Radical Mechanism in the Elimination of 2-Arylsulfinyl Esters

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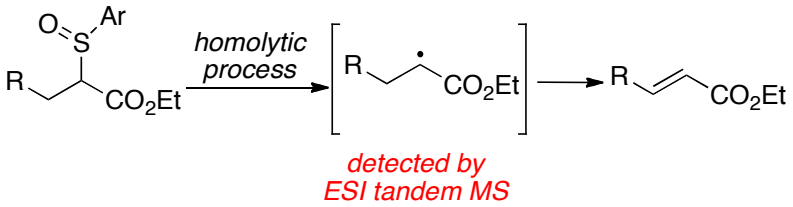
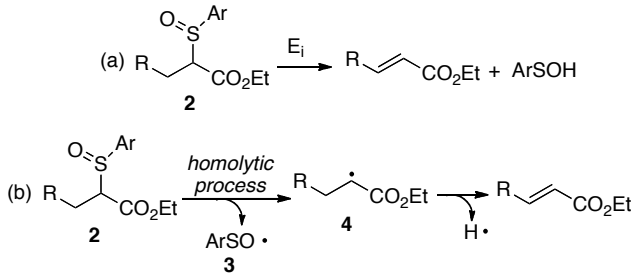


Abstract- The mechanism of the dehydrosulfenylation of 2-arylsulfinyl esters was investigated. The reaction was found to follow a homolytic cleavage mechanism as verified by electrospray ionization tandem mass spectrometry and experimental work. Rearranged sulfoxides are obtained as by-products during the elimination reaction.

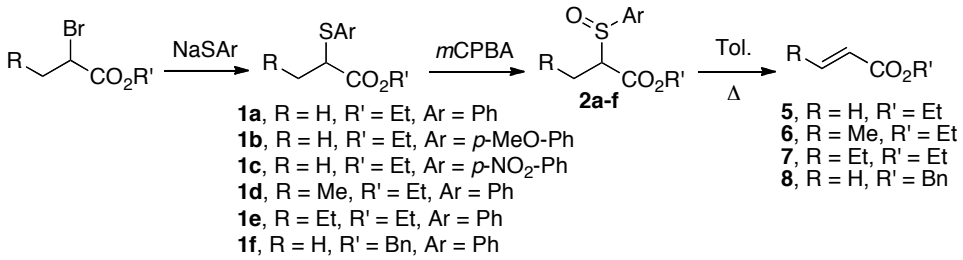
Elimination reactions of sulfoxides and sulfones are well known reactions in synthetic organic chemistry.[1] Particularly, the transformation of 2-arylsulfinyl esters to afford unsaturated carbonyl compounds by elimination is a common synthetic transformation.[2-5] The elimination reaction of sulfoxides follows an Ei (elimination internal) mechanism, as demonstrated by the seminal work by Cram and Kingsbury,[6] who also suggested the existence of a competing homolytic mechanism for some sulfoxides having a group to stabilize a radical intermediate. Although extensive work has been reported for the elimination of sulfoxides through an Ei mechanism,[7-8] no convincing evidence has appeared for a radical mechanism involving any sulfinyl substrate.

In the context of our investigations with sulfoxides,[9-10] we became interested in determining the nature of the mechanism during the elimination reaction of 2-arylsulfinyl esters. We considered two plausible mechanistic routes for the elimination of a 2-arylsulfinyl ester to afford the corresponding enoate (Scheme 1): a) the concerted elimination reaction (Ei), or b) a radical process involving the homolytic scission of the C-S bond to furnish free radical **4** and aryl sulfinyl radical **3**.



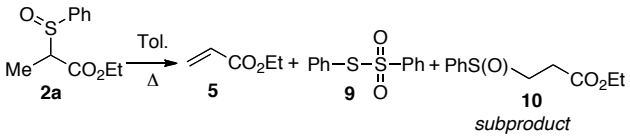
Scheme 1. Possible mechanistic routes.

We undertook the study of the elimination reaction of 2-arylsulfinyl esters with a range of R alkyl groups and Ar aryl groups attached to the sulfur atom. 2-Arylsulfinyl esters **2a-f** were prepared from the corresponding 2-bromo esters by treatment with the corresponding sodium thiophenolates, which furnished the expected thioethers **1a-f**. Upon oxidation of the thioethers, sulfoxides **2a-f** were obtained as a mixture of stereoisomers (Scheme 2).[11] Then compounds **2a-f** were submitted to elimination by heating to reflux in toluene for 5 h, affording the corresponding *E*-enoates.[12] 2-Arylsulfinyl esters **2a-c** gave rise to ethyl acrylate **5** and compounds **2d**, **2e** and **2f** afforded enoates **6**, **7** and **8** respectively as dominant products.[13]



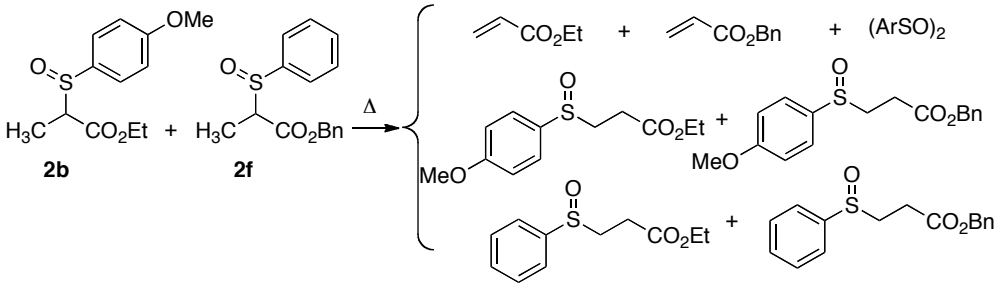
Scheme 2. Preparation and elimination of 2-arylsulfinyl esters **2a-f**.

Careful isolation of all the products obtained during the elimination reaction of compound **2a** gave the phenylthiosulfonate **9** (that partly converts to diphenyldisulfide and sulfonic acid, see below) and rearranged sulfoxide **10** as a minor product (15%) (Scheme 3). [14]



Scheme 3. Elimination reaction of compound **2a**.

It is also noteworthy that the unprecedented rearrangement of 2-arylsulfinyl ester **2a** to yield **10** provided an alternative synthetic entry to 3-arylsulfinyl ester. To determine whether the formation of minor compound **10** was an inter- or an intramolecular process, we conducted a crossover experiment between **2b** and compound **2f** (see Scheme 4).



