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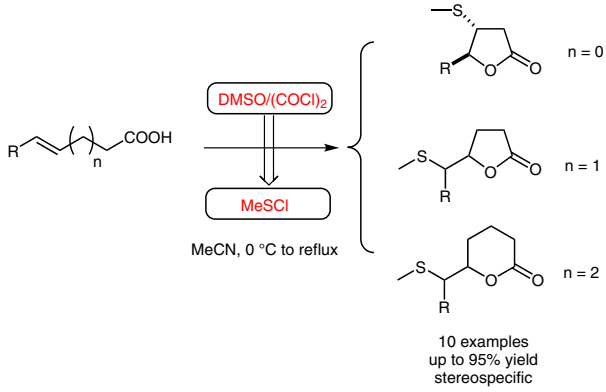
A Facile Method for the Sulfenyllactonization of Alkenoic Acids Using Dimethyl Sulfoxide Activated by Oxalyl Chloride

Ting Zhang[1]
Yifeng Dai[1]
Siwei Cheng
Yongguo Liu
Shaoxiang Yang
Baoguo Sun
Hongyu Tian*

Beijing Advanced Innovation Center for Food Nutrition and Human Health, Beijing Key Laboratory of Flavor Chemistry, Beijing Technology and Business University, Beijing, 100048, P. R. of China
tianhy@btbu.edu.cn



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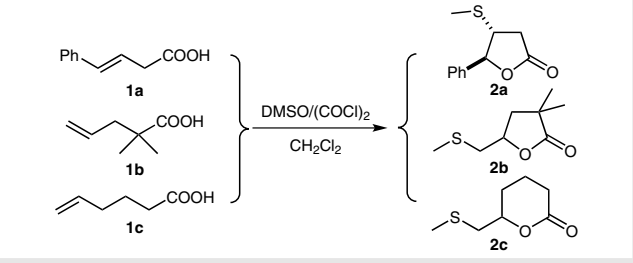
Abstract A simple approach has been developed for the sulfenyllactonization of alkenoic acids using dimethyl sulfoxide activated with oxalyl chloride, in which methanesulfenyl chloride is proposed as the intermediate.

Key words sulfenyllactonization, alkenoic acids, dimethyl sulfoxide, oxalyl chloride, methanesulfenyl chloride

Halolactonization of alkenoic acids has been well developed due to its importance and wide application in organic syntheses.[2] In contrast, sulfenyllactonization has been known to a much lesser extent with only a few examples of sulfenyllactonization having been reported so far. It was found that unsaturated acids were converted into sulfenyllactones by treatment with lead tetraacetate and disulfide in the presence of trifluoroacetic acid when Trost's group studied the hydroxysulfenylation of olefins.[3] Young et al. reported that sulfenyllactonization of alkenoic acids could be accomplished using sulfenyl chlorides derived from disulfides with complex multifunctional groups and chlorine.[4] Commercially available dimethyl(methylthio)sulfonium fluoroborate (DMTSF) was also reported to execute the sulfenyllactonization of unsaturated acids in moderate to high yields,[5] which was very straightforward, however, suffered from two major disadvantages: relatively long reaction times (1 day to 3 days) and the high price of DMTSF.

An unexpected product, 4-(methylthio)-5-methyldihydrofuran-2(3*H*)-one (a γ-butanolide) was generated when (*E*)-pent-3-enoic acid, synthesized in our laboratory, was transformed into its methyl ester by treatment with thionyl chloride in methanol. This was found to be the result of the reaction of (*E*)-pent-3-enoic acid with thionyl chloride and entrained dimethyl sulfoxide from the synthesis of (*E*)-pent-3-enoic acid, which was obtained by the Knoevenagel condensation of propanal with malonic acid in the presence of piperidinium acetate in DMSO.[6] It is well known that DMSO activated by various reagents, such as trifluoroacetic anhydride, sulfur trioxide/pyridine, thionyl chloride, and oxalyl chloride (especially known as the Swern oxidation), has been used extensively in the oxidation of primary and secondary alcohols, which is a very important and useful tool in synthetic chemistry.[7] It occurred to us that it should be a convenient approach to the sulfenyllactonization of alkenoic acids using DMSO/oxalyl chloride.

The use of three types of alkenoic acids was examined with the DMSO/$(COCl)_2$ reagent, including alk-3-enoic, alk-4-enoic, and alk-5-enoic acids (Scheme 1). The results are listed in Table 1.



