Synthesis of Diarylmethanes Similar to the Norjuliol Complex

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ABSTRACT: Leishmaniasis is a parasitic disease that kills hundreds of thousands annually, recently a compound to combat it has been isolated, called Norjuliol. We tested a possible synthesis pathway to create Norjuliol like compounds, for future Norjuliol synthesis and anti-leishmaniasis testing. The products of the different synthesis steps were characterized using proton NMR (400 MHz). The results show the hydrazone and boronic acid synthesis pathway should not be used for Norjuliol. Previous research has shown that the synthesis with methoxy groups on the boronic acid is possible, but the data collected demonstrated the reaction difficult with multiple methoxy groups. The initial testing of Norjuliol like compounds with alcohol groups against leishmaniasis has shown promise and have shown better results than the current treatment. Further testing is needed for definitive conclusions to be drawn.

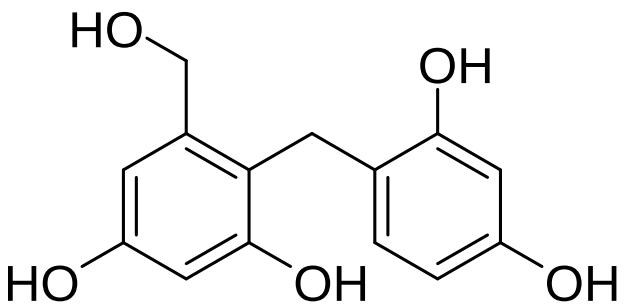
INTRODUCTION

Leishmaniasis is a neglected tropical disease according to the World Health Organization (WHO)[1] and the Centers for Disease Control and Prevention (CDC).[2] Neglected tropical disease means that there is very little research being done on the disease compared to others and that it is mainly situated in the tropics near the equator. It is a parasitic disease that is spread by female sand flies and comes in three types. Cutaneous leishmaniasis, the most common form causes skin sores that can change in size and appearance over time.[2] Mucosal leishmaniasis infects the mucous membranes of the nose, throat, and mouth.[2] The last is visceral leishmaniasis, and it is the deadliest. It infects several internal organs and if left untreated it is likely to be fatal.[2] There are cases in 90 countries and there are over normally over a million new cases every year.[2] Many of the cases of leishmaniasis are in more impoverished areas.[1] The current treatment of leishmaniasis is expensive and a form of chemo therapy, meaning the treatment is administered over a long period of time, and the body is damaged along with the parasite. Neither of these factors are good for those in impoverished areas.

Recently, an isolated compound from the fungus Geosmithia Langdonii showed promising anti-leishmaniasis properties.[3] The compound is a diarylmethane with two hydroxy groups on both rings and one with a primary alcohol (Norjuliol). Diarylmethane compounds are difficult to synthesis in addition this molecule has numerous reactive OH groups adding even more difficulty. One way to synthesize a diarylmethane with a very high yield is to use a tosylhydrazone bonded to one benzene ring and a boronic acid bonded to the other.[4] Norjuliol-like compounds have previously been synthesized successfully using this method.[5]

This research will be synthesizing Norjuliol-like as well but it will have one benzene ring without additional bromine bonded to it. The previous study focused on forming a compound that had the two benzene rings with some hydroxy groups on them and numerous bromines bonded to the rings. This research focused on

Scheme 1: Norjuliol



making a diarylmethane compound with one benzene ring that was the exact same as Norjuliol with a halogen (in this case fluorine) on the other. The molecules synthesized were characterized using proton nuclear magnetic resonance (NMR). This will help us understand the feasibility of manufacturing Norjuliol using this pathway without the extra bromine groups. If successful, this pathway can be used to develop Norjuliol for further testing and hopefully medication.