Scheme 4. Crossover experiment between **2b** and **2f.**

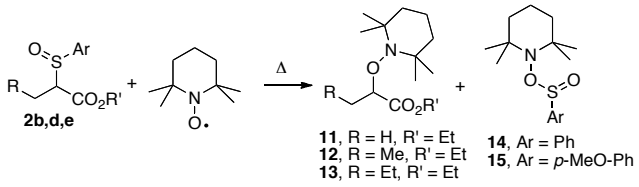
After heating of both sulfoxides **2b** and **2f**, the ^{1}H NMR or ^{13}C NMR spectra were highly crowded due to the presence of numerous species, making it difficult to identify the newly formed species. However, after removal of volatile acrylates and chromatographic separation of the fraction containing the 3-arylsulfinyl esters and the thiolsulfonate esters, electrospray ionization mass spectrometry (ESI-MS) analysis, operated in positive ion mode (ESI(+)), unravelled a rapid and direct snapshot of the formed species in the reaction mixture (see Figures S1 and

S2), and demonstrated that the rearrangement was an intermolecular rather than an intramolecular process.[15] A similar result was observed when sulfoxides **2b** and **2e** were heated at 80 ºC for 2 h as judged by ESI-MS analysis.

The corresponding 2-arylsulfonyl esters were also prepared. When 2-arylsulfonyl esters or 2-arylthioethers (**1a-f**) underwent the same experimental conditions for elimination as the sulfoxides, only starting material was recovered, thus illustrating that eliminations are a characteristic feature of only the sulfoxides.

Since the photolytic homolysis of C-S bonds have been described,[16] the elimination reactions were also performed in the absence of light. When 2-arylsulfinyl esters **2a-f** were submitted to elimination by heating in the absence of light the products were the same as in the presence of light thus ruling out a photolytic homolysis.

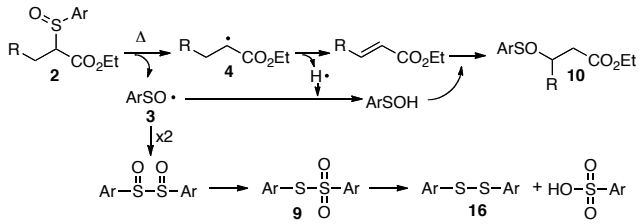
The interception of the radical intermediates would provide evidence for presence of a single-electron transfer mechanism in the elimination reaction. A nitroxyl radical (2,2,6,6-Tetramethyl-1-piperidinyloxy) **(**Tempo) succeeded in intercepting the radical intermediates derived from 2-arylsulfinyl esters **2b**, **2d** and **2e**. The reactions were investigated by electrospray ionization mass spectrometry (ESI-MS). [17] Compounds **2b**, **2d** and **2e** afforded adducts **11** and **15**, **12** and **14**, and **13** and **14** respectively. In case of the reaction using **2e** as starting material, both resulting reaction compounds **13** and **14** were isolated and fully characterized (see Supporting Information) (Scheme 5).[18]



Scheme 5. Trapping of the radical intermediates using Tempo.

These results denote the occurrence of a radical process during the elimination of 2-arylsulfinyl esters into enoates. A possible mechanism is proposed in Scheme 6. Sulfoxide **2** would give rise to radical **4** and aryl sulfinyl radical **3**. Sulfinyl radicals combine to give vicinal disulfoxides (vic-disulfoxides) which isomerize to give phenyl thiosulfonate **9**. Thiosulfonate **9** partly converts into the corresponding diaryl sulfide **16** and sulfonic acid as it is known.[19] Radical **4** would furnish the enoate. The formation of the subproduct **10** can be explained by addition of *in situ*-formed phenyl sulfenic acid to the enoate. The addition of sulfenic acids to unsaturated esters have been

demonstrated previously.[20-22] Compound **10** would be formed in a low yield due to the high tendency of sulfinyl radicals (or sulfenic acids) to afford thiosulphonates, although final reaction yields would depend on the subtle interplay between kinetics and thermodynamics of each elementary step depicted in Scheme 6.



Scheme 6. Radical Mechanism in the Elimination of 2-Arylsulfinyl Esters

In studies to determine the reaction mechanism of a multistep reaction, the identification of the intermediates is an essential process.[23] In this context, ESI-MS is a useful technique for analyzing chemical intermediates or products in diverse chemical and biochemical processes,[24-26] as illustrated above for the identification of the products formed in the crossover experiment. Although the detection of free radicals is sometimes difficult, ESI-MS has been recently employed for observing radical intermediates in some processes.[27-32] For a better understanding of the mechanism of the arylsulfinyl esters elimination depicted in Scheme 6, attempts to intercept and characterize the formed species were carried out on the basis of on-line ESI mass spectrometry and ESI tandem mass spectrometry. Closely related thermally-driven homolytic reactions have been successfully investigated by Metzger´s group by means of ESI mass spectrometry using modified ESI sources.[28] To investigate the elimination reaction, toluene solutions of **2a** were heated to 100 ºC and at different time intervals, aliquots were extracted, immediately diluted with hot acetonitrile, and analyzed by ESI(+) mass spectrometry. The obtained ESI mass spectra recorded at different intervals were nearly identical (Figure 1), with the most significant difference being the appearance of new signals corresponding to the $PhSSO_2Ph$ product as evidenced for the peaks assigned to $[PhSSO_2Ph + Na]^+$ (m/z = 273) and $[PhSSO_2Ph + K]+$ (m/z = 289). Negative ESI mass spectrum revealed the presence of sulfonic acid as $[M - H]^-$ adduct. Diphenyldisulfide was not observed in the ESI mass spectrum because it is not readily ionized upon ESI conditions.

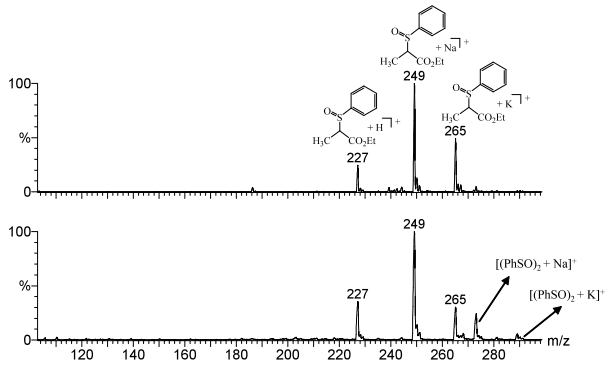


Figure 1. ESI(+) mass spectra of toluene/acetonitrile solutions of compound **2a**. Samples of the initial solution of **2a** (upper panel) and of compound **2a** after heating for 60 min (lower panel). Note that species at m/z 227, 249 and 265 in the lower panel correspond to **2a** and its rearranged isomer **10**.

