

Considering Organic Mechanisms and the Optimization of Current Flow in an Electrochemical Oxidative Condensation Reaction

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SUPPORTING INFORMATION

General Reaction Procedure

The following procedure is the optimized set of reaction conditions. This procedure was used for the three reactions using 2-aminothiophenol mixed with syringaldehyde, benzaldehyde, and 4-nitrobenzaldehyde.

A divided cell, Figure 1 in paper, was dried in an oven overnight along with two stir bars, one for each chamber of the cell. The cell can also be dried with a Bunsen burner, a procedure that can be performed in a matter of minutes rather than hours. After drying was completed septa were attached to the four ports on the cell and the reaction vessel was evacuated and subsequently purged with argon. (The reactions were run under positive argon pressure) The solvent system, 8 mL of THF and 2 mL of MeOH, was added to each chamber. Lithium perchlorate electrolyte was added to each chamber to reach a concentration of 0.5M. 2-Aminothiophenol and an aldehyde were added to the anodic chamber. Reticulated vitreous carbon electrodes (1 cm x 0.5 cm x 0.5 cm) were placed in each chamber. This was accomplished by sharpening a carbon rod, pushing the end into the RVC electrode, and then passing the carbon rod through a thermometer adapter. A constant current of 25 mA was passed through the cell until 2.1 F/mole of charge was used. This amount of charge required for the reaction can be calculated using the following equation.

Moles of compound x 2.1 F/mole x 96485 C/F = Coulombs of Current Passed

After the reaction was complete the contents of the anodic chamber were transferred to a separatory funnel at which time the contents were diluted with ethyl acetate and washed with two portions of 1N HCl, one portion of water, and one portion of brine. The organic layer was dried over MgSO₄ concentrated *in vacuo* to give the crude compound, and then purified with silica gel column chromatography to yield the final product. The following three specific examples use this general procedure.

Syringaldehyde:

The reactants used were 2-aminothiophenol (0.10 mL, 0.93 mmol) and syringaldehyde (0.191 grams, 1.05 mmol). Lithium perchlorate electrolyte was used in the anode (0.536 grams) and cathode (0.533 grams). The reaction consumed 189 coulombs, and after workup 0.250 grams of crude product mixture was obtained. The product was purified *via* silica gel chromatography with a solvent system of 6:4 ethyl acetate:hexanes to obtain 0.194 grams of the product for a 73% yield. The spectral data obtained matched that previously reported. (Nguyen, B. H.; Perkins, R. J.; Smith, J. A.; Moeller, K. D. *J. Org. Chem.* **2015**, *80*, 11953)

Benzaldehyde:

The reactants used were 2-aminothiophenol (0.03 mL, 0.28 mmol) and benzaldehyde (0.03 mL, 0.30 mmol). Lithium perchlorate electrolyte was used in the anode (0.532 grams) and cathode (0.536 grams). The reaction consumed 57 coulombs, and after workup 0.062 grams of crude product mixture was obtained. The product was purified *via* silica gel chromatography with a solvent system of 3:7 ethyl acetate:hexanes to obtain 0.038 grams of the product for a 64% yield. The spectral data obtained matched that previously reported. (Huang, J. *J. Am. Chem. Soc.* **2010**, *132*, 3674.)

4-Nitrobenzaldehyde:

The reactants used were 2-aminothiophenol (0.03 mL, 0.28 mmol) and 4-nitrobenzaldehyde (0.048 grams, 0.32 mmol). Lithium perchlorate electrolyte was used in the anode (0.539 grams) and cathode (0.536 grams). The reaction consumed 57 coulombs, and after workup 0.052 grams of crude product mixture was obtained. This was purified *via* silica gel chromatography with a solvent system of 1:1 ethyl