Scheme 1 Sulfenyllactonization of alkenoic acids with DMSO/$(COCl)_2$

Initially, we thought that the sulfenyllactonization we observed accidently might follow the mechanism similar to that in the Swern oxidation. Therefore, a typical procedure for the Swern oxidation was initially adopted as follows: a solution of $(COCl)_2$ (1.5 equiv) in CH_2Cl_2 was added dropwise to a solution of DMSO (3.0 equiv) in CH_2Cl_2 at –65 °C and about 15 minutes after the addition, a solution of (*E*)-4-phenylbut-3-enoic acid (**1a**, 1 equiv) in CH_2Cl_2 was added, and the mixture stirred at –65 °C. The reaction was moni-

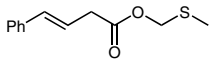
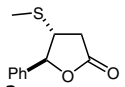
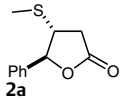
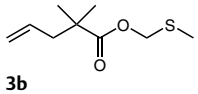
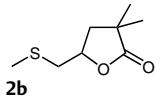
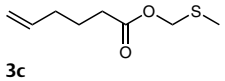
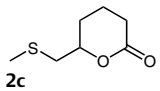
tored by ^{1}H NMR. Unfortunately, none of the desired product, 4-(methylthio)-5-phenyldihydrofuran-2(3*H*)-one (**2a**) was obtained, as expected, even after stirring for 24 hours, whereas the (methylthio)methyl ester **3a** was produced in high yield (90%) (entry 1). Then a reaction was tried at 0 °C. After stirring at 0 °C for 24 hours, the desired product **2a** was detected by ^{1}H NMR and the yield was about 11% based on the ratio of the product to the substrate in the ^{1}H NMR spectrum (entry 2). In contrast, no (methylthio)methyl ester **3a** was produced at 0 °C. Obviously, these results indicate that the reaction temperature has an important impact on sulfenyllactonization. Therefore, the reaction temperature was raised further to room temperature (about 26 °C), but with the addition temperature at 0 °C since oxalyl chloride reacts vigorously with DMSO at room temperature. The reaction was complete after about 15 hours and the desired product **2a** was obtained in 90% isolated yield (entry 3).

In our experiments, the effect of different ratios of substrate to reagent on the reaction was also investigated. Three molar ratios of 1:4:2, 1:3:1.5, and 1:2.4:1.2 (substrate/DMSO/oxalyl chloride) were examined. It was found that the former two levels gave similar results and the last level gave a relatively low yield. Hence the middle level, i.e. 1:3:1.5 (substrate/DMSO/oxalyl chloride) was adopted in the following experiments.

Based on these results from **1a**, an alk-4-enoic acid [2,2-dimethylpent-4-enoic acid (**1b**)] and an alk-5-enoic acid [hex-5-enoic acid (**1c**)] were examined. Both of them gave the corresponding (methylthio)methyl esters **3b** and **3c** in high yields by treatment with DMSO/oxalyl chloride at –65 °C (entries 4 and 6), whereas sulfenyllactones **2b** and **2c** were produced when the reactions were performed at room temperature (entry 5 and 7). The reaction with hex-5-enoic acid (**1c**) took longer (about 24 h) to go to completion, which might be attributed to the formation of the δ-lactone, 6-[(methylthio)methyl]tetrahydro-2*H*-pyran-2-one (**2c**), instead of γ-lactones **2a** and **2b** for substrates **1a** and **1b**.

In view of the relative long reaction times for the production of these sulfenyllactones, the procedure for the sulfenyllactonization was optimized further using **1b** as a model substrate. The results are listed in Table 2. Since we have observed that the reaction temperature had a significant effect on the formation of the sulfenyllactone, the reaction was attempted under reflux using CH_2Cl_2 as the solvent in order to shorten the reaction time. The result indicates that the reaction was faster under reflux than at room temperature (entries 1 and 2). Potassium carbonate was also added using acetonitrile as the solvent and 18-crown-6 as a phase-transfer catalyst in order to speed up reaction. However, the reaction time did not change much when the reaction was carried out at room temperature (entry 3). However, the reaction was found to be complete in 5 hours when the reaction mixture was heated to reflux without obvious loss of yield (entry 4). In order to identify the crucial factor affecting the reaction speed, high temperature, or potassium carbonate, or the combined action of both, one further reaction was carried out under reflux but without potassium carbonate, which gave similar results (entry 4 vs. 5). This indicates that the presence of potassium carbonate has a negligible effect on sulfenyllactonization, whereas high temperature is the crucial factor to guarantee a smooth reaction.

