Communication

Facile Synthesis of Pyrrolyl-Containing Semisquaraines in Water as Precursors for Non-Symmetric Squaraines

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Abstract: One-step reactions between squaric acid and pyrroles, such as 3-ethyl-2,4-dimethyl-pyrrole and 1,2,5-trimethylpyrrole, in water provide the corresponding pyrrol-2-yl- and pyrrol-3-yl-containing semisquaraines in high yields. These semisquaraines serve as useful precursors for the synthesis of various non-symmetric pyrrole-containing squaraine dyes.

1. Introduction

Squaraine dyes (Figure 1) could be considered privileged types of chromophores and fluorophores due to their tunable photophysical properties and diverse range of applications, which span over various areas of chemistry, biology, materials, and engineering [1–4]. Notably, non-symmetric squaraines (dyes with distinct moieties attached to the squaric acid scaffold; Figure 1) possess several advantages over symmetric squaraine dyes, including better solubility in organic solvents, as well as superior adaptability for introducing structural and functional diversity onto fluorogenic scaffolds [5]. These features and properties of non-symmetric squaraine dyes could ultimately be translated to a broader, potentially more useful, range of applications [5].
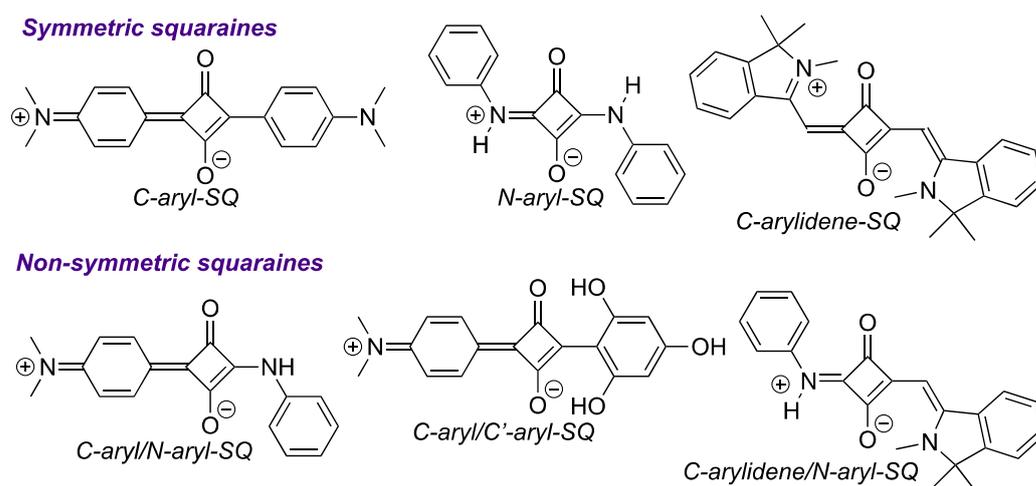

Figure 1. General examples of symmetric and non-symmetric squaraine dyes.

Importantly, from a synthetic point of view, the accessibility of non-symmetric squaraines is typically more elaborate and problematic than for symmetric squaraines. The simultaneous condensation of two different nucleophiles with squaric acid leads to mixtures of products, which are difficult to separate. Hence, most practical routes to non-symmetric squaraine dyes rely on the use of semisquaric acids (semisquaraines) as intermediate synthons. In general, the synthesis of semisquaraines can be accomplished via two-step

