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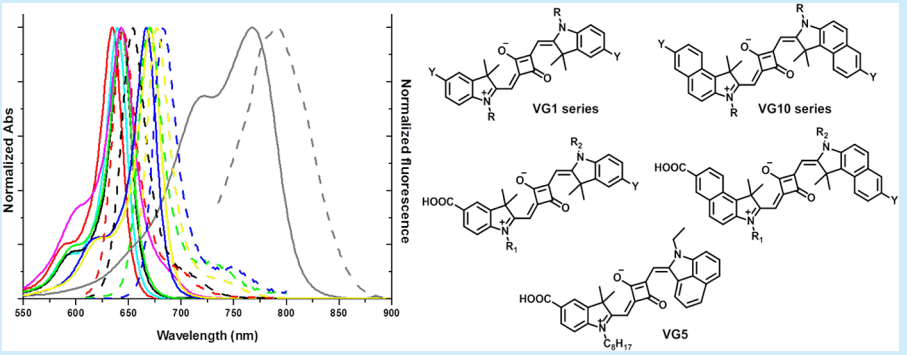
Microwave-Assisted Synthesis of Near-Infrared Fluorescent Indole-Based Squaraines

Nadia Barbero,[†] Claudio Magistris,[†] Jinhyung Park,[†,§] Davide Saccone,[†] Pierluigi Quagliotto,[†] Roberto Buscaino,[†] Claudio Medana,[‡] Claudia Barolo,*[,†] and Guido Viscardi[†]

[†]Department of Chemistry and NIS Interdepartmental Centre and [‡]Dipartimento di Biotecnologie Molecolari e Scienze per la Salute, University of Torino, Via Giuria 7, I-10125 Torino, Italy

Supporting Information



ABSTRACT: A microwave-assisted method for the preparation of a wide color range of 2,3,3-trimethylindolenine-based squaraines and their intermediates is described. This practical approach allows the rapid preparation of both symmetrical and nonsymmetrical squaraine dyes, reducing reaction time from days to minutes with more than 2-fold improvement in product yields when compared to conventional methods.

Since the first reports on the use of microwave (MW) heating to accelerate organic chemical transformations by the groups of Gedye[1] and Giguere and Majetich[2] in 1986, microwave-assisted organic synthesis (MAOS) has proven to be a powerful technique for promoting a variety of chemical reactions.[3] Microwave heating has been shown to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions compared to conventional heating methods.[4]

Squaraines are polymethine dyes obtained as dicondensation products between electron-rich substrates and squaric acid possessing sharp and intense absorption mainly localized in the red-NIR region associated with a strong fluorescence. These peculiar properties, along with wide molecular structure diversity, promoted their use as molecular components of a great number of technological applications.[5,6]

Conventional synthetic methods for the preparation of symmetrical squaraine dyes are based on the condensation between activated arenes, π-excessive heterocycles, or suitable anhydrobases and squaric acid.[7] The commonly accepted reaction mechanism involves the condensation of the first electron-rich derivative with squaric acid leading to the formation of a semisquaraine intermediate. Condensation with a second equivalent of the electron-rich molecule affords the final compound. It should be noted that the reaction of the semisquaraine with the second equivalent of electron-rich counterpart is not completely regioselective and a certain amount of the 1,2-condensation product can be formed.[8] The synthesis of unsymmetrical squaraine dyes is a little more challenging and requires the isolation of the semisquaraine intermediate and its condensation with a different activated molecule in a subsequent step, typically affording mixtures of the desired compound along with unreacted hemisquaraine and undesired symmetrical analogues. To avoid time-consuming purifications, we recently proposed crystallization methods for the purification of symmetrical squaraines which does not apply to unsymmetrical structures, where the presence of side products is too large.[9]

To date, no reactions dealing with MW synthesis of squaraines are reported in the literature even if MW was already used for the synthesis[10] and functionalization[11] of related cyanine dyes and their intermediates.[12] However, there is still a great demand for the development of a facile synthetic method for the preparation of squaraine dyes above all for their increasing use in solar cell devices[13] and PDT applications.[14]

Herein, we report a common synthetic pathway for the preparation of a wide color range of symmetrical and unsymmetrical 2,3,3-trimethylindolenine-based squaraine dyes (see Figure 1 and Figure S1; details of the substituents are

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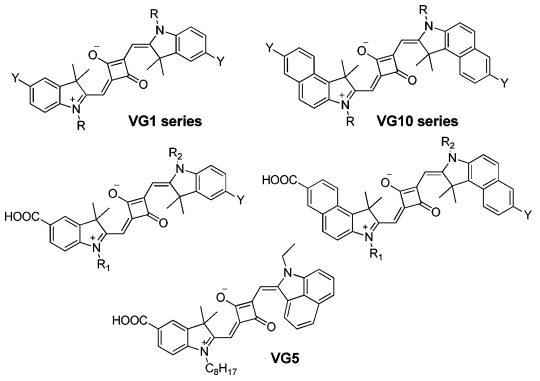


Figure 1. General structures of synthesized compounds.

reported in the Supporting Information and specified in the following tables), using MW methodologies, which offers a practical approach to the rapid preparation of a variety of squaraines. Reaction time under MW was reduced from days to minutes, with more than 2-fold improvement in product yields when compared to conventional methods. Crystallization methods were developed on the crude symmetrical and unsymmetrical products, while some unsymmetrical dyes were isolated with good purity only after column chromatography (for a detailed account, see the Supporting Information).

