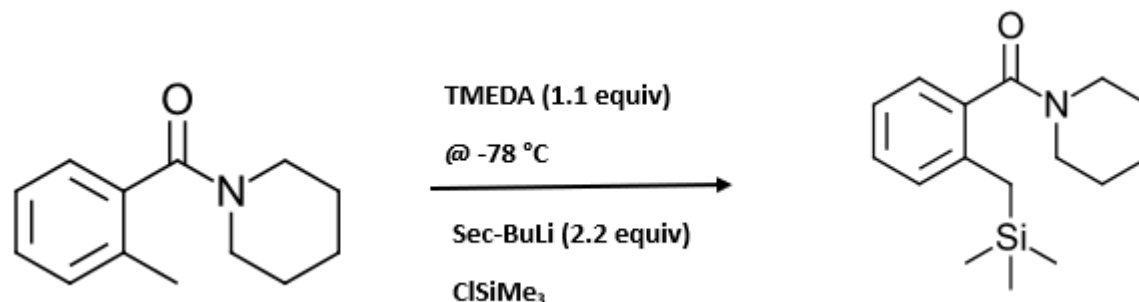


Investigation into the Antifungal Activity of 2-[(trimethylsilyl)methyl]-Tertiary Benzamides: A Directed Ortho Metalation of (2-methylphenyl)-1-piperidinylmethanone

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[Supplemental Information](#)



ABSTRACT: A general method for the synthesis of 2-[(trimethylsilylmethyl)]-tertiary benzamides was investigated involving a Directed ortho metalation (DoM) of (2-Methylphenyl)-1-piperidinylmethanone). Derivatives of these products have shown significant antifungal properties against the soil borne fungus *Gaeumannomyces graminis* which attacks wheat and other crops. This work investigates the separation of the trimethylsilane (TMS) group from the aromatic ring which has not previously been described. A proposed mechanism was investigated, and products were characterized by Fourier Transform Infrared (FTIR) spectroscopy, ¹H-NMR, and ¹³C-NMR.

Introduction

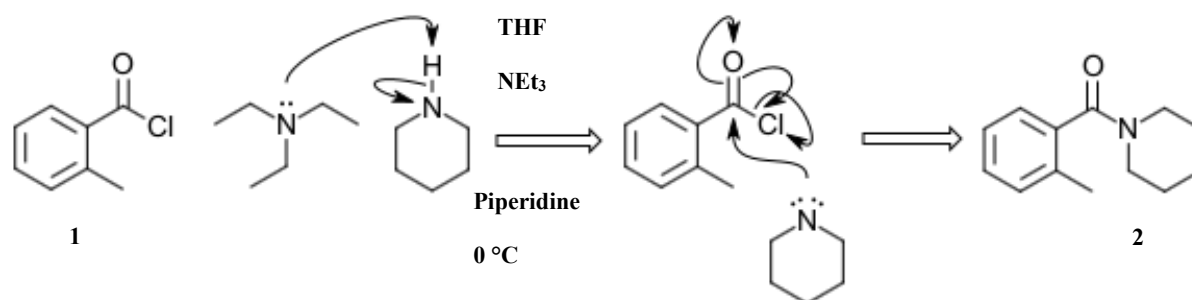
Directed ortho metalation reactions have been of great interest since the discovery in 1939 by Gilman and Wittig. Their work discovered more than 40 aromatic directing groups which are commonly used.¹ The DoM scheme is commonly linked with other coupling processes including Negishi, Suzuki-Miyaura, and Stille cross coupling which have many applications in the pharmaceutical industry.² The work by Dr. J Norman Reed and Dr. Victor Snieckus³ investigated the directed ortho metalation of a similar compound. Their work was discovered by Monsanto where they conducted extensive research into the antifungal properties of their product. The compound was patented and known by the generic name “Silthiofam” and sold under the trade name “Latitude”. Agricultural compounds have been a

topic of great interest and continue to be very important to the sustainability of crop production worldwide. This project looks to expand on the work done by Reed and Snieckus by introducing a benzylic carbon between the aromatic ring and the TMS group. The TMS group is in close proximity to the amide group which introduces steric crowding. The introduction of benzylic carbon could create a major difference in the activity of the fungicide.