Table 1 Sulfenyllactonization of Alkenoic Acids with DMSO/$(COCl)_2$ in CH_2Cl_2

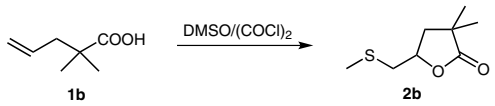
Entry	Substrate (temp, time)	Product	Yield (%)[a]
1	**1a** (–65 °C, 24 h)	 **3a**	90
2	**1a** (0 °C, 24 h)	 **2a**	11
3	**1a** (0 °C to r.t., 15 h)	 **2a**	90
4	**1b** (–65 °C, 24 h)	 **3b**	94
5	**1b** (0 °C to r.t., 18 h)	 **2b**	95
6	**1c** (–65 °C, 24 h)	 **3c**	91
7	**1c** (0 °C to r.t., 24 h)	 **2c**	91

[a] Isolated yields, except entry 2 (^{1}H NMR yield).

Sulfenyllactonizations of substrates **1a** and **1c** were also performed in acetonitrile under reflux without K_2CO_3. The reaction time for **1a** was shortened to about 3 hours, and the latter about 7 hours, whereas the yields were close to those at room temperature.

More alkenoic acids were examined in the sulfenyllactonization under the optimized reaction conditions (Table 3). Three alk-3-enoic acids, (*E*)-pent-3-enoic acid (**1d**), (*E*)-non-3-enoic acid (**1e**), and (*E*)-dodec-3-enoic acid (**1f**), were treated with the DMSO/$(COCl)_2$ reagent in acetonitrile under reflux to afford 5-alkyl-4-(methylthio)dihydrofuran-2(3*H*)-ones **2d–f** (entries 1–3). Four more alk-4-enoic acids **1g–j** were examined, which also produced γ-butanolides **2g–j** (entries 4–7). It usually took 3–4 hours to complete

Table 2 The Procedure Optimization for Sulfenyllactonization



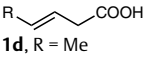
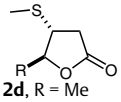
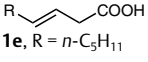
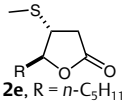
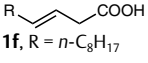
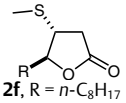
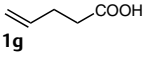
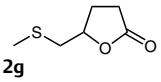
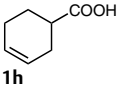
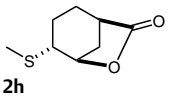
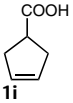
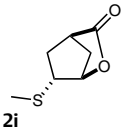
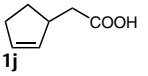
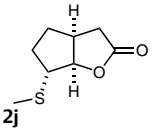
1b 2b

Entry	Conditions	Time (h)	Yield (%)[a]
1	CH_2Cl_2, r.t.	18	95
2	CH_2Cl_2, reflux	12	90
3	MeCN, K_2CO_3, 18-crown-6, r.t.	15	93
4	MeCN, K_2CO_3, 18-crown-6, reflux	5	88
5	MeCN, reflux	5	91

[a] Isolated yield.

the reactions and produced sulfenyllactones in more than 83% yield except substrates **1h** and **1i** with slightly lower yields.

Table 3 Sulfenyllactonization of Alkenoic Acids with DMSO/$(COCl)_2$ in MeCN

Entry	Substrate	Product	Yield (%)[a] (time)
1	 **1d**, R = Me	 **2d**, R = Me	85 (3 h)
2	 **1e**, R = *n*-C_5H_{11}	 **2e**, R = *n*-C_5H_{11}	84 (3 h)
3	 **1f**, R = *n*-C_8H_{17}	 **2f**, R = *n*-C_8H_{17}	88 (3 h)
4	 **1g**	 **2g**	89 (3 h)
5	 **1h**	 **2h**	78 (3.5 h)
6	 **1i**	 **2i**	76 (4 h)
7	 **1j**	 **2j**	83 (3.5 h)

