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Laboratory Experiment

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Synthesis of a Fluorescent Acridone Using a Grignard Addition, Oxidation, and Nucleophilic Aromatic Substitution Reaction Sequence

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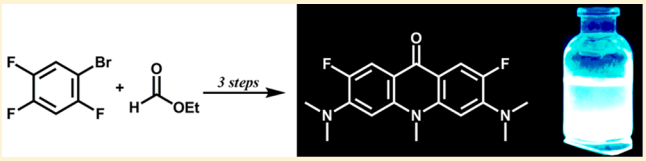
Supporting Information

ABSTRACT: A three-pot synthesis oriented for an undergraduate organic chemistry laboratory was developed to construct a fluorescent acridone molecule. This laboratory experiment utilizes Grignard addition to an aldehyde, alcohol oxidation, and iterative nucleophilic aromatic substitution steps to produce the final product. Each of the intermediates and the acridone product of the synthesis are analyzed by common techniques available in most undergraduate chemistry laboratories such as melting point, thin-layer chromatography, infrared spectroscopy, UV−vis spectroscopy, and fluorescence spectroscopy. Yields for each transformation in the synthesis are generally moderately low to good (20−90%), and nearly all of the students (>90%) who attempted the synthesis were able to produce the final acridone product.



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Heterocyclic molecules with the core structure of **1** (Figure 1), commonly referred to as "acridones", are a class of

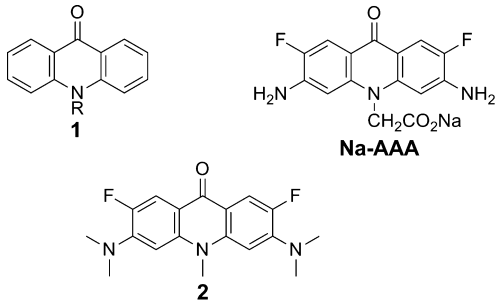

Figure 1. Structures of acridone (**1**), acridone acetic acid, sodium salt (**Na-AAA**), and fluorous acridone (**2**).

biologically active molecules found in an array of natural products, pharmaceutical drugs, and biological probes. The interaction of acridones with their cellular targets is quite diverse, and molecules within this family often display a range of activities such as antiviral,[1] antimicrobial,[2] antimalarial,[3,4] and anti-inflammatory.[5] Acridone analogs also have shown promising leads in combating cancer and have been reported to prevent tumor growth,[6] as chemical therapeutics,[7] and as treatment measures against multidrug resistance in cancer cells.[8] This pharmacologically diverse moiety, often called a "privileged structure" for its versatile activity, has been involved in several different clinical drug developments and is the core structure for the commercial antiviral drug, acridone acetic acid, sodium salt (**Na-AAA**), which is marketed with the trade name Neovir (Figure 1). Additionally, many acridone-containing molecules exhibit fluorescence in the visible region[9,10] of the electromagnetic spectrum, which is advantageous for visualizing their activity in cell cultures or in tissue samples.[4]

Unsubstituted acridone, or 9(10*H*)-acridone, was synthesized as early as 1912[11] and was reported in a 1939 *Organic Synthesis* preparation.[12] Since 1912, additional methodologies have been developed to diversify the range of acridones that can be produced through organic synthesis.[13] One intriguing methodology that has recently been described is an iterative nucleophilic aromatic substitution (S_NAr) reaction,[10] where four subsequent S_NAr reactions occur to construct a diamino substituted acridone ring. The methodology was designed to incorporate fluorine into acridones, xanthones, and thioxanthones, and works by substituting only fluorine atoms situated ortho and para to the carbonyl within fluorinated benzophenones. Meta substituted fluorine atoms do not readily undergo substitution and are retained in the final product. Intellectually, this methodology offers the ability for students to predict and test for various S_NAr substitution patterns using a single molecule and a one-pot procedure. The methodology, which requires sealed tube reaction vessels, however, is not suitable for undergraduate experimentation.

The experiment described herein adapts the iterative S_NAr reaction to fit the demands of an undergraduate laboratory setting. Acridone **2** (Figure 1) was chosen as the subject for this experiment because its synthesis (Scheme 1) incorporates several core reactions (Grignard generation, acyl addition, and oxidation of alcohols), in addition to iterative S_NAr, that are typically covered in an introductory organic curriculum.

