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The Use of Heterocycles as Important Structures in Medicinal Chemistry

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The Use of Heterocycles as Important Structures in Medicinal Chemistry

by

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Abstract

Heterocycles have many applications in the discipline of medicinal chemistry. These structures are found in various natural products with relevant biological activity. Our research group, in collaboration with two others, is particularly interested in one heterocycle, quinoline, as a scaffold for HIV-1 integrase inhibitors. A synthetic route has been developed to produce a derivatized structure on small scale. One goal of this thesis was to expand the scale of this route to provide increased quantities of the quinoline scaffold. Procedures were adapted to accommodate the increase in scale to convert commercially available anthranilic acids to quinolines via the isatoic anhydride. The quinolines could then be further derivatized to be tested as HIV-1 integrase inhibitors. At a later stage in the synthesis, the use of a masked acyl cyanide (MAC) reagent allows installation of an alpha-alkoxyester side chain onto the quinoline that is necessary for HIV inhibition. The second goal of this thesis involves heterocycles more broadly by expanding this reaction to include other heterocycles to test the generality of the method. This reaction also highlights the utility of MAC reagents as an example of umpolung chemistry, which is a reversal of polarity and bond formation compared to what is traditionally accomplished. These exciting strategies open the possibility for new reagents and strategies in organic synthesis. A series of heterocyclic structures were tested in the MAC reaction and the results of the method are discussed.

Dedication

To my late great grandmother, Great.

Her wisdom and encouragement still impact me today.

Acknowledgements

I would like the acknowledge those who have played a vital role in my completion of this thesis. First, I want to thank my advisor, Dr. Julie Pigza, for her dedication and encouragement through my time at Southern Miss. She saw potential in me that I had not seen in myself as a freshman and continued to take interest in my academic success even if that meant taking on multiple advisees. Dr. Pigza has always been willing to answer questions and make herself available no matter her schedule. Thank you to Dr. Pigza's graduate students, Jared Hume and Alison Hart for being patient and flexible over the last year. To Dr. Matthew Donahue and the rest of the Donahue and Pigza groups, thanks for making my time in the lab fun and memorable. I would also like to thank the Drapeau Center for Undergraduate Research for providing funding for this project. Thank you to the USM Honors College for providing me with support and opportunities I may not have had otherwise.

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List of Abbreviations

HIV-human immunodeficiency virus

RNA-ribose nucleic acid

DNA-deoxyribose nucleic acid

AIDS-acquired immunodeficiency syndrome

LAV-lymphoadenopathy virus

SIV-simian immunodeficiency virus

HAART-highly active antiretroviral therapy

NRTI-nucleoside reverse transcriptase inhibitor

NNRTI-non-nucleoside reverse transcriptase inhibitor

PI-protease inhibitor

INSTI-integrase strand-transfer inhibitor

CCR5-chemokine receptor antagonist

FDA-Food and Drug Administration

LEDGF-lens epithelium-derived growth factor

CCD-catalytic core domain

IBD-integrase binding domain

ALLINI-allosteric integrase inhibitor

SAR-structure-activity relationship

NCINI-non-catalytic site integrase inhibitor

MAC-masked acyl cyanide

TLC-thin-layer chromatography

PMA-phosphomolybdic acid

NMR-nuclear magnetic resonance

THF-tetrahydrofuran

DMA-*N*,*N*-dimethylaniline

NaOH-sodium hydroxide

$POCl_3$-phosphoryl chloride

DMAP-dimethylaminopyridine

EtOH-ethanol

Et_2O-diethyl ether

TBS-MAC-2-((tert-butyldimethylsilyl)oxy)malononitrile

DCM-methylene chloride/dichloromethane

NH_4Cl-ammonium chloride

Na_2SO_4-sodium sulfate

EtOAc-ethyl acetate

1.Introduction

Heterocycles are a class of molecule present in many biomolecules within the human body and contain atoms other than carbon and hydrogen within a ring. The natural presence of heterocycles as well as their complexity and ability to hydrogen bond makes them desirable structures for use as drugs. Medicinal chemists synthesize drug structures containing heterocycles that mimic the compounds found in our bodies with the goal of being able to enhance or restrict the intended function of those molecules. One heterocycle of interest is quinoline, which contains two fused six-membered benzene rings with one carbon switched out for a nitrogen. It has been identified as a scaffold for drug structures with the ability to inhibit HIV-1 integrase via binding to an allosteric site. While the allosteric site is not the active site, binding to it still affects the structure of the active site by changing the conformation of the enzyme and rendering it unable to perform its function. Quinolines can be purchased commercially or synthesized and then in each case derivatized to the final target. However, commercially available quinolines are often not as flexible as ones that can be synthesized from simpler substrates, where functional groups can be introduced at various positions. A synthetic strategy for the ability to create quinolines with substitutions at various positions has been developed on a small scale. The ability to scale up is valuable for being able to create a variety of derivatized quinolines to test as HIV-1 integrase inhibitors.

One position that is essential to inhibition of the enzyme is the 3-position of quinoline. The desired quinoline motif includes an acetic acid residue at this site. It was determined that addition of a masked acyl cyanide (MAC) reagent to the 3-position would install the correct functional group and oxidation state. It is of interest to extend

this highly valuable method to other heterocycles as well. The success of this method could potentially indicate another pathway to derivatize heterocycles useful in the synthesis of other drug structures.

2. Background

2.1 HIV Introduction

The human immunodeficiency virus, HIV, is a retrovirus, which is a virus that contains RNA that is reverse transcribed into DNA upon infection of a cell. The virus attacks the body's T-cells, white blood cells that develop in the thymus, which in turn weakens the immune system and prevents those infected from being able to fight off other infections. The body is unable to eliminate HIV and, if the disease is left untreated, it can lead to acquired immunodeficiency syndrome, or AIDS. An AIDS infection often leads to opportunistic infections and cancers because of the body's inability to counteract them.[1]

HIV was first discovered after many cases of what would later be known as AIDS were detected in 1981. The HIV-1 virus was isolated in 1983 in France and was known at the time as the lymphoadenopathy-associated virus or LAV. The virus was cloned and sequenced in 1985, making it possible for viral load and resistance tests to be developed. Sequencing allowed the relationship of HIV-1 to be determined as the cross-species transmission of the simian immunodeficiency virus, SIV. After isolation of HIV-1, it was determined that the CD4 T cell was the main receptor for HIV.[2] Since HIV was known to be cytopathic, or cause the death of cells, the discovery that CD4 cells were targeted led to the use of cell counting to monitor those diagnosed with the disease.

2.2 Statistics

More than three decades after its discovery, HIV still remains a leading cause of death around the world. A total of 1.8 million people were newly diagnosed with HIV in 2017 alone. A staggering 36.9 million people are estimated to be living with HIV while approximately 35 million are estimated to have died from AIDS-related illnesses since the beginning of the epidemic. Sub-Saharan Africa is the region known to be the most heavily infected with 66% of new infections in 2017 being located in this region.[3] The high infection rate is due to the poverty in the area which results in a lack of education, young marriage, and a sex trade.[4]

In the United States, HIV diagnoses are not equal across regions. Per 100,000 people, the South has the highest rate with 16.1%.[5] In 2014, Mississippi was ranked 9th in the nation for number of new HIV diagnoses and among metropolitan areas, Jackson was ranked 4th in the nation. In 2017, Forrest County was ranked 4th in HIV diagnoses in Mississippi.[6] These sobering statistics show how truly close to home this disease is and how it impacts the lives of many Mississippi residents.

