Synthesis of Piperidino{*o*-[(trimethylsilyl)methyl]phenyl}methanone by a Directed Ortho Lateral Lithiation Reaction

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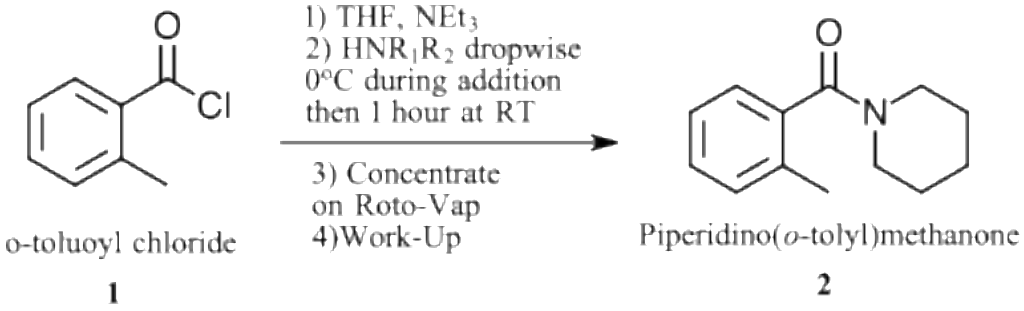
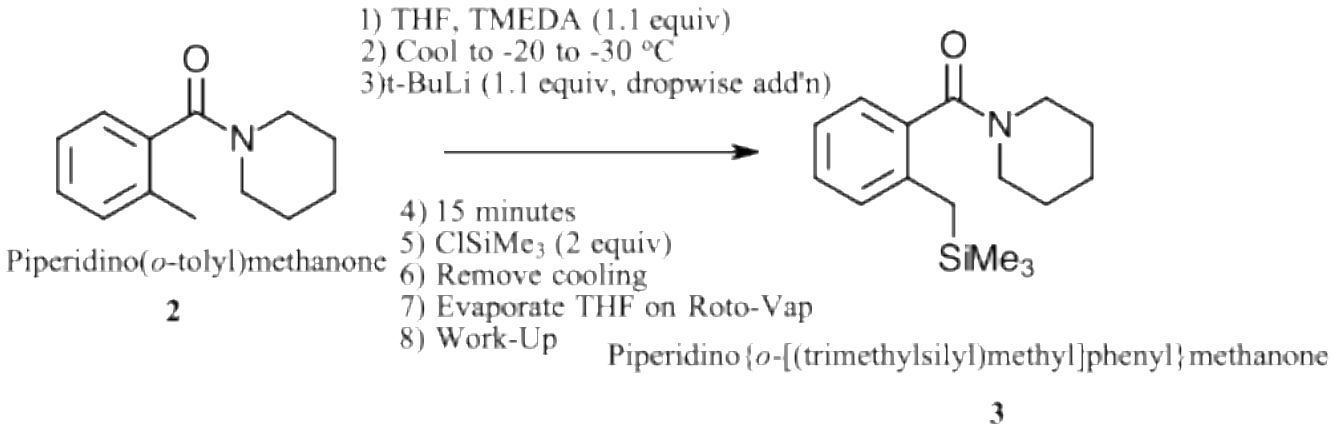
Step 1: Reaction conditions for synthesis of tertiary amide



Step 2: Benzylic Lithiation and Electrophile Reaction



ABSTRACT: A direct ortho lateral lithiation for the synthesis of Piperidino{o-[(trimethylsilyl)methyl]phenyl}methanone (**3)** (45% yield, 0.9062 g) was synthesized from a Piperidino(o-tolyl)methanone (**2) (**84% yield, 8.3846 g**).** Derivatives of these compounds have shown great promise in being used as pharmaceutical settings to help fight human diseases. This work has been adapted from the late great Victor Snieckus. The products were determined using Fourier Transformation Infrared Spectroscopy (FTIR) and Proton Nuclear Magnetic Resonance (NMR).

