1: C-2	=R^1: C-2	120.31	129.08	123.88	-	-	-
R^1: *C*H_3	40.44	40.47	55.28	55.31	56.02	-	-	-	-	14.14
R^2: C-1	-	149.20	-	149.00	-	147.09	-	-	-	-
R^2: C-2/C-6	-	116.26	-	116.21	-	118.78	-	-	-	-
R^2: C-3/C-5	-	128.65	-	*128.78*	-	129.05	-	-	-	-
R^2: C-4	-	122.93	-	123.13	-	125.79	-	-	-	-
R^2: N*C*H_3	42.58	-	42.60	-	42.74	-	43.00	42.46	42.83	42.46

[a] For R^1: 70.85 (*C*H_2), 136.96 (C-1'), 127.23 (C-2'), *128.58* (C-3'), 127.93 (C-4'). Assignments *italisized* may be vice versa.

Table 4

Main electron impact induced fragmentations *m/z*(%) in compounds **3a**-**j**.

Compound [a-j]	A^+ [a]	$[A-H]^{+\bullet}$ [b]	$[A-2H]^+$ [c]	$[A-3H]^{+\bullet}$ [d]	B^+ [e]
3a	-	204(10)	203(7)		178(100)
3b	-	-	-	-	240(6)
3c	-	191(90)	190(100)	189(10)	165(29)
3d	-	253(10)	252(7)	-	-
3e	-	297(9)	296(3)	-	271(3)
3f	240(9)	239(55)	238(19)	-	-
3g	163(27)	161(12)	161(13)	-	136(41)[f] 134(69)[g]
3h	-	151(95)	150(100)	149(6)	125(21) [h]
3i	168(83)	167(86)	166(100)	165(9)	141(26) [i]
3j	-	181(100)	180(66)	-	155(20)

[a] $A^+ = [M-PhSO_2]^+$. [b] $[A-H]^{+\bullet} = [M-PhSO_2H]^{+\bullet}$. [c] $[A-2H]^+ = [M-PhSO_2H_2]^+$. [d] $[A-3H]^{+\bullet} = [M-PhSO_2H_3]^+$. [e] $B^+ = [M-PhSO_2C_2H_3]^+$. [f] $C_8H_{10}NO^+ = [M-PhSO_2-HCN]^+$. [g] $C_8H_8NO^+ = [M-PhSO_2H_2-HCN]^+$. [h] One fourth corresponds to $C_6H_5SO^+$. [i] $C_6H_5SO_2^+$.

the nitrogen) and also CH_3N parallel to what was observed for some of our compounds as well even though the effect of the $PhS(O)_2$ substituent in **3a–j** substantially dominates the fragmentation routes found.

Most of the compounds **3a–j** gave relatively abundant molecular ions (RA 12-100%) except **3g** (2%) ,which showed also other peculiarities as discussed later. All of the compounds except **3b** exhibited the primary loss of $PhSO_2H_x$ ($[A-H]^{+\bullet}$, x = 1 and $[A-2H]^+$, x = 2, Scheme 3 and Table 4). For **3c**,**h**,**i** this ion with x = 2 forms the base peak and for **3j** the ion with x = 1 although in each compound these ions are of comparable abundance. Furthermore **3f**,**g**,**i** gave also the fragment corresponding to x = 0 (A^+) and **3c**,**h**,**i** some amount of the fragment corresponding to x = 3 ($[A-3H]^{+\bullet}$). $[A-H]^{+\bullet}$ was mainly responsible for the formation of the ions D^+, $[D-H]^{+\bullet}$, and $[D-2H]^+$, (Table 5) except **3e,** *via* loss of $[R_2NO-H]$, R^2NO, and R^2NOH, respectively. It also lost C_2H_2O (compounds **3c**,**d**,**f**,**i**,**j**) and C_2H_3O (compounds **3a**,**c**,**d**,**f–j**) leading to fragments $[C+H]^{+\bullet}$ and C^+, respectively. In the case of compounds **3c**,**e**,**f,g,i,** and **j** $[A-H]^{+\bullet}$ also lost OH giving the ions *m/z* 174, 280, 222, 145, 150 and 164, respectively (shown *in italics* in Table 6) in variable amounts (RA 2-31%).

