Synthesis of Aryl-Substituted 2,4-Dinitrophenylamines: Nucleophilic Aromatic Substitution as a Problem-Solving and Collaborative-Learning Approach

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During the first and second semesters of organic chemistry laboratory, students master the most significant techniques required in the laboratory. The third and fourth semesters of the organic chemistry laboratory focus principally on the synthesis of representative compounds and qualitative analysis. These last two semesters of organic chemistry laboratory represent very little challenge to students; the laboratory is perceived to be a weak appendix to the lecture course and emphasis is given to learning the mechanisms of reactions and technique analysis. Some instructors provide all the information about the experiment, and in several cases, the results of experiments are even specified in advance. This approach facilitates cheating among students and does not represent organic chemistry as a factual science.

In this *Journal*, several articles have been published criticizing the current way of teaching organic chemistry laboratory, which is often based on "recipes" that do not allow students to interpret results and draw conclusions from the data *(1–3)*. The organic chemistry laboratory must demonstrate how the facts described in the textbooks are obtained *(4)*. To achieve this goal, we decided to create a new approach based on a problem-solving and collaborative-learning pedagogies. We chose to study the reaction of substituted anilines with 1-halo-2,4-dinitrobenzene (Scheme 1) using (i) parallel library synthesis, (ii) different reaction conditions, and (iii) different solvents (Scheme 1). Nucleophilic aromatic substitution on activated aryl halides has been already used successfully as a learning tool in organic chemistry *(5, 6)* and physical chemistry laboratory *(7)*.

Combinatorial synthesis has been described *(8–10)* as both a powerful tool to increase creativity and a source of data to stimulate analysis and discussion from students. Determining the yield of each variation in a combinatorial library prepared by parallel synthesis has allowed students to make simple structure—reactivity relationships. Varying the temperature, solvent, duration of the reaction, leaving group in **1**, and substituent in **2** allows a nonformal reactivity study.

Experimental Procedure

Each laboratory session starts with a question to resolve, and every semester the experimental objective is changed. For example, one semester, the parallel synthesis of a series of aryl substituted 2,4-dinitrophenylamines was the objective. Other semesters, the solvent variation was the objective, and so on. This procedure prevented students from copying previous results and kept the teaching from being monotonous.

One set of experiments used 1-chloro-2,4-dinitrobenzene as compound **1**, pyridine as the base, and ethanol as the solvent but varied the substituted aniline, **2**. The substituted anilines were aniline and ortho and para isomers of chloroaniline, nitroaniline, methylaniline, aminophenol, and methoxyaniline. Each student was assigned an aniline, and all procedures were done during a 4-h experimental session. A second set of experiments examined the solvent effect. Aniline was used as the nucleophile, 1-chloro-2,4-dinitrobenzene was used as the electrophile, and pyridine was the base. Chloroform, ethyl acetate, 2-butanone, acetonitrile, methanol, and ethanol were used as solvent. A third set of experiments examined variations in compound **1** (X = F, Cl, Br, or I) with the other reagents held constant. Depending on the number of students in the laboratory, one or two nucleophiles can be chosen.

Reactions were carried out at the microscale and semi-microscale. The yield of the microscale was measured by GC and yield of the semi-microscale was measured by gravimetric analysis. The results were plotted and analyzed in a group seminar. After the results were obtained, the students were asked to plot the yield against the different physicochemical properties of the compounds.

Theory

Nucleophilic substitution reactions at aromatic carbons (S_NAr) are not feasible unless the aryl halides carry appropriate electron-withdrawing substituents. Thus, the reaction is not possible for the usual aromatic substrates in electrophilic aromatic substitution reactions *(11)*. These kinds of reactions are affected by substrate structure, the nucleophile, temperature, and leaving group *(12)*, so it is possible to make structure—reactivity studies for all of these variants. Including both ortho- and para-substituted anilines in a combinatorial study illustrates the effect of the substituent in a S_NAr reaction. The nature of the solvent also has serious repercussions in a S_NAr reaction; students were

Scheme 1. Nucleophilic Aromatic Substitution between 1-Halo-2,4-dinitrobenzene (**1**) and Substituted Anilines (**2**)
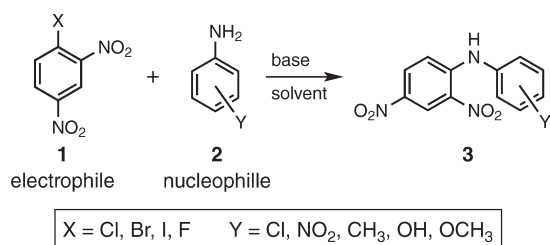
asked to infer conclusions from their results and propose possible explanations after examining literature reports.

