



A microwave-assisted and environmentally benign approach to the synthesis of near-infrared fluorescent pentamethine cyanine dyes



Eric A. Owens^{a, b, c}, Nicholas Bruschi^a, Joseph G. Tawney^a, Maged Henary^{a, b, c, *}

^a Department of Chemistry, Georgia State University, 100 Piedmont Road SE, Atlanta, GA 30303, USA

^b The Center for Diagnostics and Therapeutics, Georgia State University, 100 Piedmont Road SE, Atlanta, GA 30303, USA

^c The Center for Biotechnology and Drug Design, Georgia State University, 100 Piedmont Road SE, Atlanta, GA 30303, USA

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ABSTRACT

A time-efficient and eco-conscious microwave methodology was developed and applied to synthesize a systematic library of pentamethine cyanine dyes and their corresponding precursors. The synthesis outlined herein drastically reduced the reaction pathway for pentamethine carbocyanine dye syntheses from days to min, as well as producing increased yields (89–98%) to the conventional heating method (18–64%). Twelve examples of pentamethine cyanine dyes were synthesized by means of microwave-assisted organic synthesis which provided excellent yield in expedited reaction time and were obtained using facile isolation methods. Furthermore, three cyanines were prepared with a novel methylene dioxy heterocyclic structure which imparted an approximately 40 nm bathochromic shift compared to unsubstituted counterparts; these results were shown to be in agreement with DFT calculations and HOMO-LUMO energy differences.

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1. Introduction

Mother Nature provides our atmosphere to breathe, food required to eat and beautiful scenery to enjoy. Protecting and nurturing our environment should be a task shared by all in the research community. There are many methods for helping to preserve our precious natural resources which include the following: (1) using green solvents, (2) reducing heating times to conserve energy, (3) increasing atom efficiency by using higher yielding reaction conditions and (4) eliminating wasteful purification steps by using optimized methods that reduce side-products. These principles have been applied to the synthesis of many classes of compounds that are interesting to a broad population of the scientific community. Correspondingly, we have chosen to develop a completely benign synthetic route for the synthesis of near-infrared fluorescent compounds that have shown excellent promise in biological imaging, solar-cell technology, as chemodosimeters in sensing biologically relevant species and for non-covalent labeling of biomolecules.

Near-infrared (NIR, 640–900 nm) fluorescent chromophores have garnered considerable research interest for biomolecular labeling because of their unique red-shifted optical properties [1–4]. The majority of fluorescent sensors have shown to emit light in the visible region (400–600 nm), which forces unwanted competition with background noise that arises from inherent biomolecular auto-fluorescence. This competition disrupts the meaningful signal and can lead to extreme difficulty in signal delineation often with undesirable results [5]. To avoid the problems associated with visible-light-emitting fluorophores, molecules which absorb and emit light in the near-infrared region have been of significant interest to the scientific community. [1–3,5–7]

Specifically among the NIR emitting dyes, immense interest has been placed in the particular class of chromophores known as cyanine dyes, and they have shown extensive applications in cancer imaging, nucleic acid detection, biomolecular labeling, photographic processes, information storage and dye lasers [7–10]. Possessing relatively high molar absorption coefficients and a broad range of tunable fluorescence wavelengths (600–900 nm) cyanine dyes have been synthesized to emit light in the NIR range while maintaining biological efficacy [4,5,8–11]. Chiefly among these fluorophores, pentamethine cyanine dyes have shown significant promise for image guided surgery using NIR light [1]. Specifically, we reported several pentamethine cyanine dyes that have been

* Corresponding author. Department of Chemistry, Georgia State University, 100 Piedmont Road SE, Atlanta, GA 30303, USA. Tel.: +1 404 413 5566 (office).

E-mail address: mhenary1@gsu.edu (M. Henary).

shown to specifically locate various tissues of clinical importance during image-guided surgery [1]. Expanding upon the synthesis of pentamethine cyanine dyes as biomolecular imaging agents has been a focus of many bioorganic research labs worldwide [12,13].

The design and synthesis of various substituted pentamethine cyanines has been achieved in a combinatorial manner by changing the *N*-alkyl substituent or functionalizing different positions of the heterocyclic backbone [2,4]. It has been observed that minor structural alterations elicits a drastic biological response which makes synthesis of highly varied chemical structures very important [1]. This provides a significant rationale for developing a fast, facile and effective method for generating a library of pentamethine cyanines with high purity levels.

Synthesis of various pentamethine cyanine dyes with slightly altered connectivity has been shown to take hours to days by the conventional oil bath heating method with lengthy, difficult column chromatography that generates environmentally polluting solvent waste [2,6,14]. Cyanine dyes are sensitive to the acidic nature of silica gel, photodegrade during purification steps and cleave in the basic solutions required for their synthesis (Fig. 1); therefore, expediting the reaction time and increasing purity levels is of highly important. Recently, the implementations of microwave chemistry has helped speed reactions and decrease the environmentally harmful waste common in organic labs; it has received interest throughout the scientific community and it is very desirable to conduct synthetic protocol under microwave irradiation.

