Sulfanilamide Synthesis with a Modern Silyl-Sulfinylamine Willis Reagent

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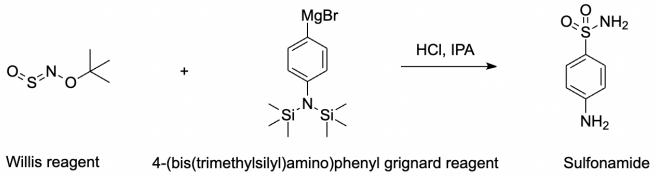
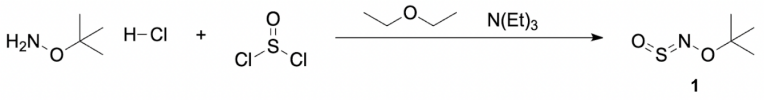
Abstract

In this experiment, a novel synthetic approach is performed to produce sulfanilamide, a “sulfa” drug that contributed to the proliferation of many antibacterials in the early 20th century. Despite the early ubiquitous use of sulfanilamide as a front-line remedy, no synthesis pathway is feasibly accomplished with safe reagents and in a timely manner. Commonly, aniline would be protected followed by sulfonation with gaseous SO_2 and deprotection. A Willis reagent allows for a modern and convenient alternate route that involves a one step addition with a Grignard to produce the final sulfonamide after workup. The generation of the short-lived Willis reagent from commercially available starting products is confirmed as well as its efficacy to add a sulfinyl group to the substrate.



Reaction Scheme 1



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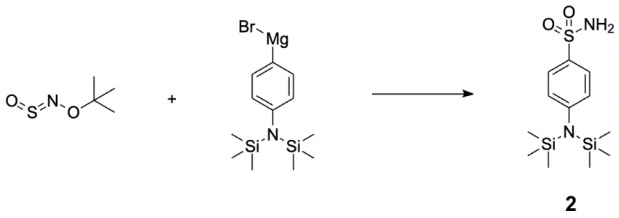

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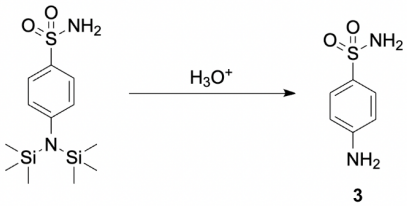


Introduction

Sulfanilamide is an aniline-derived sulfonamide and one of the first synthesized antibacterial drugs in the start of the 20th century. A limitation to antibacterial small molecule drugs is the rapid tendency for bacteria to develop anti-bacterial resistance, lending to an arms race between advances in novel drug production and evolution driving survival of the fittest by selecting for antibiotic-resistant genes. Azo dyes quickly became a desirable starting material to turn to sulfa drugs. One notable example is Prontosil which was discovered to have the same active pharmacophore as sulfanilamide.[1] The breakthrough that valuable drugs could be synthesized from seemingly tangential precursors in the early 1900s led to a proliferation of "sulfa" drugs and revolutionized the age of chemotherapeutics.[2, 3]

Despite the simplicity of the structure of sulfanilamide, the reagents in the conventional synthesis protocol are often acutely toxic and hazardous according to modern safety standards. Namely, sulfonation requires the generation of SO_2 gas *in situ*, which necessitates a great deal of patience in allowing dissolved SO_2 to react with the aniline substrate along with the risk of extreme heat generation and toxic gas evolution. Sulfonation can be conveniently performed with chlorosulfonic acid, but the reagent is violently reactive with water. In this experiment, a different synthetic angle was explored to create sulfanilamide which would be markedly more efficient and safe. This method involves a Willis reagent which performs SO_2 addition through a O-(tert-Butyl)-N-sulfinylhydroxylamine (t-BuONSO) intermediate that houses a relatively stable aqueous thionyl intermediate.[4] This eliminates the need to rely on SO_2 gas dissolved in water to nucleophilically attack the substrate, but directly substitutes the thionyl group onto O-(tert-butyl)hydroxylamine hydrochloride to form the activate sulfonation reagent t-BuONSO. The next step utilizes a grignard reagent (4-[Bis(trimethylsilyl)amino]phenylmagnesium), which overall achieves the same effect as a sulfonation. This further eliminates the need to protect the aniline with an acetamide. Overall, this approach is drastically different from the standard reaction flow to synthesize sulfanilamide[1]. This experiment details the methodology to perform this full synthesis with most emphasis on confirming the validity of the Willis reagent.

