analytical chemistry

Article

Cite This: Anal. Chem. XXXX, XXX, XXX−XXX

pubs.acs.org/ac

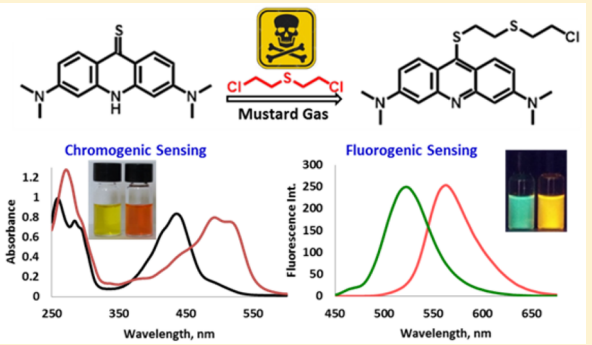
Chemodosimeter for Selective and Sensitive Chromogenic and Fluorogenic Detection of Mustard Gas for Real Time Analysis

Vinod Kumar,* Hemlata Rana, G. Raviraju, and Arvind K. Gupta

Process and Technology Development Division, Defence Research and Development Establishment, Jhansi Road, Gwalior 474002, India

Supporting Information

ABSTRACT: Since the first use of chemical warfare agents (CWA) (1915) to the recent attacks in Syria (2017) on mankind, there have been many incidents where CWA have claimed thousands of lives and left many more contaminated. In order to provide the appropriate and immediate medical counter measure to the victims, the exact classification of these chemical agents within few minutes on the field itself using a rapid and simple detection technique is extremely important to save the lives of the effected people. This has motivated all of us to explore the novel strategies/detection systems that can be field deployable with better selectivity and greater sensitivity. In view of this, we present a novel chemosensor, 3,6-bis(dimethylamino)-9(10H)-acridine thione (**1**), that can detect mustard gas and its simulant by both chromogenic and fluorogenic methods. For the first time, a single probe was able to demonstrate the detection with unprecedented selectivity over most probable interferences (nerve agents and alkylating agents) including solvents, acids, and bases which are routinely present in the environment. The desired level of sensitivity by naked eyes (0.04 mg/mL), UV spectroscopy (0.02 mg/mL), and fluorescence spectroscopy (0.005 mg/mL) makes this method truly field deployable. For the spot detection on the affected areas, a handy and potable chemosensor kit was also fabricated. This paper provides a simple, highly specific, and easy to use method in "actual sense" that not only detects the agents in the solution phase but also in the contaminated samples.



Sulfur mustard (SM) represents one of the most potential chemical warfare agents (CWAs) (Figure 1).[1,2] It is

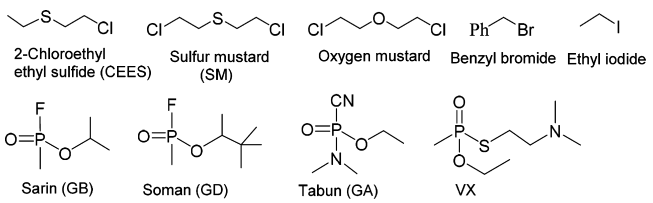
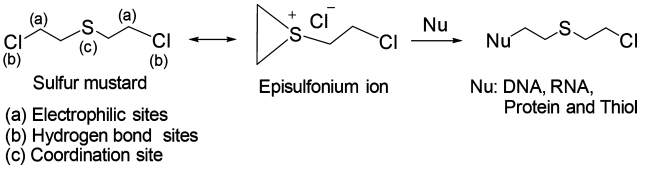


Figure 1. Chemical warfare agents and probable interferences in mustard gas detection.

colorless and odorless viscous liquid, and in impure form, it smells like garlic or horseradish, hence, named as mustard gas.[3] SM is powerful blistering agent and can damage the skin, eyes, and the respiratory system.[4] Its toxicity is due to the alkylation of guanine nucleotide in DNA, which prevents cellular division and leads to programed cell death (Scheme 1).[5] Long-term exposure even at the ppm level may be the root of the carcinogenic and mutagenic effects.[6] The lethal effect of SM is further aggravated by the fact that on dispersion in the environment, it remains active for the periods varying from hours to several weeks depending upon the environment temperature and pH of the soil.[7]

