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Recommended Citation
Quesada, Katherine; Chabeda, Daniel; Johnson, Jaeger; and Shore, Alex (2021) "Analysis of the Electronic Effects and Reactivity of Benzhydrols in the Formation of Benzhydryl Ethers," The Yale Undergraduate Research Journal: Vol. 2 : Iss. 1 , Article 34.  
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Cover Page Footnote
The author acknowledges the support of Dr. Jonathan Parr, Dr. Christine DiMeglio, Ms. Sooyun Choi, and fellow researchers Miss Alex Shore, Mr. Daniel Chabeda, and Mr. Jaeger Johnson in determining the electronic properties of benzhydryl ethers. Written for Christine DiMeglio’s course CHEM 226L: Intensive Advanced Chemistry Laboratory.

This article is available in The Yale Undergraduate Research Journal: https://elischolar.library.yale.edu/yurj/vol2/iss1/
Analysis of the Electronic Effects and Reactivity of Benzhydrols in the Formation of Benzhydryl Ethers

By Katherine G. Quesada, Daniel Chabeda, Jaeger Johnson, Alex Shore

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ABSTRACT

Benzhydryl ethers were synthesized through the use of microwave irradiation in a protic ionic liquid solvent. The resulting products were separated from the reaction mixture by vacuum filtration with a silica gel plug. The products were analyzed using GCMS and 1H NMR techniques to identify and quantify products. Analysis of the resultant data indicated the syntheses of the desired benzhydryl products were successful for 4,4-dimethoxybenzhydrol (conversion: 83% (1-propyl ether), 11% (2-propyl ether), 11% (menthyl ether)) and 4,4-dimethylbenzhydrol (conversion to desired product: 100% (1-propyl ether), 100% (2-propyl ether), 26% (menthyl ether)). However, the syntheses were unsuccessful for reactant 4,4-difluorobenzhydrol and benzhydrol. It was concluded that the electron-donating groups of 4,4-dimethoxybenzhydrol and 4,4-dimethylbenzhydrol aided in the formulation of a stable intermediate and subsequent desired product. The data support the hypothesized mechanism of protonation of the hydroxyl group of the benzhydryl with subsequent creation of a carbocation intermediate.

INTRODUCTION

Benzhydryl ethers are compounds with various synthetic and pharmaceutical uses. Synthetically, they make good use as protecting groups due to ease of removal through hydrogenolysis and in acidic conditions (Thornton & Henderson, 2013). Because of the bulky structure of the benzhydryl group, the compound is very advantageous for enantioselective syntheses or for discouraging reactions between functional groups in close proximity (Thornton & Henderson, 2013). Benzhydryl has been used for the purpose of alkylating and protecting alcohols, carboxylates, and thiols (Altimari et al., 2012). The protecting group use of benzhydryl ethers also applies to therapeutic compounds (Thornton & Henderson, 2013). Many functions of the ethers include non-nucleoside reverse transcriptase inhibition, anti-plasmodial and anti-trypanosomal action, and monoamine uptake inhibition (Brahmachari & Banerjee, 2013).

The therapeutic and medicinal functions of benzhydryl ethers stem into the development of peptide drugs. Takahashi, et al. explored the development of a good C-terminal protecting group for efficient synthesis of stable peptide drugs (Takahashi, Yano, & Fukui, 2012). The study found that benzhydryl ether derived protecting groups at the C-terminal provided an efficient synthesis of various type of terminal amide peptides (Takahashi et al., 2012). Thus, green, cost-effective, and simple synthesis of benzhydryl ethers is certainly a topic of importance for future research.

In this report, the benzhydryl ethers were synthesized in a protic ionic liquid (pIL) suspension and underwent microwave irradiation. pILs were utilized in this reaction due to their recent popularity for research due to their dual ability as a catalyst and co-solvent when used with microwave irradiation (Altimari et al., 2012). This synthesis was chosen due to its proved success in Altimari, et al. For the synthesis, the pIL chosen was triethylammonium methanesulfonate (TeaMS) due to the quick reaction time through the use of this catalyst. Additionally, this synthetic approach proved effective since it was simple to separate the pIL and the co-solvent through filtration through a plug of silica gel. This synthesis was also chosen due to its adherence to green chemistry principles because of its low production of excess waste and lack of hazardous reactants.

