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The Preparation of *meso*-Stilbene Dibromide: Scaffolding Green Chemistry Principles via an Electrophilic Addition Reaction

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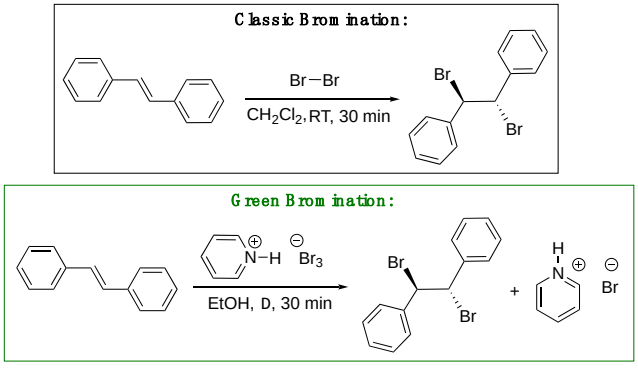
Abstract To better understand how green chemistry principles may be applied to a simple electrophilic addition reaction, students in the Green and Sustainable Chemistry course (CHEM 4000) at Georgia Gwinnett College were introduced to the bromination of *E*-stilbene in a scaffolded approach which culminated with the conduct of an experimental comparison of the classic bromination of *E*-stilbene using Br_2 in CH_2Cl_2 and the green bromination of *E*-stilbene using pyridinium tribromide in ethanol. Student teams isolated the target *meso*-stilbene dibromide product and compared the processes using the green reaction metrics of percent yield (PY), atom economy (AE), waste metric (E-factor), process mass intensity (PMI), solvent suitability (K_{ow}, log K_{ow}) and hazard classes of reactants, products and by-products. The classic bromination was determined overall to be a more efficacious reaction than the green bromination based on the PY, AE, E-factor, and PMI. On the basis of K_{ow}, log K_{ow} and the hazard classes of reactants, products and by-products, the green bromination was determined to be less hazardous than the classic bromination.

Keywords Atom economy, Waste metric, Process mass intensity, K_{ow}, *E*-stilbene, *Meso*-stilbene dibromide

1. Introduction

As part of a continuing initiative to incorporate green chemistry principles throughout the chemistry curriculum, faculty in the Department of Chemistry at Georgia Gwinnett College (GGC) developed the Green and Sustainable Chemistry course [1]. The American Chemical Society (ACS) guidelines for ACS certified chemistry programs lists green chemistry and sustainability as critical requirements for accreditation. [2] Progress in implementation of green chemistry in undergraduate chemistry curricula over the last two decades has helped enhance laboratory safety, drive facility improvements and enable faculty to infuse courses with environmentally responsible reaction alternatives. [3,4] The overarching goals of the course were to (1) expose students to the twelve Green Chemistry Principles, (2) develop student skills in the use green chemistry metrics to analyze chemical processes for their sustainability, and (3) apply these metrics to case studies in which green chemical synthesis methods and sustainable processes have been successfully employed.

As part of the course design, the instructors selected Etzkorn's text [5], which provides case studies to illustrate each of the twelve green chemistry principles. Based on the high impact practice of scaffolding on learning in chemistry [6,7], instructors then incorporated a well-known addition reaction, the bromination of 1,1'-[(E)-1,2-Ethenediyl] dibenzene, commonly known as *E*-stilbene, to scaffold throughout the course lessons in order to illustrate how green chemistry principles and specific green reaction metrics may be applied to achieve a more benign process. See Scheme 1.



Scheme 1. Classic and Green *Meso*-Stilbene Dibromide Syntheses

The green bromination shown in Scheme 1 was selected because (1) the brominating agent, pyridinium tribromide,

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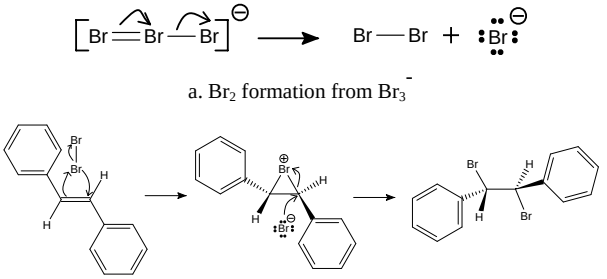
was a shelf-stable solid which students could easily handle without undue the undue hazards associated with handling liquid bromine or other in-situ bromine generating reagents [8], (2) the ethanol solvent is less toxic than methylene chloride, and (3) previous studies indicated that this green bromination gave yields in excess of 60%. [9]

