1,3-Dipolar Cycloaddition Reactions of Nitrones to Prop-1-ene-1,3-sultone

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Abstract: The reaction of prop-1-ene-1,3-sultone (**1**) with a variety of nitrones **2** afforded novel [3+2] cycloaddition products **3**, **4**, and **5** in good yield. Excellent regio- and stereoselectivity were achieved in the cycloaddition reaction with phenylnitrones.

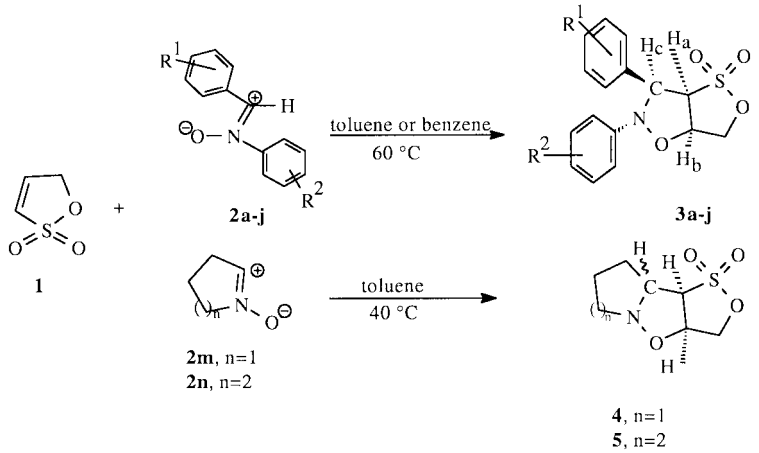
Key words: cycloaddition, nitrone, sultone, regioselectivity, stereoselectivity

Introduction

The molecule of prop-1-ene-1,3-sultone (**1**) contains a vinyl group and α-hydrogen atoms whose reactivities have been enhanced by the sulfonyl group and ring strain. These activated moieties could undergo a variety of reactions such as 1,2-addition, cycloaddition, ene reaction, Baylis–Hillman reaction etc. Therefore, it is envisioned that the sultone **1** will emerge as a versatile synthon for the construction of heterocyclic systems and functional compounds. Surprisingly, the chemistry of sultone **1** has received little attention in the literature.[1–3] As part of our research on 1,3-dipolar cycloaddition reactions, we were interested in utilizing sulfur-containing functionalities as activating groups in the design of dipolarophiles. Recently, the cycloaddition reaction of sultone **1** with nitrile oxides has been accomplished by us with satisfactory results.[4] Nitrones (or azomethine oxides) are well-known to behave as 1,3-dipoles in thermal cycloaddition reactions. As an extension of our research on 1,3-dipolar cycloaddition reactions, we report here the cycloaddition reaction of sultone **1** with various substituted phenylnitrones and cyclic (five- and six-membered) nitrones.

Cycloaddition of Phenylnitrones with Prop-1-ene-1,3-Sultone

We have successfully carried out the cycloaddition of prop-1-ene-sultone (**1**) to nitrones **2** (Scheme 1, Table 1). The reaction is conducted by heating the two reagents together in an inert solvent, commonly benzene or toluene, and the products are often easily isolated in excellent yield. As the phenylnitrones were found to be sensitive to light[5] and tend to decompose easily under thermal conditions, the reaction should proceed in the dark and under a nitrogen atmosphere. At the same time, the reaction temperature should be maintained below 60 °C. The yield of the cycloadducts can be improved by prolonging the reaction time (it usually needs 24–36 h) and adding additional amounts of the nitrones . From Table 1, we can see that the yields of adducts **3e** (57%), **3i** (56%) and **3j** (57%) are a little higher than the other adducts. The reason for this phenomenon is that the chloro and the fluoro subsitituents in nitrones **2e**, **2i**, and **2j** are capable of exerting an electron-attracting effect enhancing the positive charge on the C=N carbon and so favoring the attack of the enolate ion.



Scheme 1

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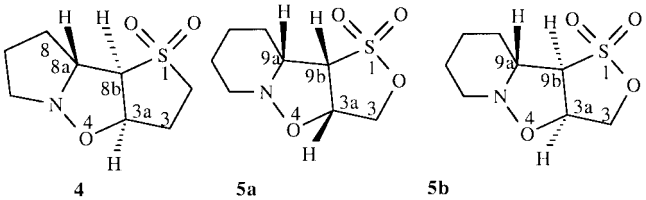
But, on the contrary, for nitrones **2k** and **2l** with electron-donating substituents [OCH_3 and (OCH_2O)], almost no cycloadducts were obtained. The adducts **3** were separated by column chromatograpy and recrystallization.

