GOLD CATALYZED SYNTHESIS OF PYRROLE AND INDOLE FUSED HETEROCYCLES VIA ALKYNE CYCLIZATION

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ABSTRACT

GOLD CATALYZED SYNTHESIS OF PYRROLE AND INDOLE FUSED HETEROCYCLES VIA ALKYNE CYCLIZATION

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New methodologies were developed for the synthesis of pyrrolo- and indolo-oxazin-1-one derivatives. In the first section of this thesis, various N-propargyl pyrrole and indole esters were efficiently converted into corresponding carboxylic acids which then underwent intramolecular cyclization reaction with AuCl₃ to give 6-exo-dig cyclization products. In the second part of the study, 6-exo-dig pyrrolo- and indolo-oxazinone derivatives were treated with TFA in order to achieve double bond isomerization. Some of the 6-exo-dig cyclic double bonds underwent isomerization to 6-endo-cyclic compounds upon treatment with TFA. The experimental results were supported by DFT calculations. Moreover, the cyclization reaction of 1-prop-2-ynyl-1H-pyrrole-2-carboxylic acid in the presence of alcohols catalyzed by Au(I) resulted in the formation of hemiacetals after cascade reactions.

Keywords: pyrrolo-oxazinone, indolo-oxazinone, gold catalyst, ring-closure reaction
ÖZ

PIROL VE İNDOL KONDENZE HETEROSİKLİK BİLEŞİKLERİN ALTIN KATALİZÖRLÜĞÜNDE SENTEZİ

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Anahtar Kelimeler: pirolo-okzazinon, indolo-okzazinon, altın katalizörü, halka kapatma reaksiyonu
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To my beloved husband ...
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LIST OF ABBREVIATIONS

TFA: Trifluoroacetic acid
THF: Tetrahydrofuran
DIPA: Diisopropylamine
TLC: Thin layer chromatography
NMR: Nuclear magnetic resonance
IR: Infrared
HRMS: High resolution mass spectroscopy
J: Coupling constant
Hz: Hertz
ppm: Parts per million
mg: miligram
mmol: milimol
CHAPTER 1

INTRODUCTION

1.1. Pyrrole

Five-membered heterocyclic molecule including sp$^2$ hybridized nitrogen atom is named as pyrrole (1). The aromaticity arises because the nitrogen atom contributes two electrons and each of the four sp$^2$ hybridized carbons contributes one π electrons to form a delocalized sextet of π electrons.$^1$

![Pyrrole](image)

The lone pair of electron on the N-atom in pyrrole participates in delocalization; thus, pyrrole is best characterized as a resonance hybrid, with contributing structures (1a-d) shown below (Scheme 1).$^1$

![Scheme 1](image)

Among numerous heterocycles, pyrrole is one of the most important heterocycles since it is found in a broad range of natural products and drugs. It is a fundamental structural subunit of heme (2) and chlorophyll (3) which are pigments esssential for life.$^2$
A lot of alkaloids that contain pyrrole moiety has been isolated from marine organism and display good biological activities. Lamellarin D (4) which was isolated from a marine mollusk, *Lamellaria*, has been shown to exhibit cytotoxicity values in the mid to-high nanomolar range (38–110 nM). Lamellarin D (4) is also a potent inhibitor of human topoisomerase I and Lamellarin H (5) is a potent inhibitor of both Molluscum contagiosum virus topoisomerase and HIV-1 integrase.

In addition, pyrrole derivatives are present in a large number of bioactive compounds including HIV fusion inhibitors and antitubercular compounds among many others. Tolmetin (6), which is in class of non-steroidal antiinflammatory medications (NSAID), can be given as example of pyrrole derived drugs. Moreover, pyrrole moiety is also of growing relevance in materials science. Derivatives of 4,4-difluoro-4-boradipyrrin system known as BODIPY (7) have a strong absorption in UV and show very intense
fluorescence. Many applications are available as chemosensors, for laser manufacture, image diagnosis, etc.\textsuperscript{6}

1.2. Indole

Indole (8) is a bicyclic heterocyclic compound containing pyrrole ring (1) with benzene ring (9) fused to \(\alpha,\beta\)-position. It is a heterocyclic system with 10 electrons arising from four double bonds and the lone pair on the nitrogen atom.\textsuperscript{7}

\begin{center}
\begin{tabular}{c c c}
\textbf{indole} & \textbf{benzene} & \textbf{pyrrole} \\
\begin{tikzpicture}[scale=0.5]
\draw[thick] (0,0) circle (1cm);
\fill (0,0) circle (0.1cm);
\node at (0,-0.5) {H};
\end{tikzpicture} & \begin{tikzpicture}[scale=0.5]
\draw[thick] (0,0) circle (1cm);
\fill (0,0) circle (0.1cm);
\node at (0,-0.5) {H};
\end{tikzpicture} & \begin{tikzpicture}[scale=0.5]
\draw[thick] (0,0) circle (1cm);
\fill (0,0) circle (0.1cm);
\node at (0,-0.5) {H};
\end{tikzpicture}
\end{tabular}
\end{center}

Indole is an important heterocycle due to natural occurrence and pharmacological activities. The simple indole derivatives are present in the form of amino acid tryptophan (10), as well as tryptamine (11) and serotonin (12). There are more complex derivatives which usually contain an additional fused ring, such as in carbazole (13) and \(\beta\)-carboline (14).\textsuperscript{8}

\begin{center}
\begin{tabular}{c c c}
\textbf{10} & \textbf{11} & \textbf{12} \\
\begin{tikzpicture}[scale=0.5]
\draw[thick] (0,0) circle (1cm);
\fill (0,0) circle (0.1cm);
\node at (0,-0.5) {H};
\end{tikzpicture} & \begin{tikzpicture}[scale=0.5]
\draw[thick] (0,0) circle (1cm);
\fill (0,0) circle (0.1cm);
\node at (0,-0.5) {H};
\end{tikzpicture} & \begin{tikzpicture}[scale=0.5]
\draw[thick] (0,0) circle (1cm);
\fill (0,0) circle (0.1cm);
\node at (0,-0.5) {H};
\end{tikzpicture}
\end{tabular}
\end{center}

Indole derivatives draw a lot of attention from scientists due to possessing a wide variety of biological activities such as anti-inflammatory, analgesic, antifungal, anticancer and antimicrobial. For example, indomethacin (15), which is non-steroidal anti-inflammatory drugs (NSAIDs), exerts anti-inflammatory and analgesic properties.\textsuperscript{9} Etodolac (16) which is used for treatment of arthritis and indolmycin (17), an antibiotic, are the drugs in sale whose structures contain indole nucleus.\textsuperscript{7,10}
1.3. Oxazinone Derivatives

1.3.1. Importance of oxazinone derivatives

Oxazinones are heterocyclic ketones derived from benzene and its reduction products by substitution of carbon atoms by one nitrogen and one oxygen.\textsuperscript{11} There are several isomeric oxazinones 18-20 shown below whose existence are dependent on the relative position of heteroatom and the double bonds. The position of atoms are indicated by numbers namely, 1,2-, 1,3- and 1,4-oxazinones (18,19,20).\textsuperscript{12}

Oxazinone heterocycles have attracted special attention because they constitute an important class of natural and non-natural products.\textsuperscript{11} Many oxazinone derivatives exhibit wide range of pharmacological properties, such as antitumor, antiviral, antithrombotic, antiinflammatory, antidiabetic and hypolipidaemic effects.\textsuperscript{13} For
example, Scheuer and coworkers\textsuperscript{14} isolated pyrrolo-oxazinone derivatives which are Lukianol A (21) and Lukianol B (22) from a Pacific tunicate. Lukianol A exhibits cytotoxic activity against a human epidermoid carcinoma cell line while Lukianol B exhibits no activity.\textsuperscript{15}

Maytansinoid based heterocycles which contain 1,3-oxazin-2-one skeleton exhibit a broad diversity of biological activity.\textsuperscript{16} Maytansine (23), the first ansa macrolide, is the first member of maytansinoid class reported to show significant in vivo tumor inhibitory activity.\textsuperscript{17}

Moreover, oxazine dyes are useful as environmental sensors partly because they can give information on local viscosity, pH value, solute concentration, and electrical potential.\textsuperscript{18} Commercial compound ATTO-655 (24) is the example for oxazine dyes which are among the best for single-molecule detection application and high resolution microscopy.\textsuperscript{19}
1.3.2. Synthesis of pyrolooxazinone and indoloazinone derivatives

In medicinal and modern synthetic chemistry, the production of appropriate nitrogen- and oxygen-containing target molecules is always a challenge. In particular, oxazinones are in continuous demand because of their known biological properties and pharmaceutical applications.\(^{20}\)

Abbiati and coworkers\(^{21}\) developed a synthetic approach for the synthesis of oxazinoindole derivatives. The cyclization of \(N\)-alkynyl-2-indolcarbaldehyde \(25\) in the presence of Na and ethyl alcohol resulted in oxazinoindole derivative \(26\) in moderate yield. According to proposed mechanism suggested by the group, the addition of alkoxide, generated in situ from alcohol by sodium, is the first probable step resulting in the formation of hemiacetal anion. The hemiacetal anion undergoes a 6-\textit{exo-dig} cyclization on the triple bond, after the izomerization, the corresponding final product \(26\) is obtained (Scheme 2).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{25}};
\node (b) at (1.5,0) {EtOH};
\node (c) at (3,0) {Na};
\node (d) at (4.5,0) {80 °C};
\node (e) at (6,0) {sealed tube, \(N_2\)};
\node (f) at (7.5,0) {48%};
\node (g) at (0,-1) {CHO};
\node (h) at (1.5,-1) {\textcolor{black}{\textbullet}};
\node (i) at (2.5,-1) {\textcolor{black}{\textbullet}};
\node (j) at (3.5,-1) {Ph};
\node (k) at (4,-1) {OEt};
\node (l) at (5,-1) {\textcolor{black}{\textbullet}};
\node (m) at (6,-1) {\textcolor{black}{\textbullet}};
\node (n) at (6.5,-1) {\textcolor{black}{\textbullet}};
\node (o) at (7.5,-1) {Ph};
\node (p) at (9,0) {\textbf{26}};
\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);
\draw[->] (d) -- (e);
\draw[->] (e) -- (f);
\end{tikzpicture}
\end{center}

\textbf{Scheme 2}

Another synthetic approach for oxazinone derivatives was reported by Fang and coworkers.\(^{22}\) 2,2,2-Trichloro-1-(1H-pyrrol-2-yl)ethanone (27) was treated with 2-chloroethanol in the presence of \(Na_2CO_3\) in DMF to afford 28 in 71% yield. The cyclization was performed in the presence of NaH in DMF to yield oxazinopyrrole derivative 29 in 80% yield (Scheme 3).
A practical and efficient synthetic approach to obtain pyrrole and indole oxazinone derivatives was enhanced by Vaillard and coworkers. These synthetic approach consisted of intramolecular Cu-catalyzed Ullmann-type reaction conditions. Pyrrole carboxlate 30 was reacted with 10 mol % of CuI in the presence of 20 mol % of L-proline and K$_2$CO$_3$ in DMF at reflux temperature to obtain pyrrolo-oxazinone derivative 31 in 72% yield. The same reaction was performed with indole carboxylate 32 in the presence of NaH instead of K$_2$CO$_3$ (Scheme 4) to obtain indolo-oxazinone 33. The use of the conventional heating and MW irradiation was also compared for these reactions. It was established that MW-assisted organic synthesis is a useful tool to achieve these reactions, rapidly and in good yields.
1.4. Alkyne cyclization reactions

1.4.1. Gold: A widely used metal

Gold has been employed for numerous applications in a variety of fields for ages by mankind. It has been used as currency and in jewellery manufacturing and decoration due to its well known malleability and resistance to tarnish. Gold has been considered of low interest in organic chemistry for a long period of time due to the reason of many misconceptions. For example, gold is undoubtedly an uncommon element, but it is more abundant than platinum, palladium, rhodium and other valuable metals that are used even in large scale processes. Besides, gold is certainly inert, but is far from being chemically useless.\(^{23}\)

Gold catalysts are generally regarded as safe and simple for treatment. The gold catalyzed reactions are normally easy to accomplish and these reactions can be performed under very mild reaction conditions with moderately short reaction times. Gold catalysts often show excellent chemoselectivity towards unsaturated C-C π systems, leaving other functional groups untouched.\(^{24}\)

Au(I) and Au(III) are the most existant states of gold catalyst. Gold catalysts, like palladium catalysts, do not undergo conventional redox catalytic cycles of oxidative addition and reductive elimination. However, gold catalysts have a tendency to stay in one oxidation state throughout the reaction. Simple halide salts such as AuCl\(_3\) was the first gold catalyst. The catalyst activity can be enhanced with phosphine or N-heterocyclic carbene ligands by creating cationic gold-species. The cationic gold-complex can be created in situ with a silver co-catalyst.\(^{25}\)
1.4.2. Gold catalyzed alkyne cyclization reactions

The most important property of gold catalysts used in organic chemistry is their π electrophilicity. Gold catalysts have even been named as π acids\(^{21}\) due to their affinity to bind to C-C multiple bonds.

