Optimizing a Lab-Friendly Radical Bromination Reaction

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Abstract

Bromination reactions are an important type of reaction in Organic Chemistry (CHEM301 and CHEM302), with a wide range of industrial applications. Several different types of bromination reactions exist, and a wide variety are used in chemistry education. At Liberty University, they are the first organic reactions discussed in the first semester of Organic Chemistry. Therefore, the laboratory component of the topic should be easy to perform and understand for the students. Currently, the laboratory experiment consists of a radical bromination of a cinnamic acid derivative (Scheme 1). NBS is the brominating agent; it is preferrable to bromine, which is highly volatile and acutely toxic. AIBN acts as a radical initiator. The process is simple: the reagents are weighed out, added to a flask, and stirred and heated in a non-halogenated solvent for forty-five minutes. The product is then precipitated in ice-cold water and isolated by vacuum filtration. The entire experiment can be completed in a three hour lab period. A similar reaction can be found in literature, which uses carbon tetrachloride as a solvent, but produces similar yields.[2] However, the final product is an uninteresting white powder almost identical to the starting material, and a decarboxylation side-reaction reduces yields unnecessarily. The purpose of the present research is to find a compound that can be brominated under the same conditions with less side-products and results in a more visibly distinct product. To find a suitable compound, numerous bromination reactions will be performed under the same constraints and conditions of the existing lab to determine which produces the product and procedure most suited for illustrating the topic to students. One reaction that has been tested is an electrophilic substitution reaction in methanol inspired by a patent.[1]

Methods

1. Literature Review

A search in the Journal of Chemical Education was performed in September 2023 with the keyword "N-bromosuccinimide".

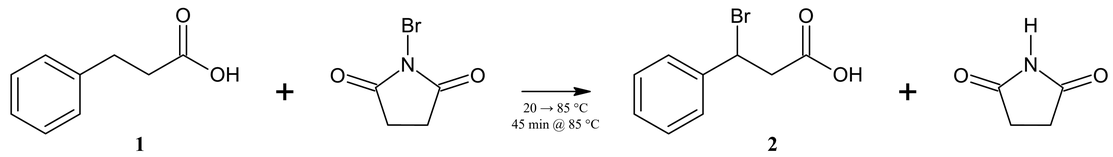
2. Laboratory Experiments

We started by substituting new compounds into the normal lab procedure. These substitutions often ran into various problems, especially during the work-up, so we made various tweaks to the procedure, such as varying the precipitation solvent. We experimented with an electrophilic substitution reaction as found in a patent (Scheme 2).[1] We explored work-up methodology, solvents and procedures for isolating and purifying the final product. We use NBS over bromine as it is safer.

Research Question

What is the best bromination reaction and procedure to fit these critera?

- Introduces chemical reactions in lab.
- Demonstrates chemical change through visible change from substrate to product.
- Able to be completed in a 3-hour lab period.
- Is economic and green.
- Has good yields and few side-products.
- Produces a product that can undergo elimination to produce another color change.



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Scheme 1. Radical Bromination of Hydrocinnamic Acid

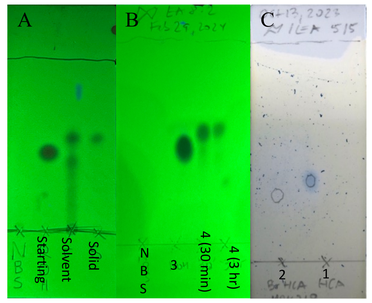


Figure 1. TLC Plates

A. Bromination of compound 3, first trial
B. Bromination of compound 3, second trial
C. Radical bromination of hydrocinnamic acid; CAM stained.