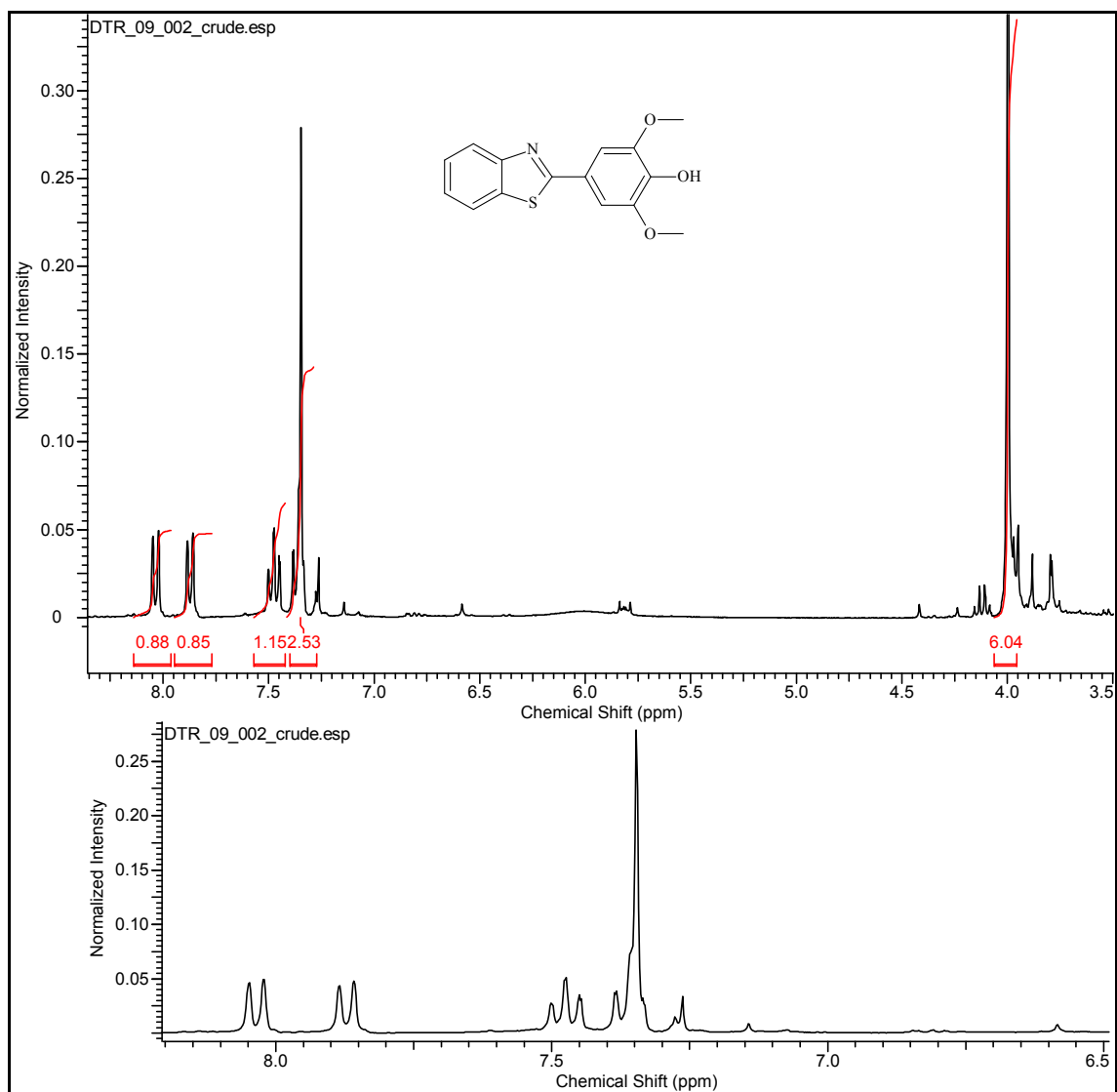
acetate:hexanes to obtain 0.045 grams of the product for a 63% yield. The spectral data obtained matched that previously reported. (Das, S.; Smanta, S.; Maji, S, K.; Smanta, P. K.; Dutta, A. K.; Srivastava, D. N.; Adhikary, B.; Biswas, P. *Tetrahedron Lett.* **2013**, *54*, 1090.)

