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An Investigation Of Electron Density And Resonance Of A 6π Conjugated System

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Abstract

Numerous 6π conjugated systems were observed during an electrocyclization-condensation reaction in order to understand resonating electrons behave in π-orbitals in the presence of withdrawing and donating substituents. The prediction that when the 6π carbanion system contains a withdrawing or deactivating residue, the density of the π-electrons will be delocalized, causing the π-electrons to be more organized and stabilizing the system. Under the notions of foundation carbanion and resonance theory, the stabilization of the carbanion system will decrease the reaction entropy, as well as hindering product formation, thus resulting in a decrease in yield under a specific time frame. In turn, We predict that donating or activating residues will contribute to a less stable, more electron dense and more entropic intermediate and these cause product formation to occur in relatively higher yields than the former case described. The electrocyclic-condensation of glycine-ethyl or metyhhyl ester hydrochloride and chalcone derivatives with varying electronic substituents is being observed and performed. In the reaction, the chalcone and glycine- ethyl ester condensed to form a secondary imine intermediate. In the same pot, this intermediate underwent an electrocyclization forming a dihydro-pyrrole. Several novel α-substituted chalcones were synthesized in good to excellent yield using a variety of methods. It was found that the specific dihydropyrrole formed was dictated by the alpha-substituent. Thus far some α-chalcones formed C-N pi bonded dihydropyrroles, whereas other α-substituted chalcones generated N-H dihydropyrroles other dihydropyrroles are being developed and the results will be reported in the future. Trends associated with the reaction of these α-substituted chalcones with various withdrawing or donating residues with glycine ethyl or methyl ester in the pyrrole formation process are provided

1. Introduction

Heterocyclic aromatic compounds, are prevalent throughout science and nature. Pyrroles specifically are used by cellular machines in vivo to synthesize biological materials. An example of this phenomenon is the utilization of pyrrole in the composition of hemoglobin (Fig. 1), an oxygen storing and transport molecule, and chlorophyll, a molecule in plants used to absorb energy from light sources. Pyrroles can also be seen in the industry, as they are used to create polymers, preservatives, and to prevent the corrosion in metals.[1,2]

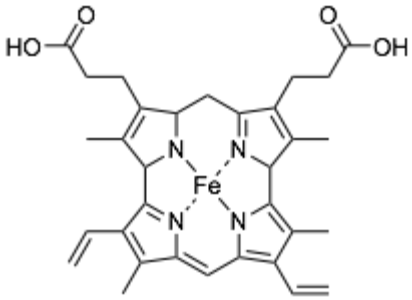


Figure 1: Structure of Fe-porphyrin subunit contains an Fe^{2+} ion complexed with four pyrroles in the coordination complex heme B. Heme B is one of the subunits of hemoglobin, an oxygen transport and storage protein.

Pyrrole and its derivatives are most famous because of their wide application in synthetic chemistry. When pyrroles are decorated with the appropriate pharmacophores, they are transformed into a curative force that can possess a diverse nature of remedial biological activity. Pyrrole derivatives possess antibiotic properties, anticancer properties, cholesterol reducing properties and HIV properties, to name a few, however the list is greatly extended pass the few properties mentioned (Fig. 2).[3] The biological potential of pyrrole derivatives should continuously be examined to expand the medicinal potential of the pyrrole.

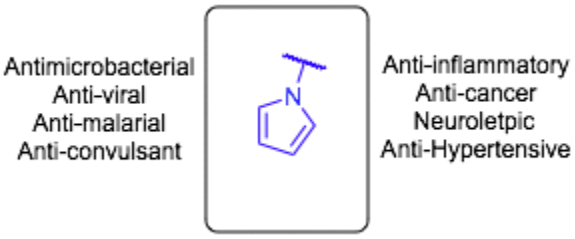


Figure 2: A diagram showing the pyrrole unit and many biological fates of pyrrole.[3]

2. Background

Many novel synthetic routes have been developed in order to synthesize some of the world's most important pyrrole derivatives. One of these important pyrrole derivatives is the cardiovascular prevention medication Atorvastatin, commonly known as *Lipitor*, the highest selling drug in all of history.[4]

In 1989 an efficient synthetic route for Atorvastatin was developed by the Warner-Lambert pharmaceutical company [5] .The synthesis made use of a Stetter reaction with a thiazolium salt for the first step, and a Paal-Knorr reaction using pivalic acid and the necessary primary amine for the last step to access the Atorvastatin pyrrole with an 81% yield.[4] A Paal-Knorr reaction utilizes a 1,4 diketone in the presence of a primary amine or ammonia. In the reaction, the primary amine attacks both carbonyl carbons, forming a unsaturated pyrrolidine intermediate. This intermediate, inevitably goes through dehydration aromatization to form the substituted pyrrole. The utilization of Paal-Knorr in the Atorvastatin reaction is highlighted in **Figure 3**.