procedures, either starting with dialkyl-squarate or squaryl dichloride (which, in turn, are synthesized by reacting squaric acid with either an alcohol or thionyl chloride or other chlorinating agent), followed by hydrolysis (Scheme 1) [5,6]. Subsequent reaction with nucleophiles at elevated temperatures in either alcohol/toluene or iso-propanol/alkyl formate mixtures leads to non-symmetric squaraines (Scheme 1). However, general, modular, and facile approaches which could enable the synthesis of structurally and functionally diverse non-symmetric squaraines are not available. Thus, the development of facile synthetic routes to various semisquaraine scaffolds is warranted.
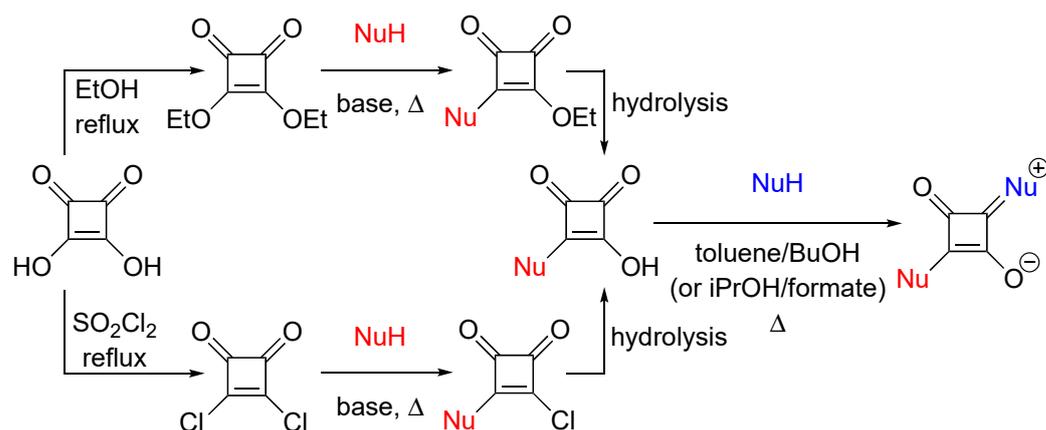
Scheme 1. Preparations of non-symmetric squaraines, via diethylsquarate (**top**) or squaryl dichloride (**bottom**), using squaric acid and various nucleophiles (NuH) as the starting materials for each step.

Furthermore, from the sustainability and green chemistry perspectives, it would be advantageous to reduce the number of synthetic steps that are required to synthesize the semisquaraine synthons as well as to eliminate or reduce the use of hazardous chemicals and solvents. This would be especially crucial because squaraine dyes are becoming integral parts in various devices and processes; thus, the possibility of conducting larger-scale syntheses of these dyes should be taken into consideration. It should also be pointed out that only a handful of studies have addressed the synthesis of symmetric squaraines from the green and sustainable chemistry perspectives [7–9]. However, to the best of our knowledge, there have been no reports on green, sustainable approaches towards non-symmetric squaraines. Here, we provide a facile, efficient, and sustainable approach to some pyrrole-containing semisquaraines, which could be used as viable synthons for the synthesis of non-symmetric squaraine dyes.

2. Materials and Methods

2.1. General Information

All reagents and solvents were purchased from the commercial sources and were used as received. NMR spectra were acquired on a Bruker Ascend 400 (400 MHz) spectrophotometer using DMSO-d6 as the solvent, and the chemical shifts are reported in ppm (δ) from the residual DMSO peak (2.51 ppm) or TMS (0.00 ppm). High-resolution mass spectra (HRMS-ESI) were acquired on an Agilent 6230 instrument at the Mass Spectrometry Facility, Louisiana State University. Microwave-facilitated reactions were conducted in CEM Discover or Discover-SP microwave synthesizers using 10 mL vials. The UV–Vis absorption spectra were measured with a Cary 60 UV–Vis spectrophotometer (Agilent Technologies). The fluorescence spectra were measured with a Cary Eclipse fluorescence spectrometer (Varian Inc., Palo Alto, CA, USA).

2.2. Synthesis of Compound **1a**

A round-bottomed flask was charged with a stirring bar, water (100 mL), and squaric acid (21.16 g, 185.5 mmol). Once the solution was brought to reflux, 2,4-dimethyl-3-ethyl-pyrrole (5.00 mL, 37.1 mmol) was added in one portion, and the reaction mixture was refluxed for 15 min. The reaction mixture was removed from heat, water (150 mL) was added, and the mixture brought to reflux. Next, while hot, the supernatant was decanted, and water (250 mL) was added to the residue, and the mixture was brought to reflux, followed by decantation. This sequence was repeated two more times (total volume of water used was 1000 mL for reaction and washings). After the final wash, the solid was filtered, then dried under vacuum to give **1a** as a green solid (7.90 g, 97%). The water washes were combined, and charcoal (10.0 g) was added. The mixture was brought to reflux, filtered while hot, and water was removed in vacuo, to give white squaric acid (16.07 g, 95% recovery).

