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Progress Toward The Synthesis Of *N*-Methyl Improgan

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Abstract

Improgan is a synthetic drug that appears to be a powerful pain reliever without the addictive properties of opiate drugs. To date, improgan has only been administered through direct injections into the brain of laboratory animals due to the fact that it does not cross the blood-brain barrier. The goal of this research is to synthesize *N*-methyl improgan, a potentially brain penetrating analogue. Replacing the N-H on the imidazole ring of improgan with an *N*-methyl group will decrease the amount of hydrogen bond donors as well as the polarity of the compound, potentially allowing it to cross the blood-brain barrier. A seven-step synthesis has been proposed in order to construct this chemical congener. The progress towards the synthesis of *N*-methyl improgan will be described in detail. The synthesis produces isomers with methylation occurring at the τ(N-1) or π(N-3) position. Different routes and conditions used to alter the ratio of the two isomers will be discussed as well as the separation of these isomers.

Keywords: Improgan, *N*-Methylation

1. Introduction

Improgan (Figure 1) is a synthetic drug that appears to be a powerful pain reliever without the addictive properties of opiate drugs like morphine.[1] To date, the target of improgan in the brain is unknown.[2] A major drawback of improgan is that it does not cross the blood-brain barrier (BBB), therefore all studies must be conducted by direct injection into the central nervous system of laboratory animals.[3] In order to optimize improgan toward potential testing on human subjects, the chemical structure of the drug must be altered in a way which allows it to enter the brain without compromising its analgesic effects. A closely related chemical congener of improgan called τ-*N*-methyl improgan (Figure 1) is suggested to improve the BBB penetration. By replacing the *N*-H on the imidazole ring of improgan with an *N*-methyl group, it will decrease the number of hydrogen bond donors as well as the polarity of drug. This substitution will increase the lipid solubility of improgan, potentially allowing it to cross the BBB. [4] A seven-step retrosynthesis is proposed for τ-*N*-methyl improgan (Scheme 1).

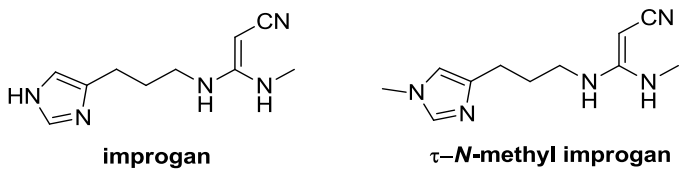
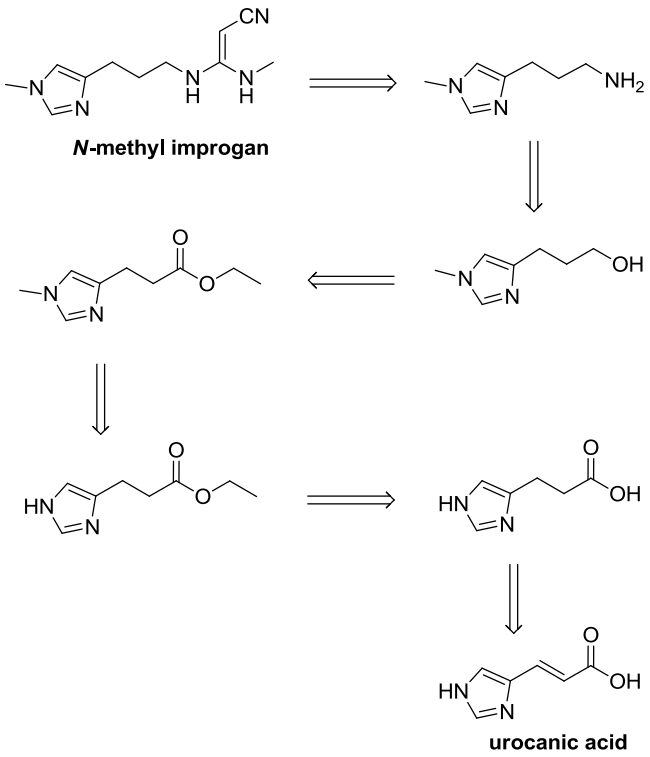


Figure 1. Chemical structures of improgan and τ-*N*-methyl improgan



Scheme 1. Proposed retrosynthesis for τ-*N*-methyl improgan

2. Materials And Methods

2.1 Materials And Instrumentation

Urocanic acid, ammonium formate, 10% palladium on carbon, Hyflo gel, hydrosulfuric acid, 60% sodium hydride, anhydrous acetonitrile, iodomethane and lithium aluminum hydride were purchased from Sigma Aldrich (St. Louis, MO). Anhydrous sodium sulfate was purchased from Fischer Scientific Company (Fair Lawn, NJ). Methanol, ethanol, dichloromethane, and chloroform were purchased from Pharmco-AAPER (Brookfield, CT). Anhydrous tetrahydrofuran was purchased from Acros Organics (Morris Plains, NJ). Silica gel and TLC plates were purchased from Sorbent Technologies (Norcross, GA). Deuterium oxide, chloroform-d, and dimethyl sulfoxide-d6 was purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA).