Compounds **3a**,**b**,**d** showed also some loss of CH_2O (Scheme 3 and Table 6, *m/z* values given *in italics*) and compounds **3a**,**b**,**d**,**j** a primary loss of R^2NOH (Scheme 3) which ion in these cases led also to ions D^+, $[D-H]^{+\bullet}$, and $[D-2H]^+$ via loss of $C_6H_ySO_2$ (y = 4–6), respectively. For **3b** D^+ was the base peak of the spectrum. It should be

Table 5

More main electron impact induced fragmentations *m/z*(%) in compounds **3a**-**j**.

Compound [a-e]	$[C+H]^{+\bullet}$	C^+	D^+	$[D-H]^{+\bullet}$	$[D-2H]^+$
3a	162(11)	161(16.5)	160(59)	159(17)	158(8)
3b	224(9)	223(10)	160(100)	159(21.5)	158(10)
3c	149(9)	148(16)	147(27)	146(10)	145(5.5)
3d	211(72)	210(65)	147(31)	146(10)	145(10)
3e	255(14)	254(2)	-	-	-
3f	197(21)	196(55)	133(38)	132(8)	131(18)
3g	-	119(60)	118(91)	117(45)	-
3h	-	108(8)	107(24)	106(3)	-
3i	125(49.5) [f]	124(33.5)	123(46)	122(7)	-
3j	139(7.5)	138(35)	137(54)	136(17)	135(21)

[a] $[C+H]^{+\bullet} = [M-PhSO_2C_2H_3O]^{+\bullet}$. [b] $C^+ = [M-PhSO_2C_2H_4O]^+$. [c] $D^+ = [M-PhSO_2-R^2NO]^+$. [d] $[D-H]^{+\bullet} = [M-PhSO_2H-R^2NO]^+$. [e] $[D-2H]^+ = [M-PhSO_2H_2-R^2NO]^+$. [f] One third corresponds to $C_6H_5SO^+$.

Table 6

Other fragments (Rel. abundance mostly > 5%) in the mass spectra of compounds **3a**-**j**.