The cyclic nitrones, which can exist only in the *E* isomeric form because of geometric constraint, are found to undergo cycloaddition reactions with high stereoselection, high yield, and fast rate.

Confirmation of the Cycloaddition Direction

The structures of cycloadducts **3** were confirmed by their ^{1}H NMR spectra. The ^{1}H NMR spectra showed that the reaction of **1** with phenylnitrones **2a**–**j** afforded only the sole regioisomeric adducts (structure **3**, not structure **3″** in Figure 1). The structural assignment of the cycloadducts **3** was corroborated using ^{1}H NMR data. The ^{1}H NMR spectra of **3** showed that the chemical shifts of H_b, which appeared as two doublets are more downfield than those for H_a. This means that the carbon bonded to H_b is connected with oxygen atom of nitrone (structure **3** in Figure 1). Owning to the paramagnetic shift caused by the adjacent oxygen atom, the H_b appeared at lower field than H_a. All of the cycloadducts show larger J_{ab} values in the range of 6.24–6.82 Hz consistent with their *cis*-orientation.[5] No exception to the rigid *cis*-stereospecificity of the addition was observed. Furthermore, the J_{ac} values of all the cycloadducts are about 6 Hz, which means that H_a and H_c are also *cis*-oriented (structure **3** not structure **3′** in Figure 1). If they were stucture **3′**, the dihedral angle between the face of the H_a and the face of the H_c would be 90°, so there would be no coupling interaction between H_a and H_c. So the cycloaddition reaction of the phenylnitrones with prop-1-ene-1,3-sultone (**1**) has not only far higher regioselectivity but also far higher stereoselectivity. The products are in accord with the regiochemistry reported for cycloaddition of nitrones to α,β-unsaturated lactones.[5] This *cis*-stereo- and regiospecificity are best explained by a concerted process.[6] While the chemical shifts for H_b of the adducts **3**, except **3e**, turn up at more downfield than H_c and H_a, the H_c (5.55 ppm) of **3e** appear at more downfield than H_b (5.36 ppm), resulting from the dichloro substituents of the phenyl ring.

For cyclic nitrones, the reaction of nitrones **2m** with **1** gave exclusively the product **4** in 78% yield. The ^{1}H NMR spectrum of compound **4** displayed the H-8b (3.95 ppm, $J_{8b,3a}$ = 7.12 Hz) as a doublet. The zero coupling constant observed for $J_{8a,8b}$ thus indicates an approximate dihedral angle of 90° between the face of H-8a and H-8b (Figure 2). However, the reaction of nitrone **2n** with sultone **1** gave a mixture (86%) of adducts **5a**, **5b** in a ratio of 68:32. The major isomer probably has the stereochemistry as depicted in Figure 2 with the H-9a and the H-9b being at the same side of the isoxazolidine ring. The reason for this conclusion is that the ^{1}H NMR spectrum of the major **5a** displayed the H-9b (3.73 ppm) as triplet ($J_{9a,9b}$ = 7.3 Hz, $J_{9b,3a}$ = 8.34 Hz).



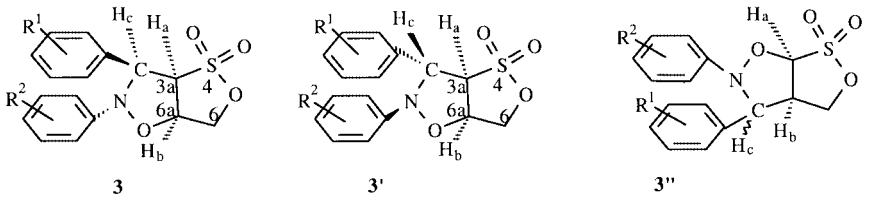
4 **5a** **5b**

Figure 2 Structures of compounds **4**, **5a** and **5b**

Table 1 Cycloaddition Conditions and Yields of Cycloadducts

Products	R^1	R^2	n	Solvent	Reaction Time (h)	Yield (%)[a]
3a	H	H	–	toluene	24	42
3b	4-Cl	H	–	toluene	24	52
3c	4-Me	H	–	toluene	28	51
3d	4-F	H	–	toluene	36	53
3e	2,4-Cl_2	H	–	toluene	36	57
3f	3-NO_2	H	–	toluene	36	41
3g	3-Me	H	–	toluene	36	53
3h	4-H	4-Cl	–	benzene	36	49
3i	4-F	4-Cl	–	benzene	36	56
3j	4-Cl	4-Cl	–	benzene	36	57
4	–	–	1	toluene	12	78
5	–	–	2	toluene	12	86

[a] Yields are based on prop-1-ene-1,3-sultone (**1**).