RESULTS AND DISCUSSION

Multiple products were synthesized through the combination of the alcohols 1-propanol (5), 2-propanol (6), and 1R, 2S, 5R-(−) menthol (7) with reactants 1-4 (Figure 1, Scheme 1). The reaction took place under microwave irradiation, and the resulting products were...
washed with diethyl ether, run through a silica gel plug to remove the proto-ionic suspension, and placed in a roto-evaporation apparatus to concentrate the final product oils. The final products (e.g. 1

5-7a) were analyzed using 1H NMR and GCMS in order to identify if the desired product was synthesized (Figure 2).

**Synthesis of 1, 5-7a.** For the reaction between 1 and 5, 1H NMR data indicated multiple products. GCMS confirmed an 11% conversion to desired product, 4,4-difluorobenzhydryl-1-propyl ether (1, 5a, R' = (CH2)2 CH3). The reaction between 1 and 6 experienced a much higher yield of the desired product, 4,4-difluorobenzhydryl-2-propyl ether (1, 6a, R' = CH(CH3)2), and GCMS analysis showed a conversion of 76% for this product. This is a different trend seen among the data set and may indicate steric and electronic contribution from the alcohol. For the reaction between 1 and 7, there was no yield of the desired product, 4,4-difluorobenzhydryl-menthyl ether (1, 7a, R'=1R, 2S, 5R-(-) menthyl).

**Synthesis of Complexes 2, 5-7a.** For the reaction between 2 and 5, 1H NMR data indicated multiple products. GCMS confirmed an 83% conversion to desired product, 4,4-dimethoxybenzhydryl-1-propyl ether (2, 5a, R' = (CH2)2 CH3). The reaction between 2 and 6 experienced a low isolated yield of 4% of 4,4-dimethoxybenzhydryl-2-propyl ether (2, 6a, R' = CH(CH3)2), and GCMS analysis showed a conversion of 11% to 2, 6a. For the reaction between 2 and 7, there was an 11% conversion to 4,4-dimethoxybenzhydryl-menthyl ether (2, 7a, R'=1R, 2S, 5R-(-) menthyl).

**Synthesis of Complexes 3, 5-7a.** For the reaction between 3 and 5, 1H NMR data showed no starting material was found in the reaction mixture. GCMS confirmed a 100% conversion to 4,4-dimethoxybenzhydryl-1-propyl ether (3, 5a, R' = (CH3)2 CH3). The reaction between 3 and 6 experienced a similar yield and conversion to desired product, 4,4-dimethoxybenzhydryl-2-propyl ether (3, 6a, R' = CH(CH3)2); GCMS analysis showed a conversion of 100% for to 3a. The reaction between 3 and 7, there was a 26% conversion to desired product 4,4-dimethoxybenzhydryl-menthyl (3, 7a, R'=1R, 2S, 5R-(-) menthyl ether).

**Synthesis of Complexes 4, 5-7a.** For the reaction between 4 and 1-propanol, GCMS confirmed a 23% conversion to desired product, benzhydryl-1-propyl ether (4, 5a, R' = (CH3)2 CH3). There was a 77% conversion of unreacted 4 in the product mixture. The reaction between 4 and 6 did not produce the desired product benzhydryl-2-propyl ether (4, 6a, R' = CH(CH3)2). GCMS analysis showed a conversion of 68% to an unknown product. There was 32% conversion of unreacted reactant 4. For the reaction between 4 and 7, there was no yield of the desired product, benzhydryl-menthyl ether (4, 7a, R'=1R, 2S, 5R-(-) menthol). GCMS data of the product mixture showed 27% conversion of unreacted 4, 26% of unreacted 7, and 48% of unknown product.

A table of all reaction data is included in the supplemental information (table S1).

The full set of data reveal that the most reactive benzhydryl was 3. Benzhydryl 2 was also reactive and produced good yield. It was determined by the observation that these two reactants reacted with all three alcohols to yield desired products. Additionally, these reactants were the only two reactants to form the desired product when reacted with the menthol. Thus, it is reasonable these two compounds formed the most stable intermediates and experienced the least steric hindrance in the reaction. It also can be seen that...
these two reactants possessed electron donating groups -CH₃ and -OCH₃. It can be hypothesized that the protonated hydroxyl group is the leaving group in the mechanism and that the electron donating groups stabilize the carbocation intermediate (Scheme 2). This possibility provides a good explanation for the low yields experienced for the electron-withdrawing group of 1 and the neutral 4, especially for the no yields derived from the attempted synthesis with menthol. The electron withdrawing groups would be detrimental to this mechanism given that these groups destabilize the benzene ring and product given the withdrawing nature. Following the hypothesized mechanism of protonation of the hydroxyl group, these reactions exhibited low yields due to either the creation of an unstable carbocation intermediate or the lack of one. This mechanistic hypothesis must be explored with further experimentation. For example, a different subset of electron donating and withdrawing benzhydrols could be researched in order to assess repetition of the electronic trends observed in this report. Additionally, a wider variety of alcohols with varying steric hindrance could be utilized to assess steric effects on reactivity. However, with the data obtained in this experiment, it is reasonable to conclude that electron-donating groups had a positive effect in the synthesis of the desired compounds.

