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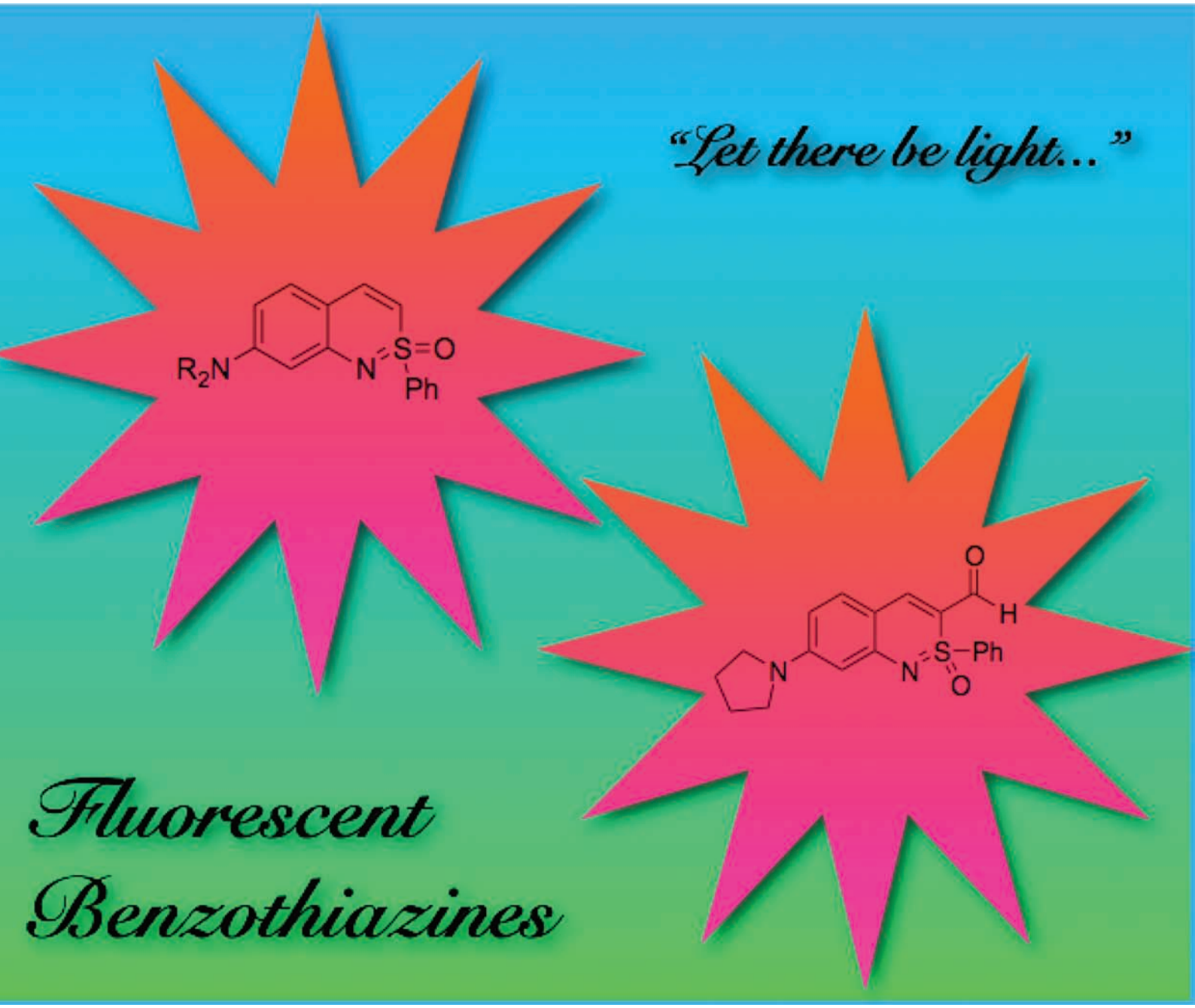

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COMMUNICATION

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COMMUNICATION

Benzothiazines in organic synthesis. Synthesis of fluorescent 7-amino-2,1-benzothiazines†

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Fluorescent 7-amino-2,1-benzothiazines were prepared in high yields using the palladium-catalyzed reaction of 4-amino-2-chlorobenzaldehydes with a sulfoximine or the reaction of 7-fluoro-2,1-benzothiazines with amines.