C-C multiple bonds of alkynes, allenes, or alkenes coordinate to gold complexes; this efficiently activates them for the attack of a nucleophile. The simplest example of a nucleophilic addition to a C-C multiple bond is shown in an organic substrate 34. First, the gold catalyst interacts with the π-system of the substrate to form the intermediate 35, and then, the nucleophile attacks. Then, the organogold intermediate 36 liberates the addition product 37 and the gold catalyst by protodemetallation.\(^{23}\)

![Scheme 5](image)

The nucleophile in the reaction can be delivered in an intramolecular or intermolecular manner. In these parts, intramolecular cyclization reactions of different compounds will be discussed.

Many methods were recently developed in this area using heteroatom nucleophiles, mainly oxygen or nitrogen. Genin and coworkers\(^{26}\) found that functionalized acetylenic acids 38 can be cyclized under extremely mild conditions, at room temperature in the presence of AuCl catalyst to generate lactones 39. The ring closure
reactions proceeded efficiently under a 5-*exo-dig* fashion, and no reaction was observed on the alkenyl moieties (Scheme 6).

![Scheme 6]

Another remarkable transformation in a one pot cascade manner was developed to synthesize highly functionalized pyrrolo[1,2-α]quinolin-1(2H)-ones by gold catalyst (Scheme 7). Zhou and coworkers\(^{27}\) suggested that the reaction of 40 with AuBr\(_3\)/AgSbF\(_6\)-catalyst system yielded 41 via intramolecular hydroamination and it was followed by a gold-catalyzed hydroarylation of 41 in the presence of 42 to give product 43 in good yield. It was necessary to use a combination of Au/Ag salts to obtain high yields, and the yield was dramatically reduced when lower temperatures were employed.

![Scheme 7]
A mild and efficient tandem cycloisomerization-hydroalkoxylation of homopropargylic alcohols 44 to tetrahydrofuranyl ethers 45 was developed by Belting and Krause. The reaction was performed in the presence of an alcohol and a dual catalyst system, consisting of a gold precatalyst and a Brønsted acid (Scheme 8). Moreover, the reaction was carried out in various solvents, including alcohol, with both terminal and internal alkynes as the substrate.

![Scheme 8](image)

Hashmi et al. studied on the formation of oxazoles via N-propargylcarboxamide cyclization 46 and used only 5 mol % of AuCl$_3$ in either MeCN or CH$_2$Cl$_2$. The methylene dihydrooxazole intermediate 47 was also trapped at lower temperatures. Isolated yields from room temperature examples were typically very good (>95%).

![Scheme 9](image)
1.5. Aim of the study

This study focused on a new gold catalyzed synthesis of oxazinone derivatives from alkynyl esters. Our aim was first to develop a new synthetic methodology for the synthesis of pyrrolo-oxazinone and indolo-oxazinone derivatives 51 starting from N-substituted propargyl esters 50 (Scheme 10).

![Scheme 10]

The object of the second part was to study the resultant product from metal-catalyzed cyclization of pyrrole carboxylic acid 52 in the presence of alcohols. Different alcohols were used to observe the product 53 (Scheme 11). In order to shed light on the mechanism of these reactions, separate reactions were performed.

![Scheme 11]
CHAPTER 2

RESULTS AND DISCUSSION

2.1. Synthesis of pyrrolo-oxazin-1-ones

2.1.1. Synthesis of 3-methylene-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one

Pyrrole ring is an electron rich heterocyclic aromatic compound. Since the positive charge is stabilized by resonance, electrophiles attack pyrrole at C-2 carbon atom. In the way of our aim for this part, acylation reaction of pyrrole (1) was carried out with trichloroacetyl chloride (54) to give 2,2,2-trichloro-(1H-pyrrol-2-yl)ethanone (55) and after that NaOMe was used to obtain starting pyrrolo-ester (Scheme 12).

Scheme 12

Pyrrole ring has slightly acidic character due to participation of nonbonding electrons on nitrogen atom to the conjugation; thus, after abstraction of proton attached to nitrogen, a substitution reaction on nitrogen atom can take place. An SN2 reaction took place in the presence of NaH and propargyl bromide to afford propargyl ester (57) (Scheme 13). The cyclization reaction of propargyl ester (57) was achieved with AuCl3 catalyst at room temperature. The resulted product was only isolated H2O addition product to alkyne units (58) in low yield. In the literature, it has been proposed that gold could catalyze the addition of water to terminal alkynes in neutral media. The expected cyclization product was not formed.
After failure of the cyclization reaction of 57 with AuCl$_3$, we turned our interest to the synthesis of the corresponding carboxylic acid. First of all, propargyl ester 57 was hydrolyzed with 2 N KOH in methanol at reflux temperature. Although, esterification reaction was successfully achieved, propargyl group was isomerized to allene at these reaction conditions. The mixture of allene carboxylic acid 60 and propargyl carboxylic acid 59 was obtained in 60% and 40% yield after 5 h (Scheme 14). The attempt to isolate 59 with column chromatography was failed.

In order to synthesize acid 59 only, we decided to apply different method. Therefore, Cs$_2$CO$_3$ was used as base for this reaction. However, a mixture of allene ester 61, carboxylic acid 60 and propargyl carboxylic acid 59 was obtained in 43%, 33% and 24% yield respectively (Scheme 15).

Therefore, the method for hydrolysis was changed and the propargyl ester 57 was hydrolyzed with K$_2$CO$_3$ in the presence of MeOH/H$_2$O to obtain carboxylic acid 59. Under this reaction conditions, carboxylic acid 59 was obtained at 80 °C in 91% yield.
The cyclization reaction of carboxylic acid 59 was decided to perform with AuCl$_3$ catalyst at room temperature. AuCl$_3$ catalyst is very preferable catalyst among other transition metal catalysts due to its resistance to air and moisture. As maintained by the result, 3-methylene-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (62) was exclusively formed in an excellent yield of 96% (Scheme 16).

![Scheme 16](image)

It was required to examine whether different metal catalysts would yield exo/endo selectivity in the alkyne activation. The pyrrole carboxylic acid 59 was reacted with various metal catalysts in chloroform at different temperatures and for different reaction times. Any selectivity was observed with metal catalysts used; the same product was formed with yields shown in Table 1. Four different catalysts were tried besides AuCl$_3$ catalyst (Table 1). N-heterocyclic carbene (NHC) complex of Au(I) provided any reaction in chloroform. Moreover, very poor yields of exo-dig cyclization product 62 was obtained by reactions with InCl$_3$ and PtCl$_2$(PPh$_3$)$_3$ as catalysts. AgOTf were also investigated and after that AuCl$_3$ was identified as the optimal choice due to the shorter reaction time, high yield, and easy isolation of the oxazinone 62.

![Scheme 17](image)
Table 1: Optimization of cyclization reaction of 59

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 AuCl₃</td>
<td>2</td>
<td>rt</td>
<td>96</td>
</tr>
<tr>
<td>2 AgOTf</td>
<td>20</td>
<td>rt</td>
<td>95</td>
</tr>
<tr>
<td>3 InCl₃</td>
<td>24</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>4 PtCl₂(PPh)₃</td>
<td>26</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>5 Au(I)</td>
<td>24</td>
<td>rt</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

The ¹H-NMR, ¹³C-NMR spectra including 2D NMR spectra (COSY, HSQC, HMBC, DEPT) were used to characterize the formed product. The disappearance of protons of propargyl group revealed the formation of the new product. Inspection of the ¹H NMR spectrum of compound 62 revealed that one of the CH₂ protons resonates at 4.7 ppm as doublet of triplets with 2.2 Hz geminal coupling and 1.1 Hz long range coupling. The other proton appears at 5.0 ppm as a broad doublet with a geminal coupling constant of 2.2 Hz (Figure 1). The DEPT-135 spectrum showed the presence of two CH₂ carbon resonances at 98.4 ppm and 45.5 ppm (Figure 2). Moreover, the HSQC spectrum confirmed the formation of proposed structure 62 (Figure 3). The correlation between CH protons with C-7 carbon atom and CH₂ proton signal with C-8 carbon atom were shown in Figure 3.
Figure 1: $^1$H-NMR Spectrum of compound 62

Figure 2: DEPT-135 Spectrum of compound 62
On the basis of these backgrounds, a proposed mechanism for the AuCl₃ catalyzed intramolecular cyclization is shown in Scheme 18. The π-activation of triple bond of carboxylic acid by AuCl₃ enhances the electrophilicity of the alkyne unit and makes it prone to intramolecular nucleophilic attack by oxygen via the 6-exo-dig cyclization to give zwitterionic intermediate 64. The following proton transfer and regeneration of catalyst yields the product 62.