With respect to variation of the nature of the halogen in compound **1**, students were asked to predict the yield of aniline substitution of 1-halo-2,4-dinitrobenzene considering the halogen leaving group. Most of the students tend to correlate the reactivity of compound **1** in a S_NAr reaction in the opposite order (I > Br > Cl > F) due to some preceding knowledge of S_N1 and S_N2 reactions; when they perform the reaction, a different trend is found.

Hazards

Wearing gloves, goggles, and a laboratory coat must be mandatory during all of the experimental work. Student must read all MSDS before laboratory session *(13)*. When it is possible, reactions should be carried out in a fume hood. Anilines are considered carcinogens in rats and contact with skin should be avoided and vapor should not be inhaled. Pyridine has a strong unpleasant odor, is highly flammable, and harmful by skin contact. 1-Halo-2,4-dinitrobenzene derivatives are highly toxic and may cause sensitization. Ethanol and methanol are highly flammable. Methanol is toxic by inhalation and skin contact. Acetonitrile and chloroform are toxic. 2-Butanone is a skin and severe eye irritant and can cause CNS depression. Ethyl acetate is skin irritant and its vapors may cause drowsiness.

Results

These series of experiments using aniline substitution of 1-halo-2,4 dinitrobenzene (**1**) through a S_NAr reaction allowed students to obtain data and to draw several conclusions. Parallel synthesis supplied a library of aryl-substituted 2,4-dinitrophenylamines (**3**). The yields were plotted against the pK_a of the different substituted anilines (Figure 1). The ortho- and para-substituted compounds were plotted on separate graphs (Figure 1, panels A and B). The yields from para-substituted anilines produced a good correlation with respect to pK_a: anilines with electron-withdrawing groups gave a lower yield than aniline and anilines with electro-donating groups gave higher yields. However, the yields from ortho-substituted anilines did not display a good relationship due to the ortho effect *(12, 14)*: all compounds gave lower yields than aniline. The ortho effect is affected by steric effects, inductive effects, mesomeric effects, hydrogen bonding, and so forth. Consequently, it was possible to conclude that pK_a alone must not be used as a guide to predict nucleophilicity of a molecule.

The solvent effect was assessed with the yield in each solvent variation and was correlated with the dielectric constant (Figure 2). The graph shows that S_NAr reactions gave better results in polar
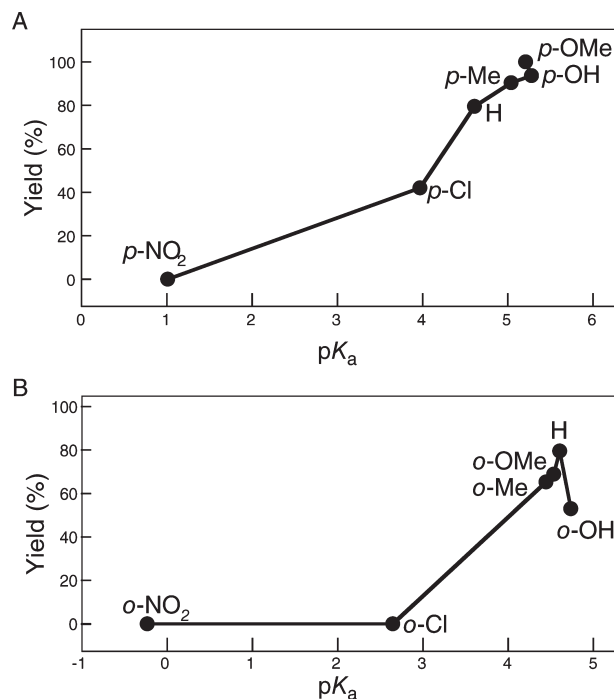

