SIU Southern Illinois University Edwardsville

Undergraduate Research Academy (URA)

Application for Student Fellowship

SEND TO CAMPUS BOX 1300
BY NOON, WEDNESDAY, MARCH 16, 2004
(Please type)

1. Name Nellie J. Shaul 2. ID#_____

3. Local Address_____

4. Local Telephone_____ 5. e-mail_____

6. Academic Major Biology/Chemistry 7. Hours Completed 97 8. GPA (4-point scale) 3.866

9. Nominated by Dr. James McClure

10. Reviewed by: (Please print)

Faculty Mentor Dr. James McClure Department Chair Dr. Robert Dixon

11. Title of Research Project Synthesis of 2-Substituted Benzofurans

Please send the original plus 10 copies of the proposal, including budget justification and cover page.

12. Budget Summary Total: $ 800
Commodities: $ 800 Contractual Services: $ N/A
Travel: $ N/A Other (specify): $ N/A

13. Valid nominations must carry all of the following approval signatures with dates:

a. Clearances (as appropriate):
Animal Care_____ Human Subjects_____ Toxic Waste_____

b. Student Nellie Shaul's Signature

c. Faculty Mentor James McClure's Signature

d. Department Chair Robert Dixon's Signature

e. Dean of College/School Carl Springer's Signature

f. Undergraduate Research Academy Interview Cindy Scarsdale's Signature

SIUE Undergraduate Assessment -&- The Undergraduate Research Academy
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THE UNDERGRADUATE RESEARCH ACADEMY
OFFICE OF UNDERGRADUATE ASSESSMENT & PROGRAM REVIEW
Cover Page (*Please type*)

STUDENT Nellie J. Shaul MENTOR Dr. James McClure

PROJECT TITLE Synthesis of 2-Substituted Benzofurans

ABSTRACT: The abstract is a brief but comprehensive summary of the contents of the proposal *in plain language*, approximately 150 words. Readers receive their first impression of the flavor of the topic from this abstract. The information in the abstract needs to be concise, well organized, self contained, and understandable to persons outside the discipline.

Benzofurans are a family of compounds that constitute an immensely valuable area of organic chemistry. Practical applications of benzofurans are found in the fields of pharmacology, agriculture and photography. Complimenting other literature methods to prepare benzofurans, our procedure will generate them using *ortho*-cresol, a relatively inexpensive starting material. The uniqueness of our study lies in the efficient way that we will be able to produce the aryloxyketone intermediate and in the protecting group that we will be using on the *ortho*-cresol. Currently, the methods available for synthesizing aryloxyketones are rather wasteful, yielding a mixture of products, the majority of which are *para* substituted instead of the necessary *ortho* conformer. The primary goal of the described research is to develop a procedure to prepare a variety of potential useful benzofurans in a more efficient, yet relatively inexpensive way, in hopes of furthering the other areas of science, as such mentioned above, that are inevitably influenced by the benzofuran structure in the products that they use.

Upon submitting this proposal, I verify that this writing is my own and pledge to fulfill all of the expectations of the Undergraduate Research Academy to the best of my abilities. I understand that failure to do so may result in return of fellowship money to the University and forfeiture of academic credit and honors recognition.

Nellie Shaul's Signature 1-13-04
Signature of the Student

I am able, willing, and committed to providing the necessary facilities and to take the time to mentor this student during this project. I verify that this student is capable of undertaking this proposed project.

James McClure's Signature 1/13/04
Signature of the Faculty Mentor

This project is within the mission and scope of this department, and the department fully supports the faculty mentor and student during this venture.

Robert Dixon's Signature
Signature of the Department Chairperson

I testify that all necessary research protocols (human, animal, toxic waste) have been fulfilled, and I support this proposed faculty-student scholarly activity as within the mission of the College/School.

Carl Springer's Signature
Signature of the Dean of the College/School

I. Introduction and Significance

The benzofurans are an important class of organic compounds. Their theoretical implications and diversity in structure exemplify their physiological and industrial significance. The study of these compounds can produce practical contributions to organic chemistry as well as to the fields of agriculture and medicine.

The basic benzofuran structure (Figure 1) contains a fused ring system.

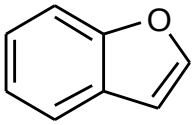


Figure 1

The structure commonly appears in natural products. For example, a crystalline 2-substituted benzofuran (Figure 2) was isolated from baker's yeast and acts as an antioxidant*.[1] As illustrated, this compound differs only in the type of substituent added to the ring.

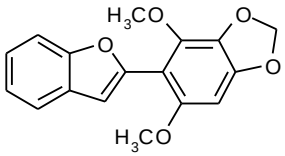


Figure 2

Substituted benzofurans exhibit a wide scope of pharmacological properties as well. Notably, amidarone is an antianginal drug that causes coronary dilation and depresses myocardial oxygen consumption, preventing further damage to heart muscles due to lack of oxygen.[1] This compound could be easily synthesized using our proposed method, with only a slight modification of the starting phenol.

