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"Covalent Assembly" Based Fluorescent Probe for the Detection of a Nerve Agent Mimic (DCP) *via* Lossen Rearrangement

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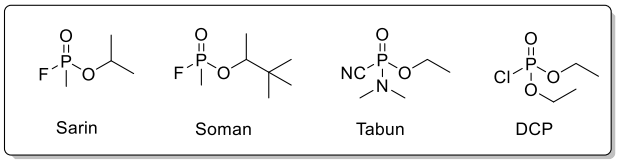
ABSTRACT: The highly selective and sensitive fluorescence "light-up" probe, 5'-(dimethylamino)-2'-formyl-*N*-hydroxy-[1,1'-biphenyl]-2-carboxamide (**PTS**), has been fabricated for the nerve agent mimic diethyl chlorophosphate (DCP). The probe is designed by combining two novel strategies of "covalent assembly" and Lossen rearrangement. The formation of a phosphoryl intermediate from DCP and a hydroxamic acid group in **PTS** yields an isocyanate that quickly undergoes the Lossen rearrangement to produce an aniline that condenses intramolecularly to a fluorescent phenanthridine system. **PTS** shows superior properties to probe DCP, such as rapid response (within 100 s), low detection limit (10.4 nM), specificity and excellent linearity (R^2=0.9993) in range of 2 μM to 16 μM. More importantly, its application of detecting DCP vapor has also been achieved with satisfying results.

Nerve agents, including Sarin, Soman, and Tabun (Chart 1), are a class of organophosphate derivatives. Their acute toxicity is mainly attributed to their strong electrophilic ability, which can easily interact with the important central nervous enzyme acetylcholinesterase, destroying nerve impulse conduction, leading to organ failure, thus causing death in a few seconds.[1-8] In World War II, these highly toxic agents served as chemical warfare agents, killing millions soldiers and civilians.[9-13] After the war, in view of the cruelty of nerve agents, a large number of these chemical weapons were destroyed by many countries. Unfortunately, it was precisely due to the horrific killing effect of nerve agents that lead terrorists to express a soft spot for nerve agents.[14-19] In the past few decades, nerve agents have been released in the public areas of some countries for creating panic, which posed a great threat to social security and human health. Therefore, it is extremely urgent to detect such highly toxic substances, and thus prevent the occurrence of tragedy.[20-22]

Chart 1. Structure of nerve agents and DCP.



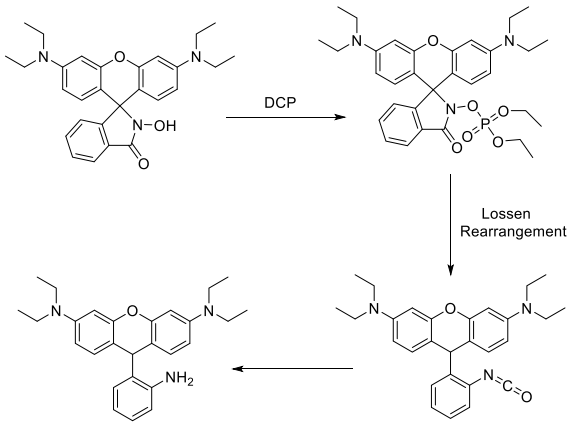
Traditional analytical methods of nerve agents mainly consist of electrochemistry[23-25], gas chromatography-mass spectrometry[26], interferometry[27] and enzymatic bio-sensing technology[28]. However, cumbersome sample pretreatment, complicated operation, and requirement for large instruments that greatly handicap their further application.[29, 30] The fluorescent probe technology, which is rapidly developed in recent years, has been widely used by researchers because of its high sensitivity, good selectivity, easy operation, low cost, and real-time situ detection in microenvironment systems.[31-34] Usually, diethyl chlorophosphate (DCP) serves as a nerve-agent mimic due to its low toxicity but similar activity to Sarin (Chart 1). By utilizing the high chemical reactivity of nerve agents, some fluorescent probes that detected DCP *via* directly phosphorylation of amino or hydroxyl groups on the probes have been fabricated.[35-39] However, these sensors still have some shortcomings in response time, sensitivity, etc.