The mechanism for the bromination of *E*-stilbene is shown in Figure 1. The Br_3^- component of the pyridinium tribromide brominating reagent dissociates giving Br_2 and Br^- (Figure 1a). As diatomic bromine is formed, the *E*-stilbene attacks the bromine to give a bromonium ion intermediate. The bromonium ring may be attacked by the bromide anion at either carbon in a stereospecific fashion to give the optically inactive [(1R,2S)-1,2-Dibromo-2-phenylethyl]benzene, commonly known as *meso*-stilbene dibromide (Figure 1b).



a. Br_2 formation from Br_3^-

b. *meso*-stilbene dibromide formation

Figure 1. *E*-Stilbene Bromination Mechanism

Table 1. Green & Sustainable Chemistry Course Outcomes

1. Apply knowledge of chemistry to green and sustainable chemistry:
• Describe and apply the 12 principles of green chemistry.
• Describe frameworks for incorporating chemical toxicity and human health considerations into product design, material selection, and supply-chain decision-making.
• Explain the environmental, economic, and societal benefits of green chemistry, sustainability, and systems thinking.
2. Demonstrate knowledge of literature applicable to the special topic and:
• Describe the latest research and regulatory developments in the field.
• Apply concepts of sustainable development to address sustainability challenges, including but not limited to barriers to implement sustainable practices, in a global context.
• Describe frameworks for incorporating chemical toxicity and human health considerations into product design, material selection, and supply-chain decision-making.
3. Demonstrate proficiency in solving chemical problems related to the special topic.
• Apply concepts of sustainable development to address sustainability challenges, including but not limited to barriers to implement sustainable practices, in a global context.
• Identify, act on, and evaluate professional and personal actions using knowledge of and appreciation for interconnections among economic, environmental and social perspectives.

One of the challenges students face in chemistry courses is understanding how to devise "green" synthesis strategies for organic molecules, both as a matter of theory in the class and as a practical application in the laboratory [10]. The preparation of *meso*-stilbene dibromide was chosen as a vehicle to improve student mastery of green synthesis principles because (1) of the ease of synthesis (single step) from simple starting materials, (2) it provided a "hook" to grab the interest of students since many have learned of alkene brominations, which are covered during the Organic Chemistry I course [11] and (3) the green brominating reagent, pyridinium tribromide, and the ethanol solvent are less toxic than the liquid bromine reagent and methylene chloride solvent used in classic brominations. [8,9]

Another factor considered during the development of this scaffolded lecture to laboratory experience was the fact that the green bromination shown in Scheme 1 was included in GGC's no-cost Undergraduate Organic Chemistry I & II Laboratory Manual [12]. Thus, students taking CHEM 4000 had previous experience with this reaction.

The student activities selected for this laboratory experience reflect the linkage with topics covered in the classroom, their practical application by experimentation and the achievement of the relevant Course Outcomes (COs) shown in Table 1 [1].

Student green bromination scaffolding activities included:

- Lesson 2 (Synthetic Efficiency): [CO #1] Students were introduced to the four major reaction types and using the bromination of *E*-stilbene as an example of addition reactions, students identified the reactants, solvents, products and by-products; given a mass of *E*-stilbene and a hypothetical yield of meso-stilbene dibromide, students then calculated theoretical yield (TY), percent yield (PY), atom economy (AE), waste (E-factor) and process mass intensity (PMI). See equations 1 - 4. Students also reviewed the retrosynthesis of the meso-stilbene dibromide product back to the starting material.

$$PY = \frac{actual\ \ mass\ (g) of\ product\ (s)}{theoretical\ \ mass\ of\ product\ (s)} * 100\% \quad (1)$$

$$AE = \frac{mass\ of\ desired\ \ product\ (s)}{\Sigma masses\ \ of\ \ all\ \ reactants} * 100\% \quad (2)$$

$$E = \frac{mass\ \ inputs - mass\ \ product\ (s)}{mass\ \ product\ (s)} \quad (3)$$

$$PMI = \frac{mass\ \ inputs}{mass\ \ product\ (s)} \quad (4)$$

- Lesson 7 (Energy Efficiency): [CO #2] Given a Hypothetical room temperature bromination of *E*-stilbene, students were asked to calculate the energy of the bromination reaction using $q = mc\Delta T$.
- Lesson 11 (Design for Degradation): [COs #2 & 3] Students were asked to consider the green and the classic brominations, determine the reaction waste products generated and discuss the waste streams for the two processes.
- Lesson 12 (Avoid Auxiliaries): [COs #1 & #2] As part of this lesson, approximately 1.5 hours were dedicated to the teams setting up the reactions, performing the brominations, isolating and characterizing the meso-stilbene dibromide product, completing the experimental worksheet [13] and discussion of the results.

2. Materials and Instrumentation

2.1. Materials

a. Experimental Instructions (adapted from the on-line Laboratory Text – Chemistry 2211K/2212K).
b. *E*-stilbene, bromine, pyridinium tribromide, methylene chloride and ethanol were purchased from Fisher Scientific Chemical company and were used as purchased.