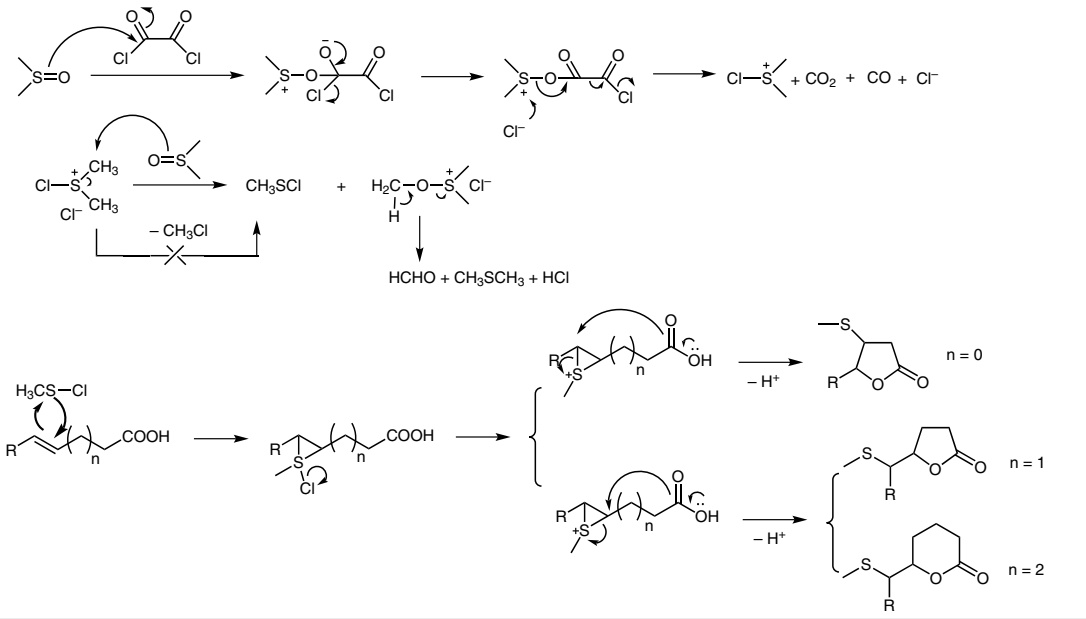
[a] Isolated yield.

Most sulfenyllactones obtained contain at least two chiral carbons except **2b**, **2c**, and **2g**. The NMR spectra and GC analysis indicated that single diastereomers were obtained for those sulfenyllactones with at least two chiral carbons. In order to determine the relative configuration of the products, a series of NOE experiments were carried out. For 5-methyl-4-(methylthio)dihydrofuran-2(3*H*)-one (**2d**), irradiation of the signal at δ = 4.40 (C*H*CH_3) gave a small enhancement of the signal at δ = 2.14 (SCH_3), and irradiation of the signal at δ = 3.06 (C*H*SCH_3) gave a small enhancement of the signal at δ = 1.46 ($CHCH_3$). These results indicate that H-C5 was *cis* to the methylthio group (SCH_3) attached to C4 and H-C4 *cis* to the methyl group attached to C5, i.e. the methylthio group (SCH_3) attached to C4 was *trans* to the methyl group attached to C5. Similarly, for all other products, irradiation of the signal of C*H* attached to ester group gave a small enhancement of the signal of the methyl of the methylthio group without exception. These results indicate that methylthio group and ester group introduced to double bond of alkenoic acids through sulfenyllactonization were located *trans*.

Possible reaction pathways for sulfenyllactonization of alkenoic acids with DMSO/oxalyl chloride are depicted in Scheme 2. At first, DMSO reacted with oxalyl chloride to produce the chlorodimethylsulfonium salt, which is the same intermediate as the Swern oxidation. Methanesulfenyl chloride, the real species for sulfenyllactonization of alkenoic acids, is formed via DMSO attack on the chlorosulfonium intermediate. The electrophilic additions of methanesulfenyl chloride to the double bonds of alkenoic acids produced thiiranium ions, which were then attacked by the carboxyl group via an intramolecular nucleophilic substitution to afford the corresponding sulfenyllactones.

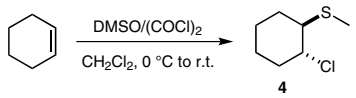
The speculation of the intervention of methanesulfenyl chloride was originally based on the reactions of (*E*)-4-phenylbut-3-enoic acids (**1a**) with DMSO/oxalyl chloride, which produced *trans*-4-(methylthio)-5-phenyldihydrofuran-2(3*H*)-one (**2a**) exclusively (Table 1, entry 1). In addition, all the sulfenyllactones with multiple chiral centers were produced as a single diastereomer. These results implied that sulfenyllactonization occurred in a stereospecific way. The intermediates thiiranium ions derived from the electrophilic additions of methanesulfenyl chloride to the double bonds of alkenoic acids gives a perfect explanation for the observed stereospecific phenomena.

In order to prove the intervention of methanesulfenyl chloride generated in situ, cyclohexene was treated following the same protocol as the above alkenoic acids (Scheme 3). *trans*-1-Chloro-2-(methylthio)cyclohexane (**4**) was obtained as expected in 89% yield, the spectroscopic data of which were consistent with those of the product prepared by the reaction of *trans*-2-(methylthio)cyclohexanol with thionyl chloride in the reference.[8] This product was also found to be prepared by the reaction of cyclohexene with Me_2S/SO_2Cl_2/DMSO reported by Bellesia et al.[9] In their work,



Scheme 2 Proposed reaction mechanism for sulfenyllactonization of alkenoic acids with DMSO/oxalyl chloride