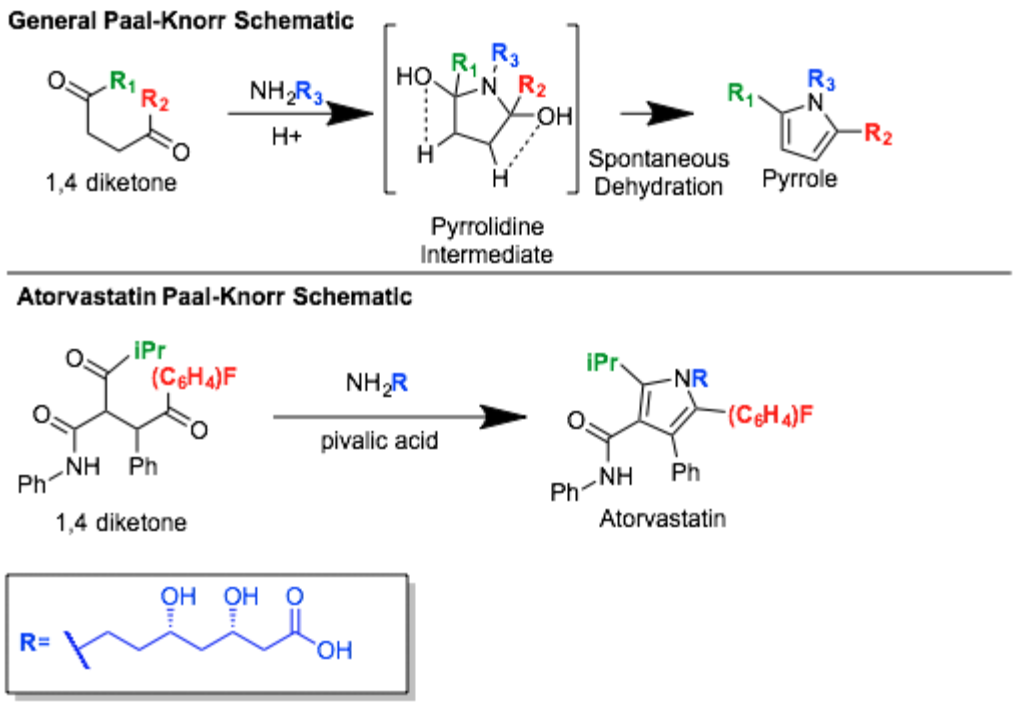


Figure 3: General Paal- Knorr synthetic schematic (**top**) to the Atorvastatin Paal- Knorr synthetic scheme (**bottom**).[5]

Historically, there are three classical approaches that are used to synthetically generate pyrroles, the most commonly applied approach being the Paal-Knorr synthetic route.[5] Many modifications have been made to the Paal-Knorr reaction and the reaction is the go-to for many medicinal chemist due to its simplicity, efficiency and use of little starting material.

Dr. Ludwig Knorr was also involved with the discovery of another classical route commonly used to synthesize pyrrole derivatives, the Knorr-Pyrrole synthesis. The reaction utilizes the condensation of an α-aminoketone and a compound containing an electron withdrawing residue (generally a carbonyl) to form an imine. The imine eventually tautomerizes to an enamine, and the π-electrons in this conformation attack the carbonyl alpha to the amine (of the α-aminoketone) causing a cyclocondensation towards the desired pyrrole. The carbonyl complex is worked up to form the pyrrole. Often times, symmetrical β-diketones are utilized as the withdrawing residue when executing this reaction. This is because the reaction lacks regioselectivity with unsymmetrical β-diketones or other withdrawing groups, which many researchers consider to be a major drawback of the reaction.[6] In addition to the lack of regioselectivity, the primary issue with the reaction is that the aminoketone is extremely prone to self-condensation.[6] To avoid the problem, the aminoketone usually is synthesized in situ but this is not a guaranteed method to avoid self-condensation. However, in 1999 the Ortega group discovered a work around the self-condensation problem with the use of an Weinreb amide (α-N,O-Dimethylhydroxylamine). Weinreb amides can prevent the over-addition of an organometallic nucleophilic to the carbonyl carbonyl, when the Weinreb amide is alpha to said carbonyl. Ortega et al. successfully used Weinreb α-aminoamides and enamines/imines to form pyrrole derivatives without the production of undesired self-condensation products ranging from 72-89% in yield.[7] The Ortega approach is compared with the general Knorr Pyrrole synthesis in **Figure 4**.

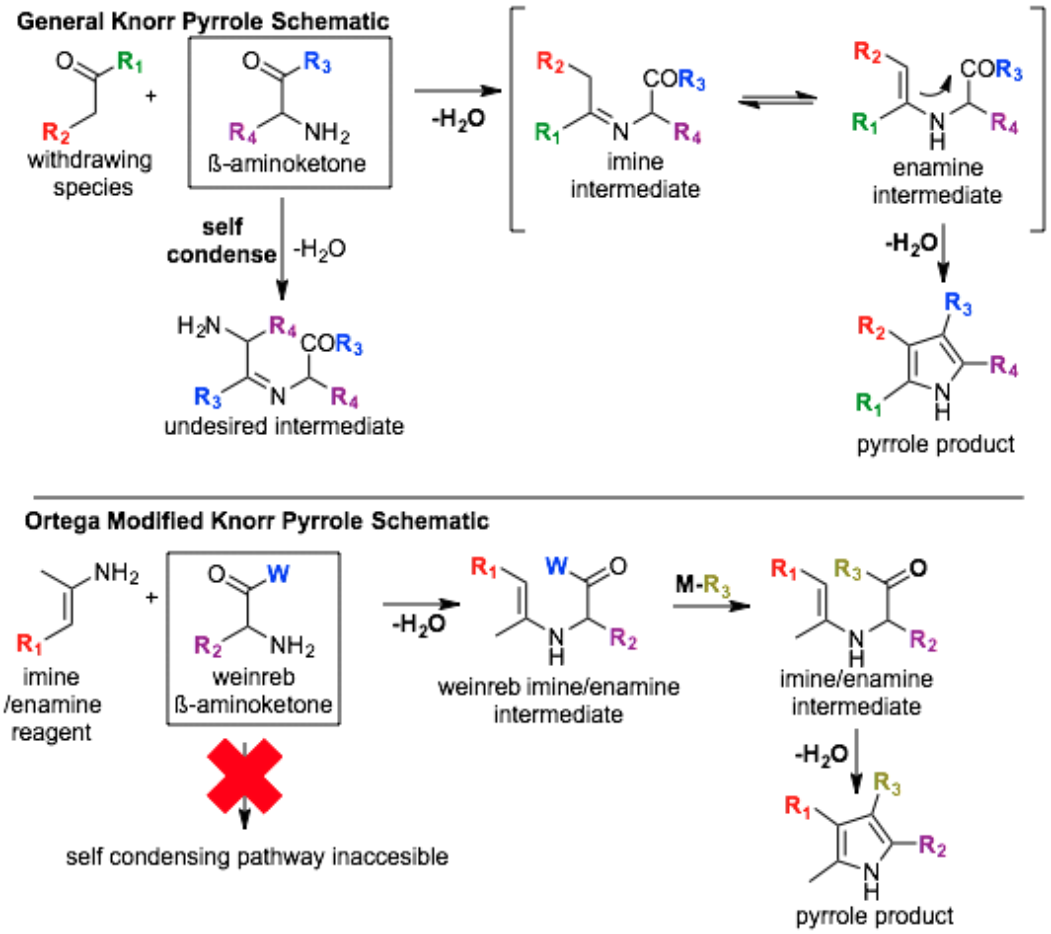


Figure 4: The Ortega Modified Schematic (**bottom**)[7] to the General Knorr Pyrrole Schematic (**top**).
W = N,O dimethoxyhydoxylamine.