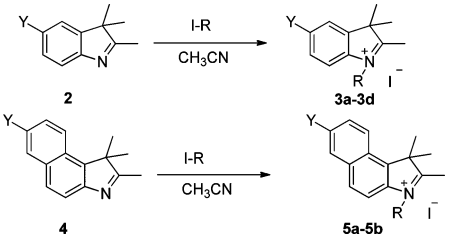
2,3,3-Trimethylindolenine and 5-carboxy-2,3,3-trimethyl-3*H*-indolenine are commercially available. For the other derivatives, we exploited the Fischer indole synthesis that, for 5-bromo derivatives (see Scheme S1), was carried out using microwaves instead of conventional heating procedures.[15]

The general synthetic procedure for symmetrical and unsymmetrical squaraines starts with the quaternization of the indolenine ring. Thanks to the nitrogen quaternization, an increase of the acidity of the methyl group will occur enabling the bridge formation.[16] Its conjugated base attacks the carbonyl of the squaric acid or the diethyl squarate. The reaction has traditionally been carried out with an excess of alkylating agent with and without solvent over several hours or days.[17]

With the purpose of investigating the reaction under microwave conditions, we first performed a screening analysis using Design of Experiment (DoE) on the reaction of 5-carboxy-2,3,3-trimethylindolenine with 1-iodooctane. The influence of temperature, time, and ratio between indolenine and solvent was investigated on the yield of the reaction, keeping the indolenine/iodooctane ratio constant (see Table S1). Heating at 155 °C for 25 min gave 62% yield as best result. Starting from these results, a more detailed D-Optimal Design[18] was set up for the reaction with 1-iododecane, introducing the ratio between indolenine and iodide as a further parameter. The results were processed statistically, in order to delete factors whose influence was unimportant (as time proved to be). The obtained model (see Figure S2) suggests optimized conditions (solvent/reagent ratio of 5, 155 °C, 40 min and large excess of iodide) that were checked experimentally, obtaining an average yield (65%) even larger than the software prediction. The optimized conditions were then applied to the other quaternization reactions using the same approach to the different iodides (see Table 1).

Compared to the classical method of synthesis, microwave-assisted quaternization afforded the target products in comparable or higher yields, dramatically shortening reaction times.[10,21] For example, in the synthesis of **3a**, reaction times decreased from 24 h (entry 1)[17d] to 9 min (entry 4). In the

Table 1. General Quaternization Synthesis of Indolenines and Benzoindolenines (for the Complete Entry List, See Table S2)



entry (compd)	Y	R	M[a]	time (min)	yield (%)
1 (**3a**)	H	C_2H_5	A	1440	59[17d]
4 (**3a**)	H	C_2H_5	B	9	91
5 (**3b**)	COOH	C_2H_5	A	1440	79[19]
7 (**3b**)	COOH	C_2H_5	B	20	94
9 (**3c**)	COOH	C_4H_9	B	20	86
10 (**3d**)	COOH	C_8H_{17}	A	660	75[17f]
11 (**3d**)	COOH	C_8H_{17}	B	25	66
24 (**5a**)	COOH	C_2H_5	B	40	77[20]
26 (**5b**)	COOH	C_8H_{17}	B	40	51[20]

[a]M: method A, Dean–Stark apparatus; B, MW heating.

synthesis of **3b**, the yield increased from 79[19] to 94%, while reaction times decreased from 24 h to 20 min. The presence of an electron-withdrawing group on the heterocycle generally results in a decrease of yields.[17b,22,23] This general trend is also evident with microwave heating. Moreover, while anhydrous conditions seem to be important in the conventional synthesis, they were uninfluential when the reaction was performed with microwaves, thus simplifying reaction conditions. The elongation on the halide chain, useful for broadening the range of structures in order to extend their potential applications, also results in longer reaction times and a decrease of yields;[19] however, again, in the quaternization with octyl iodide (**3d**) with MW, reaction times shorten from 72 h[19] to 25 min. With other indolenines, the reaction similarly profited from MW conditions. For example, the synthesis of **5a** afforded the product in 77% yield, while in the classical way the reaction simply does not proceed. This method works well with a wide variety of alkylating agents, also in the presence of sensitive functional groups like carboxyl, hydroxyl, and hexyl.