Optimization Process with Representative NMR Spectra

The following is a description of the different reactions run during optimization of the reaction and the proton NMR spectra used to determine the %-conversion reported for those reactions. When calculating the conversion of the reactions we compared the NMR peak integrations for the product relative to the thioaminal intermediate. The proton NMR spectra used are of the crude reaction mixture obtained after workup but prior to any purification. In all of the test studies, 2.1 F/mole of charge was passed through the reaction. All changes between reactions are explained below the individual spectra. Once the best set of reaction conditions was determined, the reactions were run on a preparative scale and the products isolated. The yields from the optimized reactions were reported in Scheme 7 and the associated text.

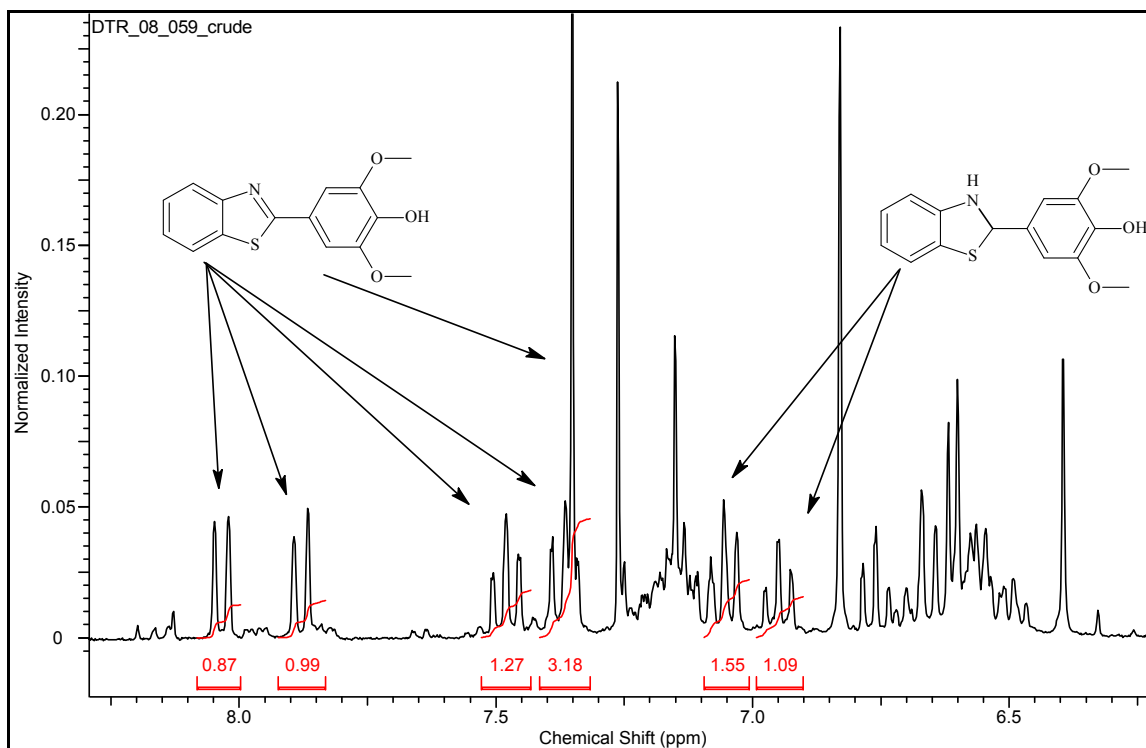
Product From Oxidation of Syringaldehyde and 2-aminothiophenol

The spectrum for the isolated product is shown below so that it can be used to identify the sired product in the spectra obtained for the crude reaction mixture. The aromatic region has been expanded because it is the region of the spectrum used to calculate percent conversion for the subsequent reactions.



