A New and Efficient Method for the Generation of Sulfene (Thioformaldehyde Dioxide)

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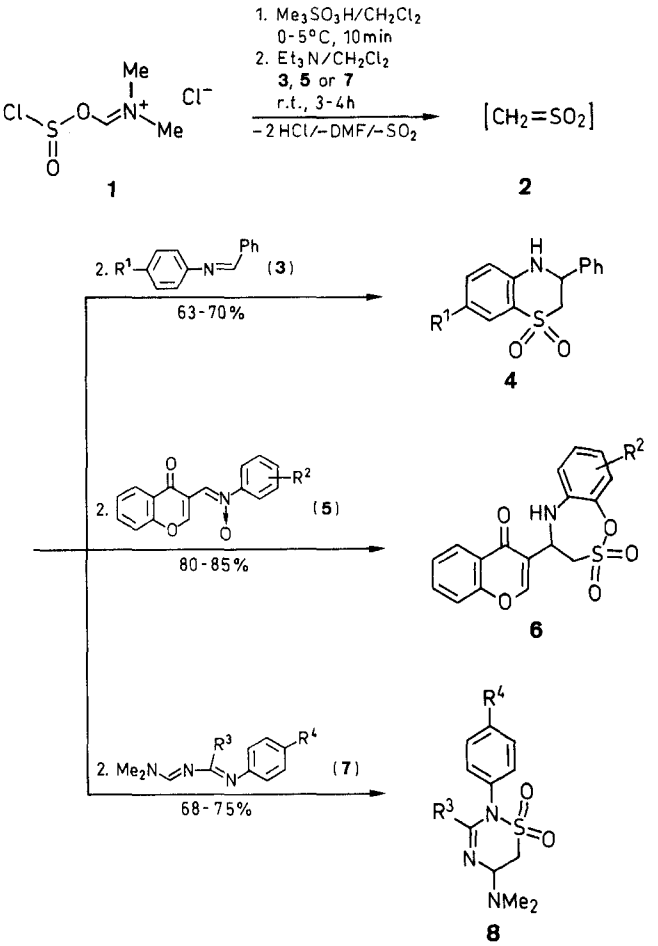
Chlorosulfonylmethylene(dimethyl)ammonium chloride (**1**) is a highly reactive dehydrating agent which provides an efficient entry to 3,4-dihydro-3-phenyl-2*H*-benzothiazine 1,1-dioxides **4**, 4,5-dihydro-4-(4-oxo-4*H*-1-benzopyran-3-yl)-3*H*-1,2,5-benzoxathiazepine 2,2-dioxides **6** and 2-aryl-5-dimethylamino-5,6-dihydro-2*H*-1,2,4-thiadiazine 1,1-dioxides **8** via cycloaddition reactions of imines **3**, nitrones **5** and 1,3-diazabutadiene derivatives **7** with in situ generated sulfene directly from the corresponding sulfonic acids. The seven-membered azasultone structural assignments are supported by spectroscopic data.

Heterocumulenes such as isocyanates, isothiocyanates, ketenes and similar compounds continue to attract increasing interest as reactive synthetic building blocks. Sulfenes, the *S,S*-dioxides of thioketones which are formally the inner anhydride of sulfonic acids[1] are also counted among the classical heterocumulenes on the grounds of their reaction behaviour, particularly at the C=S double bond. Sulfene (thioformaldehyde dioxide, $CH_2=SO_2$) was proposed by Hesse and Reichold[2] as formed by the interaction of diazomethane with sulfur dioxide. Later Stork and Borowitz[3] and independently Opitz and Adolph[4] have formed four-membered ring sulfones by interaction of enamines with methanesulfonyl chloride in the presence of a trialkylamine, presumably through a sulfene intermediate. Recently, Block and Aslam[5] have produced sulfene by treatment of (trimethylsilyl)methanesulfonyl chloride with cesium fluoride in acetonitrile, but this method has its own merit as well as limitations. Cycloaddition reactions of sulfene to the carbon–nitrogen double bond have been studied by Staudinger[6] and by Singh[7] et al. Staudinger reported that the reaction of diphenylsulfene (generated from diphenyldiazomethane and sulfur dioxide) with benzalaniline gave a four-membered cyclic compound, Tsuge[8] obtained [2+2] and/or [2+4] cycloadducts by the addition of benzoylsulfene to imines and Singh et al. reported the formation of six-membered 1,4-benzothiazines.[7]

