

Synthesis of Triarylmethane and Xanthene Dyes Using Electrophilic Aromatic Substitution Reactions

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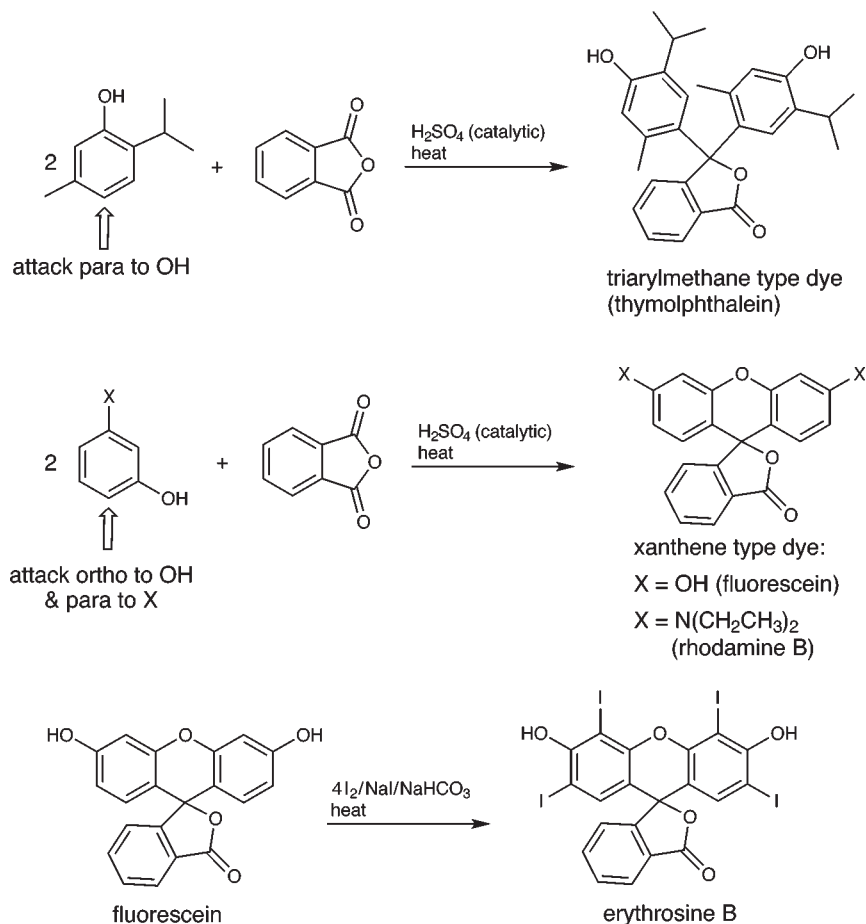
The synthesis and characterization of dye molecules has long been a popular topic in organic chemistry laboratory experiments, because such experiments allow students to see first hand that knowledge learned in organic lecture can be used to make useful and practical materials (1–9). From a more historical perspective this is also appropriate as the synthesis of commercial dyes was the impetus leading to many of the earlier discoveries in organic chemistry (10–14). In this experiment electrophilic aromatic substitution reactions, Friedel–Crafts type reactions, and halogenation are used to synthesize triarylmethane and xanthene type dyes (Scheme I).

The triarylmethane or xanthene carbon skeletons of the dyes are produced by reacting two equivalents of a substituted phenol with phthalic anhydride. The overall process is actually two sequential Friedel–Crafts type reactions that occur in the same reaction flask without having to isolate the

product of the first reaction as shown in Scheme II. Depending on the type and orientation of the substituents present on the phenol, either a triarylmethane or xanthene type dye will be produced.

