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Convenient one-step synthesis of 5-carboxy-seminaphthofluoresceins

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ABSTRACT

The one-step synthesis and characterization of a series of regioisomerically pure 5-carboxy-seminaphthofluoresceins (5-carboxy-SNAFLs) is reported. The optical properties were determined in aqueous buffer at around biological pH, and highly pH sensitive, large Stokes-shift fluorophores with emission in the deep-red to near-infrared region were identified.

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Introduction

The development and characterization of functional red and near-infrared-emitting (NIR) organic dyes with available anchoring sites is of great current interest, especially in fields such as biomedicine, biochemistry, and soft-matter science.^{1–4} Due to the low cost, reliability, and low invasiveness of fluorescent techniques in, for example, diagnostics and imaging, there is an ongoing search for new and better dyes. The importance placed on red-NIR dyes in this context is primarily due to the near-absence of biological autofluorescence in this spectral range, and the large penetration depth of NIR light in biological tissue.^{5–7}

5- and 6-carboxy-fluorescein are well-known functional dyes, with strongly pH sensitive optical properties and anchoring sites for target conjugation, and are suitable for a wide range of biological and materials science applications.^{8,9} The long history of their chemical modification of these dyes has broadened the scope of their use, however, a fundamental limitation is the relatively high-energy emission centered at approximately 520 nm. Developing robust approaches to substantially lowering the emission energy of this otherwise excellent class of dyes has thus been a topic of significant interest.^{5–15} One such approach has been to extend the fluorescein scaffold with additional benzoid rings to

one or both sides, yielding seminaphthofluorescein (SNAFL) or naphthofluorescein respectively (Fig. 1). These represent fluorescein analogs of the well-known structurally related seminaphthorhodafluor (SNARF) rhodamine derivatives (Fig. 1).

Furthermore, as a class of dyes they show tunable wavelengths, with emission ranging from the deep-red to the NIR region.^{5–13} This range of emission properties appear due to its dependence on both the geometry of the conjugated system and the position of the hydroxy group on the naphthalene moiety.^{5–7,13} The benzene unit can in general be positioned in three different ways termed type [a], [b] and [c] (Fig. 1). The importance of the benzannulation position has been studied both by semiempirical calculations and by synthesizing a large range of regioisomers of closely related seminaphthofluorene (SNAFR) derivatives.¹³ The structure of carboxy-SNAFLs diverges from SNAFRs by two additional carboxylic acids at the 3' and 5' or 6' positions (Fig. 1). SNAFR derivatives thus lack the obvious linking sites provided by the 5' or 6' carboxylic acids. In general the synthesis of seminaphtho- and naphthofluorescein requires multiple steps and, in cases where a carboxylic acid is present at the 5' or 6' positions, mixtures of the two regioisomers are formed.¹⁶ The fluorescence quantum yields are typically low in aqueous solutions (<9%). In most cases an increase in quantum yield, Stokes shifts and maximum absorption/emission peak is observed in organic solvents.⁶

In the present work we report the synthesis and optical properties of a number of 5-carboxy-SNAFL derivatives. The general synthetic approach uses the 5-carboxy-fluorescein scaffold and

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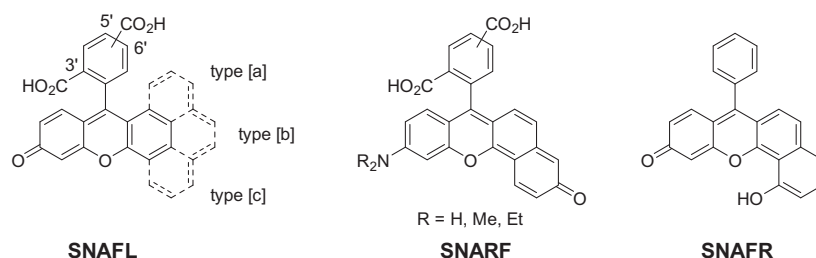


