

Flow detoxification of a sulfur mustard simulant with organometallic compounds enabled by an optimization algorithm

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SUPPORTING INFORMATION

1. General methods

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents were used as supplied. The solvents were dried before use. ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker Advance III 300 at 300 MHz and 76 MHz, respectively. Residual solvent peaks were used as the reference. Data for ^1H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sex = sextet, sept = septet, m = multiplet), coupling constant (Hz) and integration). Chemical shifts are reported in ppm relative to the signals corresponding to residual non-deuterated (CDCl_3 : $\delta = 7.26$ ppm). Analyses were performed on GC-FID thermoscientific trace 1310 equipped with Durabond DB-5MS (30 m, 0.250 mm \varnothing narrowbore, 0.25 μm film), the He vector gas flow rate of 1 $\text{ml}\cdot\text{min}^{-1}$ in split mode (50 $\text{mL}\cdot\text{min}^{-1}$) and the inlet injector temperature of 250 $^\circ\text{C}$. As FID detector, the air flow rate is at 350 $\text{mL}\cdot\text{min}^{-1}$ with vector gas at 35 $\text{mL}\cdot\text{min}^{-1}$. The temperature program was as follows, 5 minutes at 40 $^\circ\text{C}$, then a temperature rate of 15 $^\circ\text{C}\cdot\text{min}^{-1}$ until reach 150 $^\circ\text{C}$. Then, it stays at 150 $^\circ\text{C}$ for 1 minute and at a temperature rate of 25 $^\circ\text{C}/\text{min}$ until reach 300 $^\circ\text{C}$ and holds at 300 $^\circ\text{C}$ for 5 minutes. The GC-MS analysis was performed by low resolution GC-MS (Thermo scientific, TRACE 1310 gas chromatography and ISQ 7000 single Quadrupole Mass spectrometer) (HP5- MS stationary phase, l = 30 cm, d = 0.25 mm, film thickness = 0.25 μm). The temperature program was as follows, 5 minutes at 40 $^\circ\text{C}$, then a temperature rate of 15 $^\circ\text{C}\cdot\text{min}^{-1}$ until reach 150 $^\circ\text{C}$ holds at 150 $^\circ\text{C}$ for 2 minutes. All GC-sample were prepared using grade HPLC solvents from Fischer. All fluidic tubing, connections, adapters were manufactured by IDEX Health and Science. Syringe pumps were manufactured by Harvard apparatus (Pump 11) with Air Tite plastic syringe. All details regarding the modified Nelder-Mead method used in this study can be found elsewhere.¹

¹ D. Cortés-Borda, K. V. Kutonova, C. Jamet, M. E. Trusova, F. Zammattio, C. Truchet, M. Rodriguez-Zubiri and F.-X. Felpin, *Org. Process Res. Dev.*, 2016, **20**, 1979–1987.

2. Solvent screening for the neutralisation of CEES with PhLi or PhMgBr (batch conditions)

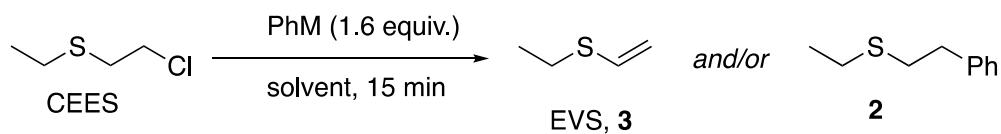
PhLi

In a 5 mL glass flask, 22 μL of CEES (1 equiv.), 21 μL of decane (0.6 equiv. internal standard), 256 μL of solvent (THF, dibutyl ether, hexane, diethyl ether or toluene) were added. Under stirring, 300 μL of PhLi solution (1 mol L⁻¹ in dibutyl ether) were added. After 15 minutes, the reaction was quenched with 0.5 mL of ethanol, and then 2 mL of diethyl ether and 2 mL of brine were added to the reaction flask. After vigorously shaking, 100 μL of the organic phase was taken, diluted to 1 mL in diethyl ether, and analyzed by GC-FID.

PhMgBr

In a 10 mL glass flask, 44 μL of CEES (1 equiv.), 42 μL of decane (0.6 equiv. internal standard), 224 μL of solvent (THF, dibutyl ether, hexane, diethyl ether or toluene) were added. Under stirring, 300 μL of PhMgBr solution (2 mol L⁻¹ in diethyl ether) were added. After 15 minutes, the reaction was quenched with 0.5 mL of ethanol, and then 4 mL of diethyl ether and 2 mL of water were added to the reaction flask. After vigorously shaking, 200 μL of the organic phase was taken, diluted to 1 mL in diethyl ether, and analyzed by GC-FID.