3 **3'** **3"**

Figure 1 Possible structures of adducts **3**

Conclusions

In conclusion, 1,3-dipolar cycloaddition of compound **1** with phenylnitrones **2a–j** gave the corresponding isoxazolidines regio- and stereospecifically in 41–60% yields. The cyclic nitrones, because of structrural constraint,[7] undergo cycloaddition much faster and with higher yields than phenylnitrones.

Table 2 Physical Constants of Nitrones **2a–l**

Nitrone	R^1	R^2	Method	Mp (°C) Found	Mp (°C) Reported
2a	H	H	A	114	116[13]
2b	4-Cl	H	A	152–154	152[14]
2c	4-Me	H	A	92–93	94[15]
2d	4-F	H	A	136–138	138[15]
2e	2,4-Cl_2	H	A	92–93	93[16]
2f	3-NO_2	H	A	152–153	151[17]
2g	3-Me	H	A	83–85	85[16]
2h	H	4-Cl	B	181–182	181[18]
2i	4-F	4-Cl	B	151–152	152[18]
2j	4-Cl	4-Cl	B	170–172	173[18]
2k	4-OMe	H	A	116–117	117[15]
2l	3,4-(OCH_2O)	H	A	131–132	133[15]

Mps were determined with a Thomas-Hoover melting point apparatus. ^1H and ^{13}C NMR spectra were determined with a Bruker AC-P200 in $CDCl_3$ solution. Chemical shifts are reported in ppm (δ) downfield from Me_4Si. Elemental Analyses were performed on Yanaco Chn Cor Der MF-3 apparatus. Petroleum ether used refers to the fraction boiling at 60–90 °C.

Nitrones 2; General Procedures[8]

Method A, for 2a–g, 2k,l[9]

A vigorously stirred mixture of nitrobenzene (26 g, 0.21 mol), NH_4Cl (13 g, 0.24 mol) and H_2O (400 mL) was maintained below 60 °C whilst zinc dust (90%, 30.8 g, 0.42 mol) was added in small portions during 15 min. The reaction mixture was stirred for 15 min after addition was complete, filtered while still warm, and the filter cake was washed with hot water (50 mL). The combined filtrates and washings were saturated with salt, (ca. 150 g) and cooled to 0 °C, and the resulting solid was collected, dried. The crude phenylhydroxylamine was recrystallized from hexane–petroleum ether instead of benzene–petroleum ether which was reported in the literature.[12] The pure *N*-phenylhydroxylamine had mp 80 °C (Lit.[12] mp 80.5–81.5 °C). The phenylnitrones **2a–g**, **2k**,**l** were then prepared by mixing equimolar solutions of the appropriate aromatic aldehyde and phenylhydroxylamine dissolved in a minimum quantity of EtOH,[9] and allowing the mixtures to stand at r.t. overnight in the dark. The mixtures were then cooled in an ice-bath and filtered. The collected solids were recrystallized from EtOH (yields: 80–95%) (Table 2).

Method B, Using N-Arylhydroxylamines Prepared in situ for 2h–j[10]

A vigorously stirred mixture of aromatic aldehye (0.02 mol), 4-chloronitrobenzene (3.55 g, 0.023 mol), NH_4Cl (1.39 g, 0.026 mol), EtOH (13 mL) and H_2O (13 mL) was maintained below 35 °C while zinc dust (90%, 3.5 g, 0.046 mol) was added in small portions during 30 min. After gentle stirring overnight at r.t., the mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined extracts were dried, evaporated, and the residual solid was recrystallized from toluene–petroleum ether (90–95%) (Table 2).

Method C, for 2m,n[7]

Yellow HgO (3 g, 14 mmol) was added to *N*-hydroxypyrrolidine or *N*-hydroxypiperidine (5 mmol) in CH_2Cl_2 (50 mL) at 0 °C under N_2. Within 10 min the reaction was complete as indicated by TLC. Anhyd $MgSO_4$ was added to the mixture which then filtered through a bed of Celite and anhyd $MgSO_4$. The grey mercury salts were washed with cold CH_2Cl_2 (25 mL) and the solvent was removed in vacuo. The residual yellow oil was the crude cyclic nitrones, which could be used in the cycloaddition reaction.

