

FURSCA Research Program Cover Page

Name of applicant _____ Date: 2-14-2011

Graduation Year 2013 Major Chemistry

Advisor Dr. McCaffrey Advisor's Department Chemistry

Title of Project: Microwave-Assisted Solid-Supported Duff Formylation of Substituted Phenols

Grant Period: Fall _____ Spring _____ Summer _____

Summer start and end dates? date must start on Monday and end on Friday

05/23/11 – 07/29/11

Has FURSCA supported this project or projects similar to it for the applicant or advisor in the past? YES NO If yes, how is this project related to previously funded projects?

Chris Omerza did a spring 2010 proposal for the solution phase of this project. I am continuing this with the solid phase synthesis.

Does this project require IRB or IACUC approval? YES NO If yes, has approval been sought? YES NO

Does this project require chemicals or biological agents? YES NO If yes, Have you received approval to order these chemicals? YES NO

BUDGET SUMMARY

Amount(s) Requested For each line requested, briefly explain the purpose

*Most of the materials necessary for this project we have on hand

- \$37.42 m-Bromophenol, 10g, ICN203763, MP Biomedicals, No.:20376310 (chemical reagent)
- \$93.32 p-Trifluoromethylphenol, 5g, Fisher Scientific, AC17644-0010, Acros Organics, No.:176440010 (chemical reagent)
- \$164.75 Agate mortar and pestle, 2.5 inches, Fisher Scientific, 12-950A, Walter Stern, No.:400E (equipment needed for procedure)
- \$80.00 Hexamethylenetetramine, 1kg, Fisher Scientific, AC12061-0010, Acros Organics, No.:120610010 (chemical reagent)
- \$22.50, Hazard Fee
- \$22.01, Shipping charge, changes with changing gas prices

Total \$420.00

Revisions to document highlighted in yellow

Microwave-Assisted Solid-Supported Duff Formylation of Substituted Phenols

Background Information

Aromatic aldehydes are important and interesting compounds. They are found as the basis of many molecules found in nature. In addition, they are used in the organic laboratory as building blocks for a wide variety of compounds. The McCaffrey lab uses dialdehydes (molecules with more than one aldehyde functional group) as the basic building blocks for bis-phenoxy-bridged manganese dimers that are used to study fundamental magnetic interactions. The main goal in the study of these magnetic interactions is to gain a deeper understanding of the properties of the electron. The electron, being a fundamental unit of the atom, is important in every aspect of science, including: magnets and electricity in physics, mechanisms and reactivity in chemistry, and amino acid, carbohydrate, and fat interactions within the body in biology. In gaining a deeper understanding of these electrons in dialdehyde compounds, we can transpose our work to improve understanding in all areas of science, and ultimately in our understanding of the world. To make the dialdehyde starting materials, a reaction called the Duff reaction is used, shown below, Figure 1.¹ The Duff reaction can take a long time and makes unwanted side products that are mostly monoaldehydes.

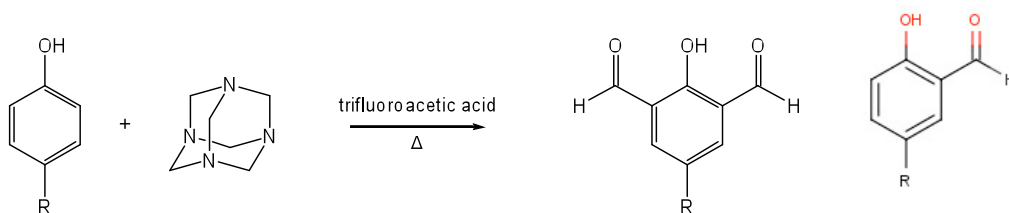


Figure 1. Duff formylation

Dialdehyde

Monoaldehyde

Purification techniques attempting to isolate the dialdehyde compound are possible, but a successful experiment would produce the pure product in higher yields with little to no side products. The purity of this dialdehyde compound is important in the synthesis of the macrocyclic complex. The R-groups include chlorine (Cl), bromine (Br), methyl (CH₃), and tert-butyl groups (C(CH₃)₃) and were chosen for their electron withdrawing or donating ability. Work is still in progress to successfully synthesize and purify the dialdehydes where the R-groups are nitro (NO₂), methoxide (OCH₃), and trifluoromethyl (CF₃).