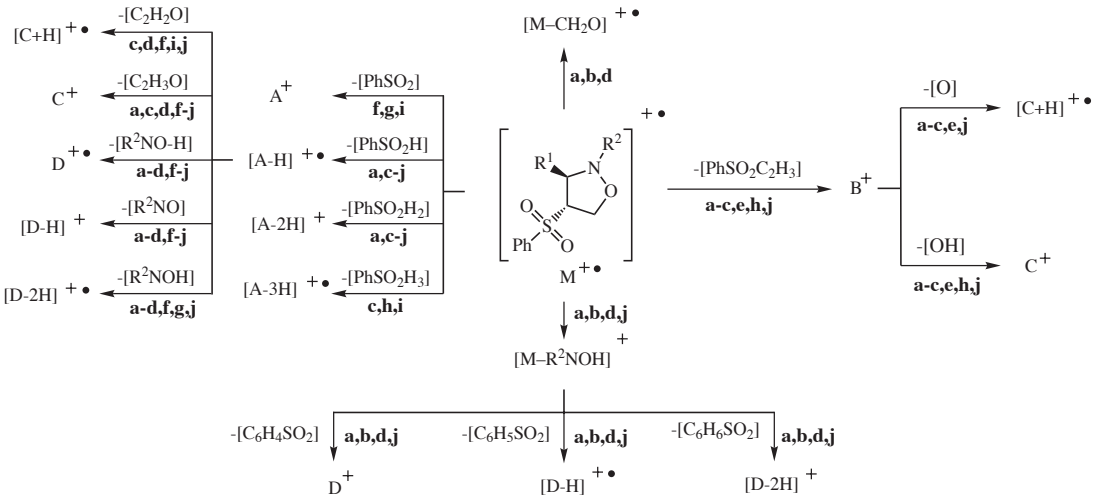
Compound	*m/z*(%)
3a	346(21), *316(0.7)*, *300(2.5)*, 149(9), 148(5.5), 146(7), 145(11), 144(8.5), 134(5), 131(5), 125(5), 118(5), 116(5), 115(4.5), 91(5), 78(8), 77(22), 51(10), 42(7)
3b	408(19), *378(9)*, *300(20)*, 237(5.5), 222(6), 193(6), 149(5), 146(7), 145(13), 144(11), 134(5), 118(10), 117(5), 116(6), 115(5), 104(6), 91(9), 78(11), 77(57), 65(5.5), 51(21), 50(5), 42(6), 39(6)
3c	333(38), *174(8)*, 164(21), 133(8), 132(8), 131(6), 125(4), 121(9), 118(3), 117(4), 116(4), 115(8), 104(6), 103(7), 91(15), 84(5), 78(16), 77(37), 65(7), 51(17), 50(5), 43(7), 42(11), 41(5), 40(6), 39(6.5)
3d	395(31), *365(1)*, *287(2)*, 224(8), 212(16), 209(6.5), 167(9), 160(13), 156(7), 142(5), 141(10), 132(8), 125(5), 115(5), 104(7), 93(11), 92(5), 91(22), 78(20), 77(100), 76(5), 65(12), 64(5), 63(6), 51(38), 50(10), 43(11), 40(8), 39(10)
3e	439(12), *280(2)*, 206(5), 164(10), 149(5), 125(6), 91(100), 78(8), 77(27), 65(10), 51(13), 44(5), 43(9), 42(7), 41(5), 40(20), 39(6)
3f	381(100), *222(14)*, 210(19), 209(5), 180(5), 147(5), 125(3.5), 118(5), 105(9), 104(6), 93(7.5), 92(5), 91(23), 78(10), 77(51), 65(8), 51(13)
3g	304(2), *274(2)*, *246(100)*, *226(3)*, *180(3)*, 147(10), *145(28)*, 134(69), 133(61), 132(5), 125(6), 106(28), 105(14), 103(32),94(5), 93(6), 92(22), 91(12), 90(5.5), 85(51), 84(48), 79(18), 78(54), 77(54), 68(14), 65(17), 64(7), 63(5), 56(5), 53(79, 52(16), 51(47), 50(11), 43(59, 42(24), 41(7), 40(12), 39(15)
3h	293(17), 94(5), 93(3), 81(7), 79(20), 78(12), 77(44), 65(7), 53(10), 52(6), 51(19), 50(5), 41(16), 41(5), 39(16)
3i	309(25), *150(6)*, 140(36), 139(25), 138(8), 111(18), 110(15.5), 109(26), 108(5), 99(14), 98(13), 97(43), 96(6), 94(6), 85(10), 84(20), 82(4.5), 79(16), 78(22), 77(95.5), 71(6), 70(5), 69(9), 67(5), 66(7), 65(15), 63(6), 58(8), 56(15), 55(5), 54(5), 53(10), 52(7), 51(54), 50(14), 45(44), 42(73), 41(10), 39(33.5)
3j	323(49), *277(3)*, 179(4), *166(5)*, *164(31)*, 152(7), 151(11), 150(7), 149(4), 125(8), 124(8), 123(14), 122(17), 121(8), 111(11), 110(4), 109(5), 104(6), 103(7), 97(25), 94(5), 91(11), 85(8), 84(9), 79(5), 78(16.5), 77(50), 71(5), 69(5), 65(8.5), 59(15), 53(13), 51(28), 50(7), 45(26), 42(19), 41(6), 39(13)

mentioned that for **3g** both C^+ and $[D+H]^{+\bullet}$ has the same nominal mass but accurate mass measurements showed that the former dominated in a ratio of 6:1. Most of the compounds, namely **3a–c**,**e**,**h**,**j**, gave also an enamine type primary fragment, namely B^+ (Scheme 3, Table 4) corresponding to the loss of $PhSO_2C_2H_3$, *i.e.* a retro-1,3-dipolar cycloaddition reaction [6]. This ion formed also an alternative route to ions $[C+H]^{+\bullet}$ (**3a–c**,**e**,**j**) and C^+ (**3a–c**,**e**,**h**,**j**) *via* loss of O and OH, respectively.

It has been reported [10] that sulfones often rearrange to sulfinic acids under electron ionization. All except **3b** of the studied compounds exhibit an ion *m/z* 125, $C_6H_5SO^+$ which in fact can result from such a rearrangement: $PhS(=O)_2- \equiv PhS(=O)O-$. However, this ion did not result directly from the molecular ion but after the loss of R^2NOH which makes it evident that some amount of the primary loss of R^2NOH occurs also in these isoxazolidines although in most cases in a concerted manner leading to the above ion and the D-type ions.

