# Optimization of bisguaiacol F Synthesis via Microwave Assistance

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## Abstract

Bisphenol A (BPA) is a monomer used to produce epoxy resins and in thermal printing processes. BPA is problematic from environmental and toxicological perspectives since it is synthesized from non-renewable sources and is an estrogenic compound. One BPA mimic that has the advantage of renewable feedstock and non-estrogenic toxicology is bisguaiacol F (BGF, 4-[(4-Hydroxy-3-methoxyphenyl)methyl]-2-methoxyphenol). The typical BGF synthesis via electrophilic coupling of vanillyl alcohol and guaiacol results in a mixture of *p,p'* and *o,p'* isomers in moderate yield following laborious workup and purification. Proposed is the process optimization of BGF preparation using microwave assisted synthesis and alternate acid catalysts. Initial efforts to scale the reaction and simplify the work-up and purification are also proposed.

## Introduction

BPA is an endocrine disruptor that binds to estrogen receptors. It may impact:

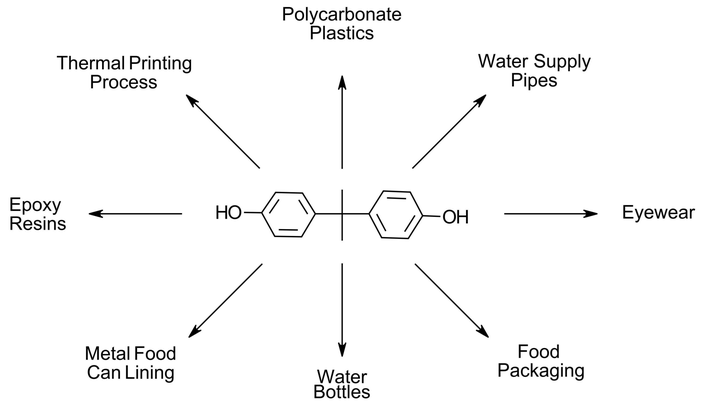
- Thyroid function
- Endocrine/pancreas
- Immune system
- Central nervous system
- Reproductive system

BGF is non-estrogenic and can be synthesized from non-petroleum source thus contributing to the growing field of green chemistry.

Microwave assisted synthesis will be used to optimize BGF synthesis. Microwave irradiation in sealed tubes rapidly heats reactions to high temperatures, dramatically reduces reaction time, and reduces side reactions to achieve higher yields of *p,p'*-BGF.

## Methods

In preliminary (control) experiments, BGF was synthesized by the electrophilic coupling of vanillyl alcohol (A) and guaiacol (B). Deionized water was used as the solvent and Amberlyst (strong acid) resin was the catalyst. The reaction was run for 48 hours at either 65 °C and 100 °C. Standard work-up and was purified using flash chromatography gave the product in moderate yield. Products were analyzed using TLC and FT-IR. Initial efforts produced moderate yields of *p,p'* and *o,p'* product.




**Scheme 1.** BGF Synthesis

**Table 1.** Control BGF Synthesis ($H_20$, Amerberlyst 15)

| Reaction | Temperature | Percent Yield | Melting Point |
|---|---|---|---|
| **1** | 65˚C | 26.7% | 82.5-95.6 °C |
| **2** | 100˚C | 56.7% | 88.4- 94.5 °C |

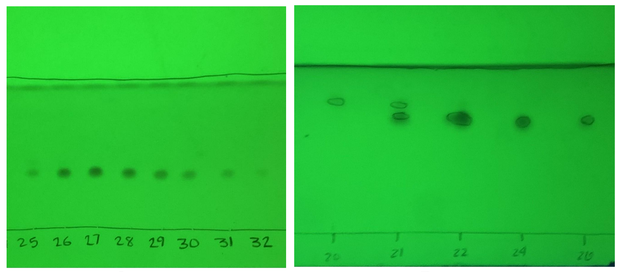



**Figure 2.** (A) **1** TLC (B) **2** TLC analysis.

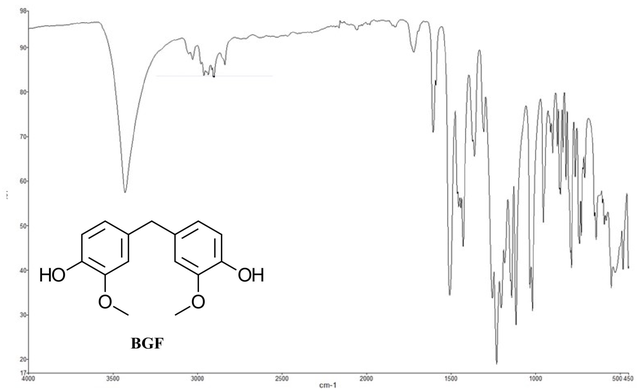



**Figure 3.** FTIR spectrum of BGF


**Figure 4.** CEM Discover 2.0 Microwave Reactor

**Table 2.** Microwave Assisted Synthesis Benefits

| CEM Discover 2.0 Microwave Reactor |
|---|
| • Rapidly reaches high temperatures |
| • Decreases reaction time |
| • Reduces side reactions |

## Proposed Work

**Step 1:**
Use water and Amberlyst to optimize microwave assisted synthesis conditions

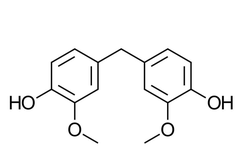
**Step 2:**
Vary polarity of solvents under optimal conditions for water

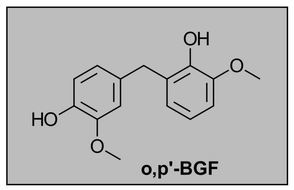
| **#1** | **#2** | **#3** |
|---|---|---|
| Amberlyst → | Amberlyst → | Amberlyst → |
| DMF | Ethanol | DME |

**Step 3:**
Use optimal solvent and reaction time to determine effect of acid sources

| **#1** | **#2** | **#3** |
|---|---|---|
| Amberlyst → | $H_2SO_4$ → | Silica Gel → |
| Solvent | Solvent | Solvent |

**Step 4:**
Optimize workup/purification of BGF




## Preliminary Results

- Control syntheses of BGF (**Scheme 1)** completed using water as the solvent and Amberlyst resin as an acid catalyst at 65 °C and 100 °C.
- BGF synthesis at 100 °C resulted a mixture of *p,p'*-BGF and *o,p'*-BGF isomers as indicated by the broader MP (88.4-94.5 °C).
- Moderate yields of BGF isomers obtained through laborious workup and purification
- The purity of both BGF products was confirmed by IR, TLC, and melting point analysis.
- FTIR and TLC of newly synthesized were compared to previously synthesized BGF that was characterized by $^1$H NMR, $^{13}$C NMR, and elemental analysis

## Future Work

1. With control conditions (water, Amberlyst resin), establish and optimize microwave assisted synthesis conditions.
   A. Time
   B. Temperature
   C. Heating rate
2. Vary the solvent polarity with optimal conditions for water
3. Use the optimal solvent and reaction conditions to evaluate different acid catalysts
   1. $H_2SO_4$
   2. Acid functionalized silica
4. Optimize BGF workup and purification.

## References and Acknowledgments

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*References:*

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