ORGANIC
LETTERS

2013
Vol. 15, No. 10
2386–2389

Cyanide Detection Using a Triazolopyridinium Salt

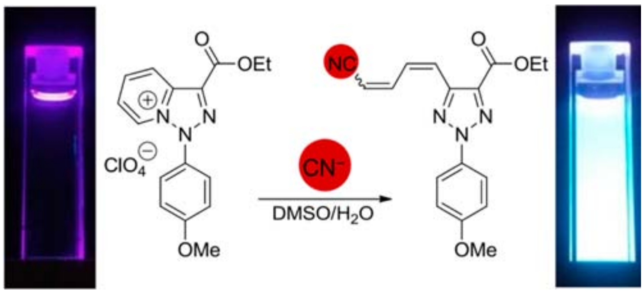
Thomas F. Robbins, Hai Qian, Xin Su, Russell P. Hughes, and Ivan Aprahamian*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States

ivan.aprahamian@dartmouth.edu

Received March 26, 2013

ABSTRACT



A triazolopyridinium salt chemodosimeter has been developed that displays a 60-fold enhancement in fluorescence upon reaction with cyanide. The novel, fast, selective and sensitive reaction-based indicator relies on the pseudopericyclic ring opening of the bridgehead nitrogen-containing detector.

Despite its toxicity,[1,2] cyanide (CN^-) is still widely used in mining, metallurgy, and various chemical industries, inevitably resulting in the pollution of water supplies.[3,4] As a result, considerable attention has been devoted in recent years to the development of CN^- sensors.[5] Traditionally, hydrogen bonding or supramolecular interactions have been used in the detection of low concentrations of cyanide in solution.[6−8] These approaches, however, usually result in poor selectivity over other common anions.[9] The burgeoning field of reaction-based indicators has made progress in this area because of the unique reactivity of CN^- toward a variety of organic functional groups[10,11] including C=O,[9,11b,11h,11j] C=N,[11f,g] and C=C.[11k,i] Other advantages of this approach include the irreversible formation of chemical bonds that can provide chemodosimetric information[10c] and lead to remediation as well as detection.[9b] There is an ever-present need to develop new reaction-based CN^- sensors, as these can help overcome lingering obstacles in its detection,[10] such as selectivity, sensitivity, response times, sensor stability, reaction conditions, etc.[11] Here we report a

---

(1) World Health Organization. *Concise International Chemical Assessment Document 61. Hydrogen cyanide and cyanides: human health aspects*; Geneva, 2004; 4−5. http://www.who.int/ipcs/publications/cicad/en/cicad61.pdf (accessed Sep. 17, 2012).

(2) Taylor, J.; Roney, N.; Harper, C.; Fransen, M.; Swarts, S. *Toxicological Profile for Cyanide*; U.S. Department of Health and Human Services: Atlanta, GA, 2006; 6−7.

(3) The United States Environmental Protection Agency has set the maximum contaminant level for CN^- in drinking water at 0.2 ppm: Kulig, K. W. *Cyanide Toxicity*; U.S. Department of Health and Human Services: Atlanta, GA, 1991.

(4) Xu, Z.; Chen, X.; Kim, H. N.; Yoon, J. *Chem. Soc. Rev.* **2010**, *39*, 127.

(5) Ma, J.; Dasgupta, P. K. *Anal. Chim. Acta* **2010**, *673*, 117.

(6) Moragues, M. E.; Martínez-Máñez, R.; Sancenón, R. *Chem. Soc. Rev.* **2011**, *40*, 2593.

(7) Wenzel, M.; Hiscock, J. R.; Gale, P. A. *Chem. Soc. Rev.* **2012**, *41*, 480.

(8) Jo, J.; Olasz, A.; Chen, C.-H.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 3620.

(9) (a) Sessler, J. L.; Cho, D.-G. *Org. Lett.* **2008**, *10*, 73. (b) Cho, D.-G.; Kim, J. H.; Sessler, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 12163.