2.2. Instrumentation

a. Melting points were obtained on an SRS Digimelt MPA160 melting point apparatus and were uncorrected.
b. IR Spectra were collected on a Thermo Scientific Nicolet iS5 FTIR (600-4000 cm^{-1} range).

3. Experimental

Students selected their lab team members. One team opted to perform the green bromination while the other team chose the classic bromination.

3.1. Green Bromination of *E*-Stilbene

Chemicals used: E-Stilbene (Fisher Scientific, CAS 103-30-0), pyridinium tribromide (Fisher Scientific, CAS 39416-48-3), 96% ethanol (Fisher Scientific, CAS 64-17-5). All chemicals were used as purchased.

Equipment used: stir/hotplate, sand bath, 10 mL round bottom flask, condenser, magnetic stir bar.

Safety notes:

a. Reaction must be carried out under the benchtop snorkel hoodlet.
b. Students must use gloves and safety goggles while carrying out the experiment.

For mole table: Use a 1:1.67 molar ratio of *E*-Stilbene: pyridinium tribromide. [12] This molar ratio was selected to ensure that a slight excess of the brominating agent was present during the reaction. *E*-Stilbene: brominating agent ratios for this reaction as high as 1:1.90 have been reported. [8]

Procedure: A 10 mL round bottom flask equipped with a stir bar was charged with 6.0 mL ethanol and *E*-Stilbene (0.205g, 1.14 mmol) and placed in the sand bath. The solution was stirred to ensure dissolution and warmed to 50℃. Then, pyridinium tribromide (0.350 g, 1.90 mmol) was added to the warm, stirring solution in small portions over a five-minute period. A condenser was affixed to the flask and the mixture stirred for 30 min.

After 30 minutes, the solution was allowed to cool to room temperature, and then placed in an ice bath to maximize crystal formation. The white crystalline product was isolated using vacuum filtration and the crystals washed with 3 x 5 mL aliquots of cold ethanol. The crystals were then dried using a Fries lamp and the percent yield and m.p. of the meso-stilbene dibromide were determined. Yield: 0.148 g (38%); melting range 239-242℃, lit. [14], m.p. 237℃. IR (cm^{-1}): 3029 (Ar-H), 3021 (Ar-H), 1497(Ar C=C), 1454 (Ar C=C), 690 (C-Br). [15]

3.2. Classic Bromination of *E*-Stilbene

Chemicals used: E-Stilbene (Fisher Scientific, CAS 103-30-0), freshly prepared 1.0 *M* solution Br_2 in CH_2Cl_2, (Br_2, 99.5%, obtained from Thermo Scientific, CAS 7726-95-6), CH_2Cl_2, (HPLC grade, Fisher Scientific, CAS 75-09-02).

Equipment used: stirplate, 10 mL round bottom flask, magnetic stir bar.

Safety notes:

a. Reaction must be carried out under the benchtop snorkel hoodlet.
b. CH_2Cl_2 is a carcinogen, students must use gloves and safety goggles while carrying out the experiment.
c. The Br_2/CH_2Cl_2 solution is hazardous; students must use caution when handling.

For mole table: Use a 1:1.5 molar ratio of *E*-Stilbene: Bromine.

Procedure: A 10 mL round bottom flask equipped with a stir bar was charged with *E*-Stilbene (0.200 g, 1.11 mmol) and 5.0 mL of dichloromethane (DCM). The mixture was stirred to ensure dissolution. Using a disposable pipette, 1 *M* bromine solution (1.65 mL, 1.65 mmol) (in DCM) was added slowly over a period of two minutes to the reaction mixture. The reaction mixture was then stirred at room temperature for 30 minutes. Upon completion, the reaction flask was chilled in an ice bath for 10 minutes. The white crystalline product was isolated via vacuum filtration. The product was washed with 3 x 5 mL portions cold water to remove any color from the crystalline material. The crystals were then dried using a Fries lamp and the percent yield and m.p. of the *meso*-stilbene dibromide were determined. Yield: 0.189 g (50%); melting range 238-241℃, lit. [14] m.p. 237℃. IR (cm^{-1}): 3030 (Ar-H), 3023 (Ar-H), 1496 (Ar C=C), 1451 (Ar C=C), 688 (C-Br). [15]

3.3. Post Experimental Activities – Worksheet Completion and Discussion

Instructors encouraged teams to work throughout the experimental process on the worksheet as the synthesis was underway. Following isolation of the product and cleanup, the student teams completed the worksheet, which is available as supplemental material [13]. Each team determined several metrics for their reaction which illustrated the "greenness" of the processes. The metrics included PY, AE, E-factor, PMI, K_{ow}, log K_{ow} and Toxicity ratings for the reactants, solvents, products and by-products. The results are found in Table 2. The worksheets were collected by the instructors for assessment as a lesson quiz.