Compound **3g** deserves a special notion. It is the only compound which shows some loss of CH_4N giving the ion *m/z* 274. In this case the base peak of the spectrum is a specially stabilized ion, *m/z* 246 corresponding to the loss of C_2H_4NO from the molecular ion (Scheme 4). This ion is also obtained via *m/z* 274 after loss of CO. Two other exceptional though not abundant ions

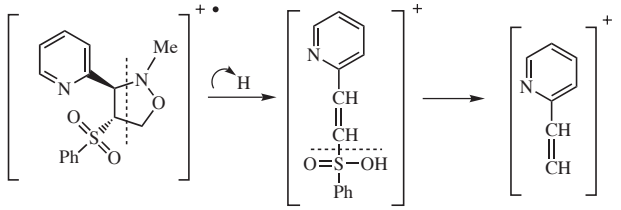
Scheme 3



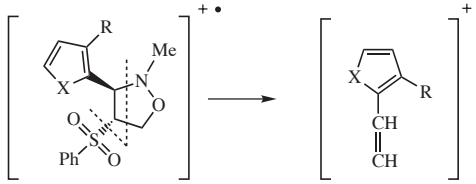
are also observed, namely *m/z* 226 (3%), corresponding to the loss of pyridyl, C_5H_4N and *m/z* 180 corresponding to the consecutive loss of of CH_2O and SO_2 or *vice versa*. Instead of ion B^+ **3g** gave ions *m/z* 136 and 134 corresponding to $[M–PhSO_2–HCN]^+$ and $[M–PhSO_2H_2–HCN]^+$, respectively.

Compounds **3h–j** also exhibit a unique secondary fragmentation *via* the $[A–H]^{+\bullet}$ ions (an alternative route for **3i** and **3j** is from the ion $[A–H–OH]^+$) due to their furyl or thiophenyl substitutions (Scheme 4). For **3h** this ion, *m/z* 93 is weak but corresponds structurally those from **3i** and **3j**. The latter compounds also give the ions *m/z* (109 or 123) ± H, respectively but **3h** only a small amount of the ion *m/z* 94(2%), $C_6H_6O^{+\bullet}$ since major part (3%) of this nominal mass corresponded to the structure $C_6H_8N^+$.

Scheme 4



3g m/z (%) 246 (100) m/z (%) 104 (32)



3h-j

3h X=O, R=H, m/z (%) 93 (3)
3i X=S, R=H, m/z (%) 109 (26)
3j X=S, R=Me, m/z (%) 123 (14)

In the case of compounds **3d** and **3e** the base peaks of the spectra were *m/z* 77 and 91. The former was fairly abundant in all of the spectra but only for **3d** (R^2 = Ph) it was the base peak. In case of **3e** the 4-$PhCH_2O$ substituent on R^1 is responsible for the formation of tropylium ion giving the base peak of the spectrum. In the latter case this explains also why D-type ions are not formed since the ion $[A–H]^{+\bullet}$ decomposes preferably to the ions *m/z* 91 and 206 ($C_{11}H_{12}NO_3^+$) of which the former predominates.

EXPERIMENTAL

General Experimental Procedures.

Melting points were determined on a Meltemp apparatus and are uncorrected. IR spectra were recorded on a Jasco 430 FT/IR instrument (KBr pellet for solids, neat for oil or liquids using NaCl disks). Preparative flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). R_f-values were determined by thin layer chromatography (TLC) on Merck silica gel 60 F_{254} and spots were visualized with UV light, iodine or potassium permanganate stain solutions.

NMR-spectra were acquired using a Bruker Avance 500 spectrometer (equipped with BBO-5mm-Zgrad probe) operating at 500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C. Spectra were recorded using $CDCl_3$ as a solvent with a non-spinning sample in 5 mm NMR-tubes. Spectra were processed by a PC with Windows XP operating system and XWin-NMR software. Proton and carbon spectra were referenced internally to TMS signal using value 0.00 ppm.