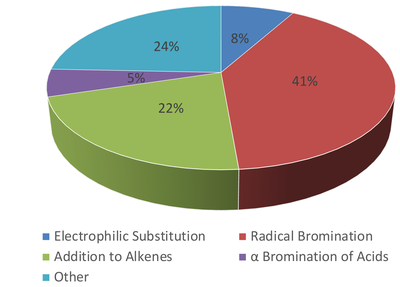


Figure 2. Bromination Reactions in the Journal of Chemical Education

The ratio of bromination reaction types in the Journal of Chemical Education (queried September 2023)

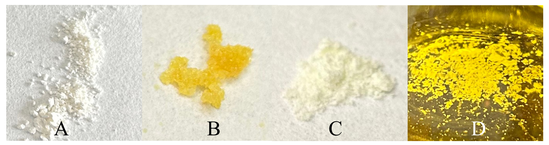


Figure 3. Bromination Products

A. Brominated hydrocinnamic acid
B. Orange crystals from the bromination of a phenol derivative.
C. Product of bromination by electrophilic substitution.
D. Brominated crystals forming in a yellow solution.

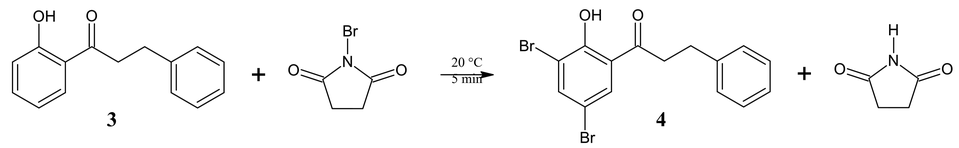
Reaction	Solvent	Reagents	Conditions	Time	Reference
Liberty University	Non-halogenated solvent	NBS, AIBN	20 °C → 85 °C	45 minutes	[3]
McGarvey & Knipe	CH_2Cl_2	NBS	N_2 atmosphere; 100W tungsten lamp	1 hour	[2]
Patent	CH_3OH	24 eq NBS	0 °C → 20 °C	24 hours	[1]

Table 1. Comparison of Lab Reactions

compound	acute toxicity	skin corrosion/ irritation	eye damage/ irritation	acute aquatic hazard	TWA[(a)]
bromine	category 1	category 1	category 1	category 1	0.1 ppm
NBS	mutagenic (germ cells)	category 2	category 2	category 1	no exposure limits

Table 2. Bromine vs. NBS Safety Data[3]

Bromine (Br_2) is an excellent source of bromine for a variety of bromination reactions. However, it is toxic, volatile, difficult to clean up, and generally unsuitable for beginner students. NBS (N-bromosuccinimide) is still a good source of bromine for brominations, but is less toxic and easier to work with.



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Scheme 2. Electrophilic Substitution Bromination of a Phenol Derivative[1]

Results

1. Literature Review of Bromination Reactions in Chemistry Education

Bromination reactions of any kind were found in the Journal of Chemistry Education. Of 37 reactions, 15 were radical brominations, 3 were electrophilic substitutions, 8 were additions to alkenes, 2 were α-brominations of carboxylic acids, and 9 were miscellaneous.

2. Exploration of New Substrates and Reaction Conditions

The present reaction used at Liberty University is a radical bromination of hydrocinnamic acid with NBS (Scheme 1). A similar procedure found in the Journal of Chemical Education, in which the same compound is brominated in carbon tetrachloride under a nitrogen atmosphere while being irradiated with a tungsten lamp; the yield was 75%. Our reaction uses a non-halogenated solvent, AIBN as a radical initiator, and heat, and results in a similar yield (74%).

A new phenol derivative is being tested as a substrate. One procedure we tried (Scheme 2) was adapted from a patent.[1] In this procedure, the substrate and 24 equivalents of NBS are stirred in methanol for 24 hours while ambiently heating from 0 °C to room temperature. In our procedure we used a smaller amount of NBS and shorter reaction times to obtain a product which is presently being analyzed (Fig. 2).

Future Work

1. Optimize reagent quantities and conditions to ensure an economic and time-efficient laboratory process.
2. Explore more options for work-up solvents and methods.
3. Explore elimination reactions for brominated products.

References

[1] Allen, et al. Preparation of 2-Arylindole- or -Benzimidazolecarboxamidines and Analogs as Serine Protease Inhibitors. International Patent WO 00/35886. 17 Dec. 1999.

[2] McGarvey, J. E. B.; Knipe, A. C. An introductory level kinetics investigation. *J. Chem. Ed.* **1980**, *57 (2)*, 155.

[3] *Organic Chemistry 1 Laboratory,* 7th ed.; Korn, M.; Academx Publishing Services: Port Charlotte, FL.