Another reaction used for the synthesis of pyrroles is the Hantzsch pyrrole synthesis. The reaction accesses the pyrrole by using an α-haloketone and a β-ketones in the presence of a primary amine or ammonia. The amine attacks one of the two carbonyls on the β-ketone, forming an imine intermediate through condensation. This process is not completely selective, so sometimes a symmetrical β-ketones is used. When the amine is tautomerized into an enamine, this route is generally considered the least efficient of the classic three due to the formation of furan molecules as a byproduct- and in some cases the main product.[6] Because of this drawback, further research has been done on the Hantzsch reaction in order to improve the yield of the synthetic approach. Despite efforts, the reaction has had little advancement relative to the other Dr. Ludwig Knorr's approaches.[6] However, In 2014 the Dos group developed an environmentally-friendly one-pot condensation reaction using an inexpensive alum catalyst and a water-PEG 400 solvent system. The group used a haloketone 3-(bromoacetyl)-coumarin derivative and the β-ketone used was acetylacetone. It was discovered that with their approach, the furan byproduct is generated in considerably lower yield. The novel approach generally yielded 83-91% of the desired pyrrole.[8] These optimizations make this reaction one of the greatest advances to the Hantzsch reaction because of its high average yield and catalyst efficiency.[9] The Dos approach is compared with the General Hantzsch pyrrole synthesis in **Figure 5**.

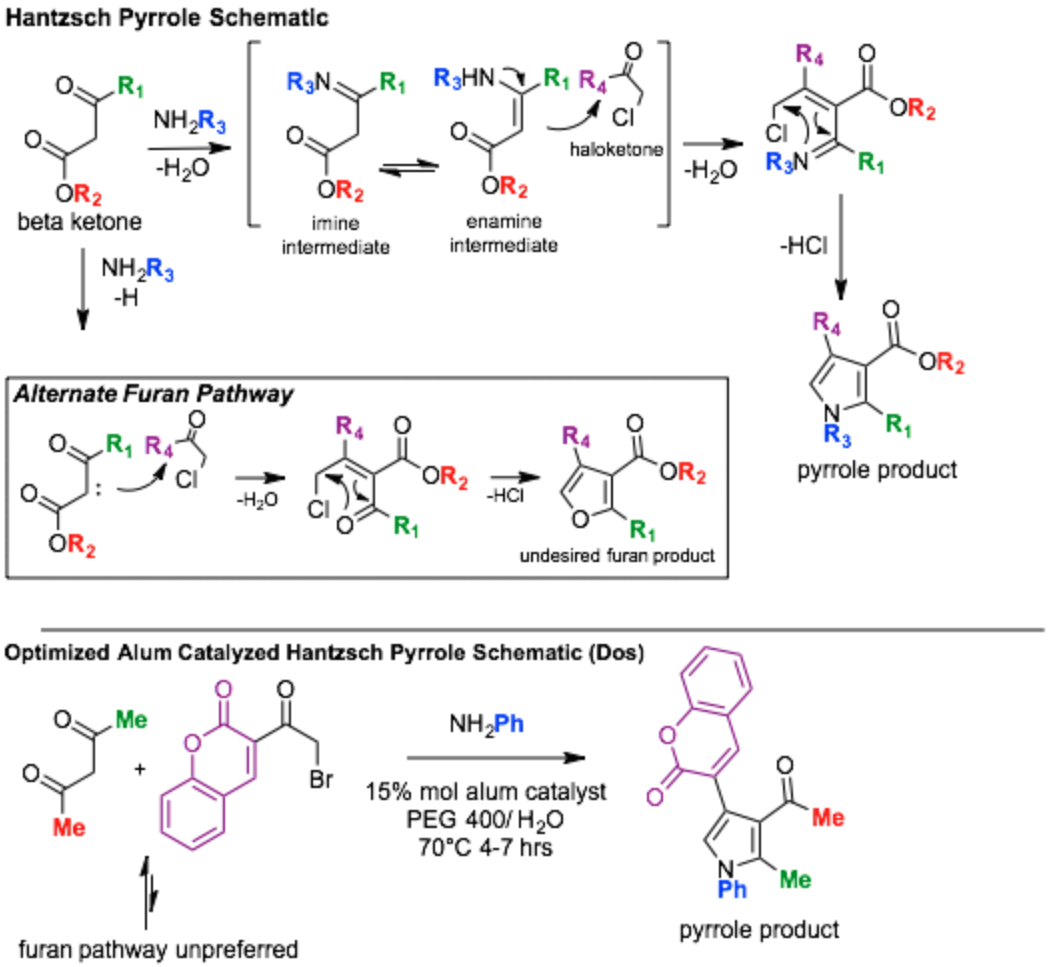


Figure 5: The advanced Hantzsch Pyrrole synthesis utilizing an alum catalyst (**bottom**)[8] to the general Hantzsch Pyrrole synthesis (**top**).

The recently discovered Barton-Zard reaction,although not used as commonly as the main three synthetic approaches, it still holds significance [6]. An extensive amount of research and many modifications have been done on this reaction, many of which were efficient.[6] Generally, the reaction produced pyrroles by reacting a nitroalkene with an α-isocyanoacetate in basic conditions as seen in **Figure 6**.

