Supporting Information

Flow neutralisation of sulfur-containing chemical warfare agents with Oxone: packed-bed vs. aqueous solution

Antonin Delaune,[a] Sergui Mansour,[a] Baptiste Picard, [a] Philippe Carrasqueira,[a] Isabelle Chataigner,[a] Ludovic Jean,[a] Pierre-Yves Renard,[a] Jean-Christophe M. Monbaliu,[b] and Julien Legros*[,a]

[a.] *Normandie Université, UNIROUEN, CNRS, INSA Rouen, COBRA laboratory, F-76000 Rouen, France E-mail : julien.legros@univ-rouen.fr.*

[b.] *Center for Integrated Technology and Organic Synthesis, MolSys Research Unit, University of Liège, B-4000 Liège (Sart Tilman), Belgium*

General information

CWA simulant PhX was synthesized according to the literature.[1] CWA simulant CEES and Oxone were purchased from Sigma Aldrich and used as provided; solvents were purchased from VWR and used without further purification. All fluidic tubing, connections, adapters were manufactured by IDEX Health and Science. Syringe pumps were manufactured by Harvard apparatus (Pump 11 Elite Dual). Air tight plastic syringe were used in all experiments.

High field ^{1}H, ^{13}C and $^{31}P\{^{1}H\}$ NMR studies were realized on a 300 MHz Bruker Spectrospin spectrometer. Chemical shifts (δ) are given in regard to TMS using solvent as internal reference, *J* coupling constants are given in Hertz. Low resolution mass spectra and gas chromatograms were acquired on a Shimadzu QP2010 hybrid ionization apparatus (HP5-MS stationary phase, l = 30 cm, d = 0.25 mm, film thickness = 0.25 µm).

All reactions were conducted at room temperature (20-25 °C) except if noted otherwise, with no particular precautions with regard to residual moisture and air. However due to the toxicity of CWA simulants, reactions were carried out under closed atmosphere in a very well-ventilated fume hood. All glassware and materials in contact of simulants were immersed in a bleach bath under the fume hood for one day before further washing and/or disposal.

[1] P.-Y. Renard, H. Schwebel, P. Vayron, L. Josien, A. Valleix and C. Mioskowski, *Chem. Eur. J.*, 2002, **8**, 2910–2916.

Preparation of enriched aqueous solution $KHSO_5$ (~28% sol.) from Oxone

Oxone (30 g) was diluted in water (17.5 mL) and cooled to 0 °C and a 35% potassium hydroxide solution (10 g) was added under strong stirring. After 1 hour, the slurry was filtered, and the resulting filtrate solution contained 28.16% of $KHSO_5$ based on iodometric titration (vide infra).

Iodometric Titration of $KHSO_5$

0.3 ± 0.05 g of $KHSO_5$ obtained by precipitation of commercial Oxone (carefully weighed at least three time), and then added to a 250 mL beaker containing 75 mL water, 10 mL of a 20% (v/v) H_2SO_4 aqueous solution, and 10 mL of 25% (w/w) KI aqueous solution under stirring. The specimen was then immediately titrated with a 0.1 M sodium thiosulfate aqueous solution until a pale yellow color was reached. 2 mL of starch indicator solution was then added, and the solution turned deep blue. Titration was maintained until a colorless endpoint that persists for at least 30 seconds.

General procedure for the neutralization of CWA simulants PhX with enriched Oxone® under batch conditions

PhX (20 mg, 0.0608 mmol) was added in a sealed tube containing $KHSO_5$ 28.16% in aqueous solution (0.1 mL, 3.65 mmol, 6 eq.) under stirring. After 10 minutes, the reaction was quenched with an aqueous solution of $Na_2S_2O_3$ (30% w/w), still under stirring. The reaction medium was extracted with ethyl acetate, and the recovered organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford pure ethyl phenylphosphonic acid as a slightly yellowish oil (10.96 mg, 98% yield).

In order to perform a kinetic study of PhX neutralization by Oxone under Batch conditions, the operation was repeated by varying the reaction time (1, 3, 5, 8 and 10 minutes).

General procedure for the neutralization of CWA simulant PhX by enriched Oxone® under flow conditions

Neat PhX was injected at a flow rate of 2.16 µL.min^{-1} for 10 minutes. Enriched Oxone (1/3 diluted) was injected at a 38.84 µL.min^{-1} flow rate for 20 minutes. These two substrates were mixed together in a PEEK T-shaped micromixer (1/16 in). The main reactor was made of a 20.38 cm long PFA tubing (OD = 1/8 in., ID = 1.56 mm, V = 410 µL). The reaction proceeded in the reactor for t^R = 10 minutes (Q_{tot} = 41 µL.min^{-1}) before being collected in a tube containing the 30% (w/w) aqueous solution of $Na_2S_2O_3$ under strong magnetic stirring in order to quench the oxidant. The reaction medium was extracted with ethyl acetate, the recovered organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford phenylphosphonic acid monethyl ester as a slightly yellowish oil (13.70 mg, 97% yield).

The flow rate values were fixed in order to perform a kinetic study of the PhX neutralization by Oxone in continuous flow and these values are given in **Table 1**. The kinetic study of the neutralization is thus carried out by varying the length of the reactor which will affect proportionally the reaction time (residence time). The values of the various parameters required for the kinetic study are summarized in **Table 2**.