All of the reactions performed were synthesized using previously reported literature procedures. The identity of all the compounds was confirmed by comparing obtained NMR data with literature values. Thin layer chromatography (TLC) was completed using glass silica gel plates (0.25, 230-400 mesh) infused with fluorescent indicator 254 nm. Column chromatography was performed using silica gel (60Å, 40-63 μm, 230 x 400 mesh).

2.2 Experimental Procedure

The isolation of the τ-alcohol **4a** from π-alcohol **4b** was performed via column chromatography (silica gel, dichloromethane:methanol=50:1 to 30:1).

3-(1*H*-imidazol-4-yl)propanoic acid (1)[5]: white solid (10.0 g, yield = 99%); ^{1}H NMR spectral data previously reported.

Ethyl 3-(1*H*-imidazol-4-yl)propanoate (2)[5]: viscous brown oil (5.9 g, yield = 93%); ^{1}H NMR spectral data previously reported.

Ethyl 3-(1-methyl-1*H*-imidazol-4-yl)propanoate (3a)[7]: brown oil (0.9 g, yield = 53% as a mixture with **3b**); ^{1}H NMR spectral data previously reported

Ethyl 3-(1-methyl-1*H*-imidazol-5-yl)propanoate (3b)[8]: brown oil (0.9 g, yield = 53% as a mixture with **3a**); ^{1}H NMR spectral data previously reported.

3-(1-methyl-1*H*-imidazol-4-yl)propanoic acid (3c)[7]: white solid (1.5 g, yield = N/A as a mixture with **3d**) ^{1}H NMR spectral data previously reported.

3-(1-methyl-1*H*-imidazol-5-yl)propanoic acid (3d)[9] : white solid (1.5 g, yield =N/A as a mixture with **3c**) ^{1}H NMR spectral data previously reported.

3-(1-methyl-1*H*-imidazol-4-yl)propanol (4a)[10]: light brown oil (0.2 g, yield = 14%). *Rf* = 0.31 (dichloromethane:methanol = 50:1); ^{1}H NMR spectral data previously reported.

3-(1-methyl-1*H*-imidazol-5-yl)propanol (4b)[11]: light brown oil (0.1 g, yield = 9%) *Rf* = 0.28 (dichloromethane:methanol = 50:1); ^{1}H NMR spectral data previously reported.

Ethyl 3-(1*H*-imidazol-4-yl)acrylate (5)[13]: white solid (6.0 g, yield = 94%); ^{1}H NMR spectral data previously reported.

Ethyl 3-(1-methyl-1*H*-imidazol-4-yl)acrylate (6a)[14]: brown oil (1.8 g, yield = 90% as a mixture with **6b**); ^{1}H NMR spectral data previously reported.

Ethyl 3-(1-methyl-1*H*-imidazol-5-yl)acrylate (6b)[15]: brown oil (1.8 g, yield = 90% as a mixture with **6a**); ^{1}H NMR spectral data previously reported.

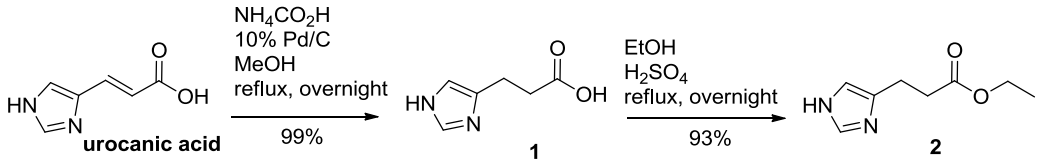
3-(1-methyl-1*H*-imidazol-4-yl)prop-2-en-1-ol (7a)[14]: brown oil (1.6 g, yield = 78% as a mixture with **7b**); ^{1}H NMR spectral data previously reported.

3-(1-methyl-1*H*-imidazol-5-yl)prop-2-en-1-ol (7b)[16]: brown oil (1.6 g, yield = 78% as a mixture with **7a**); ^{1}H NMR spectral data previously reported.