The transient radical cations PhSO· and $CH_3CH{\cdot}CO_2CH_2CH_3$ (neither as H^+, Na^+ nor K^+ adducts) could not be identified in the ESI mass spectrum directly. However, monitoring the advance of the **2a** conversion to methylacrylate and the rearranged product **10** was possible by ESI-MS, provided that both **2a** and **10** isomers at m/z = 249 displayed distinctive unimolecular dissociation upon collision-induced dissociation (CID) conditions. CID spectra of the sodium adducts of **2a** and **10** are shown in Figure 2 which allowed us to monitor the temporal evolution of the species.

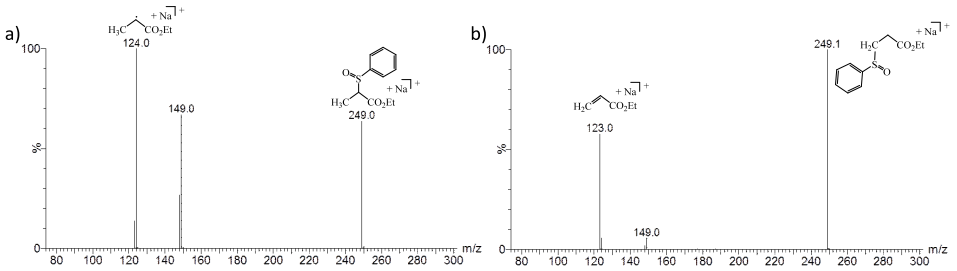


Figure 2. CID spectra of mass-selected species at a) m/z = 249 [**2a** + Na]$^+$ and b) m/z = 249 [**10** + Na]$^+$ ($E_{laboratory}$ = 15 eV)

Also helpful is the use of the MS/MS technique, where the fragment spectrum gives direct information about structural aspects of the investigated ion and can provide efficient information about mechanistic properties. It is remarkable that species [**2a** + Na]$^+$ (m/z = 249) dissociated predominantly via homolytic C-S bond cleavage affording the radical species [$CH_3CH{\cdot}CO_2CH_2CH_3$ + Na]$^+$ (m/z = 124) whereas species [**10** + Na]$^+$ (m/z = 249) dissociated via formation of the closed-shell [$CH_2CH{\cdot}CO_2CH_2CH_3$ + Na]$^+$ (m/z = 123) product ion. Moreover, at identical collision energies, it is clear that species [**2a** +Na]$^+$ is significantly easier to dissociate than [**10** +Na]$^+$ as evidenced by the relative intensity of the formed product ions. The gas-phase behavior of **2a** is reminiscent of that observed for heated solutions for which this compound is more prone to homolytically dissociate via S-C bond cleavage.

The same conditions were also used for monitoring the evolution of the reaction of 2-arylsulfinyl esters **2b-f**. It is remarkable that species [**2a-f** + Na]$^+$ unvariably dissociated predominantly via homolytic C-S bond cleavage affording the respective radical species [$RCH_2CH{\cdot}CO_2X$ + Na]$^+$ respectively, as illustrated in Figure 3 for **2b-f**. Fragmentation studies were also performed for the 2-arylsulfide esters and 2-arylsulfonyl esters but no radical intermediates were detected in their respective CID spectra. It is known that sulfides and sulfones do not eliminate as easily as sulfoxides.[33]

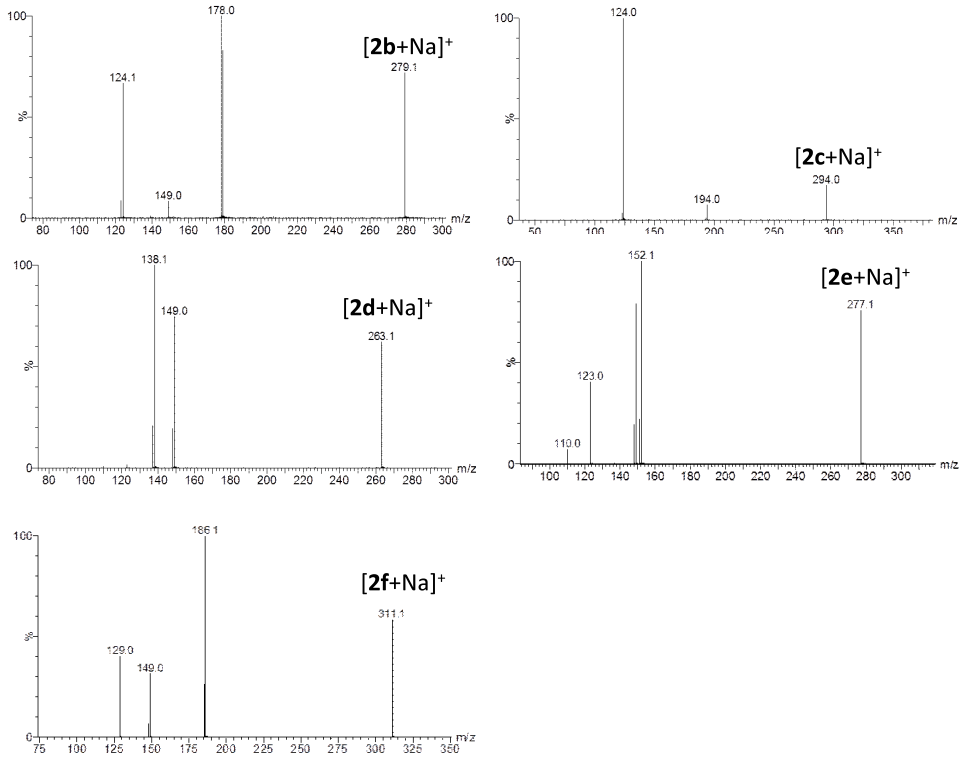
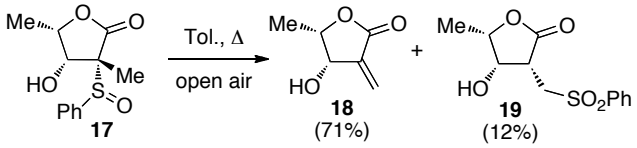