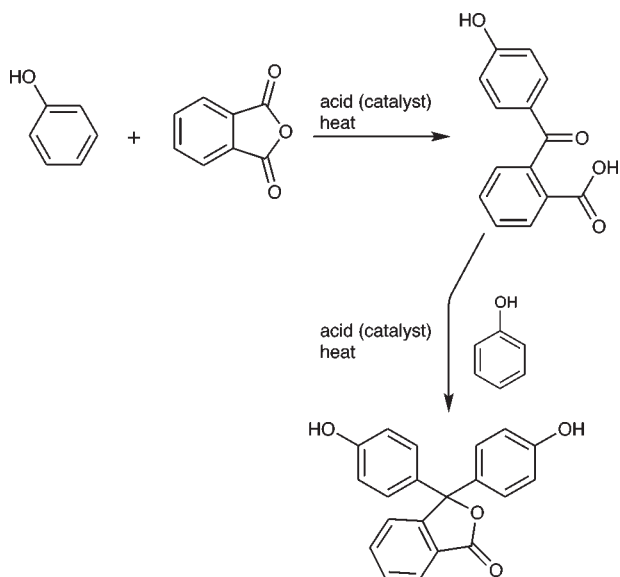
The synthesis experiments of related dyes that have appeared in laboratory texts and the literature use Lewis acids such as $ZnCl_2$, which are extremely hygroscopic and must be extensively dried before use and kept dry (2, 3). This is often inconvenient in a typical undergraduate laboratory setting. In the reactions shown here, the use of hygroscopic Lewis acids is avoided. Instead inexpensive and readily available protic acids (H_2SO_4) are used in catalytic quantities (15).

This experiment starts with inexpensive colorless substituted phenols and phthalic anhydride and uses Friedel–Crafts type reactions to produce a variety of dyes including fluorescein, rhodamine B, and thymolphthalein as shown in the first two equations in Scheme I. The synthesis of each of these three dyes are run in a test tube or small Erlenmeyer flask as a melt with a very small quantity of sulfuric acid cata-



Scheme I. Dyes synthesized in this experiment by electrophilic aromatic substitution reactions.

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Scheme II. Two-stage alkylation reaction used in formation of triarylmethane and xanthenes dyes.

lyst present. For most cases, a few drops of 2 M H_2SO_4 is sufficient to catalyze the reaction. The reactions are heated in a sand bath to a temperature between 115 °C and 190 °C depending on the dye synthesized as outlined in the Supplemental Material.^W

In addition to the Friedel–Crafts reactions shown, an aromatic halogenation reaction can be used in this experiment to convert fluorescein into erythrosine B, a red food dye (FD&C red 3), as shown in the third equation of Scheme I (16, 17). This iodination reaction, which uses molecular iodine in the presence of a weak base, can be run in a test tube. The solution is heated to a gentle boil until all the iodine has reacted.

The different dye syntheses presented here have reaction times between 30 and 80 minutes, allowing students to complete the synthesis and workup of any one of the dyes in a single laboratory session. A detailed lab procedure for each of these dyes is given in the Supplemental Material.^W

The brightly colored dyes produced in this experiment have many applications including use as food dyes, ink and paper dyes, biological staining reagents, and pH indicators. Their properties and uses are summarized in Table 1.

Hazards

The organic solvents used in this laboratory experiment (acetone, THF, hexane, diethyl ether, and methyl *tert*-butyl ether) are volatile, flammable solvents of moderate toxicity, but should prove little hazard if handled in a fume hood and disposed of properly after use. Methylene chloride is a volatile solvent that is toxic and potentially carcinogenic. The organic reagents used in this experiment are also classified as irritants with moderate toxicity. Molecular iodine (I_2) is toxic and corrosive. Students should not conduct halogenations with iodine unless closely supervised. Some of the strong acids and bases used in this experiment (H_2SO_4 and NaOH , respectively) are toxic and corrosive.

Results and Discussion

This laboratory experiment was originally developed and tested as part of an undergraduate research project and has been used in a second-semester organic chemistry laboratory course for the last two years. Most students who conducted these experiments successfully obtained the desired dye compounds.

Most yields were fairly reasonable averaging, 75.5% for fluorescein, 79.2% for erythrosine B, and 66.7% for rhodamine B.¹ The yields for thymolphthalein averaged 40.9%. This lower yield results because the reaction is stopped prematurely owing to time constraints of an organic lab period. The unconsumed starting materials from this reaction can effectively be removed during the workup. The products of each dye synthesis were reasonably pure and showed dye properties and UV–vis spectroscopy consistent with literature values and spectra taken on commercially available dye samples.