Prop-1-ene-1,3-sultone (1)[19]

Method D[1]

To a boiling solution of allyl chloride (20 g, 261 mmol) in 95% EtOH and H_2O (50 mL) was added dropwise a solution of Na_2SO_3 (15.75 g, 125 mmol, in 60 mL of H_2O). Then the reflux was continued for 4 h. The solvent was removed on a rotary evaporator and the residue was dried in vacuo. The crude products were purified by recrystallization from 95% EtOH. The total weight of sodium prop-2-ene sulfonate is 13.5 g (yield: 75%); mp 239–241°C. To a solution of sodium prop-2-ene sulfonate (5.5 g, 38.19 mmol) in H_2O (22 mL) was added Br_2 (2.06 mL) dropwise. Then, the solution was stirred for 2 h at r.t. A very little amount of Na_2SO_3 was added to decompose the excess of Br_2. The solvent was then removed in vacuo to furnish the white solid dibromosulfonate quantitatively. Without purification, the dibromosulfonate was treated with conc. HCl (22 mL) by stirring at r.t. for 1 day to give the 2,3-dibromopropane-1-sulfonic acid. Without further purification, the sulfonic acid was subjected to heating at 150–160 °C under reduced pressure and then distillation in vacuo to give the β-bromosultone (4 g, 114 °C/20 Pa). A solution of β-bromosultone (4 g) and Et_3N (4.3 mL) in benzene (150 mL) was stirred at r.t. for 4 h. After filtration of triethylamine hydrobromide and concentration of the solution, a white solid was obtained (2.4 g, 97%). Recrystallization from $CHCl_3$ gave **1** as needles; mp 81–82 °C.

Method E[21]

A mixture of $K_2S_2O_5$ (28 g) H_2O (200 mL) and 3.98 N KOH (61 mL) was placed in a 500 mL beaker. With stirring, an additional amount of $K_2S_2O_5$ (60 g) was added to the contents of the beaker. Thus, a solution of $KHSO_3$ and K_2SO_3 was formed. To a solution of propynol (40 mL) and H_2O (200 mL) in a 500 mL three-necked flask equipped with a stirrer and a dropping funnel, was added dropwise the above prepared solution of $KHSO_3$ and K_2SO_3. During the addition process, air was bubbled into the reaction bottle at 30–35 °C. The reaction mixture was stirred for 2 h at this temperature. Then aq 2 N H_2SO_4 (10 mL) was added to the solution and the SO_2 formed was released in vacuo. The residue was treated with KOH to neutralize and concentrated; then EtOH (100 mL) was added to make the K_2SO_4 separate out completely. K_2SO_4 was filtered off and washed with 50% EtOH (30 mL). The filtrate was concentrated and extracted with 70% EtOH (5 × 100 mL). The crude product obtained by removal of the solvent in vacuo was purified by recrystallization from 95% EtOH to give the potassium salt; mp 160–162 °C. The potassium salt (36 g) was treated with concd HCl (80 mL), then with MeOH (40 mL). The produced KCl was filtered off, washed with concd HCl (30 mL) and EtOH (15 mL). The combined filtrates

were concentrated in vacuo to afford crude 1-hydroxyprop-2-ene-3-sulfonic acid. The crude 1-hydroxyprop-2-ene-3-sulfonic acid was heated at 130–145 °C in an oil bath and then distilled in vacuo to give **1** (12 g); bp 118 °C/14 Pa; mp 83–84 °C.

Cycloaddition of Phenylnitrones 2a-j with Sultone 1; General Procedure

A toluene or benzene solution of nitrone **2** (1 mmol) and the sultone **1** (0.12 g, 1 mmol) was heated at 60 °C (for phenylnitrones) or 40 °C (for cyclic nitrones) for the time indicated in Table 1. During the reaction, additional amounts of nitrones (ca. 0.2 mmol) were added twice. Evaporation of the solvent and separation of the resulting brown residue by column chromatography gave the crude product, which was recrystallized from suitable solvents.