Figure 3. CID spectra of mass-selected species [**2b-f** + Na]$^+$ using a collision energy ($E_{laboratory}$) = 15 eV. Radical species detected are m/z = 124 for **2b** and **2c**, m/z = 138 for **2d**, m/z = 152 for **2e** and m/z = 186 for **2f.**

The formation of rearrangement products during the elimination of a 2-arylsulfinyl ester was also observed during the synthesis of the natural product **18** starting from sulfoxide **17**.[9] In this case, 3-arylsulfonyl lactone **19** was obtained as a minor product along with the expected α-methylene γ-butyrolactone **18** (Scheme 7) when the reaction was performed in open air. Sulfone **19** was formed in a highly stereoselective fashion as judged by single-crystal X-ray diffraction methods (see Figure S4).[34] In this case sulfone **19** was formed instead of the expected sulfoxide, following the well-known tendency of γ-hydroxy sulfides to be oxidized to sulfones instead of sulfoxides under photooxidation conditions.[35]



Scheme 7. Synthesis of compounds **18** and **19**.

In summary, the mechanism of the dehydrosulfenylation of 2-arylsulfinyl esters for furnishing enoates has been determined to be a homolytic process. The interception of the radical intermediate using a nitroxyl radical and ESI-MS and ESI tandem MS techniques were useful for drawing a comprehensive picture of the intermediates involved in the dehydrosulfenylation of 2-arylsulfinyl esters and suggest that a radical-mediated process is operative. An unprecedented transformation of 2-arylsulfinyl esters to 3-arylsulfinyl esters is also observed as a side reaction whose intimate mechanism is proposed.

Experimental Section

General Experimental Methods. All solvents used in reactions were freshly distilled from appropriate drying agents before use. ^{1}H NMR spectra and ^{13}C NMR spectra were measured in $CDCl_3$ (^{1}H, 7.24 ppm; ^{13}C 77.0 ppm) solution at 30 °C on a 300 MHz or a 500 MHz NMR spectrometer. IR spectra were recorded as oil films or KBr discs or NaCl pellets on a FT-IR spectrometer. EM Science Silica Gel 60 was used for column chromatography while TLC was performed with precoated plates (Kieselgel 60, F_{254}, 0.25 mm). Unless otherwise specified, all reactions were carried out under argon atmosphere with magnetic stirring.

Electrospray ionization mass spectrometry (ESI-MS) and electron impact mass spectrometry (EI-MS)

For the on-line reaction monitoring, ESI mass spectra were recorded using an ESI tandem mass spectrometer (quadrupole-hexapole-quadrupole). The drying gas was nitrogen. The temperature of the source block was set to 120 ºC and the desolvation temperature to 150 ºC. A capillary voltage of 3.5 kV was used in the positive scan mode and the cone voltage (U_c) was set to 15 V to control the extent of fragmentation of the identified ions. Toluene solutions of **2a-f** were heated at 100 ºC in an open vial, a drop of the solution was immediately extracted, diluted in hot CH_3CN and a positive-ion mass spectrum collected. For CID experiments, the cations of interest were mass-selected using the first quadrupole (Q1) and interacted with argon in the hexapole collision cell at variable collision energies (typically

in the $E_{laboratory}$ = 3-10 eV range) while mass analyzing the products with the second analyser. The isolation width was ca. 1 Da and argon was used as a collision gas to produce a pressure of 8 x 10^{-4} mbar.

For accurate m/z determinations (for all the compounds except for **16**) and CID experiments, an ESI tandem mass spectrometer (quadrupole-Twave-time of flight) was used. The drying gas was nitrogen. The temperature of the source block was set to 120 ºC and the desolvation temperature to 150 ºC. A capillary voltage of 3.5 kV was used in the positive scan mode and the cone voltage was set to a low value to control the extent of fragmentation (typically 15 V). Methanol sample solutions were infused via syringe pump directly connected to the ESI source at a flow rate of 10 μL/min. Mass calibration was performed using a mixture of NaOH 0.05 M: formic acid 10 % (50:50) from m/z 50 to 900. For the accurate mass measurements, a solution of leucine enkephalin (m/z = 556.2771) was introduced via the lock spray needle at a flow rate of 30 μL/min.

For an accurate m/z determination of compound **16**, a GC-EIMS was used. The GC instrumentation used was equipped with an autosampler, coupled to a TOF mass spectrometer operating in electron ionization (EI) mode. The GC separation was performed using a fused silica column (30 m x 0.25 mm i.d., 0.25 mm film thickness). The oven temperature was programmed as follows: 90 ºC (hold 1 min); 10 ºC/min to 300 ºC (hold 2 min). The total running time was 24 min. Splitless injections of 1 mL of sample extracts were carried out with an injector temperature of 300 °C and with a splitless time of 1 min. Helium 99.999 % was used as carrier gas at a constant flow of 1 mL/min. The interface and ion source temperatures were set to 260 ºC and 250 ºC, respectively. A solvent delay of 3 min was used to prevent damage in the ion source filament. TOF MS was operated at an scan time of 0.95 s in the mass range *m/z* 60-300 and using a multi-channel plate voltage of 2700 V. TOF MS resolution was about 8500 (FWHM) at *m/z* 614. Pure PFTBA (Perfluorotri-n-butylamine), used for the daily mass calibration/verification as well as for lock mass, was injected via syringe (~ 1 mL) in the reference reservoir at 30 ºC. The *m/z* monitored was 218.9856.

