

# Microscale Synthesis of 1-Bromo-3-chloro-5-iodobenzene: An Improved Deamination of 4-Bromo-2-chloro-6-iodoaniline

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The multistep synthesis of 1-bromo-3-chloro-5-iodobenzene has appeared both in this *Journal* (1) and in laboratory texts (2–3). The final step in the synthesis is the reductive deamination of 4-bromo-2-chloro-6-iodoaniline using a standard diazonium route, in which the final product is isolated by steam distillation. Not only does this require the use of gram quantities of 4-bromo-2-chloro-6-iodoaniline, but also the product, 1-bromo-3-chloro-5-iodobenzene, “has a tendency to solidify in the condenser” (3).

In an effort to eliminate the lengthy and often inefficient product isolation procedure, we sought to identify an alternative deamination method. Alkyl nitrites in *N,N*-dimethylformamide can be utilized for the reductive deamination of haloanilines (4). In this article, we report that this reaction can be performed successfully in an undergraduate laboratory using microscale techniques. The reaction time has been significantly decreased and the production isolation uses simple extraction techniques. Additionally, the scale of the experiment has been reduced to require less starting material (0.25 g).

The procedure provided utilizes commercially available isoamyl nitrite (Figure 1). Other alkyl nitrites will also work in this procedure. For example, we have obtained excellent results using *t*-butyl nitrite (85–90%), synthesized according to a published procedure (5).

## Microscale Procedure

Under a fume hood, 1.65 mL of a 0.75 M isoamyl nitrite/DMF solution<sup>1</sup> is added to a 10-mL round-bottomed flask containing a magnetic spin vane. A reflux condenser is placed on the flask and the flask is clamped in a sand bath heated to 65 °C. With the isoamyl nitrite solution stirring rapidly, a solution of 4-bromo-2-chloro-6-iodoaniline (0.25 g, 0.75 mmol) dissolved in a minimal amount of DMF (2

mL) is added dropwise to the reaction solution over a period of 5 min.<sup>2</sup> The evolution of nitrogen gas is immediate and continues until all of the aniline solution is added.<sup>3</sup> After the gas evolution is complete (~15 min), the reaction mixture is allowed to cool to room temperature and then carefully transferred to a 25-mL Erlenmeyer flask. Fifteen mL of 20% aqueous hydrochloric acid solution is added to the reaction mixture and the product is extracted from the reaction mixture into two, 10-mL portions of ether. The combined organic extract is washed with 15 mL of 10% aqueous hydrochloric acid solution, dried over anhydrous magnesium sulfate, filtered, and concentrated to yield the product as a pale copper-colored solid.<sup>4</sup> The crude product is recrystallized from methanol, using a ratio of 6 mL of methanol per gram of product, to give 1-bromo-3-chloro-5-iodobenzene as long, colorless needles (75–80%, m.p. 85–86 °C).

## Safety

Wear eye protection at all times in the laboratory. Work in a hood or in a well-ventilated area. Care must be used in handling the alkyl nitrite; inhalation of the vapor may cause severe headache and heart excitation. *N,N*-dimethylformamide is flammable and absorbed through the skin. Diethyl ether is flammable. Hydrochloric acid solutions are corrosive and toxic and can cause burns if they come in contact with your skin. Wash affected areas with copious quantities of water.

## Results and Discussions

We incorporate this experiment into our curriculum at the end of the second semester of organic chemistry laboratory as a part of a multistep synthesis (Figure 2). Our focus in the teaching laboratories is to allow students to learn chemistry by doing experiments similar to those done by practicing chemists. By including a multistep synthesis at the end of the course, students apply a variety of skills and techniques learned during the two-semester laboratory course. They are also able to see firsthand the importance of synthetic design, the importance of high yields and product purity at each step, and the dependence of the overall product yield and quality on the individual transformations. This reaction sequence provides an excellent review of the concept of group effects in electrophilic aromatic substitution reactions. In particular, it demonstrates the use of activating and deactivating groups and the use of a “traceless” directing group.

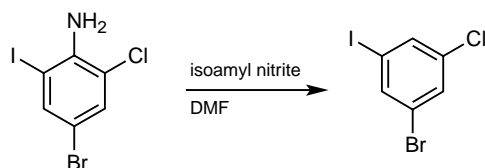


Figure 1. Reductive deamination step—the final step.

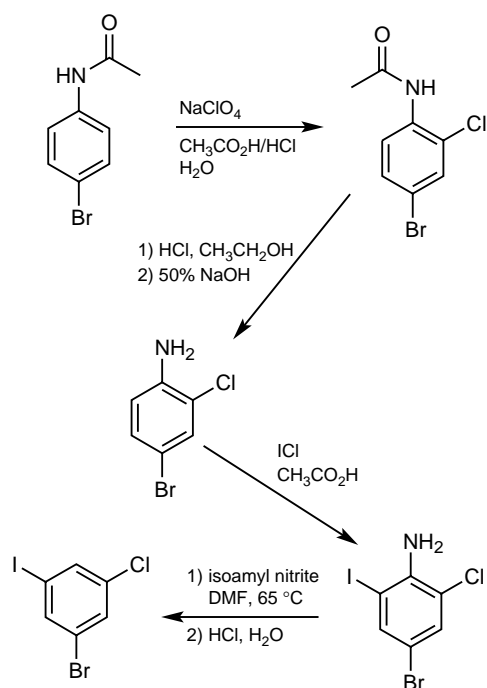


Figure 2. All steps in a multistep organic synthesis.

Most students successfully complete the entire synthetic sequence. Product yields from each of the first three steps are generally good (75–95%) providing more than enough 4-bromo-2-chloro-6-iodoaniline for the deamination reaction, the final step. In general, product yields in the final step average greater than 75%. Overall, the deamination reaction reported here has several advantages over the published methods: it requires less starting material, is operationally simpler, and gives higher yields of 1-bromo-3-chloro-5-iodobenzene.

Our students like these experiments. They work independently and enjoy putting into practice techniques learned throughout the term. At the end of the sequence, they feel that this experience gives them more insight into the profession.

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### Supplemental Material

A microscale procedure for use with standard taper glassware (0.5 g), spectral data, CAS Registry Numbers, and additional instructions for instructors are available in this issue of *JCE Online*.

### Notes

1. A stock solution, based on 10 students, of 1.5 mL (11.5 mmol) of isoamyl nitrite and 15 mL of *N,N*-dimethylformamide (DMF) is prepared by the instructor immediately prior to the laboratory period. The stock solution can be stored under nitrogen in the refrigerator for up to a week. All DMF used in the reaction should be dried prior to use (6). Our method is to allow the DMF to stand over barium oxide, followed by decantation, and distillation under reduced pressure. Dried DMF can be stored over active molecular sieves prior to use.

2. Use a 9-in. Pasteur pipet to add the solution through the top of the condenser.

3. Although nitrogen evolution is not measured quantitatively, bubbles were clearly visible in the reaction mixture.

4. Students should be directed to perform this step in the standard manner used in your laboratory. We place the dried solution in a stoppered 25-mL filter flask and connect the side arm to a vacuum source. The flask is then placed in a warm (40 °C) sand bath until the solvent is removed.

### Literature Cited

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