Table 1. Fixed flow rates of the continuous flow system

$Q_{Tot.}$	Q_{oxone}	Q_{PhX}
41µL.min^{-1}	38.84 µL.min^{-1}	2.16 µL.min^{-1}

Table 2. Parameters used for the kinetic study of the neutralization reaction

Reaction time	Length of reactor	Volume PhX injected	Volume oxone injected
1 min	2.04 cm	2.16 µL.min^{-1} for 10 minutes → 21.6 µL de PhX	Q = 38.84µL.min^{-1} for 11 minutes → 383.24 µL of $KHSO_5$ aq. sol.
2 min	4.08 cm		Q = 38.84µL.min^{-1} for 12 minutes → 466.08 µL of $KHSO_5$aq. sol.
3 min	6.12 cm		Q = 38.84µL.min^{-1} for 13 minutes → 504.92 µL of $KHSO_5$ aq. sol.
5 min	10.2 cm		Q = 38.84µL.min^{-1} for 15 minutes → 582.6 µL of $KHSO_5$ aq. sol.
7.5 min	15.3 cm		Q = 38.84µL.min^{-1} for 17.5 minutes → 679.7 µL of $KHSO_5$ aq. sol.
10 min	20.4 cm		Q = 38.84µL.min^{-1} for 20 minutes → 776.8 µL of $KHSO_5$ aq. sol.

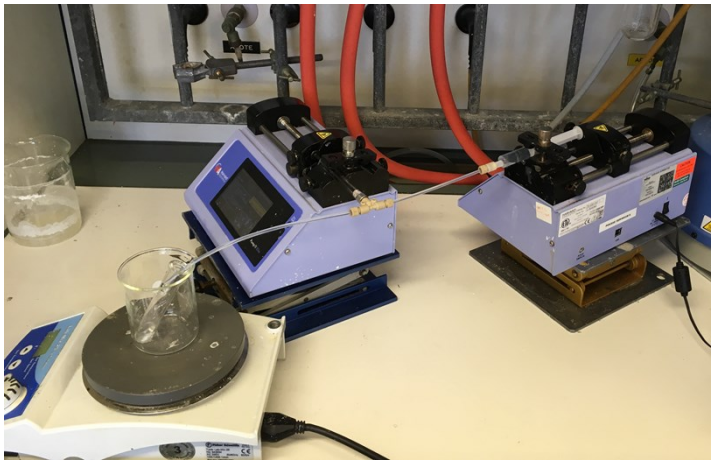
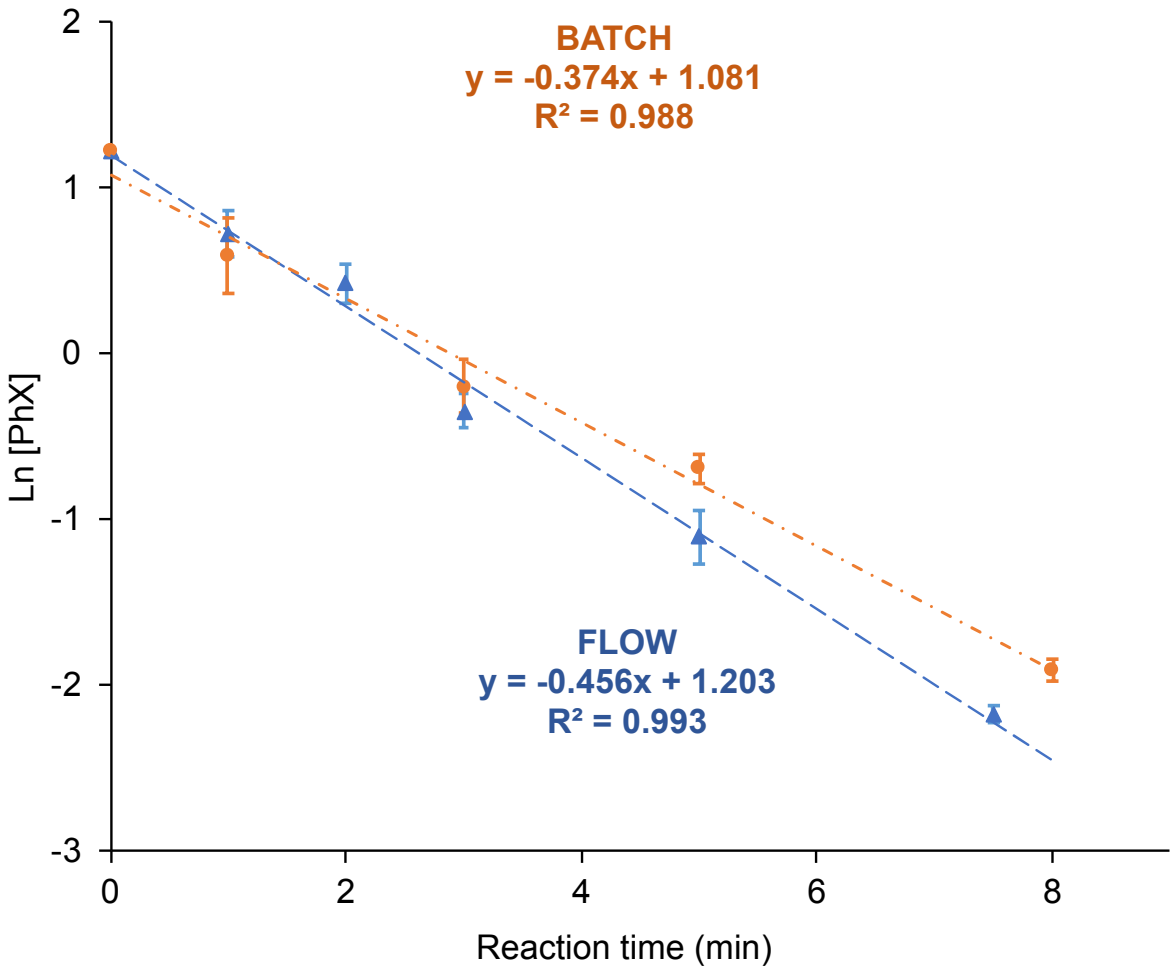


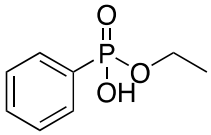
Figure 1 – Set-up for the flow neutralization of PhX with aqueous solution of $KHSO_5$ (enriched Oxone).