A second compound, Amethone is used against bronchial asthma.[1] The scope of their utility is profound, encompassing other areas such as: bactericidal and bacteriostatic activity, potent analgesic activity, and photographic processes.[1] Though our hypothesized method will not yield any of these

* A glossary has been provided for some of the scientific terminology in Appendix A after the reference section.

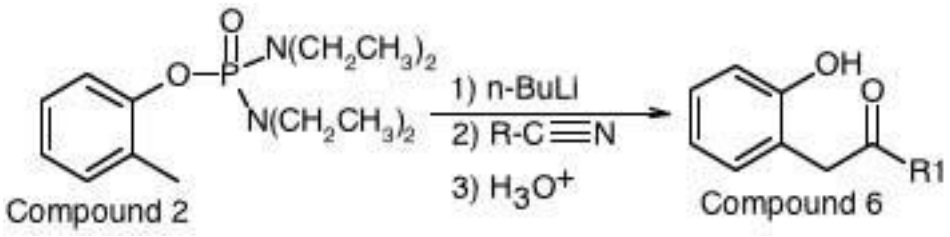
specific pharmaceutical compounds directly, simple modifications can be made to the process in order to produce them more efficiently. Overall, our procedure is a strong link in the chain of benzofuran synthesis, building on past URA work done in Dr. McClure's laboratory, and, upon hopeful completion of our research, leading to many new and exciting practical applications and research topics.

II. Literature Review

The chemical literature abounds with synthetic paths to benzofurans. Several examples treat aryloxyketones (Compound 1) with polyphosphoric acid (PPA).[1] Given the literary evidence, we are confident that this will be a straightforward procedure. The chemistry is outlined in Scheme 1. The difficulty lies in the production of Compound 1, since the predominant substitution location is at the *para* position on the ring. Aryloxyketones, however, are *ortho* substituted. The major advantage to our method versus others currently available is that it will lead to this *ortho* substituted product exclusively.[2] This is much more efficient than having a product mixture of *ortho* product and *para* product, which is not a reaction form for cyclization.

Scheme 1

Previous studies in Dr. McClure's laboratory have demonstrated that metalation of a phenol derivative can produce the required aryloxyketones, as illustrated in Scheme 2.[2]

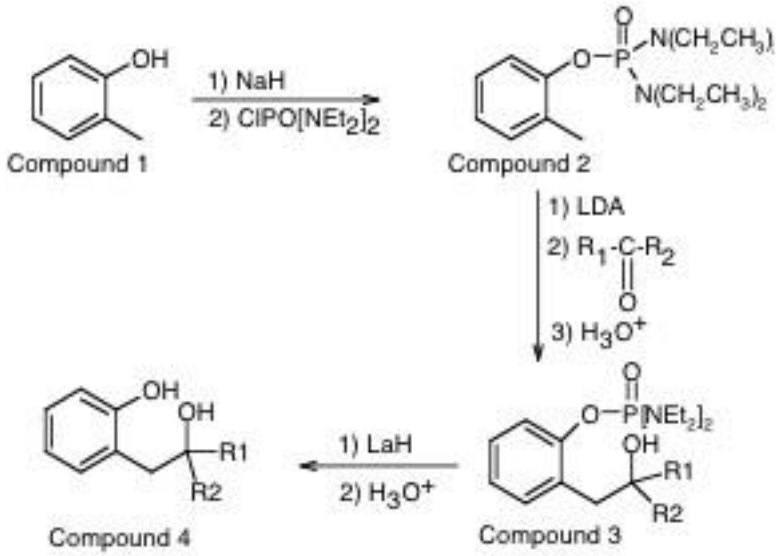


Scheme 2

The combination of these previous literature methods (Scheme 1) and results obtained by Katie Zipfel in a previous URA project conducted in Dr. McClure's laboratory (Scheme 2) suggest that a variety of benzofurans can be produced. Further details will be provided in the hypothesis.

III. Objectives and Hypothesis

Our synthesis for preparing benzofurans is outlined in Scheme 3.



Scheme 3

We will begin with the commercially available compound *ortho*-cresol (Compound 1), a derivative of phenol. We will block the OH with a tetraethyl phosphorodiamic group, yielding Compound 2, to avoid undesired side reactions. Once protected, subsequent treatment of Compound 2 with n-BuLi and condensation with a nitrile and an acid work-up will produce the aryloxyketone (Compound 3). The acid

environment affects ester hydrolysis to remove the protecting group, yielding a second intermediate structure with the alcohol group restored. Finally, the aryloxyketone will be converted to a benzofuran (Compound 4) by the addition of polyphosphoric acid (PPA). Due to the synthetic route chosen, our resulting benzofuran can be varied in its constituent side chains, modifying the resultant chemical and/or pharmacological behavior of the compound. Overall, the work described in this proposal should provide a practical route to benzofurans, generating the target compound from relatively inexpensive starting materials. In addition, a secondary objective of this research is to introduce the URA participant to a number of techniques and thought processes that are not ordinarily encountered in an undergraduate curriculum, such as NMR spectroscopy experience and advanced organic chemistry experimental procedures.