X-ray crystallography

Crystals of compound **19** are air stable and were mounted on the tip of a glass fiber with the use of epoxi cement. X-ray diffraction experiment was carried out on a diffractometer using Mo-Kα radiation (λ = 0.71073 Å) at room

temperature. The data were collected with a frame width of 0.3 º in ω and a counting time of 60 s per frame at a crystal to detector distance of 4 cm. The diffraction frames were integrated using the SAINT package and corrected for absorption with SADABS. The structures were solved by direct methods and refined by the full-matrix method based on F^2 using the SHELXTL software package. All non hydrogen atoms were refined anisotropically. Hydrogen atoms were generated geometrically, assigned isotropic thermal parameters and allowed to ride on their respective parent carbon atoms. Crystal data and structure refinement for **19**: Empirical formula $C_{12}H_{14}O_5S$; Crystal system Monoclinic; Space group P2(1); unit cell dimensions a = 4.8321(7) Å, b = 21.157(3) Å, c = 6.4661(9) Å, β= 95.816(3)°; Z = 2; theta range for data collection 1.93 to 30.49°; reflections collected 5373; independent reflections 3114 [R(int) = 0.0247]; goodness-of-fit on F^2 = 1.030; Final R indices [I>2sigma(I)] R1 = 0.0424, wR2 = 0.0928; R indices (all data) R1 = 0.0685, wR2 = 0.1034; absolute structure parameter -0.03(8); largest diff. peak and hole 0.268 and -0.180 e.$Å^{-3}$

General experimental procedure for the preparation of thioethers 1a-f:

To an ice-bath cold solution of sodium hydride (1.85 g, 46.2 mmol) (60% in mineral oil) in tetrahydrofuran (110 mL) was added drop wise the corresponding thiophenol (92.4 mmol). The resulting mixture was stirred cold with an ice-bath for 30 minutes. Then the bromoester (92.4 mmol) was added and the resulting mixture was stirred at room temperature for 72 h. Then was quenched with brine, extracted with ethyl ether (3 x 15 mL), and then the organic layers were washed with a saturated aqueous solution of sodium bicarbonate and water, dried (Na_2SO_4) and concentrated. The crude was purified through chromatography (silica-gel, hexanes/ethyl acetate (95:5)) to afford the desired compound.

Ethyl 2-(phenylthio)propanoate 1a. (yield= 12.61 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.48 (2H, m), 7.26-7.32 (3H, m), 4.11 (2H, q, J= 7.2Hz), 3.78 (1H, q, J= 6.9Hz), 1.48 (3H, d, J= 6.9Hz), 1.17 (3H, t, J= 7.2Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 133.4, 129.2, 128.3, 61.5, 45.6, 17.7, 14.3 ppm. IR (NaCl) δ 3060, 2981, 2933, 2872, 1955, 1883, 1732, 1583, 1476, 1440, 1375, 1323, 1256, 1225, 1159, 1068, 1025, 897, 859, 776, 748, 691, 596 cm^{-1}. HRMS *m/z* calcd. for $C_{11}H_{14}O_2SNa$ [$M+Na^+$]: 233.0612, found: 233.0611.

Ethyl 2-((4-methoxyphenyl)thio)propanoate 1b. (yield= 13.3 g, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (2H, d, J= 8.0Hz), 6.79 (2H, d, J= 8.5Hz), 4.06 (2H, q, J= 7.0Hz), 3.75 (3H, s), 3.57 (1H, q, J= 7.0 Hz), 1.37 (3H, d, J= 7.0Hz), 1.14 (3H, t, J= 7.5Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 160.5, 136.7, 123.4, 114.7, 61.2, 55.5, 46.2, 17.4, 14.3 ppm. IR (NaCl) δ 2927, 1727, 1591, 1493, 1461, 1286, 1247, 1172, 1029, 827 cm^{-1}. HRMS *m/z* calcd. for $C_{12}H_{16}O_3SNa$ [$M+Na^+$]: 263.0718, found: 263.0712.

Ethyl 2-((4-nitrophenyl)thio)propanoate 1c. (yield= 12.25 g, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (2H, d, J= 8.5Hz), 7.46 (2H, d, J= 9.0Hz), 4.15 (2H, m), 4.00 (2H, q, J= 7.0Hz), 1.56 (3H, d, J= 7.5Hz), 1.19 (3H, t, J= 7.0Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 144.9, 131.5, 129.3, 124.3, 62.1, 44.1, 17.6, 14.4 ppm. IR (NaCl) δ 2925, 1732, 1596, 1578, 1515, 1477, 1341, 1259, 1174, 1076, 1013, 853, 742, 683 cm^{-1}. HRMS *m/z* calcd. for $C_{11}H_{14}NO_4S$ [$M+H^+$]: 256.0644, found: 256.0647; calcd. for $C_{11}H_{13}NO_4SNa$ [$M+Na^+$]: 278.0463, found: 278.0464.

Ethyl 2-(phenylthio)butanoate 1d. (yield= 19.25 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (2H, m), 7.25 (3H, m), 4.09 (2H, dq, J= 1.2, 7.2Hz), 3.56 (1H, dd, J= 6.6, 8.4Hz), 1.70-1.95 (m, 2H), 1.15 (3H, t, J= 6.9Hz), 1.09 (3H, t, J= 7.2Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 133.7, 132.7, 128.8, 127.7, 60.9, 52.4, 25.1, 14.0, 11.7 ppm. IR (oil) δ 3079, 2970, 2936, 2877, 1959, 1884, 1735, 1583, 1480, 1443, 1368, 1343, 1300, 1234, 1209, 1160, 1091, 1026, 941, 864, 811 cm^{-1}. HRMS *m/z* calcd. for $C_{12}H_{17}O_2S$ [$M+H^+$]: 225.0949, found: 225.0953; calcd. for $C_{12}H_{16}O_2SNa$ [$M+Na^+$]: 247.0769, found: 247.0772.

Ethyl 2-(phenylthio)pentanoate 1e. (yield= 19.35 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.47 (2H, m), 7.24-7.31 (3H, m), 4.10 (2H, q, J= 7.2Hz), 3.65 (1H, dd, J= 6.6, 8.1Hz), 1.67-1.94 (m, 2H), 1.38-1.52 (m, 2H), 1.15 (3H, t, J= 6.6Hz), 0.92 (3H, t, J= 7.2Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 133.7, 132.7, 128.7, 127.6, 60.7, 50.5, 33.7, 20.5, 14.0, 13.6 ppm. IR (oil) δ 3066, 2968, 2936, 2876, 1958, 1884, 1733, 1585, 1483, 1444, 1374, 1335, 1303, 1279, 1243, 1163, 1106, 1033, 934, 860, 808 cm^{-1}. HRMS *m/z* calcd. for $C_{13}H_{19}O_2S$ [$M+H^+$]: 239.1106, found: 239.1115; calcd. for $C_{13}H_{18}O_2SNa$ [$M+Na^+$]: 261.0925, found: 261.0923.