Scheme 1. Sulfur Mustard and Its Chemical Reactivity Towards Biomolecules and Other Nucleophiles



Other vesicants such as nitrogen mustard (NM) and lewisites are also considered schedule 1 chemicals as per the Chemical Weapon Convention (CWC). However, they never had been used as a chemical weapon[8] owing to their poor stability and low persistency in the environment. In fact, NM has been used as an anticancer drug.[9] Development of British antilewisite (an antidote) further discourages the use of lewisite as a warfare agent.[10] Unfortunately, in the case of SM, no antidote or prophylactics is available as a medical counter measure to the victim of attacks.[11] In order to protect mankind from such a notorious chemical, it is necessary to develop a sensor with

Received: November 24, 2017
Accepted: December 20, 2017

DOI: 10.1021/acs.analchem.7b04882
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good selectivity and sensitivity that can detect the agent within a few minutes on the field itself.

The general techniques for SM detection are based on instrumentation[12] and chemical methods.[13] Instrumentation methods are more reliable and detect the analytes at the required level of sensitivity but are often associated with high cost, nonportability, and longer operation time and operation complexity. Subsequently, the focus was directed toward the exploration of the chemical approaches. A chemical method is considered to be the best which can provide the detection by both colorimetric and fluorescence. Colorimetric sensors, in particular, are low cost and easy-to-read even by the untrained users, whereas fluorogenic sensors deliver greater sensitivity. On the basis of chromogenic and or fluorogenic sensing, new approaches such as molecularly imprinted polymer,[14] platinum-(II) pincer,[15] dansyl ligated Au-nanoparticles,[16] Rhodamine 6G,[17] and enzyme-based strip[18] have been recently tested yet remain at the realm of proof-of-concept only. There have been continuous efforts to improve upon the associated drawbacks with existing methods.

CWA are broadly classified into two categories, nerve agents and blistering agents. Because of the strong electrophilic nature of nerve agents, the approaches for their detection have been extensively explored where a nucleophilic probe molecule reacts with electrophilic phosphorus group to induce the chemical changes within the probe thus leading to the selective optical detection.[19] On the other hand, the approaches established for blistering agents such as SM have mainly targeted electrophilic, coordination, and hydrogen bond sites (Scheme 1). Involvement of the later two sites is less likely to produce the selectivity, thus leading to large interferences. Hence, detection currently remains focused on exploitation of the electrophilic site of SM. This also encounters the interference of more reactive electrophilic agents (nerve and acetylating agents). Therefore, fine-tuning of the chemical probe and reaction conditions plays a crucial role to attain the better selectivity. In the last years, Anslyn and our group are exploring the strategies to develop selective, sensitive, and easy to use methods in "actual sense" that not only detects the chemical agents in the solution phase but also in the environmental samples. In this attempt, the first fluorescent and chromo-fluorogenic sensors with excellent selectivity and sensitivity were reported.[20] The chemosensor was effective but demanding two basic components along with a receptor. The first was the supplementary step of capping the receptor before performing sensing, and the second was the requirement of a metal−indicator complex (M−I complex) or squaraine dye (SQ) (Figure 2). Despite displaying the attractive chemistries by both the approaches, use of a signaling element was essentially required. The long synthetic method, additional steps, and use of indicator restrict these methods for practical uses.

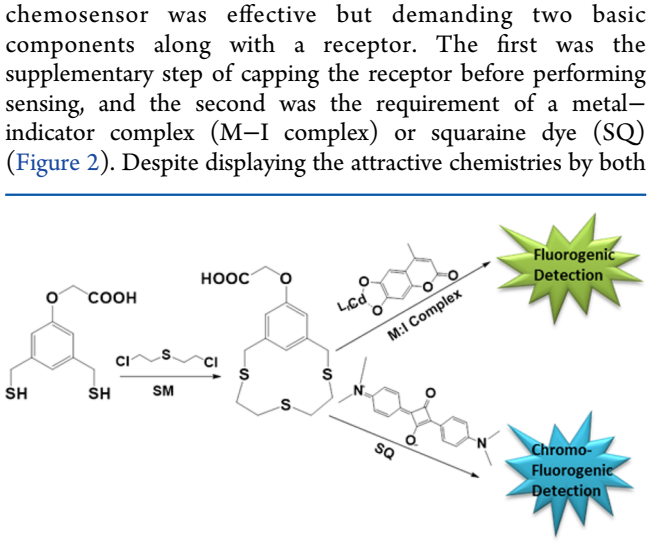

Figure 2. Illustration of Anslyn and our previous approaches.