2.3. Synthesis of Compound **4a**

A round-bottomed flask was charged with a stirring bar, water (20 mL), and squaric acid (846.5 mg, 7.42 mmol). Once the solution was brought to 80 °C, 1,2,5-trimethylpyrrole (1.00 mL, 7.39 mmol) was added in one portion, and the reaction mixture was stirred at 80 °C for 60 min. The reaction mixture was removed from heat, cooled to room temperature, and filtered. Next, the precipitate was washed with water (3 × 10 mL). Then, the precipitate was washed with diethyl ether (2 × 5 mL) and dried under vacuum to give **4a** as a maroon solid (1.27 g, 84%).

2.4. General Synthetic Procedure for Synthesis of Compounds **6**–**18**

A microwave vial was charged with a stirring bar, semisquaraine (50.0 mg, **1a** or **4a**), 1-BuOH (0.6 mL), and nucleophile (1.5 eq.), sealed, and subjected to MW irradiation at 90 °C for 30 min or 90 min. After the reaction was cooled to room temperature, the reaction mixture was filtered, washed with appropriate solvent, and the resulting solid was dried under vacuum, recrystallized, or subjected to column chromatography to give respective squaraine dyes as colored solids in 25–90% yield.

The Supplementary Materials contains detailed information on the synthesis, characterization, and spectral data of the reported compounds.

3. Results and Discussion

In an effort to develop modular syntheses of non-symmetric squaraines, we envisioned using squaric acid monoamines (i.e., N-alkyl/aryl-containing semisquaraines) as synthons for preparation of non-symmetric squaraines, because these semisquaraines could be prepared by simply reacting squaric acid with the amines either under thermal or microwave irradiation heating [10,11]. Regretfully, we found that the amine-containing semisquaraines were unreactive towards a number of amines (Scheme S1). However, when the amine-containing semisquaraines were reacted with kryptopyrrole (2,4-dimethyl-3-ethyl-pyrrole), either no reaction or the formation of symmetric kryptopyrrolyl-containing squaraine was noted (Scheme S1).

In view of the aforementioned results, we hypothesized that pyrrolyl-containing semisquaraines might be viable synthons for the synthesis of non-symmetric squaraines. In addition, pyrrole-containing squaraine dyes possess a variety of useful properties and have a wide range of applications [12–16]. Therefore, we decided to investigate the synthesis of a common pyrrole-containing synthon that would be suitable for the modular, efficient, facile, and divergent synthesis of non-symmetric squaraines. Accounts in the literature utilize a multistep procedure for obtaining pyrrole-containing semisquaraines (Scheme 2, top) [17–21]. In an effort to develop a more facile approach, we decided to explore the synthesis of **1a** directly using squaric acid and kryptopyrrole (Scheme 2, bottom). We hypothesized that due to the poor solubility of squaric acid and good miscibility of kryptopyrrole with organic solvents, a higher local concentration of kryptopyrrole (as well

as high nucleophilicity of this pyrrole) around squaric acid might favor the formation of symmetric 1,3-bis-kryptopyrrol-2-yl squaraine **1b** (Scheme 2, bottom). Indeed, a reaction between equimolar amounts of squaric acid and kryptopyrrole in several organic solvents led to formation of **1b** as the major product, which was consistent with accounts in the literature [16,22].

