

Designing and Using a Safer, Greener Azole Oxamide for Chemiluminescence Demonstrations

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S Supporting Information

ABSTRACT: The oxamide of 1*H*-benzotriazole, identified with the guidance of Green Chemistry Principle no. 4, was successfully employed in chemiluminescence demonstrations. Its synthesis is highly convenient, as it can work without sacrificial bases.



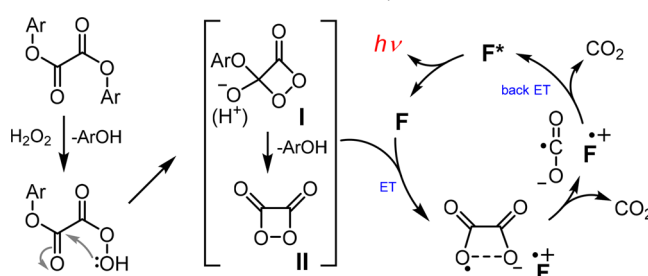
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Preparing a glowing lightstick in the lab may appear to be a simple task, but the underlying chemical mechanism is quite complex, and choosing the appropriate reagents or reaction conditions may not be quite as simple.¹ In these systems, emission of visible light is often achieved by electronic transitions within an organic compound characterized by extensive conjugation, called the fluorescer (F). When some energy is transferred to F, an electron jump may occur, resulting in a short-lived excited state (F*) that will relax back to the ground state, emitting a photon of light. The term chemiluminescence (CL), i.e., light emission from a chemical reaction, is used when a chemical reaction serves as the energy source.¹ This phenomenon resembles the well-known flame tests for metal recognition, in which the flame energy promotes electronic transitions.

The most efficient known nonenzymatic chemiluminescent system is based on the reaction between an oxalic acid derivative and hydrogen peroxide.² The ensuing unstable peroxyoxalate decomposes exergonically to CO₂ via intermediate I or II (Scheme 1). An appropriate F can mediate the decomposition of I or II through electron interchange, giving rise to chemically initiated electron exchange luminescence (CIEEL).³

Since I or II can also decompose by alternative routes, to obtain efficient luminescence through CIEEL, the electrophilicity of the starting oxalate and the reaction conditions must be carefully tailored. For example, oxalyl chloride is highly reactive and produces only a short luminescence flash, while alkyl oxalate esters do not react at all.^{2b} Suitable compounds are activated esters such as bis(2,4,6-trichlorophenyl)oxalate (TCPO) and bis(2,4-dinitrophenyl)oxalate (DNPO), shown

Scheme 1. Mechanism of the Peroxyoxalate CIEEL Process^a



^aF is the fluorescer, a substance able to convert chemical energy into light ($h\nu$). Electron transfer (ET) and the related return process (back ET) describe the interchange processes between I or II and F.

in Figure 1. Activated amides like 1,1'-oxalyldiimidazole (ODI) can work pretty well too.⁴

Peroxyoxalate CL has been employed in several analytical and commercial applications^{5,6} as well as for didactical demonstrations,⁷ adding high attractiveness to chemical sciences. Anyway, a safety issue comes out when classical oxalates (TCPO and DNPO) are employed because the parent phenols, generated as byproducts of the chemiluminescence demonstration (ArOH in Scheme 1), are toxic and/or suspected carcinogens.^{8a} Accordingly, these systems are not suitable for use in schools, nor should they be marketed.^{8b} ODI

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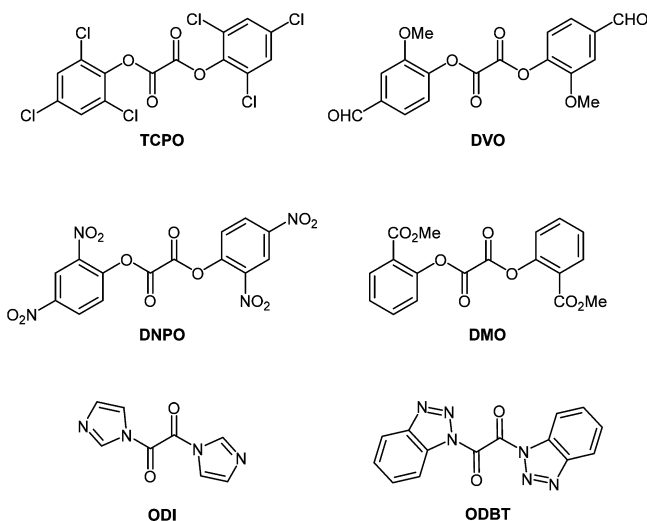


