Reaction Monitoring

International Edition: DOI: 10.1002/anie.201702744
German Edition: DOI: 10.1002/ange.201702744

# Oxidative Neutralization of Mustard-Gas Simulants in an On-Board Flow Device with In-Line NMR Monitoring

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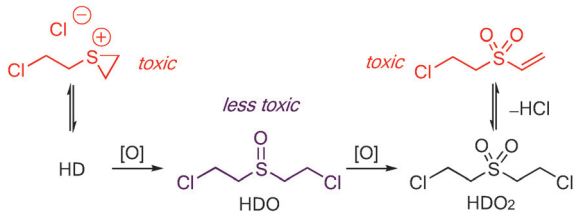
**Abstract:** *The fast and effective neutralization of the mustard-gas simulant 2-chloroethyl ethyl sulfide (CEES) using a simple and portable continuous flow device is reported. Neutralization takes place through a fully selective sulfoxidation by a stable source of hydrogen peroxide (alcoholic solution of urea–$H_2O_2$ adduct/$MeSO_3H$ freshly prepared). The reaction progress can be monitored with an in-line benchtop NMR spectrometer, allowing a real-time adjustment of reaction conditions. Inherent features of millireactors, that is, perfect control of mixing, heat and reaction time, allowed the neutralization of 25 g of pure CEES within 46 minutes in a 21.5 mL millireactor ($t^R = 3.9$ minutes). This device, which relies on affordable and nontoxic reagents, fits into a suitcase, and can be deployed by police/military forces directly on the attack site.*

The use of chemical weapons by terrorist groups has become a plausible threat since several chemical warfare agents (CWA) are currently available to perpetrators, including mustard compounds with the simplest bis(2-chloroethyl) sulfide as prominent member.[1,2] This blister agent is well-known under common names such as mustard agent, yperite or HD; this viscous liquid is used as a weapon through dispersion by spraying or explosion, hence the denomination "mustard gas". The extreme toxicity of HD is due to the equilibrium with the strongly electrophilic episulfonium form, which also makes it carcinogenic (Scheme 1). Conventional processes for the destruction of large quantities of mustard agents (e.g. shells from World War I, Syrian stockpiles) require highly secure sites, specifically dedicated for this purpose. The neutralization/destruction of chemical warfare agents is generally conducted under harsh conditions, that is, direct pyrolysis, hydrolysis in strongly basic solutions or transformations with aggressive oxidants.[3–6] The limited solubility of HD in water explains the poor efficiency of the hydrolysis path. In contrast, oxidation has to be regarded as the method of choice to neutralize this CWA, at least if the process retained is very selective toward the sulfoxide, since overoxidation affords a highly toxic sulfone (Scheme 1).




***Scheme 1.*** Oxidation of mustard gas yperite (HD) into the corresponding sulfoxide (HDO) and sulfone ($HDO_2$).

In recent years, the academic community has made progresses towards the implementation of highly selective sulfoxidation of HD simulants with peroxides, singlet oxygen, hypochlorite, for instance, in the presence of metal promoters (including polyoxometallates and metal–organic frameworks) or in microemulsion media.[7–17] However, most of these protocols are unsuited for large scales or use in real situation. Considering that the terrorist threat would most likely embody the form of a small and concealable chemical bomb introduced into a densely populated area, the possibility of intervening directly on site represents a decisive advantage. Therefore, the deployment of robust and transportable equipment allowing a rapid and selective oxidation of mustard gas is of utmost importance. Continuous flow devices fulfil all these requirements: they are compact systems which allow high control on reaction time as well as on heat and mass transfer, and the process can be easily up-scaled without optimization of new conditions.[18,19] Moreover, hazardous chemicals such as oxidants are easily handled in a flow system,[20–24] and it offers the possibility of automation and in-line analysis.[25–27] Herein we show that the fast neutralization of sulfur mustard simulants can be achieved by fully selective oxidation in a flow apparatus monitored by an in-line $^1$H NMR low-field instrument (Scheme 2).

The toolbox of organic chemists overflows with oxidants, among which hydrogen peroxide is certainly one of the most convenient to use, especially under its UHP form (urea-$H_2O_2$

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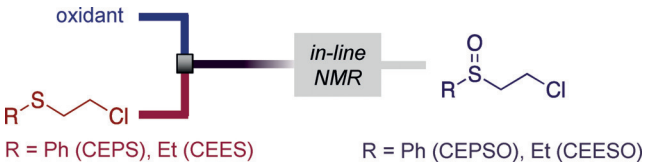
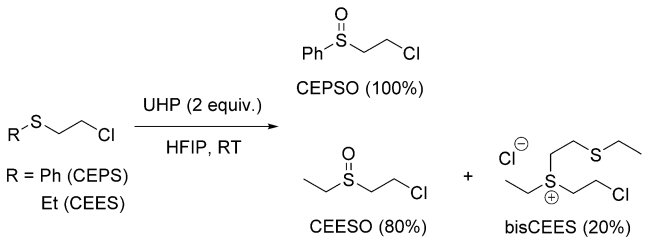