Benzyl 2-(phenylthio)propanoate 1f. (yield= 17.59 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.44 (10H, m), 5.11 (2H, s), 3.85 (1H, d, J= 7.2Hz), 1.52 (3H, d, J= 7.2Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 135.5, 133.2, 133.0, 128.9, 128.5, 128.2, 128.0, 66.7, 45.3, 17.3 ppm. IR (oil) δ 3061, 2986, 2936, 1959, 1888, 1735, 1586, 1480,

1443, 1380, 1324, 1268, 1162, 1063, 1029, 1004, 954, 898, 780 cm^{-1}. HRMS *m/z* calcd. for $C_{16}H_{17}O_2S$ $[M+H^+]$: 273.0949, found: 273.0946; calcd. for $C_{16}H_{16}O_2SNa$ $[M+Na^+]$: 295.0769, found: 295.0770.

General experimental procedure for the preparation of sulfoxides 2a-f:

To a -10ºC cold solution of thioether (0.95 mmol) in CH_2Cl_2 (5 mL) was added a solution of *m*-CPBA (77% pure) (177 mg, 0.79 mmol) in CH_2Cl_2 (4 mL). The resulting mixture was stirred at -10ºC for 30min and then was quenched with saturated aqueous solution of sodium bicarbonate, extracted with CH_2Cl_2 (3 x 15 mL), and then the organic layers were sequently washed with brine and saturated aqueous solution of sodium bicarbonate and water, dried (Na_2SO_4) and concentrated. The crude was purified through chromatography (silica-gel, hexanes/ethyl acetate (7:3)) to afford the desired sulfoxide.

Ethyl 2-(phenylsulfinyl)propanoate 2a. (yield= 178 mg, 83%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.45 (5H, m) (major and minor), 4.12 (2H, m) (major and minor), 3.81 (1H, q, J= 6.5Hz) (major), 3.49 (1H, q, J= 7.0Hz) (minor), 1.49 (3H, d, J= 7.0Hz) (major), 1.32 (3H, d, J= 7.5Hz) (minor), 1.21 (3H, t, J= 6.5Hz) (minor), 1.18 (3H, t, J= 7.0Hz) (major). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 168.1, 142.6, 140.9, 134.5, 132.1, 131.9, 129.7, 129.5, 129.3, 125.5, 125.1, 66.2, 64.1, 62.1, 62.0, 14.3, 14.2, 10.0, 9.1 ppm. IR (NaCl) δ 3051, 2988, 2926, 1968, 1895, 1724, 1577, 1472, 1445, 1371, 1316, 1254, 1215, 1165, 1083, 1045, 1017, 920, 889, 858, 749, 691 cm^{-1}. HRMS *m/z* calcd. for $C_{11}H_{14}O_3SNa$ $[M+Na^+]$: 249.0556, found: 249.0557.

Ethyl 2-((4-methoxyphenyl)sulfinyl)propanoate 2b. (yield= 124 mg, 51%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (2H, d, J= 8.5Hz) (major), 7.52 (2H, d, J= 8.5Hz) (minor), 7.00 (2H, d, J= 8.5Hz) (major and minor), 4.04-4.20 (2H, m) (major and minor), 3.85 (3H, s) (major and minor), 3.78 (1H, q, J= 7.0Hz) (major), 3.47 (1H, q, J= 8.0Hz) (minor), 1.50 (3H, d, J= 7.0Hz) (major), 1.27 (3H, d, J= 7.0Hz) (minor), 1.23 (3H, t, J= 7.0Hz) (minor), 1.15 (3H, t, J= 7.0Hz) (major). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 168.3, 162.7, 133.2, 131.5, 127.3, 126.9, 114.9, 114.8, 66.3, 64.3, 61.9, 55.8, 14.3, 14.3, 10.4, 8.9 ppm. IR (KBr) δ 3096, 3069, 2981, 2940, 2842, 1727, 1598, 1500, 1459, 1306, 1258, 1173, 1092, 1024, 834, 793, 626 cm^{-1}. HRMS *m/z* calcd. for $C_{12}H_{17}O_4S$ $[M+H^+]$: 257.0848, found: 257.0849; calcd. for $C_{12}H_{16}O_4SNa$ $[M+Na^+]$: 279.0667, found: 279.0656.

Ethyl 2-((4-nitrophenyl)sulfinyl)propanoate 2c. (yield= 160 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (2H, d, J= 8.5Hz) (major), 8.30 (2H, d, J= 9.0Hz) (minor), 7.82 (2H, d, J= 9.0Hz) (major), 7.77 (2H, d, J= 9.0Hz) (minor), 4.04-4.15 (2H, m) (major and minor), 3.84 (1H, q, J= 7.0Hz) (major), 3.48 (1H, q, J= 7.0Hz) (minor), 1.41 (3H, d, J= 7.5Hz) (major), 1.30 (3H, d, J= 7.0Hz) (minor), 1.17 (3H, t, J= 7.5Hz) (minor), 1.15 (3H, t, J= 7.5Hz) (major). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 168.3, 149.7, 147.9, 126.6, 126.2, 127.3, 125.6, 125.0, 65.6, 63.7, 62.5, 62.3, 14.2, 9.4, 9.0 ppm. IR (NaCl) δ 3101, 2985, 1732, 1603, 1579, 1527, 1475, 1450, 1398, 1347, 1150, 1089, 1054, 1011, 1017, 853, 743, 723, 684 cm^{-1}. HRMS *m/z* calcd. for $C_{11}H_{14}NO_5S$ $[M+H^+]$: 272.0593, found: 272.0580; calcd. for $C_{11}H_{13}NO_5SNa$ $[M+Na^+]$: 294.0412, found: 294.0405.

Ethyl 2-(phenylsulfinyl)butanoate 2d. (yield= 187 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.66 (5H, m) (major and minor), 3.95-4.10 (2H, m) (major and minor), 3.48 (1H, dd, J= 5.0, 10.0Hz) (major), 3.39 (1H, dd, J= 5.0, 9.5Hz) (minor), 2.06-2.16 (1H, m) (major and minor), 1.76-1.90 (1H, m) (major and minor), 1.12 (3H, t, J= 7.5Hz) (major), 1.06 (3H, t, J= 7.5Hz) (minor), 1.03 (3H, t, J= 7.0Hz) (major), 1.00 (3H, t, J= 7.5Hz) (minor). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 166.7, 142.2, 141.1, 131.7, 131.4, 129.9, 128.9, 124.8, 124.7, 73.5, 70.6, 61.3, 20.3, 18.7, 13.8, 11.5, 11.3 ppm. IR (oil) δ 3066, 2975, 2940, 2880, 2088, 1972, 1894, 1726, 1638, 1581, 1476, 1448, 1374, 1335, 1258, 1202, 1163, 1089, 1039, 952, 860, 815 cm^{-1}. HRMS *m/z* calcd. for $C_{12}H_{17}O_3S$ $[M+H^+]$: 241.0898, found: 241.0900; calcd. for $C_{12}H_{16}O_3SNa$ $[M+Na^+]$: 263.0718, found: 263.0722.