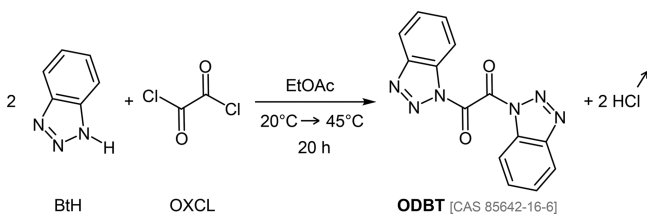
Figure 1. Active compounds used in peroxyoxalate chemiluminescence systems. Typical examples (TCPO, DNPO, ODI) and greener alternatives (DVO, DMO, ODBT) are shown.

(Figure 1) has similar issues, as the parent imidazole may be associated with birth defects (GHS code H360D).^{8a}

The green chemistry (GC) approach strives to achieve sustainability at the molecular level, reducing hazards across all of the life-cycle stages.⁹ The Twelve Principles of Green Chemistry address a range of ways to improve the safety and sustainability of chemical substances. The indications within GC Principle no. 4 (GC4), *safer products by design*, prove to be rather useful upon inspection of the compounds shown in Figure 1. A common structural feature responsible for the desired function (activated oxalate) and a molecular portion responsible for side effects (leaving groups, LGs) can be promptly identified. In agreement with that, oxalic acid derivatives containing less toxic LGs were recently studied, such as divanillyl oxalate (DVO) (LG = vanillin)^{10a} and dimethylsalicyl oxalate (DMO) (LG = methyl salicylate).^{10b,c} Going on with this line of thought, it was observed that benzoazoles sometimes have a better toxicological profile than the corresponding azoles, so 1,1'-oxalyldibenzotriazole (ODBT, 1,2-bis(1*H*-benzo[*d*][1,2,3]triazol-1-yl)ethane-1,2-dione) (Figure 1) was identified as a safer, promising agent. Furthermore, it proved to be a very efficient chemiluminescent agent. Known 1,1'-oxalyldibenzoimidazole (ODBI, 1,2-bis(1*H*-benzo[*d*]-imidazol-1-yl)ethane-1,2-dione) appeared to be safe as well,¹¹ but in our hands gave only short-lived luminescence (see the Supporting Information).

The synthesis of ODBT (Scheme 2) is practical and follows a standard method for the acylation of amines but intriguingly does not require the use of any sacrificial base.¹² This seems to

Scheme 2. Synthetic Method To Prepare ODBT from BtH and OXCL



be related to the thermal decomposition of the triazolium salt that occurs shortly after formation. Oxalyl chloride (OXCL), as a 1 M solution in EtOAc, is added dropwise at room temperature to a stirred solution of benzotriazole (BtH) in EtOAc. After the mixture is heated at 45 °C overnight, ODBT is cleanly formed and then isolated by simple filtration (92% yield).

The opportunity to avoid the addition of the sacrificial base improves the sustainability of the method on three sides:⁹ (i) current safety data sheets (SDSs) indicate that Et₃N is less safe than oxalyl chloride (GC3: *less hazardous chemical synthesis*);^{8a} (ii) no ammonium chloride is generated (GC1: *waste prevention instead of remediation*); and (iii) as a consequence (ii), the aqueous wash can be avoided, with good workup simplification (GC1). As a final note regarding the solvent, GC5 (*safer solvents and auxiliaries*) spurred us to change the originally employed Et₂O to EtOAc.¹²

DEMONSTRATION

For the CL test, ODBT (50 mg), 9,10-diphenylanthracene (1 drop of a 0.02 M solution), and H₂O₂ (1 drop of a 35% aqueous solution) were suspended in BuOAc (5 mL) inside a 10 mL vial with a screw cap. Addition of Na₂HPO₄ (10 mg) and a drop of 10% aqueous NaOH started the luminescence. An intense blue light, sustained by gentle heating and shaking, was visible for at least 30 min in a darkened room.