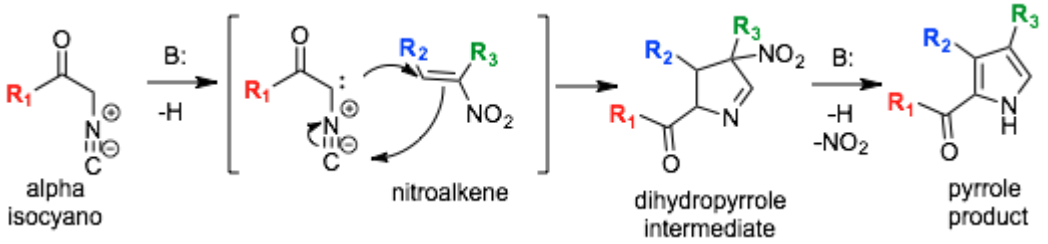


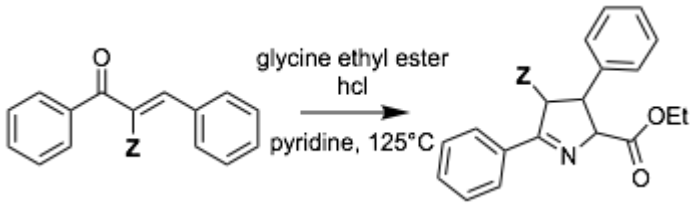
Figure 6: General Barton-Zard Reaction [6]

Besides these four reactions, there are still various synthetic approaches that can be employed to access pyrrole derivatives. Cycloadditions, Zavyalov Reactions, Piloty–Robinson Reactions and cyclocondensation reactions are just a few more examples of established approaches for pyrrole synthesis.

2.1 Investigation

This project has a primary focus and a secondary focus. The primary focus is to investigate how electron density plays a role in the electrocyclization of a 6π species. The secondary goal is synthesize novel dihydropyrroles that can simply be oxidized to create novel pyrroles or used for the synthesis of other molecules.

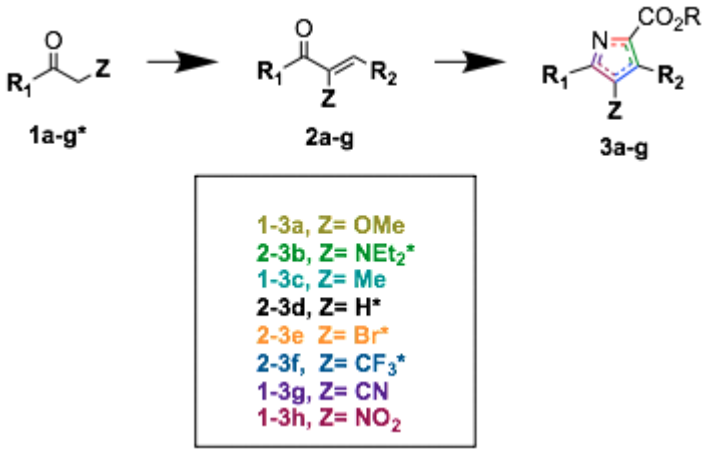
The cyclo-condensation of glycine-ester hydrochloride and chalcone derivatives with varying electronic substituents is the reaction of interest. Methods developed by Opatz et al. (Scheme 1) will be used to perform the cyclocondensation.[10]



Scheme 1. Generalized Schematic of Cyclocondensation for our project derived from Opatz et al.[10]

Reaction Sequence can be broken in two 3 major synthetic phases. (Scheme 2):

1. Synthesis of a necessary acetophenone derivative. **(1a-g)**.
2. Synthesis of a novel chalcone derivative **(2a-g)** using the acetophenone derivative.
3. Synthesis of a novel dihydro-pyrrole **(3a-g)** using the chalcone derivative.

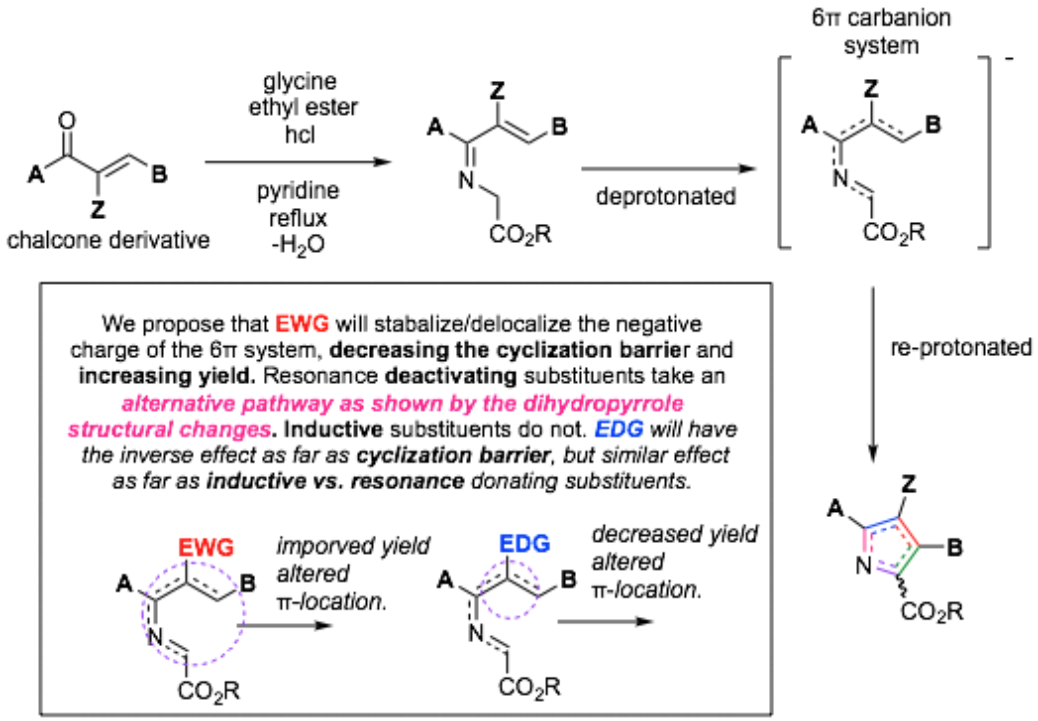


Scheme 2. Generalized schematic of the investigation pathway for chalcones (**2a-g)** and dihydropyrrole (**3a-g**). *Derivatives do not require synthesis of acetophenone in order to access chalcone molecules.