Literature syntheses of pyrrolyl-containing semisquaraines
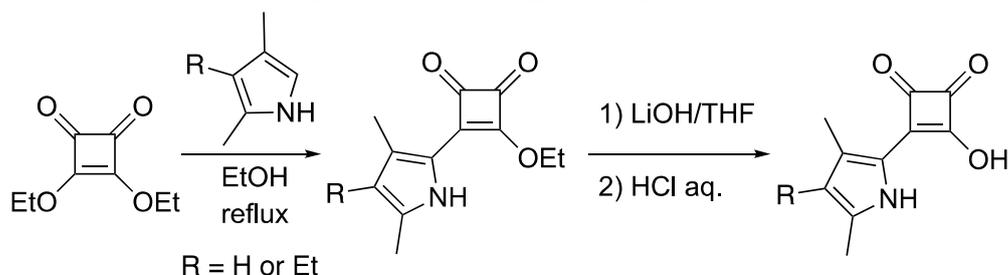
Proposed synthesis of kryptopyrol-2-yl semisquaraine
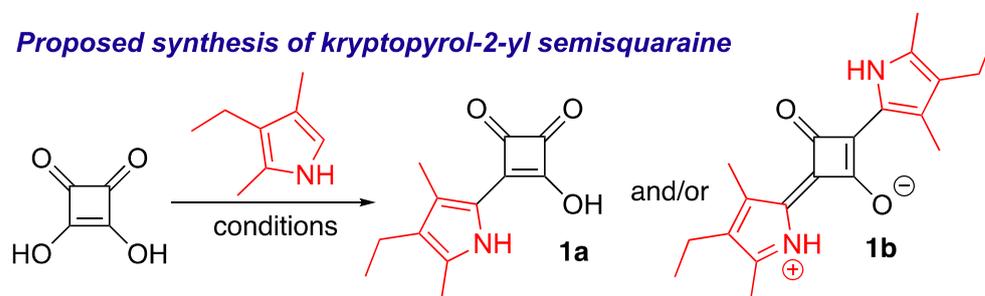
Scheme 2. Syntheses from the literature [18–20] (**top**) and this study (**bottom**) of pyrrole-containing semisquaraines.

Arguably, in water, where the solubility of squaric acid would be higher than that of the pyrrole, the scenario could be reversed, which, in turn, should favor the formation of kryptopyrrole semisquaraine **1a**. We found that, in water, **1a** was obtained as the major product, although a substantial amount of **1b** was still observed (Table 1, entry 1). Multiple attempts to separate semisquaraine **1a** from squaraine **1b** either via recrystallization or by washing with a range of organic solvents (including chloroform, acetone, diethyl ether, and petroleum ether) proved inefficient and non-sustainable. We also attempted to prepare **1a** using the slow addition of kryptopyrrole to an equimolar amount of squaric acid, albeit with limited success, as the formation of **1a** was accompanied by the formation of a number of unidentified products, which proved difficult to remove in a facile and efficient manner. However, progressively increasing the amount of squaric acid (from 2 to 5 eq.) completely suppressed the formation of **1b** (entries 2–5). Subsequently, we varied the reaction time (entries 5–8); the corresponding results revealed the reaction completion to occur within 15 min. The reaction proved inefficient when the concentration of kryptopyrrole was lowered to 0.037 M (entry 9); concentrations higher than 0.37 M were not tested to retain the solubility of squaric acid. We also conducted this reaction under room temperature (entry 10), and although **1a** formed as the major product, the overall results appeared to be inferior to those obtained under reflux conditions. Thus, 15 min reflux and 5 eq. of squaric acid (entry 7) appeared to be optimal conditions for the synthesis of **1a**. To demonstrate the scalability of this process, the synthesis of **1a** was also conducted on a multigram-scales (i.e., 1 mL (7.4 mmol), and 5 mL (37.1 mmol) scales); in both cases, **1a** was obtained in high yields (entries 11 and 12), thus indicating the robust nature of this process, and potential industrial applicability.

Table 1. Synthesis **1a**: optimization studies [a].
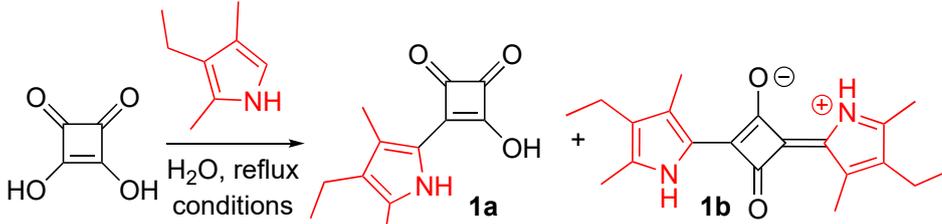
Entry	Squaric Acid, eq.	Reaction Time, min	Yield, % [b] (1a:1b) [c]
1	1	120	80 (75:25)
2	2	120	91 (98:2)
3	3	120	87 (98:2)
4	4	120	97 (98:2)
5	5	120	95 (100:0)
6	5	30	91 (100:0)
7	5	15	92 (100:0)
8	5	5	84 (100:0)
9 [d]	5	5	15 (95:5)
10 [e]	5	300	47 (97:3)
11 [f]	5	15	99 (100:0)
12 [g]	5	15	97 (100:0)