In case of internal alkynes, two isomeric E- and Z-oxazinones during the cyclization reaction can be formed. However, we observed exclusive formation of a single isomer. The anti intramolecular addition of the carboxylic acid to the gold-alkyne intermediate 63, forms an intermediate 64 where the substituent is in the endo-position. Removal of gold results in the formation of Z-isomer. Therefore, we assign the endo-configuration to the formed oxazinones.
2.1.2. Synthesis of (3Z)-3-ethylidene-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one

Having established efficient steps and conditions for the synthesis of oxazinone 62, we wanted to evaluate the substrate scope. Therefore, propargyl ester 67 was synthesized in 96% yield from the reaction of methyl 1H-pyrrole-2-carboxylate (56) with 1-bromobut-2-yn (66) in the presence of NaH as a base. The following step was the synthesis of the corresponding carboxylic acid 68 by applying the same conditions which was used for propargyl ester 57. The yield of 68 was very high (95%) so that the compound could be used for the cyclization reaction without additional purification (Scheme 19).
After that, it was desired to investigate cyclization reaction of carboxylic acid 68 with AuCl₃ at room temperature. However, two cyclization products were observed by ¹H NMR spectrum after 2 h. Cyclization product 69 with an oxazinone structure was formed as the major product in 85% isolated yield, but 7-endo cyclization product 70 was proposed as the minor product. Since the isolation of 70 failed after chromatographic purification, the structure was deduced by ¹H NMR spectrum of the mixture which is shown in Figure 4. The olefinic proton of 70 resonates at 5.5 ppm as triplet of quartets with coupling constants of 6.7 Hz and 0.8 Hz. The methylene protons resonate at 4.5 ppm as doublet (6.7 Hz).
2.1.3. Synthesis of 6,7-dibromo-3-methylene-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one

To synthesize further oxazinone derivatives, ester 71 was synthesized from reaction of 56 with bromine in AcOH according to literature. Pyrrole generally reacts with electrophiles at C-2 carbon in preference to C-3 carbon since the positive charge in the intermediate for C-2 substitution is delocalized more extensively on the pyrrole ring. Therefore, the active carbons of pyrrole for electrophilic addition are C-5 and C-4 carbons for compound 56. Since C-2 position was occupied with an ester group, bromination took place at these carbons. The 1H NMR spectrum clearly showed the disappearance of two protons resonating at aromatic region which supports the formation of brominated compound 71 (Scheme 21).

![Figure 4: 1H NMR spectrum of compound 69 and 70](image-url)

**Scheme 21**

\[
\text{56} + \text{Br}_2 \xrightarrow{\text{AcOH}} \text{71}
\]
After synthesis of the brominated ester 71, substitution of propargyl group was carried out in presence of NaH to obtain 72 in 96% yield. Then, the hydrolysis of 72 with K$_2$CO$_3$ was achieved to give carboxylic acid 73 in good yield.

![Scheme 22](image)

Carboxylic acid 73 did not dissolve in CHCl$_3$ for cyclization reaction, therefore, the reaction of carboxylic acid 73 with AuCl$_3$ was performed in MeOH at room temperature. The pyrrolo-oxazinone 74 was synthesized in 95% yield.

![Scheme 23](image)

2.1.4. Synthesis of methyl 6,8-dimethyl-3-methylene-1-oxo-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate

The condensation of α-amino ketones with carbonyl compounds containing active α-methylene groups is generally known as the Knorr pyrrole synthesis. It involves the condensation of a β-keto ester 75 with an α-amino ketone 76 (Scheme 24).
The amino ketone 76 is commonly prepared in situ by nitrosation and reduction of a second molecule of the β-keto ester with Zn dust in AcOH (Scheme 24). The reaction mechanism of the synthesis of pyrrole derivative is shown in Figure 25.
After successful synthesis of substituted ester 77, the same methodology was applied to synthesize further oxazinone derivatives. The substitution of propargyl group with NaH took place in 94% yield and hydrolysis of N-alkynyl ester 78 was selectively occurred on the ester group attached to C-2 carbon. Because of reactivity difference of the carbonyl groups, the semi ester formation was observed for this reaction. Carbonyl group which is bonded to C-2 carbon of pyrrole is more electropositive due to less delocalization of lone pairs of nitrogen on the carbonyl group attached to C-2 carbon atom than carbonyl group attached to C-3 carbon atom. Therefore, carboxylic acid formation 79 occurs from the carbonyl group attached to C-2 carbon atom.

Scheme 26

When hydrolysis step was achieved, cyclization reaction with AuCl₃ was performed and two cyclization products were detected from ¹H NMR spectrum. The major product was 6-exo-dig cyclization product 80, the minor product 81 was the isomerization product of 80. The yields were calculated from the crude ¹H NMR spectrum due to failure of the isolation of these cyclization products from column chromatography (Scheme 27). Therefore, the mixture was treated with TFA at room temperature to obtain 81. These part will be explained in detail in section 2.3.
2.1.5. Synthesis of starting materials with Sonogashira coupling reaction to synthesize oxazinone derivatives

To test the scope of this cyclization reaction we decided to synthesize further ester derivatives having aromatic groups attached to the terminal carbon atom of acetylene unit. Therefore, Sonogashira coupling reactions were performed.

Sonogashira coupling is an appropriate method for constructing new C-C bonds. There are some variations of Sonogashira cross-coupling reactions reported in the literature, but copper-cocatalyzed Sonogashira cross-coupling reaction was going to be underlined here. Using Pd catalyst and CuI cocatalyst in the presence of a base is one modification of Sonogashira coupling reactions, in which terminal alkynes and aryl halides undergo cross-coupling reaction.35

Reagents were selected to afford a representative example both in terms of reactivity and convenience. Although aromatic iodides react more readily under the applied conditions, aryl bromides are available in extreme numbers and their use is more economical. Therefore, we applied Sonogashira coupling to methyl 1-prop-2-ynyl-1H-pyrrole-2-carboxylate (57) to generate 82b by using bromotoluene. However, the yield of this reaction under selected conditions was very low, 12% (Scheme 28).

![Scheme 28](image)

In order to increase the yield, we decided to apply the same reaction conditions with aryl iodides. Thus, iodobenzene and iodotoluene were used to obtain coupling products 82a and 82b. The yields of these reactions were moderately high which is shown in Scheme 29.
The $^1$H and $^{13}$C NMR spectra supported the formation of compound 82a and 82b. Especially, the disappearance of one proton resonance at around 2.5 ppm clearly indicated incorporation of alkyne functionalities into the molecule.

Scheme 29

The hydrolysis of ester derivatives 82a and 82b was performed with K$_2$CO$_3$, however, the synthesis of carboxylic acids failed due to less basicity of K$_2$CO$_3$ for these molecules. Therefore, KOH in methanol was used as a base instead of K$_2$CO$_3$ to synthesize corresponding carboxylic acids 83a and 83b (Scheme 30).

Scheme 30

The scope of having these coupling products was to investigate the effect of aromatic systems on cyclization reaction. As a result of conjugation of C-C triple bond with benzene, the yields of cyclization reaction with AuCl$_3$ at room temperature were very low after 24 h. Thus, heat was applied in order to increase the yields. Carboxylic acids 83a and 83b were reacted with 3 mol % AuCl$_3$ at 50 °C for 24 h to yield 84a and 84b in 73% and 67% yields, respectively (Scheme 30).
2.2. Synthesis of indolo-oxazinone derivatives

2.2.1. Synthesis of 3-methylene-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one and (3Z)-3-ethylidene-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one

Treatment of carboxylic acids with an alcohol in the presence of a strong acid as catalyst results in the formation of esters, along with the elimination of water. This reaction is known as Fischer esterification. The overall reaction is reversible and in order to effort the completion of the reaction, it is necessary to use Le Châteliers principle, which can be done either by continuously removing the water formed from the system or by using a large excess of the alcohol. Driving the reaction forward is usually accomplished by using the alcohol as solvent.

So as to obtain starting ester derivative of indole 85, Fischer esterification was performed in EtOH as solvent with catalytic amount of H$_2$SO$_4$ (Scheme 31).

![Scheme 31](image)

Same steps were followed to synthesize N-substituted ester derivatives of indole. Substitution of alkynyl groups was achieved in the presence of NaH with propargyl bromide and 1-bromobut-2-yne to obtain 87a and 87b. The hydrolysis of ester derivatives 87a and 87b yielded corresponding carboxylic acids 88a and 88b in high yields. The cyclization reactions with AuCl$_3$ at room temperature were performed in either MeOH or CHCl$_3$ and associated indolo-oxazinone derivatives 89a and 89b were synthesized in 99% and 97% yield respectively (Scheme 32).
2.2.2. Synthesis of 3-methylene-1-oxo-3,4-dihydro-1H-[1,4]oxazino[4,3-
aj]indole-10-carbaldehyde

Introduction of formyl group from the amide nitrogen to a substrate carbon atom has proved useful in organic synthesis since its discovery by Vilsmeier and Haack in 1927. The Vilsmeier-Haack reaction is used to convert an electron rich aromatic ring to an aryl aldehyde using DMF, an acid chloride, and aqueous work-up.

Vilsmeier-Haack reaction was applied for the formylation of indole derivative 86 to give ethyl 3-formyl-1H-indole-2-carboxylate (90) in moderate yield (Scheme 33). Electrophiles attack indole at C-3, rather than at C-2. For a reaction at C-3, the energy of activation of the intermediate is lowered because it is possible to delocalize the positive charge through resonance involving the nitrogen lone pair of electrons. This favourable situation is not possible in the corresponding intermediate for attack at C-2. Any attempt to delocalize the positive charge would now disrupt the 6 π electron system of the benzene ring.
After the synthesis of starting formylated ester derivative 90, the propargyl group was substituted with NaH in DMF to yield 91 in 72% yield. Hydrolysis with K$_2$CO$_3$ in MeOH/H$_2$O to obtain 92 was achieved in 97% yield. Using 3 mol % AuCl$_3$, oxazinone derivative 93 was synthesized at room temperature in 92% yield (Scheme 34).
2.3. TFA catalyzed isomerization reactions of oxazinone derivatives

Acids are important catalysts for double bond isomerization of olefinic hydrocarbons and therefore the reactions involving these catalysts received the predominant attention in literature. The catalytic isomerization reactions were studied by using either Brönsted acid and Lewis acids and various examples have been published by many groups.

Since it’s discovery in 1922, trifluoroacetic acid has proved to be a significant chemical with very distinctive properties. Because of its interesting properties, such as low toxicity, solubility in organic solvents, and strength, trifluoroacetic acid (TFA) is considered to be a special reagent for promotion of numerous organic reactions.

In this topic, trifluoroacetic acid was used to synthesize isomerization products from oxazinone derivatives which were synthesized from the reaction of carboxylic acids with AuCl₃.

Firstly, oxazino derivative 62 was reacted with excess TFA at room temperature in CHCl₃, and cyclic product 94 was isolated in 89% yield. The ¹H NMR spectrum of compound 94 shown in Figure 5 was in agreement with the proposed structure. The appearance of CH₃ protons at 2.1 ppm and the resonance of one sp² hybridized CH proton at 6.7 ppm supported the formation of the endo-cyclic oxazinone derivative 94.

![Scheme 35](image-link)
The investigation of isomerization of exo-cyclic products was performed for the other pyrrolo- and indolo-oxazinone derivatives. The products, crude yields and isolated yields were shown in Table 2. As it can be seen from the Table 2, while some of the oxazinone derivatives underwent isomerization reaction with TFA, some of them did not. Phenyl substituted oxazinone derivatives 84a and 84b were fully recovered after treatment with TFA (Scheme 36).

Scheme 36
In order to investigate the reason for these results, theoretical calculations were performed with Gaussian 09. Products were optimized in the gas phase with DFT, B3LYP at 6-31G** level in Gaussian 09. The calculations showed that 94 is about 10.6 kcal/mol more stable than 62. However, in the case of 84a and 95, it was also found that the endo-cyclic isomers 95 thermodynamically about 4.8 kcal/mol is more stable than the exo-cyclic isomer 84a (Figure 6).