^{1}H-NMR spectra were acquired with single-pulse excitation, 30° flip angle and with spectral width of 8 kHz consisting of 64 k data points (digital resolution 0.12 Hz/pt). No apodisation was applied prior to Fourier transformation. ^{13}C-NMR proton-decoupled spectra were acquired with single-pulse excitation, 30° flip angle and with spectral width of 30 kHz consisting of 64 k data points (digital resolution 0.46 Hz/pt). 1 Hz exponential weighting was applied prior to Fourier transformation. Gradient selected DQF-COSY spectra were acquired with cosygpmfqf

pulse program (pulse programs refer to original ones installed by Bruker), with spectral widths of 6.7 kHz, 1024×128 data points and processed with zero-filling (×1, ×8) and non-shifted sine weighting applied in both dimensions prior to Fourier transformation. Gradient selected NOESY spectra were acquired with noesygpph pulse program, with spectral widths of 5 kHz, 1024×128 data points and processed with zero-filling (×1, ×8) and shifted (SSB 2) qsine weighting applied in both dimensions prior to Fourier transformation. Gradient selected ^{1}H-^{13}C HSQC spectra were acquired with hsqcetgpsisp.2 pulse program (using shaped pulses), with spectral widths of 6.7×27.5 kHz, 1024×256 data points, 145 Hz one-bond coupling constant and processed with zero-filling (×1, ×4) and shifted (SSB 2) qsine weighting applied in both dimensions prior to Fourier transformation. Gradient selected ^{1}H-^{13}C HMBC spectra were acquired with hmbcgplpndqf pulse program, with spectral widths of 6.5×28 kHz, 1024×128 data points, 10 Hz long-range coupling constant and processed with zero-filling (×2, ×8) and shifted (SSB 2) qsine weighting applied in both dimensions prior to Fourier transformation.

Mass spectra were measured on a VG ZabSpec mass spectrometer (Micromass, Manchester, UK) equipped with Opus V3.3X program package. For low-resolution EI spectra (70 eV) and metastable ion analyses (*B*/*E* and B^2/E linked scans in the first field-free region), the resolution was approximately 3,000 (at 10% peak height), the acceleration voltage was 8 kV, and the ionization current was 200 μA. For accurate mass measurements, the resolution was in the range of 8,000–12,000 (measured at 10% peak height) and voltage scanning or peak-matching techniques were applied using PFK as a source of reference signals. For all experiments, samples were introduced *via* a solids inlet system; the temperature of the ion source was 433 K.

General Procedure for Preparation of **3a–j**.

A 1-substituted *N*-methyl (or phenyl) methanimine *N*-oxide (**1**, 1 mmol if not otherwise stated) was added to a solution of phenyl vinyl sulfone (**2**, 168 mg, 1 mmol if not otherwise stated) in dry toluene (10 mL) and the mixture was heated to reflux for overnight. The progress of the reaction was monitored by TLC. Then the reaction mixture was concentrated *in vacuo* and the crude product purified by flash column chromatography using a mixture of *n*-hexane (*n*H) and ethyl acetate (EA) to give the products.

(3*R**,4*R**)-3-(4-*N*,*N*-Dimethylphenyl)-2-methyl-4-(phenylsulfonyl)-isoxazolidine (**3a**).

N-Methyl-4-(*N*,*N*-dimethylamino)-benzylidene amine *N*-oxide (**1a**) gave **3a** after the flash chromatography (*n*H:EA 2:1) as a yellowish solid (190 mg, 55%). Mp 116-117 °C. R_f : 0.55 (*n*H:EA 2:1). IR (KBr): ν(cm^{-1}) 2922, 1614, 1447, 1309 (SO_2, symmetric), 1147 (SO_2, asymmetric). HRMS: $M^{+\bullet}$ $C_{18}H_{22}N_2O_3S$, Calcd. 346.1351, Obsd. 346.1351.

Anal. Calcd. for $C_{18}H_{22}N_2O_3S$ (MW 346.44). C 62.40; H 6.40; N 8.09; S 9.25. Found: 62.25; H 6.30; N 8.24; S 9.40.

(3*R**,4*R**)-3-(4-*N*,*N*-Dimethylphenyl)-2-phenyl-4-(phenylsulfonyl)-isoxazolidine (**3b**).

