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

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The reaction of prop-1-ene-1,3-sultone **1** with a variety of nitrile oxides **3** afforded novel [3+2] cycloaddition products **4** in good yield. The cycloaddition reaction achieved excellent regioselectivity.

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Introduction.

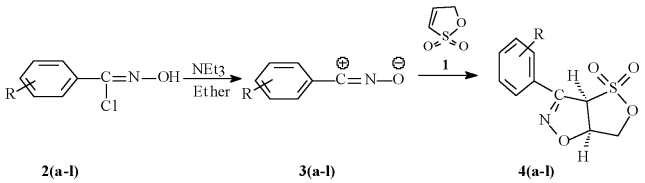
The molecular structure of prop-1-ene-1,3-sultone **1** contains a vinyl group and α-hydrogen atoms whose reactivates have been enhanced by the sulfonyl group and ring strain. These activated moieties could undergo a variety of reactions such as 1,2-addition, cycloaddition, ene reaction and Baylis-Hillman 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. However, only limited papers in literature for the investigation of the chemistry of sultone **1** are reported [1-3]. For instance, W. M. Lee and his co-workers reported the Diels-Alder reaction of **1** with a variety of dienes [1]. F. Bianca *et al*. described the Michael reaction of thiophenol or methanol with **1** in the presence of sodium methylate to give the saturated sultones [2]. The limited studies on the chemistry of **1** promote us to explore its reactivity. As part of our research on 1,3-dipolar cycloaddition, we are interested in utilizing sulfur-containing functionalities as activating groups in the dipolarophile design. So we choose sultone **1** as the dipolarophile and studied its cycloadditon reaction with benzonitrile oxides. The 1,3-dipolar reaction of sultone **1** with nitrile oxides gave substituted isoxazolines, which are versatile intermediates for the syntheses of natural products and biologically active compounds [4]. Similar reactions of **1** with other 1,3-dipoles are under investigation in our laboratory.

Results and Discussion.

Cycloaddition of Benzonitrile Oxide with Prop-1-ene-1,3-sultone.

We have successfully carried out the cycloaddition reactions of prop-1-ene-1,3-sultone **1** with dipoles **3**. The reaction sequence is shown in Scheme 1. The results are summarized in Table 1. The principal advantages of this reaction are: the operation is simple, the reaction proceeds smoothly under mild conditions, and the yield and purity of the corresponding cycloadducts **4** are excellent. Further more, the cycloaddition reaction has been proved to proceed regiospecifically, which is confirmed by the ^{1}H NMR spectra and an X-ray crystal structure (Figure 1). The main by-products of the cycloaddition reaction are the dimers (furoxan) of the dipolars. For example, we have obtained compound **5** (Scheme 2) which is the dimer of nitrile oxide **3a** (Scheme 2). The melting point of compound **5** is 113-114 °C the same as the reported value [5]. When **1** is treated with 4-nitrophenyl nitrile oxide, there is almost no cycloadducts produced, because the dimerization of this nitrile oxide occured so rapidly. In order to decrease the dimerization reaction, we have carried out the cycloaddition reactions by the dipolars **3** generated "*in situ*" with triethylamine from chloro-benzaldoxime [5,6]. In addition, dropping a solution of triethylamine in ethyl ether at an appropriate rate can also increase the yield of cycloadducts, and usually, the dropping process prolonged to 2 hours.

Scheme 1



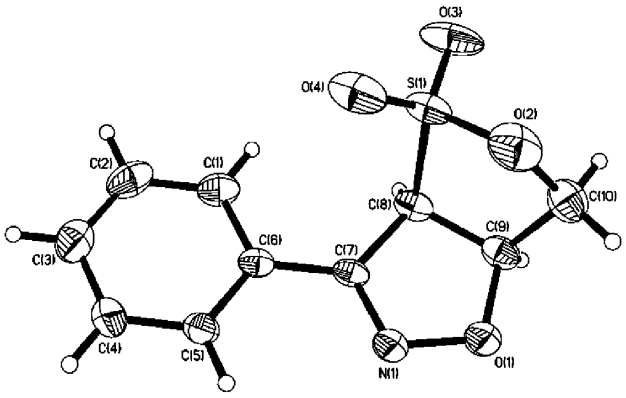
where: R= a.H; b.4-Cl; c.3-Cl; d.3-NO_2; e.2-Cl; f.2,4-Cl_2; g.4-CH_3; h.3-CH_3; i.4-F; j.3-Br; k.4-CH_3O; l.3,4-(OCH_2O)