2,3-Diphenyl-6a,3a-dihydro-5,4-oxathiain-4,4-dioxide[3,4-*d*]-isoxazolidine (3a)

Recrystallized from EtOAc–petroleum ether (1:3); white crystals; mp 147–148 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.25–7.45 (m, 5 H_{arom}), 6.8–7.2 (m, 5 H_{arom}), 5.42 (dd, *J* = 3.21, 6.68 Hz, 1 H, H-6a), 4.79 (d, *J* = 6.32 Hz, 1 H, H-3), 4.64 (d, *J* = –11.07 Hz, 1 H, H-6), 4.48 (dd, *J* = 3.21, –11.07 Hz, 1 H, H-6), 4.22 (t, *J* = 6.68, 6.32 Hz, 1 H, H-3a).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 146.7, 131.64, 129.77, 128.65, 128.03, 119.2 (arom), 79.26 (C-6a), 71.21 (C-3), 70.32 (C-6), 69.32 (C-3a).

Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41. Found: C, 60.51; H, 5.01; N, 4.64.

3-(4-Chlorophenyl)-2-phenyl-6a,3a-dihydro-5,4-oxathiain-4,4-dioxide[3,4-*d*]isoxazolidine (3b)

Recrystallized from EtOAc–petroleum ether (1:3); white crystals, mp 164–165 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.9–7.4 (m, 9 H_{arom}), 5.43 (dd, *J* = 3.52, 6.55 Hz, 1 H, H-6a), 4.77 (d, *J* = 5.9 Hz, 1 H, H-3), 4.6 (d, *J* = –11.033 Hz, 1 H, H-6), 4.52 (dd, *J* = 3.52 Hz, –11.033 Hz, 1 H, H-6), 4.13 (t, *J* = 6.55, 5.9 Hz, 1 H, H-3a).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 146.3, 137.02, 131.34, 129.69, 128.65, 127.13, 119.2 (arom), 79.34 (C-6a), 72.01 (C-3), 70.72 (C-6), 69.33 (C-3a).

Anal. Calcd for $C_{16}H_{14}ClNO_4S$: C, 54.62; H, 4.02; N, 3.98. Found: C, 54.51; H, 3.96; N, 4.05.

3-(4-Methylphenyl)-2-phenyl-6a,3a-dihydro-5,4-oxathiain-4,4-dioxide[3,4-*d*]isoxazolidine (3c)

Recrystallized from EtOAc–petroleum ether (1:3); white crystals; mp 123–124 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.96–7.4 (m, 9 H_{arom}), 5.39 (dd, *J* = 3.33, 6.57 Hz, 1 H, H-6a), 4.77 (d, *J* = 6.27 Hz, 1 H, H-3), 4.59 (d, *J* = –11.06 Hz, 1 H, H-6), 4.45 (dd, *J* 3.33, –11.06 Hz, 1 H, H-6), 4.17 (t, *J* = 6.57, 6.27 Hz, 1 H, H-3a), 2.34 (s, 3 H, CH_3).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 146.74, 138.90, 132.96, 129.99, 128.66, 127.58, 124.98, 119.22 (arom), 79.16 (C-6a), 72.41 (C-3), 70.71 (C-6), 69.46 (C-3a).

Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.48; H, 5.18; N, 4.37.

3-(4-Fluorophenyl)-2-phenyl-6a,3a-dihydro-5,4-oxathiain-4,4-dioxide[3,4-*d*]-isoxazolidine (3d)

Recrystallized from EtOAc–petroleum ether (1:3); white crystals, mp 182–183 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.9-7.5 (m, 9 H_{arom}), 5.38 (dd, *J* = 3.54, 6.82 Hz, 1 H, H-6a), 4.76 (d, *J* = 6.25 Hz, 1 H, H-3), 4.59 (d, *J* = –11.19 Hz, 1 H, H-6), 4.46 (dd, *J* = 3.54, –11.19 Hz, 1 H, H-6), 4.17 (t, *J* = 6.82, 6.25 Hz, 1 H H-3a).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 162.30, 131.61, 130.51, 129.23, 128.11, 124.71, 117.23 (arom), 79.84 (C-6a), 72.01 (C-3), 70.21 (C-6), 69.24 (C-3a).