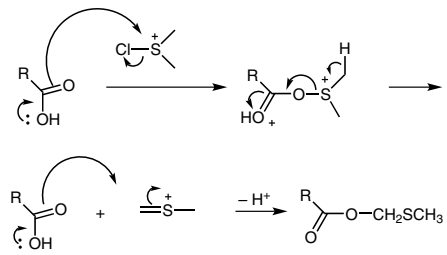
a series of β-chloroalkyl sulfides were obtained from alkenes by treatment with Me_2S/SO_2Cl_2/DMSO, in which methanesulfenyl chloride was considered as the key intermediate. The pathway of the formation of methanesulfenyl chloride was deduced to be via DMSO attack on the chlorodimethylsulfonium salt derived from the reaction Me_2S with SO_2Cl_2. As shown by Bellesia et al., the crucial role of DMSO in the formation of methanesulfenyl chloride was also observed in our experiments. At first, reaction of DMSO and oxalyl chloride in different molar ratios was attempted. Almost no reaction occurred when the molar ratio of DMSO to oxalyl chloride was less than 1. This result indicates that the excess of DMSO against $(COCl)_2$ was necessary for the reaction to occur. Therefore, it could be concluded that methanesulfenyl chloride did exist as a crucial intermediate in the process of the reaction and two equivalents of DMSO were required for the formation of this intermediate, among which one was for the production of the chlorodimethylsulfonium salt and the other was needed to convert this salt into the active species.



Scheme 3 The reaction of cyclohexene with DMSO/oxalyl chloride

Initially, the reactions were carried out followed the order of addition as that of the Swern oxidation, i.e. DMSO was added to the solution of $(COCl)_2$ in CH_2Cl_2 before the above mechanism was proposed. A byproduct, chloromethyl methyl sulfide was usually detected when the molar ratio of DMSO to oxalyl chloride was less than 2, which should be produced by the chlorodimethylsulfonium salt via Pummerer's rearrangement. After the role of DMSO was recognized in the formation of methanesulfenyl chloride intermediate, the order of addition was inverted, i.e. $(COCl)_2$ was added to the solution of DMSO in CH_2Cl_2 with the molar ratio of 2:1 (DMSO/oxalyl chloride), which avoided the formation of chloromethyl methyl sulfide.

A possible pathway to these (methylthio)methyl esters (Table 1, entries 1, 4, and 6) is shown in Scheme 4. The nucleophilic attack of the carboxyl group of the substrates on the chlorodimethylsulfonium salt produced the intermediate of acyloxysulfonium salt, which underwent Pummerer rearrangement to afford the corresponding esters. The formation of (methylthio)methyl esters indicated that no methanesulfenyl chloride was produced via DMSO attack on the chlorodimethylsulfonium salt at –65 °C. During retrieval of the literature, we found in Ghosh's work that they reported the synthesis of (methylthio)methyl esters under Swern oxidation conditions.[10] It was found that the yields of



Scheme 4 The pathway of the formation of (methylthio)methyl alkenoate

(methylthio)methyl esters were not affected when the reaction time was shortened from 24 hours to 30 minutes after the addition of alkenoic acids to the DMSO/$(COCl)_2$ reagent. Obviously, the results we obtained at –65 °C were in agreement with Ghosh's work.

In conclusion, alkenoic acids can be converted into sulfenyllactonates via thiiranium ions by methanesulfenyl chloride generated in situ by the reaction of DMSO and oxalyl chloride. The reaction temperature makes significant impact on this reaction. It presents very good generality for various unsaturated acids, such as alk-3-enoic, alk-4-enoic, and alk-5-enoic acids and affords the corresponding sulfenyllactones in good yields under mild conditions.

^{1}H NMR spectra were recorded on a Bruker AV300 or AV600 spectrometer. ^{13}C NMR spectra were recorded at 100 MHz. The residual solvent peak was used as an internal reference. HRMS data were obtained on a Solarix XR or Autoflex III Mass Spectrometer. Analytical TLC was performed with precoated TLC plates, silica gel 60F-254, layer thickness 0.25 mm. Flash chromatography separations were performed on 230–400 mesh silica gel. Reagents and solvents are commercial grade and were used as supplied. Compounds **1a–c** are commercially available and were purchased from Sigma-Aldrich.

(*E*)-Alken-3-enoic Acids 1d–f; General Procedure

To a 250-mL round-bottomed flask equipped with a condenser and a bubbler connected to the exit of the condenser was added a solution of malonic acid (26 g, 0.25 mol), piperidinium acetate [from piperidine (0.22 g) and AcOH (0.15 g, 2.5 mmol)], and aliphatic aldehyde (0.125 mol) in DMSO (100 mL). The mixture was stirred at 40 °C for 2 h. Then, the solution was heated in an oil bath at 100 °C. A rapid evolution of CO_2 was observed. Heating was maintained until the evolution of CO_2 ceased. The solution was cooled to r.t., poured into cold water (200 mL) and extracted with Et_2O. The combined extracts were washed with water and brine, dried (anhyd $MgSO_4$), and evaporated under reduced pressure. The residue was distilled under vacuum to give the (*E*)-alk-3-enoic acid.