2.3 HIV Life Cycle

HIV is spread through the exchange of bodily fluids through blood transfusions, sexual intercourse, contaminated needles, or from mother to child during pregnancy. As a virus by definition, HIV is not able to sustain on its own and requires a host cell to reproduce. HIV targets the CD4 helper T-cells in the host, which are responsible for regulating immune responses in the body. As the number of HIV virus particles increases and CD4 cells are destroyed, the host's immune system is weakened. Once inside a CD4 cell, HIV takes over the cell's ability to transcribe and translate its own DNA and in turn produces more virus particles (Figure 2.1). Early stage replication involves the virus

binding to the cell surface up through viral DNA integration to the host DNA. Late stage replication is the beginning of viral transcription and ends with the release of the fully developed virion.[7]

Binding of the virus to the CD4 receptor also involves a co-receptor, CCR5 (C-C motif chemokine receptor 5).[8,9] CD4 binding causes a conformation change in the HIV-Env trimer, a glycoprotein on the surface of viruses, which then interacts with the co-receptor causing the virus coating to fuse with the cell membrane.[10] Fusion with the membrane causes the transfer of the material inside the viral particle into the cytoplasm. Once the genetic material is inside the cell, the single strand RNA is transcribed into double stranded DNA via an enzyme called reverse transcriptase, that is characteristic of retroviruses like HIV. After reverse transcription, the viral capsid has to be disassembled and this is known as uncoating. Capsids have been shown to remain in the cytoplasm for several hours giving HIV a critical stability necessary for infection. This step is closely tied to the reverse transcription and the integration of viral DNA. Now that the viral genetic material is double stranded DNA, it can be incorporated into the host DNA by way of the integrase enzyme. As the host cell's DNA is replicated, the viral DNA is replicated along with it.[8]

Transcription involves the conversion of DNA into RNA. Segments of RNA encode for viral components called Tat, Rev, and Nef. Tat functions for viral transcription and RNA elongation. Rev monitors the transport of RNA into the cytoplasm. Nef causes the cell to be less detectable by the immune system, therefore making the cell a more effective producer of viral particles. These components are assembled in a complex process involving many proteins. Gag and Gag-Pol precursors

multimerize via interactions between the Gag proteins. These precursors are concentrated in lipid rafts in the cell membrane. Glycoproteins are used to build platforms through interactions with the matrix proteins. Then two copies of viral RNA are accumulated with viral proteins at the plasma membrane and form a membrane-coated spherical particle.[8] The viral particles are then released after HIV's Vpu transmembrane protein overcomes the cell's tetherin protein.[11] These particles are not infectious until they are mature after a viral protease protein cleaves Gag and Gag-Pol precursors to their mature form.[8]

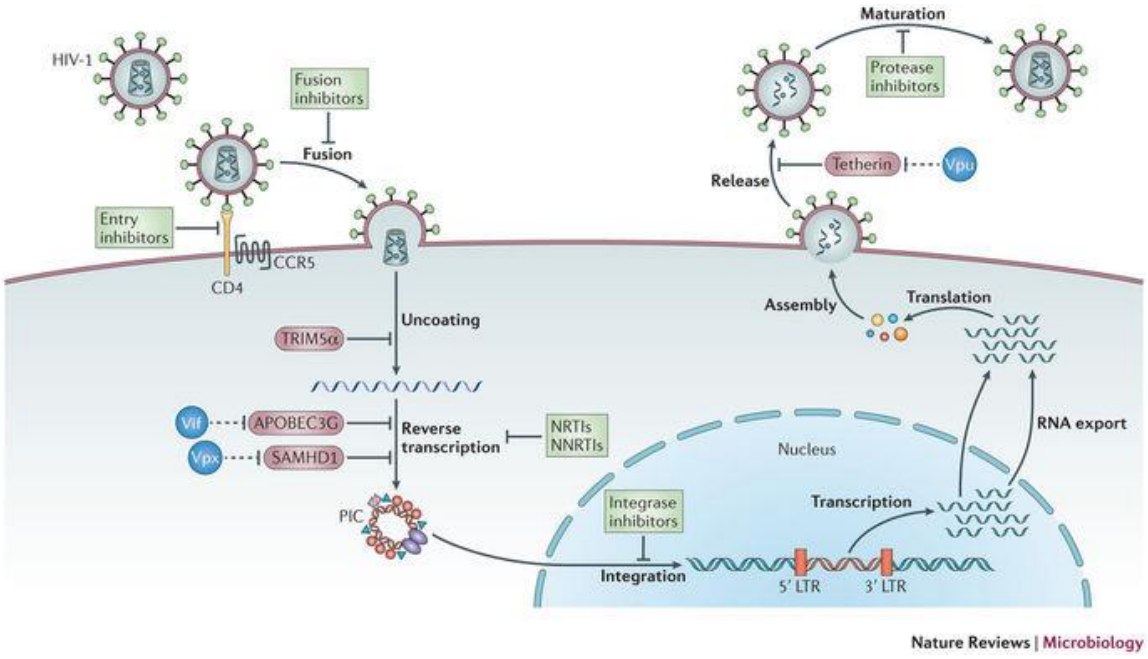


Figure 2.1: HIV Life Cycle[2]

2.4 HIV Treatments

HIV has several factors that contribute to its ability to continue to thrive over the years. HIV has a high mutation rate of 1 error per 10,000 nucleotides, a short generation time, and a large virus production of $2x10^9$ particles per day. Therefore, treatment strategies for HIV often contain a cocktail of drugs that serve to target multiple phases of the life cycle. This approach is known as HAART, or highly active antiretroviral

therapy.[8,12] There are seven types of drug classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand-transfer inhibitors (INSTIs), chemokine receptor antagonists (CCR5), fusion inhibitors (FIs), and entry inhibitors (CD4-directed post-attachment inhibitors). These seven classes target five phases of the HIV reproductive cycle as shown in Figure 2.1.[13] Currently, the US Food and Drug Administration (FDA) has approved a total of 22 medicines to treat HIV. One drug regimen assigned to a patient usually consists of three medicines from two or more drug classes (Table 2.1).[14]

Name	**NRTI**	**nNRTI**	**INSTI**	**Pharmacokinetic enhancer**
Triumeq	Abacavir	Lamivudine	Dolutegravir	--
Juluca	--	Rilpivirine	Dolutegravir	--
Stribild	Tenofovir disoproxil fumarate/emtricitabine	--	Elvitegravir	Cobicistat
Genvoya	Tenofovir alafenamide/ emtricitabine	--	Elvitegravir	Cobicistat
Atripla	Tenofovir disoproxil fumarate/emtricitabine	Efavirenz	--	--
Complera	Tenofovir disoproxil fumarate/emtricitabine	Rilpivirine	--	--
Odefsey	Tenofovir alafenamide/ emtricitabine	Rilpivirine	--	--
Biktarvy	Tenofovir alafenamide/ emtricitabine	--	Bictegravir	--

Table 2.1: Common HAART HIV-1 Treatments

Each drug class is briefly described in the following section including their role in preventing the replication of HIV. NRTIs were the first available drug class. They are structurally similar to DNA nucleoside bases and prevent proviral DNA from being synthesized by incorporating themselves as a faulty bases into the growing chain.

