

# Synthesis of Squaraine Dyes

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Squaraine dye is a popular class of contrast near-infrared (NIR) dyes. Squaraine dyes have shown the ability to be modified with various heterocycles. The indole moiety is the most notable heterocycle incorporated in squaraine dyes.

Keywords: squaraine dye ; synthesis ; optical properties ; near-infrared region ; indole ; quinoline

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## 1. Introduction

Small molecular organic dyes are a research hotspot. There have been various classes of dyes reported over the years. Squaraine dyes are one of the popular classes of near-infrared dyes that have been described. The unique characteristic that differentiates them from other dyes is the central linking unit; this unit is known as a squaraine, where the name for these dyes is obtained. The core unit is composed of an unsaturated, four-membered ring <sup>[1][2][3]</sup>. This unique linking core unit provides the properties associated with squaraine dyes. Some of their other characteristics are sharp absorption bands, a high molar extinction coefficient, and photoconductivity abilities <sup>[4][5][6]</sup>.

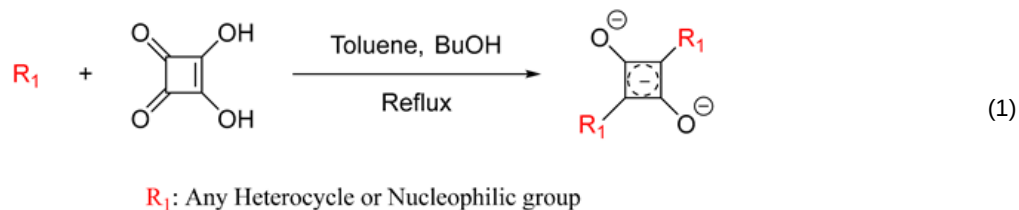
The squaraine core is composed of a four-membered ring that is electron-deficient when incorporated into the dye <sup>[7]</sup>. The electrons in the squaraine core are delocalized, allowing them to encompass the whole conjugated system. This squaraine core is capped with donor units, forming a donor-acceptor-donor system, allowing the dye to be stabilized by a  $\pi$ -conjugated system <sup>[1][7]</sup>. The squaraine core scaffold is zwitterionic and has multiple resonances, due to the delocalized electrons <sup>[8][9][10]</sup>. The zwitterionic nature is an essential part of the dye, as it facilitates electron movement through the scaffold <sup>[2][3]</sup>. The targeting specificity of the squaraine dyes can be improved through conjugation by synthesizing them with various possible functional groups. The overall optical characteristics of the compound may be affected by the addition of heterocycles and functional groups. Regardless of the varying functional groups and heterocycles, squaraine dyes benefit from excellent chemical and photophysical properties <sup>[2][3]</sup>.

The use of near-infrared squaraine dyes aims to achieve absorbance and fluorescence in the near-infrared region (NIR), and this region ranges from 650 to 1700 nm <sup>[11][12]</sup>. This region is optimal for biomedical <sup>[11][12]</sup> and solar energy applications <sup>[13]</sup>. In terms of biomedical applications, the region enables a higher signal-to-noise ratio for bioimaging. This is due to the limited autofluorescence of biological molecules, resulting in reduced light scattering in this region <sup>[14]</sup>. Red shifting into the NIR range allows greater penetration of light into tissues, allowing for better spatial visualization <sup>[14][15]</sup>. Solar radiation is composed of about 50% near-infrared light <sup>[16]</sup>. To create an efficient solar cell, the light-absorbing materials need to absorb light in this region <sup>[17]</sup>. In addition, the lower-energy photons of NIR result in a higher short-circuit current density <sup>[18]</sup>.

In recent years, the indole heterocycle has been a popular donor unit for squaraine dyes. There have been numerous applications in various fields reported for this class <sup>[4][19][20][21]</sup>. In comparison, when looking at other heterocycles, such as quinoline- and perimidine-based squaraine dyes, there are only a few scattered reported dyes and associated applications. This is the case even though they have exciting and notable optical properties that differ from indole-based squaraine dyes.