3. Results & Discussion

It was predicted that when the 6π carbanion system contains with a withdrawing or deactivating residue, the density of the π-electrons will be delocalized, causing the π-electrons to be more organized and stabilizing the system. Under the notion that electrocyclic systems are thermodynamic, the stabilization of the carbanion system will increase the reaction entropy as lowering the system's cyclization barrier, resulting in a increase in dihydroproduct yield under a specific time frame. Thus, donating or activating residues will contribute to a less stable, more electron dense and more entropic intermediate. Under the same notion that electrocyclic systems are thermodynamic, localization should cause dihydropyrrole formation to occur in relatively lower yields. Granted, similar yields may have discrepancies, there appears to be an agreeable linear trend in regards to electronic substituents. Expectedly, when comparing similar A/B rings, the α-OMe dihydropyrrole has produced the lowest yield thus far (5%), the α-Me has produced the second lowest yield thus far (9%) and the α-CN has produced the highest yield thus far (31%). Although not all data points

have been collected, the hypothesis will be affirmed if the reference (α-H) remains in the middle of the linear trend. Serendipitously, research of these electronic conditions have also revealed that the location of the π-bond in the dihydropyrrole product is dependent on its electronic substituent, it is most likely that the theory discussed above is affecting the the electron flow shown in **Scheme 3.** Three different π-confirmations have been characterized so far. Such variance implies that the electronic substituents are altering the mechanism of the electrocyclic-condensation reaction. It should be highlighted that the α-Me dihydropyrrole gives the same π-confirmation as the reference. This may imply that the mechanism can be only manipulated when the electronic substituents are electronic by primarily resonance and not inductivity, however this assertion cannot be said with confidence until the α-CF_3 analog has been synthesized. Altered location of these π-bonds can be found in the data below.



Scheme 3: Detailed Schematic of Cyclocondensation for our project derived from Opatz et al.[10]

The progress of each reactions are observed using thin-layer chromatography. Each compound was purified using a variety of techniques such as liquid-liquid extraction, filtration, recrystallization, trituration and column chromatography. Each compound will be characterized using infrared radiation and nuclear magnetic resonance spectroscopy techniques. **Table 1** includes all the intended products as well as respective yields and times that it took to achieve each yield. This research is still in progress.

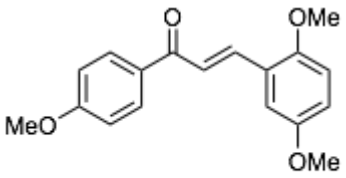
Table 1: Experimental yields and reaction times for compounds synthesized thus far. Blue boxes correspond with acetophenone derivatives. Yellow boxes correspond with chalcone derivatives. Red boxes correspond correspond with dihydropyrrole derivatives. **N/A** implies that this derivative is not requisite for the total pathway of the reaction sequence. For **1d** it means that this compound was pre-made. **"--"** implies that data has not been attained for this derivative. **Undeter.** Implies that yield has not been determined, but the compound was characterized. **O.N.** means that this reaction was ran overnight.

Aceto.	Yield	Time	Chalc.	Yield	Time	Dihydr.	Yield	Time
1a	76%	2 h	2a	66%	O.N.	3a	5%.	24 h
1b	N/A	--	2b	undeter.	2 d	2b	--	24 h
1c	77%	O.N.	2c	31%	1d	3c	9%	24 h
1d	N/A	--	2d	82%	3 h	3d	16%	24 h
1e	N/A	--	2e	--	--	3e	--	
1f	N/A	--	2e	undeter.	2 d	3e	--	24 h
1g	45%	1.5 h	2f	76%	5 min	3f	53%.	24 h
1h	44%	12 h	2g	undeter.	12h	3g	--	2 4h

4. Experimental

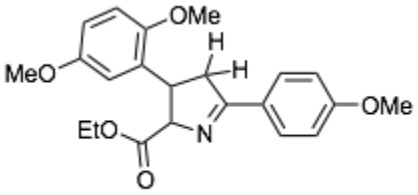
General Dihydropyrrole Procedure [10]. To a 3 neck vessel charged with 5 ml pyridine and 50 mg of molecular sieves was added 0.54 mmol of the **respective chalcone** and 0.54 mmol of glycine ethyl ester hydrochloride. This solution was stirred and refluxed for 24 hrs at 130°C. Once complete the reaction was allowed to cool for 10 min to reach room temperature. The reactions were diluted with DCM and washed with water. The water partition was extracted x2 with DCM. The combined organic partitions were dried over Na_2SO_4 anhydrous and concentrated under reduced pressure to yield. The dihydropyrroles were purified using Column Chromatography and characterized using H^1-NMR. The respective dihydropyrroles appear as dark brown and dark orange waxes.

4.1 Reference Compounds



(*E*)-3-(2,5-dimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one

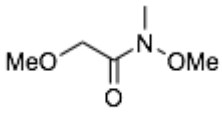
In an open vessel, 33.3 mmol of the acetophenone and 1. eq of the benzaldehyde was dissolved in 20 mL of EtOH. 10 mL of 15 N NaOH was added dropwise, and additional 15 N NaOH was continuously added until a moiety began to form in the bottom of the vessel. Once the moiety began to solidify into yellow solids, the reaction was allowed to run for an hour, and a generous amount of ice was added to the reaction. The yellow solids were filtered from solution and recrystallized to receive the desired chalcone as pure. The product was used in the next step without further analysis.



ethyl 3-(2,5-dimethoxyphenyl)-5-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylate

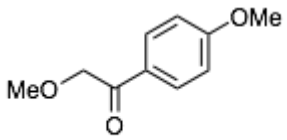
Synthesized using ***General Dihydropyrrole Procedure***. Product confirmed using Proton NMR Spectroscopy. (16%) **^{1}H NMR** (400 MHz, CDCl3) δ **7.86-7.84** (d, 2H), **6.94-6.92** (d, 2H), **6.79-6.76** (m, 3H), **4.98-4.96** (d, 2H)**, 4.25-4.20** (q, 2H), **4.04-3.99** (dd, 1H), **3.85** (s, 3H), **3.74** (s, 6H), **3.54-3.47** (dd, 1H), **3.23-3.16** (dd, 1H), **1.30-1.25** (t, 3H).