NNRTIs bind at an allosteric pocket of the reverse transcriptase dimer, changing the conformation of the enzyme and altering the active site. PIs are competitive inhibitors of HIV protease and prevent Gag and Gag-Pol polypeptides from being cleaved. INSTIs target the active site of the HIV integrase enzyme and bind metal ions in the active site, which prevents binding to the host DNA. CCR5 antagonists interact with the CCR5 co-receptors and prevent the binding of viral particles to the CD4 cells. Only one FI is on the market due to its complicated production and inconvenient administration (subcutaneous injection). It functions by preventing the conformation change of necessary proteins that allow the binding of HIV particles to the cell membrane. The first CD4 post-attachment inhibitor was approved in March 2018 and prevents the CD4 receptor-HIV complex from interacting with its intended co-receptor.[14]

2.5 Integrase Inhibitors

The unique structure of HIV-1 integrase is not similar to any human enzymes, which means that there is a low risk of adverse effects from medications targeting this enzyme. There are only three FDA approved medications that target the integrase enzyme. All three are INSTIs that act at the active site, and include raltegravir, elvitegravir, and dolutegravir. Unfortunately, resistance to two of these drugs, raltegravir and elvitegravir, has been discovered, creating a need for more medications in this drug class.[14] Since the viral mutations have affected the active site, other potential sites for enzyme inhibition must be explored.[15]

The activity of integrase is monitored by various proteins. Human lens epithelium-derived growth factor (LEDGF) and endogeneous transcriptional coactivator (p75) have been found to be important co-factors in the integration of viral DNA. The

interaction between two of the integrase protein domains, the catalytic core domain (CCD) and the integrase binding domain (IBD), have revealed necessary protein-protein interactions. The LEDGF/p75b complex stabilizes the interactions between domains and helps to form the functional tetramer. Targeting this allosteric pocket could be a way to prevent the enzyme function and avoid viral mutations at this site.[16]

Allosteric integrase inhibitors (ALLINIs) have been found to compete with LEDGF/p75 binding interactions and are capable of disrupting enzyme function.[17,18] These inhibitors work through a dual mode of action - they prevent the interaction of integrase and viral DNA and inhibit the integrase-LEDGF binding.[19] A high-throughput screen (HTS) was carried out using the Boehringer Ingelheim compound collection to identify hits based on a quinoline scaffold resembling compound **1**. Analogues were synthesized to do structure-activity relationship (SAR) studies to determine leads. SAR studies involve modifying a portion of the drug and then re-submitting it to testing to see if the change increases its potency and/or favorable properties. The conclusion of the studies produced compound **2** (BI-224436) as the first non-catalytic site integrase inhibitor (NCINI) to advance to a phase 1 clinical trial.[20]

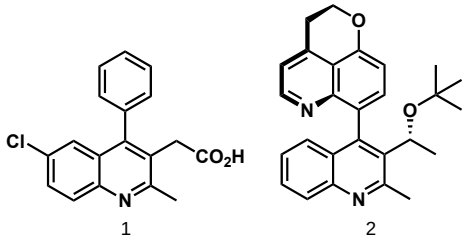


Figure 2.2: Quinoline scaffold and BI-224436

2.6 Umpolung Chemistry

Organic synthesis reactions are commonly based on the polar nature of bonds and the interactions between electrophiles, the electron accepting component, and nucleophiles, the electron donating component.[21] Umpolung chemistry involves the inversion of polarity as to what is traditionally thought of as electrophile versus nucleophile (in other words, the reversal of positive and negative, respectively, as in Figure 2.2). This technique is highly useful in organic chemistry bond-forming processes by allowing seemingly impossible transformations usually prohibited by traditional reactivity rules. One example of an umpolung process involves the use of an acyl anion equivalent.[22] Technically, the acyl anion itself does not exist in the reaction, but rather, a substrate is used such that bond formation appears to have resulted from the acyl anion. The substrate that "acts" as an acyl anion is called an acyl anion synthetic equivalent or synthon. These synthons have the power to be a traceless linchpin and join two separate molecules without ever being a distinct acyl anion. Masked acyl cyanides (MACs) are acyl anion synthons that are capable of acting as nucleophiles and electrophiles, allowing a chemist to customize the nucleophile and electrophile to be utilized.[23] For example, when a MAC reagent is reacted with an aldehyde electrophile and then an alcohol nucleophile, they can be used to install an α-alkoxy ester functional group to a molecule.[24]

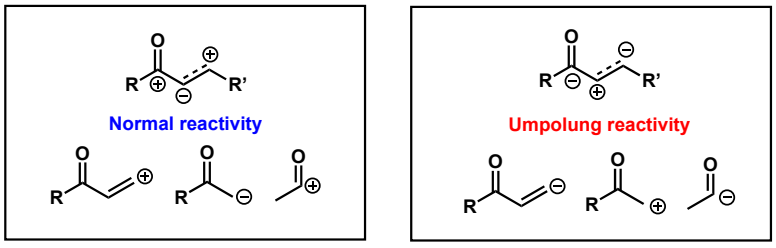


Figure 2.3: Comparison of normal and umpolung reactivity

2.7 Heterocycles in Drug Structures

A heteroatom is any atom other than carbon and hydrogen. This term is used because carbon and hydrogen make up the largest percent of organic compounds. Examples of common heteroatoms found in organic compounds include largely oxygen and nitrogen, but also halogens, phosphorus, and sulfur. Heteroatoms provide molecules with diversity and enhanced polarity to perform their intended biological functions and to design new therapeutics. Heterocycles, which are ring molecules containing at least one heteroatom, are present in over 70% of all drug structures.[25] They are a component of seven of the top ten prescribed drugs in 2016, demonstrating their importance in medicinal chemistry (heterocycles within each structure are highlighted in blue, Figure 2.4).[26] Drugs are often made to mimic structural motifs of the body's natural nucleic acids, amino acids, and carbohydrates. In this way, heterocycles serve as bioisosteres, or biologically similar functional groups, in drug candidates to ensure they will have similar function in the body. Their usefulness stems from the ability to form noncovalent interactions in the body via hydrogen bonding, whether that is as hydrogen-bond acceptors (heteroaromatics) or donors (saturated nitrogen heterocycles). The ability to hydrogen bond can improve qualities necessary for drug molecules such as lipophilicity, polar surface area, and oral bioavailability.[27]

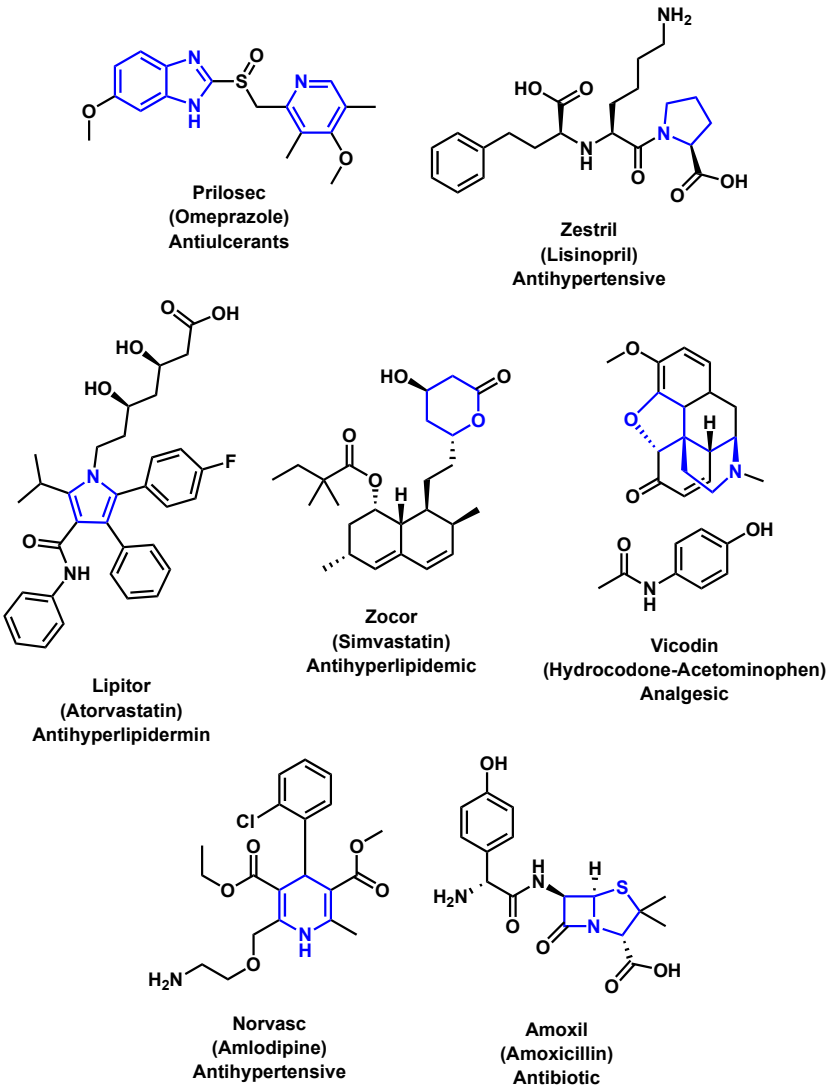


Figure 2.4: Top 10 drugs from 2016 containing heterocycles

3. Materials and Methods

3.1 Materials

Starting materials and solvents were purchased from commercial vendors and used without purification unless noted. Thin-layer chromatography (TLC) was performed using Sorbent Technologies 250 μm glass-backed UV254 silica plates. The plates were first visualized by fluorescence upon 254 nm irradiation. The plates were then dipped in phosphomolybdic acid (PMA) stain followed by heating. Column chromatography was