Here we wish to report a new and efficient one-pot method for the in situ generation of sulfene directly from the corresponding sulfonic acid using the less explored [(chlorosulfinyloxy)methylene]dimethylammonium chloride[9] (**1**) as the dehydrating agent, without the use of an acid chloride. This method appears to be very convenient and facile as a large excess of cyclodehydrating agent is not required, it also involves mild reaction conditions and a simple workup affording the products in high yield.

Generation of the sulfene **2** and its cycloaddition reactions with imines **3** were carried out by the dropwise addition of a dichloromethane solution of dehydrating agent **1** to a dichloromethane solution of methanesulfonic acid, followed by *N*-benzylideneaniline (**3a**) and dry triethylamine. The product could be purified by preparative TLC to obtain **4a** as a white crystalline solid, mp 184–186°C in 70% yield. The IR spectra of this product show sharp bands at ν = 3150, 1310–1365 and 1145–1170 cm^{-1} indicating the presence of an an associated –NH and a sulfone group, respectively. This reaction did not yield [2+2] cycloadducts, instead 1,4-benzothiazines **4** were obtained perhaps through the rearrangement of the anticipated cycloadducts (Scheme). The structural assignment for **4** is fully established by comparing the physical and spectroscopic results with an authentic sample.[7]



3, 4	R^1	5	R^2	6	R^2	7, 8	R^3	R^4
a	H	a	4-Me	a	8-Me	a	Ph	H
b	OMe	b	4-OMe	b	8-OMe	b	Ph	4-CH_3
c	NO_2	c	4-Cl	c	8-Cl	c	Ph	4-Cl
d	Cl	d	2-OMe	d	6-OMe	d	SMe	H
		e	H	e	H	e	SMe	4-Cl

Scheme

Then we turned our attention to effect the cycloaddition of sulfene with a 1,3-dipolar system namely *N*-[4-oxo-4*H*-1-benzopyran-3-ylmethylene]arylamine *N*-oxides. Though sulfene readily undergoes [2+2] or [2+4] cy-

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cloadditions, there are only two known examples of a [2+3] cycloaddition.[10,11] We selected 4-oxo-4*H*-1-benzopyranyl-substituted nitrones **5**, as bifunctional substrates, where the sulfene could react either at the 4*H*-1-benzopyran-4-one double bond or at the nitrone function. Moreover, 4*H*-1-benzopyran-4-ones bearing electron-withdrawing substituents at C-3 are capable of reacting as a Michael acceptor[12] or a heterodiene[13] and undergo various rearrangements on treatment with nucleophiles.[14] However, their use as 2π-components in [4+2] cycloadditions has received surprisingly little attention.[15] Cycloaddition reactions were realized by the dropwise addition of a dichloromethane solution of reagent **1** to a stirred dichloromethane solution of methanesulfonic acid **2** at 0°C, followed by *N*-[4-oxo-4*H*-1-benzopyran-3-yl-methylene]-4-methylphenylamine] oxide (**5a**)[16] and dry triethylamine. After usual workup the product could be purified by preparative TLC to give the 4*H*-1-benzopyran-4-one-liked azasultone **6a** as a light yellow crystalline solid mp 172–173°C in 85% yield. The structural assignment for **6** is fully established on the basis of elemental analysis and spectroscopic results. The mass spectrum of **6a** gave M^+ at $m/z = 357$. The ^{1}H NMR spectrum exhibits a singlet at $\delta = 2.29$(3 H), a doublet at $\delta = 3.76$ (1 H), two double doublets centered at $\delta = 3.76$ and $\delta = 4.98$ (2 H), a multiplet at $\delta = 4.25$ (1 H) and a complex multiplet at $\delta = 6.75$–8.25 (8 H). The diagnostic azomethine proton which was present in the nitrone **5a** at $\delta = 8.85$ was absent, whilst the appearance of this proton at $\delta = 4.25$ as a multiplet showed that cycloaddition had occurred at the nitrone function. The IR spectra of this product shows sharp bands at $\nu = 1375$, 1170 and 3300 cm^{-1} indicating the presence of a sulfone group and an associated –NH group, respectively. From these spectroscopic results the seven-membered azasultone structure **6a** was confirmed. Similarly, other azasultones **6b–e** were prepared and their characteristics are recorded in the experimental section. When the same reaction was performed by using methanesulfonyl chloride/triethylamine as the dehydrohalogenating agent for the generation of sulfene and its subsequent cycloaddition reaction with nitrones **5**, the corresponding azasultones **6** were obtained in poor yield. Reaction between the nitrone **5a** and methanesulfonyl chloride was carried out by dissolving it in equimolar quantities in chloroform and stirring the mixture under nitrogen for 5 hours; usual workup gave **6a** in 25% yield. The structural assignment of this product was confirmed by comparing with the azasultone **6a**, prepared directly from methanesulfonic acid.