Ethyl 2-(phenylsulfinyl)pentanoate 2e. (yield= 222 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.65 (5H, m) (major and minor), 3.88-4.10 (2H, m) (major and minor), 3.53 (1H, dd, J= 5.5, 10.0Hz) (major), 3.43 (1H, dd, J= 5.0, 9.0Hz) (minor), 2.02-2.10 (1H, m) (major and minor), 1.73-1.84 (1H, m) (major and minor), 1.28-1.48 (2H, m) (major and minor), 1.09 (3H, t, J= 7.0Hz) (major), 1.03 (3H, t, J= 7.5Hz) (minor), 0.91 (3H, t, J= 7.0Hz) (major), 0.88 (3H, t, J= 7.5Hz) (minor). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 166.8, 142.3, 141.7, 131.7, 131.5, 129.0, 128.8, 124.8, 124.7, 72.1, 68.8, 61.2, 28.7, 27.0, 20.3, 13.8, 13.5 ppm. IR (oil) δ 3062, 2968, 2940, 2879, 2095, 1972, 1891, 1729, 1585, 1469, 1447, 1377, 1335, 1275, 1247, 1191, 1156, 1089, 1057, 941, 860, 825 cm^{-1}. HRMS *m/z* calcd. for $C_{13}H_{19}O_3S$ $[M+H^+]$: 255.1055, found: 255.1053; calcd. for $C_{13}H_{18}O_3SNa$ $[M+Na^+]$: 277.0874, found: 277.0876.

Benzyl 2-(phenylsulfinyl)propanoate 2f. (yield= 192 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.55 (10H, m) (major and minor), 5.10 (1H, d, J= 12.0Hz) (major), 5.10 (1H, d, J= 12.0Hz) (minor), 5.00 (1H, d, J= 12.0Hz) (major), 4.99 (1H, d, J= 12.0Hz) (minor), 3.82 (1H, q, J= 7.2Hz) (major), 3.50 (1H, q, J= 7.2Hz) (minor), 1.41 (3H, d, J= 6.9Hz) (major), 1.26 (3H, d, J= 7.2Hz) (minor). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 167.5, 142.0, 140.2, 134.9, 131.7, 131.5, 129.1, 128.9, 128.6, 128.5, 128.4, 128.3, 125.0, 124.6, 67.4, 67.3, 65.4, 63.5, 9.4, 8.6 ppm. IR (oil) δ 3067, 3036, 2939, 1965, 1894, 1732, 1583, 1499, 1477, 1449, 1380, 1318, 1222, 1163, 1050, 998, 957, 920, 848, 820, 777 cm^{-1}. HRMS *m/z* calcd. for $C_{16}H_{17}O_3S$ [$M+H^+$]: 289.0898, found: 289.0894; calcd. for $C_{16}H_{16}O_3SNa$ [$M+Na^+$]: 311.0718, found: 311.0713.

Experimental procedure for elimination

A mixture of compound **2** (1 mmol) in toluene (6 mL) was heated at 110 ºC for 5h (in case of compounds **2a**, **2b**, **2c** and **2f** the reaction was performed in a sealed flask to avoid acrylate loss). Then the resulting crude mixture was purified through chromatography (silica-gel, hexanes/ethyl acetate (1:1), (1:2) and ethyl acetate) to afford the corresponding enoate.

***S*-phenyl benzenesulfonothioate 9.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13-7.51 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 136.6, 133.6, 131.4, 129.4, 129.0, 128.8, 127.9, 127.6, 127.2 ppm. IR (NaCl) δ 3064, 1580, 1445, 1323, 1144, 1076, 1021, 748, 688 cm^{-1}. HRMS *m/z* calcd. for $C_{12}H_{10}O_2S_2Na$ [$M+Na^+$]: 273.0020, found: 273.0026.

Diphenyl disulfide 16. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13-7.17 (2H, m), 7.21-7.24 (4H, t, J = 8.5Hz), 7.42 (4H, d, J = 8.5Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 129.0, 127.6, 127.2 ppm. IR (NaCl) δ 3064, 1946, 1864, 1800, 1735, 1574, 1470, 1432, 1379, 1298, 1068, 1017, 896, 787, 735, 686, 605 cm^{-1}. HRMS (EI) *m/z* calcd. for $C_{12}H_{10}S_2$ [M]: 218.0224, found: 218.0210.

2-(Ethoxycarbonyl)ethyl benzenesulfenate 10. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61-7.62 (2H, m), 7.49-7.54 (3H, m), 4.11 (2H, q, J= 7.5Hz), 3.22 (1H, m), 2.97 (1H, m), 2.84 (1H, m), 2.54 (1H, m), 1.22 (3H, d, J= 7.5Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 143.4, 131.5, 129.6, 124.4, 61.4, 51.5, 26.5, 14.4 ppm. IR (NaCl) δ 2963, 1733, 1445,

1373, 1260, 1087, 1045, 799, 750, 691 cm^{-1}. HRMS *m/z* calcd. for $C_{11}H_{14}O_3SNa$ $[M+Na^+]$: 249.0561, found: 249.0561.