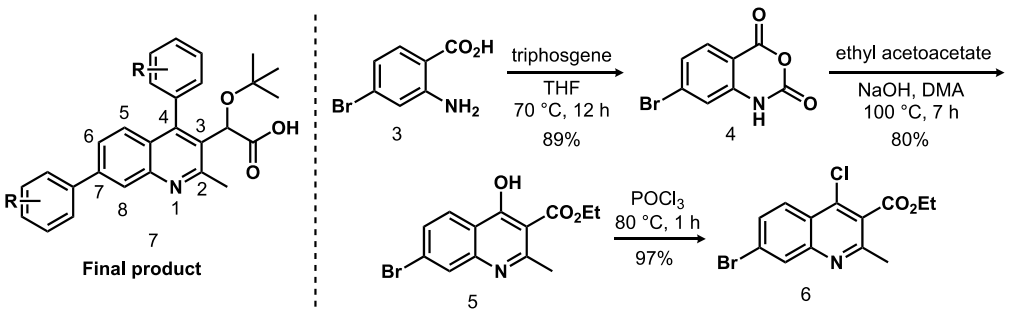
performed using Sorbent Technologies 40-63 μm, pore size 60 Å silica gel with solvent systems indicated. All yields refer to isolated material that is chromatographically (TLC) and spectroscopically (^{1}H NMR) homogenous.

3.2 Analysis and Characterization

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker UltraShield Plus 400 MHz spectrometer and chemical shifts are recorded in parts per million from an internal deuterated solvent peak of chloroform (7.26 ppm) or dimethylsulfoxide (2.50 ppm) on the δ scale and are reported as follows: chemical shift [multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant(s) in hertz, integration, interpretation]. Carbon (^{13}C NMR) data were recorded on the same instrument at a frequency of 100 MHz and are reported as follows: chemical shift (multiplicity as determined from DEPT-135 and DEPT-90 NMR (quaternary (s), methine (d), methylene (t), methyl (q)).

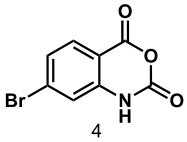
3.3 Large Scale Synthesis of Derivatized Quinoline

The synthetic route (Scheme 3.1) has the goal of synthesizing the final quinoline product **7** on large scale. It begins with 5-bromoanthranilic acid **3** (25 g) and converts it to an isatoic anhydride **4** using triphosgene in tetrahydrofuran (THF). The isatoic anhydride **4** (10 g) was transformed to quinoline **5** with ethyl acetoacetate in dimethylaniline (DMA) catalyzed by sodium hydroxide (NaOH). The alcohol group on the 4-position was chlorinated using phosphoryl chloride ($POCl_3$) on a 10 g scale. The resulting quinoline was further derivatized by a graduate student to produce the desired final product **7.**

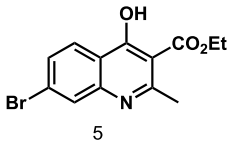


Scheme 3.2: Large scale synthesis of derivatized quinoline

Experimental Information

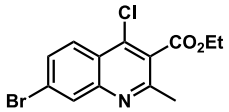


7-Bromo-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (4): 2-Amino-4-bromobenzoic acid (0.115 mol, 1 eq) was added to a 1000 mL 3 neck round bottom flask with a stir bar. THF (350 mL) was then added to the flask. Triphosgene (0.115 mol, 1 eq) was dissolved in THF (50 mL) and was added to the 3 neck flask via addition funnel. A reflux condenser was added and the flask was heated to 70 °C and stirred for 20 hours. The reaction was cooled to room temperature and transferred to a 4 L beaker with distilled water (400 mL). The beaker was stirred with mechanical stirring for 6 hours. The solid was filtered out using a Buchner funnel and washed with water. The solid was collected and stirred with methanol (50 mL) for 10 minutes then re-filtered and washed with methanol. The solid was collected and dried under high vacuum to produce 24.6908 g (89%) of a pearlescent solid. Characterization data can be found in the literature.[28]



Ethyl 7-bromo-4-hydroxy-2-methylquinoline-3-carboxylate (5): 7-Bromo-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (0.04 mol, 1 eq), ethyl acetoacetate (0.08 mol, 2 eq), and DMA (0.6 M) were added to a 250 mL round bottom flask with stir bar. NaOH (0.04 mol, 1 eq) was then added to the flask, followed

by a reflux condenser, and the reaction was heated to 100 °C for 7 hours. The reaction was allowed to cool then was transferred to a 600 mL beaker with distilled water (250 mL) and stirred with mechanical stirring overnight. The white solid was filtered using a Buchner funnel and washed with distilled water. The solid was collected and dried under high vacuum to afford 10.2777 g (80%). Characterization can be found in literature.[29]



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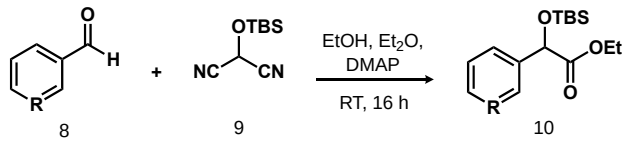
Ethyl 7-bromo-4-chloro-2-methylquinoline-3-carboxylate (6): Ethyl 7-bromo-4-hydroxy-2-methylquinoline-3-carboxylate (0.03 mole, 1 eq) and $POCl_3$ (0.5 M) were added to a 250 mL round bottom flask containing a stir bar. The reaction was heated to 80 °C for 1 hour, at which time TLC was used to check for completion. The reaction was heated for 1 hour increments until complete. Once complete, the reaction was cooled to room temperature and then transferred to a separatory funnel and added dropwise to an ice bath in a 4 L beaker due a large exotherm. The initial flask and separatory funnel were rinsed with distilled water. Then 10 M NaOH was added to neutralize the reaction. The reaction was filtered using a Buchner funnel and a tan solid was isolated and dried under high vacuum to produce 10.1834 g (97%). Characterization data can be found in literature.[29]

3.4 MAC Addition to Aromatic Heterocycles

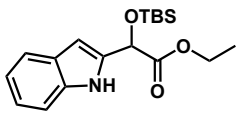
Masked acyl cyanide reagents (MAC) can be added to heterocyclic aldehydes (Scheme 3.2). The reaction utilizes 4-dimethylaminopyridine (DMAP) as the base to deprotonate the MAC reagent and ethanol (EtOH) serves to capture the acyl cyanide formed *in situ.* The method from literature was adapted to this procedure.[25]



Scheme 3.2: Generalized scheme for MAC addition to heterocyclic aldehydes

Experimental Information

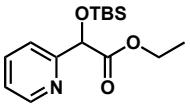
General procedure: To a 5 mL conical vial and spin vane were added 2-((tert-butyldimethylsilyl)oxy)malononitrile **9** (0.32 mmol, 1.05 eq), aldehyde starting material **8** (0.3 mmol, 1 eq), diethyl ether (Et_2O, 0.15 M), EtOH (0.9 mmol, 3 eq), and DMAP (0.75 mmol, 2.5 eq). The reaction was stirred at room temperature for 16 hours. TLC was used to monitor starting material consumption, and in cases where this was difficult due to overlap of spots, ^{1}H NMR was taken (and compared to the ^{1}H NMR of the starting materials). After completion of the reaction, it was added to a 30 mL separatory funnel and extracted using dichloromethane (DCM, 3 x 10 mL portions) and the combined organic layers were then washed with saturated aqueous ammonium chloride (NH_4Cl, 10 mL). The organic layer was collected, dried over sodium sulfate (Na_2SO_4) and concentrated under air. After confirming reaction completion by crude ^{1}H NMR, the concentrated organic layer was dissolved in DCM and loaded onto a 4 g column packed with SiO_2 and hexanes. The products were eluted with a mixture of ethyl acetate (EtOAc) in hexanes.