Kinetic measurements under flow conditions			
Reaction time (min)	[PhX] (mol/L)	Ln [PhX]	Standard deviation
0	3.43	1.232560261	0
1	1.9208	0.652741766	0.1386218
	2.1952	0.786273159	
	2.0923	0.738263939	
2	1.5435	0.434052565	0.120457641
	1.4063	0.340962142	
	1.6464	0.498591086	
3	0.686	-0.376877651	0.104788231
	0.6174	-0.482238167	
	0.8232	-0.194556094	
5	0.2744	-1.293168383	0.162095476
	0.2058	-1.580850456	
	0.5145	-0.664559724	
7.5	0.1029	-2.273997636	0.052394115
	0.1715	-1.763172012	
	0.0686	-2.679462744	
10	0	-	-
	0	-	

Kinetic measurements under batch conditions			
Reaction time (min)	[PhX] (mol/L)	Ln [PhX]	Standard deviation
0	3.43	1.232560261	0
1	1.6121	0.477537677	0.224920141
	2.058	0.721734637	
	1.7836	0.578633794	
3	0.686	-0.376877651	0.157182346
	0.9947	-0.005314095	
	0.7889	-0.237115709	
5	0.4116	-0.887703275	0.086319774
	0.5145	-0.664559724	
	0.5831	-0.539396581	
8	0.1715	-1.763172012	0.071401144
	0.2058	-1.580850456	
	0.0686	-2.679462744	
10	0	-	-
	0	-	



Phenylphosphonic acid monethyl ester: Starting from PhX (25 mg), phenylphosphonic acid monethyl ester was obtained directly as a slightly yellowish oil (13.70 mg, 97%). NMR data were consistent with literature.[2]



^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.64 (s, 1H), 7.84 – 7.77 (m, 2H), 7.54 – 7.49 (m, 1H), 7.44 – 7.38 (m, 2H), 4.10 – 4.0 (m, 2H), 1.27 (t, *J* = 7.5 Hz, 3H).

^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$): δ = 20.40 (s).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 132.27 (d, *J* = 2.25 Hz), 131.48 (d, *J* = 9.75 Hz), 129.23 (d, *J* = 196.5 Hz), 128.43 (d, *J* = 15 Hz), 62.06 (d, *J* = 5.25 Hz), 16.32 (d, *J* = 6 Hz).

General procedure for the neutralization of CWA simulants CEES by enriched Oxone® in batch conditions

CEES (40 µL, 0.343 mmol) was added with KHSO5 28.16% in aqueous solution (0.580 mL, 2.07 mmol, 6 eq.) in a sealed tube and stirred for 10 minutes. After 10 minutes, the reaction was quenched with an aqueous solution of $Na_2S_2O_3$ (30% w/w), still under stirring. The reaction medium is extracted with ethyl acetate, dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. NMR and GC-MS analysis showed that the majority of the CEES was over-oxidized to sulfone ($CEESO_2$), the other part did not react.

General procedure for the neutralization of CWA simulants CEES by regular Oxone® under flow conditions

- **Packed-bed column preparation:**

The oxone was ground with a mortar and pestle. After inserting a fritted and about 3-4 mm of sand into a 70 mm column (13 mm ID, volume V = 9.3 mL), oxone (5.6 g, 18.2 mmol) was conditioned by tapping on the bench and priming with ethanol. The column was sealed with an end-cap after adding about 5-8 mm of sand. The column was then packed by flowing ethanol through the column at 1 $ml.min^{-1}$ until no air bubbles were observed. The volume of

[2] Y. Park, I. Jeon, S. Shin, J. Min and P. H. Lee, *J. Org. Chem.*, 2013, **78**, 10209–10220.

the column, averaging 4.8 mL, was determined from the difference between the anhydrous and wet weights divided by the density of the solvent (EtOH).

- **General procedure for the flow oxidation of CWA simulant CEES by Oxone:**

The CWA simulant CWA (50 mg, 0.4 mmol) was dissolved in a solution of ethanol/trifluoracetic acid (1:1 v/v, 2 mL). After flushing the column with ethanol, the reagent solution was introduced in an Air-Tight plastic syringe (2.5 mL) and injected through the column with a flow rate of 1 $mL.min^{-1}$ by using syringe pump. When injected, a solution of ethanol/trifluoroacetic acid (1:1 v/v, 10 mL) is introduced with an Air-Tight plastic syringe into the device at a flow rate of 1 $mL.min^{-1}$ to rinse it. The solution was collected in a round bottomed flask containing an aqueous solution of $Na_2S_2O_3$ (30% w/w), under stirring. The solution was neutralized with aqueous solution of K_2CO_3, extracted with 25 mL of ethyl acetate, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a pure product, analyses by GC-MS and NMR. CEESO was obtained as a slightly reddish oil (55.1 mg, 98% yield).

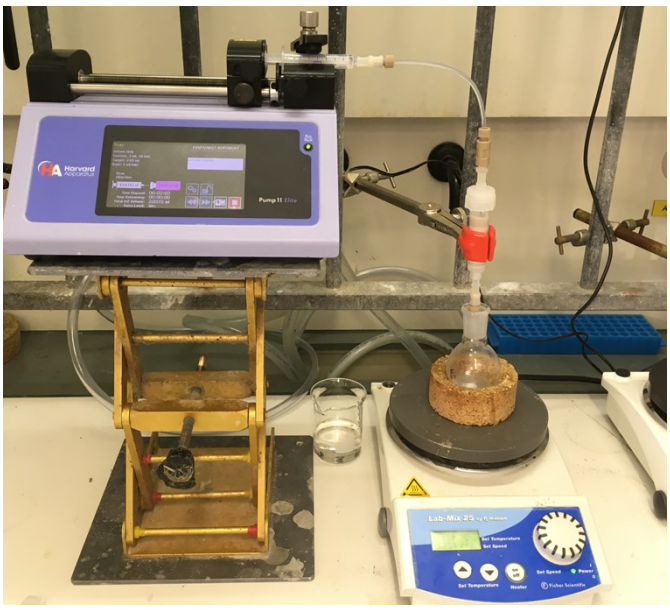
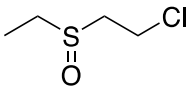


Figure 2 - Device for CEES flow neutralization with Oxone®

CEESO: Starting from CEES (50 mg), CEESO was obtained directly as a slightly reddish oil (55.1 mg, 98%). NMR data were consistent with literature.[3]

[3] B. Picard, B. Gouilleux, T. Lebleu, J. Maddaluno, I. Chataigner, M. Penhoat, F.-X. Felpin, P. Giraudeau and J. Legros, *Angew. Chem. Int. Ed.*, 2017, **56**, 7568–7572.