Table 1

Cycloaddition Conditions and Yields of Cycloadducts **4**

Compounds	R	Reaction Time (h) [a]	Yield(%) [b]
4a	H	20	47
4b	4-Cl	29	80.4
4c	3-Cl	20	66.3
4d	3-NO_2	23	52.8
4e	2-Cl	25	51.3
4f	2,4-Cl_2	24	48.5
4g	4-CH_3	18	55.3
4h	3- CH_3	23	55.8
4I	4-F	12	75.9
4j	3-Br	22	51.2
4k	4-CH_3O	20	71.4
4l	3,4-(OCH_2O)	24	80

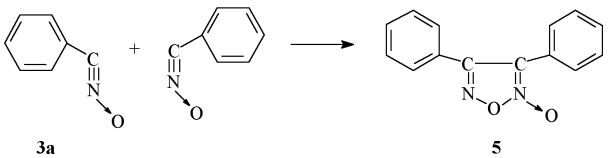
[a] The reaction proceeded at the room temperature; [b] Calcaulated on sultone **1**.



Selected bond distance (Å) and angles (°): C(6)–C(7) =1.454(4), C(7)-C(8) =1.512(4), C(8)-C(9) =1.523(5), C(9)-C(10) = 1.501(5), C(7)-N(1) =1.280(4), N(1)-O(1) =1.401(3), O(1)-C(9) =1.459(4), C(8)-S(1) =1.804(3), S(1)-O(2) =1.577(3), O(2)-C(10) =1.458(5); C(6)-C(7)-C(8) =126.2(3), C(7)-C(8)-C(9) =102.1(3), C(8)-C(9)-C(10) =109.2(3), C(6)-C(7)-N(1) =121.2(3), N(1)-O(1)-C(9) =110.1(2), C(9)-C(8)-S(1) =103.8(2), C(7)-C(8)-S(1)=112.5(2)

Figure 1. X-ray structure of compound **4a**.

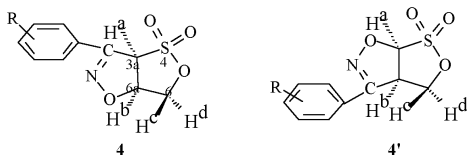
Scheme 2



Confirmation of the Cycloaddition Direction.

The reaction of **1** with nitrile oxides afforded only one regioisomeric adduct (structure **4**, not structure **4'** in Scheme 3). The structural assignment of the cycloadducts **4** was corroborated using proton nmr data. The ^{1}H NMR spectra of **4** showed that the chemical shift of H^b, which appeared as double doublet, resonates farther down field than that of H^a. This shows that the carbon bonded to H^b is connected to the oxygen atom of the nitrile oxide (structure **4** in Scheme 3). Owing to paramagnetic shift caused by the adjacent oxygen atom, the resonance corresponding to H^b appears at a lower field than that of H^a. All of the cycloadducts show large J_{ab} values (8.69-9.35 Hz) consistent with their *cis*-orientation [7,8]. No exception to the rigid *cis*-stereospecificity of the addition was observed. The dihedral angle between the C-H bonds corresponding to H^b and H^c is almost 90°, hence coupling is not observed between H^b and H^c.

Scheme 3



To further ascertain the configuration of **4**, a single-crystal X-ray diffraction study was performed on **4a**. The crystal was grown from toluene and petroleum ether (1:2), and is shown in Figure 1. Crystallographic analysis shows that the nitrile oxide carbon is bonded to the unsaturated carbon connected to the $–SO_3$ group, while the oxygen of nitrile oxide is bonded to the other unsaturated carbon of the sultone. This shows that the cycloaddition reaction between substituted benzonitrile oxide and prop-1-ene-1,3 sultone **1** takes place with high regioselectivity. The products are consistent with the regiochemistry reported for cycloaddition of benzonitrile oxides to α,β-unsaturated lactones [9]. This *cis*-stereospecificity and regiospecificity is best explained by a concerted process [9].

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting-point apparatus. IR spectra were recorded on a Bruker EQUINOX55 spectrometer. ^{1}H NMR spectra were determined with a Bruker AC-P200 in $CDCl_3$. ^{13}C NMR were determined with a Bruker AC-P200 in $(CD_3)_2CO$ solution. Elemental Analyses were performed on Yanaco Chn Cor Der MF-3 apparatus. X-ray reflection from compound **4a** was measured on the Bruker Smart 1000 single-crystal diffractometer.

Various substituted benzonitrile oxides **3** have been widely employed as 1,3-dipoles. There are several methods for their preparation, dehydrohalogenation of the corresponding hydroximic acid halide with base is the more usual method [10,6]. Cycloaddtion reactions were carried out at room temperature with an excess of dipole **3(a-l)** generated "*in situ*" with triethylamine from chloro-benzaldoxime [6].

Preparation of Prop-1-ene-1,3-sultone.

Among numerous synthetic methods [1,11-12], two routes attracted our attention. Of those, we repeated and improved on two methods (A and B).

Method A [1].

