IDENTIFYING OPTIMAL CONDITIONS FOR THE BORON TRIFLUORIDE CATALYZED ELECTROPHILIC AROMATIC SUBSTITUTION REACTION

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Abstract
Electrophilic Aromatic Substitution Reactions (EAS) are widely studied, typically straightforward, and high yielding; however, an EAS reaction utilizing boron trifluoride diethyl etherate as a Lewis acid catalyst has variable temperature and time reported in literature reports. The goal of this study is to find optimal conditions for an EAS with boron trifluoride as a Lewis acid catalyst by conducting several reactions, under different conditions, of resorcinol with phenyl acetic acid in boron trifluoride to form 1-(2,4-dihydroxyphenyl)-2-phenylethanone, Compound 2. To find the optimal conditions, phenylacetic acid and resorcinol were reacted for varying times and at varying temperatures. Each reaction was followed with the same purification steps that were identified as most successful in our previous unpublished study.[1,2] After 15 reactions, it was concluded that the highest yielding and most pure product was formed when phenylacetic acid and resorcinol reacted in boron trifluoride at 110 °C for 30 minutes.

Introduction

A fundamental problem in organic research is the formation of carbon-carbon bonds. The Electrophilic Aromatic Substitution (EAS) reaction provides a synthetically important way to substitute an aromatic ring, a moiety relevant in drugs, polymers, materials, and more. Student researchers in the Ferguson lab have synthesized several analogues of Compound **1** (2-(4-bromophenyl)-1-(2,4-dihydroxyphenyl)ethan-1-one), which was identified as a possible TRAF6 inhibitor by Zarzycka *et al*[3] (Figure 1). The synthesis of these analogues requires the addition of resorcinol to the carbonyl of the properly substituted phenylacetic acid through a boron trifluoride catalyzed electrophilic aromatic substitution. Despite electrophilic aromatic substitution (EAS) reactions typically being straightforward and well-researched, this particular EAS reaction using boron trifluoride (BF_3) as a Lewis acid catalyst is performed under widely varying conditions throughout literature. Studies have reported successful synthesis under varying temperature conditions. Reported temperatures include 60 °C[4], 75°C[5], 80°C[6], 85 °C[7], 100 °C[8], and reflux conditions.[9,10,11] In addition to the discrepancies in recorded temperatures, reaction times also differ greatly, including 15 minutes[10], 1.5 hours[11], 1.75 hours[7], 2 hours[8], 4 hours[5], 8 hours[6], and 24 hours.[9] In an effort to uncover optimal reaction conditions regarding yield and purity, we proposed four temperature variables - room temperature (~20 °C), 60 °C, 110 °C, and 126 °C (b.p. of BF_3 diethyl etherate) - and five time variables - 30 minutes, 1 hour, 1.5 hours, 2 hours and 3 hours. The suggested variables covered a large portion of the ranges reported in the literature to identify what combination yielded the most success. In addition to the reaction condition variables, the addition of molecular sieves was proposed to investigate if moisture in the reaction mixture rendered the catalyst ineffective via the hydrolysis of boron trifluoride, affecting the efficacy of the syntheses.[12] While this work focuses on adjusting the reaction conditions of this EAS reaction, others in the field have examined the effects of the presence of activating and deactivating groups on product yields.[13]

Identifying a clear methodology for this reaction will allow chemists from all disciplines to perform high yielding EAS reactions in a solvent free system. Furthermore, the work of this study could contribute to developing a reliable methodology to use in undergraduate teaching labs to provide early exposure of the common EAS reaction.

Experimental Methods

Resorcinol and phenylacetic acid are reacted to form 1-(2,4-dihydroxyphenyl)-2-phenylethanone (**2**) following the same procedure for all time and temperature variables (Figure 2). The time variables investigated were 30 minutes, 1 hour, 1.5 hour, 2 hours, and 3 hours. The temperature variables investigated were room temperature (~20 °C), 60 °C, 110 °C, and reflux (126 °C). The 30 minute time variable led to the purest product after a single crystallization and the 1.5 hour time variable was the highest yielding reaction with minimal impurities. Product was only obtained at 110 °C and 126 °C. Thus, reactions were repeated at these temperatures utilizing the same procedure, but with flame-dried 3Å molecular sieves added to the round bottom flask.

Procedure: To a 3-neck round bottom flask affixed with a magnetic stir bar, thermometer, and reflux condenser was added 0.25 g (1.84 mmol) phenylacetic acid (Sigma-Aldrich, Milwaukee, WI) and 0.222 g (2.02 mmol) resorcinol (Sigma-Aldrich, Milwaukee,
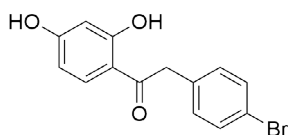
Figure 1. Structure of Compound **1**, (2-(4-bromophenyl)-1-(2,4-dihydroxyphenyl)ethan-1-one).[3]
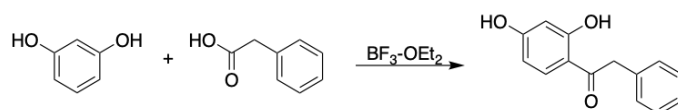
Figure 2. Synthetic scheme for the synthesis of 1-(2,4-dihydroxyphenyl)-2-phenylethanone,**2.**