Table 1. Solvent screening for the neutralisation of CEES with PhMgBr and PhLi under batch conditions.¹



| Entry | PhM | Solvent | CEES | EVS, 3 | 2 |
|-------|---------------------|------------------|-------------|---------------|--------------|
| 1 | PhMgBr ² | THF | 95.0% | 0.3% | 4.7% |
| 2 | | Dibutyl ether | 1.8% | 2.5% | 95.7% |
| 3 | | Diethyl ether | 8.4% | 2.2% | 89.3% |
| 4 | | <i>n</i> -Hexane | 0.3% | 2.5% | 97.1% |
| 5 | | Toluene | 0.1% | 1.2% | 98.6% |
| 6 | PhLi ³ | THF | 0.4% | 88.2 % | 11.4% |
| 7 | | Dibutyl ether | 81.7% | 10.5% | 7.8% |
| 8 | | Diethyl ether | 77.4% | 19.4% | 3.8% |
| 9 | | <i>n</i> -Hexane | 73.0% | 5.0% | 22.0% |
| 10 | | Toluene | 64.2% | 5.1% | 30.6% |

¹ Reactions were performed on a 0.19 and 0.37 mmol scale of CEES in 0.256, and 0.224 mL of the indicated solvent for reactions with PhLi and PhMgBr, respectively, in a bath thermostated at 20 °C. Reaction was monitored by gas chromatography using decane (0.6 equiv.) as internal standard. ² Provided as a 2 M solution in diethyl ether. ³ Provided as a 1 M solution in dibutyl ether.

3. Kinetic studies under batch conditions

PhLi

In a 5 mL glass flask, 1 mL of PhLi (1.6 M in dibutyl ether) were added on a 1 mL solution containing CEES (0.16 M) and decane (0.08 M) in THF. The reaction was quenched with 0.5 mL of ethanol, and then 2 mL of diethyl ether and 2 mL of brine were added to the reaction flask. After vigorously shaking, 100 μ L of the organic phase was taken, diluted to 1 mL in diethyl ether, and analyzed by GC-FID.

PhMgBr

In a 5 mL glass flask, 1 mL of PhMgBr (2.5 M in diethyl ether) were added on a 1 mL solution containing CEES (0.25 M) and decane (0.125 M) in toluene. The reaction was quenched with 0.5 mL of ethanol, and then 2 mL of diethyl ether and 2 mL of brine were added to the reaction flask. After vigorously shaking, 100 μ L of the organic phase was taken, diluted to 1 mL in diethyl ether, and analyzed by GC-FID.

4. Kinetic studies under flow conditions

PhLi

The flow system was composed of two 5 mL Air Tite plastic syringes, charged on two syringe pumps (Pump 11 Elite) and connected to a PEEK T-shaped mixer and a 0.79 mL PFA tubular microreactor (L = 100 cm, ID = 1 mm, OD = 1.59 mm). A solution of PhLi (1.6 M in dibutyl ether) was injected in the first inlet and a solution of CEES (0.16 M) and decane as internal standard (0.08 M) in THF in the second inlet. The two solutions were injected at the same flow rate. The outlet of the reactor was collected in an aliquot and quenched with 0.5 mL of ethanol. The reaction outcome was analysed by GC-FID. The samples were prepared by the same way as described above.

| Time of reaction (min) | Flow rate (ml/min) |
|------------------------|--------------------|
| 0.5 | 1.58 |
| 1 | 0.79 |
| 2 | 0.39 |
| 3 | 0.26 |
| 4 | 0.20 |
| 5 | 0.16 |
| 7 | 0.11 |
| 10 | 0.08 |

PhMgBr

The flow system is composed of two 5 mL Air Tite plastic syringes, charged on two syringe pumps (Pump 11 Elite) and connected to a PEEK T-shaped mixer and a 0.79 mL PFA tubular microreactor (L = 100 cm, ID = 1 mm, OD = 1.59 mm). A solution of PhMgBr (2.5 M in diethyl ether) was injected in the first inlet and a solution of CEES (0.25 M) and decane as internal standard (0.125 M) in toluene in the second inlet. The two solutions were injected at the same flow rate. The outlet of the reactor was

collected in an aliquot and quenched with 0.5 mL of ethanol. The reaction outcome was analysed by GC-FID. The samples were prepared by the same way as described above.

| Time of reaction (min) | Flow rate (ml/min) |
|------------------------|--------------------|
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| 3 | 0.26 |
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| 7 | 0.11 |
| 10 | 0.08 |

For the kinetic curves the area of CEES, on the chromatogram, were normalized dividing by the decane area. The kinetic curves were fitted using the software OriginLab considering first-order kinetics. All fittings presented $r^2 \geq 0.96$.

$$AN_t = AN_{ti} + (exp^{-kt} * (AN_{t0} - AN_{ti}))$$

Where :

AN_t = Normalized area at time "t".

AN_{t0} = Normalized area at time "zero".