## 2. Synthesis

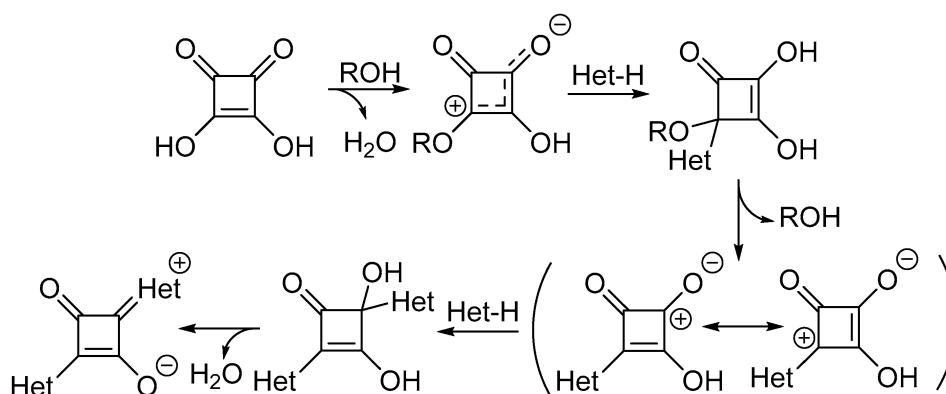
There are two different classes of squaraine dyes: symmetrical and unsymmetrical. The symmetrical squaraine dyes contain identical donor units on each side, while the unsymmetrical, as the name suggests, contain two different donor groups. Typically, the donor units are bound to the first and third positions of the squaraine unit, due to their desirable, red-shifted optical properties compared to the 1,2 regioisomer <sup>[22]</sup>. For symmetrical squaraine dyes, the synthesis involves the condensation reaction in a single-pot reaction mixture <sup>[23]</sup>, as utilized in Equation (1).



Equation (1): general synthesis of symmetrical squaraine dyes.

Symmetrical squaraine dyes use a standard synthetical process regardless of the heterocycle. The first accepted synthesis of squaraine dyes was reported by Treibs and Jacob in 1965 [24]. The synthesis utilized acetic anhydride as the solvent to form the dye, which is traditionally used for cyanine synthesis. In 1966, a new solvent system was introduced that used the azeotropic principle to produce the squaraine dye; the updated solvent system used an n-butanol–benzene mixture [23]. However, due to the carcinogenic properties of benzene, toluene was utilized instead for the synthesis [25]. This solvent system can azeotropically remove water residue from the reaction and allow a high-temperature system for the condensation reaction. The use of butanol and toluene or benzene (2:1 to 1:1) is the common solvent system for squaraine dye synthesis. In addition, bases such as TEA or quinolone can be incorporated to facilitate the reaction. Most synthetic yields for symmetrical squaraine dyes hover around 60% [26].

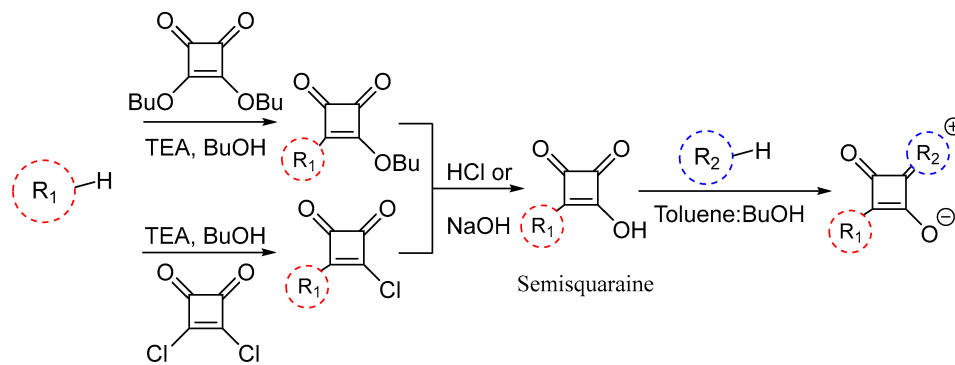
Symmetrical squaraine dyes are synthesized with the activation of squaric acid by the butanol or another alkyl alcohol group. This activates the central moiety for the nucleophilic attack by the electron-rich donor unit. This forms the semisquaraine intermediate, which is short-lived, as another nucleophilic attack from the other donor unit follows it [27]. This results in the formation of the dye and the release of water as a byproduct (**Scheme 1**) [27].



