THE DUFF REACTION: RESEARCHING A MODIFICATION

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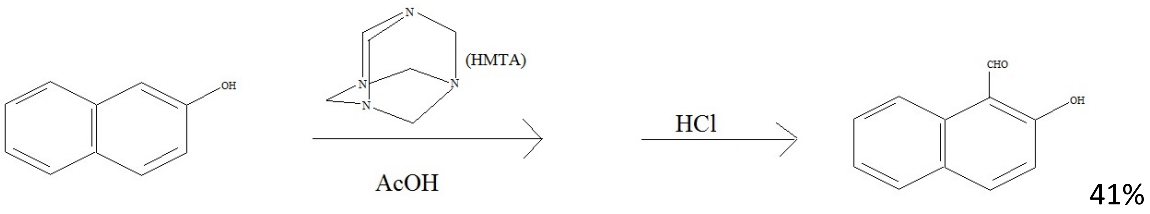
Background

Aldehydes are compounds that are commonly used and synthesized in chemistry. Most reactions that form aromatic aldehydes, such as Gattermann and Koch, and Reimer-Tiemann reactions place the aldehyde in the para position in relation to an electron donating group present on the ring or, produce a mixture of para and ortho products. The Duff reaction allows for the formation of aromatic aldehydes almost exclusively in the ortho position in relation to an electron donating group present on the ring using hexamethylenetetramine (HMTA). The down side is that the yields obtained using this method are low, usually ranging from 15-20%.[1] Even though the yields are low, the reaction is still useful. Chartterjee and Biswas used the Duff reaction to form indole-3-carboxaldehydes and compared it to the Vilsmeirer-Haack formylation. While the Duff reaction did not have as high a yield it was an easier reaction to conduct.[2] Lindoy, Meehan, and Svenstrup used a modified version of the Duff reaction for the mono and diformylation of 4-substituted phenols. Acetic acid was replaced with anhydrous trifluoroacetic acid. The selectivity was able to be controlled by the amount of time the solution was heated at reflux.[3] Masurier determined that the Duff reaction was able to produce formyl amido-IP compounds, unless they were substituted at position 5 which caused peri-annelation. IP compounds are also known as imidazo[1,2-a]pyridinic compounds.[4]

This topic was of interest due to the need for 2-hydroxy-1-naphthaldehyde as part of a previous project. The Duff conducted using typical reaction conditions produced a low yield of the desired product, but the reaction was attempted again with dimethydichlorosilane and the yield was significantly increased. It was then wondered if this result was reproducible and if it could then be applied to other compounds. This then formed the thesis of my project.

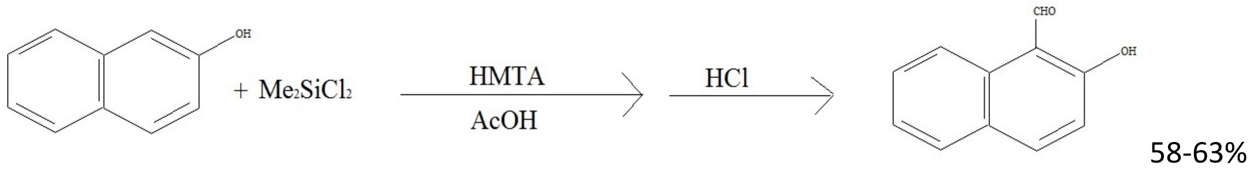
Results

The Duff reaction using 2-naphthol resulted in the formation of 2-hydroxy-1-naphthaldehyde with a yield of 41% (I).



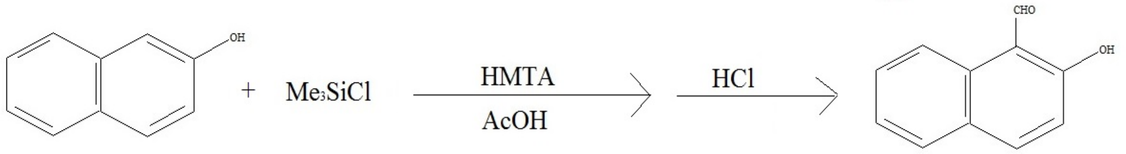
I

The reaction was ran again with the addition of dimethyldichlorosilane (II). The yields that were obtained using dimethyldichlorosilane were 58-63% for two reactions.