The development of new fluorescent materials is mandated by the continuing and growing interest in the application of optical devices and sensors, particularly in the context of materials development and biological chemistry.[1] Fluorescent species that are properly functionalized can potentially serve as sensors for detecting anything from the occurrence of biological metabolites to tumors and as components in electronic materials.[2] Our interest in this area arose from our long-standing involvement in the synthesis and application of various 2,1-benzothiazines[3] and the fact that we have known for quite some time that many of these compounds are fluorescent.

In the present study, we decided to attempt to emulate certain coumarins that have been developed in the context of fluorescent sensors.[4] For example, **1** (Fig. 1) has recently been introduced as a fluorescent probe for the detection of Cu(II).[5] We thought that benzothiazines generically represented by **2** (Fig. 2) would exhibit enhanced and useful fluorescent properties and thus decided to synthesize several examples of such species.

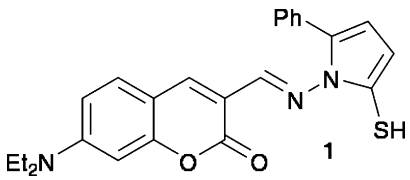


Fig. 1 A coumarin-based fluorescent sensor.

Typically, our approach to benzothiazine synthesis has involved the Buchwald–Hartwig coupling of *ortho*-bromobenzaldehydes with sulfoximines such as **3** (Fig. 3).[6] We recently reported a new approach to sulfoximines and benzothiazines that conveniently made use of chloroarenes.[7] For example, heating of a toluene solution of *o*-chlorobenzophenone (**4**) with **3** in the presence of a Pd source and the ligand RuPhos afforded the benzothiazine **5** in 77% yield (Scheme 1). Though we were not certain that the methodology would be applicable to synthesis of aminobenzothiazines, we decided to attempt to expand the scope of the methodology in this direction.

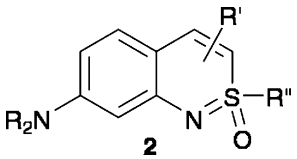


Fig. 2 Generic, fluorescent 2,1-benzothiazine.

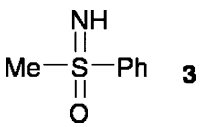
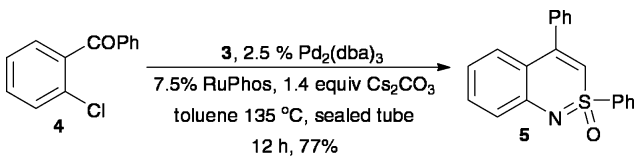


Fig. 3 The sulfoximine used in this study.



Scheme 1 Benzothiazine synthesis from a chloroarene.

The aldehydes used in this study were prepared from 2-chloro-4-fluorobenzaldehyde *via* simple, but effective, nucleophilic aromatic substitution. Thus, heating aldehyde **6** with an amine in DMF in the presence of K_2CO_3 afforded 4-amino-2-chlorobenzaldehydes in excellent yield, as summarized in Table 1. In general, only secondary amines were effective in this reaction. Primary amines such as benzylamine and *n*-propylamine appeared to give imines in the process, and the latter were unreactive with respect to the desired nucleophilic aromatic substitution.