Scheme 37

In spite of the thermodynamically stability of 84a, the isomerization reaction of 84a in the presence of TFA did not yield the endo-cyclic product 95. The reason of obstruction can be explained with the stability of carbocations generated after protonation of the double bond. Since benzylic carbocation is more stable than tertiary carbocation, the rearrangement would not occur (Scheme 37).
Table 2. Crude and isolated yields of reaction of oxazinones with TFA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization products</th>
<th>Isomerization products</th>
<th>Crude Yield (%)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="95.png" alt="Image" /></td>
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<td>-</td>
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<tr>
<td>2</td>
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<td><img src="96.png" alt="Image" /></td>
<td>-</td>
<td>-</td>
</tr>
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<td><img src="99.png" alt="Image" /></td>
<td>84</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td><img src="89b.png" alt="Image" /></td>
<td><img src="100.png" alt="Image" /></td>
<td>37</td>
<td>21</td>
</tr>
</tbody>
</table>
2.4. Reaction of 1-prop-2-ynyl-1H-pyrrole-2-carboxylic acid with gold(I) in the presence of alcohol

Gold-catalyzed reactions allow simple starting materials to be turned into complex products under mild conditions. Moreover, cationic gold acts as a soft and carbophilic Lewis acid and is regarded one of the most strong activators of C-C multiple bonds. Consequently, gold-catalysis plays an important role in the development of new methodologies to form CO, C-N and C-C bonds in more convenient ways.\(^1\)

In this topic, it was decided to react \(N\)-propargyl carboxylic acid 59 with gold(I) catalyst instead of gold(III) catalyst. When gold(I) catalyst which has \(N\)-heterocyclic carbene moiety was only used, it was observed that gold catalyst was unreactive as shown at Table 1. In literature, it has been shown that many gold(I) catalyzed cyclization reactions have been performed in the presence of a silver cocatalyst such as AgOTf, AgClO\(_4\).\(^2\)

Therefore, the cyclization reaction of 59 was carried out with Au(I) and AgOTf as cocatalyst in CHCl\(_3\) at room temperature. NMR spectral analysis of the reaction mixture showed that the product 101 was unexpectedly formed as the major product in 51% yield along with the cyclization product 62 in 10% yield. The formation of the product 101 can be explained by the incorporation of ethanol (<1%) which is used as stabilizer in CHCl\(_3\). Moreover, the product 102 which is the hydrolysis product of 101 was observed in \(^1\)H-NMR spectrum of the mixture in 39% yield. In order to isolate 101, column chromatography was used, however, the hydrolysis product 102 was quantitatively isolated instead of 101 (Scheme 38).

![Scheme 38](image-url)
When the reaction of 59 was performed with Au(I)/AgOTf catalyst system in ethanol free CHCl₃, due to the lack of nucleophile only cyclization products 94 and 62 were formed in 83% and 17% yields, respectively (Scheme 39).

\[
\begin{align*}
\text{59} & \quad \xrightarrow{3 \text{ mol % Au(I)}} \quad \text{5 mol % AgOTf} \\
& \quad \xrightarrow{\text{dry CHCl}_3} \quad 62 \ (17\%) \quad + \quad 94 \ (83\%)
\end{align*}
\]

**Scheme 39**

Two different reactions were performed in order to reveal the mechanism for the formation of the products. Firstly, deuterium labeling experiment was carried out to unveil the reaction mechanism. The reaction of 59 was carried out in deuterated methanol (CD₃OD) under the same reaction conditions. When the ¹H NMR spectrum of the reaction mixture was examined, the formation of 103 and 104 were observed in 65% and 35% yields, respectively. However, 103a and hydrolysis product 104a were observed besides the deuterated products 103b and 104b due to the water present in methanol-d₄. The amount of deuterium atom in 103 and 104 attached to the methylene group as –CH₂D was calculated as about 64% (Scheme 40).

\[
\begin{align*}
\text{59} & \quad \xrightarrow{3 \text{ mol % Au(I)}} \quad \text{5 mol % AgOTf} \\
& \quad \xrightarrow{\text{CD₃OD (2 equiv)}} \quad 103 \ (65\%) \quad + \quad 104 \ (35\%)
\end{align*}
\]

**Scheme 40**

In order to verify the involvement of 62 to the reaction as the intermediate, the product 62 was reacted with 3 mol % Au(I) and 5 mol % AgOTf in the presence of EtOH under the same reaction conditions. As a result of this reaction, the products 101 and 102 were formed in yields of 39% and 61%, respectively (Scheme 41).
The following gold-catalyzed cascade reaction mechanism was proposed based on all this information obtained. The proposed mechanism is shown in Scheme 42. The $\pi$ coordination of alkynyl group to $N$-heterocyclic carbene cationic gold complex produces the alkyne $\pi$-complex 105. A 6-\textit{exo-dig} cyclization by nucleophilic attack of the carboxyl oxygen forms the vinylgold oxazinium ion which undergoes proton transfer to release the oxazinone product 62 and regenerates the gold cation catalyst. In the following step, the double bond is activated by $\pi$-coordination of the gold catalyst. Addition of oxygen of alcohol to the double bond by the support of gold cation yields hemiacetal 101 and regenerates the gold cation.

Scheme 42
To investigate the incorporation of alcohol for this reaction, PrOH, $i$-PrOH, and $t$-BuOH were reacted with 59 in the presence of Au(I)/AgOTf catalyst system at room temperature. As the crude $^1$H NMR spectrum of these reactions were examined, three products hemiacetals 106, oxazinone 62 and hydrolysis product 102 were observed (Scheme 43).

The yields of the reactions which were calculated from crude NMR spectrum are shown in Table 3. As can be seen from Table 3, when the bulkiness of the alcohol increased, the yield of the hemiacetal decreased and the formation of the hydrolysis product 102 increased. Moreover, the yield of oxazinone 62 increased. These results showed that the rate of the addition of alkoxy group decreased and the stability of hemiacetal also decreased due to the bulkiness of the alcohol.

**Table 3.** Crude yields of the reaction of 59 with Au(I)/AgOTf in the presence of alcohols

<table>
<thead>
<tr>
<th>R</th>
<th>Crude Yield of 106 (%)</th>
<th>Yield of 62 (%)</th>
<th>Yield of 102 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CH$_2$CH$_2$CH$_3$</td>
<td>64</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>-CH(CH$_3$)$_2$</td>
<td>28</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>-C(CH$_3$)$_3$</td>
<td>trace</td>
<td>40</td>
<td>60</td>
</tr>
</tbody>
</table>
CHAPTER 3

CONCLUSION

We developed a general synthetic methodology for the synthesis of pyrrolo- and indolo-oxazin-1-one derivatives. These compounds show potential for possessing biological activity since there are many biologically active compounds in literature having the similar framework with these molecules.

In the first part of this study, we focused on the synthesis of pyrrolo- and indolo-oxazin-1-one derivatives. First, the ester derivatives were synthesized using the methods of acylation of pyrrole, bromination of pyrrole, Fischer esterification and Vilsmeier Haack reaction. Then, pyrrole and indole ester derivatives were treated with alkynyl bromide in the presence of NaH in DMF to synthesize N-substituted alkynyl esters. N-alkynyl pyrrole and indole esters were hydrolyzed giving the carboxylic acids which were the key compound for the synthesis of oxazinone derivatives. Treating the carboxylic acids with 3 mol % AuCl₃ gave 6-exo-dig cyclization products.

Scheme 44
Then the obtained products were converted into the \textit{endo}-cyclic products. To achieve this goal, 6-\textit{exo-dig} cyclization products were reacted with TFA at room temperature in CHCl$_3$. Some of the \textit{exo}-cyclic double bonds underwent isomerization to \textit{endo}-cyclic compounds upon treatment with TFA, while some did not. In order to investigate the reason for these results, theoretical calculations were performed with Gaussian 09 and DFT studies.

\begin{center}
\textbf{Scheme 45}
\end{center}

Moreover, the cyclization reaction of carboxylic acid 59 was carried out with Au(I) and AgOTf as cocatalyst in CHCl$_3$ at room temperature in the presence of alcohols. Hemiacetal derivatives formed after gold-catalyzed cascade reactions.

\begin{center}
\textbf{Scheme 46}
\end{center}
CHAPTER 4

EXPERIMENTAL SECTION

4.1. General Methods
All reagents were used as purchased from commercial suppliers without further purification. Proton nuclear magnetic resonance spectra (\(^1\)H NMR) were recorded on an instrument 400 MHz and chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual CDCl\(_3\) as an internal standard. The \(^{13}\)C-NMR spectra were recorded on an instrument 100 MHz and are reported in ppm using solvent as an internal standard (CDCl\(_3\)). Column chromatography was performed on silica gel (60-mesh). TLC was carried out on 0.2 mm silica gel 60 F254 analytical aluminum plates. High resolution Mass spectra were recorded by LC-MS TOF electrospray ionization technique.

Chemicals and all solvents were commercially available and used without further purification. Infrared (IR) spectra were recorded in the range 4000-600 cm\(^{-1}\) via ATR diamond. Melting points were measured using melting point apparatus and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary vacuum evaporator.

4.2. Synthesis of 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone (55)\(^{30,31}\)
To a stirred solution of 2,2,2-trichloroacetyl chloride (25.5 mL, 0.227 mol) in dry ether (45 mL) was added pyrrole (14.3 mL, 0.206 mmol) at 0 °C dropwise in an ice bath and the mixture was stirred for 2 d. After completion of the reaction, brine solution (300 mL) was added to the solution. The mixture was extracted with ethyl acetate (3 × 100 mL) and water (100 mL). The combined organic extracts were dried over MgSO\(_4\) and the solvent was evaporated to give 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone (55) as brown solid (43.6 g, 99%).
**4.3. Synthesis of methyl 1H-pyrrole-2-carboxylate (56)**

To a stirred solution of 55 (31.87 g, 0.150 mol) in methanol (50 mL) was added a solution of NaOMe solution in methanol (50 mL), prepared by dissolving Na (3.46 g, 0.150 mol) in methanol, dropwise at 0 °C for 3 h. The solvent was evaporated and diluted HCl (50 mL) was added to residue. The mixture was extracted with ethyl acetate (3 × 150 mL) and dried over MgSO₄. Evaporation of solvent gave methyl 1H-pyrrole-2-carboxylate (56) as a brown solid (16.5 g, 88%).

**4.4. General procedure for propargylation of pyrrole and indole derivatives.**

To a stirred solution of substituted methyl 1H-pyrrole-2-carboxylate (5 mmol) in DMF (10 mL) was added solid NaH (8 mmol) portionwise at 0 °C over 30 min. The reaction mixture was stirred at room temperature for 30 min. followed by dropwise addition of propargyl bromide or 1-bromobut-2-yne (6 mmol) in DMF (5 mL). The resulting mixture was stirred at room temperature for 2 d. Water (30 mL) was added, and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (4 × 25 mL) and dried over MgSO₄. Evaporation of solvent gave propargyl esters.