***Scheme 2.*** An integrated flow system with in-line NMR monitoring for the sulfoxidation of mustard simulants chloroethyl phenyl sulfide (CEPS) and chloroethyl ethyl sulfide (CEES).

adduct; m.p. 90 °C), a very stable solid, hence transportable, source of anhydrous hydrogen peroxide. Whereas $H_2O_2$ generally requires the assistance of a promoter for efficient oxygen transfer, it has been shown that the simple use of hexafluoroisopropanol (HFIP) as solvent was able to efficiently activate the oxidant;[28–31] this activation is mostly due to an increase of the electrophilicity of peroxide oxygen through strong H-bonding with the solvent.[31,32] Notably, Bégué and co-workers reported that complete oxidation of various sulfides into sulfoxides was attained within only 5 minutes reaction time.[28] Hence, a preliminary experiment involving mustard gas simulants (CEPS and CEES) and a solution of UHP (2 equiv) in HFIP was run in a classical batch setup (Scheme 3).




***Scheme 3.*** Oxidation of half-mustards CEPS and CEES with UHP in HFIP.

Full conversion of both substrates rapidly occurred and CEPS underwent fully selective sulfoxidation (CEPSO). However CEES, the closest analogue of the real warfare agent HD,[33] was converted into sulfoxide CEESO (80 %), along with 20 % of a dimeric sulfonium salt (bisCEES), whose formation has already been described, among several products, during hydrolysis.[34] A blank NMR experiment was then performed by diluting CEES in pure HFIP and after only 5 minutes, the dimeric sulfonium salt (bisCEES), was formed selectively. The possible reversible dimerization of the bisCEES in the presence of UHP was evaluated on a benchmark test, but unfortunately, after 15 days of stirring the dimeric sulfonium salts remained very stable. Thus, to avoid this competitive and irreversible dimerization affording a compound of unknown toxicity, we switched to the less polar solvent methanol,[35,36] in the presence of methanesulfonic acid as proton donor to dissociate/activate UHP. Actually, CEES proved to remain stable in a MSA/methanol mixture for hours in the absence of oxidant. These new conditions (methanol/MSA/UHP) were implemented in a two-stream flow reactor shown on Figure 1. Neat CEES

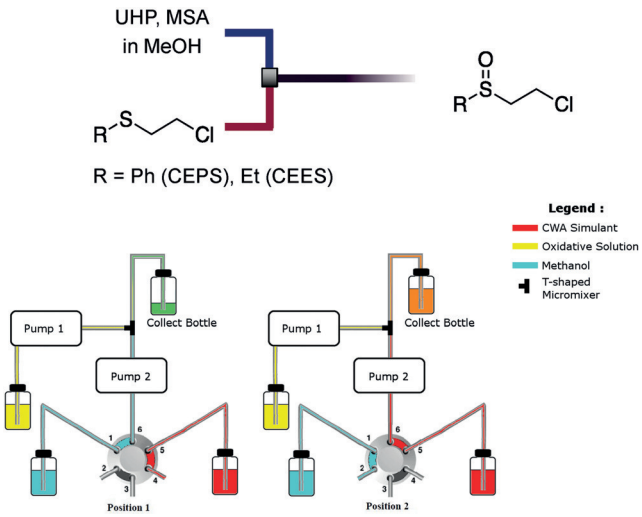



***Figure 1.*** Continuous flow set-up for the oxidation of half-mustards CEPS and CEES with UHP/MSA in methanol. See the Supporting Information for details.

(23.36 mL, 0.2 mol), was pumped at a flow rate of 0.5 mL min$^{-1}$ and met in a T-shaped mixer a solution of UHP (1.3 equiv), MSA (2.6 equiv) in MeOH (30 equiv) pumped at a flow rate of 5 mL min$^{-1}$. The resulting stream entered in a PFA tubing reactor (ID = 1.6 mm, L = 10.7 m, $V$ = 21.5 mL) with a residence time of $t^R$ = 3.9 minutes. The reactor outlet was then collected into a bottle containing 40 mL of 10 % (w/w) aqueous $NaHSO_3$. Therefore, a simple extraction afforded the corresponding sulfoxide CEESO in > 99 % yield. Similar results (conditions and yield) were obtained with CEPS.[37,38]