Then, we selected 1,3-diazabutadienes **7** (which have not received much attention compared to their 1,2- and 1,4-diazabutadiene analogues).[17] Also, there are conflicting reports in the case of the reaction of ketenes with 1,3-diazabutadienes.[18] The reaction was carried out by dropwise addition of a dichloromethane solution of dehydrating agent **1** to a dichloromethane solution of methanesulfonic acid followed by 5-methyl-1,2-diphenyl-1,3,5-triaza-1,3-hexadiene (**7a**) and dry triethylamine (Scheme). The product was purified by preparative TLC to give previously known 2-phenyl-5-dimethylamino-5,6-dihydro-2,3-diphenyl-2*H*-1,2,4-thiadiazine 1,1-dioxide (**8a**) as a crystalline solid mp 121–122°C in 75% yield (Lit.[19] mp 121–122°C). The structure of **8a** was confirmed by comparing the physical and spectroscopic data with an authentic sample.[18] Similarly, other thiadiazine 1,1-dioxides **8b–e** were prepared and their characteristics are recorded in the experimental section.

In conclusion, the present report offers a new alternative and efficient method for the generation of sulfene[20] and the preparation of various 1,4-benzothiazines, benzoxathiazepine 2,2-dioxides and thiadiazine 1,1-dioxides, wherein workup is simpler, reaction conditions are mild and afford virtually pure products in excellent yields.

Melting points were determined using a Büchi melting point apparatus and are uncorrected. The IR spectra were recorded in KBr discs on a Perkin-Elmer 237B IR spectrophotometer. Microanalyses were performed on a Perkin-Elmer 240C analyser. The ^{1}H NMR spectra were recorded on Bruker 270 MHz and 90 MHz spectrometers using TMS as internal standard. The imines described in this report were prepared from freshly distilled primary amines and aldehydes through known methods and their melting points agree with those recorded in the literature. All nitrones **5** used were freshly recrystallized before use and their properties checked by elemental analyses and spectroscopic data. Solvents were dried according to literature procedures.

Chlorosulfonylmethylene(dimethyl)ammonium Chloride (1)
In a 25 mL pressure equalising funnel, dry benzene (10 mL) DMF (2 mL, 20.4 mmol) and $SOCl_2$ (1.6 mL, 22 mmol) were added consecutively. After 5 min two phases were separated and the reagent (lower layer) was used directly for the cyclodehydration reactions.

3,4-Dihydro-3-phenyl-2*H*-benzothiazine 1,1-Dioxide (4a); Typical Procedure:
To a solution of $MeSO_3H$ (0.96 g, 10 mmol) in abs. CH_2Cl_2 (20 mL) was added dropwise at 0–5°C, freshly prepared reagent **1** (2.88 g, 15 mmol). After stirring at this temperature for 10 min, freshly prepared *N*-benzylideneaniline (**3a**) (1.81 g, 10 mmol) was added dropwise followed by dry Et_3N (2.02 g, 20 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was then stirred at r.t. for 4 h. On completion, the mixture was quenched with H_2O (15 mL), extracted with CH_2Cl_2 (2 × 40 mL). The organic extract was washed with cold H_2O (2 × 30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to furnish a residue which was purified by preparative TLC (silica gel; $CHCl_3$). The product 1,4-benzothiazine **4a** was obtained as a white crystalline solid; mp 184–186°C (Lit.[7] mp 184°C), yield: 1.81 g (70%).