With the aminobenzaldehydes **7** in hand, we proceeded to examine their ability to participate in our benzothiazine synthesis. Under conditions that were essentially the same as those developed recently, almost all of the aminobenzaldehydes afforded benzothiazines upon reaction with **3** in the presence of a Pd source and RuPhos as the ligand. The results are summarized in Table 2. However, aldehyde **7e**, in which the amino group bore two allyl substituents, did not work well in this reaction. Switching to

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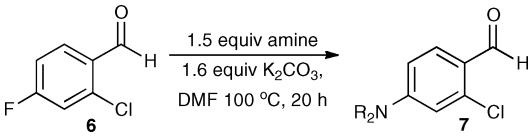
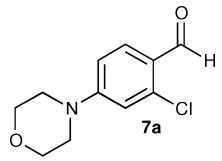
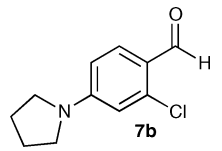
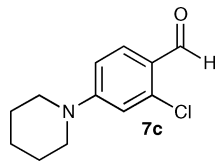
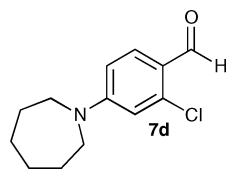
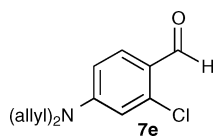
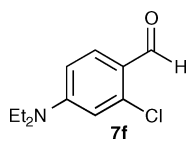
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data for all new compounds. See DOI: 10.1039/c1ob06051a

Table 1 Preparation of aminobenzaldehydes

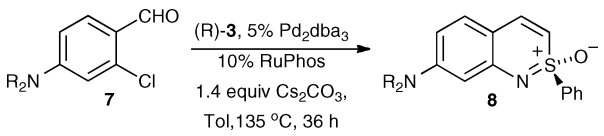


Entry	Amine	Product	Yield (%)
1	morpholine	 **7a**	87
2	pyrrolidine	 **7b**	97
3	piperidine	 **7c**	87
4	azepine	 **7d**	85
5	diallylamine	 **7e**	98
6	diethylamine	 **7f**	94

the bromo analogue of **7e**, namely **9e**, was also not productive. Consumption of the starting material was observed in this case, but none of the desired product was obtained. However, the yield of **8e** could be increased to 83% with **9e** by conducting the reaction employing "old" reaction conditions, using $Pd(OAc)_2$ as the Pd source and racemic BINAP as the ligand. It would appear that this catalyst system is still competent to perform oxidative addition on the carbon–bromine bond of **9e** but is less suited for the formation of a π-allyl intermediate arising from oxidative addition into the carbon–nitrogen bond of the latter. This assumes that the problems with **7e** and **9e** involved deallylation, something that still must be determined.

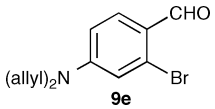
Another route to the target benzothiazines was also considered. We earlier reported the synthesis of **10**,[7] and decided to explore its ability to undergo simple aromatic nucleophilic substitution. Thus, **10** was treated with a variety of amines in the presence of K_2CO_3

Table 2 Synthesis of benzothiazines from aminobenzaldehydes



Entry	Substrate	Product	Yield (%)
1	**7a**	**8a**	98
2[a]	**7b**	**8b**	93
3	**7c**	**8c**	82
4	**7d**	**8d**	62
5[a]	**7e**	**8e**	0[b]
6[a]	**9e**[d]	**8e**	0[b]
7[a,c]	**9e**[d]	**8e**	83
8	**7f**	**8f**	88

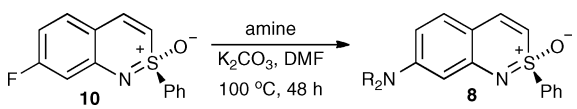
[a] Racemic sulfoximine was used. [b] Complete conversion of the aryl halide was observed, but none of the expected product was obtained. [c] A combination of 5% $Pd(OAc)_2$ and 7.5% BINAP was used as catalyst. [d]



at 100 °C in DMF. The results of this study are shown in Table 3. Overall, the yields for the benozothiazines were good-to-excellent. Diallylamine failed to give rise to **8e** under these conditions for reasons that are not yet clear. In addition, both diphenylamine and dicyclohexylamine were not competent nucleophiles in this process, perhaps due to a steric effect.

