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Greening the organic chemistry laboratory: a comparison of microwave-assisted and classical nucleophilic aromatic substitution reactions

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ABSTRACT

An experiment is described for the undergraduate organic chemistry lab which compares microwave-induced organic reaction enhancement (MORE) to that of more traditional synthetic procedures. MORE and traditional reflux procedures for substituting thiocyanate, ethylamine and diethylamine nucleophiles for bromide in nucleophilic aromatic substitution reactions on 1-bromo-2,4-dinitrobenzene are given. Recrystallization affords products of sufficient purity for characterization by ^{13}C NMR, mass spectrometry and melting point. As students compare the two synthetic methods, MORE procedures are consistently observed to be quicker, easier, greener and result in higher yields. Student instructions, instructor notes and example NMR and mass spectra obtained by students are provided in Supplemental material.

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The UN World Decade of an Education for Sustainable Development ended in 2014, and in that time, a curricular revolution has been realized where green chemistry content has become imbedded into undergraduate chemistry (1–16). Future chemists will decide whether chemistry will develop with sustainability as part of the focus, but only if they have a strong foundation on sustainability issues and the meaning of making green chemistry development decisions. The third annual American Chemical Society Green Chemistry Summer School participants noted that incorporation of a general knowledge of green chemistry should begin at the undergraduate level and continue through graduate course work (4). These curricular developments are greatly facilitated by the fact that contemporary laboratory students have come to expect to be educated in an environmentally sustainable fashion (17). Furthermore, it has been noted that, rather than developing new techniques, achieving greener chemistry in many cases will simply require a redirection of current techniques (18).

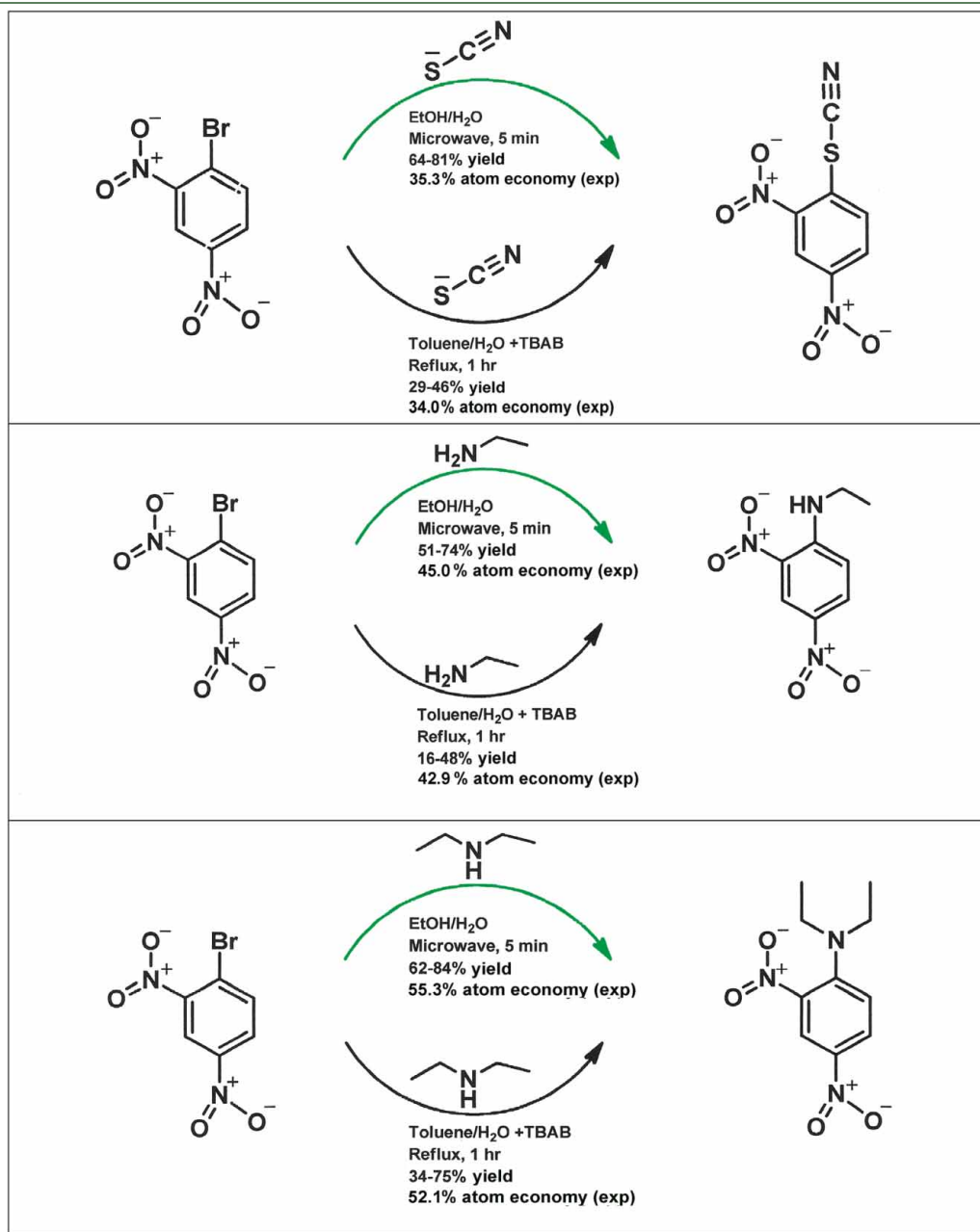
In Haack's editorial in this journal (19), it is noted that laboratory methodology leading to greener results is critical to current educational practice. The present study has thus become a pivotal experiment in our green chemistry initiatives in that it demonstrates to the student a modern technique (microwave heating) that consistently gives greener results (higher yielding, greater atom economy, uses less power and less