N-Phenyl-4-(*N*,*N*-dimethylamino)-benzylidene amine *N*-oxide (**1b**, two mmols of starting materials were used) gave **3b** after the flash chromatography (*n*H:EA 3:1) and recrystallization from benzene-light petroleum as yellow needles (208 mg, 51%). Mp 172-175 °C. R_f: 0.46 (EA:*n*H 1:1). IR (KBr): ν (cm^{-1}) 2922, 1614, 1447, 1309 (SO_2, symmetric), 1147 (SO_2, asymmetric). HRMS: $M^{+\bullet}$ $C_{23}H_{24}N_2O_3S$, Calcd. 408.1508, Obsd. 408.1501.

Anal. Calcd. for $C_{23}H_{24}N_2O_3S$ (MW 408.52). C 67.62; H 5.92; N 6.86; S 7.85. Found: C 67.40; H 5.76; N 6.90; S 7.72.

(3*R**,4*R**)-3-(4-Methoxyphenyl)-2-methyl-4-(phenylsulfonyl)-isoxazolidine (**3c**).

N-Methyl-4-(methoxy)-benzylidene amine *N*-oxide (**1c**, 0,25 mmols of starting materials were used) gave **3c** after the flash chromatography (*n*H:EA 2:1) as a yellow solid (62 mg, 55%). Mp 146-147 °C. R_f : 0.62 (EA:*n*H 1:1)**,** IR (KBr): ν (cm^{-1}): 3050, 2845, 1615 , 1445 , 1295 (SO_2, symmetric), 1142 (SO_2, asymmetric). HRMS: $M^{+\bullet}$ $C_{17}H_{19}NO_4S$, Calcd. 333.1035, Obsd. 333.1037.

Anal. Calcd. for $C_{17}H_{19}NO_4S$ (MW 333.402). C 61.24; H 5.74; N 4.20; S 9.62. Found: C 61.40; H 5.82; N 4.12; S 9.76.

(3*R**,4*R**)-3-(4-Methoxyphenyl)-2-phenyl-4-(phenylsulfonyl)-isoxazolidine (**3d**).

N-Phenyl-4-(methoxy)-benzylidene amine *N*-oxide (**1d**) gave **3d** after the flash chromatography (*n*H:EA 3:1) and recrystallization from benzene-light petroleum as yellow needles (200 mg, 50%). Mp 145-146 °C. R_f : 0.61 (EA:*n*H 1:1). IR (KBr): ν (cm^{-1}) 3415, 3056 , 1611 ,1486, 1309 (SO_2, symmetric), 1147 (SO_2, asymmetric). HRMS: $M^{+\bullet}$ $C_{22}H_{21}NO_4S$, Calcd. 395.1191, Obsd. 395.1191.

Anal. Calcd. for $C_{22}H_{21}NO_4S$ (MW 395.47). C 66.82; H 5.35; N 3.54; S 8.11. Found: C 66.62; H 5.16; N 3.70; S 8.30.

(3*R**,4*R**)-3-(3-Methoxy-4-phenoxyphenyl)-2-methyl-4-(phenylsulfonyl)isoxazolidine (**3e**).

N-Methyl-(3-methoxy-4-phenoxy)-benzylidene amine *N*-oxide (**1e**) gave **3e** after the flash chromatography (petroleum ether 40-60 °C: EA 2:1) as a yellow solid (276 mg, 63%). Mp 115-117 °C. R_f: 0.77 (EA:*n*H 2:1). IR (KBr): ν (cm^{-1}) 3050, 2959, 1604, 1454, 1305 (SO_2, symmetric), 1153 (SO_2, asymmetric). HRMS: $M^{+\bullet}$ $C_{24}H_{25}NO_5S$, Calcd. 439.1453, Obsd. 439.1452.

Anal. Calcd. for $C_{24}H_{25}N_2O_5S$ (MW 437.53). C 65.58; H 5.73; N 3.19; S 7.29. Found: C 65.42; H 5.73; N 3.30; S 7.42.

(3*R**,4*R**)-3-(2-Hydroxyphenyl)-2-phenyl-4-(phenylsulfonyl)-isoxazolidine (**3f).**

N-(2-hydroxyphenyl)-benzylidene amine *N*-oxide **(1f)** gave **3f** after the flash chromatography (*n*H:EA 2:1) as a dark coloured oil (48 mg, 13%). R_f : 0.46 (EA:*n*H 1:1). IR (KBr): ν (cm^{-1}) 3411 (OH), 1596, 1447, 1307 (SO_2, symmetric), 1149 (SO_2, asymmetric). HRMS: $M^{+\bullet}$ $C_{21}H_{19}NO_4S$, Calcd. 381.1035, Obsd. 381.1037.