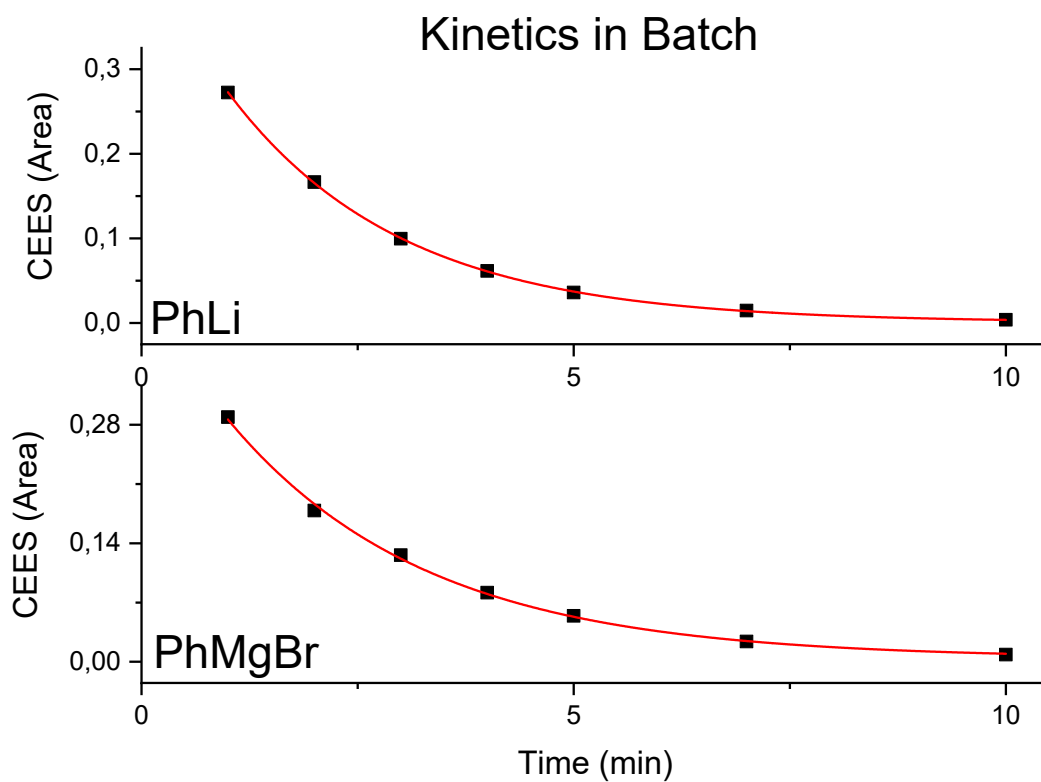
AN_{ti} = Normalized area at "infinite time"