Figure 1. The microscale experimental yield versus the pK_a of the different substituted anilines to form compound **3**: (A) para-substituted anilines and (B) ortho-substituted anilines. The pK_a values were obtained from the Scifinder database under the section of predicted properties.
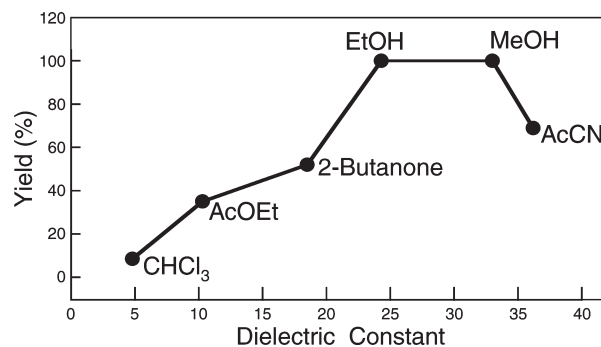

Figure 2. Microscale yield versus the dielectric constant of the solvent demonstrating the solvent effect in a S_NAr reaction between 1-chloro-2,4-dinitrobenzene and aniline.

solvents versus nonpolar solvents. Methanol and ethanol, which conferred better results, are polar protic solvents, and acetonitrile is a polar aprotic solvent. Other studies have shown that the best solvents to carry out this reaction are polar aprotic solvents *(15)*; even so, this unexpected behavior for acetonitrile has previously been reported *(16)*. In this case, students perform an exhaustive bibliographical revision and can suggest other solvents to include in the laboratory session.

The halogen-leaving group in **1** was used as another variation. Students have a propensity to confound the leaving group order in a S_NAr reaction. The trend observed in our results was that reactions gave higher yields following this order: I ≈ Cl < Br ≪ F (Figure 3). This tendency generally seems unusual to students because F is the poorest leaving group among halogens in aliphatic nucleophilic substitutions reactions. Nucleophilic attack
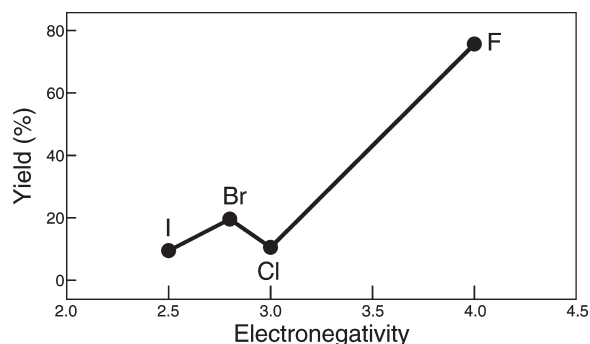
Figure 3. Microscale yield versus the electronegativity of each halogen leaving group on **1** in the S_NAr reaction with 1-halo-2,4-dinitrobenzene and aniline.

on halodinitrobenzenes is the rate-limiting step, and the recovery of aromaticity is achieved when the leaving group is lost. Fluorine gives better yields because it facilitates the rate-limiting step of the reaction.

In all of the variations, experiments were performed at the microscale and semi-microscale. The microscale yield was measured directly, without workup, by GC using an internal standard calibration. The use of the GC equipment was done by a qualified technician, but interested students were motivated to perform the analysis by themselves with proper assistance. The semi-microscale yield was determined by gravimetric analysis after workup of the reaction. The semi-microscale experiments represented a challenge to students because a general protocol to isolate the products was not given. Consequently, on the semi-microscale, there was no relationship between the yield and other properties because of experimental error: principally wet products, products contaminated with starting material, and student error.

Students were assessed by experimental work, a laboratory report, and a seminar. The seminar was the most useful tool in assessing the understanding of the experiment. During the seminar, with help of the professor, students arrived at the correct conclusions from the data. The seminar also allowed students to practice their communicative skills and to present experimental work. In general, graphics were well presented and the literature search was extensive.

The new approach was initially not well liked by the students because it was a drastic change in their routine laboratory work. After the course was over, the students commented that these kinds of experiments illustrate of how science in real life is. An analysis of their own work represents a useful form of self-evaluation; the awareness of their limitations motivated them to do better laboratory work and to generate more accurate results to be used in a collaborative study. At the end of the course, a majority of the students developed critical organic chemistry laboratory techniques and increased their group work skills. Understanding of the experiment was complete and the retention of knowledge was good. The retention was evaluated by asking students randomly during the course, without repercussion in the final grade, about an experiment, which showed us that the concepts were well retained.

Acknowledgment

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Supporting Information Available

Student handout; notes for the instructor. This material is available via the Internet at http://pubs.acs.org.