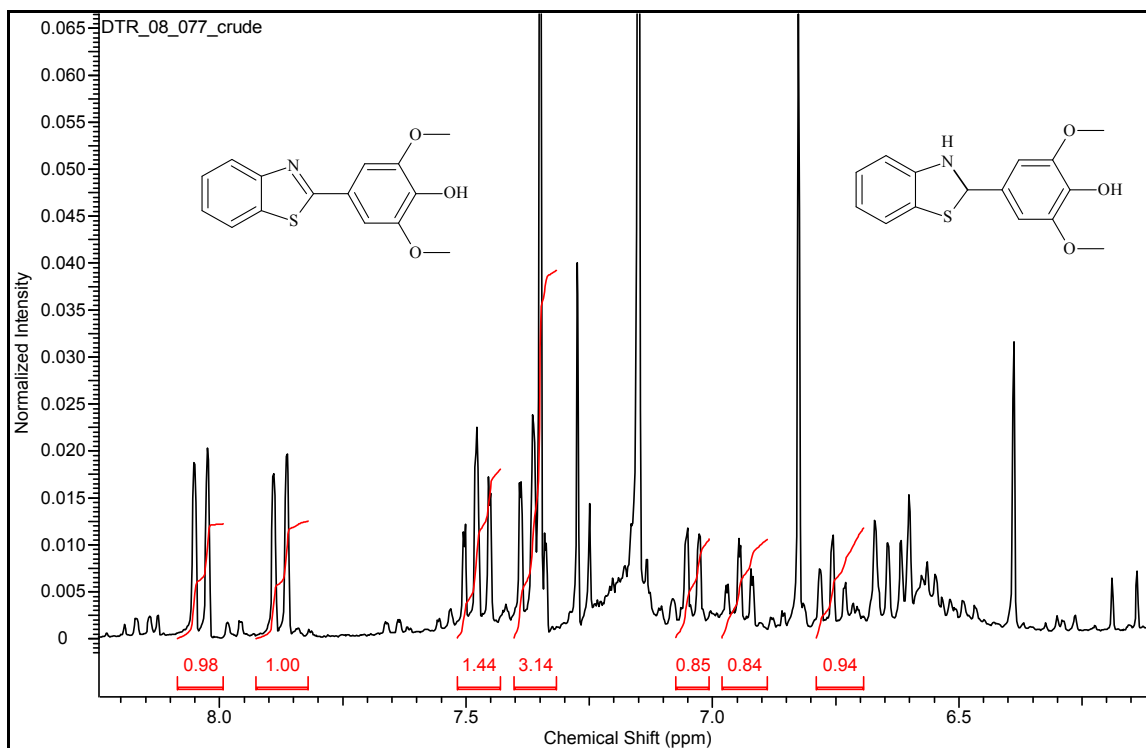
Mediated Reaction: Copper Acetate Added in Undivided Cell at 25mA

In the spectrum shown on the following page, peaks are evident for both the product and the thioaminal intermediate. In this spectrum, not all of the peaks for the thioaminal are visible because of some of the impurities formed. The thioaminal will be easier to identify in the spectrum run on the cleaner reactions illustrated below. Irrespective of the impurities, the product and thioaminal peaks that can be observed indicate a 1:1 mixture of those materials and hence a 50% conversion for the reaction.



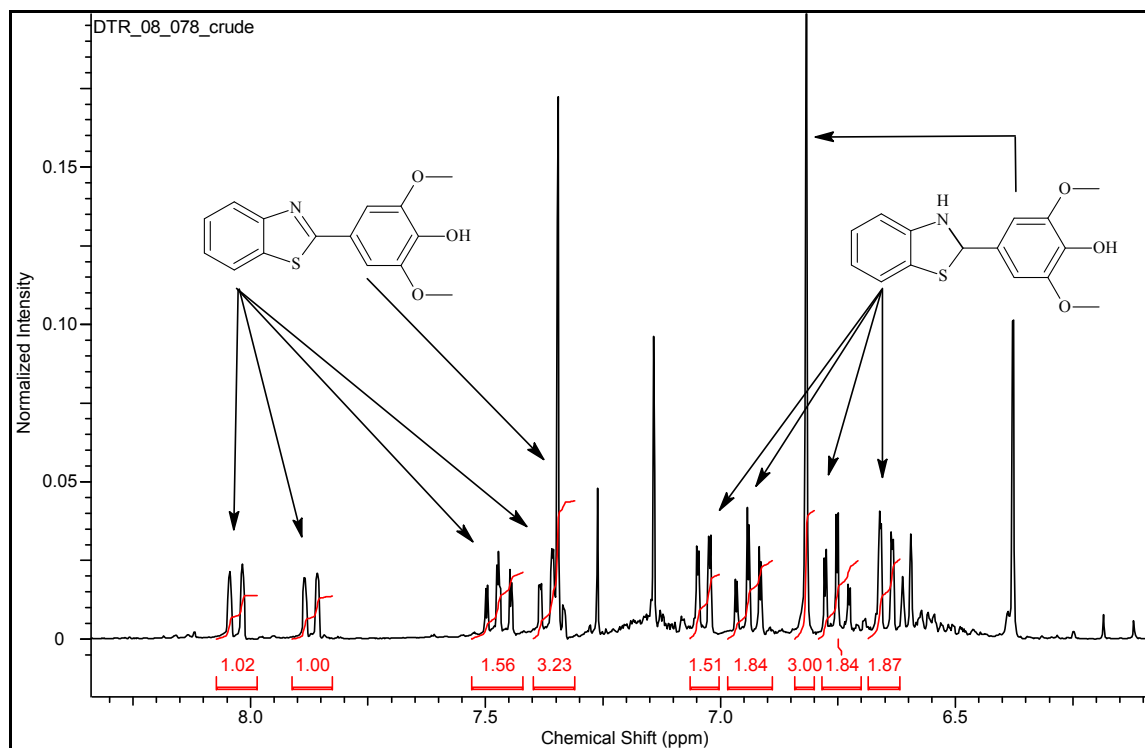
Cu(OAc)₂ Mediated Reaction with MgSO₄ Based Performation of the Thioaminal: Undivided Cell at 25mA