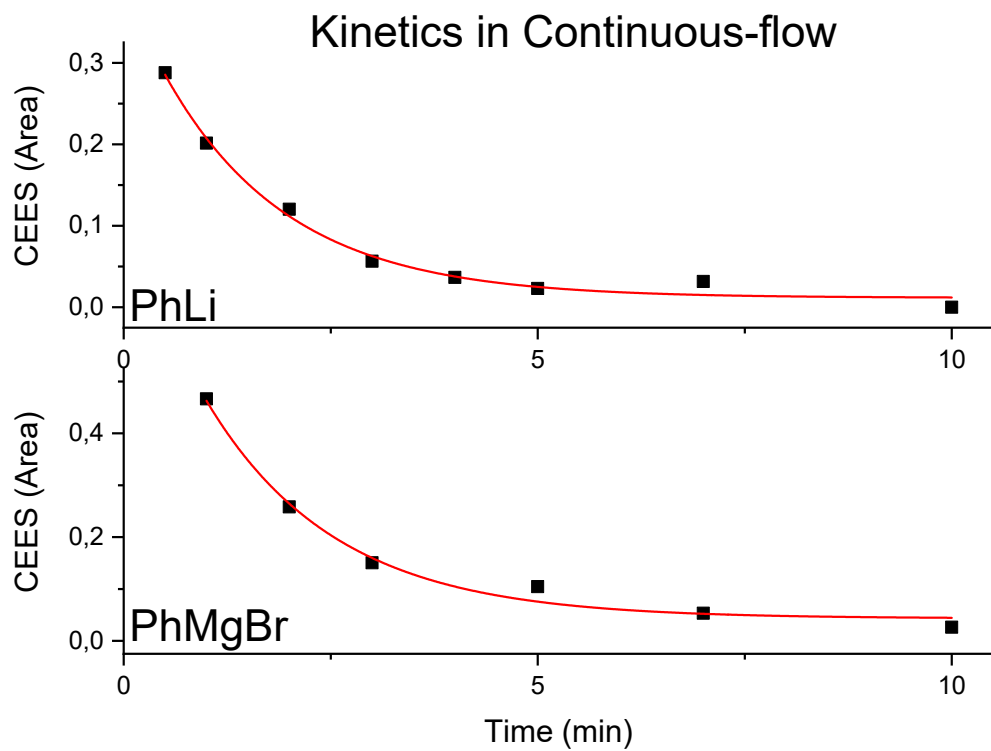
k = rate constant

t = time

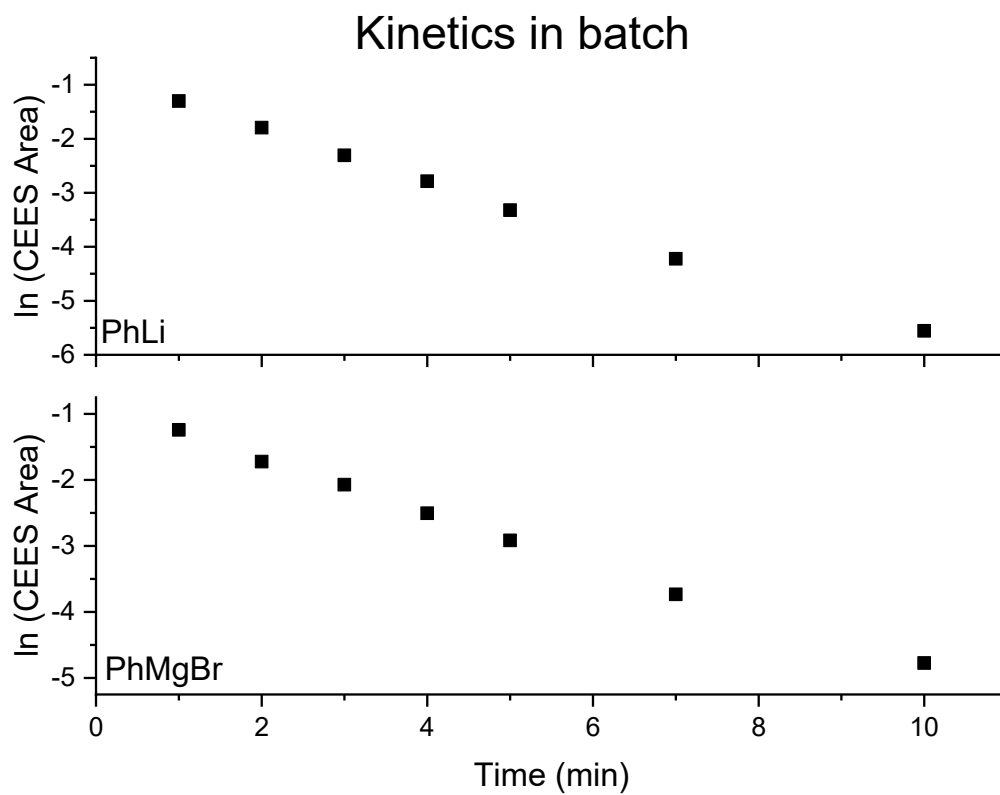
| Reactions in batch conditions | | | |
|-------------------------------|------------------------|-----------------------------|------------------------|
| Neutralizing agent : PhLi | | Neutralizing agent : PhMgBr | |
| Time (min) | CEES (Normalized area) | Time (min) | CEES (Normalized area) |
| 1 | 0.2724 | 1 | 0.28895 |
| 2 | 0.16641 | 2 | 0.17864 |
| 3 | 0.0996 | 3 | 0.12601 |
| 4 | 0.06155 | 4 | 0.0817 |
| 5 | 0.03609 | 5 | 0.05414 |
| 7 | 0.01467 | 7 | 0.02387 |
| 10 | 0.00386 | 10 | 0.00844 |

| Reactions in flow conditions | | | |
|------------------------------|------------------------|-----------------------------|------------------------|
| Neutralizing agent : PhLi | | Neutralizing agent : PhMgBr | |
| Time (min) | CEES (Normalized area) | Time (min) | CEES (Normalized area) |
| (min) | PhLi | (min) | PhMgBr |
| 0.5 | 0.28773 | 1 | 0.46663 |
| 1 | 0.20137 | 2 | 0.25818 |
| 2 | 0.12033 | 3 | 0.15041 |
| 3 | 0.05657 | 5 | 0.10438 |
| 4 | 0.03668 | 7 | 0.05332 |
| 5 | 0.02301 | 10 | 0.0264 |
| 7 | 0.03171 | --- | --- |
| 10 | 0 | --- | --- |