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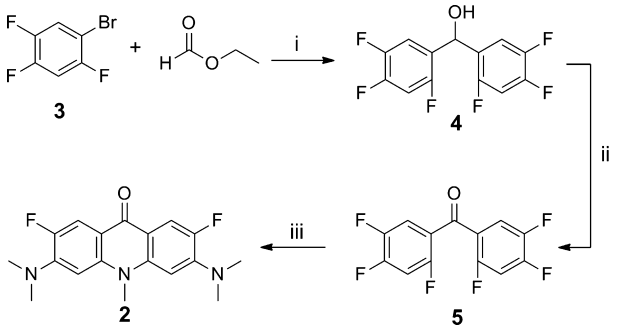
Scheme 1. Synthesis of Acridone 2[a]



[a]Conditions: (i) Mg, THF, 0 °C, 2 equiv of **3**, ethyl acetate 1 equiv., 10% (m/v) aqueous NH_4Cl; (ii) TEMPO, 0.7 M aqueous NaOCl, KBr, $NaHCO_3$, CH_2Cl_2; (iii) DMF, 10 M aqueous KOH, reflux for 12 h.

Additionally, the experiment relies on a range of analytical methods (melting point, thin-layer chromatography (TLC), UV−vis, and infrared (IR) spectroscopy) to characterize the intermediates and final product of the synthesis. Furthermore, acridone **2**, when dissolved in organic solvents, exhibits blue−violet fluorescence (λ_{ex} = 384 nm, λ_{em} = 441 nm),[10] which incorporates fluorometry into the experiment as well. Considering the variety of laboratory and spectroscopic techniques utilized for the synthesis and characterization of **2**, the experiment is most suitable as a final project for an introductory organic laboratory curriculum but could also be used as an advanced organic chemistry laboratory experiment. Overall, the experiment provides a structured method to perform the chemical synthesis of a biologically interesting fluorophore while it illustrates the utility of several reactions that students have studied in the lecture component of a course.

The synthesis of acridone **2** (Scheme 1) exposes undergraduate students to a new range of synthetically derived molecules and reaction conditions that have not been described in chemical education literature. While undergraduate synthesis experiments report the preparation of 9(10*H*)-acridone[14,15] and 10-methyl-9(10H)-acridone,[14] acridones with multiple substituents, which represent all known acridones with biological activity, have not been reported. Additionally, the use of an iterative S_NAr reaction has not been reported for an undergraduate synthesis experiment despite the pedagogical value this reaction has in teaching relative rates of substitution in S_NAr reactions with respect to an electron withdrawing group. The synthesis also highlights strategies for carrying out both oxidation of a secondary alcohol and the generation of dimethylamine for undergraduate students. The 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/NaOCl-catalyzed oxidation reaction, reported in the chemical education literature in 1991,[16] has seen very little representation in undergraduate synthesis experiments since, despite its wide range of use in synthetic organic chemistry.[17] While TEMPO catalyst paired with O_2/Cu^+ has recently been reported as a "green" alternative to chromium-based oxidants,[18] the use of commercial NaOCl solution paired with TEMPO catalyst illustrates to students how a tangible item, bleach, can be used to carry out an oxidation reaction. Furthermore, the base promoted decomposition of N,N-dimethylamine (DMF) introduces a method to chemical education literature by which a common solvent can decompose to form an amine nucleophile.

Beyond pedagogical considerations, the synthesis of **2** also has several practical features as an undergraduate organic chemistry experiment. Nearly all of the materials and chemicals used, with the exception of TEMPO and 1-bromo-2,4,5-trifluorobenzene (**3**), are typically stocked in the inventory of undergraduate laboratories. Although TEMPO and 1-bromo-2,4,5-trifluorobenzene are not commonplace in undergraduate laboratories, both chemicals are commercially available from multiple chemical suppliers and can be purchased for less than $1 per gram. In addition, the purification of all intermediates and the final product in the experiment are performed without the use of column chromatography; thus, expenses associated with solvents, equipment, silica, etc. are avoided. Lastly, the total experiment is completed within three sequential 3-h laboratory sessions; no students to date were unable to finish the experiment due to time constraints.