Anal. Calcd for $C_{16}H_{14}FNO_4S$: C, 57.31; H, 4.21; N, 4.18. Found: C, 57.03; H, 3.98; N, 4.27

3-(2,4-Dichlorophenyl)-2-phenyl-6a,3a-dihydro-5,4-oxathiain-4,4-dioxide[3,4-*d*]isoxazolidine (3e)

Recrystallized from EtOAc–petroleum ether (1:4); white crystals; mp 155–156 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.9–7.5 (m, 8 H_{arom}), 5.55 (d, *J* = 3.33 Hz, 1 H, H-3) 5.36 (dd, *J* = 6.24, 3.35 Hz, 1 H, H-6a), 4.66 (d, *J* = –11.15 Hz, 1 H, H-6), 4.52 (dd, *J* = –11.15, 3.35 Hz, 1 H, H-6), 4.21 (dd, *J* = 6.24, 3.33 Hz, 1 H, H-3a).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 146.34, 135.32, 134.11, 132.74, 130.08, 128.92, 127.80, 124.14, 117.04 (arom), 79.63 (C-6a), 70.09 (C-3), 69.24 (C-6), 67.29 (C-3a).

Anal. Calcd for $C_{16}H_{13}NO_4Cl_2S$: C, 49.76; H, 3.39; N, 3.63. Found: C, 49.8; H, 3.405; N, 3.54.

3-(3-Nitrophenyl)-2-phenyl-6a,3a-dihydro-5,4-oxathiain-4,4-dioxide[3,4-*d*]isoxazolidine (3f)

Recrystallized from toluene; white crystals; mp 143–144 °C.

^{1}H NMR (200 MHz,$CDCl_3$): δ = 6.9–8.4 (m, 9 H_{arom}), 5.47 (dd, *J* = 3.13, 6.66 Hz, 1 H, H-6a), 4.94 (d, *J* = 6.19 Hz, 1 H, H-3), 4.62 (d, *J* = –11.12 Hz, 1 H, H-6), 4.51 (dd, *J* = 3.13, –11.12 Hz, 1 H, H-6), 4.16 (t, *J* = 6.66, 6.19 Hz, 1 H, H-3a).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 148.76, 145.71, 138.00, 134.04, 130.37, 128.98, 125.84, 124.05, 122.53, 119.65 (arom), 79.35 (C-6a), 71.42 (C-3), 70.01 (C-6), 69.92 (C-3a).

Anal. Calcd for $C_{16}H_{14}N_2O_6S$: C, 55.48; H, 4.07; N, 8.09. Found: C, 55.53; H, 3.92; N, 7.99

3-(3-Methylphenyl)-2-phenyl-6a,3a-dihydro-5,4-oxathiain-4,4-dioxide[3,4-*d*]isoxazolidine (3g)

Recrystallized from EtOAc–petroleum ether (1:4); white crystals, mp 114–115 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.9–7.3 (m, 9 H_{arom}), 5.37 (dd, *J* = 3.26, 6.66 Hz, 1 H, H-6a), 4.7 (d, *J* = 6.24 Hz, 1 H, H-3), 4.59 (d, *J* = –11.08 Hz, 1 H, H-6), 4.45 (dd, *J* = 3.26, –11.08 Hz, 1 H, H-6), 4.16 (t, *J* = 6.66, 6.24 Hz, 1 H, H-3a).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 146.88, 139.16, 136.12, 129.80, 129.19, 128.68, 128.19, 124.88, 124.69, 119.04 (arom), 79.26 (C-6a), 72.49 (C-3), 70.81 (C-6), 69.41 (C-3a).

Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.585; H, 5.2; N, 4.3

2-(4-Chlorophenyl)-3-phenyl-6a,3a-dihydro-5,4-oxathiain-4,4-dioxide[3,4-*d*]isoxazolidine (3h)

Recrystallized from EtOAc–petroleum ether (1:3); white crystals, mp 166–167 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.7–7.4 (m, 9 H_{arom}), 5.31 (dd, *J* = 3.65, 6.68 Hz, 1 H, H-6a), 4.66 (d, *J* = 6.17 Hz, 1 H, H-3), 4.52 (d, *J* = –11.05 Hz, 1 H, H-6), 4.43 (dd, *J* = 3.65, –11.05 Hz, 1 H, H-6), 4.10 (t, *J* = 6.68, 6.17 Hz, 1 H, H-3a).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 144.61, 131.65, 129.77, 129.21, 128.03, 125.34, 119.32 (arom); 79.26 (C-6a), 72.22 (C-3), 70.12 (C-6), 69.67 (C-3a).

Anal. Calcd for $C_{16}H_{14}ClNO_4S$: C, 54.62; H, 4.02; N, 3.98. Found: C, 54.62; H, 3.93; N, 3.87.