EXPERIMENTAL SECTION

Chemicals and Materials. All chemicals and reagents were bought from Aldrich, Fluka, and Fisher Scientific and used without further purification. Solvents such as methanol (CH_3OH), chloroform ($CHCl_3$), dimethyl sulfoxide (DMSO), and dimethylformamide (DMF) were purchased from S D Fine Chem. Ltd., India, and dried as per the standard methods before using. UV−vis and fluorescence measurements spectra were recorded on an Agilent Technologies, Cary 100 UV−vis spectrophotometer and PerkinElmer, LS-55, U.K., respectively, equipped with a quartz cuvette (path length = 1 cm, at 25 °C). IR spectra were recorded on a PerkinElmer model BXII FTIR spectrophotometer using KBr pellets. NMR was recorded on a Bruker 400 MHz spectrometer using trimethysilane (TMS) as an internal standard. Mass analysis was performed on Orbitrap mass spectrometer of Thermo Scientific and MALDI TOF analyzer (AB Sciex)

Synthesis of 3,6-Bis(dimethylamino)-9(10H)-acridine Thione 1. In total, 500 mg of 3,6-bis(dimethy1amino)acridine and 66 mg of resublimed sulfur was thoroughly mixed with the help of a mortar and pestle. This was then poured into a round-bottom flask and the flask was heated at 205 °C in an oil bath. The flask was kept at the same temperature for 30 min. The flask was allowed to cool down. The dark purple residue formed which was recrystallized from DMF to give 3,6-bis(dimethylamino)-9(10H)-acridine thione **1** as a reddish brown solid. Yield, 65%; melting point, 361−362 °C. ^{1}H NMR (400 MHz; DMSO-*d6*): δ = 11.66 (br, 1H, NH); 8.65 (d, 2H,); 6.88 (d, 2H); 6.39 (s, 2H); 3.08 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δc: 195.6, 153.4, 139.0, 132.3, 120., 111.1, 94.1, 40.4. Mass analysis: (ESI$^+$) 298.14 $(M + H)^+$.

Preparation of Portable Chemosensor Kit. A probe solution (0.15 mM) in MeOH containing KOH (1.0 mM) was spread over a silica coated TLC plate (2 in. × 1 in. and 5 in. × 1 in.) and the solvent was evaporated with the blow of nitrogen. These kits were used for on spot detection of SM along with other relevant environment contaminants.

Safety Statement. Mustard gas and nerve agents were prepared in an Organization for the Prohibitions of Chemical Weapon (OPCW) declared facility and are deadliest in nature. Therefore, a recommended operating procedure must be followed during the preparation and use of the chemical agents. Proper protective gears and equipment should be used while handling the agents for synthesis and analytical research.

RESULTS AND DISCUSSION

Design and Synthesis of Chemical Probe. With an approach to integrate both the components (receptor and indicator) in a single probe molecule, we used the chemistry established by Elslager (1962) which describes the S-alkylation of acridine thione.[21] We have successfully utilized this strategy by reacting the electrophilic episulfonium intermediate of SM (Scheme 1) in an ionizing solvent with a good nucleophile such as thiolate anion of acridine thione (Figure 3). While designing the approach, the basic idea was to break the conjugation within the indicator and to incorporate a sulfur nucleophile which on reaction with SM will trigger the regain of conjugation, hence the optical properties. Thus, 3,6-bis-