MATERIALS AND METHODS

Chemical Preparation

General Procedure for Hydrazone Creation. A mixture of the appropriate benzaldehyde (1 mmol), p-toluene-sulfonyl-hydrazide (186.23 mg, 1 mmol), in 10 ml of methanol was brought to reflux and stirred until reaction completed (30-60 min). Remaining methanol was evaporated off, and product was left to dry overnight. 2,4-methoxy: H NMR (400 MHz) δ 8.15 (s, 1H), 7.84 (d, J = 8.24 Hz, 2H), 7.78 (d, J = 8.70 Hz, 1H), 7.29 (d, J = 8.24 Hz, 2H), 6.51 (dd, J = 2.29, 8.70, 2.29 Hz, 1H), 6.38 (d, J = 2.29 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 2.39 (s, 3H). C NMR (100 MHz)

Coupling of Hydrazone and Boronic Acid Procedure. A mixture of the 2,4-methoxy-tosylhydrazone (202.27 mg, 2/3 mmol), 2-fluoro-phenyl-boronic acid (139.92 mg, 1 mmol), potassium

carbonate (138.21 mg, 1 mmol), and 5 ml of dioxane was brought to reflux (at ~110 ºC) and monitored by TLC. When the reaction is complete and then cooled to room temperature it was separated into layers with dichloromethane and saturated $NaHCO_3$ solution. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with two portions of saturated NaCO3 solution, one of brine, then dried with MgSO4 and filtered. The filtered solution was then run through a silica gel column for purification. Coupling product: H NMR (400MHz) δ 7.16 (1st Multiplet, 2H), 7.14 (1st Multiplet, 2H), 7.12 (1st Multiplet, 2H), 7.11 (1st Multiplet, 2H), 7.09 (1st Multiplet, 2H), 7.03 (2nd Multiplet, 3H), 7.01 (2nd Multiplet, 3H), 6.99 (2nd Multiplet, 3H), 6.97 (2nd Multiplet 3H), 6.46 (d, J = 2.21 Hz, 1H), 6.41 (dd, J = 2.29, 8.24, 2.29 Hz, 1H), 3.92 (s, 2H), 3.79 (s, 6H).

Figure 1

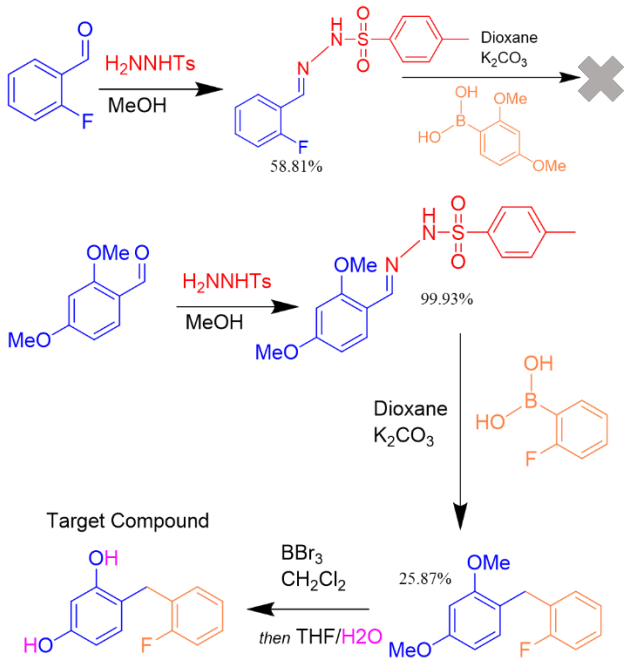


Figure 1. Overall Synthesis: This is the overall synthesis pathway that was used in this research. The first pathway shown on top was unsuccessful at the coupling stage, represented by the gray "x" mark. The second pathway shown below that did have a successful coupling reaction. The pathways begin by making a tosylhyrdazone with one of the benzene rings of the desired product and then coupling it with the other ring in the form of boronic acid. The final step is removing the methoxy protecting groups and making them OH groups by using BBr_3. Initially 2-fluoro-benzaldehyde was used to make the hydrazone. The reaction was fairly successful with a yield of 59%. The coupling reaction of this hydrazone was unsuccessful. The second hydrazone was made with 2,4-dimethoxy-benzaldehyde, and practically had a perfect yield (99.93%). This time the coupling reaction was successful. However, the yield for the coupling reaction was only about 26%. There was not enough time remaining to remove the protecting groups after the successful coupling reaction