The CL test can be easily scaled up 10 or 20 times and shows good sensitivity to product impurities, so it can also be used as a qualitative analytical tool. IR spectroscopy as well as melting point determination can be used if a more quantitative approach is preferred (see the Supporting Information). The substitution of 9,10-diphenylanthracene with fluorescers coming from renewable resources such as chlorophyll¹ can be a further step toward sustainability (GC7: *use of renewable feedstocks*).

HAZARDS

As often happens with organic compounds, all substances including solvents (except oxalyl chloride) are flammable (H225, H226), so sparks or flames must be avoided. Oxalyl chloride is a toxic volatile acyl chloride, so contact with skin or eyes (H314), inhalation (H331, H335), and ingestion (H302) must be avoided. It must be handled with gloves, safety goggles, and possibly behind the glass of an extractor hood. Using a premade 1 M solution facilitates handling. Concentrated aqueous H₂O₂ used in the CL tests is corrosive (H302) and can cause serious eye damage (H318), so it requires gloves and safety goggles. The 10% aqueous NaOH solution behaves similarly (H314). Ordinary attention must be taken with BtH (eye irritant, H319; harmful for ingestion or inhalation, H302 and H332; harmful for aquatic organisms, H412), EtOAc (eye irritant, H319; may cause drowsiness or dizziness, H336), and BuOAc (H336). As a solid nonvolatile compound, ODBT should be safe in handling and should display little toxicity. With regard to its structural feature of three adjacent nitrogen atoms, it must be noted that like other acylbenzotriazoles, which have been extensively used as “tamed acyl chlorides” by Katritzky and co-workers,^{12,13} ODBT should possess considerable stability and a good safety profile.¹⁴

CONCLUSIONS

ODBT constitutes an appealing example of a chemiluminescent agent with very low toxicity that is easy to prepare and able to generate an intense and durable visual effect. In contrast to similar agents, its synthesis does not require sacrificial bases, resulting in considerable advantages with regard to handling of toxic reagents, generated wastes, and workup practice. This experiment was successfully proposed within the Applied Organic Chemistry course taught in the third year of the B.Sc. in Chemistry. It fits well with use in universities as well as in high school laboratories, as it is cheap, avoids problematic reagents, uses green and recyclable solvents, and does not require refined analytics.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.6b01010.

Further information on materials, detailed experimental procedures, and IR spectra of products and reagents (PDF, DOC)

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Notes

The author declares no competing financial interest.