3,4-Dihydro-7-methoxy-3-phenyl-2H-benzothiazine 1,1-Dioxide (**4b**): yield: 1.90 g (66%), mp 212–214°C (Lit.[7] mp 214°C).

3,4-Dihydro-7-nitro-3-phenyl-2H-benzothiazine 1,1-Dioxide (**4c**): yield: 2.04 g (65%), mp 113–114°C (Lit.[7] mp 113°C)

7-Chloro-3,4-dihydro-3-phenyl-2H-benzothiazine 1,1-Dioxide (**4d**): yield: 1.90 g (63%), mp 133–135°C (Lit.[7] mp 135°C).

4,5-Dihydro-8-methyl-4-(4-oxo-4*H*-1-benzopyran-3-yl)-3*H*-1,2,5-benzoxathiazepine 2,2-Dioxides (6a); Typical Procedure:
To a solution of $MeSO_3H$ (0.96 g, 10 mmol) in abs. CH_2Cl_2 (20 mL) was added dropwise, freshly prepared reagent **1** (2.88 g, 15 mmol) at 0°C. The reaction mixture was stirred at this temperature for 10 min and then nitrone **5a** (R^2 = 4-Me, 2.79 g, 10 mmol) was added dropwise followed by dry Et_3N (2.02 g, 20 mmol) in CH_2Cl_2 (10 mL). This mixture is then further stirred at r.t. for 3 h (monitored vide TLC). On completion, the mixture was quenched with cold H_2O (15 mL), extracted with CH_2Cl_2 (2 × 40 mL) and washed with H_2O (2 × 30 mL). The extract was then dried (Na_2SO_4) and evaporated under reduced pressure to furnish a solid material which was recrystallized from MeOH. The product **6a** was obtained as a light yellow crystalline solid; yield: 3.03 g (85%) mp 172–173°C.

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$C_{18}H_{15}NO_5S$ (357.3) calc. C 60.50 H 4.20 found 60.63 4.29

MS: $m/z = 357$ (M^+).

^1H NMR (270 MHz, $CDCl_3$): $\delta = 2.29$ (s, 3 H, CH_3), 3.76 (dd, 1 H), 4.08 (d, 1 H), 4.25 (m, 1 H), 4.98 (dd, 1 H), 6.75–8.25 (m, 8 H).

4,5-Dihydro-8-methoxy-4-(4-oxo-4H-1-benzopyran-3-yl)-3H-1,2,5-benzoxathiazepine 2,2-Dioxide **(6b)**:

yield: 2.98 g (80%); mp 162–163 °C.

$C_{18}H_{15}NO_6S$ (373.3) calc. C 57.90 H 4.02 found 58.05 4.16

MS: $m/z = 373$ (M^+).

^1H NMR (270 MHz, $CDCl_3$): $\delta = 3.74$ (dd, 1 H), 3.82 (s, 3 H, OCH_3), 4.10 (d, 1 H), 4.27 (m, 1 H), 5.04 (dd, 1 H), 6.72–8.20 (m, 8 H).

8-Chloro-4,5-dihydro-4-(4-oxo-4H-1-benzopyran-3-yl)-3H-1,2,5-benzoxathiazepine 2,2-Dioxide **(6c)**:

yield: 3.12 g (83%); mp 205–206 °C.

$C_{17}H_{12}ClNO_5S$ (377.7) calc. C 54.11 H 3.18 found 54.21 3.23

MS: $m/z = 377$ (M^+).

^1H NMR (270 MHz, $CDCl_3$): $\delta = 3.76$ (dd, 1 H), 4.06 (d, 1 H, 4.28 (m, 1 H), 5.02 (dd, 1 H), 6.70–8.10 (m, 8 H).