With the benzothiazines in hand, we measured both their absorption and emission properties in chloroform. As can be seen from the entries given in Table 4, Stokes shifts were in the 100–130 nm range for the series of compounds **8a–8g**. Such shifts, coupled with the possibility of modification of the benzothiazine framework, suggest that compounds of this class might be manipulated to yield tailored emissions. Toward that end, we deprotonated **8b**[8] at the 3 position and trapped the resulting organolithium with DMF to give aldehyde **11** in 60% unoptimized yield (Scheme 2). Whilst changes in the spectral data for **11** were not dramatic, this modification produced clear bathochromic

Table 3 Nucleophilic aromatic substitution reactions of **10**[a]



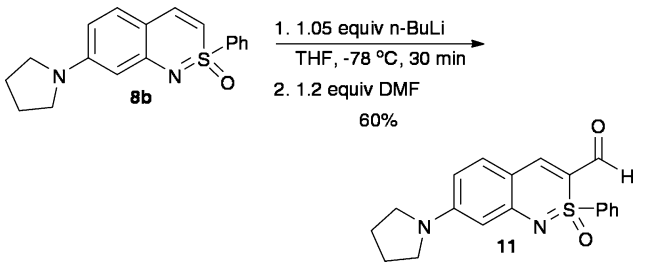
Entry	Amine	Product	Yield (%)
1[b]	morpholine	**8a**	50[c]
2	morpholine	**8a**	98
3	pyrrolidine	**8b**	97
4	piperidine	**8c**	90
5	azepine	**8d**	72
6	diallylamine	**8e**	0
7	diethylamine	**8f**	88
8	benzylamine	**8g**	75
9	diphenylamine	**8h**	0
10	dicyclohexylamine	**8i**	0

[a] Most reactions were performed with enantiomerically pure (*R*)-**10**. [b] The reaction was performed for only 36 h. [c] A 36% yield of **10** was recovered.

Table 4 Absorption and fluorescence data for benzothiazines[a]

Entry	benzothiazine	ε^b	λ_{abs} (nm)	λ_{em} (nm)	Φ_F[c]
1	**8a**	1.82	356	487	0.035
2	**8b**	2.52	370	472	0.069
3	**8c**	2.26	364	480	0.040
4	**8d**	3.20	373	474	0.065
5	**8e**	1.67	364	477	0.058
6	**8f**	2.65	370	474	0.053
7	**8g**	1.54	355	483	0.050
8	**11**	5.67	430	504	0.070

[a] Benzothiazines (10 μM) in chloroform were studied at 25 °C. [b] Molar absorptivity in units of 10^4 M^{-1} cm^{-1}. [c] Fluorescence quantum yields (±6–8%).



Scheme 2 Modification of benzothiazine **8b**.

shifts, accompanied by a marked reduction in the Stokes shift to 74 nm (Table 4, entry 8). It is thus quite conceivable that a combination of reasoned analysis and empirical observation will allow us to build a library of fluorophores from this benzothiazine scaffold that could prove useful for various applications.

To further illustrate the fluorescence features of these compounds, we show images of the benzothiazines under ambient and long-wavelength UV (365 nm) lighting (Fig. 4). As would be expected from the values in Table 4, benzothiazines **8a–g** fluoresce blue, while **11** emits blueish-green light. As intimated previously,

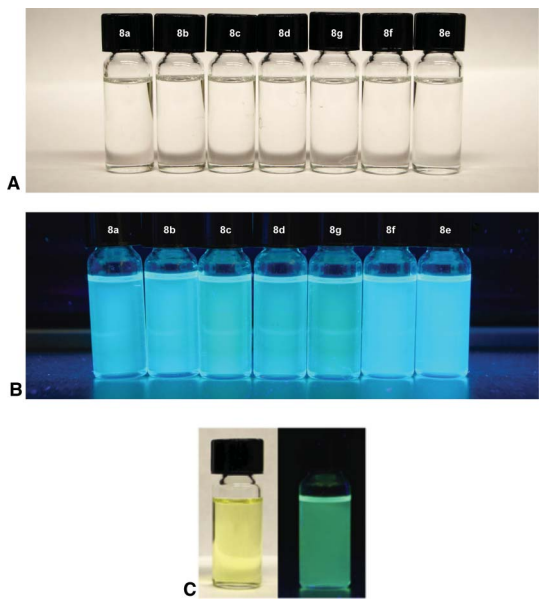


Fig. 4 10 μM $CHCl_3$ solutions of **8a–8g** in normal light (A) and under UV lamp excitation (B). Images of **11** (10 μM in $CHCl_3$) under these respective conditions (C).

proper manipulation of the chromophore in benzothiazines of this class should produce interesting and useful fluorophores.