^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.00 – 3.85 (m, 2H), 3.10 – 2.95 (m, 2H), 2.78 (q, *J* = 7 Hz, 1H), 1.35 (t, *J* = 9 Hz,3H).

$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ = 54.31 (CH_2), 46.28 (CH_2), 37.07 (CH_2), 6.8 (CH_3).

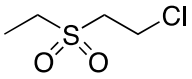
GC (50-250 DB5 method): Observed retention time: 7.044 min.

MS (EI/quadrupole) m/z (%): 63(100), 76(40), 78(40), 112(40), 114(15), 140(30), 142 (15).

General procedure for the synthesis of $CEESO_2$

$KMnO_4$ (1.5 g, 9.5 mmol) is dissolved in a water/acetonitrile mixture (1:3 v/v, 20 mL) in a 100 mL round bottomed flask. The CWA simulant CEES (63 mg, 0.5 mmol) is then added. The medium is then cooled to 0°C by an ice bath, and concentrated sulfuric acid (1.1 mL, 20mmol) is added dropwise (Caution is advised when adding the acid to keep the medium cold during addition, to avoid explosive manganese heptoxyde formation). After 17 h, the reaction is quenched with an aqueous solution of sodium bisulfite (40% w/w) until full discoloration. The resulting mixture is extracted with ethyl acetate and concentrated to afford a pure product, analyses by GC-MS and NMR. Starting from CEES (63 mg), $CEESO_2$ was obtained directly as a pale-yellow liquid (74 mg, 95%). NMR data were consistent with literature.[3]

$CEESO_2$: Starting from CEES (63 mg), $CEESO_2$ was obtained directly as a pale-yellow liquid (74 mg, 95%).



^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (t, *J* = 7.5 Hz, 2H), 3.38 (t, *J* = 7.5 Hz, 2H), 3.10 (q, *J* = 7 Hz, 2H), 1.41 (t, *J* = 7 Hz, 3H).

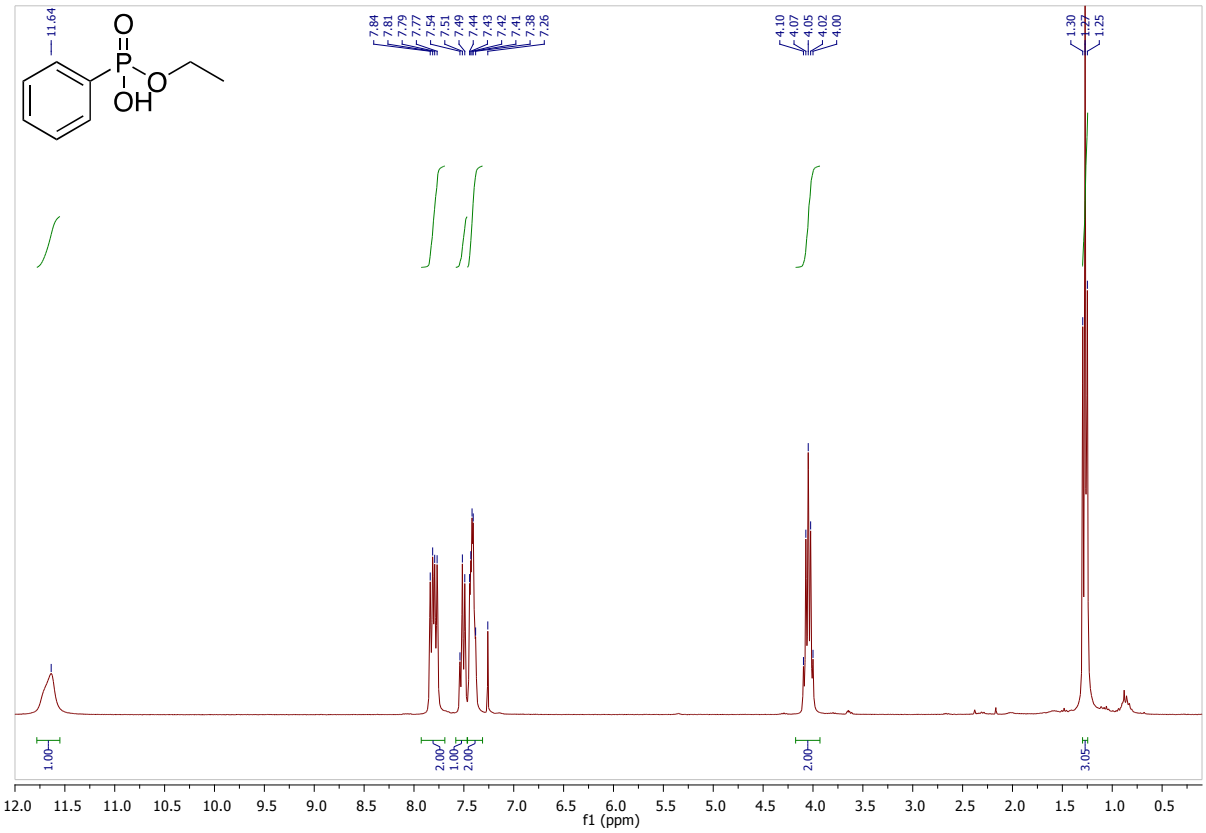
$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ = 54.21 (CH_2), 49.03 (CH_2), 36.01 (CH_2), 6.64 (CH_3).