Experimental Methods

In a 50mL erlenmeyer flask, O-(tert-Butyl)hydroxylamine hydrochloride (450mg, 3.58mmol, 1 equiv) was dissolved in 15mL dichloromethane and cooled to 0 °C in an ice bath. After the solution was fully dissolved, triethylamine (1.5mL, 11mmol, 3 equiv) was added and a white solid precipitate was observed. After letting the solution sit for

10 minutes, thionyl chloride was added (0.263μL, 3.58mol, 1 equiv) over 30 minutes dropwise with a syringe. The reaction was stirred for 2 hours on ice while letting the ice bath melt to reach room temperature. The reaction mixture was diluted with roughly 15mL of diethyl ether, filtered through celite and the solvent evaporated under reduced pressure. The crude mixture from Day 1 was purified with distillation (72°C, 40mbar) to yield a colorless liquid **1** (0.500g, 103% yield). The intermediate was stored at -20°C.

42.5mg (314μmol, 1 equiv) of **1** was dissolved in 1.2mL THF in a glass vial and cooled to -78 °C in dry ice and acetone. Subsequently added 600μL of 0.5M 4-[Bis(trimethylsilyl)amino]phenylmagnesium bromide (0.1g, 0.3mmol, 1 equiv) solution to the glass vial and the reaction was then taken out of the dry-ice-acetone bath and allowed to warm to room temperature and stirred for 24h to yield **2**. The resulting product would be purified with flash chromatography.

To work up **2**, 2x volume isopropanol would have been added as well as a few drops of dilute hydrochloric acid with stirring for 30 minutes. Filtering through celite and evaporating the solvent off with a rotavap would have produced the deprotected product **3,** but only **2** could be obtained and without mass characterization.

O-(tert-Butyl)hydroxylamine hydrochloride: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.07 (s, 2H), 3.11 (s, 1H), 1.42 (s, 4H).

1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H).

4-[Bis(trimethylsilyl)amino]phenylmagnesium bromide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (dt, J = 6.6, 3.7 Hz, 1H), 1.81 (tt, J = 5.2, 2.1 Hz, 1H).

2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1H), 3.68 (s, 8H), 1.79 (s, 9H).

None of the products or starting materials could be identified on IR and GCMS.

Results and Discussion

Reaction Scheme 1:

Several optimizations were necessary in order to obtain a pure form of t-BuONSO that could be used in the subsequent steps in the synthesis. Stirring the reaction for one hour after dropwise addition of thionyl chloride did not yield a significant peak in the NMR spectrum, where it was evident that the starting product still dominated as the major species. Furthermore, adding an arbitrary amount of diethyl ether allowed the

precipitate to crash out after stirring the reaction, but filtration and evaporation of solvent resulted in a uniform layer of yellow crystals on the surface of the flask. The mass of the crystals greatly exceeded the expected product, suggesting that there was a significant amount of triethylammonium precipitate that was not neutralized and extracted away from the desired product.

Repeating the experiment with two hours of stirring and excess diethyl ether allowed for a yellow liquid to be obtained after addition of reagents, stirring, filtering, and evaporating the solvent. Distilling under the short path distillation apparatus yielded no distillate, however, and the few drops of liquid that remained in the flask evolved some gas, likely SO_2, and turned brown when reaching the theoretical boiling point of t-BuONSO. Two influential factors were hypothesized to be the volume of distillate being too little to distill over as well as the quality of the thionyl chloride being used, as there was little to no gas effervesced during dropwise addition of thionyl chloride, and temperature increase was mild.

Using a new thionyl chloride and measuring an aliquot of the new amount in a nitrogen-filled environment was drastically influential in the visual course of the reaction. Gas evolution was seen upon each dropwise addition of thionyl chloride to O-(tert-butyl)hydroxylamine hydrochloride, and the resulting liquid to be distilled in the short path distillation distilled at exactly 72°C and was clear. Roughly 0.500g of liquid was collected in duplicate trials, and the peaks obtained from an ^1H NMR matched what was expected for both the starting material and the Willis reagent (see Experimental Figures 1 and 2).

