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Communication

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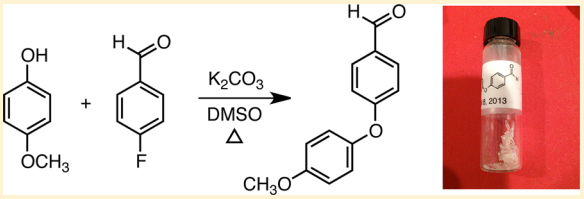
One Step Preparation of a Crystalline Product by Nucleophilic Aromatic Substitution

Douglass F. Taber* and Samantha J. Brannick

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, United States

Supporting Information

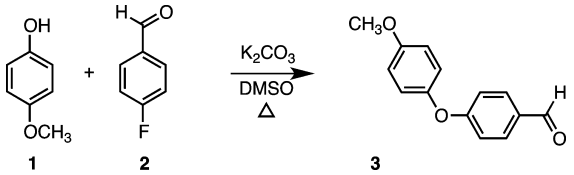
ABSTRACT: Nucleophilic addition of 4-methoxyphenol to 4-fluorobenzaldehyde leads to crystalline 4-aryloxybenzaldehyde. This preparation can be carried out in a single laboratory period with an overnight (or longer) crystallization.



KEYWORDS: *Second-Year Undergraduate, Organic Chemistry, Laboratory Instruction, Addition Reactions, Aldehydes/Ketones, Aromatic Compounds, Crystals/Crystallography, Phenols, Synthesis, Mechanisms of Reactions*

Nucleophilic aromatic substitution is commonly taught in the second semester of a second-year undergraduate organic chemistry course. Although this reaction has been discussed before in this journal,[1] and several laboratory experiments have been developed,[2] none of these have met the criteria of a simple coupling that can be carried out in a single step to generate a crystalline product. A literature search uncovered the displacement illustrated in Scheme 1.[3] This preparation can easily be accomplished in a 3 h laboratory period with consistently good student results. Three different lab sections with a total of ∼25 students have successfully carried out this synthesis.

Scheme 1. Preparation of the 4-Aryloxybenzaldehyde



EXPERIMENT

Students work individually. They mix 4-fluorobenzaldehyde (**2**) (2.0 mmol), 4-methoxyphenol (**1**) (2.0 mmol), and potassium carbonate (excess) in a test tube (12 mL), add dimethyl sulfoxide (2 mL), and heat the mixture in a bath at 140 °C bath for at least 30 min. After cooling in an ice-water bath (minimum of 10 min), water (6 mL) is added, and the mixture is thoroughly stirred. The precipitated light brown solid is dried on filter paper following removal of the liquid layer. Students record the weight, percent yield, and melting point range of the crude 4-aryloxybenzaldehyde (**3**).

Students suspend the light brown solid in heptanes (1 mL) in a test tube (12 mL) and add dichloromethane (2 mL) to dissolve. The solvent is allowed to evaporate in a fume hood (overnight or longer). Crystals slowly form and grow, beautifully coating the sides of the test tube. The impurities end up in the bottom of the test tube. The crystals are washed quickly with 95% ethanol and spread on a piece of filter paper to dry. Students record the weight, percent yield, and melting point range of the purified 4-aryloxybenzaldehyde (**3**).

HAZARDS

Chemicals required are dichloromethane, heptane, 4-methoxyphenol, potassium carbonate, 4-fluorobenzaldehyde, and dimethyl sulfoxide. Dichloromethane, heptane, 4-fluorobenzaldehyde, and 4-methoxyphenol are irritants, as is product **3**. When dealing with any of the solvents or reagents in this laboratory exercise, standard safety precautions apply. Solvents should be handled in a fume hood. Wear protective gloves and proper protective clothing. Avoid direct ingestion or inhalation of any solvents or reagents. Note that dimethyl sulfoxide is readily taken up through the skin and penetrates latex gloves. It is best handled by a dispensing pipet.

RESULTS AND DISCUSSION

The literature protocol[3] for the coupling of **1** with **2** to give **3** employed dimethylacetamide as the reaction solvent with a reaction time of five to 10 h. In dimethyl sulfoxide, the reaction was complete in 30 min. The reaction was easily carried out in a small open test tube. The crude product (photo in Supporting Information) was precipitated by dilution of the reaction mixture with water. The range of yields that students obtained was 0.15−0.47 g with an average of 0.24 g. The theoretical yield is 0.46 g. Melting points for the crude product clustered from around 51−56 °C to 69−70 °C.

Slow evaporation of a solution of the crude product in dichloromethane/heptane yielded large pale yellow crystals of product **3** (photo in Supporting Information). This crystal-

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lization worked best when all of the solvent was allowed to evaporate, which was usually overnight. The range of yields that students obtained was 0.08−0.38 g (18−83%) with an average of 0.19 g (42%); melting points for the product clustered from around 52−59 °C to 64−65 °C compared to the literature value of 62−64 °C.[3] The protocol for simple crystallization outlined here will have many applications in the undergraduate organic laboratory course.

This laboratory experiment highlights the ability of even a simple carbonyl to activate a benzene ring for nucleophilic subsitution. It also illustrats the superior reactivity of aromatic fluorides in nucleophilic addition/elimination, encouraging discussion of why that might be so. In particular, fluoride ion is not an effective S_N2 leaving group but is readily susceptible to β-elimination. Students were assessed for their understanding of the reaction with a set of prelab questions. The experiment was short enough that the students could discuss the reaction as a group with the teaching assistant before commencing work.

This experiment is easy to carry out, using only the simplest of glassware (two 12 mL test tubes); thus, it could be adopted in even the lowest-funded student laboratory course.

■ ASSOCIATED CONTENT

Supporting Information

Student instructions, student prelab questions and answers, instructor notes with photos of the crude and final product, CAS registry numbers, and ^{1}H NMR and ^{13}C NMR spectra of the product. This material is available via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: taberdf@udel.edu.

Notes

The authors declare no competing financial interest.

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