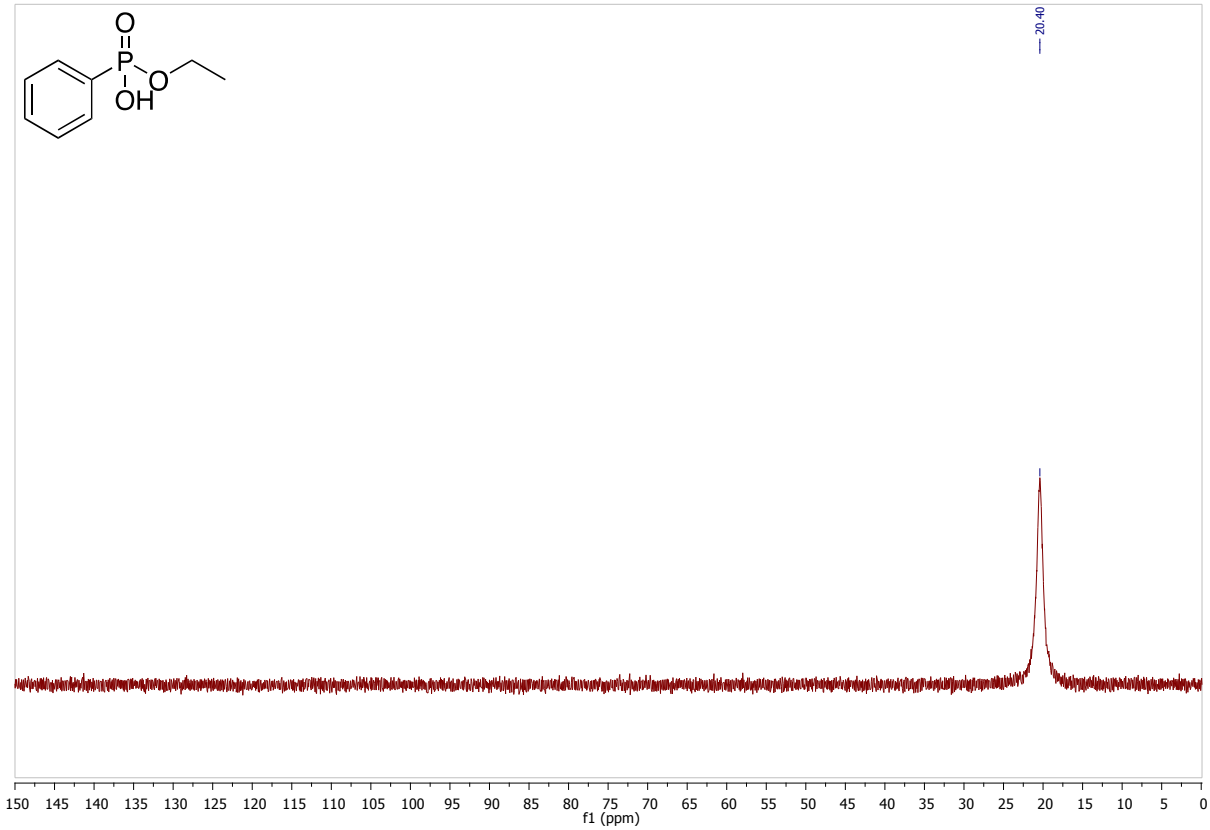
GC (50-250 DB5 method): Observed retention time: 7.227 min.

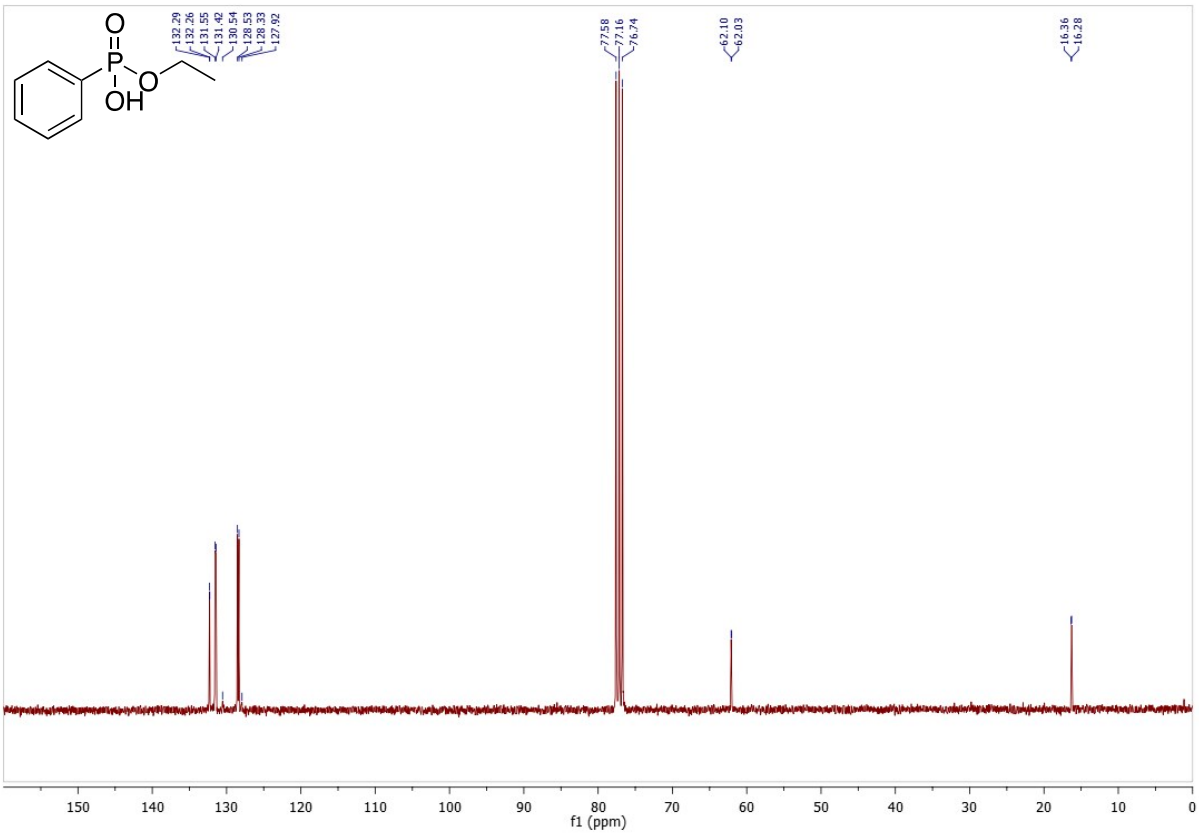
MS (EI/quadrupole) m/z (%): 63(100), 65(30), 128(40), 130(15).