DOI: 10.1021/acs.analchem.7b04882
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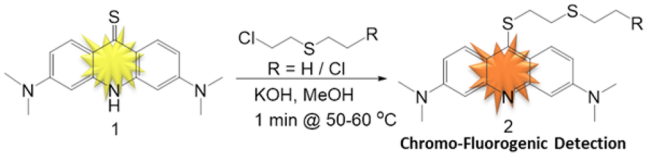
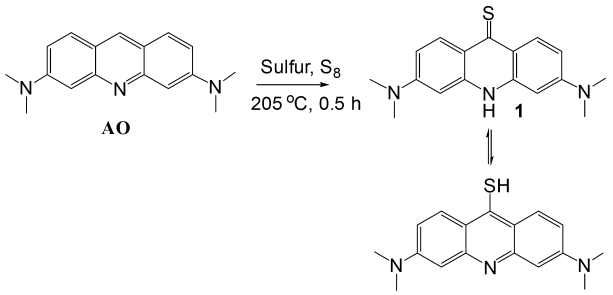


Figure 3. Schematic presentation of optical detection of sulfur mustard.

(dimethylamino)-9(10H)-acridine thione **1** on interaction with SM generates chromogenic and fluorogenic responses within a minute with good selectivity and sensitivity.

The synthesis of probe **1**[21] was realized from commercially available acridine orange base (**AO**) in a single easy step (Scheme 2) in good yields by heating with sulfur at 205 °C for 0.5 h.

Scheme 2. Synthesis of Chemical Probe 1 from AO



In cases of SM detection, most of the developed approaches primarily focus on the demonstration of proof-of-principle with its surrogate (CEES) only (not with real warfare, SM). Consequently, many times the experimental setting changes while implementing the concept on the real agent. Because SM being bialkylating in nature is less reactive ($t_{1/2}$, 8.5 min at 25 °C in H_2O) due to the presence of additional chloride atom (-I effect) as compared to CEES ($t_{1/2}$, 44 s at 25 °C in H_2O).[22] Therefore, it is important to note that in the reaction based chemical sensing, use of CEES is not an ideal situation. In view of this, we have conducted our studies with both CEES and SM in order to provide the experimental conditions that can be used as such even at the site of attack.

Chromo-Fluorogenic Detection and Selectivity Studies. First, we inspected the colorimetric and fluorescence responses of probe **1** (0.15 mM) with SM (3.0 mM) in the methanolic solution of potassium hydroxide (1.0 mM, optimized concn) at 60 °C. On interaction, the color of **1** changes from yellow to orange within a minute with change in fluorescence emission from green to yellow under a hand-held UV lamp (Ex. 365 nm) (insets of Figures 4 and 5). The UV–vis absorption spectra revealed that upon addition of SM (0.62 mM) to **1** (0.03 mM) in the presence of KOH (0.2 mM), the absorption peaks shifted bathochromically from 443 to 502 and 518 nm through an isosbestic point at 465 nm. Initially, emission peak of **1** (4.0 μM) in the presence of KOH (0.026 mM) was observed at 515 nm (Ex. 465 nm), upon the addition of SM (0.075 mM) a red shift of 40 nm was witnessed with new emission peak at 555 nm (Ex. 518 nm). As shown in the Figures 4 and 5, the probable interferences such as nerve agents (sarin, soman, tabun, and VX), alkylating agents (oxygen mustard, benzyl bromide, and ethyl iodide), and acid remain silent with **1** under similar reaction conditions by naked eyes