3. Results

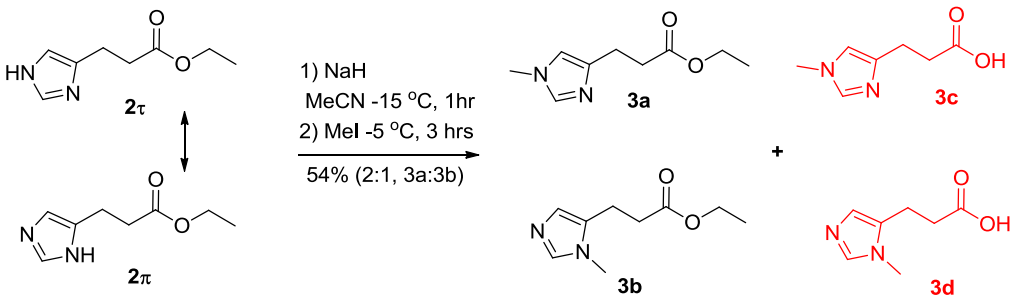
3.1 Path A

The alkene in urocanic acid was reduced using ammonium formate, 10% palladium on carbon, in methanol to form the alkane **1** in 99% yield.[5] Compound **1** underwent esterification using ethanol and concentrated sulfuric acid producing imidazole ester **2** in 93% yield (Scheme 2).[5]



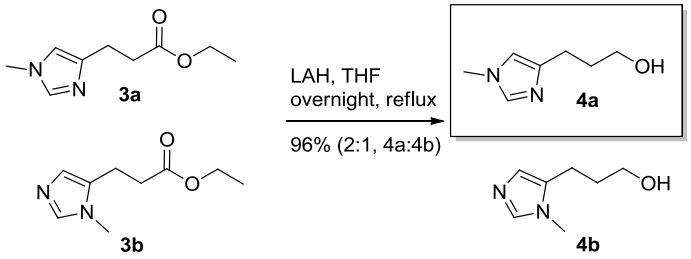
Scheme 2: Alkene reduction of urocanic acid followed by esterification

Due to tautomerization, when imidazole ester **2** was methylated using 60% sodium hydride, methyl iodide in acetonitrile,[6] a mixture of τ-methylated imidazole ester **3a** and π-methylated imidazole ester **3b** was produced in 54% yield with a ratio of 2:1, **3a**[7]: **3b**.[8] In an attempt to decipher why the yield was low, major byproducts were isolated and analyzed. The identity of these byproducts was determined to be the acid derivatives **3c**[7] and **3d**[9] (Scheme 3).



Scheme 3: *N*-Methylation of imidazole ester

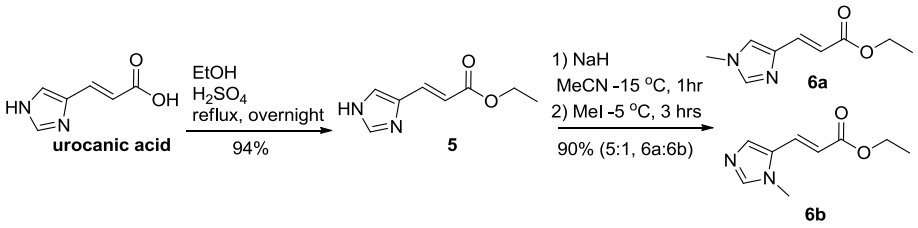
The *N*-methylated imidazole esters **3a** and **3b** were reduced as a mixture to alcohols **4a**[10] and **4b**[11] using lithium aluminum hydride in tetrahydrofuran[5] in 96% yield maintaining the ratio of 2:1, **4a**: **4b** (Scheme 4). The τ-isomer (**4a**) was successfully separated from the π-isomer (**4b**) using column chromatography.



Scheme 4: Ester reduction of methyl imidazole ester

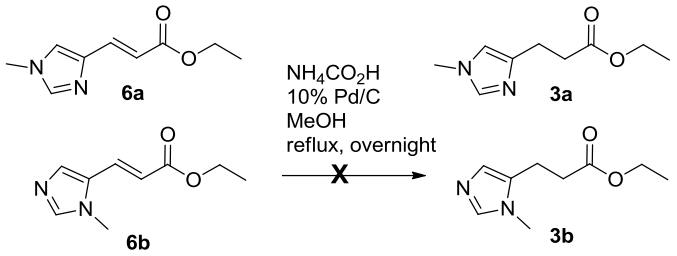
3.2 Path B

An alternative path was attempted to improve the ratio of the methylated τ-isomer. Urocanic acid underwent esterification using ethanol and concentrated sulfuric acid[12] producing the unsaturated imidazole ester **5**[13] in 94% yield. Compound **5** was methylated using 60% sodium hydride, methyl iodide in acetonitrile,[6,7] producing a mixture of unsaturated *N*-methyl imidazole esters **6a**[14] and **6b**[15] in 90% yield with a ratio of 5:1, **6a**: **6b** (Scheme 5).