2-(4-Chlorophenyl)-3-(4-fluorophenyl)-6a,3a-dihydro-5,4-oxathiain-4,4-dioxide[3,4-*d*]isoxazolidine (3i)
Recrystallized from EtOAc–petroleum ether (1:3); brown crystals, mp 91–92 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.7–7.5 (m, 8 H_{arom}), 5.39 (dd, *J* = 3.17, 6.67 Hz, 1 H, H-6a), 4.74 (d, *J* = 6.17 Hz, 1 H, H-3), 4.62 (d, *J* = –11.04 Hz, 1 H, H-6), 4.49 (dd, *J* = 3.17, –11.04 Hz, 1 H, H-6), 4.16 (t, *J* = 6.67, 6.17 Hz, 1 H, H-3a).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 164.11, 144.90, 131.16, 130.63, 129.61, 129.47, 128.82, 120.65, 116.68, 116.24 (arom), 79.24 (C-6a), 72.12 (C-3), 70.25 (C-6), 69.56 (C-3a).

Anal. Calcd for $C_{16}H_{13}ClFNO_4S$: C, 51.97; H, 3.54; N, 3.79. Found: C, 51.98; H, 3.71; N, 4.04.

2-(4-Chlorophenyl)-3-(4-chlorophenyl)-6a,3a-dihydro-5,4-oxathiain-4,4-di-oxide[3,4-*d*]isoxazolidine (3j)
Recrystallized from EtOAc–petroleum ether (1:3); brown crystals; mp 125–126 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.8–7.4 (m, 8 H_{arom}), 5.35 (dd, *J* = 3.48, 6.46 Hz, 1 H, H-6a), 4.71 (d, *J* = 5.73 Hz, 1 H, H-3), 4.59 (d, *J* = –11.02 Hz, 1 H, H-6), 4.49 (dd, *J* = 3.48, –11.02 Hz, 1 H, H-6), 4.15 (t, *J* = 6.46, 5.73 Hz, 1 H, H-3a).

^{13}C NMR(200 MHz, $CDCl_3$): δ = 144.83, 135.20, 133.94, 130.62, 129.63, 129.01, 128.84, 120.56 (arom), 79.31(C-6a), 71.97 (C-3), 70.18 (C-6), 69.62(C-3a).

Anal. Calcd for $C_{16}H_{13}Cl_2NO_4S$: C, 49.75; H, 3.39; N, 3.63. Found: C, 49.75; H, 3.68; N, 3.5.

Cycloaddition of Cyclic Nitrone 2m to Sultone 1; (3a*R, 8a*S**, 8b*S**)-Octahydro[3,4-*d*]pyrrolo[2,3-*a*]pyridine[1,2-*b*]isoxazol-2,1-oxathiain-1,1-dioxide (4)**
To a solution of nitrone **2m** (0.18 g, 2.2 mmol) in toluene (20 mL) was added sultone **1** (0.12 g, 1 mmol) and the mixture was kept at 40 °C for 12 h. Removal of the solvent gave the crude product, which was purified by column chromatography (eluent: petroleum ether–EtOAc, 2:1); yield: 0.16 g (78%); white crystals; mp 138–139 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.14 (m, 1 H, H-3a), 4.41–4.44 (m, 2 H, H-3), 4.07 (t, *J* = 7.52 Hz, 1 H, H-8a), 3.95 (d, *J* = 7.12 Hz, 1 H, H-8b), 3.36 (m, 1 H, H-6), 3.11 (m, 1 H, H-6), 2.13 (m, 2 H, H-8), 1.8 (m, 2 H, H-7).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 78.51 (C-3a), 73.05 (C-8a), 70.12 (C-3), 69.67 (C-8b), 55.79 (C-6), 29.33 (C-8), 23.81 (C-7).

Anal. Calcd for $C_7H_{11}NO_4S$: C, 40.96; H, 5.40; N, 6.83. Found: C, 40.97; H, 5.48; N, 6.75.

Cycloaddition of Cyclic Nitrone 2n to Sultone 1; (3a*R, 9a*R**, 9b*S**)-Octahydro[2,3-*a*]pyridine[3′,4′:4,5]isoxazolo-2,1-oxathiain-1,1-dioxide (5)**
To a solution of nitrone **2n** (0.21 g, 2.2 mmol) in toluene (20 mL) was added sultone **1** (0.12 g, 1 mmol) and the mixture was kept at 40 °C for 12 h. Removal of the solvent gave the crude product, which was purified by column chromatography (eluent: petroleum ether–EtOAc, 2:1); yield of **5a**/**5b**: 0.19 g (86%). The ^{1}H NMR spectra of the crude cycloaddition products revealed the presence of two isomers **5a** and **5b** in a ratio of 68:32. We were unable to isolate the two isomers either by crystallization or by column chromatograpy.