organic solvent) when compared to a traditional synthetic technique (reflux). While not an in-depth study of green chemistry metrics such as the excellent paper by Gabriela et al. (20), the results of this quick series of experiments introduces green chemistry to our third-year advanced organic chemistry laboratory that otherwise concentrates on traditional synthetic and characterization techniques. The advantages of using the less hazardous solvent ethanol (microwave) over toluene (reflux) and the decreased time and complexity involved in the microwave synthesis over the reflux synthesis make an excellent demonstration to our students that, perhaps, many traditionally accepted syntheses should be re-examined as new methodology is developed. Furthermore, the present study serves as an excellent introduction to microwave-induced organic reaction enhancement (MORE) which has been shown to be very useful in affecting the pathway of a reaction, the products formed and, especially, reaction times. As such, MORE techniques are appearing more often in the chemical literature (21–38). In one study (39), the authors report that the time and yield of their own previously developed synthesis of 2-chloromethylbenzothiazole from ortho-aminothiophenol and polyphosphoric acid, which gives a reasonable yield of 62% after 8 h of reflux at 180°C, improves to a 90% yield with only 10 min of microwave irradiation. Thus, for select reactions, higher yields, faster reaction times, and the ability to minimize the use of hazardous

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Table 1. Nucleophilic aromatic substitution reaction using each of three nucleophiles (thiocyanate, ethylamine and diethylamine) comparing microwave-assisted procedures to traditional reflux heating techniques.

organic solvents has begun to establish microwave-assisted procedures as a leader in green chemistry techniques (40). The present experiment thus provides the impetus for students to research the microwave effect (41) as well as the 12 principles of green chemistry (42). Our students complete this experiment with oral presentations, and in our experience, this often leads to a student discussion of the how many experiments might be modified with sustainability in mind. Furthermore, the present study expands published nucleophilic aromatic substitution procedures (43) to include the synthesis of 2,4-dinitro-*N,N*-diethylaniline as well as provides

detailed work-up and spectroscopic characterization of all of the products in this experiment.