In order to generate the crude reaction mixture shown below, the reaction was first stirred with MgSO₄ for 2 hours prior to the electrolysis with a copper acetate mediator. The product peaks and the thioaminal peaks are in a ratio of ~1.09:0.88 or 55% conversion. There are still impurity peaks in the 6.4-6.9 and 7.1-7.3 ppm regions, and the preformation of the thioaminal appeared to have little impact on the current efficiency of the reaction.



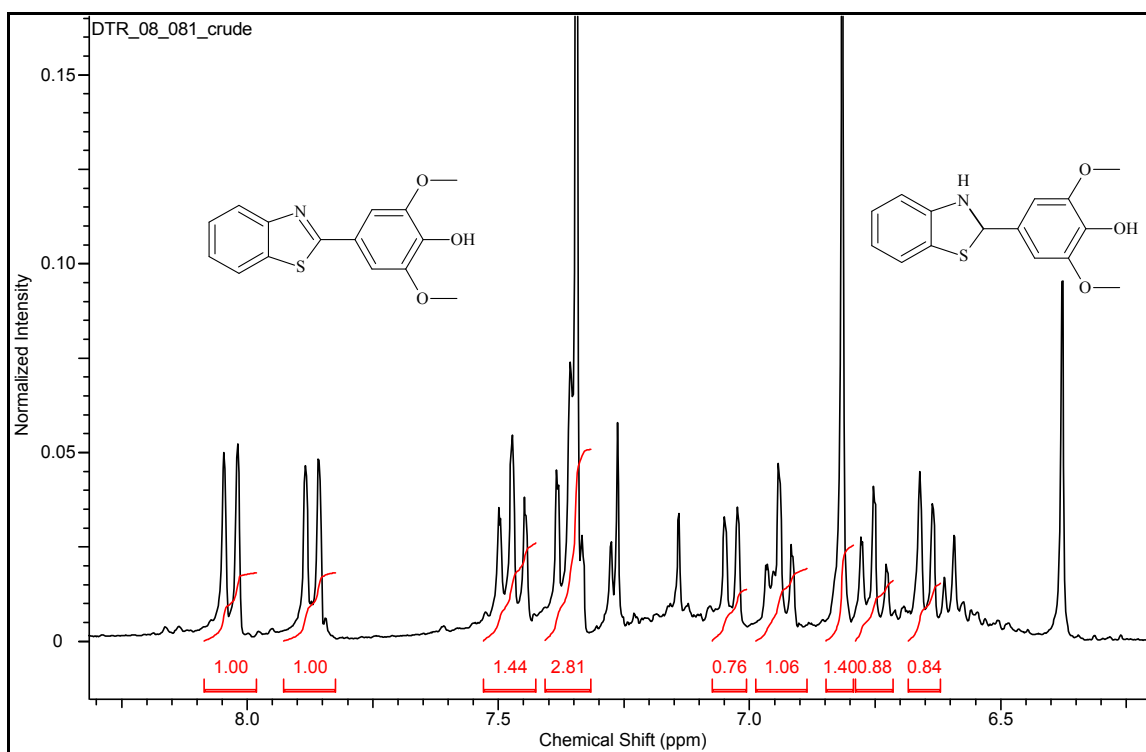
Direct Oxidation with preformation of the thioaminal: Undivided Cell at 25mA