**Scheme 1.** Proposed mechanism for synthesis of squaraine dyes [27].

The first unsymmetrical squaraine dye was reported in 1968 by Treibs and Jacob, only a couple years after their initial reporting of symmetrical squaraine dye [28]. The synthesis of unsymmetrical squaraine dyes utilizes a different process than its symmetrical counterpart, but mechanistically, they are comparable. The synthesis for unsymmetrical squaraine dye is a multistep process that complicates the synthesis process [29]. For the synthesis, a modified squaric acid is utilized to reduce the reactivity and slow the reaction down. This allows the formation of the semisquaraine product in a higher yield. If the unmodified squaric acid is used, the semisquaraine would be produced in lower yields of the squaraine dye. Modifying the squaric acid includes capping the hydroxyl group with a short alkyl chain or replacing with hydroxyl group with halogens, usually chlorine [30].

The basic synthesis of unsymmetrical squaraine dye entails the formation of the semisquaraine followed by the condensation of the second donor unit with the semisquaraine to form the unsymmetrical squaraine dye (**Scheme 2**). However, before the second condensation occurs, the modified squaric acid needs to contain the hydroxyl group, allowing the semisquaraine to become more reactive for the condensation reaction. This process can be carried out using acid or base hydrolysis [30][31]. The overall yield depends on the donor units. The yield usually ranges from 49% to 20%, but it could be even lower [30]. The lower yields are due to the multiple purification processes needed at each step before proceeding to the next.



**Scheme 2.** General synthesis of unsymmetrical squaraine dyes.

Squaraine dyes can have modified squaraine cores incorporated within them. Squaric acid can be modified with different groups such as methoxy, amines, dicyanomethylene, and others [32]. Additions of alkoxy or amino groups can be achieved after the dye has been synthesized [33]. This will result in the formation of the semisquaraine, which can be reacted with the other heterocycle [33].

In addition to forming the dyes using the traditional reaction method, the Dean–Stark apparatus, an alternative method of microwave irradiation, has been used to synthesize the dye. As is known, microwave heating significantly reduces the total reaction time [34]. Barbero et al. reported this to be true for synthesizing symmetrical and unsymmetrical squaraine dyes. In addition, the yield of symmetrical squaraine dyes is higher when the microwave method is used, and similar results are seen for unsymmetrical dyes [26]. The reaction time for unsymmetrical dyes drastically changes, due to acid or base hydrolysis not being needed for the reaction, as shown in **Table 1**. As seen in **Table 1**, there is a significant reduction in reaction time for all the dyes, with timing saving of over 300% on the lower end.

**Table 1.** Comparison of the reaction time and yield between traditional method and microwave method. The reaction time accounts for the complete synthesis of symmetrical dyes, whereas the reaction time for unsymmetrical dye is from the semisquaraine group containing ethyl ether (-OEt) [28].

	R <sub>1</sub>	Y <sub>1</sub>	R <sub>2</sub>	Y <sub>2</sub>	Trad. Rt (min)	MW Rt (min)	Trad. Yield (%)	MW Yield (%)
Sym.	-C <sub>8</sub> H <sub>17</sub>	-COOH	-C <sub>8</sub> H <sub>17</sub>	-COOH	1080	25	46	73
	-C <sub>10</sub> H <sub>21</sub>	-COOH	-C <sub>10</sub> H <sub>21</sub>	-COOH	360	20	54	63
	-C <sub>2</sub> H <sub>5</sub>	-Br	-C <sub>2</sub> H <sub>5</sub>	-Br	1440 [35]	30	84 [35]	82
	-C <sub>2</sub> H <sub>5</sub>	-COOH	-C <sub>2</sub> H <sub>5</sub>	-COOH	1080	20	58	99
Unsym.	-C <sub>8</sub> H <sub>17</sub>	-COOH	-C <sub>2</sub> H <sub>5</sub>	Benzo-[c,d]indole	180	60	10	15

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