INTRODUCTION Directed ortho metalation reactions have been widely studied since their discovery in 1939, with applications in pharmaceutical synthesis and herbicide development. Victor Snieckus was one of the earlier contributors to these reactions with his application in directed lithiation of *N,N*-dimethylbenzamides by treating it with sec-BuLi to produce ortho lithiated amides.[1] After his passing in late 2020, his work has been continued on at various institutions to further the use of directed ortho metalations. For example, there have been five compounds in recent years that have shown promise as therapeutic agents for the treatments of human diseases.[2] Furthermore, benzamides play a crucial role in pharmaceutical settings. According to studies, there are some benzamide derivates that may have effects when it comes to heart failure.[3] Due to these potentially life-altering effects, it is imperative to study direct ortho metalations and gain a deeper understanding to further carry Victor Snieckus' legacy. In this experiment, a Piperidino{o-

[(trimethylsilyl)methyl]phenyl}methanone (**3)** was synthesized from a Piperidino(o-tolyl)methanone (**2).** To determine if the correct product was synthesized, the products were examined using Fourier Transform Infrared Spectroscopy (FTIR) and Nuclear Magnetic Resonance (NMR).

MECHANISM The starting material **2** was prepared in step 1. Triethylamine was used to remove a proton from piperidine and turn it into a nucleophile. Once piperidine was a nucleophile, it attacked the carbonyl carbon on **1** which then produced **2**. This tertiary amide was used to create the final product **3**. Sec-butyllithium (sec-BuLi) was added in a solution of **2** and THF and TMEDA. The TMEDA was used to help direct the sec-BuLi to the ortho position of the benzoyl group. The N on piperidine helped orient the sec-BuLi to the ortho position of the benzene. Additionally, the use of cold reaction conditions helped reduce the reactivity of sec-BuLi to allow reaction with the desired ortho position. Once Li was attached, the carbon was nucleophilic and performed an SN2 reaction with $ClSiMe_3$ to produce **3**.

RESULTS/DISCUSSION FTIR was used to confirm the presence of functional groups in the two products synthesized (**2** and **3**). However, the presence of functional groups does not necessarily mean that the correct product was synthesized. To further confirm the product was synthesized, ^{1}H NMR was used to confirm correct orientation of groups.

The tertiary amide **2** was synthesized as proven by IR and NMR. Product **2** was synthesized with a 84% yield and final mass of 8.3846 g. Using FTIR, functional groups were identified confirming the synthesis of **2**.[4] There is a presence of characteristic peaks such as the tertiary amide carbonyl at 1626.37 cm^{-1} and a C-N stretch at 1270.14 cm^{-1} which confirms the addition of the piperidine to the *o*-toluoyl chloride. Using ^{1}H NMR, we can confirm the orientation of the groups. In Figure 2, the presence of various signals is observed. Additionally, the signals present as multiplets which indicate the presence of impurities and steric hindrance. The solvent $CDCl_3$ was also observed around. 7 ppm, it is shown to coincide with the aromatic protons. The aromatic hydrogens were assigned one peak although, each hydrogen is in its own environment, but those signals did not resolve well.

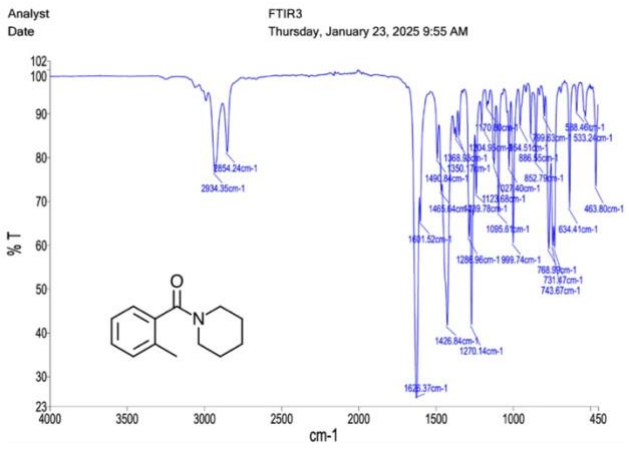


Figure 1. IR spectrum of **2** obtained using FTIR showing the expected functional groups.

Table 1. Summary of functional groups observed by FTIR of **2** shown in Figure 1.

Type of Bond	Wavenumber (cm^{-1})	Intensity
C-H stretch	2934.35	Weak
C=C stretch	1601.52	Medium
C=O (3° Amide)	1626.37	Strong
C-N stretch	1270.14	Strong

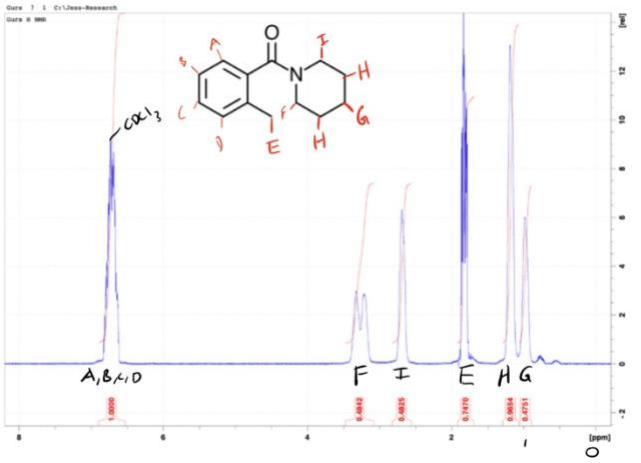


Figure 2. ^{1}H NMR spectrum of **2** showing presence of expected signals represented in *Table 2 in S1*.