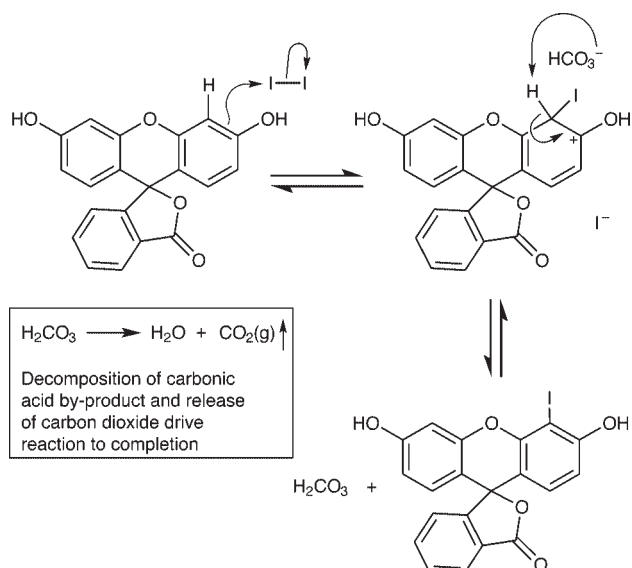
Conducting this experiment demonstrates a wealth of chemical concepts to the students including substituent effects in electrophilic aromatic substitution reactions, equilibria and how to push a reaction towards completion (Le Châtelier's principle), acid–base chemistry of organic compounds, UV–vis spectroscopy, and resonance forms.

When considering the electrophilic aromatic substitution reactions used in the synthesis of these dyes, it is important to understand how substituents effect the reactivity of the aromatic ring in terms of activating or deactivating the ring and in terms of regioselectivity (ortho, para directing versus meta directing). The activating and deactivating ef-

Table 1. Dye Properties and Uses

Compound	Color	Uses
Erythrosine B (FD&C Red 3)	Bright red	Food dye; dye for inks and paper; cosmetics and drug dye; biological cell stain; silk and wool dye
Fluorescein	Yellow–orange (strong green fluorescence upon exposure to long-wave UV light)	Due to strong fluorescence and low toxicity can be used to examine wells, to trace stream flow, in sea rescue markers, etc.; fluorescent labeling of biological compounds; detection of corneal abrasions; dye for drugs and cosmetics
Rhodamine B	Magenta (orange fluorescence)	Laser dye; dye for inks and paper; cosmetics dye; biological cell stain; dye for wool and cotton; crayons
Thymolphthalein	Colorless (acidic and neutral pH) Deep Blue (transition pH 8.8–10)	pH indicator

NOTE: Data from refs 17–20.

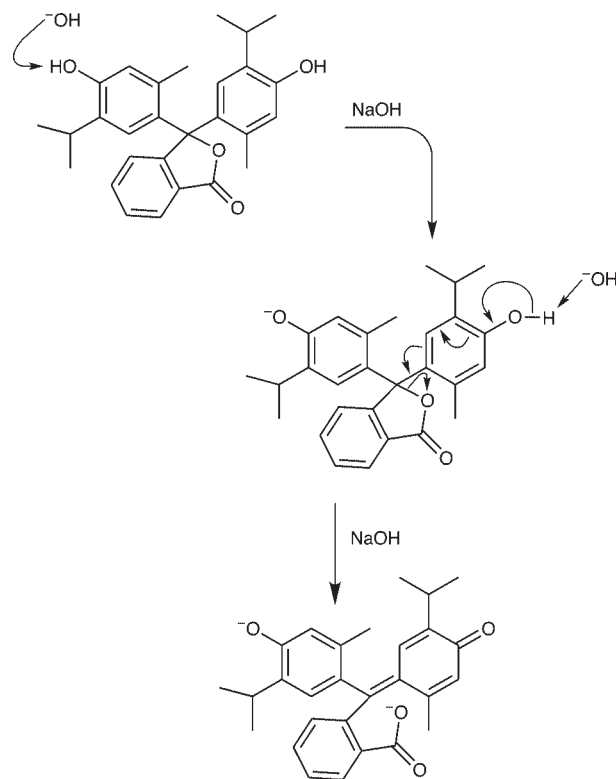


Scheme III. The use of a weak base to drive the iodination of fluorescein to completion.

fects of the substituents are demonstrated by the fact that in all the reactions used to make dyes in this experiment, substitution always occurs on the phenolic aromatic rings and never on the aromatic rings containing carbonyl groups (such as the phthalic anhydride) (21, 22). This difference in reactivity is because the phenols have strongly activating groups (OH and NR_2) while the other aromatic rings are strongly deactivated by electron withdrawing carbonyl containing substituents.