In 2010, Han's group developed a novel approach to detect DCP *via* a Lossen rearrangement of rhodamine-hydroxamate (Scheme 1). As they have claimed, hydroxamic acid was able to be converted to phosphoryl intermediate and then self-rearrange into the corresponding isocyanate, for which it was employed as the target site of DCP.[40] In addition, Yang developed a sensing reaction *via* a "covalent-assembly" approach, which results in fluorimetric signal from zero background.[41, 42] So, inspired by the research findings of the above-mentioned two groups, here, our group designed and manufactured an eye-catching probe **PTS** for highly specific and sensitive detection of DCP, which combined these two strategies of "Lossen rearrangement" and "covalent-assembly". We supposed that once the hydroxamic acid group in **PTS** bound with DCP, the new formed phosphoryl intermediate would undergo Lossen rearrangement swiftly to afford the corresponding isocyanate that was inclined to further react with water to release NH_2 group, and then covalently assembled with formyl to afford the strongly fluorescent phenanthridine derivative (Scheme 3).

EXPERIMENTAL SECTION

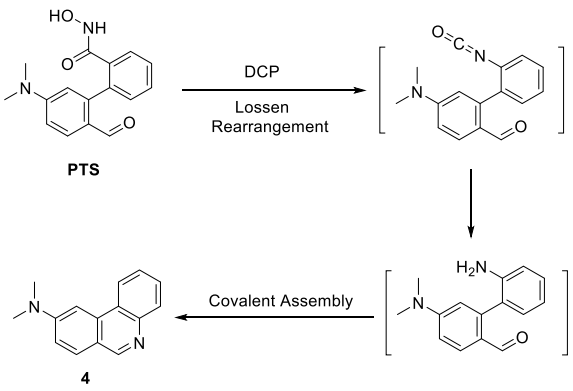
Materials and Measurements. All chemicals were purchased from commercial sources and were used directly. Solvent (Analytical Grade) was purchased from Beijing chemical

Scheme 1. Detection of DCP *via* Lossen rearrangement.



Scheme 2. The "Covalent Assembly" approach.

Scheme 3. Proposed recognition process of PTS for DCP.



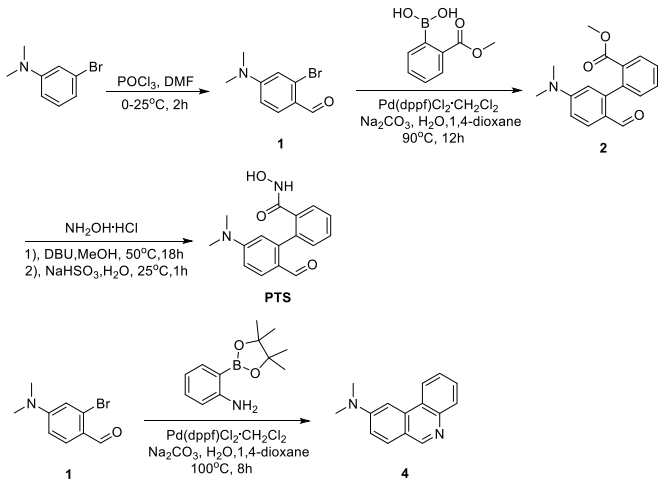
Regent Co. NMR and HRMS were recorded on a Bruker AM-400 Nuclear Magnetic Instrument and Mass Spectrometer, respectively. Shimadzu UV-1800 Spectrophotometer and Hitachi F-4500 Fluorescence Spectrophotometer were used to measure the UV-vis and fluorescence spectra, respectively.

Synthesis of PTS. The synthetic procedure of probe **PTS** and its related compounds were shown and outlined in Scheme 4, and their chemical structures were all confirmed by NMR and HRMS (SI, Figure. S1-S9).