To a boiling solution of allyl chloride (20 g, 261 mmol) in 95% EtOH (100 mL) 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). The mixture was then allowed to continue refluxing 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 with 95% EtOH, resulting in 13.5 g of sodium prop-2-ene sulfonate (yield 75%); mp 239-241 °C. To a solution of sodium prop-2-ene sulfonate (5.5 g, 38.19 mmol) in water (22 mL) was added Br_2 (2.06 mL) dropwise. The solution was then stirred for 2 h at r.t. A very little amount of Na_2SO_3 was added to decompose the excess 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 one 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 followed by

Table 2

Physical and Spectral Data of New Compounds **4**

Products [a]	Mp(°) [b]	IR (cm^{-1}), (KBr)	^{1}H NMR (200 MHz), δ	^{13}C NMR (200 MHz), δ
4a	145-147	1637, 1558, 1347, 1157	7.8-7.4(5H, m), 5.74 (1H, dd, *J* 8.87, *J* 3.71 Hz), 5.16 (1H, d, *J* 8.87 Hz), 4.76 (1H, d, *J* -11.05 Hz), 4.64 (1H, dd, *J*=3.71, *J*= -11.05 Hz)	152.6, 130.9, 128.8, 127.9, 126.7, 86.8, 72.3, 67.3
4b	211-212	1597, 1563, 1346, 1156	7.66 (2H, d, *J* 8.44 Hz), 7.43 (2H, d, *J* 8.44 Hz), 5.77 (1H, dd, *J* 9.13, *J* 3.22 Hz), 5.12 (1H, d, *J* 9.13 Hz), 4.76 (1H, d, *J* -11.05 Hz,), 4.64 (1H, dd, *J* 3.22, *J* -11.05 Hz)	151.6, 137.0, 129.7, 127.1, 87.4, 72.4, 67.0
4c	168-169	1587, 1558, 1349, 1161	7.24-7.77 (4H, m), 5.75 (1H, dd, *J* 9.06, *J* 3.08 Hz), 5.12 (1H, d, *J* 9.06 Hz), 4.79 (1H, d, *J* -11.2 Hz), 4.64 (1H, dd, *J* 3.08, *J* -11.2 Hz)	151.8, 135.2, 131.5, 130.3, 127.5, 126.6 , 87.5, 72.5, 66.9
4d	175-177	1610, 1560, 1348, 1179	7.36-8.62 (4H, m), 5.87 (1H, dd, *J* 9.14, *J* 3.13 Hz), 5.22 (1H, d, *J* 9.14 Hz), 4.83 (1H, d, *J* -11.31 Hz), 4.64 (1H, dd, *J* 3.13 , *J* -11.31 Hz)	151.5, 139.5, 133.9, 131.4, 125.9, 124.4, 122.4, 87.9, 73.8, 66.8
4e	140-142	1586, 1560, 1363, 1157	7.24-7.73 (4H, m), 5.81 (1H, dd, *J* 8.69, *J* 3.08 Hz), 5.72 (1H, d, *J* 8.69 Hz), 4.76 (1H, d, *J* -11.2 Hz), 4.58 (1H, dd, *J* 3.08, *J* -11.2 Hz)	150.7, 133.1, 132.8, 132.2, 131.5, 128.2, 126.9, 87.1, 72.6, 68.3
4f	137-138	1588, 1562, 1366, 1159	7.24-7.70 (3H, m), 5.8 (1H, dd, *J* 9.11, *J* 3.15 Hz), 5.66 (1H, d, *J* 9.11 Hz), 4.79 (1H, d, *J* -11.1 Hz), 4.6 (1H, dd, *J* 3.15, *J* -11.1 Hz)	149.9, 137.4, 134.1, 133.3, 131.1, 128.6, 125.9, 87.2, 72.6, 68.1
4g	185-186	1610, 1561, 1373, 1159	7.61 (2H, d, *J* 8.17 Hz), 7.25 (2H, d, *J* 5.57 Hz), 5.74 (1H, dd, *J* 9.09, *J* 3.13 Hz), 5.13 (1H, d, *J* 9.09 Hz), 4.73 (1H, d, *J* -11.3 Hz), 4.61 (1H, dd, *J* 3.13, *J* -11.3 Hz), 2.37 (3H, s)	152.2, 142.0, 130.3, 127.9, 125.4, 86.9, 72.2, 67.3, 21.3
4h	158-159	1607, 1558, 1368, 1156	7.23-7.55 (4H, m), 5.70 (1H, dd, *J* 9.24, *J* 3.25 Hz), 5.14 (1H, d, *J* 9.24 Hz), 4.74 (1H, d, *J* -11.1 Hz), 4.62 (1H, dd, *J* 3.25 Hz, *J* -11.1 Hz), 2.37 (3H, s)	152.4, 139.5, 132.3, 129.6, 128.3, 125.3 86.9, 72.3, 67.3, 21.2
4i	211-212	1602, 1560, 1349, 1158	7.68-7.7 (4H, dd), 5.74 (1H, dd, *J* 9.11, *J* 3.13 Hz), 5.13 (1H, d, *J* 9.11 Hz), 4.81 (1H, d, *J* -11.1 Hz), 4.64 (1H, dd, *J* 3.13, *J* -11.1 Hz)	151.4, 162.3, 130.5, 130.3, 124.7, 117.0, 116.6, 87.2, 72.4, 67.3
4j	161-163	1588, 1554, 1348, 1160	7.24-7.93 (4H, m), 5.78 (1H, dd, *J* 9.35, *J* 3.27 Hz), 5.12 (1H, d, *J* 9.35 Hz), 4.78 (1H, d, *J* -11.2 Hz), 4.63 (1H, dd, *J* 3.27, *J* -11.2 Hz)	151.3, 134.4, 131.8, 130.4, 127.0, 123.2, 87.5, 72.5, 66.8
4k	186-187	1608, 1557, 1345, 1160	7.66 (2H, d, *J* 8.7 Hz), 6.95 (2H, d, *J* 8.7 Hz), 5.71 (1H, dd, *J* 9.26, *J* 3.18 Hz), 5.12 (1H, d, *J* 9.26 Hz), 4.76 (1H, d, *J* -10.99 Hz,), 4.60 (1H, dd, *J* 3.18, *J* -10.99 Hz), 3.85 (3H, s).	151.8, 162.6, 129.7, 120.1, 115.2, 86.7, 72.2, 67.5, 55.8
4l	204-205	1611, 1558, 1345, 1160	6.80-7.31 (3H, m), 6.02 (2H, s), 5.74 (1H, dd, *J* 8.88, *J* 3.34 Hz), 5.08 (1H, d, *J* 8.88 Hz,), 4.75 (1H, d, *J* -11.08 Hz), 4.59 (1H, dd, *J* 3.34, *J* -11.08 Hz	151.9, 150.8, 149.2, 123.5, 122.1, 109.2, 107.1, 102.8, 86.9, 72.2, 67.5