The instructors and students then discussed the results. For PY and AE, values approaching 100% are desired. It was clear that the green bromination had lower PY and AE values than the classic bromination. Students were asked what factors might have led to the differences. One reason proposed was that the pyridinium tribromide was not as

effective as a brominating agent as Br_2. Another reason suggested was that the polarity of the ethanol solvent might somehow slow the reaction. Finally, it was noted that the reaction time was limited to 30 minutes, which is shorter than similar bromination reactions reported in the literature. [9] Students were then asked how the reaction conditions might be modified to improve the PY and AE, to which they responded that raising the reaction temperature and/or extending the reaction time might improve both the PY and the AE for both reactions. In addition, since the product is somewhat soluble in ethanol, reducing the volume of cold ethanol used when washing the product could improve the actual yield as well. [9,16]

Table 2. Green Metrics

Metric	Green Bromination	Classic Bromination
PY	38%	50%
AE	27%	41%
E	2.75	1.46
PMI	3.75	2.46
K_{OW}	0.49 (ethanol)	17.8 (CH_2Cl_2)
Log K_{OW}	-0.31 (ethanol)	1.25 (CH_2Cl_2)
Toxicity[a]	**Ethanol** – Cat 2/2A (flammable/irritant) **Pyridinium tribromide** – Cat 1/1B (corrosive/eye damage) **Pyridinium bromide** – Cat 1/1B (corrosive/eye damage)	**CH_2Cl_2** – Cat 2/2A (carcinogen/irritant) **Bromine** – Cat 1/1A (acute inhalation hazard/eye & skin damage)
	Stilbene – Cat 2/2A (eye irritant/aquatic hazard) **meso-Stilbene Dibromide** – Cat 1/1B (eye damage/skin corrosive)	

[a]Obtained from safety data sheets (SDS).

The E-factor and PMI metrics were likewise discussed, where values close to 1.00 are desired. For the green bromination, an E-factor value of 2.75, whereas for the classic bromination a value of 1.46 indicate that the classic reaction had a lower overall waste impact. This was expected since the green bromination product yield was lower. Similarly, the PMI values for the green and classic brominations were 3.75 and 2.46, respectively, again indicating that the green bromination's lower yield contributed to the higher PMI value. [9,16]

The solvent characteristics as well as reactant, product and by-product toxicities were discussed. The metric K_{OW} (*n*-octanol/water partition coefficient) and log K_{OW} for ethanol and dichloromethane were compared to assess the hydrophilic/hydrophobic nature of the solvents. Since small values of K_{OW} (negative values for log K_{OW}) indicate hydrophilic tendencies, the ethanol (log K_{OW} = - 0.31) is more hydrophilic than dichoromethane and would not be prone to large bioconcentration in aquatic life. Dichloromethane (log K_{OW} = 1.25), on the other hand, is more hydrophobic and would be more likely absorbed through the skin, posing a greater contact hazard. It is also a carcinogen. Thus, even though the hazard class for both solvents is 1/1A, ethanol can be viewed as a more environmentally friendly solvent.

With respect to the brominating agents, pyridinium tribromide (hazard class 1/1B) is classified as a corrosive and can cause damage to the eyes, while the more dangerous reagent Br_2 (hazard class 1/1A) is designated as an acute inhalation hazard and can cause eye and skin damage upon contact. The by-product of the green bromination, pyridinium bromide (hazard class 1/1B) is classified as a corrosive and can cause damage the eyes upon contact.

E-stilbene (hazard class 2/2A) is an eye irritant and aquatic hazard while the more toxic *meso*-stilbene dibromide (hazard class 1/1B) can cause eye damage and is corrosive to the skin.

4. Laboratory Experience Impact on Student Understanding of Green Chemistry Principles

Following the laboratory exercise, students were asked to reflect on whether they viewed the experiment as a valuable part of the course. Students unanimously responded that they enjoyed the hands-on, real-world application of green chemistry principles. When asked if they would like to have additional experiments incorporated into the course, they indicated that they would. In the end of course survey, students gave similar positive responses to the bromination reaction scaffolding approach.

5. Conclusions

This marks the first year that the Green and Sustainable Chemistry course was offered at GGC. The scaffolding of green and classic electrophilic *E*-stilbene bromination reactions throughout the course provided students with a means to utilize green chemistry principles and parameters to compare simple reactions. Course outcome assessment data suggests that students applied green chemistry metrics successfully as part of a live laboratory in which they compared two types of brominations. Overall, student surveys show that the use of the bromination scaffold was as a vehicle for learning how green chemistry principles may be applied to make reactions more environmentally responsible.

ACKNOWLEDGEMENTS

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