Reaction Scheme 2 and 3:

The NMR spectrum of the 4-[Bis(trimethylsilyl)amino]phenylmagnesium bromide suggests an impure starting material or a completely different material than the ordered compound. This is most suggested by the fact that there are no representative hydrogens in the aromatic region. However, the trimethyl groups seemed intact as the number of hydrogens and chemical shift seemed to match what would be expected (see Experimental Figure 3). Nonetheless, after the Willis Reagent was isolated, the reaction between the Willis reagent and 4-[Bis(trimethylsilyl)amino]phenylmagnesium bromide seemed to result in the addition of the sulfamide group. The chemical shifts of the peaks in the parent molecule did not change, and only the addition of an amide peak at δ7.20 with 2 hydrogens appeared, which is consistent with the Willis reaction (see Experimental Figure 4). Overall, this suggests that the Willis reagent performed its

role successfully, which could be confirmed in future experiments using techniques other than IR or GCMS. Running this product on a silica column or working it up with hydrochloric acid and isopropyl alcohol is reported to deprotect the trimethyl groups and yield the desired sulfanilamide.[4]

Conclusion

In this experiment, the Willis reagent was successfully created from O-(tert-Butyl)hydroxylamine hydrochloride after iterating various methods to maximize purity and volume of the liquid before and after distillation. This product is able to add a sulfinyl group to its complementary substrate, where follow up characterizations can confirm the validity of sulfanilamide formation. This use of the Willis reagent can be explored and extended to other sulfanilamide derivatives beyond what is reported by Davies et al. to potentially form new active forms of antibiotics and therapeutics.[4]

References

(1) Bentley, R. Different Roads to Discovery; Prontosil (Hence Sulfa Drugs) and Penicillin (Hence β-Lactams). *Journal of Industrial Microbiology & Biotechnology* **2009**, *36* (6), 775–786.

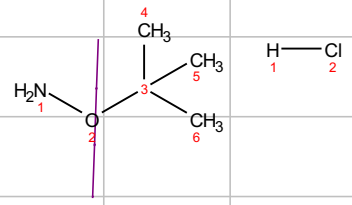
(2) Turkmen, H.; Zengin, G.; Buyukkircali, B. Synthesis of Sulfanilamide Derivatives and Investigation of in Vitro Inhibitory Activities and Antimicrobial and Physical Properties. *Bioorganic Chemistry* **2011**, *39* (3), 114–119.

(3) Emmett, E. J.; Willis, M. C. The Development and Application of Sulfur Dioxide Surrogates in Synthetic Organic Chemistry. *Asian Journal of Organic Chemistry* **2015**, *4* (7), 602–611.

(4) Davies, T. Q.; Tilby, M. J.; Skolc, D.; Hall, A.; Willis, M. C. Primary Sulfonamide Synthesis Using the Sulfinylamine Reagent *n*-Sulfinyl-*o*-(*Tert*-Butyl)Hydroxylamine, *t*-Buonso. *Organic Letters* **2020**, *22* (24), 9495–9499.

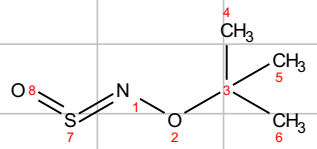
finalprojday4

^{1}H NMR (400 MHz, cdcl$_3$) δ 12.07 (s, 2H), 3.11 (s, 1H), 1.42 (s, 4H).



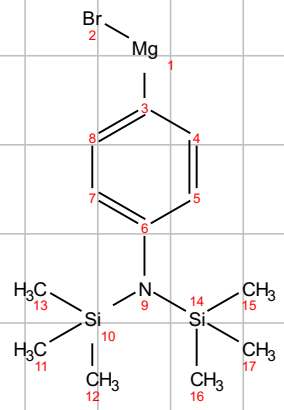
finalprojday8methoxygood

^{1}H NMR (400 MHz, cdcl$_3$) δ 1.40 (s, 1H).



finalprojday8grigstart

^{1}H NMR (400 MHz, cdcl$_3$) δ 3.72 (dt, J = 6.6, 3.7 Hz, 1H), 1.81 (tt, J = 5.2, 2.1 Hz, 1H).



^{1}H NMR (400 MHz, cdcl$_3$) δ 7.20 (s, 1H), 3.68 (s, 8H), 1.79 (s, 9H).