[a] Conditions: kryptopyrrole (1.5 mmol), [kryptopyrrole] = 0.37 M; [b] isolated yield; [c] **1a**:**1b** ratio was determined by ^{1}H NMR using the integration of NH resonances of **1a** (NH) and **1b** (2NHs); [d] [kryptopyrrole] = 0.035 M; [e] reaction was performed at room temperature; [f] 1 mL (kryptopyrrole: 0.91 g, 7.4 mmol) scale reaction; [g] 5 mL (kryptopyrrole: 4.57 g, 37.1 mmol) scale reaction.

The substantial excess of squaric acid used in the synthesis of **1a** deems this process unsustainable, unless squaric acid could be recovered and reused. Thus, we turned our attention to the recovery of the unreacted squaric acid. Simply removing the water in vacuo and washing the residue with acetone gave squaric acid with a 98% recovery, i.e., over 3.9 eq. of squaric acid (out of possible 4.0 eq.) were recovered. Although the color of the recovered squaric acid turned out to be pale green, which was not consistent with the authentic/commercial sample (i.e., white), the squaric acid exhibited properties and chemical reactivity (e.g., the reaction of recovered/"pale green" squaric acid with kryptopyrrole under the optimized conditions gave **1a** in an approximately 95% yield) that were identical to an authentic sample (Figure S1). However, when water (i.e., combined fractions from the reaction and the washings) was treated with charcoal, followed by the removal of water in vacuo, recovered squaric acid was obtained as a white solid (95% recovery; i.e., 3.8 eq. of squaric acid were recovered out of possible 4.0 eq.), whose spectral and physical characteristics were also in line with those of the authentic sample (Figure S1).

In addition, we determined the green chemistry metrics for this process [23,24], and compared them to the literature preparation of **1a** [18] (Table 2; see Supplementary Materials for considerations, calculations, and detailed results). The method developed here had an E-factor value of 0.2, atom economy of 92.4%, mass intensity of 3.1, and process mass intensity value of 46.9, which were all superior to those obtained from the literature protocol [18].

Table 2. Green chemistry metrics for the synthesis of **1a**.

Metrics	Literature Procedure [18]	Our Procedure
E-factor	6.2	0.2 [a]
Atom economy	63.0	92.4
Mass intensity	75.6	3.1 [a]
Process mass intensity	82.3	44.8 [a]

[a]—the recovered squaric acid.