CONCLUSION

The attempted syntheses of 1, 5-7a; 2, 5-7a; 3, 5-7a; and 4, 5-7a provided a basis for the analysis of electronic effects of 1-4. The 1H NMR and GCMS data supported the conclusion that 2 and 3 provided the best methods for synthesis of the desired benzhydryl ethers while 1 and 4 experienced lower yields. Additionally, the alcohols can be ranked in reactivity from 5 > 6 > 7. This is most likely due to steric hindrance and electronic effects of the individual properties of each alcohol. It was determined that electronics played a role in the stabilization of the unknown intermediate and that electron-donating groups were the preferred substituents for a successful synthesis.

EXPERIMENTAL

General Methods

All syntheses were carried out in a proto-ionic triethylammonium methanesulfonate suspension and underwent microwave irradiation.

Microwave irradiation. The reactions, in a microwave vial, underwent microwave irradiation in a Biotage Initiator + microwave with 30 seconds of mixing prior to 1H NMR analysis. The reactants and products were analyzed in a CDCl₃ solvent using a Magritek Spinsolve 60 MHzz spectrometer. GCMS analysis. The products, were analyzed using a ThermoScientific Focus DSQ II.

Evaporation. The diethyl ether was evaporated from the product solution in a BUCHI Rotavapor-200.

Synthesis of the benzhydryl ethers. To a microwave vial, 1.00 mmol of alcohol, 0.54 mmol of the benzhydryl derivative under microwave irradiation and 0.54 mmol of benzhydryl derivative under microwave irradiation at 80°C with 30 seconds of stirring prior to reaction.

### Table 1. Conversion and Yield of 1a, 2a, 3a, 4a.

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Alcohol</th>
<th>Conversion</th>
<th>Yield</th>
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<tr>
<td>1</td>
<td>5</td>
<td>11%</td>
<td>6%</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>76%</td>
<td>68%</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>83%</td>
<td>92%</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>11%</td>
<td>4%</td>
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<tr>
<td>2</td>
<td>7</td>
<td>11%</td>
<td>10%</td>
</tr>
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<td>3</td>
<td>5</td>
<td>100%</td>
<td>61%</td>
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<td>3</td>
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<td>100%</td>
<td>60%</td>
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<tr>
<td>3</td>
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<td>24%</td>
</tr>
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<td>4</td>
<td>5</td>
<td>23%</td>
<td>13%</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Reactions were performed with 1.00 mmol of alcohol, 0.25 mL of triethylammonium methanesulfonate, and 0.54 mmol of benzhydryl derivative under microwave irradiation at 80°C with 30 seconds of stirring prior to reaction.
after evaporating the diethyl ether in the rotovap. This procedure was reproduced with 1-4 with each alcohol to attempt the syntheses of products 1a-, 2a, 3a, and 4a.

1, 5a. 1H NMR (400 MHz, CDCl3): 0.93-1.55 (0.97H), 2.25-2.59 (0.88H), 3.34-3.73 (0.32H), 5.82-6.00 (1.00H), 6.90-7.62 (8.93H). GCMS: 261.89 m/z (21.98%), 219 m/z (78.02%).

1, 6a. 1H NMR (400 MHz, CDCl3): 0.19-0.86 (11.5H), 0.98-1.75 (2.06H), 1.81-2.56 (10.94H), 2.81-3.42 (3.20H), 4.41-5.55 (2.50H), 6.23-7.19 (7.94H). GCMS: 219.89 m/z (21.98%), 261.88 m/z (78.02%).

1, 7a. 1H NMR: 0.78-1.20 (2.19), 1.28-1.67 (3.36), 2.81-1.95 (1.00), 3.04-3.57 (2.11), 3.65-3.79 (0.73), 5.90-6.04 (0.15), 6.89-7.69 (1.81). GCMS: 138 m/z (38.71%), 219 m/z (54.26%).