Purity is not the only problem with our current methods of formylating these substituted phenols. Personal experience of working with these compounds in the McCaffrey lab has shown results of particularly low yields for the desired product. Previous researchers in the McCaffrey lab have also found that yields for the dialdehyde product range from 10-40%, depending on the type of substituent (R-group in figure 1) present in the reaction.²

This summer, I propose to research a new technique for the synthesis of the dialdehyde compound. Recent work on the Duff Formylation of porphyrins has shown improved yields with the use of a solid silica gel as a support as opposed to the use of a solvent such as trifluoroacetic acid.³ I would like to apply this technique to our compounds to see if we can increase the yields and decrease the time of the reaction. The hope of this new technique is to improve the yields and the selectivity of the dialdehyde compound synthesis. **The improvement in the versatility of a procedure is instrumental in the progress of scientific theory. Justification through experimentation can open new doors for the use of the Duff Formylation in numerous aspects of science: biology, chemistry, and biochemistry.**

Methodology

The new synthesis technique offers a significant improvement in the yield of the desired product. For formylation of porphyrins bonded to different metal complexes, yields were consistently in the 50-60% range. To repeat their process on my own compounds, I plan to scale my work on the substituted phenols to the amounts presented in the work on the formylated porphyrins. Ratios of compounds from the two experiments are presented in table 1 below. In the current experiment hexamethylenetetraamine (HMTA, the second molecule in Figure 1) is hard to dissolve in large quantities so we are limited in the molar ratio that we can add to the reaction. With the new solid support synthesis more HMTA can be used and will hopefully allow us to increase the yield of the dialdehyde.

Table 1. Molar ratio of compound for the current experiment in black. Experiment from which new techniques will be used are given in red.

Compound	p-NO ₂ Phenol	HMTA	Trifluoroacetic acid (solvent)	Metalloporphrin	HMTA	Silica (solid support)
Mole Ratio	1:	4	xs	1:	25	xs

Instead of dissolving the compounds in a solvent, the starting materials, p-NO₂ phenol and HMTA, will be ground together with an agate mortar and combined with silica gel in a microwave tube. Microwave settings will be crucial to the success and purity of the experiment. Research on the formylation of porphyrins recommends 200 watts, 111° C, and 18 minutes. I will start with their settings and experiment with different times, temperatures, and power settings including my current settings of 250 watts, 100° C, and 60 minutes. Determining the proper microwave settings will allow me to synthesize the compound in the highest yield and with the largest amount of the dialdehyde compound.

Success of the experiment will be determined with the aid of spectroscopic data analysis. Proton NMR, Infrared Spectroscopy, and Gas Chromatography will be used to determine the products present at the completion of the reaction. This data can be used to determine what materials are present in the product and how pure our desired product actually is. With success in the nitro substituted product, I would like to attempt the formylation with other substituents as mentioned earlier (OCH₃, Br, Cl, NO₂, CH₃, C(CH₃)₃, and CF₃).

Idealistic conditions would allow me to finish about two to three reactions per day. Pending microwave times and workup of the reactions, it will take about an hour to run the actual reactions, and 2-3 hours to do all of the spectral analysis.

Once I have successfully synthesized the dialdehyde compounds, I will use them in a metallation reaction that can be viewed in Figure 2 below. I would like to focus the majority of my remaining time on synthesizing the nitro substituted complex. In the grand scheme of things, the nitro compound is one of the last complexes we need to synthesize to analyze how these different R-groups effect magnetic exchange.