To evaluate the scope of this reaction (under optimized conditions, Table 1, entry 7), we used several pyrroles to prepare the corresponding pyrrolyl-semisquaraines (Scheme 3). The choice of pyrroles was driven by commercial availability and cost, which was set to be comparable to that of kryptopyrrole (Table S1). Surprisingly, the reaction between 2,4-dimethylpyrrole and squaric acid led only to minute amounts of the corresponding semisquaraine **2a**, while symmetric squaraine **2b** was obtained as the major product (Scheme 3B; Figure S2). Although conducting the reaction at room temperature obtained **2a** as the major product, a relatively low yield of this process made it inferior to the synthesis of **1a**. Notably, the preparations of **2a** in the literature rely on a two-step process (Scheme 2) [19–21]. Reactions between squaric acid and 2-ethylpyrrole (Scheme 3C) turned out to be inefficient, because we were unable to obtain pure semisquaraine **3a** from a complex mixture of products that also included the symmetric squaraine **3b**.
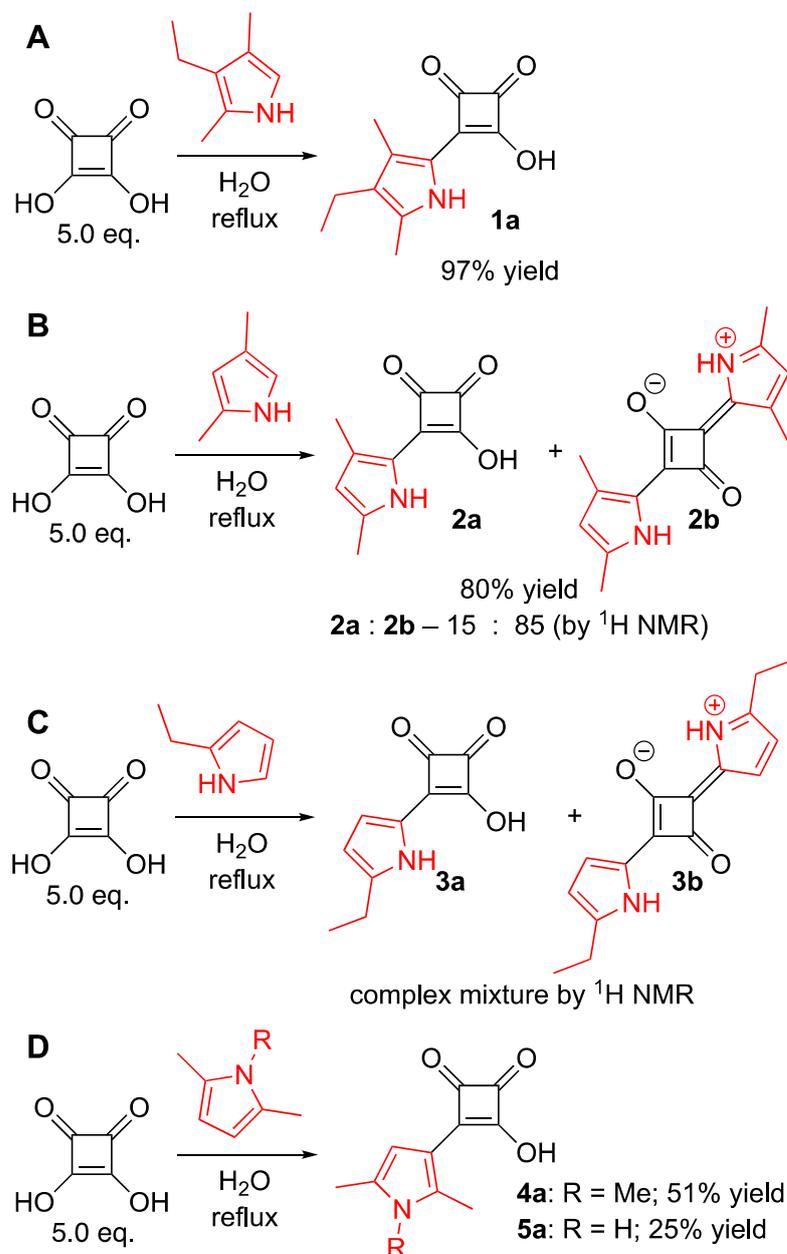
Scheme 3. Optimized synthesis of **1a** (Table 1, entry 7) (**A**) and the attempted syntheses of other pyrrol-2-yl- and pyrrol-3-yl semisquaraines (**B–D**). The **2a:2b** ratio was determined by ^{1}H NMR using the integration of NH resonances of **2a** (NH) and **2b** (2NHs).

However, the reaction of 1,2,5-trimethylpyrrole and 2,5-dimethylpyrrole with squaric acid led to the formation of semisquaraines **4a** and **5a**, respectively, albeit in low yields (Scheme 3D). These low yields were attributed to higher solubilities of these semisquaraines in water as compared with **1a**. In addition, it appeared that minute amounts of squaric acid were still present in those products, and squaric acid could not be easily removed without further decreasing the yield of the desired semisquaraines.