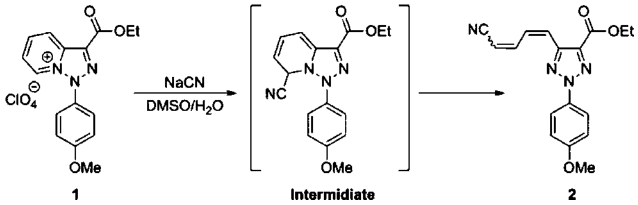
(10) (a) Cho, D.-G.; Sessler, J. L. *Chem. Soc. Rev.* **2009**, *38*, 1647. (b) Jun, M. E.; Roy, B.; Ahn, K. H. *Chem. Commun.* **2011**, *47*, 7583. (c) Du, J.; Hu, M.; Fan, J.; Peng, X. *Chem. Soc. Rev.* **2012**, *41*, 4511. (d) Chan, J.; Dodani, S. C.; Chang, C. J. *Nat. Chem.* **2012**, *4*, 973.

(11) (a) Tomasulo, M.; Raymo, F. M. *Org. Lett.* **2005**, *7*, 4633. (b) Sun, Y.; Wang, G.; Guo, W. *Tetrahedron* **2009**, *65*, 3480. (c) Kim, D.-S.; Chung, Y.-M.; Jun, M.; Alm, K. H. *J. Org. Chem.* **2009**, *74*, 4849. (d) Kim, Y.; Zhao, H.; Gabbaï, F. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 4957. (e) Kim, Y.; Huh, H.-S.; Lee, M. H.; Lenov, I. L.; Zhao, H.; Gabbaï, F. P. *Chem.—Eur. J.* **2011**, *17*, 2057. (f) Kim, H. J.; Ko, K. C.; Lee, J. H.; Lee, J. Y.; Kim, J. S. *Chem. Commun.* **2011**, *47*, 2886. (g) Lv, X.; Liu, J.; Liu, Y.; Zhao, Y.; Sun, Y.-Q.; Wang, P.; Guo, W. *Chem. Commun.* **2011**, *47*, 12843. (h) Yuan, L.; Lin, W.; Yang, Y.; Song, J.; Wang, J. *Org. Lett.* **2011**, *13*, 3730. (i) Dong, Y.-M.; Peng, Y.; Dong, M.; Wang, Y.-W. *J. Org. Chem.* **2011**, *76*, 6962. (j) Khatua, S.; Samanta, D.; Bats, J. W.; Schmittel, M. *Inorg. Chem.* **2012**, *51*, 7075. (k) Dong, M.; Peng, Y.; Dong, Y.-M.; Tang, N.; Wang, Y.-W. *Org. Lett.* **2012**, *14*, 130.

10.1021/ol4008298

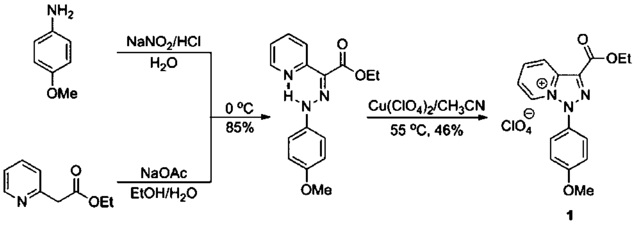
new fluorescence turn-on chemodosimeter that exhibits fast, sensitive, and selective detection of CN^- under mild conditions. The reaction-based system relies on a well established and studied ring-opening reaction of bridgehead nitrogen-containing azolopyridinium salts (Scheme 1).[12]

Scheme 1. Reaction-Based Detection of CN^- Using the Triazolopyridinium Salt **1**