RESULTS AND DISCUSSION

Synthesis Pathway

Figure 1 shows the overall synthesis pathways that were conducted and the percent yields of the compounds that were produced. Both pathwaysinvolve the combination of two benzene rings to make a diarylmethane following the procedure from Barluenga et Al.[4] Where an initial hydrazone was made with one of the benzene rings and coupled with a boronic acid with the other. The initial pathway was unsuccessful at the coupling step. It is theorized that this was unsuccessful due to the two methoxy groups on the boronic acid making it a weaker nucleophile. The fluorine boronic acid did not have this problem and the methoxys made the second hydrazone a better electrophile, thus the coupling reaction of the second synthesis pathway proceeded smoothly.

The yield for the second hydrazone reaction was very high while the yield for coupling was 26%. This appears at odds previous works where the yields for the coupling reaction were only very rarely below 60% and never below 50%. These drastic differences are most likely due to not monitoring the reaction by GC-MS(GC-MS was able to double check whether all of the initial reactants had reacted yet). Overall, the coupling reaction was successful and demonstrates that this process of synthesizing diarylmethanes is efficient. Further study is needed to determine if these reactions would be appropriate for Norjuliol synthesis.

NMR Data of Product 1 and Yields

The first hydrazone synthesized (Figure 2) used 2-fluoro for its benzaldehyde and the NMR data found was similar to the spectra of other literature such as McMahon et. al. There were two triplets while the rest of the peaks were doublets or singlets. The hydrogens with both of their adjacent carbons being bonded to a hydrogen are the two triplet peaks that are boxed in green. The less shielded of the two, on the left, is most likely the hydrogen in the para position where there is more of an interaction with fluorine. The data acquired was what was expected, although there were some differences such as the interference from fluorine and the lack of the NH peak in the early 11 parts per million. The ^{1}H NH peak did not show in our NMR due to the hydrogen deuterium exchange between the NH hydrogen and the deuterated chloroform it was dissolved in.

Figure 2

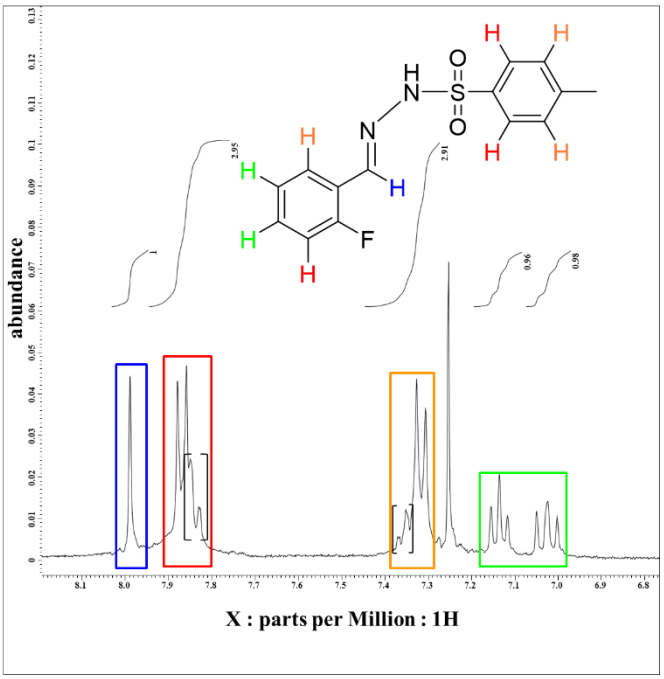


Figure 2. Synthesis of Hydrazone: This is the aromatic region of the proton NMR of the product created from the mixture of 2-fluoro-benzaldehyde and p-toluene-sulfonyl-hydrazide. The two triplet peaks correspond to the two green hydrogens on the left benzene ring since those are the only hydrogens with two hydrogen atoms on carbons adjacent to their own. The orange hydrogens correspond to the orange boxed peaks since they are the most shielded hydrogens on the benzene rings other than the triplet peaks. The red hydrogens are much less shielded than the orange ones due to their close proximities to oxygen or fluorine. The most deshielded hydrogen must be the blue one since it is bound to an imine and is in proximity of the very electronegative fluorine. The peaks in brackets are due to interference by fluorine on the hydrogens on its benzene ring (the one unlabeled peak is the chloroform-d used as the solvent for the NMRs).