11

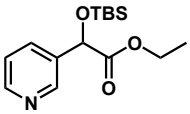
Ethyl-2-((tert-butyldimethylsilyl)oxy)-2-(1H-indol-3-yl) acetate (11): The starting material was 3-indolecarboxaldehyde. The concentrated organic layer produced a orange-brown oil. The column was run with 50 mL each of hexanes then 5-10-20% EtOAc/hexanes. The product-rich fractions were collected and concentrated under air to produce a green oil (0.0359 g, 36%

yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.12 (s, 1H), 7.82 (d, *J*=7.8 Hz, 1H), 7.35 (d, *J*=8.2 Hz, 1H), 7.27 (d, *J*=4.3 Hz, 1H), 7.20 (ddd, *J*=7.7, 7.5, 1.3 Hz, 1H), 7.13 (dd, *J*=7.5, 7.4 Hz, 1H), 5.53 (s, 1H), 4.15 (dq, *J*=7.2, 7.1 Hz, 1H), 4.14 (dq, *J*=7.3, 7.1 Hz, 1H), 1.22 (t, *J*=7.8, 7.1 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.5 (s), 136.4 (s), 125.6 (s), 122.7 (d), 122.2 (d), 120.3 (d), 119.8 (d), 115.1 (s), 110.1 (d), 69.3 (d), 61.0 (t), 29.7 (s), 25.8 (d), 18.7 (q) 14.3 (q), -5.0 (q), -5.1 (q).



12

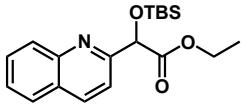
Ethyl-2-((tert-butyldimethylsilyl)oxy)-2-(pyridine-2-yl) acetate (12): The starting material was 2-pyridinecarboxaldehyde. The organic layer was concentrated under air to produce a yellow/orange solid. The column was run with 50 mL each of hexanes then 5-10-20% EtOAc/hexanes. The fractions containing product were collected and concentrated under air to produce a yellow oil (0.0327 g, 37% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.52 (ddd, *J*=4.8, 1.8, 0.8 Hz, 1H), 7.71 (ddd, *J*=8.0, 7.8, 1.8 Hz, 1H), 7.58 (d, *J*=7.9, 1H), 7.20 (ddd, *J*=7.5, 4.9, 1.2 Hz, 1H), 5.34 (s, 1H), 4.19 (dq, *J*=14.3, 7.2 Hz, 1H), 4.17 (dq, *J*=14.2, 7.1 Hz, 1H), 1.22 (t, *J*=7.2, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.4 (s), 159.0 (s), 148.9 (d), 137.0 (d), 123.0 (d), 120.9 (d), 76.3 (d), 63.4 (t), 25.8 (q), 18.4 (s), 14.2 (q), -4.9 (q), -5.1 (q).



13

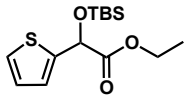
Ethyl-2-((tert-butyldimethylsilyl)oxy)-2-(pyridine-3-yl) acetate (13): 3-Pyridinecarboxaldehyde was the starting material. The organic layer was concentrated under air to produce a yellow solid. The column was run with 50 mL 9% EtOAc/hexanes and 100mL 12% EtOAc/hexanes to produce a yellow oil (0.0639 g, 72% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.71(d, *J*=2.36 Hz, 1H), 8.55 (dd, *J*=4.9, 1.6 Hz, 1H), 7.82 (dt, *J*=8.0, 1.7 Hz, 1H), 7.28 (ddd, *J*=8.0, 4.8, 0.5 Hz, 1H), 5.24 (s, 1H),

4.19-4.12 (m, 2H), 1.22 (t, *J*=7.1 Hz, 3H), 0.91 (s, 9H), 0.14 (s, 3H), 0.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.4 (s), 149.4 (d), 148.1 (d), 134.8 (s), 133.9 (d), 123.4 (d), 72.4 (d), 61.5 (t), 25.7 (d), 18.3 (s), 14.1 (d), -5.1 (q), -5.2 (q).



14

Ethyl-2-((tert-butyldimethylsilyl)oxy)-2-(quinolin-yl) acetate (14): The starting material was 2-quinolinecarboxaldehyde. The column was run with 50 mL each of hexanes then 5-10% EtOAc/hexanes to afford a yellow oil (0.0342 g, 33% yield). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 8.19 (d, *J*=9.1 Hz, 1H), 8.10 (dd, *J*=8.2, 0.8 Hz, 1H), 7.81 (dd, *J*=8.0, 1.2 Hz, 1H), 7.73 (d, *J*=8.5 Hz, 1H), 7.71-7.69 (m, 1H), 7.54 (ddd, *J*=8.7, 7.5, 1.2 Hz, 1H), 5.51 (s, 1H), 4.19 (dq, *J*=14.3, 7.5 Hz, 1H), 4.17 (dq, *J*=14.2, 7.5 Hz, 1H), 1.21 (t, *J*=8.0, 7.2 Hz, 3H), 0.93 (s, 9H), 0.16 (s, 3H), 0.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 171.1 (s), 159.0 (s), 147.3 (d), 137.0 (d), 129.5 (d), 129.4 (d), 127.8 (d), 127.6 (d), 126.6 (s), 118.7 (d), 77.0 (d), 61.3 (t), 30.9 (s), 25.7 (q), 18.3 (q), -4.9 (q), -5.1 (q).



15

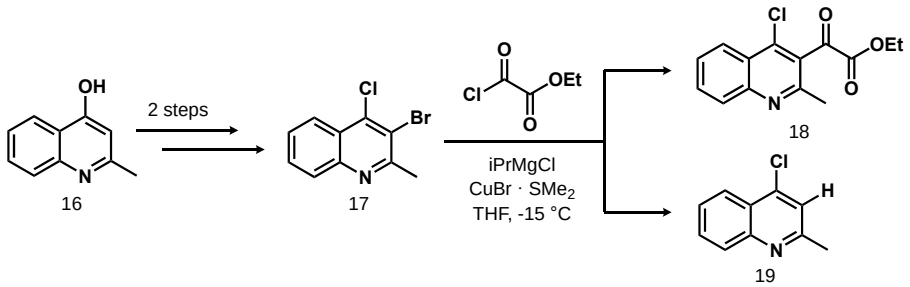
Ethyl-2-((tert-butyldimethylsilyl)oxy)-2-(thiophen-2-yl) acetate (15): The starting material was 2-thiophenecarboxaldehyde. The column was run with 50 mL each of hexanes then 5-10% EtOAc/hexanes to produce a yellow brown oil. (0.0216 g, 24% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.25 (dd, *J*=5.1, 1.2 Hz, 1H), 7.06 (dt, *J*=3.5, 1.5, 1.0 Hz, 1H) 6.96 (dd, *J*=5.2, 3.6 Hz, 1H), 5.46 (d, *J*=0.8, 1H), 4.21 (dq, *J*=7.2, 1.7 Hz, 1H), 4.20 (dq, *J*=7.1, 1.7 Hz, 1H), 1.27 (t, *J*=7.2 Hz, 3H), 0.94 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.1 (s), 142.8 (s), 126.6 (d), 125.3 (d), 124.5 (d), 71.0 (d), 61.4 (t), 61.4 (t), 25.7 (q), 18.4 (s), 14.1 (q), -5.1 (q), -5.3 (q).