We have recently reported the synthesis and photophysical properties of water-soluble triazolopyridinium salts[13] derived from our hydrazone-based switches.[14] We hypothesized that the ring-opening reaction in these systems would lead to conjugated triazole-based derivatives that can potentially be emissive[15] and, hence, used in CN^- sensing. Our choice of a sensor was based on how the emission properties of the newly formed cyano-containing triazole derivative might be best distinguished from the emission properties of the starting material. The triazolopyridinium salts emit blue light upon excitation,[13] and we anticipated that the extended π-conjugation in the cyano adduct will lead to a bathochromic shift. A recent report showed that having a *p*-OMe substituted phenyl ring at the N-2 position of the triazole ring can lead to enhanced emission.[15a] On the other hand, and based on our previous results,[13] this substituent was expected to quench the emission of the triazolopyridinium dye through charge transfer. Hence, we decided to incorporate a *p*-OMe substituent in our design (Scheme 2) to enhance the change in emission upon reaction with CN^-. Moreover, we added an ethyl ester group at position C-5 to increase the conjugation in the system. This rational design has led us to compound **1**, which was synthesized in a few simple steps (Scheme 2): *p*-Anisidine was treated with conc. HCl in H_2O and then with $NaNO_2$ at 0 °C to give the *p*-anisidenediazonium chloride salt. A solution of ethyl−2-(pyridin-2-yl)acetate that was pretreated with sodium acetate was then added to this solution to afford the hydrazone precursor. The latter was subsequently oxidized with 4 equiv of $Cu(ClO_4)_2 \cdot 6H_2O$ in CH_3CN at 55 °C to give **1** as an off-white solid in 46% yield. Both **1** and the hydrazone precursor were characterized using NMR spectroscopy and ESI-MS (Supporting Information).

Scheme 2. Synthetic Route towards the Triazolopyridinium Salt **1**



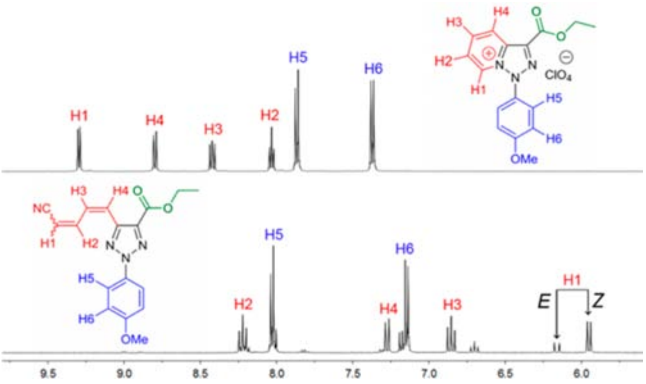


Figure 1. ^1H NMR spectra (DMSO-d_6 at 294 K) of (a) **1** and (b) a crude mixture of *E*/*Z* isomers of **2**, obtained after adding 1 equiv of NaCN to **1**.

^1H NMR spectroscopy studies in DMSO-d_6 suggest that the ring-opening reaction reported in the literature for analogous azolopyridinium salts[12] occurs rapidly with **1** as well. The ^1H NMR spectrum changes immediately upon the addition of 1 equiv of NaCN to **1** (Figure 1). The appearance of upfield alkene signals implies the formation of **2** (Scheme 1), which equilibrates over time to give an 85:15 mixture of the *Z* and *E* isomers, respectively. This assignment was inferred from the coupling constants of the signals at 5.94 and 6.17 ppm, J = 10.9 and 16.1 Hz, respectively (Supporting Information, Figure S4). Compound **2** was isolated as an inseparable mixture of *Z* and *E* isomers and characterized by NMR spectroscopy and ESI-MS (Supporting Information).

---

(12) (a) Gelleri, A.; Messmer, A.; Nagy, S.; Radics, L. *Tetrahedron Lett.* **1980**, *21*, 663. (b) Messner, A.; Hajós, G.; Timari, G. *Tetrahedron* **1992**, *48*, 8451. (c) Riedl, Z.; Hajós, G.; Messmer, A.; Kollenz, G. *J. Heterocycl. Chem.* **1993**, *30*, 819. (d) Béres, M.; Hajós, G.; Riedl, Z.; Timári, G.; Messmer, A.; Holly, S.; Schantl, J. G. *Tetrahedron* **1997**, *53*, 9393. (e) Bátori, S.; Gács-Baitz, E.; Bokotey, S.; Messmer, A. *Tetrahedron* **2003**, *59*, 4297. (f) Kotschy, A.; Faragó, J.; Csámpai, A.; Smith, D. M. *Tetrahedron* **2004**, *60*, 3421. (g) Palkó, R.; Riedl, Z.; Egyed, O.; Fábián, L.; Hajós, G. *J. Org. Chem.* **2006**, *71*, 7805. (h) Takács, D.; Király, P.; Nagy, I.; Bombicz, P.; Egyed, O.; Riedl, Z.; Hajós, G. *J. Organomet. Chem.* **2010**, *695*, 2673.