II

While this was an improvement on the yield it was believed that it could be increased more. Dimethyldichlorosilane was exchanged for trimethylsilyl chloride (III). This caused the yield to increase ranging from 65-74% for three reactions.

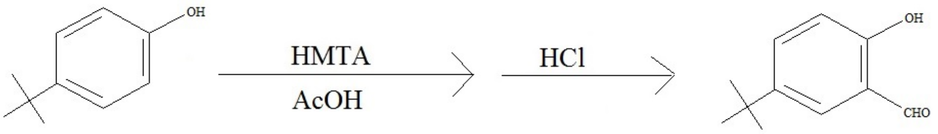


65-74%

III

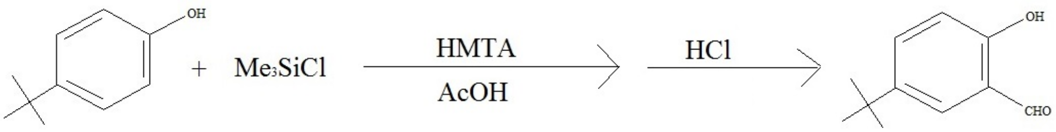
It was determined that trimethylsilyl chloride was achieving better yields. The modified reaction was then applied to several compounds to investigate its effects. ^{1}H NMR indicated some impurities, most of which were due to the solvent used for ^{1}H NMR.

The reaction was conducted with 4-tert-butylphenol as the starting compound. With the Duff reaction 5-tert-butylsalicylaldehyde was produced with a yield of 74-76% for two reactions (IV). The modified reaction was able to achieve a yield of 75-86% for two reactions (V).



74-76%

IV

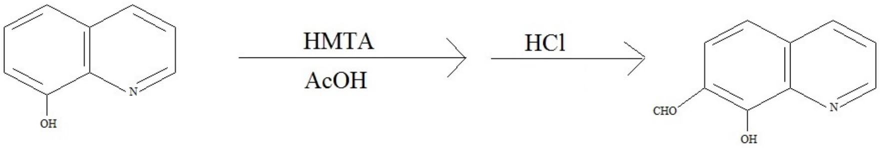


75-86%

V

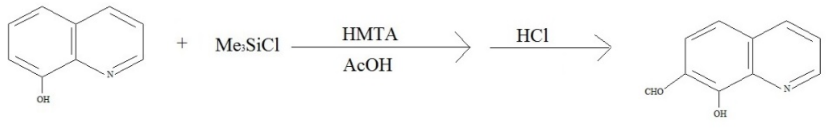
^{1}H NMR indicated that the product obtained was a mixture starting material and the desired compound.

8-Hydroxyquinoline was used as the starting material for the next set of reactions. Precipitate formed after the solution was cooled, but it was too fine to be collected by filtration. This lead to the solutions being cooled overnight allowing for larger particles of precipitate to form. It was then able to be collected by filtration. The Duff reaction produced 8-hydroxy-7-quinolinecarboxaldehyde with yields ranging from 20-33% for three reactions (VI). The modified reaction produced yields of 19-25% for three reactions (VII).



20-33%

VI

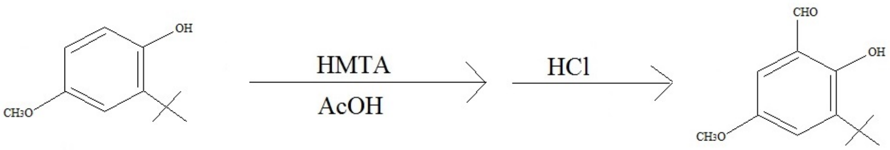


19-25%

VII

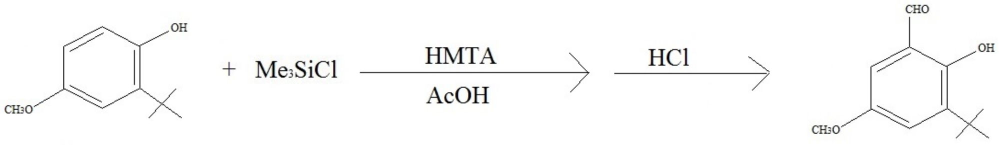
^{1}H NMR indicated that the products were so impure that it was too difficult to distinguish product from impurity

The final starting material used during the research was butylated hydroxyanisole. The Duff reaction and the modified reaction produced 3-(1,1-dimethylethyl)-2-hydroxy-5-methoxy-benzaldehyde in relatively high yields. The Duff reaction produced yields ranging from 58-81% for four reactions (VIII). The modified reaction produced yields of 77-89% for three reactions (IX).