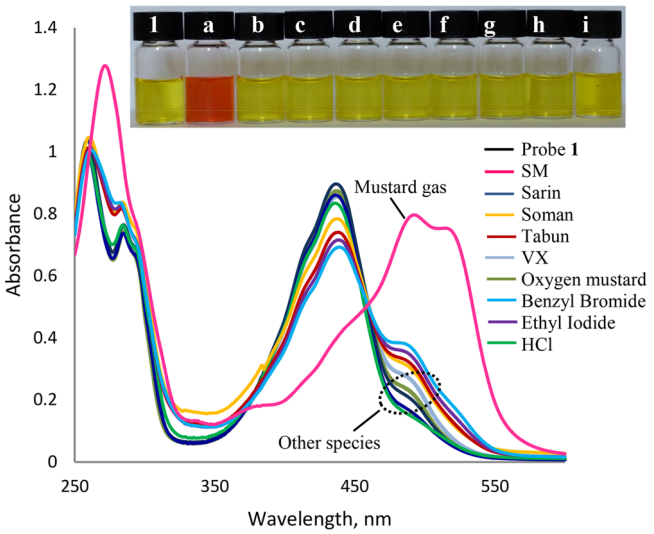


Figure 4. Absorption spectra of **1** at 0.03 mM in methanol containing KOH (0.2 mM) in the presence of 0.62 mM of SM, sarin, soman, tabun, VX, oxygen mustard, benzyl bromide, ethyl iodide, and HCl. Inset: from left to right, only **1** (0.15 mM) in MeOH in the presence of KOH (1.0 mM) and **1** with 3.0 mM of (a) SM, (b) sarin, (c) soman, (d) tabun, (e) VX, (f) oxygen mustard, (g) benzyl bromide, (h) ethyl iodide, and (i) HCl.

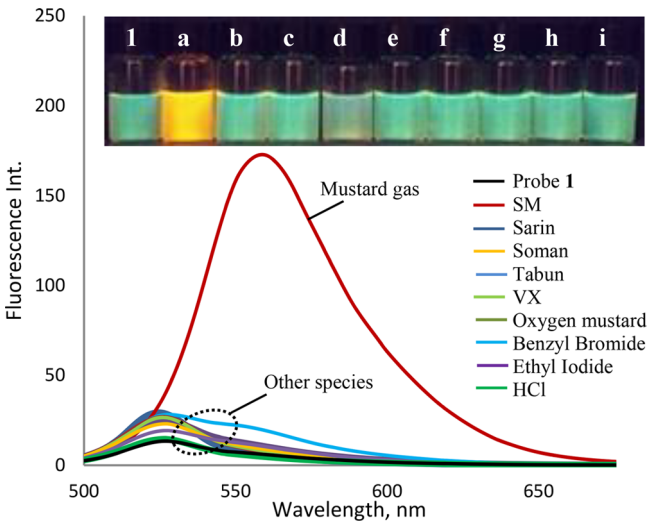


Figure 5. Fluorescence spectra of **1** (4.0 μM) in methanol containing KOH (0.026 mM) in the presence of 0.075 mM of SM, sarin, soman, tabun, VX, oxygen mustard, benzyl bromide, ethyl iodide, and HCl. Inset: Illumination of the same vials as in inset of Figure 4 under hand-held UV lamp (Ex, 365 nm) from left to right, only **1** (0.15 mM) in MeOH in the presence of KOH (1.0 mM) and **1** with 3.0 mM of (a) SM, (b) sarin, (c) soman, (d) tabun, (e) VX, (f) oxygen mustard, (g) benzyl bromide, (h) ethyl iodide, and (i) HCl (λ_{ex}, 518 nm; λ_{em}, 555 nm).

from both the color and fluorescence emission. Similarly, UV and fluorescence spectroscopy results also pronounce no response of the interfering species under study with **1**, indicating no reaction between these species and probe **1**.

Next, we examined the visual and UV–vis absorbance responses of **1** with varying concentrations of SM. **1** (0.15 mM) was allowed to react at 60 °C for 1 min each time with concentration of SM varying from 0.06 mM to 0.72 mM and absorbance spectra of each solution were recorded. There is an

DOI: 10.1021/acs.analchem.7b04882
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enhancement of absorbance peak upon each addition (0.06 mM) of SM solutions and finally it becomes saturated at 0.6 mM as can be seen in Figure 6b. Furthermore, the fluorescence