(*E*)-Pent-3-enoic Acid (1d)

[CAS Reg. No.: 1617-32-9]

Colorless oil; yield: 8.5 g (68%); bp 60–65 °C/0.4 kPa.

All measured values were identical to those in the literature.[6]

(*E*)-Non-3-enoic Acid (1e)

[CAS Reg. No.: 4124-88-3]

Colorless oil; yield: 15.6 g (80%); bp 94–95 °C/0.4 kPa.

All measured values were identical to those in the literature.[11]

(*E*)-Dodec-3-enoic Acid (1f)

[CAS Reg. No.: 4998-72-5]

Colorless oil; yield: 18.8 g (76%); bp 113–119 °C/0.014 kPa.

All measured values were identical to those in the literature.[12]

Methylthio-Substituted Lactones 2a–j; General Procedure

To a solution of DMSO (2.3 mL, 30 mmol, 3.0 equiv) in CH_2Cl_2 (30 mL) cooled at –0 °C was added dropwise a solution of oxalyl chloride (1.3 mL, 15 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL). After 10 min, a solution of alkenoic acid (10 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added. The mixture was then allowed to warm up to r.t. and stirred overnight. Et_3N (7.0 mL, 50 mmol, 5.0 equiv) was added in one portion. After stirring for 20 min, the mixture was diluted with CH_2Cl_2 (60 mL). The organic layer was successively washed with sat. aq NH_4Cl solution (50 mL) and brine (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, petroleum ether/EtOAc 10:1) afforded the corresponding sulfenyllactone.

In an optimized procedure, CH_2Cl_2 was replaced by MeCN and the reaction mixture was heated to reflux after addition of substrate.

trans-4-(Methylthio)-5-phenyldihydrofuran-2(3*H*)-one (2a)

Light yellow oil; yield: 1.87 g (90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (m, 5 H), 5.28 (d, *J* = 6.9 Hz, 1 H), 3.38 (td, *J* = 8.4, 6.9 Hz, 1 H), 3.03 (dd, *J* = 18.0, 8.4 Hz, 1 H), 2.64 (dd, *J* = 18.0, 8.4 Hz, 1 H), 2.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.23, 137.52, 128.94, 128.78, 125.69, 86.11, 48.26, 35.77, 14.24.

HRMS (EI): *m*/*z* $[M]^{+\bullet}$ calcd for $C_{11}H_{12}O_2S$: 208.05525; found: 208.05517.

3,3-Dimethyl-5-[(methylthio)methyl]dihydrofuran-2(3*H*)-one (2b)

Colorless oil; yield: 1.65 g (95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.61 (dq, *J* = 9.6, 6.0 Hz, 1 H), 2.83 (dd, *J* = 14.1, 5.7 Hz, 1 H), 2.72 (dd, *J* = 14.1, 6.3 Hz, 1 H), 2.23 (dd, *J* = 12.9, 6.0 Hz, 1 H), 2.20 (s, 3 H), 1.90 (dd, *J* = 12.9, 9.6 Hz, 1 H), 1.29 (s, 3 H), 1.27 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.27, 76.28, 42.32, 40.20, 38.48, 24.74, 24.45, 16.56.

HRMS (EI): *m*/*z* $[M]^{+\bullet}$ calcd for $C_8H_{14}O_2S$: 174.0715; found: 174.0716.

6-[(Methylthio)methyl]tetrahydro-2*H*-pyran-2-one (2c)

Colorless oil; yield: 1.45 g (91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.40 (dddd, *J* = 10.5, 6.9, 5.1, 3.3 Hz, 1 H), 2.73 (dd, *J* = 14.1, 5.4 Hz, 1 H), 2.63 (dd, *J* = 14.1, 6.6 Hz, 1 H), 2.53 (dt, *J* =17.7, 5.7 Hz, 1 H), 2.39 (ddd, *J* = 17.7, 9.0, 7.2 Hz, 1 H), 2.11 (s, 3 H), 2.01 (m, 1 H), 1.71–1.94 (m, 2 H), 1.59 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.89, 79.79, 38.83, 29.23, 26.58, 18.08, 16.67.