High-field NMR spectra

Phenylphosphonic acid monethyl ester






O
P
O
OH
132.29
132.26
131.55
131.42
130.54
128.53
128.33
127.92
77.58
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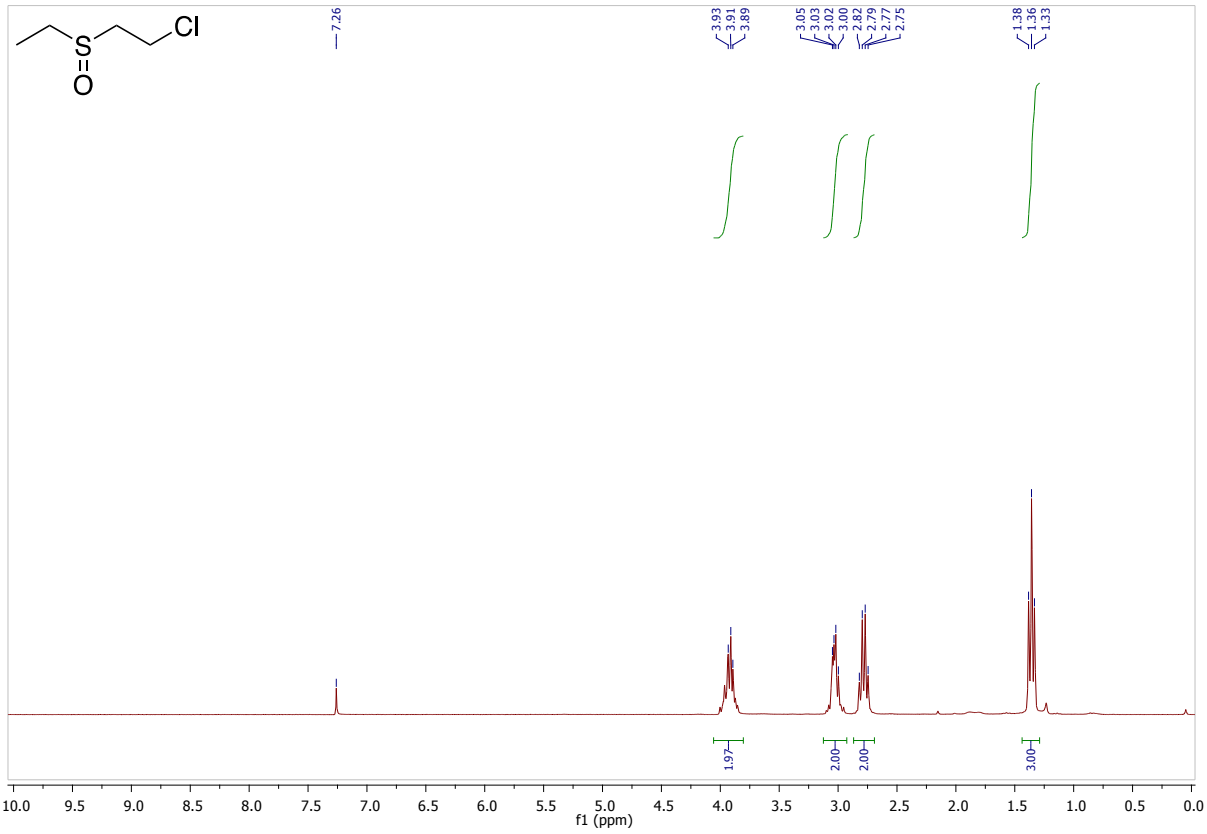
76.74
62.10
62.03
16.36
16.28
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