(13) Su, X.; Liptak, M. D.; Aprahamian, I. *Chem. Commun.* **2013**, *49*, 4160.

(14) (a) Landge, S. M.; Aprahamian, I. *J. Am. Chem. Soc.* **2009**, *131*, 18269. (b) Su, X.; Aprahamian, I. *Org. Lett.* **2011**, *13*, 30. (c) Su, X.; Robbins, T. F.; Aprahamian, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 1841. (d) Landge, S. M.; Tkatchouk, E.; Benítez, D.; Lanfranchi, D. A.; Elhabiri, M.; Goddard, W. A., III; Aprahamian, I. *J. Am. Chem. Soc.* **2011**, *133*, 9812. (e) Su, X.; Lessing, T.; Aprahamian, I. *Beilstein J. Org. Chem.* **2012**, *8*, 872. (f) Ray, D.; Foy, J. T.; Hughes, R. P.; Aprahamian, I. *Nat. Chem.* **2012**, *4*, 757. (g) Su, X.; Lõkov, M.; Kütt, A.; Leito, I.; Aprahamian, I. *Chem. Commun.* **2012**, *48*, 10490. (h) Yang, Y.; Hughes, R. P.; Aprahamian, I. *J. Am. Chem. Soc.* **2012**, *134*, 15221.

(15) (a) Yan, W.; Wang, Q.; Lin, Q.; Li, M.; Petersen, J. L.; Shi, X. *Chem.—Eur. J.* **2011**, *17*, 5011. (b) Jo, J.; Lee, H. Y.; Liu, W.; Olasz, A.; Chen, C.-H.; Lee, D. *J. Am. Chem. Soc.* **2012**, *134*, 16000.

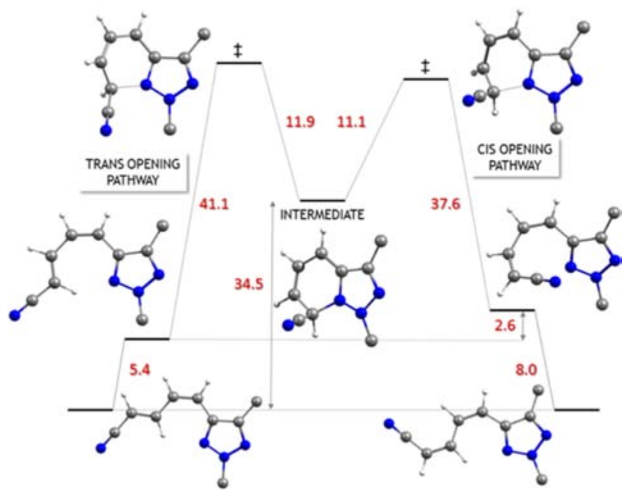
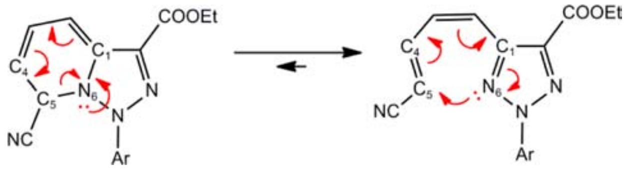


Figure 2. Free energy landscape calculated (DFT/B3LYP-D3/6-311++G**)(DMSO) for opening of cyanotriazole intermediate via pseudopericyclic pathways to give *Z*- and *E*-products. Values of ΔG are in kcal·mol^{-1}. The ester and aryl groups were removed for the sake of clarity. See Supporting Information Figure S19 for full structures.