The directing effects of the substituents are revealed by the regioselectivity observed in the products of the electrophilic aromatic substitution reactions. In the Friedel–Crafts reactions, the new C–C bonds are only formed at the most highly activated positions (ortho–para) to the strongest activating group (OH or NR_2). The directing effect of the strongly activating OH group can also be seen in the halogenation of fluorescein to form erythrosine B. The iodination only occurs ortho to the OH groups owing to the directing effects of this substituent.

The conversion of fluorescein to erythrosine B is also a good demonstration of LeChâtelier's principle, where a reaction with an unfavorable equilibrium can be pushed to completion. Most organic chemistry texts state that owing to an unfavorable equilibrium that favors the starting materials halogenation reactions with molecular iodine (I_2) do not work. Direct iodination using I_2 will only work if strong oxidants such as nitric acid are added to convert I_2 to I^+ or if the more reactive ICl gas is used (21, 22). However, this is not necessary for cases where the aromatic ring is heavily activated with either hydroxy or amino groups. In these cases, the halogenation reaction with I_2 will work in the presence of a weak base such as NaHCO_3 . This might be contrary to what students expect because commonly acid catalysts are employed in electrophilic aromatic substitution reactions. The base used in this case helps this usually unfavorable reaction run to completion in two ways. Normally, in the absence of a base, an iodination reaction would be expected to produce hydroiodic acid (HI) as a byproduct. The addition of sodium



Scheme IV. Formation of blue-colored thymolphthalein dianion.

bicarbonate would irreversibly remove this byproduct from the reaction and release carbon dioxide gas from the reaction flask. According to LeChâtelier's principle we would expect the reaction to generate more products in an attempt to reestablish equilibrium as shown in Scheme III. Also, deprotonation of acidic phenol proton in the starting material will form the corresponding phenoxide anion. The negatively charged oxygen of the phenoxide anion is an extremely good activating substituent (better than a hydroxy or amine group), which will accelerate the rate of this reaction and allow it to occur under more reasonable conditions and in a relatively short period of time (23, 24). Therefore, rather than using an acid to activate the electrophile, a base is used to activate the nucleophile.

Additionally, the products formed illustrate important concepts in acid–base reactivity of organic compounds, as well as how molecules with conjugated π systems interact with ultraviolet and visible light. Several of the dyes produced have distinct pH-dependant color and solubility changes in aqueous solutions and so are commonly used as pH indicators.

Thymolphthalein, for example, is a common pH indicator that is colorless under neutral conditions and intensely blue colored under basic conditions. The formation of the vivid blue color is due to deprotonation of its mildly acidic phenolic groups to form the corresponding dianion as shown in Scheme IV. The increase in conjugation present in the dianion can explain why it absorbs light in the visible region and is colored (25–27).

In addition to their color, dyes have other interesting physical properties. For example, dilute solutions of fluorescein and rhodamine B fluoresce strongly (green and orange-

red, respectively) when exposed to UV light or sunlight. The fluorescence of these compounds can easily be demonstrated by exposing dilute solutions to an UV light source or to direct sunlight.

Conclusion

This experiment is an effective demonstration of how ideas and concepts learned in organic chemistry lecture are used to make practical materials that find use in our everyday lives. In doing so, it shows students that organic chemistry is a vibrant field worthy of study. This experiment demonstrates a range of chemical topics, including the usefulness of electrophilic aromatic substitution reactions (Friedel–Crafts and halogenation reactions), chemical equilibrium and application of LeChâtelier's principle, fluorescence, acid–base chemistry of organic molecules, resonance and conjugation, and UV–vis spectroscopy.

This experiment has been used as an undergraduate research project as well as in the second-year organic chemistry laboratory and has received considerable positive feedback from the students. The intense fluorescence of fluorescein that causes dilute aqueous solutions to appear orange at some viewing angles and glowing green at other viewing angles surprises and fascinates many students. The visual impact of converting colorless organic molecules into vibrant colored dye molecules draws students interest into what is occurring in the experiment.

Acknowledgment

The author would like to acknowledge Suzanne Rudnick for the dye photographs in this article.

^uSupplementary Material

Background material for the students and detailed instructions as well as instructor notes, pictures, and UV–vis spectral data are available in this issue of *JCE Online*.

Note

1. The experiment was tested in the spring 2004 (57 students) and spring 2005 (47 students) second-semester organic laboratory. The rhodamine B example, which is essentially a variant of the fluorescein procedure, was not used in these laboratory sections but was run by several students to test the written procedure.

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