Figure 3

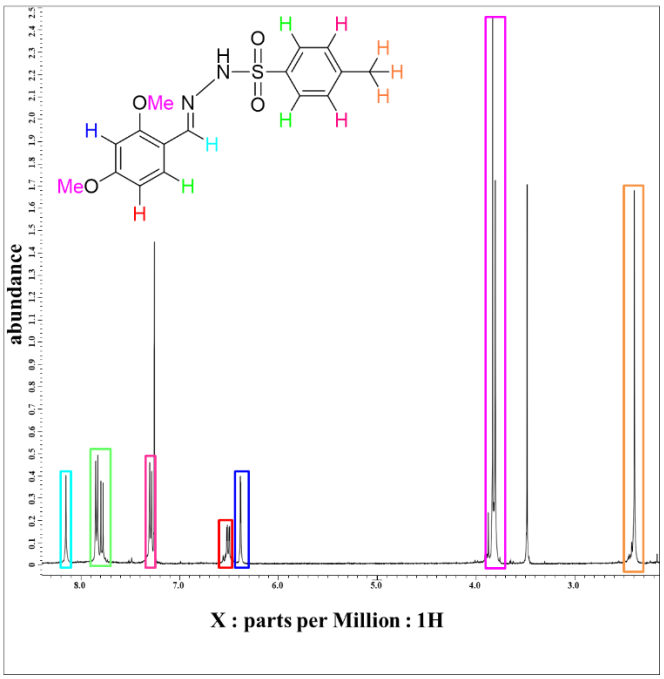


Figure 3. Reversed Hydrazone: This is the proton NMR of the product created from mixing 2,4-di-OMethyl-Benzaldehyde and p-toluene-sulfonyl hydrazide. The most downfield peak in cyan once again is the hydrogen off of the imine (normalized peak). The furthest upfield peak represents the orange colored hydrogens due to it integrating to 3. The magenta peaks are the hydrogens from the O-methyl groups due to them integrating to 6. The hydrogen in red has a doublet of doublets peaks to represent it due to the coupling from the hydrogens in the ortho and meta positions on the benzene ring. The hydrogen in blue also has a slight doublet due to it being coupled from a hydrogen in the meta position and none in the ortho position. Both of the two recently mentioned hydrogens are upfield from the aromatic region due to the shielding from the oxygens that are bonded to adjacent carbons. (The peaks that are not outlined are D-chloroform and methanol)

NMR Data of Product 2 and Yields

The second hydrazone synthesized (Figure 3) used 2,4-methoxy for its benzaldehyde. Unlike the previous hydrazone synthesized there was no previous literature to compare the spectrum to. The peaks when integrated did contain the 17 hydrogens expected (this is excluding the NH peak). The NMR data also had two peaks that were exceptionally similar to the previous NMR with the imine hydrogen being just above 8ppm and methyl group on the hydrazone showing up at nearly 2.4ppm with an integration of 3H. The large peaks boxed in magenta represent the methoxy groups since they integrate to 6H, are far from the aromatic region hydrogens, and is near the methyl group. The peaks in the aromatic region are all doublets, as expected since there is mainly only one adjacent carbon bonded to hydrogen. The peaks are at similar ppm to the previous hydrazone being around 7.8 and 7.3ppm. The only surprising peaks

were the doublet of doublets around 6.5ppm and the doublet around 6.4ppm. These peaks, boxed in red and blue respectively, represent the hydrogens next to the methoxy groups on the benzene ring. Most likely they are below the usual aromatic region due to the methoxy groups repelling the hydrogens' electrons causing more shielding. The hydrogen between the methoxy groups is a doublet rather than a singlet because of the coupling between the hydrogen in the meta position from it on the ring, the doublet of doublets is not a doublet for the same reasons. It is interesting to note that this hydrazone synthesis had a yield greater than 90% and it required no purification other than the removal of the solvent. Due to how efficient the reaction is, it would be intriguing to see what other useful or significant compounds can be made with hydrazones.