To provide more quantitative information about the photoluminescence efficiencies of benzothiazines **8a–8g** and **11**, fluorescence quantum yields (Φ_F) were determined for the fluorophores dissolved in chloroform under ambient conditions using quinine sulfate in 0.1 M H_2SO_4 as the fluorescence quantum yield standard (Φ_F = 0.577;[9] see Supporting Information (SI) for details†). The obtained Φ_F values for **8a–8g** and **11** are presented in Table 4.

Benzothiazines **8a–8g** and **11** show fair-to-good fluorescence efficiency as evident by these values. In fact, the mean value of Φ_F is 0.053 for **8a–8g** compared to 0.070 for **11**, illustrating that the aldehyde moiety does appear to enhance the fluorescence efficiency to any extent. Most noteworthy, the aldehyde functionality of **11** significantly red shifts both absorbance and fluorescence emission bands as shown in Fig. 5. This we attribute to the extended conjugation which simply results in a narrowing of the energy gap between the ground and excited states. In a practical sense, the excitation profile for **11** is moved away from the UV to become well matched to inexpensive visible light sources, particularly light-emitting diodes (LEDs), a boon for future applications in sensing and imaging.[10]

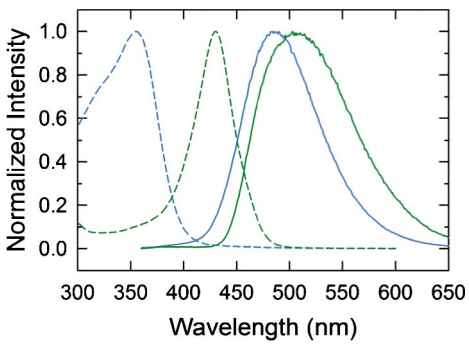


Fig. 5 Normalized UV-vis absorbance (dashed lines) and fluorescence emission spectra of **8a** (blue curves) and **11** (green curves) in chloroform. Photoluminescence spectra were acquired for excitation at 350 nm.

In a preliminary exploration of the solvatochromic behavior of these benzothiazines using a Lippert–Mataga treatment, which determines general solvent effects (*i.e.*, static dielectric constant, ε, and refractive index, n) on the Stokes shift (refer to SI†), we found a noteworthy and unanticipated lack of correlation between Stokes shifts for the representative benzothiazine **8a** and the orientational polarizability of the solubilizing milieu. This strongly hints at the notable absence of solvent effect on the photophysical properties of our benzothiazines. The fluorescence emission maxima of **8a** were found to marginally red shifted; however, in hexane (493 nm), a nonpolar solvent, as compared to methanol (480 nm), a polar-protic solvent or acetonitrile (485 nm), a polar-aprotic solvent. This may suggest an uncommon (but small) decrease in the dipole moment of the fluorophore in the excited-state as compared to that in the ground state. In a larger sense, these results hint at an intriguing role for the $–S^+–O^-$ moiety in controlling the fluorescence characteristics of the benzothiazines.

In summary, we have synthesized 7-amino-2,1-benzothiazines using two different approaches and demonstrated that these compounds exhibit fluorescent properties in combination with large Stokes shifts. We further modified one of the benzothiazines

via metalation chemistry, showing strongly red shifted spectral features as a result. Further studies expanding the palette of benzothiazine-based fluorophores and their application are in progress and will be reported in due course.

This work was supported by the National Science Foundation to whom we are grateful. We thank Professor Timothy E. Glass and his coworkers Mr. Zhang Shaohui and Mr. Kenneth Hetti for assistance with obtaining fluorescence data.

Notes and references

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