CEESO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O
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3.93
3.91
3.89
3.05
3.03
3.02
3.00
2.82
2.79
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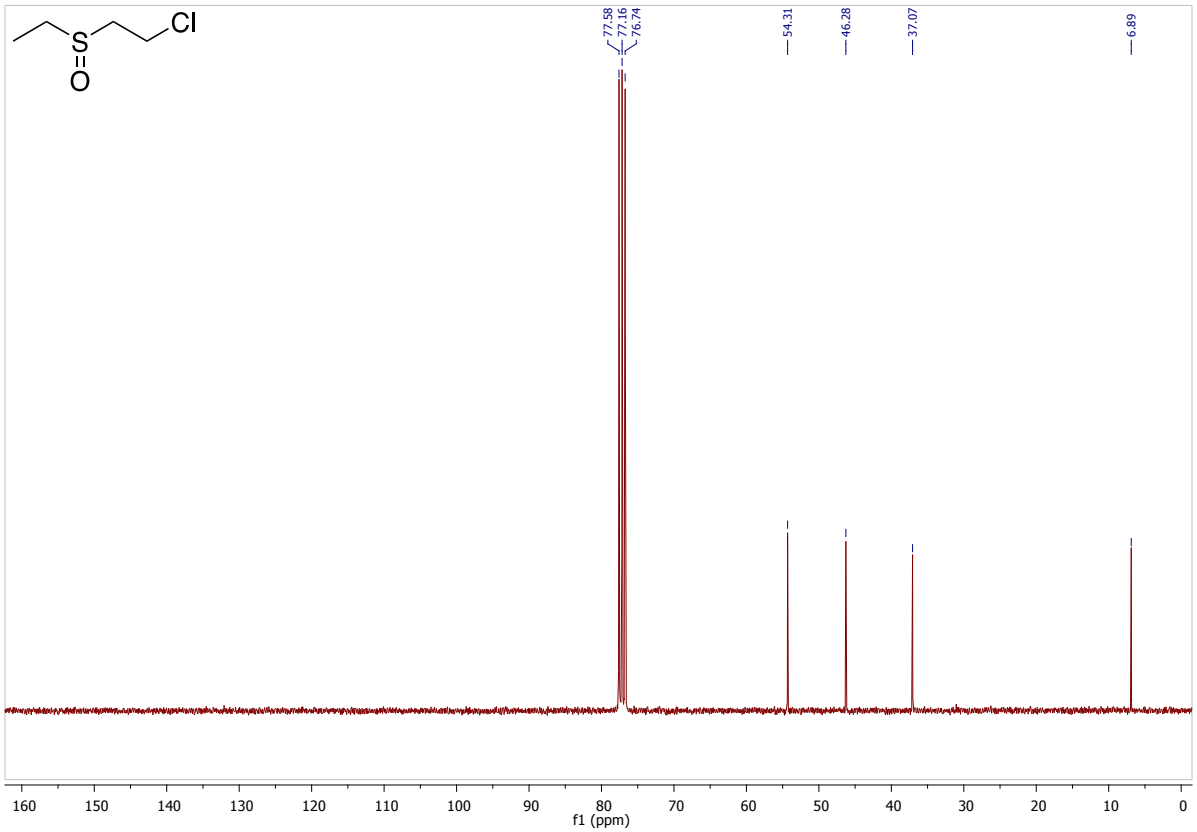
2.75
1.38
1.36
1.33
1.97
2.00
2.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Cl
S
O
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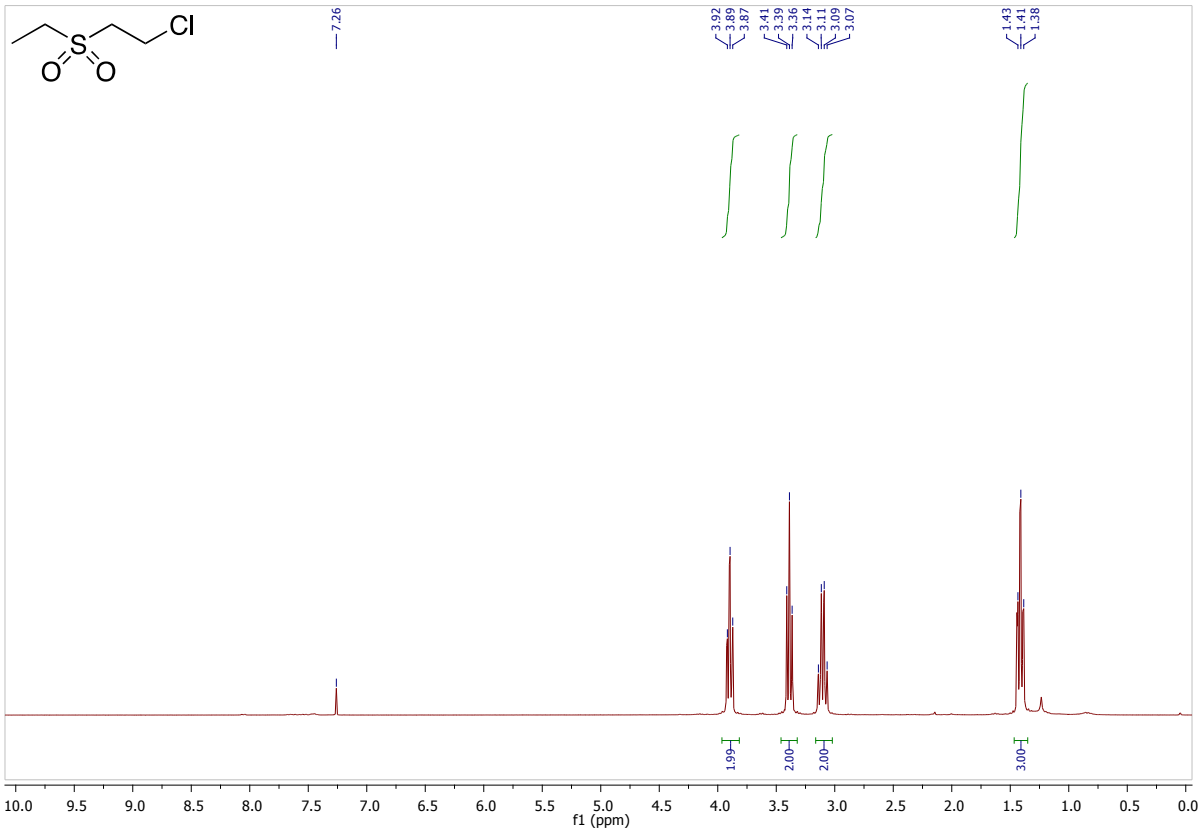
46.28
37.07
6.89
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