[a] Satisfactory elemental analyses obtained: C ± 0.28; H ± 0.26; N ± 0.26; [b] Solvents for recrystallization: **4a**: toluene-PE (1:2); **4b**, **4c**, **4d**, **4i**, **4j**, **4k** and **4l**: toluene; **4e**, **4f**, **4g**, **4h**: PE-EtOAc (3:1).

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 chloroform gave **1** as needle crystals, mp 81-82 °C.

Method B [12].

A mixture of $K_2S_2O_5$ (28 g), H_2O (200 mL) and 3.98 *N* KOH (61mL) was placed in a 500 mL beaker. With stirring, an additional amount of $K_2S_2O_5$ (60 g) was added to the mixture. Thus forming a solution of $KHSO_3$ and K_2SO_3. 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 dropping process, air was bubbled into the reaction bottle at 30-35 °C, and the reaction mixture was stirred for 2 h at this temperature. Then, aqueous 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 by 70% ethanol (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 conc. HCl (80 mL), then with EtOH (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 1-hydroxyprop-2-pene-3-sulfonic acid. The crude 1-hydroxyprop-2-pene-3-sulfonic acid was heated at 130-145 °C in oil bath and then distilled *in vacuo* to give **1** (12 g), b.p. 118 °C/14 Pa, mp 83-84 °C.

General Procedure for Preparation **4a-l** (Scheme 1).

To a mixture of prop-1-ene-1,3-sultone **1** (0.12 g, 1 mmol) in 4 mL CH_2Cl_2 and substituted chloro-benzaldoxime **2** (1.2 mmol) in 10 mL ethyl ether was added dropwise a solution of triethylamine (0.121 g, 1.2 mmol) in ethyl ether (5 mL). The reaction mixture was stirred at room temperature for the time indicated in Table 1. The triethylamine hydrochloride was filtered off and the solvent was concentrated. The residue was purified by column

chromatography, then by recrystallization from suitable solvent (Table 2) to give the title compound **4**. The physical and Spectroscopic Data of compounds **4** are shown in Table 2.

Crystallographic Data for 4a [13].

$C_{10}H_9NO_4S$: Mr = 239.25, T = 293 ± 2 K, monoclinic, P2(1)/C, a = 5.223(4)Å, b = 16.949(12)Å, c = 11.857(9)Å, α = 90°C, β = 102.256(12) °C, γ = 90°C, μ = 0.313 mm^{-1}, V = 1025.7(13) $Å^3$, Z = 4, Dx=1.549 $Mg.m^{-3}$, F (000) = 496. Crystal size: 0.45×0.15×0.06 mm, θ range for data collection: 2.13 to 25.02. Full Matrix Least Squares on F^2 for refinement.

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