4. Results and Discussion

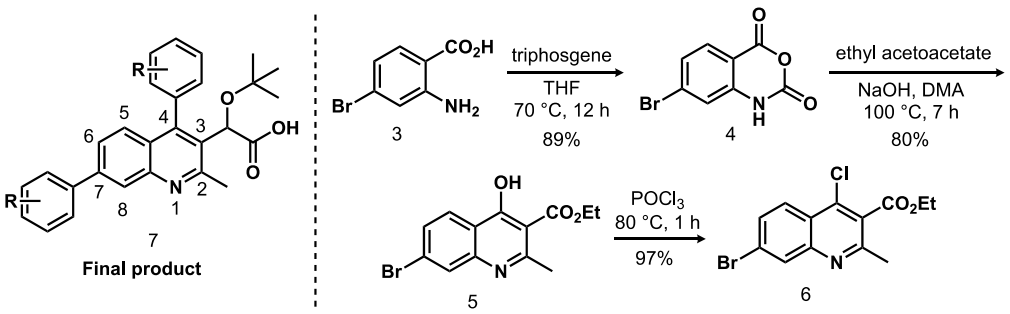
4.1 Large Scale Synthesis of Derivatized Quinoline

The new route utilizing various anthranilic acids to form the quinolines through an isatoic anhydride (**3** → **6**) allows substitution that using a commercially available quinoline **16** cannot (Schemes 4.1 and 4.2). First, the prior route utilized quinoline **16** which only allows functionalization at the 4-position (where the OH group is attached, Scheme 4.1). In addition, the prior route used a Grignard reaction (**17** → **18**) to install the side chain at the 3-position. However, during this reaction, a byproduct **19** was observed with no substitution at the 3-position and the yield of the reaction suffered as the scale of the reaction increased (Scheme 4.1). The prior route still allowed the Pigza, Donahue, and Kessl groups to fully explore substitution at the 4-position.[29]

The new route has addressed both the generality of functionalizing at other positions and approached installation of the 3-position in an alternative manner (Scheme 4.2). The ability to produce a quinoline scaffold that can be derivatized at the 5-, 6-, 7-, and 8-positions in large scale is beneficial for the capacity to produce many different derivatives for testing as potential HIV integrase inhibitors. The current route will discuss 7-position substitution, due to starting with bromoanthranilic acid **3**, which is commercially available. The other anthranilic acids are also available, allowing for exploration of the previously mentioned sites.



Scheme 4.3: Grignard reaction after halogenation of commercially available quinoline



Scheme 4.4 Large scale synthesis of quinoline ester

The sequence as shown in Scheme 4.2 was carried out with the goal of demonstrating that each step could be done on a large scale. The formation of the isatoic anhydride **4** was completed once, and the conversion to the quinoline **5** and chlorination were done twice to produce about 20 g of **6**. This increase in scale led to the need for larger glassware and more careful handling of hazardous reagents. The synthesis began with anthranilic acid **3**, which was reacted with triphosgene in THF. An addition funnel was used to ease the slow addition of the large volume of triphosgene, which was dissolved in THF to allow a more homogeneous mixture. Exposure to the hazardous fumes of triphosgene was minimized by weighing the solid quickly and then doing all further procedures in the fume hood. The work-up following the reaction was a simple filtration, though a large Buchner filter was required. The isolated pearlescent solid **4** was easily scraped out of the funnel into a large round bottom flask and put under high vacuum overnight to remove solvent, resulting in a fluffy solid.

The second step involved the formation of quinoline **5**. All reagents were added to a 250 mL round bottom flask which was then fitted with a reflux condenser since the reaction was heated to a high temperature. After quenching with distilled water and mechanical stirring overnight, the white precipitate was filtered out. The precipitate was

gummy and placed in a large round bottom that put under high vacuum overnight. During the first few hours, the round bottom was scraped periodically to allow more exposure to the vacuum. The formation of the quinoline involved only one hazardous reagent, *N*,*N*-dimethylaniline (DMA). The exposure to this reagent was minimized by using a syringe to collect it from the solvent bottle, and this was done in the hood.

The third step involved converting the alcohol **5** to the chloride **6** using phosphoryl chloride ($POCl_3$). Both starting material and $POCl_3$ were added to a 250 mL round bottom flask, and a condenser was used while the reaction was heated. The work-up involved the addition of water and was more complicated on large scale due to the HCl gas byproduct that forms and the exothermic reaction that results. The quench was completed in the hood and added to ice instead of just water. The quench was done in a very large container to account for the increase in volume of melted ice. The reaction was added through a separatory funnel to control the rate and to make sure it did not add too fast causing the quench to heat up too quickly. Once all of the reaction had been added, 10 M NaOH was added to neutralize the solution, and the pH was monitored using pH strips until a pH of 7 was reached. Once the solution was neutralized, a tan solid crashed out that was easily removed via Buchner funnel that was then dried under high vacuum overnight in a large round bottom flask. From the ester, seven more steps are needed to fully derivatize the quinoline scaffold to be an effective HIV integrase inhibitor.

Data analysis

Proton NMR (^{1}H NMR) was used to confirm the formation of all products. All characterizations were completed by a previous graduate student's work, so all spectra collected were compared to confirm the identity of products.[29] The spectra for isatoic

anhydride **4** contained the necessary aromatic peaks and amine N-H peak with the proper integrations. The formation of the quinoline **5** was confirmed by the formation of new peaks characteristic of the ethyl side chain as well as the methyl group. The chlorination of the alcohol also caused a downfield shift in all peaks. A stack plot was used to compare the starting material and product to determine the reaction had occurred.

4.2 MAC addition to aromatic heterocycles

Masked acyl cyanide (MAC) reagents, such as **9**, allow the addition of a one carbon nucleophile to a substrate, via the addition of a carbonyl (C=O) in which the carbon acts both as a nucleophile (-) and an electrophile (+) (Figure 4.1a). The normal reactivity of a C=O group is to act just as an electrophile (+). As an example, reactions in organic chemistry usually utilize 1,3-additions when involving C=O functional groups (Figure 4.1b, normal reactivity). This is due to the polarity of the C=O functional group which results in the carbon having a partial positive charge. The use of some reagents results in a polarity reversal and the ability to perform 1,2-additions (Figure 4.1b, umpolung reactivity). This reversal of polarity, or umpolung reactivity, allows for new bond disconnections to be realized that do not rely on the traditional methods of polarity. MAC reagents are an example of this, serving as a carbon monoxide equivalent.