In order to implement this technology in cyanine synthesis, we have harnessed the ability of our reaction mixture to absorb microwave energy. Electromagnetic irradiation of molecules results in rapid, volumetric heating caused by the dielectric effect which yields the final compounds without the need for column purification that may jeopardize the chemical integrity of the compounds from photodegradation or decomposition on the silica

matrix [9]. The pentamethine class of cyanine dyes has not been optimized using MAOS. Utilizing a green approach, an entire synthetic pathway has been designed to prepare pentamethine cyanines with diverse chemical structures. Specifically, in the final synthetic step, using the CEM Discover LabMate several different substituted pentamethine cyanine dyes have been synthesized within 20 min in analytical purity without column purification. In comparison to the conventional heating method, the syntheses described herein provide drastically decreased reaction times and comparable or increased yields (89–98% in the final step, 80–91% overall).

2. Results and discussion

2.1. Eco-friendly synthesis of pentamethine cyanine fluorophores

The common synthetic method for the preparation of pentamethine cyanines begins with the formation of the terminal heterocyclic moieties. The four heterocycles used to afford the compounds were synthesized according to Scheme 1 and Equation (2). We optimized each step for the synthesis beginning with heterocyclic formation and begins when substituted phenylhydrazines are refluxed in glacial acetic acid with 3-methyl-2-butanone to afford **1** and **2**. This reaction affords the desired indolenine compounds in good yield, but this method requires extended periods of reaction time exceeding 24 h and excess acetic acid as solvent. Our green microwave method employs water as an environmentally conscious solvent and a catalytic (0.1 mol eq.) amount of sulfuric acid to achieve quantitative conversion in 10 min. The second synthetic step is the quaternization of the indolenine nitrogen atom. A classical method for this synthesis is mixing the two reagents in acetonitrile and refluxing until the reaction goes to completion. The volatile nature of short chain

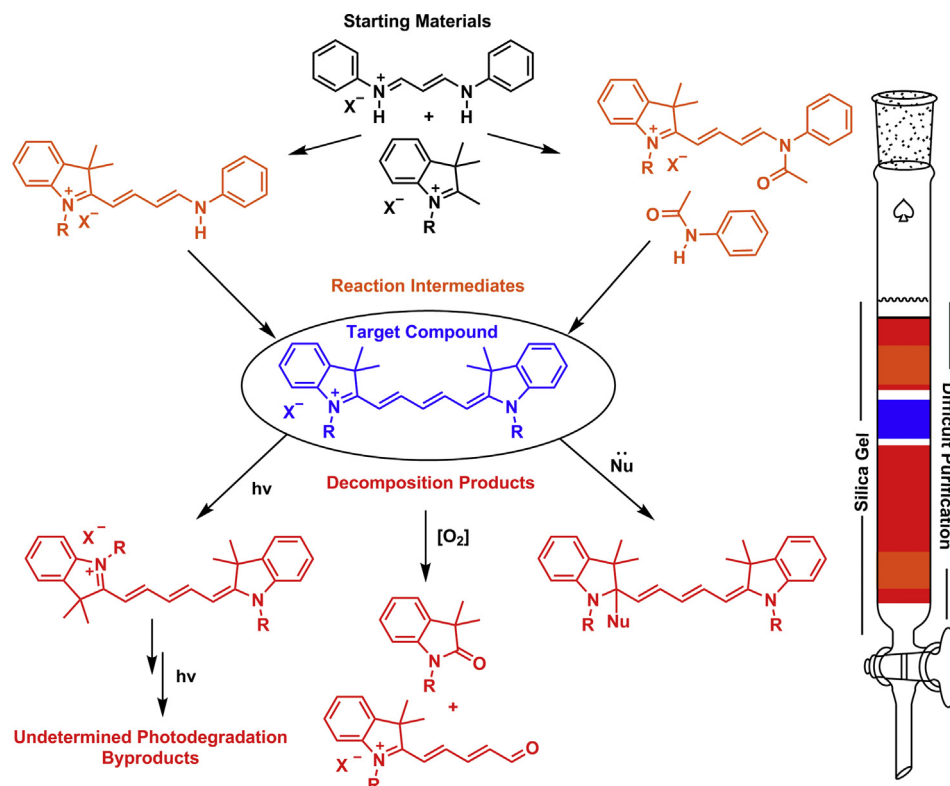


Fig. 1. The reaction intermediates and postulated degradation products that form during either the classical heating method of synthesis or purification of cyanine dyes that lead to difficulty in obtaining analytically pure compounds for biological testing.

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