The experiment is designed to have three overarching goals. The primary goal is for students to perform a multistep synthesis successfully. Another goal is for students to deduce the purity and identity of products generated from each step of the synthesis using melting point, TLC, UV−vis, fluorescence, and IR spectroscopy. Students also analyze ^{1}H NMR idealized spectra of **2**, **4**, and **5**. The final goal is for students to construct a reasonable mechanism for all of the reactions used in the synthesis. In particular, students should be able to explain a double addition of the Grignard reagent to an ester, the catalytic cycle of TEMPO and how it can be used to oxidize primary and secondary alcohols, and the substitution pattern observed for iterative nucleophilic aromatic substitution.

EXPERIMENT

Students work in groups of two or three. The synthesis requires three, 3-h laboratory periods. Students also obtain idealized ^{1}H NMR spectra for **5**, **4**, and **2** as a handout. A detailed description of the experiment is in the Supporting Information.

Synthesis of 4

To a round-bottom flask equipped with a magnetic stir bar, and a Claisen head with a rubber septum and a drying tube, students add magnesium turnings, a small crystal of iodine, and anhydrous tetrahydrofuran (THF); the mixture is stirred for a few minutes, and **3** (8.0 mmol) is added via a syringe through the rubber septum dropwise. After addition of **3** is complete, the mixture is stirred for 10 min and set in a water bath at 35 °C for 30 min. Ethyl formate (4.0 mmol) is added by syringe over 1 min, and the reaction is stirred for 30 min. HCl (0.1 M) is added; the aqueous fraction is separated from the organic layer, the aqueous layer is extracted with diethyl ether, and the combined organic layers are dried. The organic solvents are removed on a steam bath, the product is weighed to determine the yield of **4**, and a TLC is run using ethyl acetate in hexanes. The product is stored in a vial.

Synthesis of 5

Students dissolve alcohol **4** in CH_2Cl_2 and transfer the resulting solution to an Erlenmeyer flask containing a stir bar. To the same Erlenmeyer flask is sequentially added TEMPO (0.19 mmol), KBr (0.084 mmol), $NaHCO_3$ (0.75 g, 8.9 mmol), deionized water (5 mL), and an aqueous solution of NaOCl (10 mL, 7.2 mmol). The biphasic mixture is vigorously stirred, and the reaction is monitored using TLC. Once the reaction is determined to be complete, the aqueous fraction is separated from the organic layer and is extracted with CH_2Cl_2. The combined organic layers are washed with brine solution, dried,

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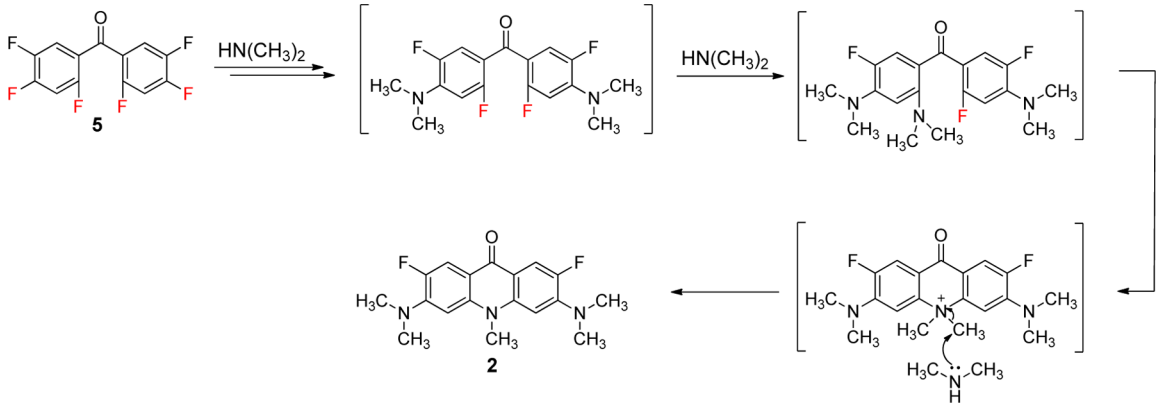
Scheme 2. Conversion of Benzophenone 5 into Acridone 2 via Iterative S_NAr[a]



[a]Fluorine atoms colored in red are susceptible to substitution with dimethylamine.

and concentrated on a steam bath. The residual oil is diluted with hexane to induce crystallization, and the crystals are collected by vacuum filtration. The product is weighed to determine the yield of **5** and is characterized by melting point and IR spectroscopy. The product is used directly in the following reaction.