WI). The reaction vessel was sealed with septa and then vacuumed and purged with nitrogen for 3 cycles. Once an air-free environment is sufficiently achieved in the reaction vessel, nitrogen flow remained at a rate of 1 bubble/sec and 4.5 mL of boron trifluoride diethyl etherate (Sigma-Aldrich, Milwaukee, WI) was added via syringe and needle. The red-orange reaction mixture was then heated to the designated temperature variable and allowed to stir according to the designated time variable. At the end of the appropriate reaction time, the nitrogen flow was ceased, and the reaction vessel was removed from the heat. The solution was then poured into ice water (20 mL) and the flask was rinsed with de-ionized water. The mixture was then washed twice with chloroform (20 mL portions) and dried over sodium sulfate (Na_2SO_4). Volatiles were removed via evaporation under reduced pressure and the resulting residue was recrystallized from chloroform/cold hexanes. The product obtained had a melting range of 107.6-110.9 °C and the physical appearance and percent yield varied by reaction condition, listed in the tables in the results and discussion section. FTIR (neat): v_{max} 3156 (br), 2723, 2605, 1621, 1600, 1585, 1575, 1495, 1454 cm⁻¹; ¹H NMR, 75 MHz (DMSO-d_6): δ = 4.30 (s, 2H), 6.26 (s, 1H), 6.41 (d, *J* = 8.7 Hz, 1H), 7.30 (m, 5H), 7.96 (d, *J* = 8.6 Hz, 1H), 10.70 (s, 1H), 12.52 (s, 1H) ppm; ¹³C-NMR, 300 MHz (DMSO-d_6): δ = 199.62, 162.49, 162.13, 132.71, 131.09, 127.05, 125.88, 124.09, 109.72, 105.80, 99.99, 41.61 ppm.

Results and Discussion

The time variable reactions, conducted at ~110 °C, or just under boiling, all indicate a successful synthesis with the target product present. While all of the ¹H NMR spectra indicate target product with limited impurities, the 30 minute, 1 hour, and 1.5 hour spectra indicated the least amount of side products and impurities, with the 30 minute reaction spectrum indicating an almost complete absence of side products. As the length of reaction time increased to 2 hours and especially the 3 hours, significantly more side products and impurities were present. Given the limited impurities present in the spectra and the 33% yield of the 1.5 hours reaction, it was decided that it was the best time variable to use to investigate the temperature variable reactions (Table 1). Of the four temperature variable reactions, only two were successful in forming the target product. Both the room temperature and 60 °C spectra indicated that the reaction did not proceed as a mixture of

the two starting materials was present with little evidence that the target product formed. The 110 °C and 126 °C reaction spectra both indicate that the target product was formed with limited side products or impurities (Table 2).

To further probe the ideal pairing of time and temperature to produce a pure and high yielding product, the best reaction conditions from the isolated time and temperature experiments were repeated to test for confounding influences. The purity of the 30 minute reaction and the high yielding nature of the 110 °C and 126 °C reactions prompted investigation into the combination. Spectra from these pairings indicated successful syntheses with no side products formed. The success from the 30 minute and 1.5 hour reactions at high temperatures prompted a final investigation on the role of water in the hydrolysis of boron trifluoride (Table 3). When adding molecular sieves to absorb moisture in the reaction vessel, the yield and purity of the 1.5 hour reactions did not change significantly; however, the yield of the 30 minute reactions dropped considerably, possibly due to deposition of product onto the beads.

Temp.	Physical Appearance	Percent Yield
~20 °C	Shiny white solid	Product not obtained
60 °C	White/pink crystalline solid	Product not obtained
110 °C	Orange and yellow solid	33%
126 °C	Orange and yellow solid	45%

Table 2. Results from the temperature variable reactions reacted for 1.5 hours.

Temp	Time (hours)	Sieves	Yield	Physical Appearance
110 °C	0.5	Yes	17%	Orange/red oil
		No	48%	Orange/red solid
126 °C	0.5	Yes	23%	Orange/red oil
		No	36%	Yellow/orange solid
110 °C	1.5	Yes	28%	Orange oil
		No	33%	Orange and yellow solid
126 °C	1.5	Yes	44%	Orange oil with red and yellow solids
		No	45%	Orange and yellow solid

Table 3. Results from the paring of time and temperature variables with and without molecular sieves.

Time	Physical Appearance	Percent Yield
30 minutes	Red and orange/yellow solid	30%
1 hour	Red and orange/yellow solid	20%
1.5 hour	Orange and yellow solid	33%
2 hours	Dark red oil	35%
3 hours	Dark red oil	29%

Table 1. Results from the time variable reactions conducted at 110 °C.

If that was the case, such product deposition would have been lost when sieves were removed during the purifying crystallization step. Overall, when considering purity, yield, and ease of reaction, the 30 minute reaction at 110°C is the best condition to form the target product, **2**.

Conclusion

The overarching goal of this study was to determine the ideal reaction conditions for an electrophilic aromatic substitution reaction utilizing boron trifluoride as a Lewis acid catalyst, employing the reaction of phenylacetic acid and resorcinol as a representative example. Through a series of repeated reactions, applying different time and temperature variables, the optimal reaction conditions, according to purity and yield of the product, were identified to be 30 minutes at 110 °C. The results of this study are highly dependent on the reaction variables investigated, therefore, a larger range of times and temperatures may further indicate ideal conditions for this reaction. Future studies could investigate the role of other elements of the reaction on purity and yield including amount of boron trifluoride, purification process, and the presence/absence of other activating or deactivating groups on the resorcinol ring. However, our current findings contribute to a fuller understanding of the boron trifluoride catalyzed EAS reaction, which has useful implications in drug discovery and chemical education.

Acknowledgements

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