Figure 4

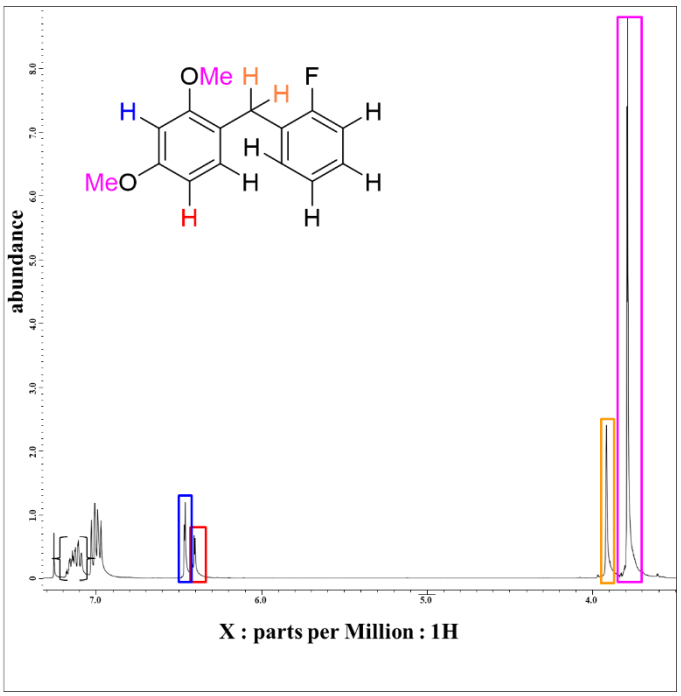


Figure 4. Coupling Synthesis: This is the proton NMR of the product created from the coupling reaction of the reversed hydrazone and 2-fluoro phenyl boronic acid, and after purifying by column chromatography. The peak outlined in magenta integrates to 6 so it represents the 6 hydrogens from the two O-methyl groups. The singlet in orange integrates to two and is relatively upfield so it represents the two hydrogens on the bridging carbon. The red and blue hydrogens are similar to how they were in the reversed hydrogen. The doublet of doublets is the hydrogen affected by the ortho and meta coupling. While the slightly doublet blue peak is the hydrogen that only has a coupling in the meta position. The multiplet in brackets is affected by the fluorine similarly to how a couple of peaks in the first hydrazone were.

NMR Data of Product 3 and Yields

The only one of the two coupling reactions that was successful synthesized the molecule in Figure 4. The two methoxy peaks are again around 3.7ppm. Now there is also a peak that integrates to 2H at around 3.9ppm that represents the hydrogens on the bridging carbon of the two benzene rings. There is also the reappearance of the doublet of doublets and the doublet around 6.4 and 6.5ppm. The integrations of the peaks show that there are only the 15 hydrogens expected. The analysis of the coupling NMR became more difficult for the peaks in the aromatic region due to there being two multiplets that are difficult to distinguish as individual hydrogens. The multiplet in brackets also appears to have the fluorine interference that was observed in the first hydrazone. It would be interesting to see what information a ^{19}F NMR would show if used to analyse the compound. This coupling reaction appears to have been successful demonstrating the viability of this diarylmethane synthesis pathway. The unsuccessful attempt was monitored by TLC and showed that after refluxing there was starting material present and no product (the hydrazone and boronic acid).

CONCLUSION

The synthesis of diarylmethane compounds using hydrazones and boronic acids has shown success. However, our results suggest this method is not suitable for Norjuliol synthesis due to the 0% yield of the first coupling reaction. As demonstrated in the first synthesis pathway, the two methoxy groups on the boronic acid prevented the coupling reaction from occurring. Norjuliol has multiple hydroxyl groups on both rings which are methoxy protecting groups until after the coupling reaction. So, no matter which ring is used to create the initial hydrazone, the boronic acid would have methoxy groups. Previous research has shown that the reaction can be successful with one methoxy group. More research must be done before this synthesis pathway can be used to produce Norjuliol, or a separate pathway must be implemented.

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Fort Lewis College Chemistry Department

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