**4.5. Synthesis of methyl 1-prop-2-ynyl-1H-pyrrole-2-carboxylate (57)**
To a stirred solution of methyl 1H-pyrrole-2-carboxylate (56) (12.02 g, 96.16 mmol) in DMF (30 mL) was added solid NaH (3.46 g, 144.25 mmol) portionwise at 0 °C over 30 min. followed by dropwise addition of (80%, 10.67 mL, 120.2 mmol) in DMF (10 mL). After work-up as described above, propargyl ester 57 was isolated as pale yellow viscous liquid (14.82, 94%).

\[
\begin{align*}
\text{1H NMR} & \ (400 \text{ MHz, CDCl}_3) \ \delta \ 7.04 \ (\text{dd, } J_{5,4} = 2.7 \text{ and } J_{5,3} = 1.8 \text{ Hz, } 1\text{H, H-5}), \ 6.89 \ (\text{dd, } J_{3,4} = 4.0 \text{ and } J_{3,5} = 1.8 \text{ Hz, } 1\text{H, H-3}), \ 6.09 \ (\text{dd, } J_{4,3} = 4.0 \text{ Hz, } J_{4,5} = 2.7 \text{ Hz, } 1\text{H, H-4}), \ 5.09 \ (\text{d, } \text{J} = 2.6 \text{ Hz, } 2\text{H, CH}_2), \ 3.73 \ (\text{s, } 3\text{H, -OCH}_3), \ 2.35 \ (\text{t, } \text{J} = 2.6 \text{ Hz, } 1\text{H, C≡CH}).
\end{align*}
\]

\[
\begin{align*}
\text{13C NMR} & \ (100 \text{ MHz, CDCl}_3) \ \delta \ 161.5, 127.9, 121.6, 118.5, 108.6, 78.3, 73.8, 51.1, 38.1.
\end{align*}
\]

4.6. General procedure for hydrolysis of esters to carboxylic acids

To a solution of propargyl esters (5 mmol) in methanol (5 mL) was added K$_2$CO$_3$ (12 mmol) in MeOH/H$_2$O (20 mL) mixture and the solution was heated at reflux temperature for 1 d. Then, a solution of diluted HCl was added until the reaction media was acidic. The mixture was extracted with EtOAc (3 × 80 mL) and then with water (30 mL). The combined organic extracts were dried over MgSO$_4$ and the solvent was evaporated to give the corresponding acids.

4.7. Synthesis of 1-prop-2-ynyl-1H-pyrrole-2-carboxylic acid (59)$^{43}$

A solution of 57 (2.02 g, 12.4 mmol) in methanol (5 mL) was reacted with K$_2$CO$_3$ (3.757 g, 27.24 mmol) in MeOH/H$_2$O (40 mL) as described above. 59 was isolated as a white solid (1.67 g, 91%).

\[
\begin{align*}
\text{1H NMR} & \ (400 \text{ MHz, CDCl}_3) \ \delta \ 7.14 \ (\text{dd, } J_{5,4} = 2.7 \text{ Hz, } J_{5,3} = 1.8 \text{ Hz, } 1\text{H, H-5}), \ 7.08 \ (\text{dd, } J_{3,4} = 4.0 \text{ Hz, } J_{3,5} = 1.8 \text{ Hz, } 1\text{H, H-3}), \ 6.16 \ (\text{dd, } J_{4,3} = 4.0 \text{ Hz, } J_{4,5} = 2.7 \text{ Hz, } 1\text{H, H-4}), \ 5.11 \ (\text{d, } J = 2.6 \text{ Hz, } 2\text{H, -CH}_2), \ 2.39 \ (\text{t, } \text{J} = 2.6 \text{ Hz, } 1\text{H, C≡CH}).
\end{align*}
\]

\[
\begin{align*}
\text{13C NMR} & \ (100 \text{ MHz, CDCl}_3) \ \delta \ 165.9, 129.2, 120.9, 120.8, 109.1, 77.9, 74.1, 38.4.
\end{align*}
\]
4.8. General Procedure for gold-catalyzed cyclization of carboxylic acids

To a stirred solution of carboxylic acid (1 mmol) in chloroform (5 mL) was added 3 mol % AuCl$_3$ at room temperature and the reaction mixture was stirred for 2 h. After completion of the reaction, controlled by TLC, the solvent was evaporated to give the cyclization products, which was crystallized from appropriate solvent.

4.9. Synthesis of 3-methylene-3,4-dihydro-1$H$-pyrrolo[2,1-c][1,4]oxazin-1-one (62)

A stirred solution of 59 (75 mg, 0.5 mmol) in chloroform (5 mL) was reacted with 3 mol % AuCl$_3$ (4 mg) as described above to give the cyclization product 7. The crude product was crystallized from chloroform under the hexane atmosphere to get analytically pure sample. Colorless needles (72 mg, 96%) from CHCl$_3$/n-hexane, m.p. 65-67 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.13 (dd, $J_{8,7} = 4.0$ and $J_{8,6} = 1.5$ Hz, 1H, H-8), 6.89 (dd, $J_{6,7} = 2.5$ and $J_{6,8} = 1.5$ Hz, 1H, H-6), 6.34 (dd, $J_{7,8} = 4.0$ and $J_{7,6} = 2.5$ Hz, 1H, H-7), 5.02 (bd, $^2J_{\text{gem}} = 2.2$ Hz, 1H, H-1), 4.76 (bs, 2H, CH$_2$), 4.70 (dt, $^2J = 2.2$ Hz, $^4J_{1,4} = 1.1$ Hz, 1H, H-1'). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.2, 148.6, 124.9, 118.0 (2C), 111.7, 98.3, 45.5

IR (ATR) 3114, 2994, 1721, 1663, 1532, 1485, 1399, 1329, 1245, 1206, 1175, 1064, 882, 732.

HRMS calcd for (C$_8$H$_7$NO$_2$) [M + H]$^+$: 150.0550; Found: 150.0556.

4.10. Synthesis of methyl 1-but-2-ynyl-$1H$-pyrrole-2-carboxylate (67)

A stirred solution of methyl $1H$-pyrrole-2-carboxylate (56) (0.300 g, 2.4 mmol) in DMF (5 mL), NaH (92 mg, 3.8 mmol), and 1-bromobut-2-yne (0.275 ml, 0.414 g, 3.1 mmol) in DMF (2 mL) were reacted as described above to give 67. Yellow viscous liquid (410 mg, 96%).
**4.11. Synthesis of 1-but-2-ynyl-1H-pyrrole-2-carboxylic acid (68)**

A solution of methyl 1-but-2-ynyl-1H-pyrrole-2-carboxylate (67) (0.354 g, 2 mmol) in methanol (3 mL) was hydrolyzed with K2CO3 (0.607 g, 4.4 mmol) in MeOH/H2O (8 mL) mixture as described above to give 68. Pale yellow plates (310 mg, 95%), m.p. 133-135 °C from methanol.

**1H NMR** (400 MHz, CD3OD) δ 7.17–7.14 (m, 1H, H-5), 6.94 (dd, J3,4 = 3.9 and J3,5 = 1.8 Hz, 1H, H-3), 6.14 (dd, J4,3 = 3.9 and J4,5 = 2.7 Hz, 1H, H-4), 5.11 (q, J5,1 = 2.4 Hz, 2H, CH2), 1.83 (t, J5,4 = 2.4 Hz, 3H, CH3).

**13C NMR** (100 MHz, CD3OD) δ 164.1, 129.5, 123.0, 119.9, 109.1, 81.9, 75.0, 39.2, 3.1.

**IR** (ATR) 3352, 2921, 2617, 1663, 1532, 1436, 1320, 1259, 1109, 1073, 885, 741, 727, 612.

**HRMS** calcd for (C9H9NO2) [M - H]+: 162.0561; found: 162.0591.


A stirred solution of 1-but-2-ynyl-1H-pyrrole-2-carboxylic acid (68) (100 mg, 0.61 mmol) in chloroform (4 mL) was reacted with 3 mol % AuCl3 (5.5 mg) at room
temperature as described above to give 69. The compound was purified by silica gel column chromatography eluting with dichloromethane. Viscous oil (85 mg, 85%).

\[^{1}\text{H NMR}\ (400 \text{ MHz, CDCl}_3) \delta 7.12 (\text{dd, } J_{3,4} = 4.0 \text{ and } J_{3,5} = 1.4 \text{ Hz, 1H, H-3}), 6.86 (\text{dd, } J_{5,4} = 2.5 \text{ and } J_{5,3} = 1.4 \text{ Hz, 1H, H-5}), 6.31 (\text{dd, } J_{4,3} = 4.0 \text{ and } J_{4,5} = 2.5 \text{ Hz, 1H, H-4}), 5.08 (\text{qt, } J_{\text{H,CH}_3} = 6.9 \text{ and } 4J_{\text{H,CH}_2} = 1.1 \text{ Hz, 1H, C=CH}), 4.66 - 4.68 (\text{m, CH}_2), 1.78 (\text{dd, } J_{\text{CH}_3,\text{H}} = 6.9 \text{ Hz, } 5J_{\text{CH}_3,\text{CH}_2} = 1.1 \text{ Hz, 3H, -CH}_3).\]

\[^{13}\text{C NMR}\ (100 \text{ MHz, CDCl}_3) \delta 155.8, 141.7, 124.5, 118.6, 117.7, 111.4, 109.3, 46.2, 9.8.\]

**IR** (ATR) 1732, 1694, 1532, 1483, 1397, 1338, 1306, 1169, 1095, 1054, 964, 883, 735.

**HRMS** calcd for (C\(_9\)H\(_9\)NO\(_2\)) [M + H\(^+\): 164.0706; found: 164.0689.

4.13. **Synthesis of methyl 4,5-dibromo-1\textit{H}-pyrrole-2-carboxylate (71)**

To a stirred solution of methyl 1\textit{H}-pyrrole-2-carboxylate (56) (0.400 g, 3.2 mmol) in acetic acid (15 mL) was added a solution of Br\(_2\) (0.327 mL, 6.4 mmol) and the reaction was stirred for 1 d at 55 °C. After completion of the reaction which controlled by TLC paper, removal of solvent under reduced pressure gave the crude as 0.937 g. Separation of the product with column chromatography on silica gel eluted with hexane:ethyl acetate (3:1) afforded methyl 4,5-dibromo-1\textit{H}-pyrrole-2-carboxylate (71) as a pale yellow solid (0.84 g, 93%).

\[^{1}\text{H NMR}\ (400 \text{ MHz, CDCl}_3) \delta: 9.78 (\text{bs, 1H, NH}), 6.81 (\text{d, } J = 2.9 \text{ Hz, 1H, CH}), 3.81 (\text{s, 3H, -OMe})\]

\[^{13}\text{C NMR}\ (100 \text{ MHz, CDCl}_3) \delta: 160.9, 124.2, 118.5, 107.7, 101.2, 52.6.\]


A stirred solution of methyl 4,5-dibromo-1\textit{H}-pyrrole-2-carboxylate (71) (0.283 g, 1 mmol) in DMF (5 mL) was reacted with NaH (0.036 g, 1.5 mmol) and propargyl
bromide (80%, 0.110 ml, 1.25 mmol) as described above to give the propargyl ester 72. Pale yellow needles from diethyl ether, (0.308 g, 96%), m. p. 82-84 °C.

\[ \text{1H NMR} (400 MHz, CDCl}_3 \delta 7.04 (s, 1H, H-3), 5.30 (d, J = 2.5 Hz, 2H, CH}_2), 3.85 (s, 3H, OCH}_3), 2.32 (t, J = 2.5 Hz, 1H, C≡CH). \]

\[ \text{13C NMR} (100 MHz, CDCl}_3 \delta 159.9, 123.2, 120.2, 113.1, 100.0, 77.5, 72.8, 51.7, 37.7. \]

\[ \text{IR} (ATR) 2922, 1697, 1508, 1433, 1391, 1320, 1253, 1204, 1114, 1089, 937, 821, 747. \]

4.15. **Synthesis of 4,5-dibromo-1-prop-2-ynyl-1H-pyrrole-2-carboxylic acid (73)**

Methyl 4,5-dibromo-1-(prop-2-yn-1-yl)-1H-pyrrole-2-carboxylate (72) (0.294 g, 0.916 mmol) in methanol (3 mL) was hydrolyzed with K$_2$CO$_3$ (0.278 g, 2 mmol) in MeOH/H$_2$O (14 mL) as described above to give the corresponding acid 73. White powder (0.254 g, 90%) from diethyl ether, m.p. 186-189 °C.

\[ \text{1H NMR} (400 MHz, CD}_3\text{OD} \delta 7.05 (s, H-3), 5.36 (d, J = 2.4 Hz, 2H, CH}_2), 2.75 (t, J = 2.4 Hz, 1H, C≡CH). \]

\[ \text{13C NMR} (100 MHz, CD}_3\text{OD} \delta 162.1, 125.3, 121.1, 113.7, 100.5, 78.9, 74.0, 38.4. \text{IR} (ATR) 3280, 2847, 1669, 1525, 1420, 1319, 1258, 1215, 1134, 980, 936, 890, 756, 697. \]

\[ \text{HRMS} \text{ calcd for } (C}_8\text{H}_5\text{Br}_2\text{NO}_2 \text{ [M} - \text{H]}^+: 303.8614; \text{ found: 303.8650.} \]

4.16. **Synthesis of 6,7-dibromo-3-methylene-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (74)**

A stirred solution of 4,5-dibromo-1-(prop-2-yn-1-yl)-1H-pyrrole-2-carboxylic acid (73) (0.123 mg, 0.4 mmol) in methanol (5 mL) was reacted with 3 mol % AuCl$_3$ (3.6 mg) as described above to give the cyclization product 74. Yellow needles (0.117 g, 95%) from CHCl$_3$/n-hexane, m.p. 149-152 °C.
1H NMR (400 MHz, CDCl3) δ 7.11 (s, 1H, H-8), 5.03 (bd, 2J1,1' = 2.5 Hz, 1H, H-1), 4.75 (dt, 2J1,1' = 2.5 Hz, 4J1,4 = 1.1 Hz, 1H, H-1'), 4.62 (bs, 2H, H-4).