HRMS (EI): *m*/*z* $[M]^{+\bullet}$ calcd for $C_7H_{12}O_2S$: 160.0558; found: 160.0555.

trans-5-Methyl-4-(methylthio)-5-dihydrofuran-2(3*H*)-one (2d)

Light yellow oil; yield: 1.24 g (85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.40 (m, 1 H), 3.06 (q, *J* = 8.4 Hz, 1 H), 2.92 (dd, *J* = 17.7, 8.4 Hz, 1 H), 2.54 (dd, *J* = 17.7, 8.4 Hz, 1 H), 2.14 (s, 3 H), 1.46 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.39, 81.56, 46.67, 35.93, 19.79, 13.92.

HRMS (EI): *m*/*z* $[M]^{+\bullet}$ calcd for $C_6H_{10}O_2S$: 146.03960; found: 146.03944.

***trans*-4-(Methylthio)-5-pentyldihydrofuran-2(3*H*)-one (2e)**

Light yellow oil; yield: 1.70 g (84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.27 (ddd, *J* = 8.1, 6.3, 4.2 Hz, 1 H), 3.11 (td, *J* = 8.1, 6.3 Hz, 1 H), 2.92 (dd, *J* = 17.7, 8.1 Hz, 1 H), 2.53 (dd, *J* = 17.7, 8.1 Hz, 1 H), 2.13 (s, 3 H), 1.56–1.82 (m, 2 H), 1.20–1.56 (m, 6 H), 0.87 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.57, 85.26, 44.74, 35.87, 34.34, 31.32, 25.02, 22.34, 13.85 (CH_3S and CH_3CH_2).

HRMS (EI): *m*/*z* [M]$^{+\bullet}$ calcd for $C_{10}H_{18}O_2S$: 202.10220; found: 202.10215.

***trans*-4-(Methylthio)-5-octyldihydrofuran-2(3*H*)-one (2f)**

Light yellow oil; yield: 2.14 g (88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.27 (ddd, *J* = 8.1, 6.6, 4.2 Hz, 1 H), 3.11 (td, *J* = 8.1, 6.6 Hz, 1 H), 2.92 (dd, *J* = 18.0, 8.1 Hz, 1 H), 2.53 (dd, *J* = 18.0, 8.1 Hz, 1 H), 2.13 (s, 3 H), 1.56–1.82 (m, 2 H), 1.16–1.56 (m, 12 H), 0.86 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.58, 85.28, 44.76, 35.89, 34.40, 31.73, 29.28, 29.18, 29.08, 25.36, 22.55, 14.01, 13.87.

HRMS (EI): *m*/*z* [M]$^{+\bullet}$ calcd for $C_{13}H_{24}O_2S$: 244.14915; found: 244.14915.

5-[(Methylthio)methyl]dihydrofuran-2(3*H*)-one (2g)

Colorless oil; yield: 1.30 g (89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.71 (qd, *J* = 7.2, 5.4 Hz, 1 H), 2.84 (dd, *J* = 14.1, 5.1 Hz, 1 H), 2.74 (dd, *J* = 14.1, 6.3 Hz, 1 H), 2.52–2.65 (m, 2 H), 2.34–2.47 (m, 1 H), 2.20 (s, 3 H), 2.02–2.12 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.78, 79.80, 38.68, 28.56, 26.89, 16.80.

HRMS (EI): *m*/*z* [M]$^{+\bullet}$ calcd for $C_6H_{10}O_2S$: 146.0402; found: 146.0403.

(1*R,4*R**,5*R**)-4-(Methylthio)-6-oxabicyclo[3.2.1]octan-7-one (2h)**

Colorless oil; yield: 1.34 g (78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.78 (t, *J* = 4.5 Hz, 1 H), 3.08 (t, *J* = 4.5 Hz, 1 H), 2.59 (m, 1 H), 2.25 (m, 2 H), 2.04–2.20 (m, 1 H), 2.14 (s, 3 H), 1.76–1.93 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.40, 79.16, 43.83, 38.59, 32.63, 24.78, 23.14, 15.64.

HRMS (EI): *m*/*z* [M]$^{+\bullet}$ calcd for $C_8H_{12}O_2S$: 172.0558; found: 172.0559.

(1*R,4*S**,6*R**)-6-(Methylthio)-2-oxabicyclo[2.2.1]heptan-3-one (2i)**

Colorless oil; yield: 1.20 g (76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.74 (br s, 1 H), 3.07 (m, 1 H), 2.85 (m, 1 H), 2.12–2.31 (m, 5 H), 2.04 (d, *J* = 10.8 Hz, 1 H), 1.55 (dt, *J* = 13.5, 4.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.31, 82.01, 45.27, 41.14, 37.01, 31.16, 16.21.

HRMS (EI): *m*/*z* [M]$^{+\bullet}$ calcd for $C_7H_{10}O_2S$: 158.0402; found: 158.0401.