After the benzylic lithiation and nucleophilic attack, product **3** was synthesized. Product **3** was synthesized with a 45% yield and final mass of 0.9002 g. The product is confirmed by FTIR and ^{1}H NMR. The IR spectrum obtained shows a characteristic peak at 836.14 cm^{-1} confirming the presence of a Si-C bond. Furthermore, the functional groups shown in **2** are still present. Specifically, the tertiary amide carbonyl at 1741.32 cm^{-1} and a C-N stretch at 1246.01 cm^{-1}. This further confirms that a trimethylsilyl group was added as opposed to the entire structure changing. From the ^{1}H NMR spectrum, the orientation of the functional groups can be observed further confirming that **3** was synthesized. First, an IR table of common solvents and impurities to determine impurities present in **3** was used.[5] Then, three impurity peaks were observed, two for ethyl acetate and one for tert-butyl and reported in *Table 4 in S1*. In addition to the signals present in Figure 2, new signals were obtained around 1.5 ppm representing hydrogen peaks from the piperidine. The spectra showed poor resolution. Apart from the impurities present, the NMR spectra was used to further confirm **3**. From the IC column, it was shown that multiple tubes contained the desired product. Two tubes were further examined with IR and NMR. The IR spectrum for the two did not differentiate enough to confirm which one was **3**. To confirm which was the correct product, NMR was used and the characteristic singlet near 0 ppm was used to confirm the presence of **3** and the other IR and NMR spectra were confirmed to be impurities (0.1924 g 10% yield).

3 has not previously been reported in literature.

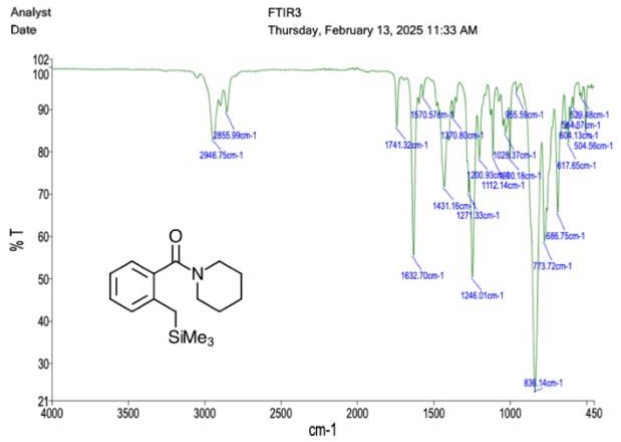


Figure 3. IR spectrum of **3** obtained using FTIR showing the expected functional groups.

Table 2. Summary of functional groups observed by FTIR of **3** shown in Figure 3.

Type of Bond	Wavenumber (cm^{-1})	Intensity
C-H stretch	2946.75	Weak
C=O	1741.32	Weak
C=C	1632.70	Medium
C-N stretch	1246.01	Medium
C-Si	836.14	Strong

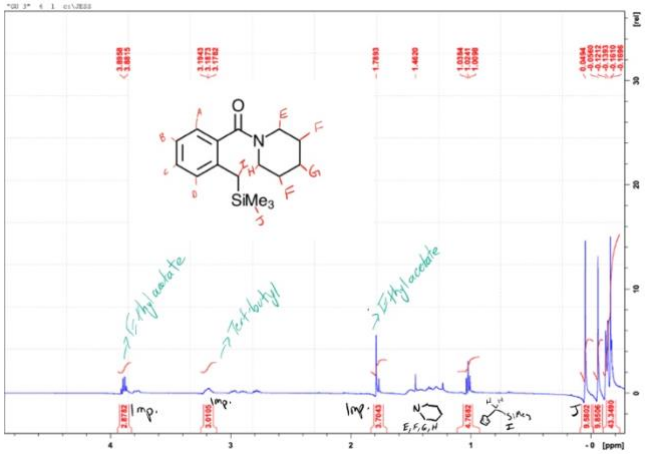


Figure 4. Alliphatic ^{1}H NMR spectrum of **3** showing presence of expected signals represented in *Table 4 in S1*.