In this reaction, the syringaldehyde and 2-aminothiophenol were stirred for 18 hours with MgSO_4 in order to preform the thioaminal. A direct electrolysis was run without any added mediator. The reaction was surprisingly clean showing only the product and thioaminal intermediate. Note that none of the impurities seen with reactions using the copper acetate mediator are present. The product peaks and the thioaminal peaks are in a ratio of $\sim 1.13:1.68$ for a 40% conversion.



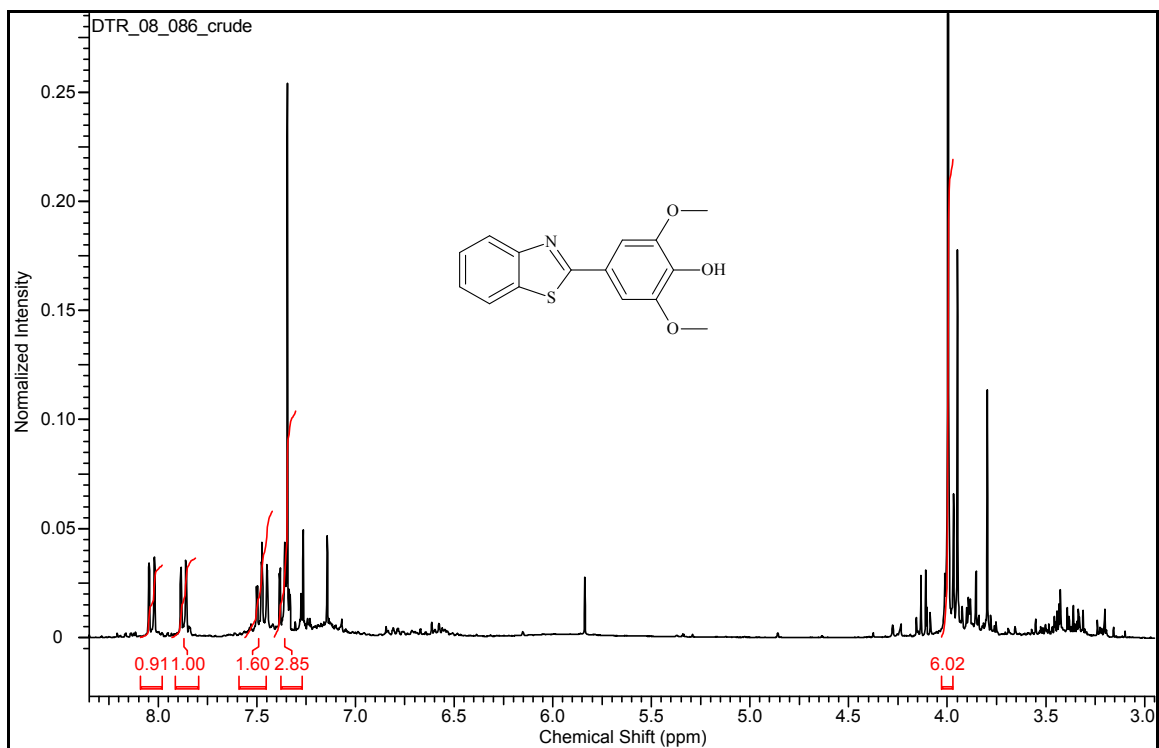
Direct Oxidation with preformation of the thioaminal and an increase in electrolyte concentration (25 mA):

This reaction used the exact same conditions as the previous reaction except for an increase in electrolyte concentration from 0.1M to 0.5M. This change in electrolyte concentration did have a positive effect on the reaction, with product peaks and the thioaminal peaks being in a ratio of ~1.04:0.82 for a 56% conversion. The positive change in the reaction was consistent with a stable radical cation being reduced at the cathode. The increase in electrolyte aids in the removal of a second electron from the intermediate and slows migration of the charged species to the cathode. Still higher concentrations of electrolyte did not further improve the reaction.