2, 5a. 1H NMR: 0.72-1.20 (3.0H), 1.23-2.09 (2H), 3.24-3.67 (2.0H), 3.67-3.99 (6H), 5.21-5.55 (1H), 6.67-7.14 (4H), 7.14-7.52 (4H). GCMS: 285.89 m/z (13.06 min, 83.16%).

2, 6a. 1H NMR: 1.12-1.61 (6H), 3.44-3.79 (1H), 3.79-4.08 (6H), 5.34-5.62 (1H), 6.73-7.14 (4H), 7.18-7.58 (4H). GCMS: 285.87 m/z (12.67 min, 11.19%).

2, 7a. 1H NMR: 0.70-1.43 (3.5H), 1.58-1.98 (5.0H), 2.34-2.46 (6.37H), 3.33-3.67 (1.96H), 5.19-5.56 (1.00H), 7.01-7.38 (9.80H). GCMS: 253.85 m/z (100%).

3, 5a. 1H NMR: 0.83-1.20 (3.02H), 1.53-1.88 (2.06H), 2.34-2.46 (6.40H), 3.42-4.06 (1.00H), 5.43-5.71 (0.84H), 9.06-9.56 (8.70H). GCMS: 253.87 m/z (12.67 min, 11.19%).

3, 6a. 1H NMR: 1.15-1.63 (4.96H), 2.35-2.62 (6.40H), 3.42-4.06 (1.00H), 5.43-5.71 (0.84H), 9.06-9.56 (8.70H). GCMS: 253.67 m/z (88.13%); 254.28 m/z (11.87%).

3, 7a. 1H NMR: 0.44-0.72 (0.97H), 0.78-1.22 (18.63H), 1.26-2.33 (11.57H), 2.36-2.60 (6.24H), 3.31-3.87 (1.50H), 5.35-5.68 (0.58H), 5.82-6.03 (0.40H), 7.04-7.55 (8.00H). GCMS: 138.21g (48.53%); 405.91 m/z (25.33%); 349.76 m/z (26.14%).

4, 5a. 1H NMR: 2.09-2.46 (1.31H), 5.84-6.19 (1.00H), 7.08-7.74 (12.05H). GCMS: 183.70 m/z (77%); 226.10 m/z (23%).

4, 6a. 1H NMR: 2.14-2.28 (1.21H), 5.84-6.17 (0.91H), 7.15-7.85 (10.00H). GCMS: 183.85 m/z (32%); unidentified (206.04 m/z, 355-428 m/z).

4, 7a. 1H NMR: 0.82-1.25 (41.40), 1.27-1.88 (54.62), 1.93-2.71 (9.76), 2.76-3.04 (13.85), 3.05-3.85 (31.55), 3.87-4.38 (7.59), 5.88-6.14 (1.00), 7.17-7.74 (13.09), 9.29-10.40 (3.93). GCMS: 183.85 m/z (27%), 138.16 m/z (26%), unidentified (119.96 m/z, 48%).

ACKNOWLEDGMENTS
The author acknowledges the support of Dr. Jonathan Parr, Dr. Christine DiMeglio, Ms. Sooyun Choi, and fellow researchers Miss Alex Shore, Mr. Daniel Chabeda, and Mr. Jaeger Johnson in determining the electronic properties of benzhydryl ethers.

