Method Of Synthesizing Tetrazines

Tech ID: 22813 / UC Case 2012-252-0

BACKGROUND

Nitrogen-rich tetrazines, have broad applications in biochemistry including small-molecule imaging, genetically targeted protein tagging, post-synthetic DNA labeling, nanoparticle-based clinical diagnostics, *in-vivo* imaging, as well as significant use in materials science, coordination chemistry, and the production of high energy materials such as those used in specialty explosives research. Among other uses, tetrazines can serve as coupling agents for molecular imaging compounds such as fluorophores or magnetic contrast agents, or even as ligands for metal catalysts or inorganic materials such as metal-organic frameworks. Tetrazines are also valuable synthetic intermediates, and have been elegantly deployed on route to several natural product syntheses. Despite the promise of tetrazines, the lack of convenient synthetic methods is a significant roadblock to their broader use and study.

TECHNOLOGY DESCRIPTION

Researchers at the University of California have discovered that Lewis acid metal catalysts, most notably divalent nickel and zinc salts, can catalyze the one-pot synthesis of 1,2,4,5-tetrazines directly from commercially available starting materials. The reaction is a single step process with a high yield. This methodology should greatly improve the accessibility of tetrazines, allowing the synthesis of compounds previously unobtainable in useful quantities, and lead to further exploration of their applications.

STATE OF DEVELOPMENT

A direct demonstration of the process has been published using a variety of reactants and catalysts. Additional studies with the technique show how bioorthogonal conjugations may be performed in labeling reactions to synthesize cyclopropene tags useful for live-cell imaging. More recently, studies have examined applications for agricultural chemistry with the synthesis of cyclopropenes capable of delaying the ripening of fruits, vegetables, and ornamental flowers. More details are available at; J. Yang, M. R. Karver, W. Li, S. Sagu, N. K. Devaraj "Metal-Catalyzed One-Pot Synthesis of Tetrazines Directly from Aliphatic Nitriles and Hydrazine" **Angew. Chem. Int. Ed.**, 2012, 51(21), 5222-5225. A demonstration of using the technique to make cyclopropene tags is available at; J. Yang, J. Šečkutė, C. M. Cole, N. K. Devaraj "Live-Cell Imaging of Cyclopropene Tags with Fluorogenic Tetrazine Cycloadditions" **Angew. Chem. Int. Ed.**, 2012, 51(30), 7476-7479

RELATED MATERIALS

- Šeckute J., Devaraj N.K. “Expanding room for tetrazine ligations in the in vivo chemistry toolbox” Curr Opin Chem Biol. 2013 Oct;17(5):761-7. doi: 10.1016/j.cbpa.2013.08.004 - 09/07/2013
- Šeckute J., Yang J., Devaraj N.K. “Rapid oligonucleotide-templated fluorogenic tetrazine ligations” Nucleic Acids Res. 2013 Aug;41(15):e148. doi: 10.1093/nar/gkt540 - 06/17/2013

OTHER INFORMATION

http://devarajgroup.ucsd.edu/index.html

http://cen.acs.org/articles/90/i18/Streamlining-Tetrazine-Synthesis.html

INTELLECTUAL PROPERTY INFO

U.S. rights available. A published patent application detailing this technology is available (hyperlink below under Patent Status).

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	9,533,957	01/03/2017	2012-252

CONTACT

University of California, San Diego
Office of Innovation and Commercialization
innovation@ucsd.edu
tel: 858.534.5815.



INVENTORS

- Devaraj, Neal Krishna

OTHER INFORMATION

CATEGORIZED AS

- **Biotechnology**
  - Other
- **Imaging**
  - Molecular
- **Materials & Chemicals**
  - Biological
  - Chemicals
  - Other
- **Medical**
  - Imaging
- **Research Tools**
  - Reagents

RELATED CASES

2012-252-0

University of California, San Diego
Office of Innovation and Commercialization
9500 Gilman Drive, MC 0910, ,
La Jolla,CA 92093-0910

Tel: 858.534.5815
innovation@ucsd.edu
https://innovation.ucsd.edu
Fax: 858.534.7345

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