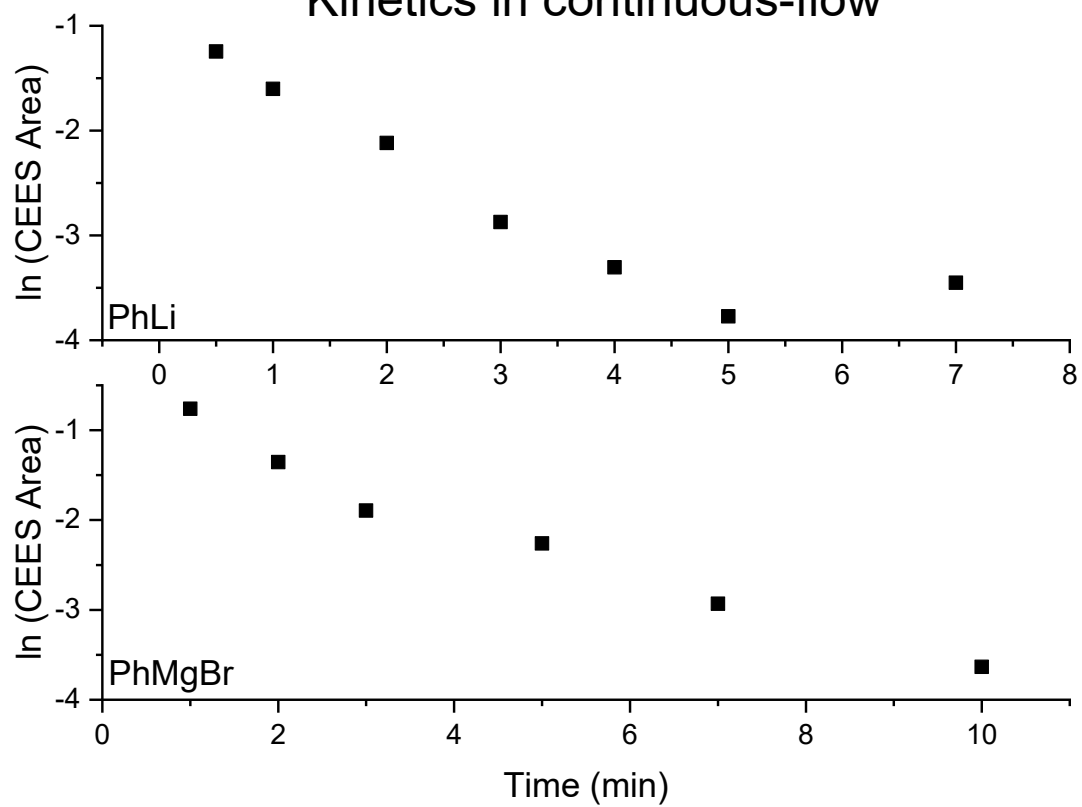




Kinetics graphs – linear

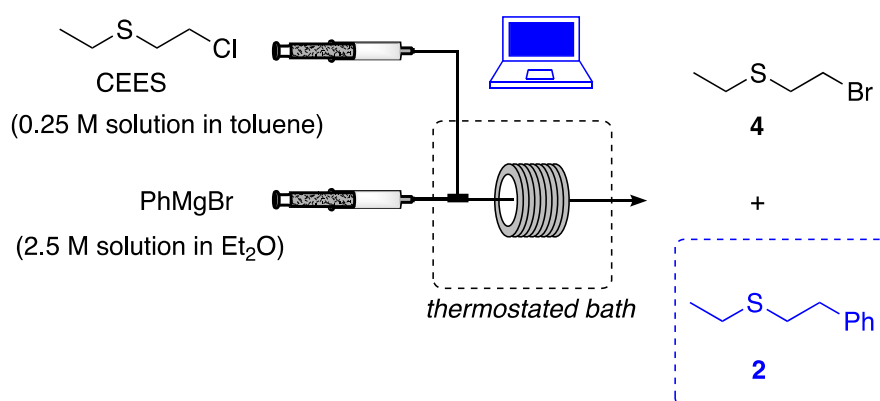


Kinetics in continuous-flow



5. Algorithm-assisted optimization of the flow neutralisation of CEES with PhMgBr to afford 1-ethylthio-2-phenylethane (2)

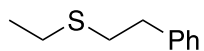
The flow system is composed of two 5 mL Air Tite plastic syringes, charged on two syringe pumps (Harvard Pump 11 Elite) and connected to a PEEK T-shaped mixer (90°) and a 0.79 mL PFA tubular microreactor (L = 100 cm, ID = 1 mm, OD = 1.59 mm) immersed in a thermostated bath. A solution of PhMgBr (2.5 M in diethyl ether) was injected in the first inlet (flow rate Q_1) and a solution of CEES (0.25 M) and decane as internal standard (0.125 M) in toluene in the second inlet (flow rate Q_2). The residence times and number of equivalents of reagents were modified by adjustments of the flow rates Q_1 and Q_2 . The outlet of the reactor was collected in flask filled with ethanol. The reaction was monitored by GC-FID ($t_R = 14.84$ min).