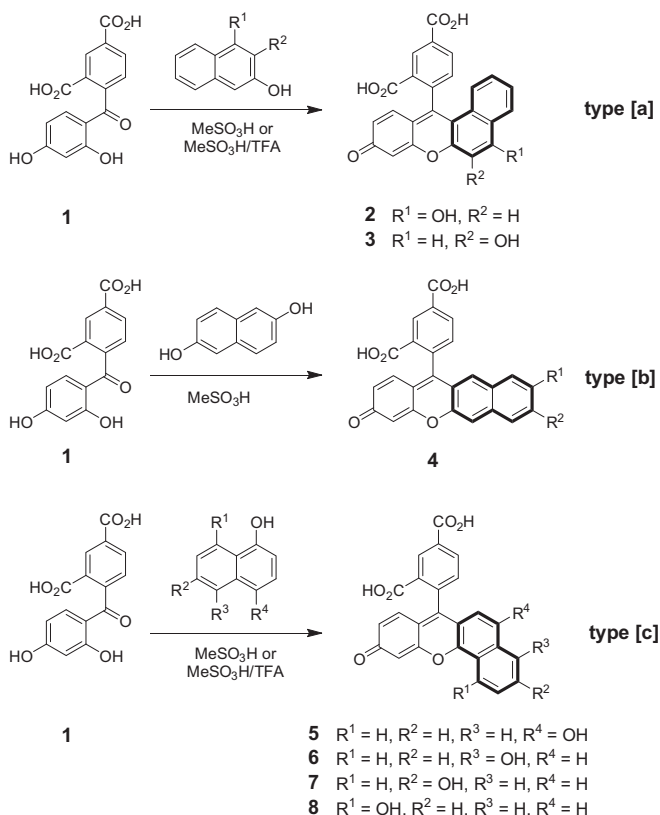
Fig. 1. Structures of type [a], [b] and [c] seminaphthofluorescein (SNAFL), seminaphthorhodafluor (SNARF) and seminaphthofluorone (SNAFR).

extends it by a benzene unit, enabling the use of well-known chemistry from 5-carboxy-fluorescein to synthesize the newly developed dyes. Depending on the direction of benzannulation, and in particular the position of the naphthol, the compounds exhibit deep-red to NIR emission with large Stokes shifts and pK_a values around 8.

Results and discussion

The synthetic approach described herein is based on previous work, where we reported the condensation between 2- and 4-(2,4-dihydroxybenzoyl)isophthalic acid and a number of resorcinol derivatives.^{9,17} The reaction between electron-rich dihydroxynaphthalene (naphthalene-1,3-diol) was found to proceed in high yield and could be easily purified by precipitation to yield 5-carboxy-SNAFL-2.

To further investigate the scope of the reaction, the condensation between 4-(2,4-dihydroxybenzoyl)isophthalic acid (**1**) in methanesulfonic acid (or a 1:1 mixture with TFA), and the 10 regioisomers of dihydroxynaphthalene (Scheme 1 and Table 1)



Scheme 1. Synthesis of type [a], [b] and [c] 5-carboxy-SNAFLs 2–8.

Table 1
Yields, solvents and reaction times.

5-Carboxy-SNAFL	Yield (%)	Solvent	Time (h)
2 ^a	79	MeSO ₃ H	1 week ^c
3	29	MeSO ₃ H/TFA	24
4	80	MeSO ₃ H	12
5	74	MeSO ₃ H/TFA	20
6	75	MeSO ₃ H	3
7	79	MeSO ₃ H/TFA	24
8	59 ^b	MeSO ₃ H/TFA	2

^a Ref. 9.

^b Based on limiting dihydroxynaphthalene.

^c Not tested using TFA.

was examined. Using this procedure, 7 new benzannulated 5-carboxy-SNAFLs (**2–8**) were produced.^{18,19} To the best of our knowledge this constitutes the largest set of type [c] isomers of SNAFL (**5–8**) with the hydroxyl group located at 4 different positions.⁶ 2,7-Dihydroxynaphthalene gave a 1:1 mixture of regioisomeric 5-carboxy-SNAFLs (LCMS, not shown), however, the isomers were not separated. Only trace amounts of the desired product were observed using 1,2- and 1,7-dihydroxynaphthalene (LCMS).

X-ray quality crystals of carboxy-SNAFL-5 co-crystallized with acetic acid were obtained (Fig. 2). The conjugated system is twisted

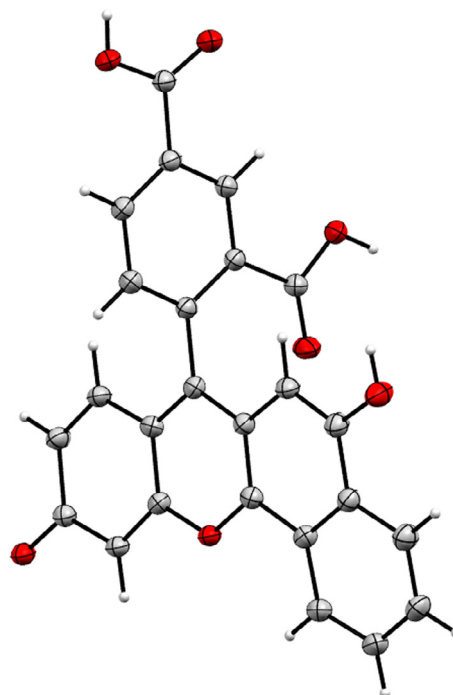


Fig. 2. Single crystal X-ray structure of carboxy-SNAFL-5 (co-crystallized with one acetic acid molecule which has been omitted for clarity).

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