Mechanistic Aspects

The starting material **2** was first synthesized according to scheme 1. Triethylamine was used as a base to abstract a proton from piperidine creating a negative charge. The charged piperidine was then used as a nucleophile to attack the acyl halide of the o-toluoyl chloride to afford the desired product **2**.

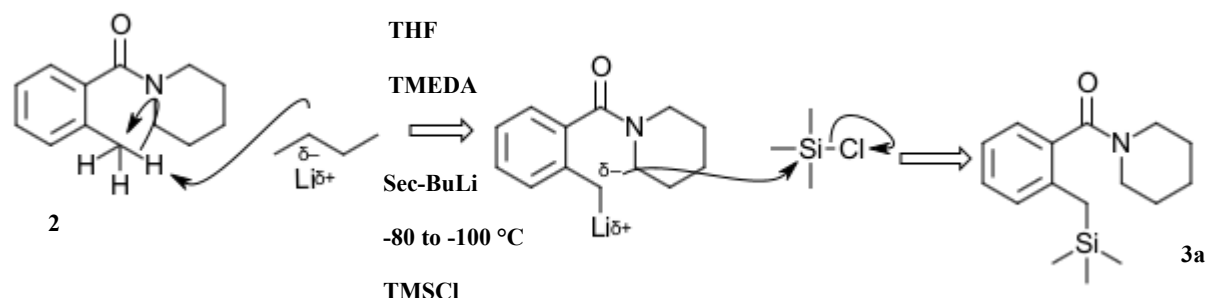
Scheme 1. Synthesis of tertiary amide



The tertiary amide product **2** was then used as starting material for the directed ortho metalation. A solution of 1.4 M sec-butyllithium was used to deprotonate the benzylic carbon, which forms the lithiated intermediate. The lithium near the benzylic carbon creates a partial negative charge which acts as a

nucleophile to attack the silicon in the TMSCl group. The chlorine on TMSCl leaves as a leaving group and the desired product **3** is synthesized. The TMEDA was to ensure completion of the reaction by modifying the pH of the reaction.

Scheme 2. Directed ortho metalation of tertiary amide product.



Results/Discussion

FTIR spectra were used to confirm presence of groups within **2**. The FTIR spectra cannot say for certain if the products were formed because all functional groups identified are present in the products and reactants. Although the presence of a carbonyl stretch at lower frequencies does indicate the presence of an amide. There was a presence of a carbonyl stretch at 1712.93 cm⁻¹ which could indicate some impurities present since the amide peak was observed at a lower frequency as expected (1626.92 cm⁻¹). However, the ¹H-NMR spectra were able to confirm that the desired product was synthesized. The integration of peaks was not consistent in each case, so peaks were assigned by expected chemical shift then integration was considered. Splitting patterns were not recognizable and peaks were either labeled singlet or multiplet. Acetone was also identified in the spectra as a solvent impurity which could broaden peaks and affect integration ratios. Each peak was assigned to a group of hydrogens. Although the hydrogens grouped together are not exactly equivalent, they are in similar chemical environments. The experimental ¹H-NMR was very similar to the NMR spectra of **2** retrieved from literature⁵ further confirming the desired product was synthesized. The ¹³C-NMR further confirmed **2** was successfully synthesized. Each peak corresponded to a carbon with minimal noise and no impurities detected. The spectra were also very similar to the spectra retrieved from literature⁵.

Spectra Characterization **3a**

FTIR was also used to confirm presence of functional groups within **3a**. Since no new functional groups were

identified in the spectra the products cannot be confirmed using FTIR spectroscopy. There was still a small peak present at 1741.96 cm⁻¹ which could still indicate impurities present. The ¹H-NMR was able to confirm the presence of a silyl group indicated close to 0 ppm. The spectra displayed broad peaks with no identifiable splitting present. Peaks were assigned by chemical shift then integration if possible. Three peaks located at 0.9760, 1.3071 and 4.1781 ppm were unable to be assigned and were labeled impurities. The ¹³C-NMR also displayed unknown peaks which were not predicted. The spectra did confirm the presence of a methylsilyl group due to the large peak at ~0 ppm. Impurities within the spectra were located between 0-50 ppm indicating possible changes to methyl groups (13 and 59 ppm). All of the spectra do confirm the presence of the desired product with some impurities present.