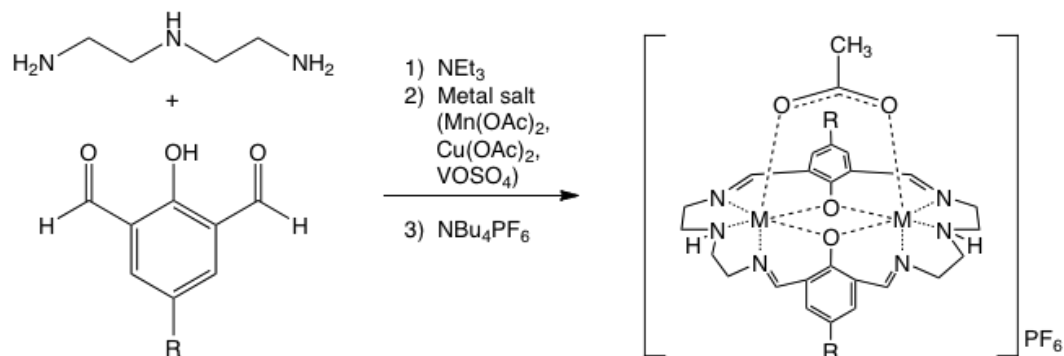


Figure 2. Metallation reaction with dialdehyde compounds

Metallation reactions to study magnetic exchange are not the only use of these aldehyde compounds. Salicylaldehydes and α,β -unsaturated aldehydes have been experimented with in other substitution reactions. One instance involves the formation of coumarin.⁴ Coumarin is an important molecule. It is the precursor to the formation of Coumadin, which is a commonly prescribed blood thinner. Formation of this product is difficult with current processes and has resulted in low yields. The development of a better synthesis technique could improve these yields.

Proposed Outcomes

The research to be conducted over the summer should provide evidence for a more effective method of formylating substituted phenols. If successful, the technique can be applied to a range of different substituent groups, as well as with different positioning of these groups including ortho, para, and meta phenols (figure 3).

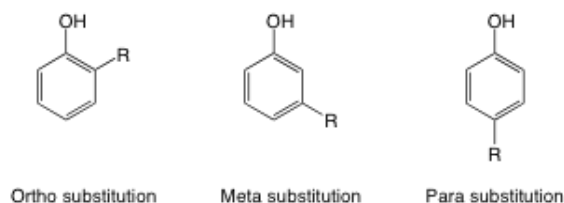


Figure 3. R-group nomenclature for substituted phenols

The overall goal of the research is to formulate a basis upon which I could write an honors thesis. I would also like to present the results of my work at Elkin Isaac and the national Meeting of the

American Chemical Society. If successful, the research is also intended to be published and used in future experiments concerning metallation reactions and substituent effects on magnetism.

Schedule

Week 1 – Start working with the nitro-substituted phenol, optimizing isolation of products and spectral analysis

Week 2- Formylation of nitro-substituted phenol, work up, spectroscopic analysis.

Week 3, 4 and 5 - Formylation of para-substituted phenols (Figure 1), work up, spectroscopic analysis.

Week 6 and 7- Formylation of ortho and meta-substituted phenols (Figure 2), work up, spectroscopic analysis.

Week 8 - Testing the general applicability of this reaction to other compounds

Week 9 and 10- Metallation reactions with successfully formylated dialdehydes.

References

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- ¹ Lindoy F, Leonard, Meehan V, George, Svenstrup Niels. Mono- and Diformylation of 4-Substituted Phenols: A New Application of the Duff Reaction. *Synthesis*, **1998**, 1029-32.
 - ² a) Omerza, C.R., Qureshi, W.Z., McCaffrey, V.P. "Formylation of substituted phenols using microwave irradiation" Poster at 239th American Chemical Society National Meeting – San Francisco CA, March 21-25, 2010. b) Herrman, N.W.C, Kelly, S.E., Fehir Jr., R., Soler, M., McCusker, J.K., McCaffrey, V.P. "Magnetic coupling of substituted bis-phenoxy-bridged dimanganese macrocyclic complexes" Poster at 239th American Chemical Society National Meeting – San Francisco CA, March 21-25, 2010.
 - ³ Yaseen, Muhammad, Mukhtar Ali, Muhammad NajeebUllah, Munawar Ali Munawar, and Irshad Khokhar. 2009. Microwave-Assisted Synthesis, Metallation, and Duff Formylation of Porphyrins. *Journal of Heterocyclic Chemistry*, **2009**, 251-55.
 - ⁴ Toräng, J., Vanderheiden, S., Nieger, M. and Bräse, S. (2007), Synthesis of 3-Alkylcoumarins from Salicylaldehydes and α,β -Unsaturated Aldehydes Utilizing Nucleophilic Carbenes: A New Unpoled Domino Reaction. *European Journal of Organic Chemistry*, 2007: 943–952.