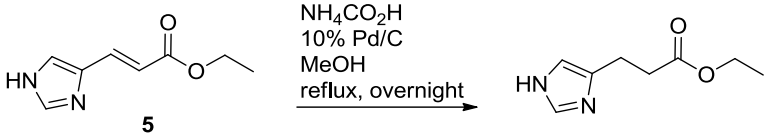
Scheme 5: Esterification of urocanic acid followed by *N*-methylation

An attempt was made to reduce the alkene double bond in compounds **6a** and **6b** as a mixture using ammonium formate, 10% palladium on carbon, in methanol to produce the saturated *N*-methyl imidazole esters **3a** and **3b** .The reaction was unsuccessful therefore further investigation is necessary (Scheme 6).



Scheme 6: Unsuccessful alkene reduction of *N*-methyl imidazole esters

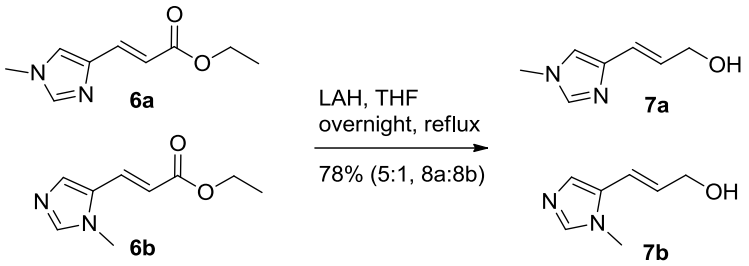
The alkene in imidazole ester **5** was successfully reduced to an alkane using ammonium formate, 10% palladium on carbon in methanol (Scheme 7).



Scheme 7: Reduction of alkene in imidazole ester

3.3 Path B1

Due to the failed alkene reduction (Scheme 6), an alternative path was executed. Compounds **6a** and **6b** were reduced using lithium aluminum hydride in tetrahydrofuran[5] to alcohols **7a**[14] and **7b**[16] in 78% yield with a ratio of 5:1, **8a**:**8b** (Scheme 8).

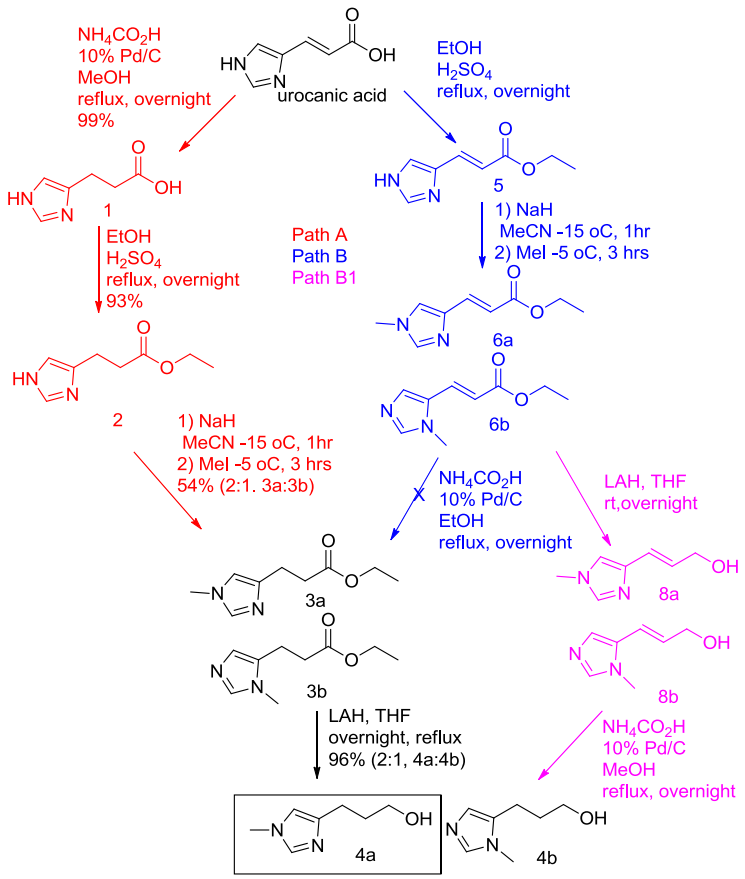


Scheme 8: Ester reduction of *N*-methyl imidazole ester

4. Discussion

During *N*-methylation of imidazole ester **2** (Path A), the reaction resulted in a 2:1 ratio of the τ- isomer to π- isomer **3a**:**3b**. When the *N*-methylation imidazole ester **5** (Path B) took place, the reaction produced a 5:1 ratio of the τ- isomer to π- isomer **6a**:**6b** (Scheme 9). The τ-position on the imidazole ring is less sterically hindered then the π-position but due to the small size of the methyl group, methylation was able to occur at both of the positions. One difference