4.1.1 alpha-methoxy compounds



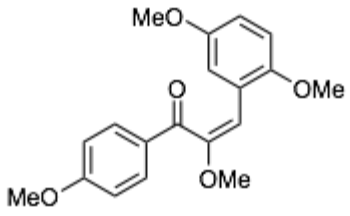
N,2-dimethoxy-*N*-methylacetamide ***[11]***

To a stirring solution of 67 mmol of the Weinreb amide in 100 mL DCM in a vessel with a drying tube extension was added 38.3 mmol ***2-methoxyacetyl chloride***. This solution was stirred for 6 hrs, then partitioned with 150 mL water and DCM (150 mL x3) and dried over $MgSO_4$ (anhydrous). The organic partition was evaporated under reduced pressure to yield pure ***N*,2-dimethoxy-*N*-methylacetamide** as a loose red wax. The product was confirmed using Proton NMR spectroscopy (65%). **^{1}H NMR** (400 MHz, CDCl3) δ **4.23** (s, 2H), **3.70** (s, 3H), **3.48** (s ,3H), **3.21** (s, 3H).



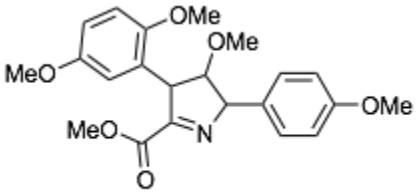
2-methoxy-1-(4-methoxyphenyl)ethan-1-one ***[12]***

In an inert environment, 27.6 mmol of **4-Bromoanisole** and 12 mL of 2.5 BuLi in hexane reacted for 10 min in 50 mL of THF (anhydrous) at 78 °C. The solution turned into a cream-like substance, and 24.8 mmol of ***N*,2-dimethoxy-*N*-methylacetamide** was added to the mixture and stirred for 4 hrs and allowed to warm to RT (room temperature). The reaction was then quenched with NH_4Cl, partitioned with 100 mL each of H_2O, dilute HCl, Brine, and diethyl ether. The aqueous partition was then with diethyl ether (100 mL x2) and the organic partitions were combined. The organic partition was dried under $MgSO_4$ (anhydrous) and evaporated under reduced pressure to yield ***2-methoxy-1-(4-methoxyphenyl)ethan-1-one*** as fluid amber or yellow wax. The product was confirmed by Proton NMR spectroscopy (77%). **^{1}H NMR** (400 MHz, CDCl3) δ **7.95-7.92** (d, 2H), **6.96-6.94** (d, 2H), **4.68** (s ,2H), **3.88** (s, 3H), **3.51** (s, 3H).



(*E*)-3-(2,5-dimethoxyphenyl)-2-methoxy-1-(4-methoxyphenyl)prop-2-en-1-one ***[13]***

In an inert environment 19 mmol of ***2-methoxy-1-(4-methoxyphenyl)ethan-1-one*** was reacted with 1 eq of 2.5 dimethoxybenzaldehyde and 35 eq. of 10 M NaOH in 150 mL MeOH overnight. In 10 m a wax formed, and 20 m a pale yellow solid began to crash out of the wax. The solid was vacuum filtered and determined to be ***(E)-3-(2,5-dimethoxyphenyl)-2-methoxy-1-(4-methoxyphenyl)prop-2-en-1-one*** via Proton NMR spectroscopy (66%). **^{1}H NMR** (400 MHz, CDCl3) δ **7.98-7.96** (d, 2H), **7.85** (s, 1H), **7.98-7.96** (d, 2H), **6.87-6.79** (m, 3H), **3.90** (s ,3H), **3.82** (s, 3H), **3.75** (s, 3H).

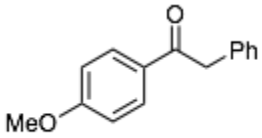


methyl 4-(2,5-dimethoxyphenyl)-3-methoxy-2-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyrrole-5-carboxylate

Synthesized using ***General Dihydropyrrole Procedure***. Product confirmed using Proton NMR Spectroscopy. (5%) **^{1}H NMR** (400 MHz, CDCl3) δ **7.90-7.88** (d, 2H), **6.87-6.85** (d, 2H), **6.75-6.71** (m, 3H), **5.11-5.10** (d, 1H)**, 4.83-4.82** (d, 1H) 3.78-3.63 (m, 13H), **3.28-3.27** (m, 3H).

4.1.2 alpha-phenyl compounds

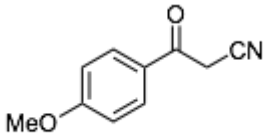
Scheme 5: Synthetic route of the acid towards the alpha-phenyl-acetophenone.



1-(4-methoxyphenyl)-2-phenylethan-1-one

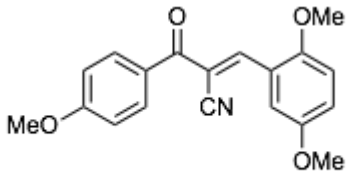
In an inert environment, 63.9 mmols of **phenylacetic acid** was reacted with 1 eq. of thionyl chloride in 1 eq. of anisole under reflux for 1 hr. Once the solution turned an intense dark red the reaction was brought down to RT and 0.5 eq (assume 100% yield of acid chloride) of ZnO was added in three parts to the vessel at -20 °C and allowed to stir overnight. The viscous red solution was diluted with 20 mL of DCM and was washed with concentrated $NaHCO_3$ (40 mL x3) and then washed with water (40 mL x2). The organic partition was evaporated under reduced pressure to receive a wax. The wax was then triturated with 1:1 DiEt/ Hexanes to afford the product ***1-(4-methoxyphenyl)-2-phenylethan-1-one as*** buff-colored crystals. The product was confirmed using Proton NMR spectroscopy (21%).**^{1}H NMR** (400 MHz, CDCl3) δ **8.02-8.00** (d, 2H), **7.34-7.24** (m, 5H), **6.95-6.93** (d, 2H), **4.25** (s, 2H), **3.87** (s ,3H).