13C NMR (100 MHz, CDCl3) δ 153.4, 147.2, 119.7, 119.5, 109.6, 102.3, 100.1, 45.4.

IR (ATR) 3134, 1726, 1670, 1536, 1460, 1388, 1340, 1303, 1261, 1193, 1128, 1075, 992, 895, 731.

HRMS calcd for [M - H]-: 303.8614; found: 303.8647.

4.17. Synthesis of dimethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (77)\textsuperscript{44}

To a mixture of methylacetoacetate (75) (17.2 ml, 0.16 mol) and acetic acid (40 ml) was added an aqueous solution of NaNO\textsubscript{2} (5.52 g, 0.08 mol) in water (10 mL) over 30 min at 0 °C. The yellowish reaction mixture was stirred for 2.5 h at 10 °C. Then, Zn powder (10.46 g, 0.16 mol) was added to this solution portionwise at room temperature and the resulting mixture was then heated to 50 °C for 10 min. to allow excess amount of Zn powder to react completely. Heating was then continued at 95 °C for 1 h. After cooling to room temperature, the yellowish precipitate was collected and washed with ice water (300 mL) to give dimethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (77). Pale yellow powder (7.6 g, 45%).

1H-NMR (400 MHz, CDCl3) δ 9.26 (bs, 1H, NH), 3.79 (s, 3H, OMe), 3.75 (s, 3H, OMe), 2.48 (s, 3H, CH\textsubscript{3}), 2.44 (s, 3H, CH\textsubscript{3}).

13C-NMR (100 MHz, CDCl3) δ 165.9, 162.3, 159.2, 139.4, 131.1, 117.8, 113.4, 51.3, 50.7, 14.2, 12.0.

4.18. Synthesis of dimethyl 3,5-dimethyl-1-prop-2-ynyl-1H-pyrrole-2,4-dicarboxylate (78)

A stirred solution of dimethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (77) (3.011 g, 14.26 mmol) in DMF (27 mL), solid NaH (0.683 g, 28.45 mmol), and propargyl bromide (80%, 2.23 mL, 24.95 mmol) were reacted as described above to give
dimethyl 3,5-dimethyl-1-(prop-2-yn-1-yl)-1H-pyrrole-2, 4-dicarboxylate (78). Pale yellow cubic crystals (3.336 g, 94%) from EtOAc, m. p. 98-100 °C.

\[ \text{H} \text{NMR (400 MHz, CDCl}_3\text{)} \delta 5.09 (d, J_{1,3} = 2.5 \text{ Hz}, 2\text{H}, \text{CH}_2), 3.80 (s, 3\text{H}, \text{OCH}_3), 3.75 (s, 3\text{H}, \text{OCH}_3), 2.54 (s, 3\text{H}, \text{CH}_3), 2.46 (s, 3\text{H}, \text{CH}_3), 2.21 ( t, J_{3,1} = 2.5 \text{ Hz}, 1\text{H}, \text{H}-3). \]

\[ \text{C NMR (100 MHz, CDCl}_3\text{)} \delta 165.8, 162.4, 141.5, 131.9, 119.2, 113.3, 78.3, 72.2, 51.1, 50.8, 34.8, 12.7, 11.8. \]

IR (ATR) 3283, 2956, 2364, 1688, 1540, 1432, 1287, 1248, 1217, 1180, 1136, 1102, 770, 628.

HRMS calcd for [M + H]^+ : 250.1074; found: 250.1058.


A solution of dimethyl 3,5-dimethyl-1-(prop-2-yn-1-yl)-1H-pyrrole-2,4-dicarboxylate (78) (1.226 g, 4.92 mmol) in methanol was reacted with K$_2$CO$_3$ (1.5 g, 10.82 mmol) in MeOH/H$_2$O (30 mL) as described above. The mono acid 79 was separated by column chromatography on silica gel eluting with hexane/EtOAc (1:1) to yield 4-(methoxycarbonyl)-3,5-dimethyl-1-(prop-2-yn-1-yl)-1H-pyrrole-2-carboxylic acid (79). White powder (0.185 g, 16%) from CHCl$_3$/n-hexane, m.p. 165-167 °C.

\[ \text{H NMR (400 MHz, CD}_3\text{COCD}_3\text{)} \delta 5.34 (d, J_{1,3} = 2.5 \text{ Hz}, 2\text{H}, \text{CH}_2), 3.80 (s, 3\text{H}, \text{OCH}_3), 2.85 (t, J_{3,1} = 2.5 \text{ Hz}, 1\text{H}, \text{H}-3), 2.64 (s, 3\text{H}, \text{CH}_3), 2.56 (s, 3\text{H}, \text{CH}_3). \]

\[ \text{C NMR (100 MHz, CD}_3\text{COCD}_3\text{)} \delta 166.0, 163.1, 142.3, 132.1, 120.1, 113.9, 79.7, 73.7, 50.9, 35.1, 12.9, 11.8. \]

IR (ATR) 3272, 2620, 1699, 1645, 1540, 1486, 1432, 1373, 1262, 1219, 1148, 1112, 920, 783, 705, 661.

4.20. Synthesis of methyl 3,6,8-trimethyl-1-oxo-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (81)

A stirred solution of 4-(methoxycarbonyl)-3,5-dimethyl-1-prop-2-ynyl-1H-pyrrole-2-carboxylic acid (79) (70 mg, 0.3 mmol) in chloroform (4 mL) was reacted with 3 mol % AuCl₃ (2.7 mg) as described above. The analysis of the mixture with ¹H-NMR indicated the presence of two cyclization products 80 and 81. Then, the crude product was reacted with TFA in CHCl₃ at room temperature to give methyl 3,6,8-trimethyl-1-oxo-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (81). Pale yellow cubical crystals (60 mg, 86%) from chloroform/n-hexane, m.p. 182-184 °C.

¹H NMR (400 MHz, CDCl₃) δ 6.56-6.58 (m, 1H), 3.79 (s, 3H, -OCH₃), 2.62 (s, 3H, CH₃), 2.50 (s, 3H, CH₃), 2.07 (d, J = 1.0 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ 165.3, 155.3, 141.8, 133.3, 132.4, 115.4, 112.7, 101.3, 51.1, 17.1, 12.1, 11.0.

IR (ATR) 1726, 1684, 1557, 1406, 1252, 1191, 1130, 1027, 983, 953, 786, 746. HRMS calcd for (C₁₂H₁₃NO₄) [M + H]+: 236.0917; found: 236.0905.

4.21. Synthesis of methyl 1-(3-phenylprop-2-ynyl)-1H-pyrrole-2-carboxylate (82a)¹⁵

To a solution of methyl 1-prop-2-ynyl-1H-pyrrole-2-carboxylate (57) (0.5 g, 3.06 mmol) in dry THF (7 mL) and dry diisopropyl amine (3 mL, 0.021 mmol) was added iodobenzene (0.625 g, 3.06 mmol), palladium acetate (9 mg, 0.04 mmol), cuprous iodide (4.6 mg, 0.024 mmol) and triphenyl phosphine (15 mg, 0.057 mmol). The mixture was heated at reflux temperature for 24 h. After evaporation of the solvent, H₂O (50 mL) was added to the residue and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over MgSO₄. Removal of the solvent under the reduced pressure gave the crude product (0.650 g). The residue was purified by silica gel column chromatography eluting with 5:1 hexane/EtOAc to afford methyl 1-(3-phenylprop-2-ynyl)-1H-pyrrole-2-carboxylate (82a) (0.494 g, 67%) as a yellow liquid.
\[ ^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta 7.38 – 7.34 (m, 2H), 7.25 – 7.21 (m, 3H), 7.16 (dd, \text{J}_{5,4} = 2.7 \text{ and J}_{5,3} = 1.8 \text{ Hz, 1H, H-5}), 6.92 (dd, \text{J}_{3,4} = 4.0 \text{ and J}_{3,5} = 1.8 \text{ Hz, 1H, H-3}), 6.11 (dd, \text{J}_{4,3} = 4.0 \text{ and J}_{4,5} = 2.7 \text{ Hz, 1H, H-4}), 5.32 (s, 2H, \text{CH}_2), 3.75 (s, 3H, \text{OCH}_3). \]

\[ ^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3) \delta 166.1, 131.8, 129.2, 128.7, 128.3, 128.0, 122.4, 121.7, 118.5, 108.5, 85.9, 83.2, 39.3. \]

4.22. Synthesis of 1-(3-phenylprop-2-ynyl)-1H-pyrrole-2-carboxylic acid (83a)

A solution of methyl 1-(3-phenylprop-2-ynyl)-1H-pyrrole-2-carboxylate (82a) (0.238 g, 1 mmol) in methanol (3 mL) was reacted with 2 N KOH in MeOH (4 mL) and H\(_2\)O (0.5 mL) mixture as described above to give 83a. Yellow cubical crystals (0.187 g, 83\%) from chloroform, m.p. 146-148 °C.

\[ ^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta 7.40 – 7.36 (m, 2H), 7.27 – 7.22 (m, 4H, 3 arom. 1 pyrrole), 7.09 (dd, \text{J}_{3,4} = 4.0 \text{ and J}_{3,5} = 1.8 \text{ Hz, 1H, H-3}), 6.17 (dd, \text{J}_{4,3} = 4.0 \text{ and J}_{4,5} = 2.7 \text{ Hz, 1H, H-4}), 5.32 (s, 2H, \text{CH}_2). \]

\[ ^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3) \delta 166.1, 131.8, 129.2, 128.7, 128.3, 122.4, 121.7, 118.5, 108.5, 85.9, 83.2, 39.3. \]

IR (ATR) 2868, 2624, 1663, 1534, 1441, 1326, 1266, 1114, 1075, 907, 752, 729, 689.

HRMS Calcd for (C\(_{14}\)H\(_{11}\)NO\(_2\)) [M - H]\(^+\): 224.0717; Found: 224.0724.