4,5-Dihydro-6-methyl-4-(4-oxo-4H-1-benzopyran-3-yl)-3H-1,2,5-benzoxathiazepine 2,2-Dioxide **(6d)**:

yield: 2.92 g (82%); mp 166–167 °C.

$C_{18}H_{15}NO_5S$ (357.3) calc. C 60.50 H 4.20 found 60.61 4.31

MS: $m/z = 357$ (M^+).

^1H NMR (270 MHz, $CDCl_3$): $\delta = 2.30$ (s, 3 H, CH_3), 3.75 (dd, 1 H), 4.03 (d, 1 H), 4.24 (m, 1 H), 4.96 (dd, 1 H), 6.70–8.22 (m, 8 H).

4,5-Dihydro-4-(4-oxo-4H-1-benzopyran-3-yl)-3H-1,2,5-benzoxathiazepine 2,2-Dioxide **(6e)**:

yield: 2.74 g (80%); mp 195–196 °C.

$C_{17}H_{13}NO_5S$ (343.3) calc. C 59.77 H 3.78 found 59.86 3.65

MS: $m/z = 343$ (M^+).

^1H NMR (270 MHz, $CDCl_3$): $\delta = 3.78$ (dd, 1 H), 4.10 (d, 1 H), 4.26 (m, 1 H), 5.10 (dd, 1 H), 6.72–8.23 (m, 9 H).

Reaction Between Nitrone 5 and Methanesulfonyl Chloride:

Nitrone **5a** (2.79 g, 10 mmol) and $MeSO_2Cl$ (1.14 g, 10 mmol) were added to anhydr. $CHCl_3$ (15 mL) in a 50 mL flask at −10 °C, under N_2 atmosphere. To this mixture dry Et_3N (2.02 g, 20 mmol) in $CHCl_3$ (10 mL) was added dropwise with constant stirring. After 5 h, $CHCl_3$ was removed and the residue was treated with benzene. The precipitated hydrochloride was filtered and the solution was concentrated under reduced pressure and chromatographed using $CHCl_3$ as eluent. Yield 0.89 g (25%).

5-Dimethylamino-5,6-dihydro-2,3-diphenyl-2*H*-1,2,4-thiadiazine 1,1-Dioxides (8a); Typical Procedure:

To a solution of $MeSO_3H$ (0.96 g, 10 mmol) in abs. CH_2Cl_2 (25 mL) was added at 0–5 °C, freshly prepared **1** (2.88 g, 15 mmol), after stirring at this temperature for 10 min, freshly prepared **7a** (2.51 g, 10 mmol) in CH_2Cl_2 (10 mL) was added dropwise followed by dry Et_3N (1.52 g, 15 mmol) in CH_2Cl_2 (15 mL). The resulting mixture was then stirred at r. t. for 4 h. Workup as above gave **8a**; yield: 2.46 g (75%) yield, mp 121–122 °C (Lit.[19] mp 121–122 °C).

5-Dimethylamino-5,6-dihydro-2-(4-methylphenyl)-3-phenyl-2H-1,2,4-thiadiazine 1,1-Dioxide **(8b)**:

yield: 2.40 g (70%); mp 110–111 °C (Lit.[19] mp 111–112 °C).

2-(4-Chlorophenyl)-5-dimethylamino-5,6-dihydro-3-phenyl-2H-1,2,4-thidiazine 1,1-Dioxide **(8c)**: yield: 2.46 g (68%); mp 114–115 °C (Lit.[19] mp 115–116 °C).

5-Dimethylamino-5,6-dihydro-3-(methylthio)-2-phenyl-2H-1,2,4-thiadiazine 1,1-Dioxide **(8d)**:

yield: 2.25 g (75%); mp 110–111 °C (Lit.[19] mp 111–112 °C).

2-(4-Chlorophenyl)-5-dimethylamino-5,6-dihydro-3-(methylthio)-2H-1,2,4-thiadiazine 1,1-Dioxide **(8e)**: yield: 2.14 g (72%); mp 109–110 °C (Lit.[19] mp 109–110 °C).

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