Symmetrical squaraine dyes are usually obtained by classical heating over several hours (18 h[24]) by reacting squaric acid with a 2-fold excess of the heterocyclic quaternary ammonium salts in polar solvents such as acetic acid or high boiling point alcohols such as butanol, often in a mixture with aromatic hydrocarbons such as toluene or benzene in order to azeotropically remove the water formed in the condensation reaction (Dean–Stark apparatus).[16] In the case of MW heating, squaric acid with a 2-fold excess of the quaternized indolenine and benzoindolenine is overheated, in a closed vessel, in a 1-butanol/toluene mixture (1:1, v/v), drastically reducing reaction time and increasing yields (Table 2).[20,21] By choosing the right amount of solvent to be used, we were able to obtain the direct crystallization of the desired squaraine dye in the reaction vessel during the cooling time. This crystallized product shows a high purity (see Figure S3), avoiding the need for expensive and time-consuming column chromatography purification.

This simple and general method works well for differently functionalized (benzo)indolenines and opens up the way to further modification in order to tune molecular properties as

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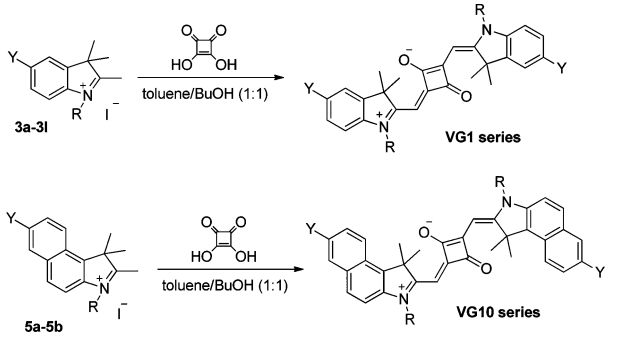
Table 2. General Synthesis of Symmetrical Squaraines (VG1 and VG10 Series)[a]

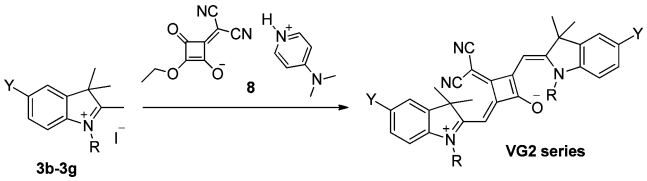


entry (compd)	R	Y	M[b]	time (min)	yield (%)
1 (**SQ-NH**)	H	H	A[c]	120	77[24]
2 (**SQ-NH**)	H	H	B	20	61[25]
3 (**Br-NH**)	H	Br	B	30	66
4 (**R1**)	C_2H_5	H	A	480	45[26]
5 (**R1**)	C_2H_5	H	B	15	48
6 (**VG1-C2**)	C_2H_5	COOH	A	1080	58[19]
7 (**VG1-C2**)	C_2H_5	COOH	B	20	99
8 (**Br-C2**)	C_2H_5	Br	B	30	82
9 (**Br-C4**)	C_4H_9	Br	A		
10 (**Br-C4**)	C_4H_9	Br	B	30	69
11 (**VG1-C8**)	C_8H_{17}	COOH	A	900	69[9]
12 (**VG1-C8**)	C_8H_{17}	COOH	A	1080	46[19]
13 (**VG1-C8**)	C_8H_{17}	COOH	B	25	73
14 (**VG1-C10**)	$C_{10}H_{21}$	COOH	A	360	54[5]
15 (**VG1-C10**)	$C_{10}H_{21}$	COOH	B	20	63
16 (**VG1-C12**)	$C_{12}H_{25}$	COOH	A	1080	55[19]
17 (**VG1-C12**)	$C_{12}H_{25}$	COOH	B	15	28
18 (**Br-C12**)	$C_{12}H_{25}$	Br	B	30	72
19 (**VG1-H6**)	C_6H_9	COOH	B	20	68
20 (**VG10-C2**)	C_2H_5	COOH	A	960	32[20]
21 (**VG10-C2**)	C_2H_5	COOH	B	40	90
22 (**VG10-C8**)	C_8H_{17}	COOH	A	960	35[20]
23 (**VG10-C8**)	C_8H_{17}	COOH	B	40	63

[a]Indolenine/squaric acid (1:1), toluene/butanol (1:1). [b]M: method A, Dean–Stark apparatus, 120 °C; method B, MW, 160 °C. [c]A: under acid catalysis.

desired.[27] In fact, this procedure can be successfully applied for the synthesis of core-substituted squaraines[28] (Table 3).