Synthesis of 2

To a round-bottom flask containing two boiling stones, students add a solution of benzophenone **5** dissolved in DMF (4 mL) along with aqueous KOH (10 M) (20 mmol). A condenser is added to the round-bottom flask; the mixture is refluxed for 15 min, and a second aliquot of aqueous KOH (20 mmol) is added. The mixture is refluxed for an additional 12 h and diluted with ice−water; the precipitate is collected by vacuum filtration. The filtered precipitate is transferred to an Erlenmeyer flask and recrystallized from dimethyl sulfoxide (DMSO); crystals of **2** are collected by vacuum filtration and washed with water and diethyl ether. The product is weighed to determine the yield; **2** is characterized by melting point, IR and UV−vis spectroscopy, and fluorimetry.

HAZARDS

Laboratory safety is critical to minimize the effects of hazardous chemicals. Goggles, gloves, and lab coats should be worn at all times in the laboratory, and all solvents and other volatile chemicals (such as TEMPO) should be handled in a regularly certified fume hood. The laboratory instructor and students should consult the Material Safety Data Sheets (MSDS) in regards to the hazards of each chemical before starting each reaction (a summary of the hazards for each chemical is reported in the Supporting Information). Chemicals of particular concern are hexanes, which are highly flammable solvents and known to be toxic to the peripheral nervous system; potassium hydroxide, which can cause severe burns upon contact; TEMPO, which can cause skin burns and eye damage; dichloromethane, which can cause skin and eye damage and may be carcinogenic; iodine, which can cause serve burns and eye damage; and magnesium/ethyl formate/diethyl ether/THF, which are highly flammable. THF and diethyl ether are known to form explosive epoxides in the absence of a stabilizer or upon prolonged exposure to oxygen gas and, therefore, should be checked for peroxide buildup on a routine basis. The hazards of compounds **2**, **4**, and **5** generated in the synthesis are not fully known. Consequently, **2**, **4**, and **5** should be handled in a fume hood, and care should be taken to avoid contact with gloves and clothing. Safety regulations must be satisfied upon the disposal of waste products.

RESULTS AND DISCUSSION

The acridone synthesis experiment has been performed 38 times by more than 100 students over six academic terms. Overall, 92% of the syntheses gave the final acridone product, **2**. For those 8% of students who obtained unusually low yields or committed errors that resulted in substantial loss of material, they were supplemented with premade intermediates.

All of the students had prior knowledge of melting point, TLC, UV−vis, IR, and ^{1}H NMR analysis and were able to characterize and determine a general degree of purity for **4**, **5**, and **2** successfully. Additionally, the majority of the students were able to assign chemical shifts correctly from the NMR handout to all hydrogen atoms within structures of **4**, **5**, and **2**.

Part A: Grignard Generation and Addition into Ethyl Formate

In the first part of the synthesis, students generated a Grignard reagent from 2,4,5-trifluorobromobenzene (**3**) using standard conditions.[19] The Grignard reagent produced undergoes double addition with ethyl formate to generate alcohol **4**. Some of the students had low yields (<20%) for this step, and, in general, these unsuccessful attempts resulted from failing to maintain anhydrous reaction conditions or inadequate maintenance of reaction temperatures. By adhering strictly to the procedure, students obtained 50−80% yields to provide sufficient alcohol **4** to complete the synthesis of **2**. Depending on the purity of **4**, the product was isolated as an oil or a solid and was characterized by melting point (if a solid) and TLC within the 3-h laboratory session in which the reaction was run.