Experimental procedure for trapping the radical

A mixture of compound **2e** (500 mg, 1.96 mmol) and 2,2,6,6-Tetramethyl-1-piperidinyloxy **(**Tempo) (614 mg, 3.93 mmol) in toluene (10 mL) was heated at 80 ºC for 2h. Then the resulting crude mixture was carefully concentrated under vacuum and then purified through chromatography (silica-gel, hexanes/ethyl acetate (95:5)) to afford compound **13** (17 mg, 3 %) as an oil and compound **14** (60 mg, 11 %) as a white solid. Recrystallization of **14** from CH_2Cl_2/Hexanes gave white prismatic crystals (m.p. = 128-130 ºC)

Ethyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pentanoate 13. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (1H, dd, J = 6.6, 7.5 Hz), 4.15 (2H, q, J = 7.2 Hz), 1.74-1.85 (2H, m), 1.01-1.48 (23H, m), 0.91 (3H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 85.5, 60.1, 40.3, 34.2, 33.6, 33.0, 20.2, 17.9, 17.1, 14.2, 13.9 ppm. IR (KBr) δ 2974, 2933, 2876, 1748, 1466, 1381, 1366, 1269, 1245, 1184, 1133, 1105, 1058, 1031, 993, 976, 963, 929, 881, 857, 793, 752, 722, 681, 650 cm^{-1}. HRMS *m/z* calcd. for $C_{16}H_{32}NO_3$ $[M+H^+]$: 286.2382, found: 286.2377.

2,2,6,6-tetramethylpiperidin-1-yl benzenesulfinate 14. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82-7.89 (2H, m), 7.39-7.47 (3H, m), 1.66 (6H, s), 1.57 (12H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 131.2, 128.5, 126.0, 60.8, 43.8, 31.1, 16.7 ppm. IR (KBr) δ 3069, 3035, 2984, 2944, 2916, 2879, 1404, 1394, 1245, 1204, 1184, 1139, 1095, 1071, 980, 922, 786, 766, 715, 701, 626, 613 cm^{-1}. HRMS *m/z* calcd. for $C_{15}H_{23}NO_2SNa$ $[M+Na^+]$: 304.1347, found: 304.1348.

(4S,5S)-dihydro-4-hydroxy-5-methyl-3-methylenefuran-2(3H)-

one (18) and (3R,4S,5S)-dihydro-4-hydroxy-5-methyl-3-((phenylsulfonyl)methyl)furan-2(3H)-one (19). An oxygen-flushed mixture of compound **17** (124 mg, 0.48 mmol) in toluene (8 mL) was heated at 110 ºC for 5h. Then the solvent was removed under vacuum and the resulting mixture was purified through chromatography (silica-gel, hexanes/ethyl acetate (1:1), (1:2) and ethyl acetate) to afford 44 mg (71%) of compound **18** as a colorless oil and 16 mg (12%) of compound **19** as a white solid. Recrystallization from $CHCl_3$/Hexanes gave white needles (mp = 117-

120 ºC).

Spectroscopic data of **18**: $[\alpha]_{20}^{D}$ = -97.26 (c = 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (1H, d, J= 2.1 Hz), 5.97 (1H, d, J=1.5Hz), 4.83 (1H, d, J= 5.7 Hz), 4.65 (1H, dq, J= 6.0, 6.6 Hz), 1.34 (3H, d, J= 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 138.8, 126.3, 78.4, 69.7, 14.3. IR (NaCl) δ 3439, 3015, 2930, 1756, 1672, 1387, 1263, 1186, 1103, 1045, 958, 910, 861, 821, 784 cm^{-1}. HRMS *m/z* calcd for $C_6H_8O_3Na$ [M + Na^+]: 151.0371, found: 151.0354.

Spectroscopic data of **19**: $[\alpha]_{26}^{D}$ = -33.94 (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (2H, d, J= 7.2 Hz), 7.72 (t, 1H, J= 7.5 Hz), 7.61 (t, 2H, J= 7.8 Hz), 4.72 (m, 1H), 4.63 (m, 1H), 3.56 (m, 2H), 3.26 (m, 1H), 2.93 (d, 1H, J = 4.2 Hz), 1.49 (3H, d, J= 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 138.4, 134.5, 129.7, 127.8, 79.6, 70.1, 51.2, 42.7, 13.6 ppm. IR (NaCl) δ 3350, 2949, 2836, 1764, 1656, 1449, 1412, 1117, 1033 cm^{-1}. HRMS *m/z* calcd. for $C_{12}H_{14}O_5SNa$ [M+Na^+]: 293.0460, found: 293.0429.

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Supporting Information Available: Crystallographic data (CIF), graphical NMR spectra of all compounds and ORTEP representations. This material is available free of charge via the Internet at http://pubs.acs.org.

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11- An aproximately 3:2 mixture of stereomeric sulfoxides was obtained in all cases (see Supporting Information).

12- The elimination reactions afforded *trans* isomers as the reaction product, the corresponding *cis* isomers were never observed (NMR spectra) nor even in trace amounts. The elimination reactions were also performed at 80 ºC and the result was similar to the one carried out at 110 ºC also in this case only *trans* enoates were obtained.

13- Compounds **5**-**8** were identifed based on NMR (see Supporting Information) comparing with prior literature. For compound **5**: *Aldrich Library of* ^{13}C *and* ^{1}H *FT NMR spectra*, 1, 973C. For compound **6**: Nishizawa, M.; Hirakawa, H.; Nakagawa, Y.; Yamamoto, H.; Namba, K.; Imagawa. H. *Org. Lett.* **2007**, *9*, 5577–5580. For compound **7**: Kandula, S.R.V.; Kumar, P. *Tetrahedron:Asymmetry* **2005**, *16*, 3268–3274. For compound **8**: Pittelkow, M.; Christensen*, J. B. Org. Lett.* **2005**, *7*, 1295-1298.

14- Rearranged sulfoxides similar to **10** from the elimination reactions of compounds **2b-2f** have been detected as traces by NMR and MS of the crude.

15- Compound **10** was isolated from the crossover experiment reaction mixture depicted in scheme 4, and compared with authentic sample already isolated and characterized.

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17- ESI-MS has shown to be a good technique for the detection of radicals by Tempo combination: Zhang, X.; Wang, H.; Guo, Y. *Rapid Commun. Mass Spectrom.* **2006**, *20*, 1877–1882.

18- Nitroxides as **11** are radical initiators (*Macromolecules* **1997**, *30*, 6445-6450). When the elimination reaction to trap the radical intermediate was performed at 110 ºC then compounds **14-15** were detected but **11-13** were not. Finally compounds **11-13** could be detected when the reaction was carried out at 80 ºC.

19- Phenyl disulfide was isolated and charaterized (see Supporting Information) and phenyl sulfonic acid was detected by ESI-MS. For references related to the conversion of thiosulfonates into disulfides see: Pinnick, H. W.; Reynolds, M. A.; McDonald, R. T.; Brewster, W. D. *J. Org. Chem.* **1980**, *45*, 930-932 and cites herein.

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