To better understand the energetics and stereochemistry of the ring-opening reaction (Scheme 1) DFT calculations (B3LYP-D3/6311++G**) were carried out using a DMSO solvent model.[16,17] The energetics are summarized in Figure 2. The ring opening is thermodynamically favorable by 34.5 kcal/mol for both *Z* and *E* isomers. However, opening to give the *Z* isomer is kinetically favored by 0.8 kcal·mol^{-1} with very large barriers for reclosure, consistent with the observed *Z*/*E* isomer ratio of 85:15 being kinetically controlled. Application of NBO techniques (Supporting Information, Figures S28−S31 and Table S1) to the transition state illustrates that the reaction follows a pseudopericyclic pathway[18] (Scheme 3), and not a disrotatory electrocyclic ring-opening reaction as previously suggested.[12a,b] In the ring-closing direction, population of the C_4-C_5 π^* orbital occurs by depletion of electron density in the original N_6 lone pair (not the C_1-N_6 π orbital) to give the new C_5-N_6 σ-bond. The C_1-N_6 π orbital evolves into the new N_6 lone pair. Thus the transformation includes eight electrons in a cyclic orbital array and takes place in concert because it is not subject to the Woodward−Hoffmann rules. Full details of this analysis are provided in the Supporting Information.

Scheme 3. Pseudopericyclic Pathway for Ring Opening/Closing



The photophysical properties of **1** and **2** were studied in aqueous DMSO (Figure 3a). The emission intensity of **1** is much lower than that for the previously reported derivative that lacks the *p*-OMe substituent.[13] As expected this group quenches the emission of **1** by enhancing the charge transfer from the phenyl ring to the triazolopyridinium subunit. The addition of 2 equiv of NaCN to **1** affords **2**, which upon excitation at 330 nm yields a 60-fold increase in fluorescence relative to **1** at $\lambda_{\max} = 504$ nm (Figure 3a). Compound **2** has a broad emission ranging from 400−620 nm and a quantum yield of 0.45 ± 0.02, which is 15 times higher than that of **1** (0.03 ± 0.02). An accurate estimation of the Stokes shift was precluded by the absorption of DMSO below 350 nm. However, when the spectroscopic analysis was carried out in acetonitrile a “mega” (larger than 100 nm)[19] Stokes shift of 177 nm (56,500 cm^{-1}) (Supporting Information, Figure S10) was measured. Such large Stokes shifts and broad emission profiles have been reported previously for other triazole-based systems.[15a]

Compound **1** exhibits a turn-on response upon the addition of NaCN, enabling its visual detection upon excitation in the UV range (Figure 3b). Because of the unique fluorescent properties of **2**, a limit of detection (LOD) of 0.2 ppm (8.46 μM) in DMSO/H_2O (99:1) was determined for CN^- (Supporting Information, Figure S7), which is at the level set by the United States Environmental Protection Agency.[3] Moreover, the reaction between **1** and

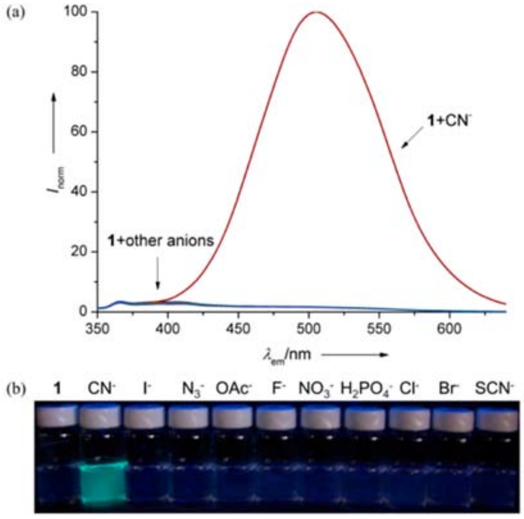


Figure 3. (a) Fluorescence intensity spectra of **1** (2.5×10^{-5} M in DMSO/H_2O (99:1)) recorded after the addition of 2 equiv of the sodium salts of various anions (**1** alone, CN^-, I^-, N_3^-, AcO^-, F^-, NO_3^-, $H_2PO_4^-$, Cl^-, Br^-, and SCN^-). (b) Fluorescence change of **1** observed upon excitation at 365 nm after the addition of various anions (conditions identical to those described above).