These developments can be supported by the implementation of in-line analytical methods capable of monitoring the reaction on the fly. This enables the real-time characterization of reaction products, kinetic studies and the optimization of the reaction conditions. Obviously, high-field NMR spectrometers are not portable, but recent years have witnessed the use of compact NMR spectrometers for these purposes, either under a by-pass configuration[39–42] or within a flow chemistry platform.[43] We incorporated such a low-field NMR system within our continuous flow system in order to evaluate the residence time $t^R$ at which the maximal conversion of CEES into the sulfoxyde CEESO is achieved (Figure 2). However, performing the reaction with short $t^R$ (less than 1 minute) in our setup involved high flow-rates, which significantly impact the sensitivity and the resolution of the NMR experiments. A first feature—commonly called "inflow effect"—is the continuous replenishment of the excited spins by unexcited ones. The latter must spend a sufficient time within the pre-polarization volume to reach their full thermal polarization. When the flow rate is too high, the saturated spins are refreshed by non-polarized ones leading to a loss of sensitivity.[44–46] Another feature involved by flow NMR—known as "outflow effect"—makes the use of high-flow regimes even more problematic. When the receiver is open during the detection of a flowing sample, some polarized and excited spins leave out the sensitive volume before the end of

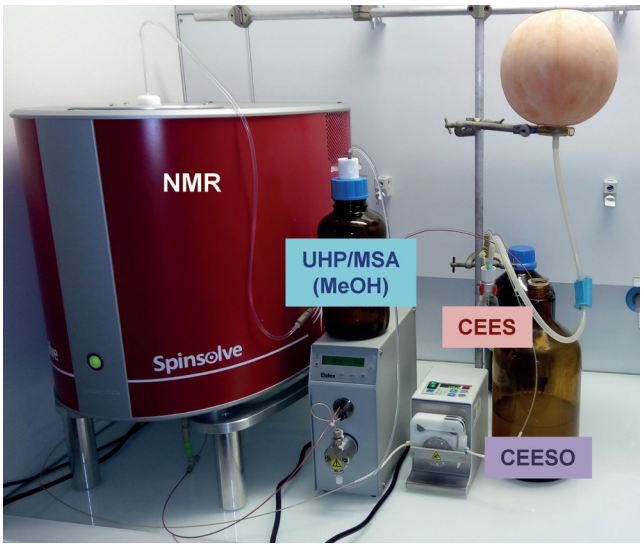



***Figure 2.*** Continuous flow system including a benchtop NMR spectrometer directly connected to the outlet of the reactor.

the acquisition.[44,46] This phenomenon leads to a reduction of the effective transverse relaxation time and involves a significant line-broadening. Here, these limitations were circumvented by finely tuning the flow system, consisting in reducing the reactor volume and previously dissolving the neat CEES in methanol (further details are available in the Supporting Information). Thanks to this optimization, it was possible to assess the conversion rate on a range of $t^R$ from 16.2 to 100.8 s without exceeding a flow-rate of 3 mL min$^{-1}$, which is an acceptable flow regime in our NMR flow system regarding the aforementioned limitations. The benchtop NMR spectrometer employed in this study (Spinsolve from Magritek) works at 43.62 MHz, relies on a permanent magnet and works without deuterated solvents.[47] This reduces the cost of the monitoring and avoids undesired isotopic effects. The downside of using non-deuterated methanol is the overlap between the huge solvent signal and the resonances of interest. This drawback became even more critical at high flow-rates (e.g. 3 mL min$^{-1}$) due to the inherent line broadening occurring with flowing samples.[44,45] To outmatch this limitation, we implemented a tailored NMR pulse sequence capable of suppressing multiple solvent resonances at low magnetic field under flow conditions. The experiment combined a continuous presaturation with a WET-180-NOESY Scheme that we recently described (see the Supporting Information for pulse sequence and parameters).[46] The WET-180 block,[48] added during the preparation step, combines a train of selective shaped pulses applied together with gradient spoilers to selectively disperse the longitudinal component of the solvent magnetization. The Scheme includes a hard 180° pulse directly after the last selective pulse with a modification of the flip angle providing a narrower residual solvent signal with a cleaner phase. This block was followed by a NOESY excitation with a two-step phase cycling leading to a reduction of the faraway solvent effect and a flatter baseline close to the residual solvent signal.[49] As a result of the efficient solvent signal suppression, the CEESO peak at 3.8 ppm could be detected and monitored through the flow reaction. The experiments were carried out at decreasing flow rates, that is, at increasing residence times. The overlapping triplets at 1.25 ppm—arising from the overlaps between the methyl groups of CEES and CEESO—progressively turned into a simple triplet matching with the disappearance of CEES (Figure 3). The conversion rate as a function of $t^R$ was monitored by computing the ratio between the peak area of the signals at 3.8 and 1.25 ppm for each kinetic point. Figure 3 displays the percentage of sulfoxide computed for six different residence times: full conversion is reached within 67 s, stressing the efficiency of the neutralization method.