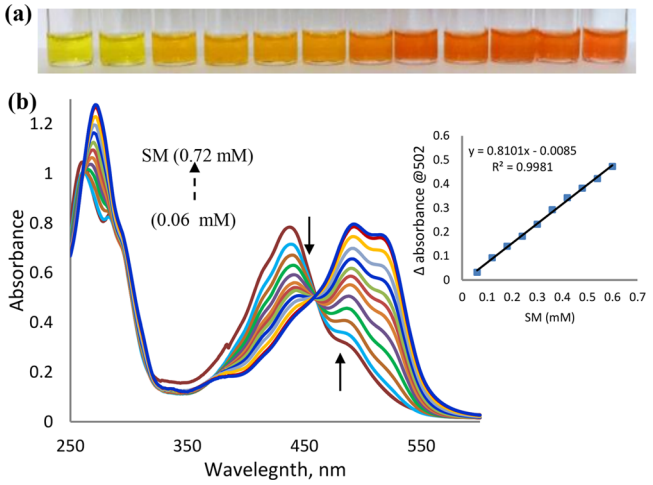

Figure 6. (a) Chromogenic response of **1** (0.15 mM) in the presence of KOH (0.2 mM) with subsequent addition of SM (from 0 to 0.02−0.22 mg (0.3−3.3 mM), left to right). (b) Absorption spectra of **1** 0.03 mM in methanol containing KOH (0.2 mM) upon the gradual addition of the solutions of SM (0.06−0.72 mM). Inset: Showing the linear calibration curve as the fuction of SM concentration with regression coefficient (R^2) 0.998.

titrations were also conducted under similar reaction conditions to observe the response of **1** (4 μM) with the aliquots of SM from 7.5 μM to 90 μM. Upon each addition of analyte (7.5 μM), a regular enhancement in the fluorescence intensity took place and then it got saturated with 75 μM (Figure 7b). Figures 6a and 7a show that the systematic color changes occurred from yellow to orange as also observed with naked eye and

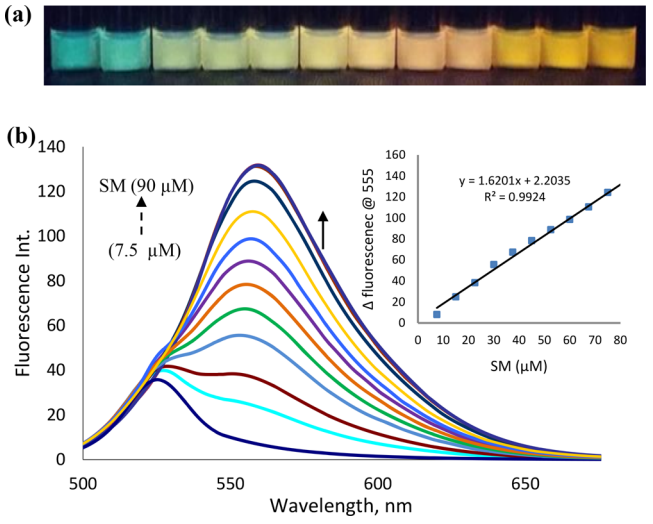

Figure 7. (a) Fluorescence response under hand-held UV lamp (Ex: 365 nm) of **1** (0.15 mM) in the presence of KOH (0.2 mM) with subsequent addition of SM (from 0 to 0.02−0.22 mg (0.3−3.3 mM), left to right). (b) Fluorescence spectra of dye **1** (4 μM) in methanol containing KOH (0.026 mM) upon the gradual addition of SM solutions (7.5−90 μM). Inset: Showing the linear calibration curve as a function of SM concentration with regression coefficient (R^2) 0.992. (λ_{ex}, 518 nm; λ_{em}, 555 nm).

under a UV lamp (Ex. 365 nm) with **1** and varied concentrations of SM (0.3−3.3 mM).

As a part of our chemosensor design, the reaction of **1** with SM or CEES is conducted deliberately in MeOH in the presence of base such as KOH which serves two purposes. First, it facilitates the reaction by abstracting a proton from −SH of acridine motif and thus enhancing its nucleophilicity. Second, more reactive electrophiles (nerve agents) and acids will be easily neutralized by methanolic KOH even before reacting with **1** thus allowing SM and CEES to react. Less reactive electrophiles (oxygen mustard, benzyl bromide, and ethyl iodide) could not react with **1** at 60 °C in a minute as no response is observed. SM is quite reactive as compared to other alkylating agents such as oxygen mustard, benzyl bromide, and ethyl iodide. This is attributed to the fact that sulfur atom in SM undergoes neighboring group participation forming electrophilic three-membered episulfonium ion (Scheme 1) thus making mustard gas extremely reactive for nucleophilic attack over these analytes including oxygen mustard.[23] Given sensing conditions, i.e., 60 °C for 1 min is not sufficient for **1** to react with these less reactive anlaytes. Although, performing the reaction under harsh conditions such as high temperature (80 °C) and prolong reaction time (16 h) may also lead to product formation,[20] which is not the desired situation in our case.