IV. Materials, Procedures, and Time Line

The SIUE Department of Chemistry and Dr. McClure's laboratory are equipped to execute the proposed research. The Chemistry Department stockroom can supply almost all of the glassware and reagents. Only a few reagents will need to be purchased, as outlined in the budget justification section.

Beginning in August of 2004, the first weeks of this research project will be spent learning the basic principles and mastering the techniques for conducting research and analyzing the results using Nuclear Magnetic Resonance (NMR) spectroscopy. Initial work will involve preparation of protected *o*-cresol (Compound 2). Since it is only a slight modification of the work performed by Katie Zipfel, this part of the procedure should only take one to two months. Each new nitrile will then be condensed with our protected *o*-cresol reagent. This portion should last approximately two to three months. Following condensation, we will affect the acid hydrolysis over a period of one to two months to remove the protecting group. Finally, another one to two months will be required for the addition of the PPA to cyclized the aryloxyketone and isolate our products. Analysis of experimental results will include proton,

carbon-13, and phosphorus-31 NMR spectroscopy. After becoming familiar with the physical properties of the new compounds in each part of the procedure, the experiment will be repeated for improved yields. Following these general procedures, the duration of the project will be six to nine months.

The successful completion of this project should prove to be a significant contribution to the chemical literature. A description of this work will be presented at either a local or national American Chemical Society meeting. A manuscript will also be submitted for publication in a refereed journal.

V. References

1. Mustafa, A. Benzofurans. New York: Interscience, 1974.

2. McClure, J. R. and Zipfel, K., unpublished results.

3. Dashan, L. and Trippett, S. *Tetrahedron*. Vol. 24, No. 19 (1983): 2039.

4. McClure, J. R. and Baker, S., unpublished results.

5. McClure, J. R., Harpstrite, S., and Zobrist, J., unpublished results.

6. Singh, V. B. and Vaughan, W. E. M. *Brit. J. Pharmacol*. Vol. 39, (1970): 657; *Chem. Abstr*. Vol. 73, (1970): 97166.

7. Watanbe, M. et al. *Chemical & Pharmaceutical Bulletin*. Vol. 37, No. 9 (1989): 2564.

8. Watanbe, M. et al. *Chemical & Pharmaceutical Bulletin*. Vol. 38, No. 10 (1990): 2637.

9. Weston, A. *J. Am. Chem. Soc.* Vol. 69, (1947): 980.

VI. Appendix A – Glossary

1. Acidic effects – A deprotonation or removal of a hydrogen (H^+) ion.
2. Acidic environment – In the presence of H^+/H_3O^+ ions; A pH level less than 7.
3. Analgesic – A medication that reduces or eliminates pain.
4. Antioxidant – A substance that protects body cells from the damaging effects of oxidation.
5. Condensation – A reaction where two or more molecules combine into a larger molecule, often with the loss of a small molecule (usually water).
6. Coronary dilation – Opening of the blood vessels.
7. Derivative compounds – A group of compounds that share one or more common characteristics or functionalities, varying from each other and the parent compound by modified substituents.
8. Functionality – A site of chemical reactivity in a molecule.
9. Myocardial – Of or associated with the muscular tissue of the heart.
10. n-BuLi – A strong base, useful in metalation as a source of a metal (Lithium).
11. Nitrile – A hydrocarbon chain with a nitrogen atom triple-bonded to the terminal carbon.
12. *ortho* – A 1,2 positioning of substituents on a ring compound (if each of the atoms composing the ring were numbered, the substituents would be adjacent), not favored under normal reaction conditions.
13. *ortho*-cresol (*o*-cresol) – A derivative of the parent compound phenol, with a methyl (CH_3) group at the *ortho* position.
14. *para* – a 1,4 positioning of substituents on a ring compound, favored under normal reaction conditions.
15. Phenol – A six-carbon ring compound with an alcohol (OH) functionality attached to one of the ring carbons, stabilized by double bonds.
16. Protecting group/Directing group – A class of compounds that can be added to the alcohol group of phenol that serves two purposes: to block the OH group from reaction with any further reagents and to direct an added electrophile to the *ortho* position on the ring.

17. Side reactions – Reactions that take place in the reaction vessel other than the primary, desired reaction. They yield varying minor products that must be separated from the product desired.

VII. Budget Justification

Amount	Description	Unit Price	Total
500 g	*o*-cresol	$22.70	$22.70
1.0 kg	Phosphorus oxychloride	$19.60	$19.60
2.0 L	Diethyl amine	$41.90	$41.90
2 x 800 mL	Butyllithium	$68.20	$136.40
1.0 kg	Polyphosphoric acid	$31.20	$31.20
1.0 L	Benzonitrile	$117.20	$117.20
10 g	4-biphenylcarbonitrile	$92.20	$92.20
25 g	1-cyanonaphthaline	$51.20	$51.20
100 g	2-cyanopyridine	$18.90	$18.90
100 g	4-cyanopyridine	$11.10	$11.10
3 x 1.0 L	Ethylene glycol dimethyl ether	$77.80	$233.40
100 mL	N, N-dimethylformamide	$24.20	$24.20
		Total	$800.00