Nucleophilic aromatic substitution reactions offer a useful way to functionalize an aromatic ring. In this experiment, the aromatic ring is activated by the electron withdrawing nitro groups ortho and para to a good leaving group (bromide), rendering the aromatic ring susceptible to substitution by the chosen nucleophile. Table 1 depicts the nucleophilic aromatic substitutions described, the substitution of thiocyanate, ethylamine or diethylamine nucleophiles onto 1-bromo-2,4-dinitrobenzene, which proceed through formation of an

intermediate Meisenheimer complex (44). As summarized in Table 1, each of the three different nucleophilic aromatic substitution reactions routinely proceed faster, use a more environmentally friendly reagent and solvent system, and result in a greater yield and atom economy using microwave techniques when compared to heating by conventional means. The reported results in Table 1 are tabulated based on student data ($n = 26$ students) accumulated over four consecutive semesters of a third-year advanced organic chemistry lab course. A single student can accomplish any pair of reactions, including work-up and characterization, in two three hour lab periods. Besides providing the opportunity for the development of both traditional and microwave synthetic techniques, this experiment also allows for the reinforcement of a mechanism typically covered in the lecture component of a second- and/or third-year organic chemistry course. A simple re-crystallization from ethanol affords products of sufficient purity for structural determination by spectroscopic means (^{13}C NMR and mass spectrometry).

Experiment

Working individually, each student is assigned a particular nucleophile (either ethylamine, diethylamine or potassium thiocyanate) and completes both the microwave (using the CEM Discover SP microwave reactor) and traditional syntheses as outlined in Table 1. In both cases the crude product is recrystallized from ethanol. Both reactions can be routinely completed in two lab periods; in week one, the student completes the syntheses and subsequent purifications. Characterization by ^{13}C NMR, mass spectrometry and melting point is accomplished in the second week. The entire procedure, detailed instructors notes and example student spectra are given in Supplemental material.

Results and discussion

Product yields for each nucleophile are displayed in Table 1, with reaction times of 5 min leading to yields of 51–84% for the microwave-assisted reactions compared to 16–75% yield for reactions conducted under traditional reflux for one hour. Students are directed to research the 12 principles of green chemistry, with many metrics being discussed, but the majority of students revealing the greater atom economies, higher yields and less hazardous solvents associated with the microwave-assisted synthesis. In their discussions, a number of students speculate on other ways to improve on green metrics such as atom economy and E-factor. Class presentations of results confirm that the microwave-assisted procedures generally

allow for simpler, faster, greener and better yielding reactions. Removal of toluene solvent was noted as a complication in some of the traditional syntheses, perhaps being a primary factor resulting in lower yields and a longer product work-up.

For characterization of products, students will select a method(s) of characterization based on their existing knowledge, the nature of their reactions and the available instrumentation. ^{13}C NMR, mass spectrometry and melting point are examples of techniques that can be used. For example, substitution of the thiocyanate nucleophile for the bromine leaving group can be verified by the appearance of a peak in the sp-hybridized region of the ^{13}C NMR spectrum (Figure A-1 to Figure B-1 in Supplemental material) coupled with an appropriate mass spectrum from GC-MS analysis. Likewise, melting points of all products can be easily compared to literature values.

Conclusion

An experiment comparing microwave-assisted and classical nucleophilic aromatic substitution reactions has been developed for a senior organic chemistry lab. Students can complete this experiment in two lab periods, revealing that the use of microwave-assisted techniques results in safer, faster and greener reaction conditions with significantly higher product yields.

Supplemental data and research materials

A student handout, instructor notes, a list of experimental hazards and a full list of equipment and chemicals required, melting points as well as example student spectra (MS, ^{13}C NMR) can be seen in the Supplemental material for this manuscript. This is available on the Taylor & Francis website, doi: 10.1080/17518253.2015.1065010

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Disclosure statement

No potential conflict of interest was reported by the authors.

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