REFERENCES

- (1) Kuntzleman, T. S.; Rohrer, K.; Schultz, E. The Chemistry of Lightsticks: Demonstrations To Illustrate Chemical Processes. *J. Chem. Educ.* **2012**, *89*, 910–916.
- (2) (a) Chandross, E. A. A new chemiluminescent system. *Tetrahedron Lett.* **1963**, *12*, 761–765. (b) Ciscato, L. F. M. L.; Augusto, F. A.; Weiss, D.; Bartoloni, F. H.; Albrecht, S.; Brandl, H.; Zimmermann, T.; Baader, W. J. The chemiluminescent peroxyoxalate system: state of the art almost 50 years from its discovery. *ARKIVOC* **2012**, *2012* (iii), 391–430. (c) Orosz, G. The role of diaryl oxalates in peroxyoxalate chemiluminescence. *Tetrahedron* **1989**, *45*, 3493–3506.
- (3) Schuster, G. B. Chemiluminescence of organic peroxides. Conversion of ground-state reactants to excited-state products by the Chemically Initiated Electron-Exchange Luminescence mechanism. *Acc. Chem. Res.* **1979**, *12*, 366–373.
- (4) Rauhut, M. M.; Bollyky, L. J.; Maulding, D. R.; Clarke, R. A.; Roberts, B. G.; Semsel, A. M.; Villanova, A. M.; Whitman, R. H. *Chemiluminescent Materials*; Technical Report No. 10, Contract No. 4200[00]; American Cyanamide Company: Stamford, CT, 1965; <http://www.dtic.mil/dtic/tr/fulltext/u2/626295.pdf> (accessed March 2017).
- (5) For analytical applications, see: (a) Stigbrand, M.; Pontén, E.; Irgum, K. 1,1'-Oxalyldiimidazole as chemiluminescence reagent in the determination of low hydrogen peroxide concentrations by flow injection analysis. *Anal. Chem.* **1994**, *66* (10), 1766–1770. (b) Gohda, R.; Kimoto, K.; Santa, T.; Fukushima, T.; Homma, H.; Imai, K. Optimization of the reaction conditions for the peroxyoxalate chemiluminescence detection system of fluorescent compounds in a High-Performance Liquid Chromatography. *Anal. Sci.* **1996**, *12*, 713–719.
- (6) For examples of “lightstick” illumination devices, see: <https://getcyalume.com/> (accessed March 2017).
- (7) Mohan, A. G.; Turro, N. J. A facile and effective chemiluminescence demonstration experiment. *J. Chem. Educ.* **1974**, *51* (8), 528–529.
- (8) (a) Up-to-date SDSs were all taken from Sigma-Aldrich (www.sigmaaldrich.com). (b) de Oliveira, T. F.; da Silva, A. L. M.; de Moura, R. A.; Bagattini, R.; de Oliveira, A. A. F.; de Medeiros, M. H. G.; Di Mascio, P.; de Arruda Campos, I. P.; Barretto, F. P.; Bechara, E. J. H.; de Melo Loureiro, A. P. Luminescent threat: toxicity of light stick attractors used in pelagic fishery. *Sci. Rep.* **2015**, *4*, 5359.
- (9) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998. (b) Anastas, P. T.; Eghbali, N. *Green Chemistry: Principles and Practice*. *Chem. Soc. Rev.* **2010**, *39*, 301–312.
- (10) (a) Jilani, O.; Donahue, T. M.; Mitchell, M. O. A greener chemiluminescence demonstration. *J. Chem. Educ.* **2011**, *88*, 786–787. (b) Cambrea, L. R.; Davis, M. C.; Groshens, T. J.; Meylemans, H. A. A Soluble, Halogen-Free Oxalate from Methyl Salicylate for Chemiluminescence Demonstrations. *J. Chem. Educ.* **2013**, *90* (9), 1253–1254. Also see: (c) Lee, J. H.; Kim, Y. T.; Hong, Y.-S.; Suh, H. S.; 1,1'-Oxalyldisodiumbenzoate derivatives, method for preparation thereof and chemiluminescent composition containing the same. Patent WO2008/062957A1, 2008.
- (11) Maulding, D. R.; Clarke, R. A.; Roberts, B. G.; Rauhut, M. M. Chemiluminescence from reactions of electrophilic oxamides with hydrogen peroxide and fluorescent compounds. *J. Org. Chem.* **1968**, *33* (1), 250–254.
- (12) Katritzky, A. R.; Levell, J. R.; Pleyne, P. M. General synthesis of unsymmetrical tetrasubstituted oxamides via 1,1'-(1,2-dioxoethane-1,2-diyl)bis-1H-benzotriazole. *Synthesis* **1998**, *1998*, 153–156.
- (13) (a) Katritzky, A. R.; Angrish, P.; Suzuki, K. The efficient preparation of di- and tripeptides by coupling *N*-(Cbz or Fmoc- α -aminoacyl)benzotriazoles with unprotected amino acids. *Synthesis* **2006**, *3*, 411–424. (b) Katritzky, A. R.; Manju, K.; Singh, S. K.; Meher, N. K. Benzotriazole mediated amino-, amido-, alkoxy- and alkylthio-alkylation. *Tetrahedron* **2005**, *61*, 2555–2581.
- (14) Malow, M.; Wehrstedt, K. D.; Neuenfeld, S. On the explosive properties of 1H-benzotriazole and 1H-1,2,3-triazole. *Tetrahedron Lett.* **2007**, *48*, 1233–1235.