| Experiment | Time (min) | PhMgBr (equiv) | T (°C) | CEES (%) | 4 (%) | 2 (%) |
|------------|------------|----------------|--------|----------|-------|-----------------|
| 1 | 1 | 1.0 | 25 | 71 | 6 | 23 |
| 2 | 1 | 3.0 | 25 | 51 | 13 | 36 |
| 3 | 7 | 1.0 | 25 | 23 | 8 | 69 |
| 4 | 1 | 1.0 | 35 | 55 | 8 | 37 |
| 5 | 5 | 2.3 | 32 | 6 | 4 | 90 |
| 6 | 7 | 3.0 | 35 | <1 | <1 | 98.5 |
| 7 | 7 | 1.0 | 35 | 29 | 10 | 61 |
| 8 | 13 | 2.3 | 28 | <1 | <1 | 98.2 |
| 9 | 11 | 3.2 | 24 | 2 | 1 | 97 |
| 10 | 13.7 | 4.7 | 33 | <0.5 | 0 | >99.5 |

6. Characterizations

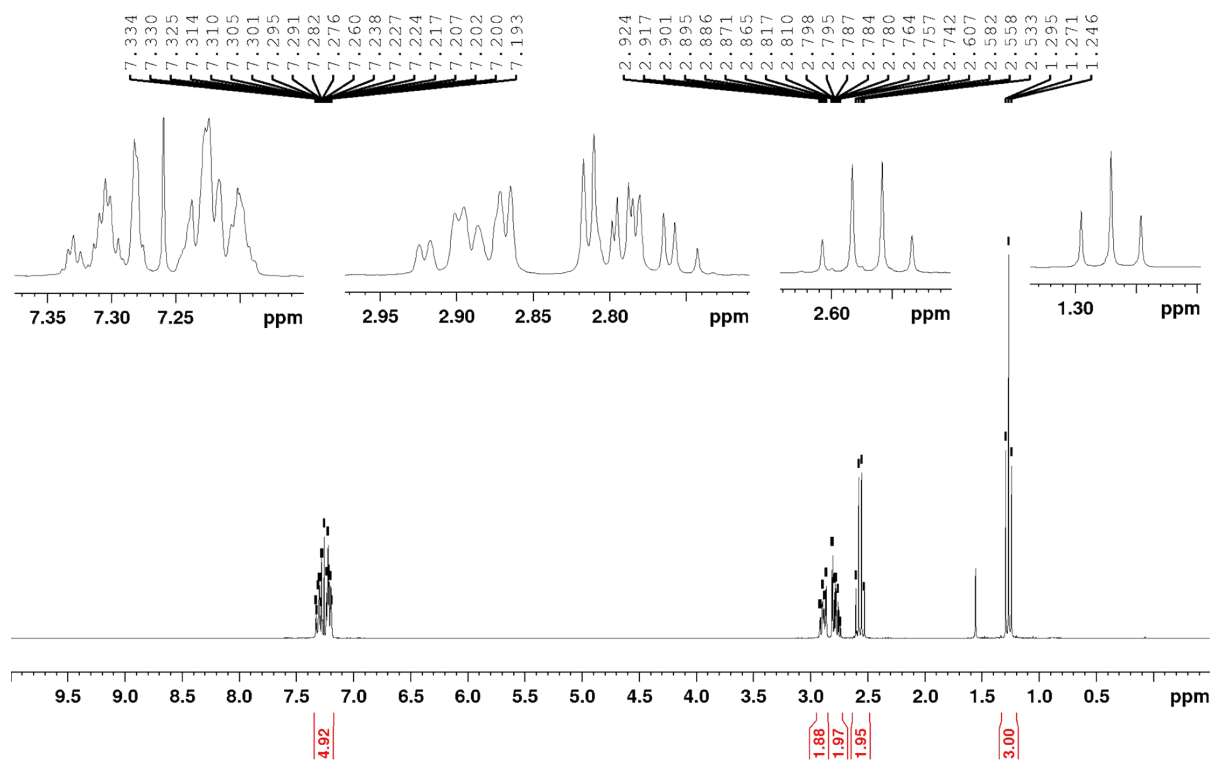
Ethyl phenethyl sulfide (2)