4.1.3 alpha-cyano compounds



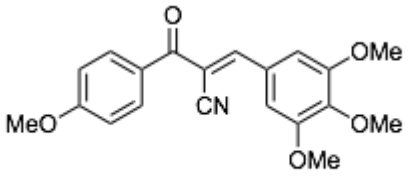
3-(4-methoxyphenyl)-3-oxopropanenitrile ***[15]***

In an inert environment 96 mmol of NaH was added to a stirring solution of 3 mL acetonitrile anhydrous in 10 mL DMSO (anhydrous). The solution was allowed to stir for 20 mins and 0.38 eq of ***methyl 4-methoxybenzoate*** was added and stirred for 1.5 hrs. The reaction was slowly quenched with water, and HCl concentrated was added until the reaction became a white thick curd like solution. The solution was washed with water (100 mL x3) and then the organic partition was washed with Brine (100 mL x3). The organic partition was then dried over $MgSO_4$ (anhydrous), and triturated with a 1:1 Hex/ DiEt solution to yield ***3-(4-methoxyphenyl)-3-oxopropanenitrile*** as a light orange yellow solid. The product was confirmed using Proton NMR Spectroscopy (45%). **^{1}H NMR** (400 MHz, CDCl3) δ **7.92-7.90** (d, 2H), **7.00-6.98** (d, 2H), **4.04** (s, 2H), **3.90** (s, 3H).

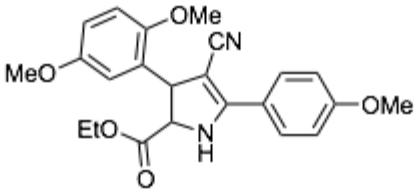


(*E*)-3-(2,5-dimethoxyphenyl)-2-(4-methoxybenzoyl)acrylonitrile ***[16]***

To a stirring solution of ***3-(4-methoxyphenyl)-3-oxopropanenitrile*** and 1 eq. of the benzaldehyde in EtOH was added 1 drop of piperidine. Mild heat was applied to the solution for 20 mins and removed to cool down to RT. Within 5 min solids had been formed. The reaction was allowed to stir until the solution was mostly solid. The yellow solid, ***(E)-3-(2,5-dimethoxyphenyl)-2 -(4-methoxybenzoyl)acrylonitrile*** was extracted, recrystallized in hot EtOH, and aired out until completely dry as a vibrant yellow solid. The product was confirmed using Proton NMR Spectroscopy (76%). **^{1}H NMR** (400 MHz, CDCl3) δ **8.50** (s, 1H), **7.95-7.92** (d, 2H), **7.12-6.90** (m, 3H), **7.09-6.99** (d, 2H)**, 3.91** (s, 3H), **3.86** (s, 3H), **3.85** (s, 3H).

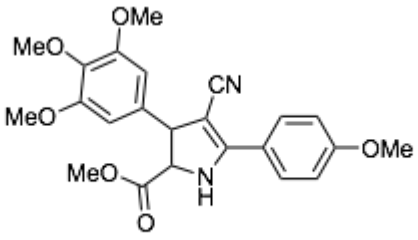


(*E*)-2-(4-methoxybenzoyl)-3-(3,4,5-trimethoxyphenyl)acrylonitrile



ethyl 4-cyano-3-(2,5-dimethoxyphenyl)-5-(4-methoxyphenyl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate

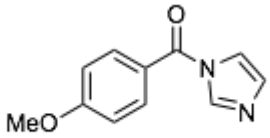
Synthesized using ***General Dihydropyrrole Procedure***. Product confirmed using Proton NMR Spectroscopy. 46% (**^{1}H NMR** (400 MHz, CDCl3) δ **7.79-7.77** (d, 2H), **6.99-6.95** (d, 2H), **6.88-6.77** (m, 3H), **4.96-4.95** (d, 2H)**, 4.74** (s, 1H), **4.26-4.25** (m, 3H), **3.85** (s, 3H), **3.81** (s, 3H), **3.75** (s, 3H), **1.35-1.31** (t, 3H).



methyl 4-cyano-5-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate

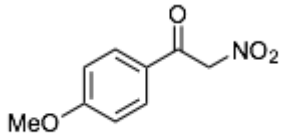
Synthesized using ***General Dihydropyrrole Procedure***. Product confirmed using Proton NMR Spectroscopy. (31%) **^{1}H NMR** (400 MHz, CDCl3) δ **7.83-7.79** (d, 2H), **7.00-6.97** (d, 2H), **6.57** (s, 2H), **4.87** (s, 1H)**, 4.53-4.52** (d, 2H), **4.35-4.33** (d, 2H), **3.86-3.82** (m, 16H).

4.1.4 alpha-nitro compounds



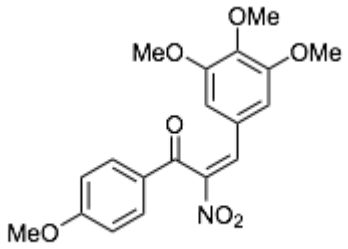
(1*H*-imidazol-1-yl)(4-methoxyphenyl)methanone ***[17]***

In an inert environment, 30.4 mmol of **4-methoxybenzoyl chloride** in 35 mL DCE (anhydrous) was added dropwise to a stirring solution of 1.25 molar eq. imidazole and 5 mL triethylamine in 35 mL DCM (anhydrous) solution held in a reaction vessel with a **gas trap**. The solution was stirred for 0.5 hrs at RT and the reaction was filtered. The organic partition was evaporated under reduced pressure to yield ***(1H-imidazol-1-yl)(4-methoxyphenyl)methanone***. (To store: purge with N_2 and store in fridge.) The product was confirmed using Proton NMR Spectroscopy.**^{1}H NMR** (400 MHz, CDCl3) δ **8.25** (s, 1H), **8.12-8.09** (d, 1H), **7.84-7.82** (d, 2H), **7.07-7.05** (d, 2H)**, 7.00-6.98** (d, 1H).