On the other hand, because the formation of symmetric squaraines, i.e., bis-1,2,5-trimethylpyrrol-3-yl- and bis-2,4-dimethylpyrrol-3-yl-squaraines, was not observed (most likely due to lower nucleophilicity of 2,5-dimethylpyrrole and 1,2,5-trimethylpyrroles as compared with kryptopyrrole) [25], we reasoned that excess squaric acid might not be required to obtain the corresponding semisquaraines. Indeed, reacting 1,2,5-trimethylpyrrole with an equimolar amount of squaric acid enabled us to obtain **4a** in an approximately 80% yield (Table S2). Similar to the synthesis of **1a** (Table 1), the synthesis of **4a** could also be done performed at elevated temperature or at room temperature, although it was found to be more facile under 80 °C (Table S2). Notably, 1 mL and 5 mL scale syntheses of **4a** proceeded in 84% and 77% yields, respectively (Table S2, entries 9 and 10), thus highlighting the scalability and robustness of this process. However, to our regret, the aforementioned conditions appeared not to be applicable for the reaction of 2,5-dimethylyrrole with an equimolar amount of squaric acid in water to produce the corresponding semisquaraine **5a**. Overall, pyrrol-2-yl- and pyrrol-3-yl-containing semisquaraines **1a** and **4a** could be obtained in a facile and efficient manner using water as the only solvent and with water being the only by-product.

As mentioned above (Scheme 1), non-symmetric squaraine dyes are typically prepared by reacting a semisquaraine with various nucleophiles in either alcohol/toluene or iso-propanol/alkyl formate mixtures under reflux (or at elevated temperatures) [5,6]. Here, we aimed to investigate the possibility of using **1a** and **4a** to generate structurally and functionally diverse non-symmetric squaraines. It is of interest to point out that although considerable research has focused on C-aryl/C'-aryl squaraines, several recent accounts have indicated that C-aryl/N-aryl-SQ (Figure 1) might exhibit unique properties, such as dual-state emission [26–28] and crystallization-induced emission [29], which could raise the demands for facile access to C-aryl/N-aryl-SQ dyes as well.

Thus, we screened several reactions between **1a** and a few *p*-substituted anilines and found out that non-symmetric C-aryl/N-aryl(alkyl)-SQ dyes could be obtained in moderate to good yields using either H_2O, n-BuOH or t-BuOH as a solvent (Table S3). Not surprisingly, and in line with previous reports [9,30], conducting the reaction under MW-heating proved to be more facile, and non-symmetric squaraines were obtained in good yields after 30 min of MW heating using n-BuOH as the only solvent (Table S3), which is designated as the "preferred/recommended" from the green chemistry and sustainability points of view [31]. With these optimized conditions at hand, a number of non-symmetric C-aryl/N-aryl(N-alkyl) squaraines were synthesized (Scheme 4). The reaction exhibited a great degree of functional group tolerance, as non-symmetric squaraines with electron-donating (**6**, **7**, **10**) and electron-withdrawing groups (**8**, **9**, **11**), as well as heterocyclic (**12**, **13**), aliphatic (**14**), and aralkyl (**15**) motifs were obtained in moderate to good yields (Scheme 4). Notably, the incorporation of NH_2 and CO_2H groups onto the squaraine scaffolds (i.e., squaraines **9** and **15**) should provide opportunities for post-functionalization, and/or conjugation to biomacromolecules or solid supports.