4.23. Synthesis of (3Z)-3-benzylidene-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (84a)

A stirred solution of 1-(3-phenylprop-2-ynyl)-1H-pyrrole-2-carboxylic acid (83a) (100 mg, 0.44 mmol) in chloroform (5 mL) was reacted with 3 mol% AuCl\(_3\) (4 mg) as described above to give the cyclization product 84a. Pale yellow plates (73 mg, 73\%) from chloroform/n-hexane, m.p. 86-88 °C.
\( ^1 \text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.63 (d, \( J = 8.1 \) Hz, 2H), 7.29 (bt, \( J = 7.8 \) Hz, 2H), 7.19 (tt, \( J = 7.4 \) and \( J = 1.0 \) Hz, 1H), 7.08 (dd, \( J = 4.0 \) and \( J = 1.5 \) Hz, 1H), 6.84 (dd, \( J = 2.5 \) and \( J = 1.5 \) Hz, 1H), 6.26 (dd, \( J = 4.0 \) and \( J = 2.5 \) Hz, 1H), 5.76 (s, 1H, H-1), 4.75 (s, 2H, H-4).

\( ^{13} \text{C NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \) 154.9, 141.1, 132.7, 129.5, 128.6, 128.0, 124.8, 118.2, 118.0, 112.8, 111.7, 46.7.

\( \text{IR (ATR)} \) 2920, 1718, 1684, 1532, 1483, 1395, 1308, 1252, 1163, 1064, 1017, 936, 857, 756, 729, 693.

\( \text{HRMS} \) calcd for \((\text{C}_{14}\text{H}_{11}\text{NO}_2)\) [M + H]: 226.0863; found: 226.0852.

4.24. **Synthesis of methyl 1-[3-(4-methylphenyl)prop-2-ynyl]-1H-pyrrole-2-carboxylate (82b)**

Cuprous iodide (4.6 mg, 0.024 mmol), triphenyl phosphine (15.0 mg, 0.057 mmol), palladium acetate (9.0 mg, 0.01 mmol) and dry diisopropyl amine (3 mL, 0.021 mmol) was added to a solution of methyl 1-prop-2-ynyl-1H-pyrrole-2-carboxylate (57) (0.5 g, 3.06 mmol) in dry THF (7 mL). Then, 4-iodotoluene (0.673 g, 3.06 mmol) was added to the reaction mixture at room temperature. The mixture was heated at reflux temperature during stirring for 24 h. After cooling to room temperature, solvent was removed under reduced pressure. H\(_2\)O (50 mL) was added to the residue and extracted with ethyl acetate (3 \times 50 mL) and lastly the combined organic layers were washed with brine (80 mL) dried over MgSO\(_4\) and removal of the solvent under the reduced pressure gave the crude product (0.695 g). Chromatography on a silica gel column eluting with hexane/EtOAc (5:1) afforded the coupling product 82b. Yellow solid (0.496 g, 64%) from EtOAc, m.p. 47-49 °C.

\( ^1 \text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.26 (bd, \( J = 8.1 \) Hz, 2H), 7.18 (dd, \( J_{5,4} = 2.7 \) and \( J_{5,3} = 1.8 \) Hz, 1H, H-5), 7.04 (bd, \( J = 8.1 \) Hz, 2H), 6.92 (dd, \( J_{3,4} = 3.9 \) and \( J_{3,5} = 1.8 \) Hz, 1H, H-3), 6.11 (dd, \( J_{4,3} = 3.9 \) and \( J_{4,5} = 2.7 \) Hz, 1H, H-4), 5.31 (s, 2H, CH\(_2\)), 3.76 (s, 3H, OCH\(_3\)), 2.27 (s, 3H, CH\(_3\)).
\textbf{13C NMR} (100 MHz, CDCl$_3$) $\delta$ 161.6, 138.8, 131.7, 129.1, 128.0, 121.7, 119.3, 118.5, 108.4, 85.8, 82.7, 51.2, 39.1, 21.5.

\textbf{IR} (ATR) 2945, 1705, 1509, 1477, 1437, 14010, 1340, 1291, 1229, 1101, 1070, 808, 756, 733, 604.

\textbf{HRMS} calcd for (C$_{16}$H$_{15}$NO$_2$) [M + H]: 254.1176; found: 254.1187.

\textbf{4.25. Synthesis of 1-[3-(4-methylphenyl)prop-2-ynyl]-1H-pyrrole-2-carboxylic acid (83b)}

A solution of methyl 1-[3-(4-methylphenyl)prop-2-ynyl]-1H-pyrrole-2-carboxylate (82b) (0.120 g, 0.5 mmol) in methanol and KOH (2 N) in MeOH (7 mL) were reacted as described above to give 1-[3-(4-methylphenyl)prop-2-ynyl]-1H-pyrrole-2-carboxylic acid (83b) Yellow needles (0.110 g, 97%) from chloroform, m.p. 139-142 °C.

\textbf{1H NMR} (400 MHz, CDCl$_3$) $\delta$ 7.27 (bd, $J = 8.0$ Hz, 2H), 7.25 (dd, $J_{5,4} = 2.7$ and $J_{5,3} = 1.6$ Hz, 1H, H-5), 7.09 (dd, $J_{3,4} = 3.9$ and $J_{3,5} = 1.6$ Hz, 1H, H-3), 7.05 (bd, $J = 8.0$ Hz, 2H), 6.16 (dd, $J_{4,3} = 3.8$ and $J_{4,5} = 2.7$ Hz, 1H, H-4), 5.31 (s, 2H, CH$_2$), 2.27 (s, 3H, CH$_3$).

\textbf{13C NMR} (100 MHz, CDCl$_3$) $\delta$ 166.2, 138.9, 131.7, 129.3, 129.1, 121.0, 120.8, 119.2, 108.9, 86.1, 82.5, 39.3, 21.5.

\textbf{IR} (ATR) 3200, 2924, 1725, 1667, 1430, 1332, 1251, 1106, 1070, 811, 760, 732, 579.

\textbf{HRMS} calcd for (C$_{15}$H$_{13}$NO$_2$) [M - H]$: 238.0873; found: 238.0891.

\textbf{4.26. Synthesis of (3Z)-3-(4-methylbenzylidene)-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (84b)}

A stirred solution of 1-[3-(4-methylphenyl)prop-2-ynyl]-1H-pyrrole-2-carboxylic acid (83b) (104 mg, 0.43 mmol) in chloroform (5 mL) was reacted with 3 mol % AuCl$_3$ (4.0 mg) as described above. The crude product (94 mg) was purified on a silica gel column eluting with n-hexane/EtOAc (5:1) to afford the cyclization product 84b. Pale yellow pellets (70 mg, 67%) from chloroform/n-hexane, m.p. 175-178 °C.
1H NMR (400 MHz, CDCl3) δ 7.61 (bd, J = 8.1 Hz, 2H), 7.20–7.13 (m, 3H), 6.91 (dd, J = 2.5 and 1.3 Hz, 1H), 6.34 (dd, J = 4.0 and J = 2.5 Hz, 1H), 5.81 (s, 1H), 4.83 (s, 2H, CH2), 2.35 (s, 3H, CH3).

13C NMR (100 MHz, CDCl3) δ 155.0, 140.4, 138.0, 129.9, 129.4, 129.3, 124.7, 118.1, 112.8, 111.6, 46.9, 21.3.

IR (ATR) 2960, 2920, 2849, 2718, 1734, 1466, 1395, 1328, 1152, 751, 731.

HRMS calcd for (C15H13NO2) [M + H]: 240.1019; found: 240.0991.

4.27. Synthesis of ethyl 1H-indole-2-carboxylate (86)\textsuperscript{38}

To a stirred solution of indole-2-carboxylic acid (85) (10.0 g, 62 mmol) in ethanol (120 mL) H2SO4 (2.5 ml) was added as catalyst. The solution was heated to reflux temperature, and then it was stirred overnight. After completion of the reaction monitored by TLC, ethanol was removed under reduced pressure and reaction medium was extracted by EtOAc and NaHCO3 for three times. The combined organic layers was dried over MgSO4 and removal of solvent under reduced pressure yielded ethyl-1H-indole-2-carboxylate (86) as a white solid (9.2 g, 78%).

1H NMR (400 MHz, CDCl3) δ: 7.69 (dd, J = 8.1, 0.9 Hz, 1H), 7.43 (dd, J = 8.3, 0.9 Hz, 1H), 7.32 (ddd, J = 8.3, 7.0, 1.1 Hz, 1H), 7.24 (dd, J = 2.0, 0.9 Hz, 1H), 7.15 (ddd, J = 8.1, 7.0, 0.9 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H, -CH2), 1.42 (t, J = 7.1 Hz, 3H, -CH3).

13C NMR (100 MHz, CDCl3) δ: 159.6, 134.4, 133.5, 124.9, 122.8, 120.1, 118.3, 109.4, 106.3, 58.6, 11.9.

4.28. Synthesis of ethyl 1-prop-2-ynyl-1H-indole-2-carboxylate (87a)\textsuperscript{46}

A stirred solution of ethyl 1H-indole-2-carboxylate (86) (0.7 g, 3.7 mmol) in DMF (6 mL), NaH (0.142 g, 5.92 mmol), and propargyl bromide (80%, 0.431 ml, 5 mmol) in DMF (3 mL) were reacted as described above to give propargyl indole derivative 87a. White powder (0.830 g, 98%) from petroleum ether m.p. 64-66 °C.
\( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.61 (bd, \( J = 8.0 \) Hz, 1H), 7.42 (dd, \( J = 8.4 \) and \( J = 0.7 \) Hz, 1H), 7.31 (ddd, \( J = 8.3, 7.0, \) and 1.1 Hz, 1H), 7.26 (d, \( J = 0.7 \) Hz, 1H), 7.11 (ddd, \( J = 8.0, 7.0, \) and 0.8 Hz, 1H), 5.36 (d, \( J_{1,3} = 2.5 \) Hz, 2H, CH\(_2\)), 4.32 (q, \( J = 7.1 \) Hz, 2H, CH\(_2\)), 2.17 (t, \( J = 2.5 \) Hz, 1H, C≡CH), 1.33 (t, \( J = 7.1 \) Hz, 3H, CH\(_3\)).

\( ^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \) 162.0, 139.0, 126.9, 126.3, 125.5, 122.8, 121.2, 111.4, 110.5, 78.8, 72.0, 60.8, 33.9, 14.3.

4.29. **Synthesis of 1-prop-2-ynyl-1H-indole-2-carboxylic acid (88a)**

A solution of ethyl 1-prop-2-ynyl-1H-indole-2-carboxylate (87a) (0.475 g, 2.1 mmol) in methanol (5 mL) was reacted with K\(_2\)CO\(_3\) (0.636 g, 4.6 mmol) in MeOH/H\(_2\)O (10 mL) mixture as described above to give indole carboxylic acid 88a. Colorless needles (0.405 g, 2.0 mmol, 97%) from chloroform, m.p. 194.0-198 °C (Lit. m.p. 190-193 °C).

\( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.66 (bd, \( J = 7.9 \) Hz, 1H), 7.46 (d, \( J = 8.0 \) Hz, 1H), 7.45 (bs, 1H), 7.38 (t, \( J = 7.7 \) Hz, 1H), 7.17 (t, \( J = 7.4 \) Hz, 1H), 5.39 (d, \( J = 2.1 \) Hz, 2H, CH\(_2\)), 2.20 (t, \( J = 2.1 \) Hz, 1H, C≡CH).