Anal. Calcd. for $C_{21}H_{19}NO_4S$ (MW 381.45). C 66.12; H 5.02; N 3.67; S 8.40. Found: C 66.30; H 5.15; N 3.48; S 8.60.

(3*R**,4*R**)-2-Methyl-4-(phenylsulfonyl)-3-(pyridin-2-yl)isoxazolidine (**3g**).

N-methyl-1-(pyridin-2-yl)-methanimine *N*-oxide (**1g**) gave **3g** after the flash chromatography (*n*H:EA 2:1) as a black solid (126 mg, 41%). Mp 119-122 °C. R_f: 0.62 (EA:*n*H 1:1). IR (KBr): ν (cm^{-1}) 2853, 1591, 1443, 1302 (SO_2, symmetric), 1154

(SO_2, asymmetric). HRMS: $M^{+\bullet}$ $C_{15}H_{16}N_2O_3S$, Calcd. 304.0882, Obsd. 304.0883.

Anal. Calcd. for $C_{15}H_{16}N_2O_3S$ (MW 304.36). C 59.19; H 5.30; N 9.20; S 10.53. Found: C 59.40; H 5.22; N 9.38; S 10.25.

(3*R**,4*R**)-3-(Furan-2-yl)-2-methyl-4-(phenylsulfonyl)isoxazolidine (**3h**).

N-methyl-1-(furan-2-yl)methanimine *N*-oxide (**1h**) gave **3h** after the flash chromatography (*n*H:EA 2:1) and recrystallization from benzene-light petroleum as white needles (125 mg, 40%). Mp 122-124 °C. R_f: 0.50 (EA:*n*H 1:1). IR (KBr): ν (cm^{-1}) 3137, 2967, 1448, 1315 (SO_2, symmetric), 1149 (SO_2, asymmetric). HRMS: $M^{+\bullet}$ $C_{14}H_{15}NO_4S$, Calcd. 293.0722, Obsd. 293.0718.

Anal. Calcd. for $C_{14}H_{15}NO_4S$ (MW 293.34). C 64.34; H 5.78; N 5.36; S 12.27. Found: C 64.50; H 5.65; N 5.50; S 12.40.

(3*R**,4*S**)-2-Methyl-4-(phenylsulfonyl)-3-(thiophen-2-yl)isoxazolidine (**3i**).

N-methyl-1-(thiophen-2-yl)methanimine *N*-oxide (**1i**) gave **3i** after the flash chromatography (*n*H:EA 2:1) and recrystallization from benzene-light petroleum as white needles (126 mg, 41%). Mp 99-101 °C. R_f: 0.49 (EA:*n*H 3:2). IR (KBr): ν (cm^{-1}) 1581, 1446, 1307 (SO_2, symmetric), 1147 (SO_2, asymmetric). HRMS: $M^{+\bullet}$ $C_{14}H_{15}NO_3S_2$, Calcd. 309.0493, Obsd. 309.0500.

Anal. Calcd for $C_{14}H_{15}NO_3S_2$ (MW 309.40). C 54.35; H 4.89; N 4.53; S 20.72. Found: C 54.20; H 5.02; N 4.70; S 20.54.

(3*R**,4*S**)-2-Methyl-3-(3-methylthiophen-2-yl)-4-(phenylsulfonyl)-isoxazolidine (**3j**).

N-methyl-1-(3-meth-ylthiophen-2-yl))methanimine *N*-oxide (**1j**) gave **3j** after the flash chromatography (*n*H:EA 2:1) and recrystallization from hexane as white needles (126 mg, 41%). Mp 87-89 °C. R_f: 0.46 (EA:*n*H 1:1). IR (KBr): ν (cm^{-1}) 3058, 2877, 1447, 1307 (SO_2, symmetric), 1153 (SO_2, asymmetric). HRMS: $M^{+\bullet}$ $C_{15}H_{17}NO_3S_2$, Calcd. 323.0650, Obsd. 323.0648.

Anal. Calcd. for $C_{15}H_{17}NO_3S_2$ (MW 323.42). C 55.70; H 5.30; N 4.33; S 19.82. Found: C 55.65; H 5.50; N 4.18; S 19.65.

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