58-81%

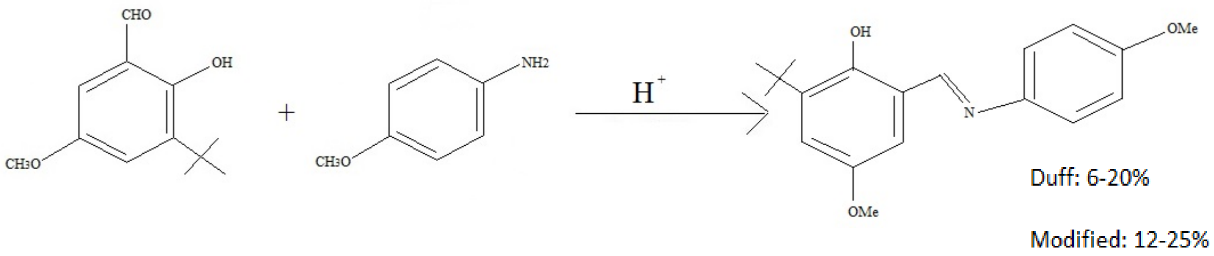
VIII



77-89%

XI

However, the ^{1}H NMR indicated that both reactions contained contaminants along with the desired product. The product was an oil which indicated that recrystallization might not have been a viable method of purification. The first attempt to purify the compound was to synthesize an oxime because oximes are normally easy to crystalize. The oxime failed to form. It was then decided to form an imine because the imine would form a crystalline structure. 2-(1,1-dimethylethyl)-4-methoxy-6-[[(4-methoxyphenyl)imino]methyl]-phenol was able to crystalize and be collected with a yield of 6-20% for the Duff reaction and 12-25% for the modified reaction (X).



Duff: 6-20%

Modified: 12-25%

X

This showed that the true yield of 3-(1,1-dimethylethyl)-2-hydroxy-5-methoxy-benzaldehyde was 4-9% for the Duff reaction and 9-13% for the modified reaction.

In conclusion, the addition of trimethylsilyl chloride was able to increase the yield for several of the compounds, although each increase was to a different extent, but not all of the compounds had an increased yield. The reason for the modest and variable yield improvement is not known

Experimental

2-Naphthol Reaction Using Trimethylsilyl Chloride

2-Naphthol (0.69 g, 4.8 mmol) and HMTA (0.68 g, 4.9 mmol) were dissolved in 10 mL acetic acid in a 50 mL round bottom flask. The solution was stirred for 5 min. Trimethylsilyl chloride (0.58 g, 5.3 mmol) was added and immediately precipitate began to form. The solution was heated at reflux for 1 h. The precipitate had dissolved and the solution was orange. 10 mL HCl (1 M) was added and the solution was heated at reflux for 45 min. 100 mL water was added to the solution which was then cooled in an ice bath. Precipitate formed and was filtered using a Bbüchner funnel and washed with water. The product was then placed on the hi-vac line to dry. The weight of 2-hydroxy-1-naphthaldehyde produced was 0.61 g. The percent yield was 74%. ^{1}H NMR δ: 7.17 (d, 1H), 7.46 (t, 1H), 7.64 (t, 1H), 7.81 (d, 1H), 8.00 (d, 1H), 8.35 (d, 1H), 10.83 (s, 1H), 13.19 (s, 1H)