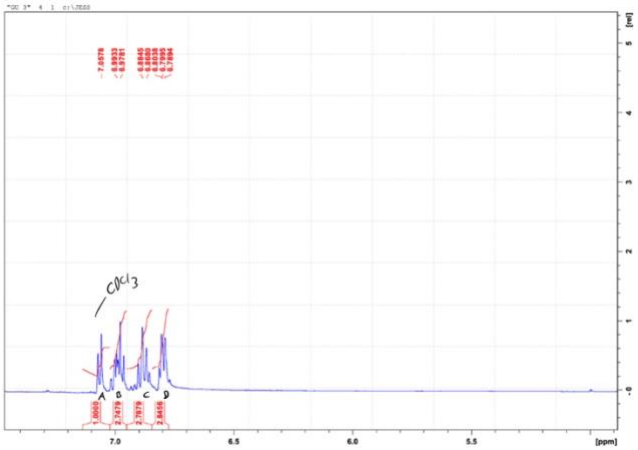


Figure 4. Aromatic ^{1}H NMR spectrum of **3** showing presence of expected signals represented in *Table 4 in S1*.

CONCLUSION The tertiary amide, **2** was synthesized following step 1 with a yield of 84% and mass of 8.3846 g. The product was confirmed using FTIR and NMR. **3** was synthesized following step 2 with a yield of 45% and mass of 0.9062 g. The directed ortho lateral metalation reaction was successful in synthesizing the desired product **3**. This product was also confirmed using FTIR and NMR. **3** has not been reported in literature. Future work would include examining **3** for viability in pharmaceutical settings. Researchers can utilize SwissADME to analyze derivates of directed ortho lateral lithiation reactions for viability as potential drugs.[6]

EXPERIMENTAL All steps were conducted in a fumehood and safety procedures were followed.

To prepare **2,** *o*-toluoyl chloride (6.4 mL) was added to THF (250 mL). To a dropping funnel with ice bath and apparatus, triethylamine (7.2 mL) was added dropwise to produce a cloudy mixture in a 500 mL RBF. Then, piperidine (5 mL) was added to the solution, while mixing to produce a very white opaque solution. The solution was then mixed for one hour. After one hour the solution was placed on the rotovap (150 rpm, 50 ºC) to evaporate the THF. Then in a separatory funnel, ethyl acetate (200 mL) was added to create a milky like solution. After the addition of water (200 mL), the milk solution turned a clear maple syrup colour. After the second wash, the solution was very clear. After the third wash, the ethyl acetate layer was dried in a 500 mL flask with sodium sulfate. The ethyl acetate was then gravity filtered into a clean 100 mL RBF and placed on the rotovap to concentrate and remove THF. The crude product (20.2896 g) was then distilled using a Kugelrohr distillation apparatus. The oily yellow product (8.3846 g) was then analyzed using FTIR and ^{1}H NMR.

To prepare **3**, the yellow oil **2** (1.49 g) was added to THF (40 mL) in a 100 mL RBF. A rubber cork was fastened onto the RBF with a syringe needle connected to a balloon full of N_2. The N_2 atmosphere was kept for the duration of the synthesis. Through the cork, with a syringe, TMEDA (1.2 mL) was added to the solution. The solution

was kept at -78 °C using dry ice and acetone. Then sec-BuLi (15 mL) was added very slowly, dropwise to the reaction. After stirring the reaction for 15 minutes at -78 °C, TMSCL (1.8 mL) was added. The maroon solution was then removed from the ice when TMSCL was finished being added. After adding NH_4Cl (40 mL), the bright yellow solution was placed on the rotovap to remove THF. The olive oil-like solution was parafilmed and stored for a week. Crude product was transferred to a 250 mL separatory funnel using ethyl acetate (50 mL), proceeded by another two ethyl acetate (2 x 50 mL) washings. The combined organic layers were washed with water (50 mL) two times followed by two times with brine (50 mL). After drying the solution with sodium sulfate and gravity filtering, the ethyl acetate was removed by rotovap. The crude product was purified by flash chromatography (EtOAc/hexanes) and analyzed using silica TLC plates. Two products were isolated since they displayed similar properties on the TLC plates (**3** oil with yellow tint 45% yield, **impure product** 9.5% yield). Products were characterized by FTIR and ^{1}H-NMR.

AUTHOR INFORMATION

Author Contributions

The manuscript was written through contributions of Gursevak Uppal and Dr. Jessica Alllingham.

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