CEESO2


Cl
S
O
O
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3.89
3.87
3.41
3.39
3.36
3.14
3.11
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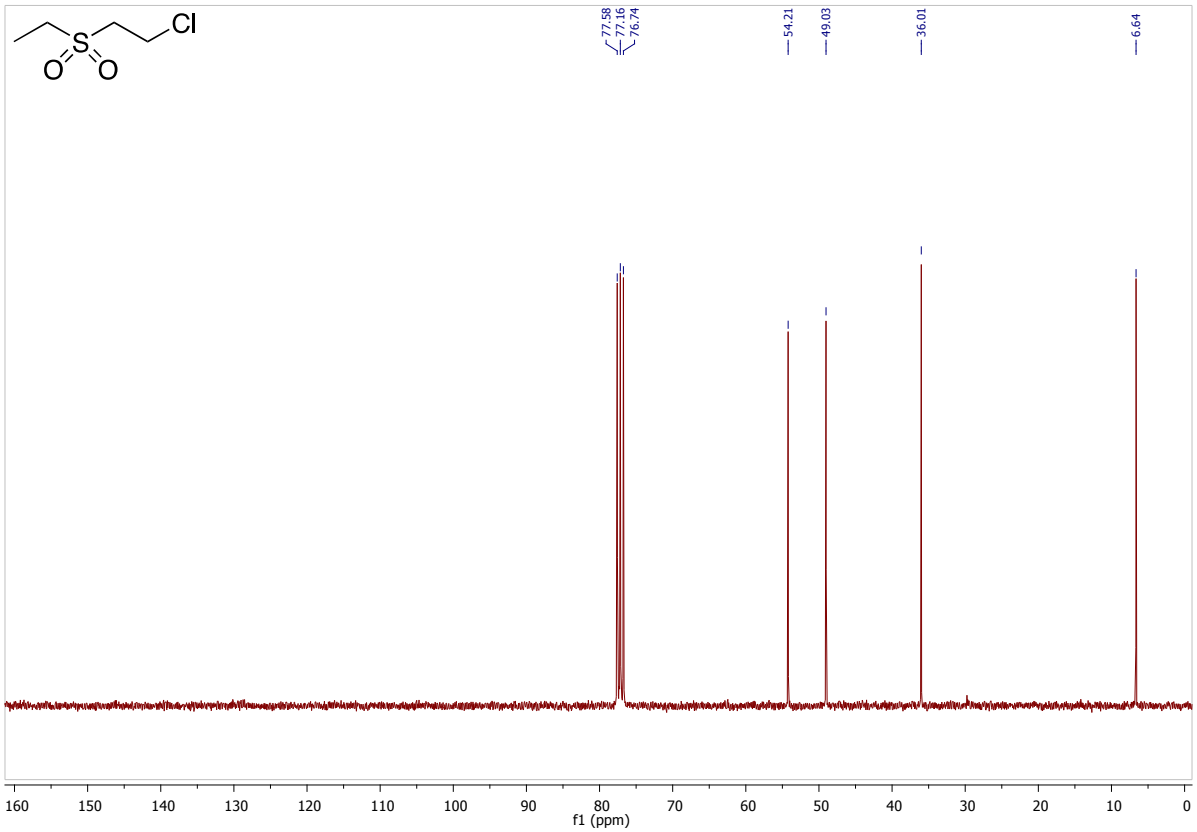
1.43
1.41
1.38
1.99
2.00
2.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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S
O
O
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77.16
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36.01
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160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Superimposition of CEES derivatives

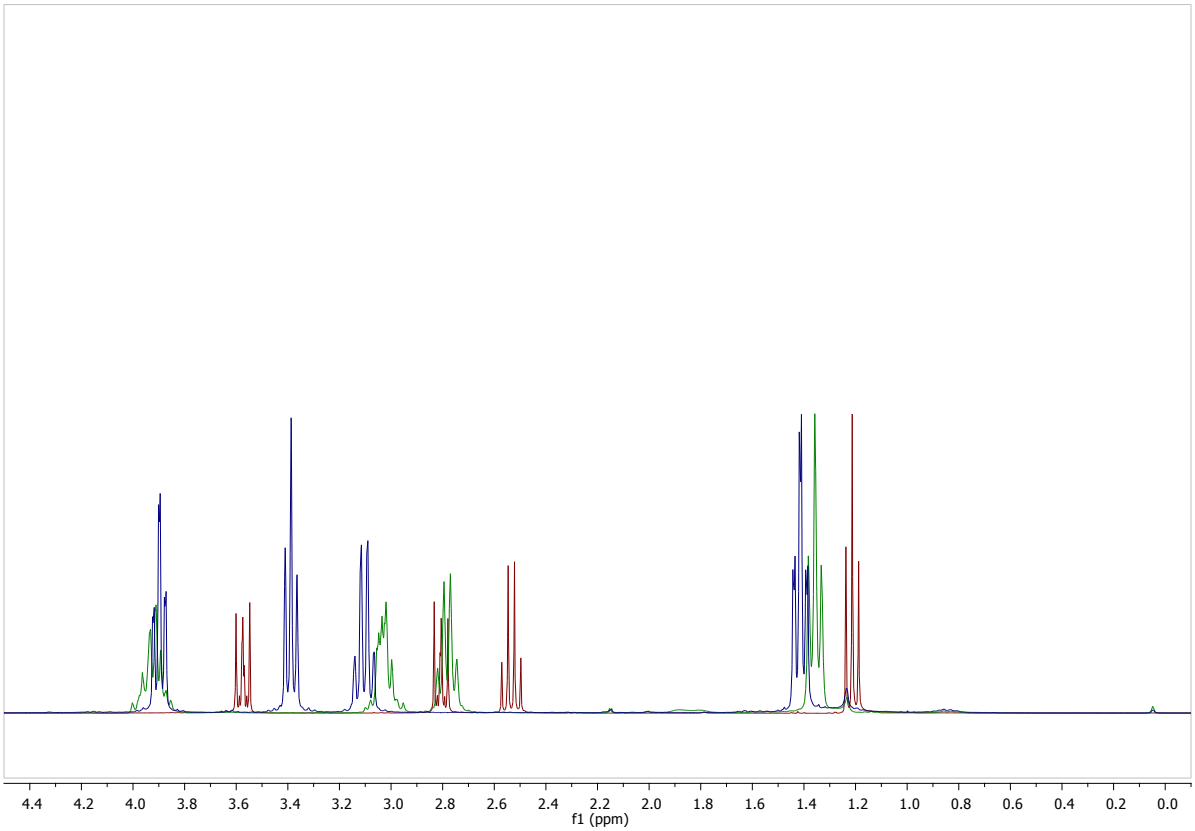

Figure 3 – Superimposition of CEES derivatives. Red signals: CEES, Green signals: CEESO, Blue signals: $CEESO_2$.