4-Tert-Butylphenol Reaction

4-Tert-butylphenol (0.72 g, 4.8 mmol) and HMTA (0.68 g, 4.9 mmol) were dissolved in 10 mL acetic acid in a 50 mL round bottom flask. The solution was stirred for 5 min. The solution was heated at reflux for 1 h. 10 mL HCl (1 M) was added and the solution was heated at reflux for 45 min. 100 mL water was added to the solution which was then cooled in an ice bath. The solution was extracted with diethyl ether (2x50 mL). The extracted ether layers were then washed with 50 mL water followed by saturated sodium bicarbonate (2x25 mL). Magnesium sulfate was added and swirled in the solution. It was filtered and the diethyl ether was evaporated using the rotovap. The product was then placed on the hi-vac line to dry. The weight of 5-tert-butylsalicylaldehyde was 0.65 g. The percent yield was 76%. ^{1}H NMR δ: 6.8 (d, 2H), 7.52 (d, 1H), 7.63 (d, 1H), 9.92 (s, 1H)

8-Hydroxyquinoline Reaction

8-Hydroxyquinoline (0.70 g, 4.8 mmol) and HMTA (0.68 g, 4.9 mmol) were dissolved in 10 mL acetic acid in a 50 mL round bottom flask. The solution was stirred for 5 min. The solution was heated at reflux for 1 h. 10 mL HCl (1 M) was added and the solution was heated at reflux for 45 min. 100 mL water was added to the solution which was then cooled in an ice bath. The solution was extracted with diethyl ether (2x50 mL). The extracted ether layers were then washed with 50 mL water followed by saturated sodium bicarbonate (2x25 mL). Magnesium sulfate was added and swirled in the solution. It was filtered and the diethyl ether was evaporated using the rotovap. The product was then placed on the hi-vac line to dry. The weight of 8-hydroxy-7-quinolinecarboxaldehyde was 0.28 g. The percent yield was 33%. H NMR δ: The compound was so impure that it was too difficult to distinguish product from impurity.

Butylated Hydroxyanisole Reaction Using Trimethylsilyl Chloride

Butylated Hydroxyanisole (0.87 g, 4.8 mmol) and HMTA (0.68 g, 4.9 mmol) were dissolved in 10 mL acetic acid in a 50 mL round bottom flask. The solution was stirred for 5 min. Trimethylsilyl chloride (0.58 g, 5.3 mmol) was added. The solution was heated at reflux for 1 h. 10 mL HCl (1 M) was added and the solution was heated at reflux for 45 min. 100 mL water was added to the solution and cooled in an ice bath. The solution was extracted with diethyl ether

(2x50 mL). It was then washed with 50 mL water followed by sodium bicarbonate (2x25 mL). Magnesium sulfate was added and swirled in the solution. It was filtered and the diethyl ether was evaporated using the rotovap. The product was then placed on the hi-vac line to dry. The weight of 3-(1,1-dimethylethyl)-2-hydroxy-5-methoxy-benzaldehyde was 0.89 g. The percent yield was 89%. H NMR δ: 1.46 (s, 7H), 3.80 (s, 4H), 6.83 (s, 2H), 7.28 (s, 1H), 9.86 (s, 1H), 11.55 (s, 1H)

Imine Formation Using 3-(1,1-Dimethylethyl)-2-Hydroxy-5-Methoxy- Benzaldehyde

3-(1,1-dimethylethyl)-2-hydroxy-5-methoxy-benzaldehyde (0.38 g, 1.8 mmol) was dissolved in minimal ethanol. P-Anisidine (0.22 g, 1.8 mmol) was added to the solution causing the solution to become dark brown-orange. 2 drops of acetic acid were added and the solution was heated at 95 ^{o}C for 1h. The solution was allowed to cool and was placed in the freezer overnight. Orange precipitate formed, was filtered using a Hirsch funnel and was washed with ice cold ethanol. The precipitate was placed on the hi-vac line. The weight of 2-(1,1-dimethylethyl)-4-methoxy-6-[[(4-methoxyphenyl)imino]methyl]-phenol was 0.13 g. The percent yield was 25%. H NMR δ: 3.83 (s, 7H), 3.87 (s, 7H), 6.74 (s, 1H), 6.97 (d, 2H), 7.05 (d, 1H), 7.34 (t, 3H), 8.61 (s, 1H), 13.67 (s, 1H)

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