---

(16) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(17) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(18) (a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650. (b) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. V. R. *J. Comput. Chem.* **1983**, *4*, 294. (c) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265.

2 equiv of CN^- occurs almost instantaneously (Figure S11). These results attest to the reactivity of **1** and show how it can be quickly used in the detection of low quantities of CN^-. To evaluate the selectivity of sensor **1**, 2 equiv of various potentially competing anions (studied as their corresponding sodium salts) including I^-, N_3^-, AcO^-, F^-, NO_3^-, $H_2PO_4^-$, Cl^-, Br^-, and SCN^- were each added to DMSO/H_2O (99:1) solutions of **1**. The fluorescent properties of the resulting solutions remained unaffected for days (Figure 3a and b and Supporting Information Figure S8) demonstrating the high selectivity of the ring-opening reaction toward cyanide.[22]

In conclusion we have shown that the triazolopyridinium salt **1** is an efficient reaction-based sensor for CN^-. A selective 60-fold increase in emission is observed upon the addition of NaCN to **1**, enabling the quick detection of 0.2 ppm of the analyte. The characterization of the fluorescent cyano adduct **2** confirmed that the ring-opening reaction of the bridgehead nitrogen is responsible for the observed sensing capability of **1**. This process was further elucidated using DFT/NBO calculations, which showed that it most likely proceeds via a pseudopericyclic pathway. We are currently working on further optimizing the conditions of this reaction in order to employ it in real-world applications.

Acknowledgment. This work was supported by Dartmouth College and the Burke Research Initiation Award. R.P.H. thanks the National Science Foundation for an operating grant that made possible the purchase of hardware and software used for the DFT calculations.

Supporting Information Available. Experimental procedures, NMR spectra, emission spectra, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(19) (a) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104. (b) Goerigk, L.; Grimme, S. *Phys. Chem. Chem. Phys.* **2011**, *13*, 6670.

(20) (a) Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325. (b) Snyder, J. P.; Halgren, T. A. *J. Am. Chem. Soc.* **1980**, *102*, 2861. (c) Dewar, M. J. S.; Healy, E. F.; Ruiz, J. *Pure Appl. Chem.* **1986**, *58*, 67. (d) Birney, D. M.; Wagenseller, P. E. *J. Am. Chem. Soc.* **1994**, *116*, 6262. (e) Birney, D. M. *J. Org. Chem.* **1996**, *61*, 243. (f) Birney, D. M.; Ham, S.; Unruh, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 4509. (g) Birney, D. M.; Xu, X.; Ham, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 189. (h) Birney, D. M. *J. Am. Chem. Soc.* **2000**, *122*, 10917. (i) Chamorro, E. J. *J. Chem. Phys.* **2003**, *118*, 8687. (j) Matito, E.; Poater, J.; Duran, M.; Solà, M. *ChemPhysChem* **2006**, *7*, 111. (k) Kearney, A. M.; Vanderwal, C. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7803. (l) Chamorro, E.; Notario, R.; Santos, J. C.; Pérez, P. *Chem. Phys. Lett.* **2007**, *443*, 136. (m) Calvo-Losada, S.; Sánchez, J. J. Q. *J. Phys. Chem. A* **2008**, *112*, 8164. (n) Ji, H.; Li, L.; Xu, X.; Ham, S.; Hammad, L. A.; Birney, D. M. *J. Am. Chem. Soc.* **2009**, *131*, 528. (o) Lemal, D. M. *J. Org. Chem.* **2010**, *75*, 6411.

(21) Martin, A.; Long, C.; Forster, R. J.; Keyes, T. E. *Chem. Commun.* **2012**, *48*, 5617.

(22) No reaction was observed between the competing anions and **1** by ^1H NMR spectroscopy. On the other hand, the hydroxide ion reacts with **1** leading to a nonemissive triazole derivative.

The authors declare no competing financial interest.