between the two compounds is that the saturated alkyl substituent on imidazole ester **2** is an electron donating group. In imidazole ester **5**, the unsaturated alkyl substituent is conjugated forming an electron withdrawing group. The effects cause by electron withdrawing are felt more strongly on the closest π-nitrogen, which causes a decrease in the amount of methylation occurring at that position. Agreeing with literature,[4] it was also observed that the ratio of the position where methylation took place was highly dependent on the temperature of the ice bath during the reaction; the lower the temperature, the greater the ratio of methylation on the τ-position.



Scheme 9: Various pathways devised to synthesize alcohol **4a**

One of the drawbacks which occurs during the *N*-methylation of imidazole ester **2** is that the ester is hydrolyzed to the acid derivatives **3c** and **3d**, forming major byproducts. Imidazole ester **2** could potentially undergo internal cyclization (Figure 2). In the presence of water, the ring would open to form the acid.

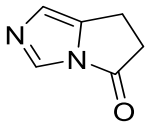
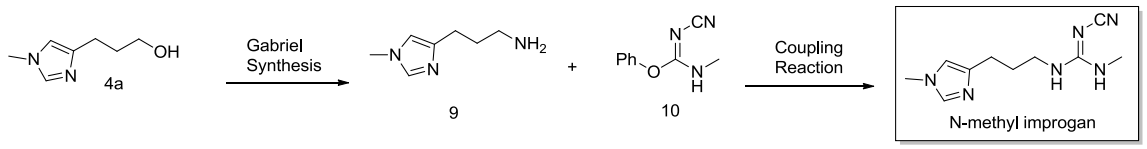


Figure 2: Proposed internal cyclization of imidazole ester **5**

Acid derivatives did not present as an issue during the *N*-methylation of the unsaturated imidazole ester **5.** Due to the presence of the *trans* double bond, imidazole ester **5** cannot undergo internal cyclization. Since the *N*-methylation of the unsaturated imidazole ester **5** in Path B produced a significantly greater ratio of the desired τ- isomer and no byproducts, it was continued to complete the synthesis. An attempt was made to reduce the double bond in *N*-methyl

imidazole esters **6a** and **6b,** yet the reaction did not work and starting material was recovered (Scheme 6). In order to determine whether the ester or the *N*-methyl group was preventing the reaction from occurring, the alkene in imidazole ester **5** was reduced (Scheme 7). This reaction was successful, which implies that the ester group is not the reason as to why the alkene reduction in *N*-methyl imidazole esters **6a** and **6b** did not occur. The reasons for this failure are under investigation. Since the double bond in *N*-methyl imidazole ester **6a** and **6b** could not be reduced, an alternative path (Path B1) has been proposed which involves reducing *N*-methyl imidazole esters **6a** and **6b** to the alcohols **8a** and **8b** first, followed by the alkene reduction to produce the *N*-methyl alcohols **4a** and **4b** (Scheme 9).

From Path A, it has been determined that the τ-alcohol **4a** can be separated from the π-alcohol **4b** using column chromatography. A Gabriel synthesis on alcohol **4a** should convert it to primary amine **9**.[17] Based on the synthesis of improgran, amine **9** can be coupled with an isourea precursor **10** to form the target compound τ-*N*-methyl improgan (Scheme 10).[17]



Scheme 10: Proposed scheme for the completion of the synthesis of *N*-methyl improgan

5. Conclusion

Various paths were performed for the synthesis of alcohol **4a**. Due to tautomerization, the synthesis produces isomers with methylation occurring at the τ- or π-position in varying ratios. The conditions in path B increased the ratio of methylation occurring at the τ-position significantly. If the alkene in compounds **8a** and **8b** is successfully reduced, Path B1 will be continued to complete the synthesis. If the reduction fails, Path A can be reinstated and used to synthesize τ-*N*-methyl improgan.

6. Acknowledgements

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7. References

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