Reactivity of SM vs CEES. With careful examination of reaction rate between SM and CEES with **1**, we observed CEES reacts at 50 °C while SM at 60 °C, as also confirmed by the lower LOD by visual and fluorescence (0.02 mg, 0.3 mM) with the naked eye. However, change in color intensity, UV absorbance, and fluorescence intensity in case of CEES are comparable to those of SM. The detailed results (data and spectra) of CEES and its comparison with SM are presented in the Supporting Information (Figures S1−S4).

Sensing Mechanism. The absorbance and fluorescence maxima of acridine orange (**AO**) (λ_{ex}, 489 nm; λ_{em}, 520 nm), probe **1** (λ_{ex}, 443 nm; λ_{em}, 515 nm) and product **2** (λ_{ex}, 502 and 518 nm; λ_{em}, 555 nm) in MeOH were observed as expected. Higher values of absorption and fluorescence maxima in the case of **2** as compared with **AO** are due to the covalently attached sulfur to acridine motif, thus enhancing absorbance and fluorescence maxima. Responses from both the spectroscopic techniques confirm the breaking of conjugation in **AO** and subsequent incorporation of sulfur within the acridine motif. The responses are further regained after the reaction with SM. Furthermore, in order to support the formation of product **2** (Figure 3) as anticipated, MALDI-MS of the **2** was recorded using α-cyano-4-hydroxycinnamic acid (CHCA) matrix and found in complete agreement (Figure S5). H^1 NMR spectroscopy also confirms the S-alkylation of the probe by CEES, as protons peaks of CEES initially appeared at δ 3.67 (t, CH_2), 2.88 (t, CH_2), 2.62 (q, CH_2), and 1.26 (t, CH_3), which after reaction shifted to δ 3.56 (t, CH_2), 2.7 (t, CH_2), 2.59 (q, CH_2), and 1.24 (t, CH_3), respectively. No significant changes in the chemical shift values of aromatic protons of both **1** and **2** were observed, hence not presented.

Sensitivity. Compared with instrumentation techniques, formation of orange color that also fluoresces under UV lamp with 0.04 mg of SM (Figures 6a and 7a) suggest the potential utility of this assay for on-spot detection with the naked eye at a concentration which is much below the level of any toxic hazards (0.2 mg). Though, from the calibration curves, the limits of detection by UV and fluorescence spectroscopy are

DOI: 10.1021/acs.analchem.7b04882
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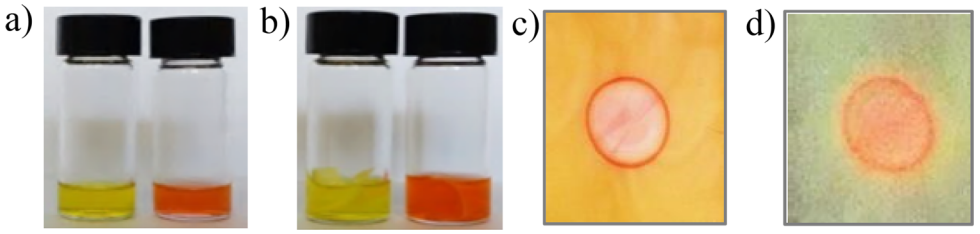

Figure 8. (a) Colorimetric responses of **1** with SM spiked soil sample (right) and unspiked soil sample (left). (b) Visual responses of dye with SM wiped filter paper (right) and without SM (left), (c) spot detection of SM on dye coated on TLC plate in visible, and (d) UV light (Ex. 365 nm).