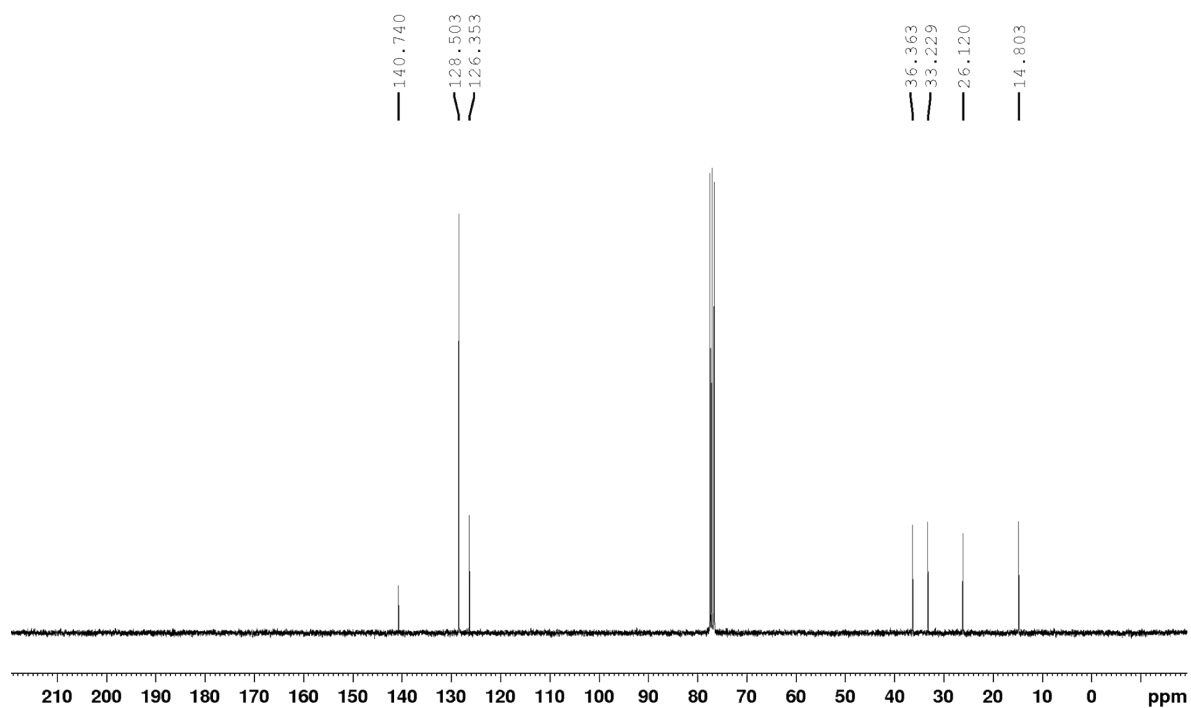


GC-FID (14.84 min), GC-MS (14.36 min).

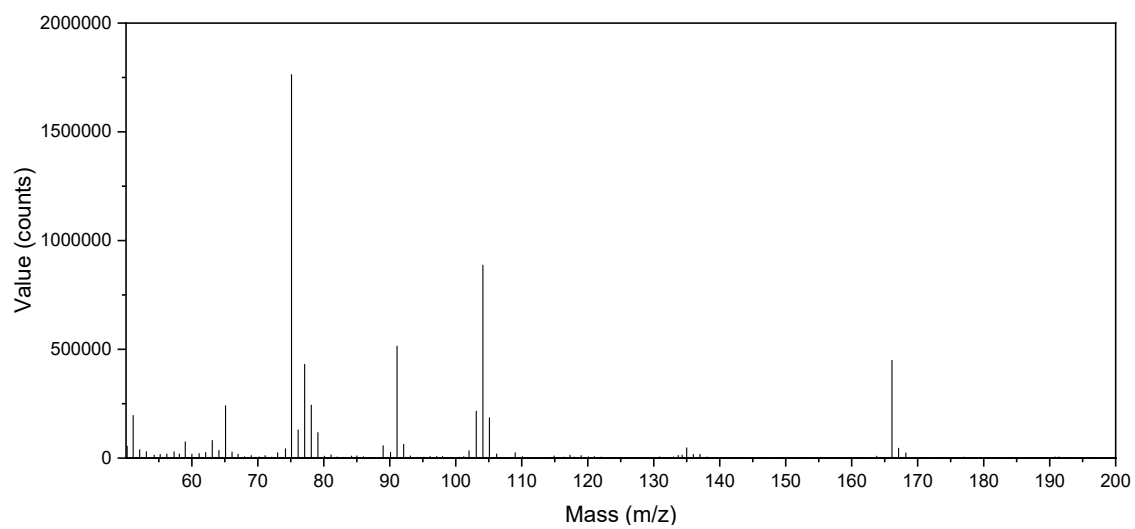
^1H NMR (300 MHz, CDCl_3): δ = 7.16-7.35 (m, 5H, ArH), 2.84-2.93 (m, 2H, CH₂), 2.73-2.83 (m, 2H, CH₂), 2.57 (q, J = 7.43, 2H, CH₂), 1.27 (t, J = 7.43, 3H, CH₃) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ = 140.7, 128.5, 126.3, 36.3, 33.2, 26.1, 14.8 ppm.