Table 3. General Synthesis of Symmetrical Squaraines with Core Functionalization



entry (compd)	R	Y	M[a]	time (min)	yield (%)
1 (**VG2-C4**)	C_4H_9	COOH	A	780	15[29]
2 (**VG2-C4**)	C_4H_9	COOH	B	30	20
3 (**VG2-Br**)	C_2H_5	Br	A	300	51[30]
4 (**VG2-Br**)	C_2H_5	Br	B	30	31

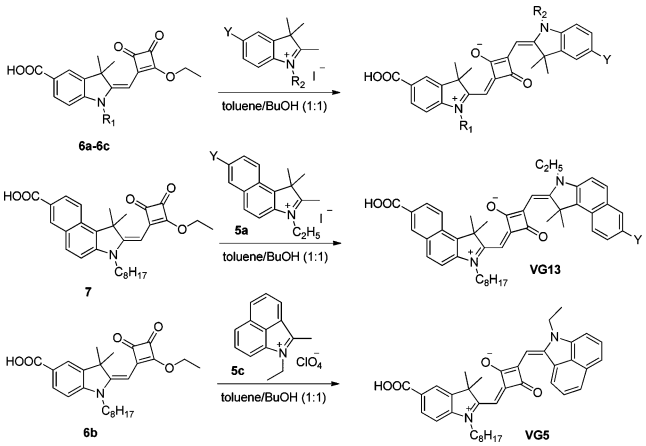
[a]M: method A, Dean–Stark apparatus; B, MW heating.

If the synthesis of symmetrical squaraines is quite easy even with conventional heating, the preparation of unsymmetrical structures required a multiple step procedure. In fact, it requires the isolation of the hemisquaraine intermediate, and its condensation with a second activated molecule in a subsequent step. Hemisquaraines are usually prepared directly in two-step protocols based on squaric acid derivatives (esters or squarylium chlorides). The hydrolysis of the resulting hemichloride or hemisquarate affords the hemisquaraine.[16]

We also tried to perform the synthesis through MW heating, in a sealed tube, of a series of differently quaternarized hemisquarates starting from diethylsquarate in ethanol and triethylamine as catalyst obtaining several kinds of hemisquarates in good yield (see Table S3).

We noticed that working at 90 °C or higher, the short-chain hemisquarate (**6a**) was not detected because we directly obtained the corresponding symmetrical squaraine (**VG1-C2**). This interesting observation inspired us to directly perform the subsequent condensation reaction on the hemisquarate, in order to obtain unsymmetrical squaraine dyes skipping the hydrolysis step (Table 4).

Table 4. General Synthesis of Unsymmetrical Squaraines



entry (compd)	R_1	R_2	Y	M[a]	time (min)	yield (%)
1 (**SQ01**)	C_8H_{17}	C_2H_5	H	A	1080	81[17f]
2 (**SQ01**)	C_8H_{17}	C_2H_5	H	B	25	69
3 (**VG1-C2-H6**)	C_2H_5	C_6H_9	COOH	A		
4 (**VG1-C2-H6**)	C_2H_5	C_6H_9	COOH	B	25	36
5 (**VG1-C8-H6**)	C_8H_{17}	C_6H_9	COOH	B	25	61
6 (**VG1-C10-H6**)	$C_{10}H_{21}$	C_6H_9	COOH	A		
7 (**VG1-C10-H6**)	$C_{10}H_{21}$	C_6H_9	COOH	B	35	52
8 (**VG13**)			H	B	35	53[20]
9 (**VG5**)				A	180	10[31]
10 (**VG5**)				B	60	15

[a]M: method A, Dean–Stark apparatus; method B, MW heating.

As an example, we synthesized **SQ01** with a slightly modified procedure from what has been reported in the literature.[9,17f] If we compare the two procedures, the one reported in literature needs a further step which consists of hydrolysis of the hemisquarate in hemisquaraine to be reactive with the quaternized salt. By using MW heating, this step can be skipped to obtain the unsymmetrical squaraine dye directly from the hemisquarate (see Scheme S2).

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In conclusion, we have developed a practical MW-assisted method for the rapid and efficient synthesis of both symmetrical and unsymmetrical differently substituted squaraines in high yield and purity. The ease of preparation and the possibility of providing a good amount of pure dyes in a short time could lead to the achievement of a large variety of novel structures that can be easily tested in technological applications such as PDT and DSC, where large amounts of these dyes are required.

■ ASSOCIATED CONTENT

Supporting Information

General procedures, experimental details, ^{1}H, ^{13}C spectra, and DoE specifications. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01453.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: claudia.barolo@unito.it.

Present Address

[§]CEA Grenoble, INAC, UMR 5819 SPrAM (CEA/CNRS/UJFGrenoble 1), Grenoble, France.

Notes

The authors declare no competing financial interest.

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