In conclusion, we have implemented a simple and mobile device allowing fast neutralization of mustard gas simulants. The neutralization occurs through complete and fully selec-

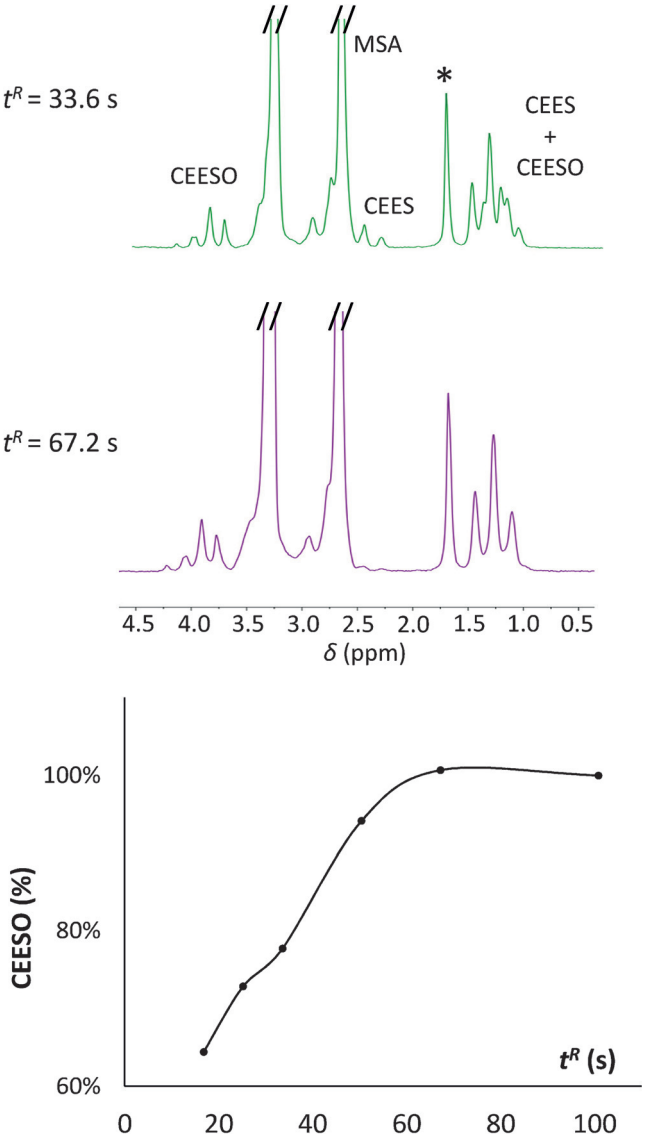



***Figure 3.*** Neutralization of CEES monitored by an in-line NMR system. Top and middle: Two NMR spectra recorded at different $t^R$. Note that the peak with a * corresponds to a $^{13}$C satellite line from the residual solvent signal at 3.3 ppm. Bottom: Percentage of CEESO as a function of the residence time.

tive sulfoxidation (>99%) in a millitube reactor using a handy oxidizing system (an alcoholic mixture of highly stable urea-$H_2O_2$ adduct and methane sulfonic acid) that can be readily prepared on demand for on site operation. Intensification at multi-gram scale has been performed and showed full reproducibility: 25 g of neat half-mustard CEES have been neutralized within 46 minutes, and kilogram scale could be reached by using adequate pumps without any further changes. When optimized, an in-line real-time monitoring of the reaction efficiency is possible thanks to tailored spectroscopic methods on a benchtop NMR spectrometer. In practice, our mobile device could be embarked in a vehicle for field intervention: the toxic agent would be directly pumped from the suspicious gear into the millireactor and neutralized on site.[50]

## Acknowledgements

The authors gratefully acknowledge support from the CNRS « Attentats Recherche » program. J.L. is grateful to Dr M. De Paolis and Dr I. Decostaire for fruitful discussions. The authors from Normandie Université also thank the Labex SYNORG (ANR-11-LABX-0029), the Région Normandie (MicroChim Project and CRUNCh network) and the European France (Manche)-England cross-border cooperation program INTERREG IV A "AI-CHEM CHANNEL" co-financed by ERDF for support. The authors from the University of Nantes acknowledge the Région Pays de la Loire (grant RésoNantes) for financial support. FXF and PG are members of the Institut Universtaire de France (IUF).

## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** chemical warfare agents · continuous flow · hydrogen peroxide · NMR spectroscopy · oxidation

**How to cite:** *Angew. Chem. Int. Ed.* **2017**, *56*, 7568–7572
*Angew. Chem.* **2017**, *129*, 7676–7680

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[50] "Mustard gas" is often used in the presence of additives to make it viscous or solid. In this case, methanol should be first introduced inside the gear by an additional pump/tubing to solubilise the CWA.

Manuscript received: March 16, 2017
Revised manuscript received: April 25, 2017
Version of record online: May 22, 2017

  