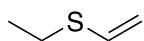


Mass Spectrum²



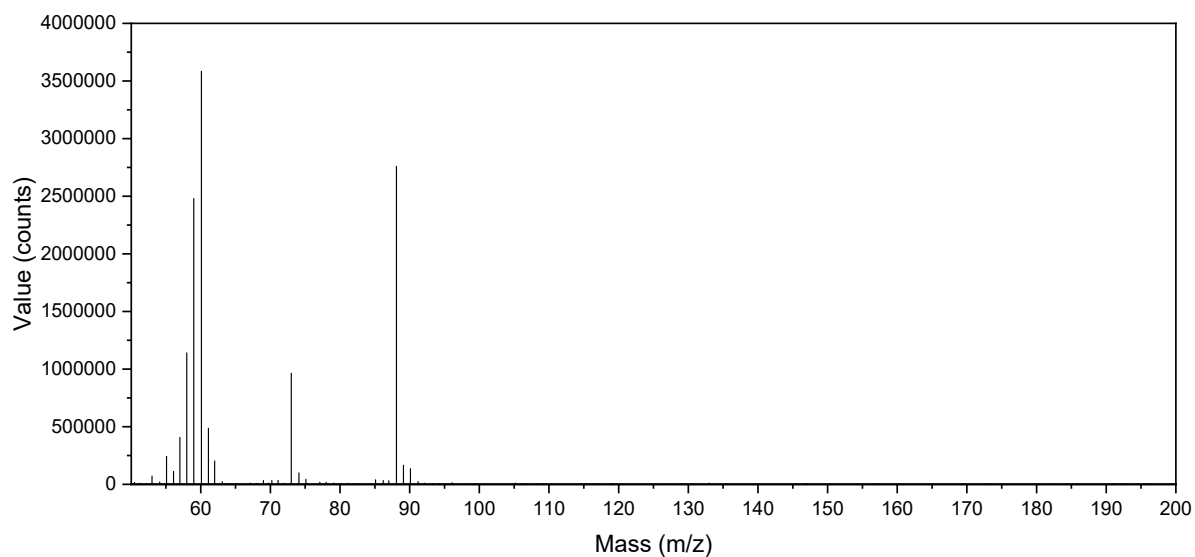
² Zorin, V. V.; Nikolaeva, S. V.; Zlotskii, S. S.; Rakhmankulov, D. L. Z. *Org. Khimii* (1985), 21(3), 660-1

Ethyl vinyl sulfide (EVS, 3)

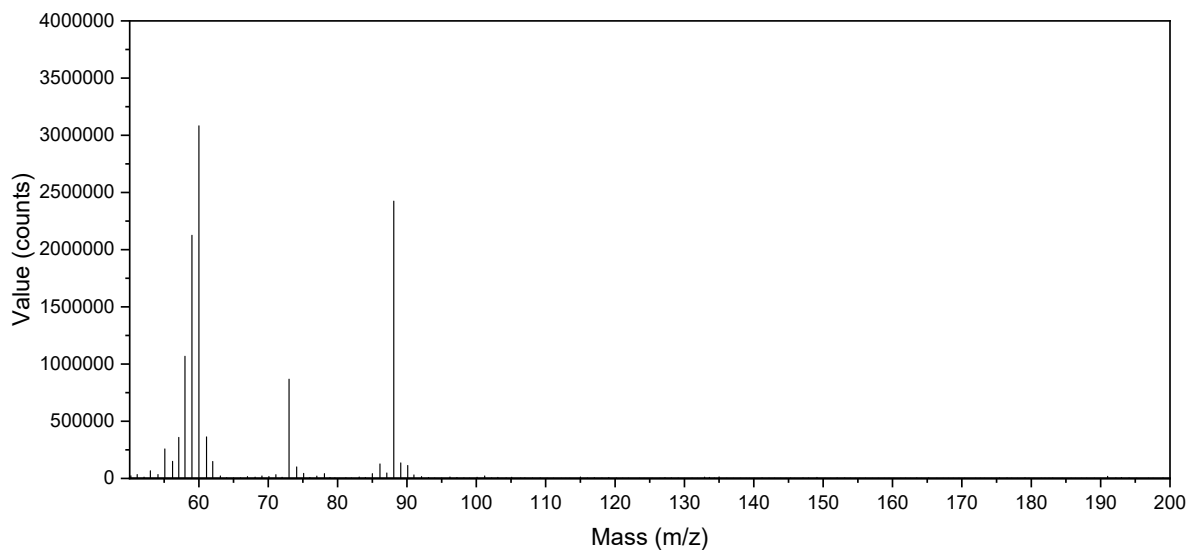


GC-FID (4.54 min), GC-MS (3.16 min). The retention time and mass spectrum were compared to a commercial sample.

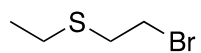
mass spectrum.



mass spectrum (authentic sample).



1-Bromo-2-(ethylthio)ethane (4)



GC-FID (10.85 min), GC-MS (10.00 min).

Mass Spectrum