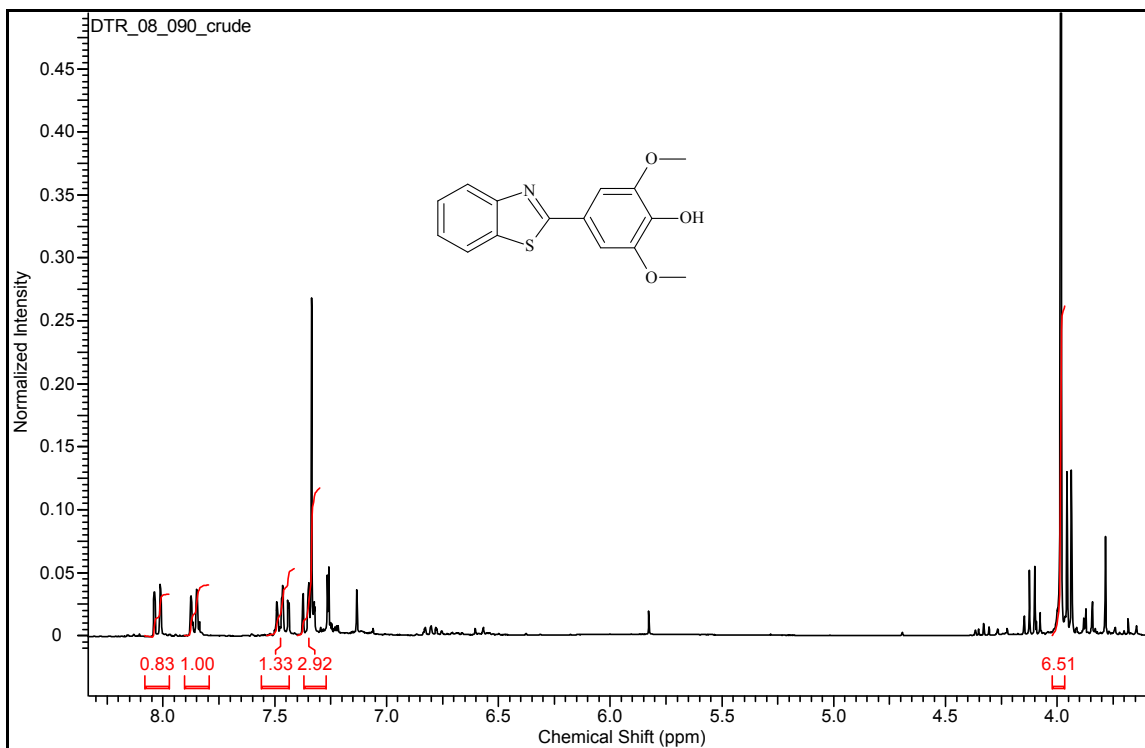
Direct Oxidation with preformation of the thioaminal: Divided Cell at 25mA

In order to improve the current efficiency of the reaction, a divided cell was used to prevent reduction of the stable radical cation intermediate at the cathode. This change led to a major improvement in the reaction. Note that in the proton NMR spectrum of the crude reaction shown below there is virtually no thioaminal present. The spectrum show only product with a few small peaks for an unidentified impurity. For all practical purposes, the reaction proceeded to 100% conversion.



Direct Oxidation with no preformation of the thioaminal: Divided Cell at 25mA

The reaction was then repeated in the divided cell without preformation of the thioaminal intermediate. This time, the reaction proceeded even more cleanly. Clearly, these were the best conditions for running the reaction.



Direct Oxidation with No MgSO₄ Incubation: Divided Cell at 40mA

When the reaction was repeated with 40 mA of current, it cleanly afforded the product with no apparent difference from the reaction run with lower current.