Spectral characterization **3b**

This product had a very similar retention time to **3a** on the TLC plates therefore spectra were obtained. The FTIR looked very similar to the spectra for **3a** except for the strong peak now present at 1736.53 cm⁻¹. It is in a similar location to the smaller peaks present in the spectra of **2** and **3a**. The ¹H-NMR spectra displayed no evidence of a methylsilyl group at ~0 ppm which confirms this is not the desired product. Peaks in the spectra are very broad and peak integrations are large. The ¹³C-NMR of this product displayed are more interesting image. Two peaks are now present in the carbonyl region along with almost double the expected peaks in the aromatic region. Multiple new peaks are also present in the 10-60 ppm region. The structure of this molecule was not deduced as it was confirmed to not be the desired product. However, discussion can

be made as to the reaction that occurred. Studies focusing on DoM have shown that multiple side reactions are possible and often competitive including ortho-Fries rearrangements, desilylation, hydrolysis, and cross coupling reactions.⁶ Due to the multiple new peaks present in the aromatic region, the cross-coupling reaction of two of the benzenes present is the most plausible.

Conclusions

The synthesized **2** was confirmed by analyzing all spectra obtained. The product was further confirmed by comparing it to spectra of the compound from literature. The DoM reaction was successful in producing a methylsilyl product (**3a**). This was confirmed by the ¹H and ¹³C NMR which also displayed some impurities present. This product has not been reported in literature.

Experimental

Synthesis of (2-Methylphenyl)-1-piperidinylmethanone (**2**)

Was prepared according to experimental procedure⁴. An oven dried 500 mL round bottom flask (RBF) was charged with 6.5 mL of *o*-toluoyl chloride (**1**) in 250 mL THF. To a dropping funnel attached to the apparatus ice cooled, 7.2 mL of triethylamine was added dropwise, then rinsed with 10 mL of THF. Then 5.1 mL of piperidine was added to the dropping funnel and was added dropwise followed by a rinse with THF. White precipitate formed upon addition of piperidine. The apparatus was removed from cooling and allowed to stir for 1h. The RBF was removed from the apparatus and rotovapped to near dryness. The crude residue was dissolved in 200 mL ethyl acetate and 200 mL of water and transferred to 500 mL separatory funnel. The ethyl acetate layer was washed with another 200 mL of water, followed by two 50 mL washings of saturated NaCl(aq) solution. The ethyl acetate layer was then dried using sodium sulphate, gravity filtered, and concentrated on the rotovap. The crude product was purified using Kugelrohr distillation (130-150 °C, 157 mtorr). Products characterized by FTIR, ¹H-NMR and ¹³C-NMR. **2** is clear, colorless oil 99% yield. The product has been reported in literature most recently by Zhang et al⁵ ¹H and ¹³C NMR spectra of this compound from their paper can be found in the supporting information. CAS number: 33388-67-9, CAS name: (2-Methylphenyl)-1-piperidinylmethanone).

Synthesis of **3a**

Was prepared according to experimental procedure⁴. An oven dried 250 mL RBF was charged with 1.48 g of **2**. The RBF was purged with N₂ and was left connected to N₂ source for duration of reaction. Using a syringe, 40 mL of THF was added followed by 1.2 mL of TMEDA. The RBF was immersed in an acetone-dry ice bath with stirring (-80 to -100 °C). Then by syringe, 11.3 mL of *sec*-BuLi (1.4 M) was added dropwise, solution turned red instantly. Reaction mixture was stirred for 15 minutes. By syringe, 1.8 mL of TMSCl was added rapidly to the reaction mixture. Reaction mixture was removed from cooling and N₂ atmosphere. Once warmed to room temperature, 40 mL of saturated NH₄Cl was added to the RBF and rotovapped to dryness. Crude product was transferred to a 250 mL separatory funnel using 50 mL of ethyl acetate, proceeded by another two 50 mL ethyl acetate

washings. The combined organic layers were washed with 50 mL water, two 50 mL washings with brine. The organic layer was then dried using sodium sulphate, gravity filtered, and concentrated to dryness on the 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 (**3a** oil with yellow tint 72% yield, **3b** 18% yield. Products were characterized by FTIR, ¹H-NMR and ¹³C-NMR. This product has not been previously reported in literature.

ASSOCIATED CONTENT

Supporting Information

The data underlying this study is available in the published article and its supporting information.

The Supporting Information is available free of charge on the ACS Publications website.

Supplemental Information ([PDF](#))

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing interests.

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