Next, the reactivity of **1a** and **4a** semisquaraines with several C-nucleophiles was explored (Scheme 4). It appeared that squaraine **16** could be obtained under similar conditions as those used with amines (i.e., N-nucleophiles) to produce squaraines **6–15**. The reaction with indolinium C-nucleophiles required the use of pyridine and MW reaction times of 90 min to give non-symmetric squaraines **17** and **18** in moderate yields (Scheme 4).
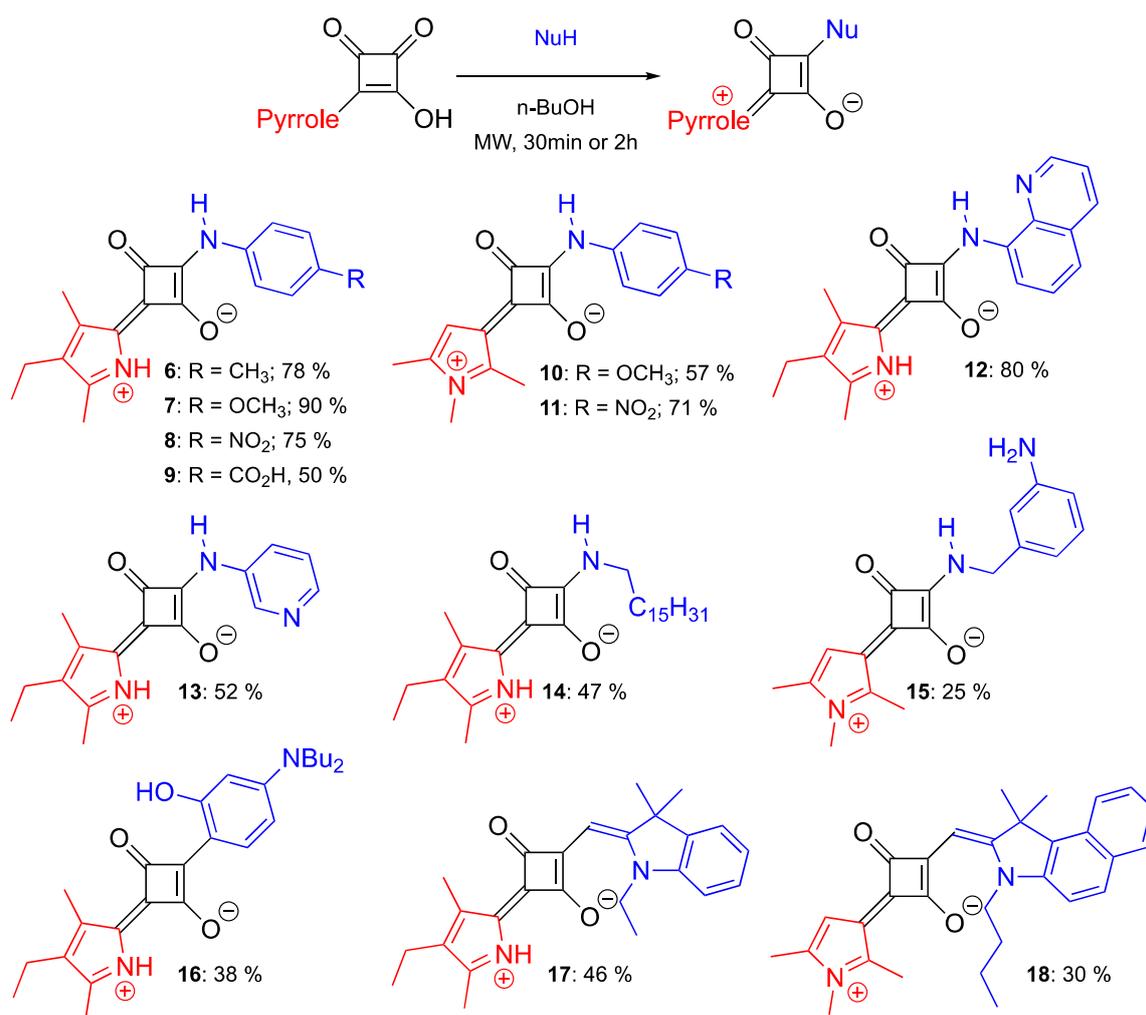
Scheme 4. Synthesis of non-symmetric squaraines from semisquaraines **1a** and **4a**. Isolated yields are given.

Some photophysical properties of non-symmetric squaraines were investigated (Table S4). In general, C-aryl/C′-aryl-squaraines appeared to exhibit absorption and emission maxima at longer wavelengths than the C-aryl/N-aryl(N-alkyl) squaraines. Complete photochemical characterization will be provided in due course.

4. Conclusions

Facile, efficient, and scalable syntheses of pyrrol-2-yl and pyrrol-3-yl semisquaraines were achieved by simply refluxing kryptopyrrole with excess squaric acid, and by refluxing 1,2,5-trimethylpyrrole with equimolar squaric acid, in water, respectively. In the case of kryptopyrrolyl-semisquaraine synthesis, the excess squaric acid could be easily recovered, with an approximately 95% efficiency) and reused without any impact on the reactivity. The synthesis of these semisquaraines had an atom economy of over 90%, with water being the only by-product. Semisquaraines were shown to undergo condensation reactions with various nucleophiles to give a range of structurally/functionally diverse non-symmetric squaraines. When amines were used as nucleophiles, efficient, facile, and chromatography-free access to C-aryl/N-aryl(N-alkyl) non-symmetric squaraines was achieved using either H_2O or n-BuOH as the only solvent.

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