Part B: Oxidation Using TEMPO and NaOCl

In the following reaction, a TEMPO-catalyzed oxidation was performed using NaOCl as a stoichiometric oxidant.[20] Commercial bleach worked well for this reaction, thus providing an economical alternative to NaOCl provided through chemical suppliers. The TEMPO/NaOCl oxidation relies on a biphasic solvent system where TEMPO is transferred between the aqueous and organic layer during its catalytic cycle.[12] Consequently, it was critical that the reaction was stirred rapidly to ensure complete conversion. For the oxidation of **4**, most students obtained benzophenone product **5** in relatively high yields (50−90%). Lower yields (<20%)

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generally resulted from the use of impure starting material **4** or from the failure to monitor the reaction correctly by TLC. The fluorous benzophenone product **5** is highly crystalline and was purified by seeding a mixture of the crude product and hexanes. Once crystallized, **5** was typically >97% pure, and students characterized the compound by melting point and IR spectroscopy.

Part C: Iterative Nucleophilic Aromatic Substitution

In the final transformation, an iterative S_NAr reaction sequence was used to construct the N,N-bridge in the center acridone ring. The reaction relies on the decomposition that occurs when a mixture of DMF and KOH is heated to provide dimethylamine that acts as the nucleophile in the reaction. This method was preferred over using commercial solutions of dimethylamine as it was more economical, convenient, and gave higher yields. Once dimethylamine is generated, four subsequent S_NAr reactions replace all of the fluorine atoms located ortho or para to the carbonyl group (Scheme 2). The first equivalents of dimethylamine reacted rapidly; however, the third addition and cyclization step required a fairly long 12 h reflux period (as discussed in the Limitations section) before a substantial quantity of **2** was formed. When precipitated from cold water and collected, students purified the acridone product by recrystallization in DMSO to give needle crystals, typically with >95% purity. After recrystallization, students obtained pure acridone **2** in low yields (20−35%), but sufficient material (100−250 mg) to perform melting point analysis, IR and UV−vis spectroscopy, and fluorimetry. Additionally, students visually demonstrated the fluorescence of **2** using a long wavelength (365 nm) UV lamp to illuminate a solution of **2** dissolved in methanol or ethanol.

LIMITATIONS

A limitation to this experiment is the 12 h reflux that was required to carry out the third synthetic transformation. While the iterative S_NAr reaction has been performed using an hour reflux, yields of **2** were typically very low (<10%). The lower yields are fairly unrewarding, but the reaction did provide proof of concept, and characterization of **2** could be carried out. An increase to a 12 h reflux time substantially improved yields but can be very difficult to perform at larger institutions where numerous sections of organic chemistry laboratory are run in the same day. For smaller institutions with more adaptability, however, the experiment can work quite well. To carry out the 12 h reflux in three lab sessions, it required that the second and the third synthetic transformations were combined into one lab session to allow for the long reflux time. Lab personnel were used to periodically check reactions when students were not available and to disassemble the reflux setup. The third laboratory session was dedicated to purifying and characterizing the physical properties of **2**.

CONCLUSION

A majority of students successfully generated, characterized, and were able to analyze correctly the ^{1}H NMR spectra from the handouts for acridone **2** and all intermediates in the experiment. Students also demonstrated a thorough understanding of each of the synthetic transformations in their laboratory reports and were able to construct detailed arrow-pushing reaction mechanisms for each step in the synthesis. Beyond simply illustrating the mechanisms, they were able to apply the mechanistic information in a way to predict products of different substrates correctly using the same reactions. In particular, students successfully predicted the products of a TEMPO/bleach reaction for primary, secondary, and tertiary alcohols, as well as the patterns of substitution for iterative S_NAr reactions applied on a range halogenated aromatics with several different nucleophiles. Overall, students scored higher on assessment questions relating to Grignard, alcohol oxidation, and nucleophilic aromatic substitution reactions than students did before this experiment was introduced into the curriculum.

In general, the three-lab-session experiment provided introductory organic chemistry students a framework for performing a multistep synthesis to produce an acridone product. The procedural simplicity and highly structured nature of the experiment provided an experience where students with little background performing multistep organic synthesis were successful in producing a complex organic molecule. Beyond the high success rate of the overall synthesis, students viewed the acridone experiment as appealing due to the interesting fluorescent nature of **2** and its relation to the pharmacologically diverse acridone family of molecules.

ASSOCIATED CONTENT

Supporting Information

Instructions and procedures for each of the synthesis reactions; student handouts for each of the synthetic transformations including prelab and postlab questions and answers to the questions, notes for the instructor; representative spectra for intermediates and acridone product. This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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