1-(4-methoxyphenyl)-2-nitroethan-1-one ***[17]***

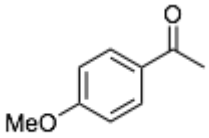
In an inert environment 17.6 mmol of NaH and 0.5 mL of NO_2Me was stirred in 20 mL DMSO (anhydrous) for 30 mins at 10 °C. Afterwards the crude **acyl imidazoles** were added dropwise over 30 mins. The reaction was allowed to warm to RT and stirred for 12h or overnight. Once complete the reaction was diluted with 150 mL EA and 150 mL of 1N HCl. This solution was extracted with EA (100 mL x3) and then washed with water (100mL x3). The organic partitions were combined and dried over $MgSO_4$ (anhydrous) and evaporated under reduced pressure. The crude wax was purified using Column Chromatography and ***1-(4-methoxyphenyl)-2-nitroethan-1-one*** eluted 4th as an orange crystalline solid. The product was confirmed using Proton NMR Spectroscopy (44%). **^{1}H NMR** (400 MHz, CDCl3) δ **7.87-7.85** (d, 2H), **7.01-6.99** (d, 2H), **5.85** (s, 2H), **3.91** (s, 3H).



(*E*)-1-(4-methoxyphenyl)-2-nitro-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one ***[16]***

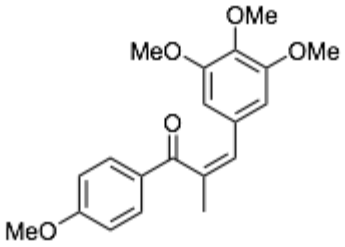
To a reaction vessel with a dean stark apparatus extension, 1.03 mmol of ***1-(4-methoxyphenyl) -2-nitroethan-1-one*** was reacted with 1.62 mmol of 2,5 dimethoxybenzaldehyde, 0.084 mmol of B-alanine and 2.8 mmol of glacial AcOH in 5 mL of benzene under reflux for 24 h. The reaction was washed (100 mL x3) with water and then extracted with EA (50 mL x3) to yield ***(E)-3-(2,5-dimethoxyphenyl)-1- (4-methoxyphenyl)- 2-nitroprop-2-en- 1-one*** as a dry reddish yellow wax. (41%) **^{1}H NMR** (400 MHz, CDCl3) δ **8.22** (s, 1H), **7.96-7.94** (d, 2H), **6.97-6.95** (d, 2H), **6.95** (s, 2H)**,** **3.88** (s, 3H), **3.85,** (s, 3H), **3.67** (s, 3H).

4.1.5 alpha-methyl compounds



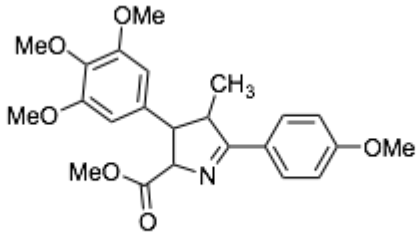
1-(4-methoxyphenyl)ethan-1-one ***[18]***

In an inert environment, 93.9 mmols of **propanoic acid** was reacted with 1 eq. of thionyl chloride in 1 eq. of anisole under reflux for 1 hr. Once the solution turned an intense dark red the reaction was brought down to RT and 0.5 eq (assume 100% yield of acid chloride) of ZnO was added in three parts to the vessel at -20 °C and allowed to stir overnight. The viscous red solution was diluted with 30 mL of DCM and was washed with concentrated $NaHCO_3$ (40 mL x3) and then washed with water (40 mL x2). The organic partition was evaporated under reduced pressure to receive a yellow liquid. The liquid was then purified using Column Chromatography receiving ***1-(4-methoxyphenyl)ethan-1-one as*** a yellow liquid. The product was confirmed using Proton NMR spectroscopy (28%).**^{1}H NMR** (400 MHz, CDCl3) δ **7.97-7.94** (d, 2H), **6.95-6.93** (d, 2H), **3.87** (s ,3H,), **2.97-2.95** (q, 2H), **1.23-1.92** (t, 3H).



(*Z*)-1-(4-methoxyphenyl)-2-methyl-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one ***[19]***

To a 3-neck vessel with a condenser was added 26 mmol of ***1-(4-methoxyphenyl)ethan-1-one*** dissolved in 15 mL EtOH. To the stirring solution was added 1 eq. of 3,4,5 trimethoxybenzaldehyde, 2 eq. Of piperidine and 1.7 eq of AcOH. The solution was stirred under reflux for 28 hrs. After the reaction was complete, the solution was washed with water x3 and the organic partition was dried with Na_2SO_4. Solvents were evaporated under reduced pressure to afford a bright yellow wax. The wax was purified via column chromatography to yield ***(Z)-1-(4-methoxyphenyl)-2-methyl-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one***. As a bright orange solid. The product was confirmed using Proton NMR Spectroscopy. (12%) **^{1}H NMR** (400 MHz, CDCl3) δ **7.81-7.79** (d, 2H), **7.05** (s, 1H), **6.98-6.95** (d, 2H), **6.65** (s, 2H), **3.90-3.87** (m, 12H), 2.30 (**s**, 3H).



methyl 5-(4-methoxyphenyl)-4-methyl-3-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylate

Synthesized using ***General Dihydropyrrole Procedure***. Product confirmed using Proton NMR Spectroscopy. (9%) **^{1}H NMR** (400 MHz, CDCl3) δ **7.83-7.79** (d, 2H), **6.96-6.93** (d, 2H), **6.41** (s, 2H), **4.93-4.91** (d, 1H)**, 3.88-3.77** (m, 15H), **3.48-3.47** (t, 1H), **3.34-3.31** (t, 1H), **1.39-1.36** (d, 3H).

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