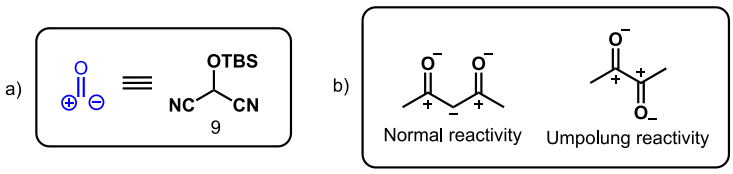
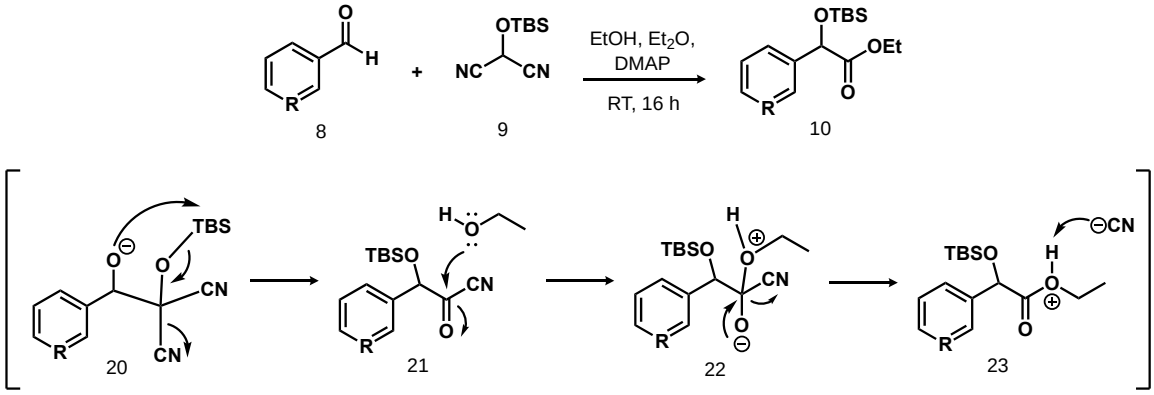


Figure 4.1: Normal and umpolung reactivity

MAC reagents have been added successfully to aldehydes as the electrophile, as shown in Scheme 4.3. First, the MAC reagent is deprotonated with a base such as

dimethylaminopyridine (DMAP) and adds to the aldehyde forming adduct **20**. A Brook rearrangement occurs, transferring the silyl group (TBS) to the alkoxide, which results in loss of a cyanide ion to form **21**. In the presence of an alcohol, in this case ethanol, acyl cyanide **21** is attacked, resulting in an intermediate **22** that collapses to form the product **10** (after proton transfer from intermediate **23**). Scheme 4.3 shows the generalized reaction and the proposed mechanism for the MAC addition.



Scheme 4.3: Generalized reaction scheme and proposed mechanism

The ability to add MAC reagents to various types of aldehydes has not been accomplished in the literature using heterocycles. Our goal for this project was to explore the MAC addition to various heterocycles. The diverse use of heterocycles in drug structures and ability to apply this method to quinolines for HIV integrase inhibition highlight the importance of this work. As such, following the reaction in Scheme 4.3, a screen of various heterocyclic aldehydes was undertaken (Table 4.1). Aldehydes **24-28** were dissolved in diethyl ether (Et_2O) and ethanol (EtOH), followed by addition of MAC **9** and then the base (DMAP). The reaction was stirred for 16 hours at room temperature then an extraction was performed. The crude material after extraction was checked by ^1H NMR and then purified using column chromatography. The results are shown in Table

4.1 and indicate purified yields after column chromatography. The yields varied a lot and for the most part were relatively low. No clear trend could be observed.

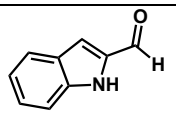
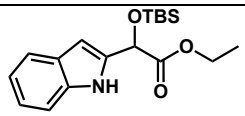
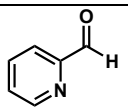
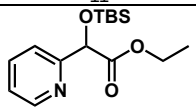
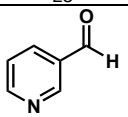
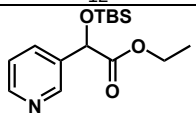
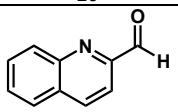
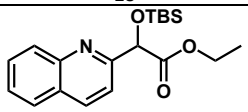
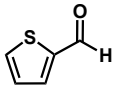
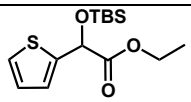
Starting material	Final product	Percent yield
 24	 11	36%
 25	 12	37%
 26	 13	72%
 27	 14	33%
 28	 15	39%

Table 4.1: Results of MAC addition to selected aromatic heterocyclic aldehydes

To further explore the conditions, pyridyl aldehydes **25** and **26** were tried with various changes in conditions before purification on silica gel (Table 4.2). For 3-pyridyl **26**, two different workup conditions were tried (entries 1 and 2). The first involved washing with water and then extracting with dichloromethane (DCM, entry 1), while the second involved washing with saturated aqueous ammonium chloride (NH_4Cl, entry 2). The two conditions did not result in a noticeable difference in yield (69% for entry 1 versus 72% for entry 2). However, 2-pyridyl aldehyde **25** resulted in noticeably lower yields under these conditions (37%, entry 3). It was therefore tried to just concentrate the

reaction and add it directly for purification, bypassing the extraction/work-up. This also resulted in a disappointing yield (14%, entry 4).

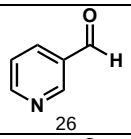
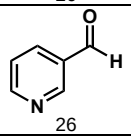
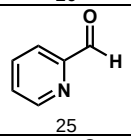
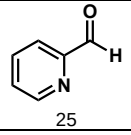
Entry	Substrate	Work-up	Extraction conditions, if applicable	Percent yield
1	 26	Extraction and column	10 mL H_2O, 3-10 mL washes DCM	69%
2	 26	Extraction and column	10 mL sat. NH_4Cl, 3-10 mL washed DCM	72%
3	 25	Extraction and column	10 mL sat. NH_4Cl, 3-10 mL washed DCM	37%
4	 25	Column only	N/A	14%

Table 4.2: Work up procedure methods

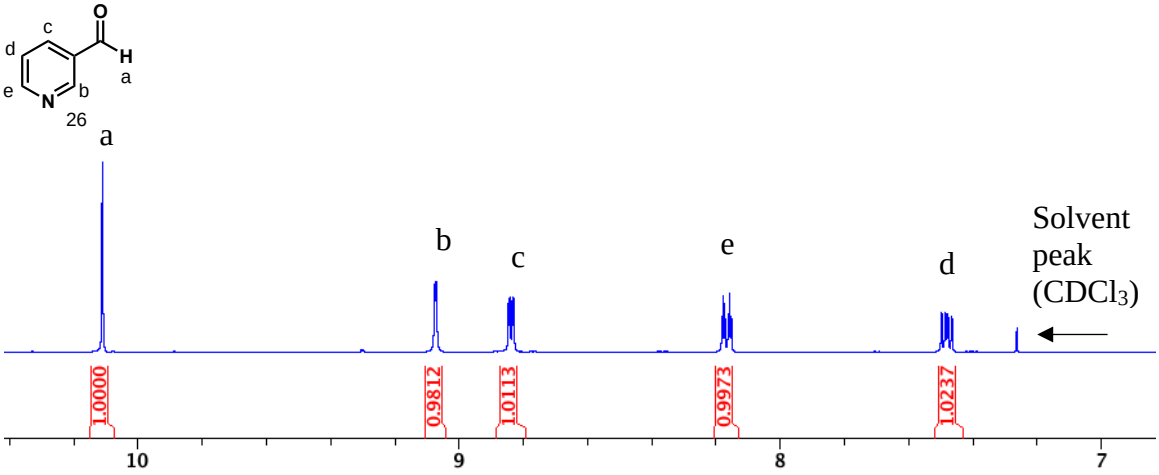
It has been seen that the reactions with aromatic heterocycles are significantly lower yielding than the non-heterocyclic aldehydes used in literature. It has been suggested that the small scale of the reactions leaves very little room for error as even small errors on a 0.03 mmol scale can have large impact on yield. It could also be possible that the lone pairs present on the heteroatoms in the structures interfere in the reaction conditions. At this point, the project was not further continued.