5a
^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.94 (dd, *J* = 8.34, 2.82 Hz, 1 H, H-3a), 4.35–4.43 (m, 2 H, H-3), 3.84 (m, 1 H, H-9a), 3.73 (t, *J* = 8.34, 7.3 Hz, 1 H, H-9b), 2.59 (m, 1 H, H-6), 2.41 (m, 1 H, H-6), 1.8 [m, 6 H, -$(CH_2)_3$-].

5b
^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.22 (m, 1 H, H-3a), 4.35–4.43 (m, 2 H, H-3), 3.67–3.74 (m, 2 H, H-9a, H-9b), 3.11 (m, 1 H, H-6), 2.79 (m, 1 H, H-6), 1.8 [m, 6 H, -$(CH_2)_3$-].

Anal. Calcd (mixture of **5a** and **5b**) $C_8H_{13}NO_4S$: C, 44.43; H, 6.06; N, 6.48. Found: C, 44.44; H, 6.06; N, 6.46.

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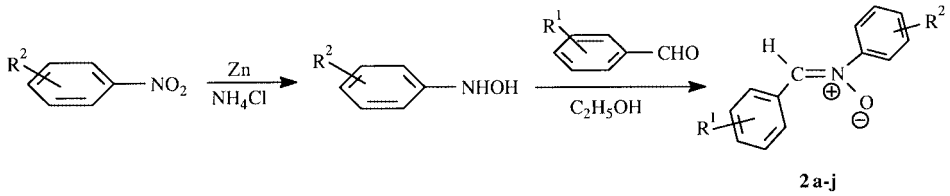
(8) The various substituted phenylnitrones **2a–l** have been widely employed as 1,3-dipoles. Three methods have been reported for their preparation.[9–11] Two routes (Method A and Method B) have been used by us (Scheme 2). Method A has two steps. In the first step, nitrobenzene was reduced by zinc dust and NH_4Cl to phenylhydroxylamine by a modified literature procedure,[12] and was purified by recrystallization. In the second step, the purified hydroxylamine was mixed with an equimolar amount of benzaldehyde to give the corresponding nitrones. Method B can be used to synthesize nitrones whose phenylhydroxylamines were unstable and can not be separated as pure intermediates. In Method B, the two steps used in Method A occur successively in one-pot. Cyclic nitrones **2m** and **2n** were prepared according to the reported procedures (Method C).[7]



Scheme 2

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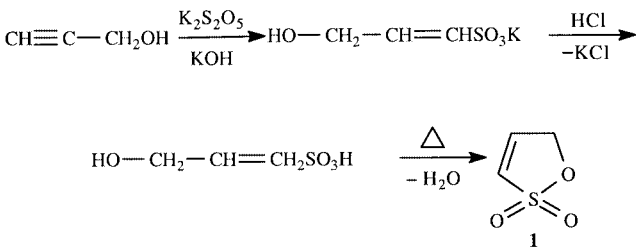
(19) Among numerous synthetic methods,[1,20,21] two routes attracted our attention. We repeated and improved the two methods [Method D (Scheme 3) and Method E (Scheme 4)].



Scheme 4

(20) (a) King, J. F.; Mayo, P. D.; Melntosh, C. L.; Smith, D. J. H. *Can. J. Chem.* **1970**, *48*, 3704. (b) Manecke, G.; Danhäuser, J.; Reich, C. *Angew. Chem.* **1958**, *70*, 503.
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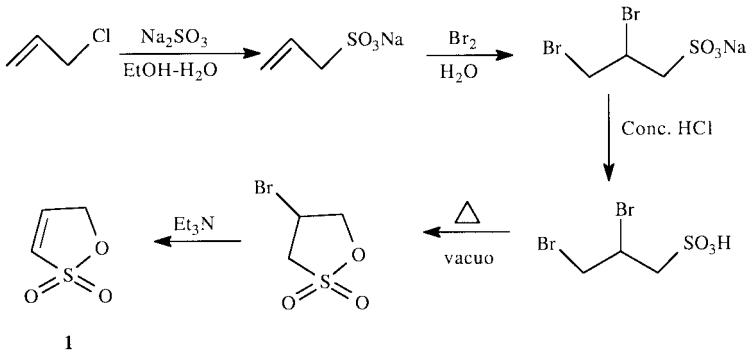

Scheme 3