REFERENCES
Table S1

<table>
<thead>
<tr>
<th>Benzhydrol Derivative</th>
<th>1-propanol</th>
<th>2-propanol</th>
<th>Menthol</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,4-difluorobenzhydrol</td>
<td>11 % conversion to 1a 6% yield of Compound 1</td>
<td>78% conversion to 1a 68% yield of Compound 2</td>
<td>no yield of 1a</td>
</tr>
<tr>
<td>MS Peaks: 261.89 (21.98%), 219 (78.02%)</td>
<td>MS Peaks: 219.89g (21.98%), 261.88g (78.02%)</td>
<td>39% conversion to unreacted menthol</td>
<td>MS Peaks: 138g (38.71%), 219g (54.26%)</td>
</tr>
<tr>
<td>H NMR: 0.93-1.55 (0.97), 2.25-2.59 (0.88), 3.34-3.73 (0.32), 5.82-6.00 (1.00), 6.90-7.62 (8.93)</td>
<td>H NMR: 0.19-0.86 (11.5), 0.98-1.75 (2.06), 1.81-2.56 (10.94), 2.81-3.42 (3.20), 4.41-5.55 (2.50), 6.23-7.19 (7.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4,4-dimethoxybenzhydrol</td>
<td>83 % conversion to Compound 4 92 % yield of 2a</td>
<td>11 % conversion to Compound 5 3% yield of 2a (spilled)</td>
<td>11 % conversion to 2a 10%yield of 2a</td>
</tr>
<tr>
<td>MS peaks: 285.89g (83.16%)</td>
<td>MS peaks: 285.87g (11.19%)</td>
<td>MS peaks: 285.87g (11.19%)</td>
<td></td>
</tr>
<tr>
<td>H NMR: 0.72-1.20 (3.0), 1.23-2.09 (2), 3.24-3.67 (2), 3.67-3.99 (6), 5.21-5.44 (1), 6.67-7.14 (4), 7.14-7.52 (4)</td>
<td>H NMR: 0.19-0.86 (11.5), 0.98-1.75 (2.06), 1.81-2.56 (10.94), 2.81-3.42 (3.20), 4.41-5.55 (2.50), 6.23-7.19 (7.94)</td>
<td>H NMR: 0.70-1.43 (3.5), 1.58-1.98 (5.0), 1.90-2.80 (8), 3.16-3.75 (3), 3.77-4.10 (6), 5.29-5.69 (1), 6.76-7.15 (4), 7.17-7.60 (4)</td>
<td></td>
</tr>
<tr>
<td>4,4-dimethylbenzhydrol</td>
<td>100% conversion to 3a 61% yield of 3a</td>
<td>100% conversion to Compound 3a 60% yield of 3a</td>
<td>49% conversion to unreacted menthol</td>
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<tr>
<td>MS Peaks: 253.85 g (100%)</td>
<td>MS Peaks: 253.67g (88.13%); 254.28 (11.87 %)</td>
<td>25 % conversion to 4,4-dimethylbenzhydrol dimer 26 % conversion to 3a</td>
<td>MS Peaks: 138.21g (48.53%); 405.91g (25.33%); 349.76g (26.14%)</td>
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<td>H NMR: 0.83-1.20 (3.02), 1.53-1.88 (2.06), 2.34-2.46 (6.37), 3.33-3.67 (1.96), 5.19-5.56 (1.00), 7.01-7.38 (9.80)</td>
<td>H NMR: 1.15-1.63 (4.96), 2.35-2.62 (6.40), 3.42-4.06 (1.00), 5.43-5.71 (0.84), 9.06-9.56 (8.70)</td>
<td>H NMR: 0.70-1.43 (3.5), 1.58-1.98 (5.0), 1.90-2.80 (8), 3.16-3.75 (3), 3.77-4.10 (6), 5.29-5.69 (1), 6.76-7.15 (4), 7.17-7.60 (4)</td>
<td></td>
</tr>
<tr>
<td>Benzhydrol</td>
<td>23% conversion to 4a 13% yield of 4a</td>
<td>68% conversion to reactant 4 No yield of desired product</td>
<td>Trace amounts of reaction mix recovered shows no yield.</td>
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<td>MS Peaks: 183.70g (77%); 226.10g (23%)</td>
<td>MS peaks: 183.85g (32%); unidentified (206.04g,-355-428g)</td>
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<td>MS Peaks: 183.85g (27%), 138.16g (26%), unidentified (119.96g, 48%)</td>
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<tr>
<td>H NMR: 2.09-2.46 (1.31), 5.84-6.19 (1.00), 7.08-7.74 (12.05)</td>
<td>H NMR: 2.14-2.28 (1.21), 5.84-6.17 (0.91), 7.15-7.85 (10.00)</td>
<td>H NMR: 0.82-1.25 (41.40), 1.27-1.88 (54.62), 1.93-2.71 (9.76), 2.76-3.04 (13.85), 3.05-3.85 (31.55), 3.87-4.38 (7.59), 5.88-6.14 (1.00), 7.17-7.74 (13.09), 9.29-10.40 (3.93)</td>
<td>H NMR: 0.78-1.20 (2.19), 1.28-1.67 (3.36), 2.81-1.95 (1.00), 3.04-3.57 (2.11), 3.65-3.79 (0.73), 5.90-6.04 (0.15), 6.89-7.69 (1.81)</td>
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