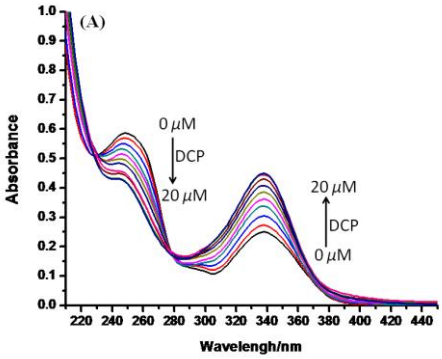
Fluorometric Assay Studies. Fluorescence assays were performed in solutions containing **PTS** (10 μM), triethylamine (TEA 20 μM) in acetonitrile. Fluorescence response was measured (λ_{ex} = 330 nm) upon addition of aliquots of a solution of DCP in acetonitrile.

RESULTS AND DISCUSSION

Scheme 4. Synthetic routes of PTS and compound 4.



UV-vis Absorption and Fluorescence Properties. The characteristics of UV-vis absorption and fluorescence emission of **PTS** (10 μM) before and after addition of DCP were carried out in acetonitrile solution containing TEA (20 μM). As shown in Figure. 1A, upon binding **PTS** to DCP (0-20 μM), the absorption signals of **PTS** at 248 nm decreased and that at 338 nm increased as a function of the increasing DCP concentration. For fluorescence emission, a proportionate increase of emission at 418 nm (Φ^{Free}=0.0001, Φ^{DCP}=0.2533) was measured (Figure. 1B), and a remarkable color change of the detection system from colorless to blue-violet was observed after exciting at 365 nm with a UV lamp (Figure. 1B, inset).



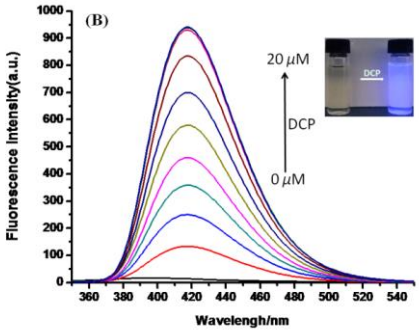


Figure 1. Absorption (A) and emission (B) of **PTS** toward to DCP (0 to 20 μM) in acetonitrile. [**PTS**] = 10 μM, [TEA] =20 μM, λ_{ex} = 330 nm, λ_{em} = 418 nm. Inset: Fluorescence color change of **PTS** in absence and presence of DCP, λ_{ex} = 365 nm.

Sensory Properties. To ascertain the sensing ability of **PTS** (10 μM), we plotted the fluorescence emission intensity at 418 nm toward different concentrations of DCP (0-20 μM) and performed a linear fit. As shown in Figure. 2, with the addition of DCP (0-20 μM), the fluorescence intensity at 418 nm increased smoothly, and a good linear relationship (R^2=0.9993) was obtained by fitting the fluorescence intensity towards DCP (2 μM to 16 μM). Meanwhile, in accordance with 3δ/slope[43], the corresponding detection limit (L_{OD}) was calculated as low as 10.4 nM.

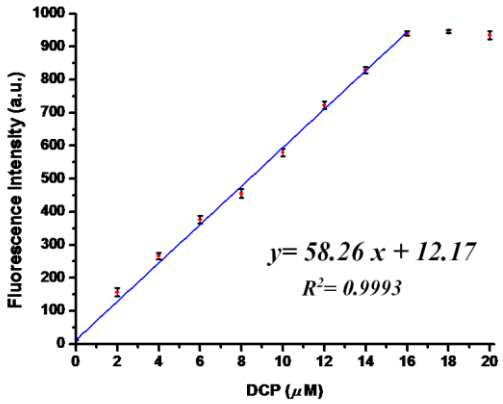


Figure 2. Linear relationship between emission and DCP ranging from 0 to 20 μM. All measurements were taken acetonitrile, [**PTS**] = 10 μM, [TEA] = 20 μM, λ_{ex}= 330 nm, λ_{em}= 418 nm.