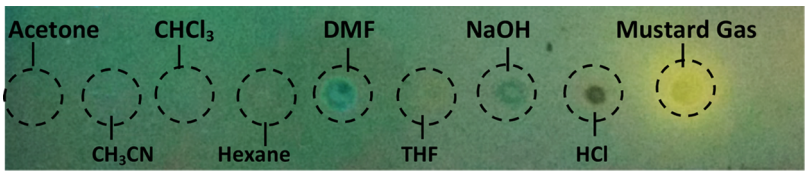

Figure 9. Illumination of dye **1** coated on TLC plate and its response with mustard gas and various interferences present in the environment.

determined to be 0.02 mg (0.3 mM) and 0.005 mg (7.5 μM), respectively.

Real Time Analysis and Portable Chemosensor Kit. With the aim of providing medical counter measure to the victims, the precise classification of the chemical agents within a few minutes at the site of attacks is imperative. Generally, it takes around a week to a month's time to identify the agents in the designated laboratories.[24] Hence, it becomes desirable for us to employ the present sensing scheme for real-time monitoring on the contaminated areas where SM may be present in the soil or on surfaces. For this purpose, the probe solution (3.0 mM) in MeOH was treated with contaminated soil and filtered; the filtrate was heated at 60 °C for 1 min. The solution turns orange from yellow while blank did not give any response (Figure 8a). In case, a surface is contaminated with SM (spray of 1 μL) that can be wiped out with filter paper or swab. It is then dipped into solution of **1** (3.0 mM) where it reacts immediately with SM under similar conditions to generate optical responses (Figure 8b).

In order to complete the swab testing analysis at the airport security and any remote locations, a ready made dye solution in the detection tube/vial will be highly beneficial; therefore, the dye stability in the solvent under testing would be crucial. Interestingly, MeOH was found to be the best solvent for this purpose as dye is stable for more than a month while it changes color in $CHCl_3$, DCM, and DMSO within 24 h, hence not recommended. Next attempt was to fabricate a handy and portable chemosensor kit, the chemical probe was deposited onto the TLC plate as it becomes a sensor kit for spot testing. A solution of SM was spotted on the its surface that was heated at 60 °C for a min, the spotted place turns orange which also emits strong fluorescence at 365 nm (Figures 8c,d). Various chemically doped test strips or detector papers generally give false positive signals even with organic solvents, acids, and bases, hence exhibit no selectivity.[13] The developed test strip shows no response with these probable environmental contaminants such as acetone, acetonitrile, chloroform, hexane, tetrahydrofuran, sodium hydroxide (1.24 mM), hydrochloric acid (1.24 mM), whereas mustard gas solution (1% in MeOH) gives yellow fluorescence (Figure 9).

CONCLUSIONS

In conclusion, we have developed the first colorimetric and fluorescent sensor for the detection of mustard gas. The chemical probe was easy to prepare, sensitive, and selective over nerve agents and alkylating agents. The reactivity of SM was also compared with that of its simulant toward the probe and the result showed that SM being bialkylating agents is less reactive than CEES. As 0.2 mg of SM can cause blistering on the skin, with our probe, a quite distinctive color appeared with 0.04 mg/mL of SM that can easily be observed with naked-eye and hand-held UV lamp. For the development of the on-field monitoring system and the fabrication of portable sensor, detection was demonstrated on SM spiked soil sample and on the contaminated surface. Furthermore, a dye coated on a TLC plate (a chemosensor kit) has demonstrated the spot testing of SM where other chemically modified detection kits or tickets give the false positive signal even with solvents, acid, and base. Our recently developed assay for chromo-fluorogenic detection and discrimination[19k,h] of real nerve agents coupled with present detection technique for SM would help us to construct a chemical warfare detection kit (CWDK) for a complete class of CW agents (nerve and blistering agents).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.analchem.7b04882.

Fluorescence spectral data of **1** with CEES and its comparison with SM and MALDI-TOF of product **2** (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: vkpal77@yahoo.co.in.

ORCID

Vinod Kumar: 0000-0001-9909-2686

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.analchem.7b04882
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■ ACKNOWLEDGMENTS

We thank Dr. D. K. Dubey, Director, DRDE, Gwalior, for his keen interest and encouragement. We also thank Dr. J. Acharya, Dr. S. I. Alam, and Mr. Ajeet Kumar for their technical support.

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DOI: 10.1021/acs.analchem.7b04882
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