(1*R,5*S**,8*R**)-8-(Methylthio)-2-oxabicyclo[3.3.0]octan-3-one (2j)**

Colorless oil; yield: 1.43 g (83%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.82 (dd, *J* = 6.6, 1.2 Hz, 1 H), 3.23 (m, 1 H), 3.04 (m, 1 H), 2.81 (dd, *J* = 18.3, 9.9 Hz, 1 H), 2.32 (dd, *J* = 18.3, 2.4 Hz, 1 H), 2.05–2.26 (m, 5 H), 1.66 (m, 1 H), 1.51 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.86, 90.08, 51.18, 37.15, 35.38, 31.82, 30.14, 14.89.

HRMS (EI): *m*/*z* [M]$^{+\bullet}$ calcd for $C_8H_{12}O_2S$: 172.0558; found: 172.0560.

(Methylthio)methyl Alkenoates 3a–c; General Procedure

To a solution of DMSO (2.3 mL, 30 mmol, 3.0 equiv) in CH_2Cl_2 (30 mL) cooled at –0 °C was added dropwise a solution of oxalyl chloride (1.3 mL, 15 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL). After 10 min, a solution of alkenoic acid (10 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added. The mixture was then stirred for 30 min at –65 °C and Et_3N (7.0 mL, 50 mmol, 5.0 equiv) was added in 1 portion. After 20 min at –65 °C, the mixture was allowed to warm up to r.t. and diluted with CH_2Cl_2 (60 mL). The organic layer was successively washed with sat. aq NH_4Cl solution (50 mL) and brine (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, petroleum ether/EtOAc 10:1) afforded the corresponding (methylthio)methyl ester.

(Methylthio)methyl (*E*)-4-Phenylbut-3-enoate (3a)

Colorless oil; yield: 2.01 g (90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.43 (m, 5 H), 6.53 (d, *J* = 15.9 Hz, 1 H), 6.31 (dt, *J* = 15.9, 6.9 Hz, 1 H), 5.19 (s, 2 H), 3.31 (dd, *J* = 6.9, 1.2 Hz, 2 H), 2.27 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.23, 136.69, 133.76, 128.53, 127.62, 126.27, 121.14, 68.54, 38.37, 15.44.

HRMS (EI): *m*/*z* [M]$^{+\bullet}$ calcd for $C_{12}H_{14}O_2S$: 222.0715; found: 222.0713.

(Methylthio)methyl 2,2-Dimethylpent-4-enoate (3b)

Colorless oil; yield: 1.76 g (94%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75 (m, 1 H), 5.13 (s, 2 H), 5.06 (m, 2 H), 2.30 (d, *J* = 7.5 Hz, 2 H), 2.23 (s, 3 H), 1.19 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.94, 133.89, 118.08, 68.04, 44.56, 42.36, 24.64, 15.26.

HRMS (EI): *m*/*z* [M]$^{+\bullet}$ calcd for $C_9H_{16}O_2S$: 188.0871; found: 188.0871.

(Methylthio)methyl Hex-5-enoate (3c)

Colorless oil; yield: 1.58 g (91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.76 (m, 1 H), 5.12 (s, 2 H), 5.00 (m, 2 H), 2.35 (t, *J* = 7.5 Hz, 2 H), 2.23 (s, 3 H), 2.09 (q, *J* = 6.9 Hz, 2 H), 1.74 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.95, 137.35, 115.27, 67.78, 33.33, 32.75, 23.74, 15.18.

HRMS (EI): *m*/*z* [M]$^{+\bullet}$ calcd for $C_8H_{14}O_2S$: 174.0715; found: 174.0715.

***trans*-1-Chloro-2-(methylthio)cyclohexane (4)**

[CAS Reg. No.: 41578-06-7]

To a solution of DMSO (8.5 mL, 120 mmol, 2.4 equiv) in CH_2Cl_2 (100 mL) cooled at –0 °C was added dropwise a solution of oxalyl chloride (5.2 mL, 60 mmol, 1.2 equiv) in CH_2Cl_2 (50 mL). After 10 min, a solution of cyclohexene (4.1 g, 50 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added. The mixture was then allowed to warm up to r.t. and stirred for 1 h. Et_3N (34.8 mL, 250 mmol, 5.0 equiv) was added in 1 portion. After stirring for 10 min, the mixture was successively washed with sat. aq NH_4Cl solution (100 mL) and brine (2 × 80 mL). The combined

organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was distilled under reduced pressure to give **4** (7.3 g, 89%) as a light yellow oil; bp 65–68 °C/0.067 kPa.

All measured values were identical to those in the literature.[9]

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588378.

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(1) These two authors contributed equally to this paper.

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