Rapid response is a critical index for reactive-type fluorescent probes, especially of significant importance for such a Nerve-agent-Probe. Therefore, time course for signaling of **PTS** with DCP was carried out. By recording fluorescence intensity change at different time intervals (20 s), a time titration curve was obtained (Figure. 3). It could be seen that the fluorescence emission enhanced swiftly and leveled off within 100 s, and remained almost unchanged even the time was extended to 5 minutes, which suggest **PTS** was an effective candidate for rapidly monitoring DCP.

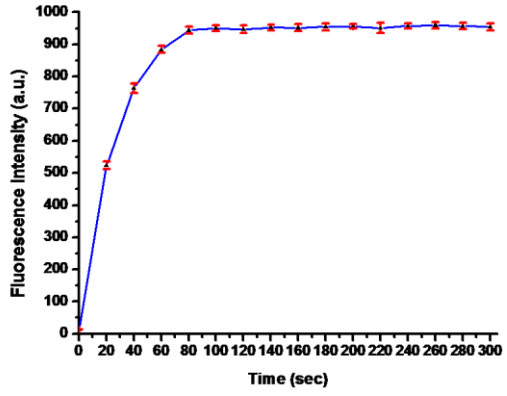


Figure 3. Time-dependent photoluminescence of **PTS** toward to DCP in acetonitrile, the spectra were recorded every 20 s (0 to 300 s), [**PTS**] = 10 μM, [DCP] = 20 μM, [TEA] = 20 μM, λ_{ex} = 330 nm, λ_{em} = 418 nm.

Selectivity is another important factor of the sensing performance. We employed some possible liquid interferents, such as phosphorus oxychloride ($POCl_3$), oxalyl chloride ($C_2O_2Cl_2$), phosphorus trichloride (PCl_3), acetyl chloride (AcCl), hydrochloric acid (HCl) and thionyl chloride ($SOCl_2$). Upon binding **PTS** with these interferents and DCP at the same condition, we could find that only DCP could cause the fluorescence emission at 418 nm, and none of these interferents casused the same fluorescence change as DCP did (Figure. 4). These results indicated that **PTS** exhibited good specificity toward DCP over other species at 418 nm with excitation at 330 nm.

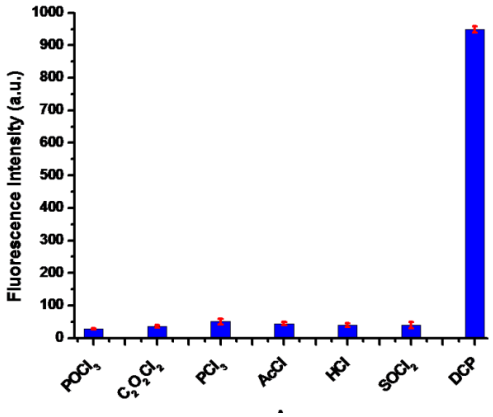


Figure 4. Fluorescence responses of **PTS** to DCP as well as other species in acetonitrile, [**PTS**] = 10 μM, [TEA] = 20 μM, [DCP] = 20 μM, [other species] = 20 μM for each, λ_{ex} = 330 nm, λ_{em} = 418 nm.

Moreover, some reported nerve agent mimic probes have been summarized to make a comparison with **PTS**, and the results were depicted in Table 1. **PTS** displayed better properties in both response time and detection limit than other probes. Therefore, **PTS** was more capable of detecting low-level nerve agent.

Mechanism Investigations. Control experiments were carried out to confirm the probe design hypotheses. The recognition mechanism was discussed through NMR and HRMS. By performing the reaction of **PTS** and DCP, we afforded compound **X**, which showed the same proton shifts as compound **4** (C) in ^{1}H NMR titration spectra (Figure. S10). In addition, compound **X** showed *m/z* 223.1229 ($M+H^+$), which was consistent with compound **4** (223.1227 $M+H^+$) in HRMS spectra (Figure. S11). All the above results indicated that **PTS** conversed to compound **4** during the process. In summary, based on covalent assembly and Lossen rearrangement, we made a feasible point for the recognition mechanism that shown in Scheme 5.