Data analysis

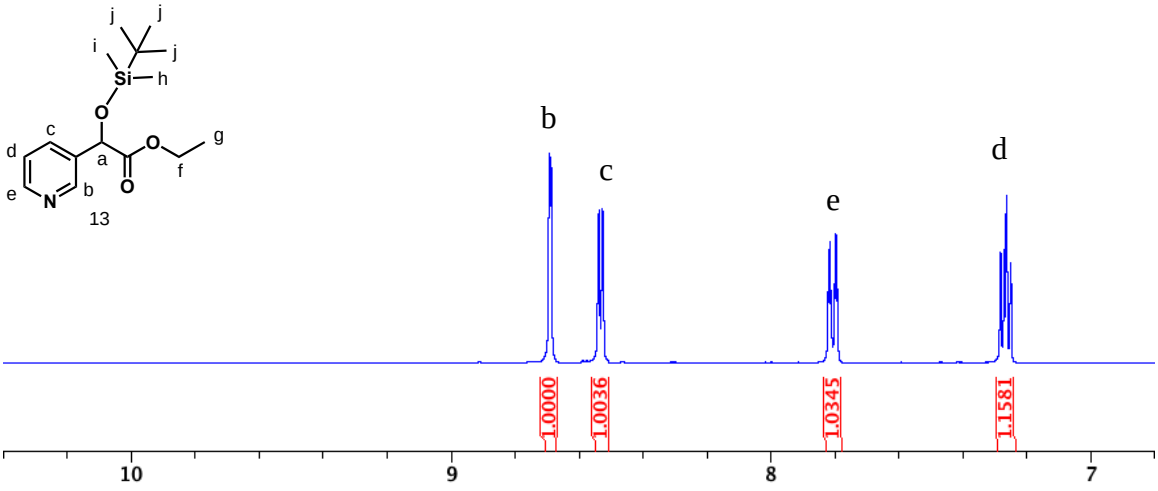
All reactions were monitored by ^1H NMR. The data below is an example using the reaction with pyridine-3-carboxaldehyde. Each substrate results in unique spectra, however, the consistent aspect is the loss of the aldehyde peak (~10 ppm) and shifting of aromatic peaks (7-9 ppm). The blow-up regions show the aldehyde and aromatic regions

of both the starting material and product NMRs to demonstrate the loss of the aldehyde peak (a) and the shift of the aromatic peaks (b-e). The full spectra shows the addition of six new peaks indicating the addition of the new side chain consisting of a TBS protecting group, adjacent hydrogen, and an ethyl group. The TBS group produces three singlets (h, i, j). The adjacent hydrogen is also a singlet (a). A quartet and triplet (f and g, respectively) are the ethyl peaks.

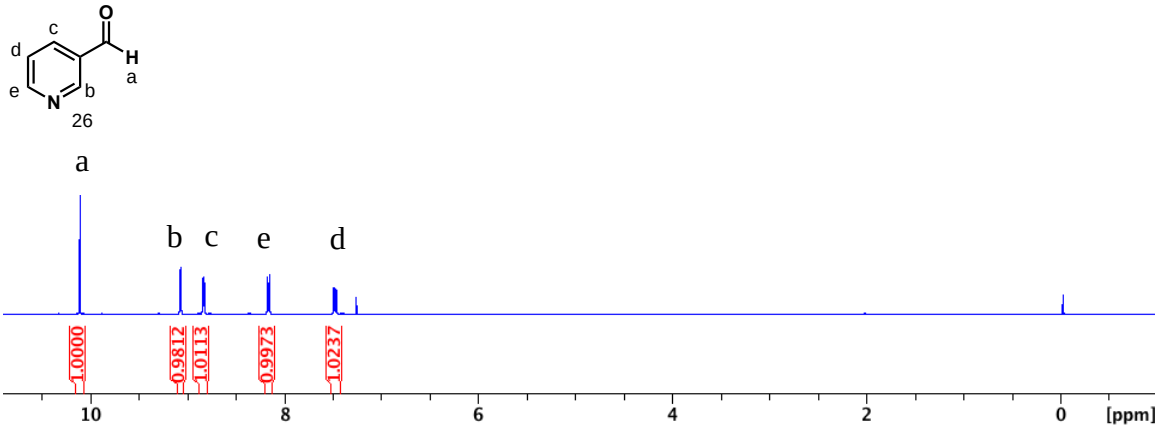
Aromatic region of pyridine-3-carboxaldehyde (starting material)



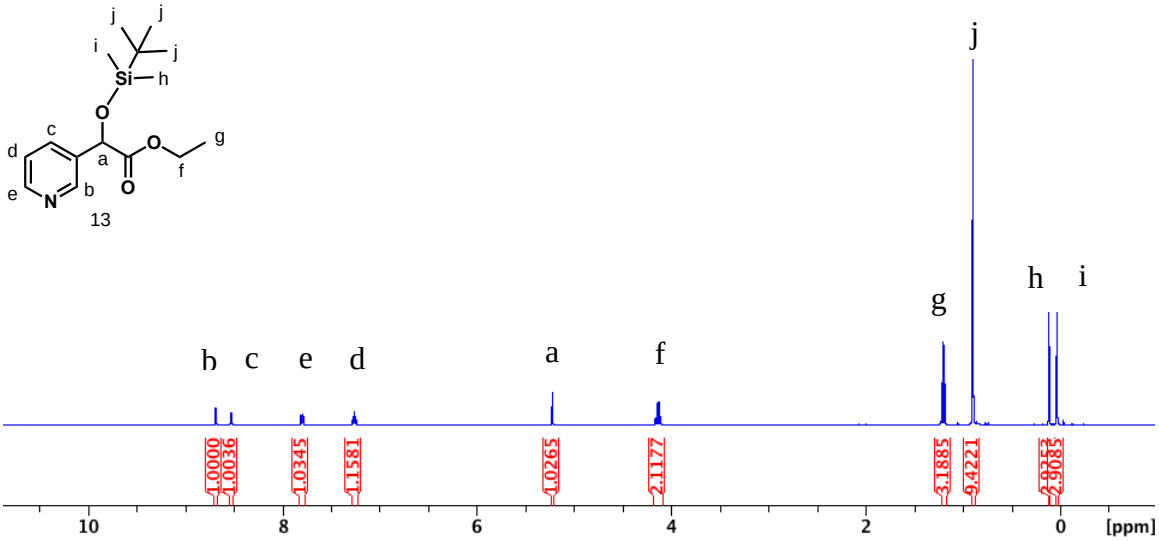
Aromatic region of ethyl-2-((tert-butyldimethylsilyl)oxy)-2-(pyridine-3-yl) acetate



Pyridine-3-carboxaldehyde (starting material) full spectrum



Ethyl-2-((tert-butyldimethylsilyl)oxy)-2-(pyridine-3-yl) acetate full spectrum



5. Conclusion

The two aims of this thesis center on the use of heterocycles in medicinal chemistry. The use of quinoline as an allosteric HIV-1 integrase inhibitor demonstrates the application of heterocycles in new areas of HIV treatment. Several derivatives with a quinoline scaffold have been synthesized through methods using commercially available quinolines as well as anthranilic acid derivatives. The method using commercially available quinolines was limited to only derivatizing certain positions and had

diminishing yields as the scale increased. The ability to synthesize quinoline derivatives on a large scale increases the possibility of its use as the scaffold for drug structures. In a research laboratory, it is useful to be able to produce large quantities to have plenty of material to subject to various tests. In addition, once a drug successfully passes through all clinical trials, it must be synthesized on a large scale to made available commercially.

One step of the quinoline derivatization involves the manipulation of the 3-position side chain. This can be done by reducing the ethyl ester to an alcohol and oxidizing to an aldehyde. Once it is an aldehyde, MAC reagents can be used to install the desired sidechain. To further explore the use of MAC reagents to oxidize aldehydes, this method was applied to various aromatic heterocyclic aldehydes. The goal with this was to expand the application of MAC beyond the substrates used in literature. TBS-protected MAC reagents successfully installed the ester sidechain to the heterocycles used though yields varied.

Work has already begun to continue the synthesis route on large scale to complete the seven steps beyond the chlorinated quinoline ester. Further work could be done to continue to optimize the conditions of the MAC addition to improve yields with heterocycles. These two projects demonstrate the diversity in the possible applications of heterocycles and possible expansions to increase their use in medicinal chemistry.

6. References

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