Practical Sensing Application. Finally, the action of DCP vapor on probe **PTS** was investigated. To make a comparison, we added **PTS** (10 μM) in acetonitrile solution containing TEA (20 μM) in two flasks, and a small bottle containing DCP was hanged up in one of them, avoiding any contact of liquid

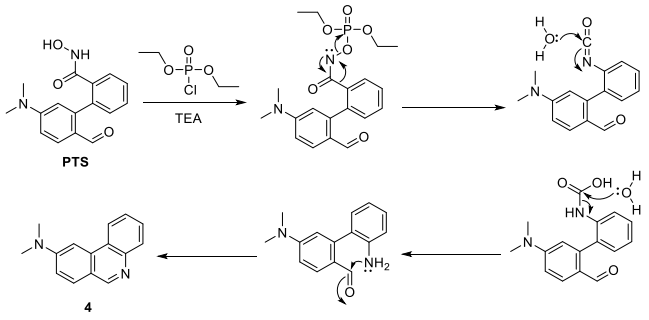
DCP with **PTS**. Both flasks were sealed from air and kept at room temperature. Once DCP fumes get into touch with the

Table 1. Comparisons of proposed method with recently reported strategies for nerve agent mimic.

Probe code	Response type	Dynamic range	Detection limit	Response time
1[2]	off-on	0 to 3 mg/L	0.71 μg/L	10 min
2[18]	on-off	0 to 3 mM	372.7 μM	—
3[15]	off-on	50 to 500 μM	44 nM	< 1 min
4[17]	ratiometric	0 to 8 μM	10 nM	> 60 min
5[20]	ratiometric	0 to 8 μM	18.86 nM	< 1 min
6[44]	off-on	0 to 60 μM	1.87 ppb	10 min
7[22]	off-on	0.2 to 1.5 mM	142 nM	—
PTS	off-on	0 to 16 μM	10.4 nM	< 2 min

"—" Not mentioned

Scheme 5. Recognition mechanism of PTS for DCP.



test solution, **PTS** in the solution will respond to them. After 10 min, the color of the flask equipped with DCP-containing bottle changed from colorless to blue-violet (The fluorescent turn-on phenomenon was similar to Figure. 1B inset under the excitation of a UV lamp at 365 nm). Furthermore, filter papers (4 cm×1 cm) were immersed in acetonitrile solution of **PTS** (50 μM) and then dried in air to prepare fluorescent test strips. After hanging on the top of DCP solution for several minutes, the fluorescent test strips showed an enhanced fluorescence intensity, which exhibited an excellent sensitivity for DCP gas (Figure. 5).

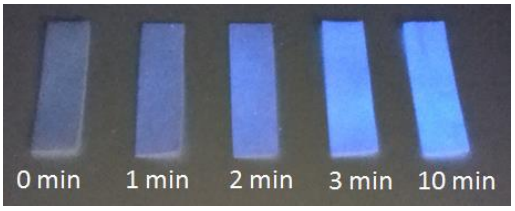


Figure 5. Display of vapour phase sensing of DCP using **PTS** coated paper strips at different times under a UV lamp.

CONCLUSION

To conclude, a novel probe **PTS**, which shows a significant fluorescence "light-up" response to nerve agent mimic (DCP), has been developed by combining "Lossen rearrangement" and "covalent-assembly". **PTS** features outstanding recognition capability, fast response (within 100 s) and low detection limit (10.4 nM) toward DCP. More importantly, the detection of DCP in gas state has also succeeded. Based on the above, we are confident that **PTS** will be an innovative probe for sensing nerve agents.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthesis details, table listing detailed comparison with some of other chemosensors, and additional figures showing NMR spectra, HRMS spectra, method for determining quantum yield (PDF).

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Notes

The authors declare no competing financial interest.

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