\( ^{13}\text{C NMR} \) (100 MHz, CD\(_3\)OD) \( \delta \) 164.8, 140.5, 128.5, 127.7, 126.3, 123.6, 122.0, 112.6, 111.8, 80.1, 73.0, 34.4.

4.30. **Synthesis of 3-methylene-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one (89a)**

A stirred solution of 1-(prop-2-yn-1-yl)-1H-indole-2-carboxylic acid (88a) (0.199 g, 1 mmol) in methanol (5 mL) was reacted with 3 mol % AuCl\(_3\) (9.1 mg) as described above to afford the cyclization product 89a. Pale yellow needles (197 mg, 99%) from chloroform/n-hexane, m.p. 201-204 °C.
**1H NMR** (400 MHz, CDCl$_3$) $\delta$ 7.67 (bd, $J = 8.0$ Hz, 1H), 7.41 (d, $J = 0.8$ Hz, 1H), 7.35 (ddd, $J = 8.4$, 7.0, and 1.0 Hz, 1H), 7.27 (dd, $J = 8.4$ and 0.8 Hz, 1H), 7.15 (ddd, $J = 8.0$, 7.0, and 1.0 Hz, 1H), 5.02 (bd, $^2J = 2.3$ Hz, 1H, C=CH), 4.81 (bs, 2H, CH$_2$), 4.74 (dt, $^2J = 2.3$ and $^4J = 1.1$ Hz, 1H, C=CH).

**13C NMR** (100.6 MHz, CDCl$_3$) $\delta$ 156.2, 148.7, 136.6, 127.2, 126.4, 123.4, 122.1, 121.8, 110.8, 110.0, 98.8, 869, 729.

**IR** (ATR) 1729, 1664, 1534, 1476, 1459, 1352, 1313, 1243, 1164, 1136, 1079, 998, 869, 729.

**HRMS** calcd for (C$_{12}$H$_9$NO$_2$) [M + H]$^+$: 200.0706; found: 200.0708.

**4.31. Synthesis of ethyl 1-but-2-ynyl-1H-indole-2-carboxylate (87b)**

A stirred solution of ethyl 1H-indole-2-carboxylate (86) (0.270 g, 1.4 mmol) in DMF (3 mL) NaH (52 mg, 2.1 mmol), and 1-bromobut-2-ynyl (0.126 ml, 0.190 g, 1.4 mmol) in DMF (2 mL) were reacted as described above to give the propargyl indole derivative 87b. White crystals like snowflake (0.240 g, 70%) from petroleum ether, m.p. 66-68 °C.

**1H NMR** (400 MHz, CDCl$_3$) $\delta$ 7.71 (bd, $J = 8.0$ Hz, 1H), 7.54 (dd, $J = 8.4$ and $J = 0.7$ Hz, 1H), 7.41 (ddd, $J = 8.2$, 7.0, and 1.0 Hz, 1H), 7.35 (d, $J = 0.7$ Hz, 1H), 7.00 (ddd, $J = 7.9$, 7.1, and 0.8 Hz, 1H), 5.39 (q, $^5J_{1,4} = 2.4$ Hz, 2H, CH$_2$), 4.40 (q, $J = 7.1$ Hz, 2H, CH$_2$), 1.75 (t, $^5J_{4,1} = 2.4$ Hz, 3H, CH$_3$), 1.42 (t, $J = 7.1$ Hz, 3H, CH$_3$).

**13C NMR** (100 MHz, CDCl$_3$) $\delta$ 162.0, 139.0, 127.0, 126.2, 125.5, 122.7, 120.9, 111.0, 110.8, 79.7, 74.2, 60.7, 34.2, 14.4, 3.6.

**IR** (ATR) 3058, 2973, 1698, 1519, 1473, 1453, 1340, 1317, 1262, 1249, 1195, 1144, 1094, 1029, 822, 766, 736.

**HRMS** calcd for (C$_{15}$H$_{15}$NO$_2$) [M + H]$^+$: 242.1176; found: 242.1174.
4.32. **Synthesis of 1-but-2-ynyl-1H-indole-2-carboxylic acid (88b)**

A solution of ethyl 1-but-2-ynyl-1H-indole-2-carboxylate (87b) (0.307 g, 1.27 mmol) in methanol (5 mL) was reacted with K$_2$CO$_3$ (0.387 g, 2.8 mmol) in MeOH/H$_2$O (10 mL as described above to give indole carboxylic acid 88b. White needle (0.405 g, 97%) from chloroform, m.p. 190-193 °C.

![1H NMR spectrum](image)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.64 (d, $J = 8.0$ Hz, 1H), 7.46 (d, $J = 8.5$ Hz, 1H), 7.42 (s, 1H), 7.34 (ddd, $J = 8.0$, 7.0, and 0.9 Hz, 1H), 7.15–7.10 (m, 1H), 5.31 (q, $^5J_{1,4} = 2.3$ Hz, 2H, CH$_2$), 1.68 (t, $^5J_{4,1} = 2.3$ Hz, 3H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.9, 139.6, 126.1, 126.0, 125.7, 123.0, 121.2, 113.5, 111.0, 80.0, 74.0, 34.3, 3.6

IR (ATR) 2851, 2513, 1654, 1518, 1482, 1438, 1264, 1206, 1142, 829, 733, 618

HRMS calcd for (C$_{13}$H$_{11}$NO$_2$) [M-H]: 212.0717; found: 212.0767.

4.33. **Synthesis of (3Z)-3-ethylidene-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one (89b)**

A stirred solution of 1-but-2-ynyl-1H-indole-2-carboxylic acid (88b) (80 mg, 0.37 mmol) in chloroform (4 mL) was reacted with 3 mol % AuCl$_3$ (3.4 mg) as described above to give the cyclization product 89b. Yellow plates (77 mg, 96%) from chloroform/n-hexane, m.p. 102-105 °C.

![1H NMR spectrum](image)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.72 (dd, $J = 8.1$, 0.7 Hz, 1H), 7.44 (s, 1H), 7.42–7.37 (m, 1H), 7.32 (d, $J = 8.4$ Hz, 1H), 7.19 (dd, $J = 8.0$ and 7.0 Hz, 1H), 5.18 (q, $J = 6.8$ Hz, 1H, C=CH), 4.77 (d, $J = 1.0$ Hz, 2H, -CH$_2$), 1.81 (dd, $J = 6.8$ and $J = 1.0$ Hz, 3H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 156.8, 141.8, 136.4, 127.1, 126.2, 123.3, 122.7, 121.6, 110.4, 110.0, 109.7, 43.1, 9.9.

IR (ATR) 2862, 1727, 1697, 1530, 1466, 1415, 1374, 1297, 1242, 1215, 1157, 1094, 1060, 812, 724.

HRMS calcd for (C$_{13}$H$_{11}$NO$_2$) [M+H]$^+$: 214.0863; found: 214.0864.
4.34. Synthesis of ethyl 3-formyl-1H-indole-2-carboxylate (90)

To a stirred solution of DMF (3 mL) was added POCl₃ (5.81 mmol, 0.533 mL) at 0 °C. After that, into this mixture, a solution of ethyl 1H-indole-2-carboxylate (86) (1.0 g, 5.3 mmol) in DMF (3 mL) was slowly added over 1 h at room temperature. Then, the reaction mixture was heated to 70 °C and stirred for overnight. After completion of the reaction monitored by TLC, the reaction mixture was poured into cold water and 2 N NaOH was added to neutralize the medium. After that, the precipitate was filtered to get ethyl 3-formyl-1H-indole-2-carboxylate (90) as a yellow powder (0.720 g, 63%).

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\text{1H NMR (400 MHz, CD}_3\text{COCD}_3) \delta 11.59 \text{ (bs, 1H), 10.62 (s, 1H, -CHO), 8.24 (d, J = 8.1 Hz, 1H), 7.49 (dd, J = 8.3, 0.7 Hz, 1H), 7.28 (ddd, J = 8.3, 7.1, 1.2 Hz, 1H), 7.19 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H, -CH}_2, 1.30 (t, J = 7.1 Hz, 3H, -CH}_3).}
\]

\[
\text{13C NMR (100 MHz, CD}_3\text{COCD}_3) \delta 187.4, 160.3, 135.9, 126.0, 125.4, 125.0, 123.4, 123.0, 119.3, 112.7, 61.7, 13.6}
\]

4.35. Synthesis of ethyl 3-formyl-1-prop-2-ynyl-1H-indole-2-carboxylate (91)

A stirred solution of ethyl 3-formyl-1H-indole-2-carboxylate (90) (0.600 g, 2.76 mmol) in DMF (6 mL), NaH (0.1 g, 4.14) and propargyl bromide (80%, 0.31 ml, 3.6 mmol) in DMF (3 mL) were reacted as described above to give propargyl derivative 91. White needles (0.510 g, 72%) from chloroform, m.p. 119-122 °C.

\[
\text{1H NMR (400 MHz, CDCl}_3) \delta 10.66 \text{ (s, 1H), 8.52 (d, J = 8.1 Hz, 1H), 7.55 (bd, J = 8.4 Hz, 1H), 7.49 (ddd, J = 8.0, 6.8, and 1.0 Hz, 1H), 7.39 (ddd, J = 8.0, 7.0, and 1.0 Hz, 1H), 5.41 (d, J = 2.5 Hz, 2H, CH}_2, 4.55 (q, J = 7.1 Hz, 2H, CH}_2, 2.33 (t, J = 2.4 Hz, 1H), 1.49 (t, J = 7.1 Hz, 3H, CH}_3).}
\]

\[
\text{13C NMR (100 MHz, CDCl}_3) \delta 188.5, 160.8, 137.4, 132.2, 126.7, 124.7, 124.4, 124.0, 120.8, 110.5, 77.5, 73.2, 62.4, 34.7, 14.2}
\]
IR (ATR) 3247, 2121, 1698, 1510, 1474, 1428, 1364, 1270, 1246, 1212, 1169, 1142, 1039, 1013, 814, 785, 705.

HRMS calcd for (C_{15}H_{13}NO_{3}) [M+H]^+: 256.0968; found: 256.0975.

4.36. **Synthesis of 3-formyl-1-prop-2-ynyl-1H-indole-2-carboxylic acid (92)**

A solution of ethyl 3-formyl-1-prop-2-ynyl-1H-indole-2-carboxylate (91) (0.255 g, 1 mmol) in methanol (4 mL) was hydrolized with K_{2}CO_{3} (0.304 g, 2.2 mmol) in MeOH/H_{2}O (10 mL) mixture as described above to give the carboxylic acid 92. Yellow powder (0.220 g, 97%) from chloroform, m.p. 190-193 °C.

**1H NMR** (400 MHz, CD_{3}COCD_{3}) δ 10.53 (s, 1H, CHO), 8.29 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.39 (ddd, J = 8.4, 7.2, and 1.1 Hz, 1H), 7.26 (bt, J = 7.6 Hz, 1H), 5.47 (d, J = 2.5 Hz, 2H, CH_{2}), 2.77 (t, J = 2.5 Hz, 1H, C≡CH).

**13C NMR** (100 MHz, CD_{3}COCD_{3}) δ 188.9, 161.8, 138.5, 133.7, 127.3, 125.7, 125.0, 123.7, 121.0, 112.3, 79.0, 74.5, 35.3.

IR (ATR) 3264, 2375, 2315, 1685, 1559, 1518, 1458, 1373, 1333, 1272, 1252, 1215, 1176, 1040, 898, 810, 744, 679.

HRMS calcd for (C_{13}H_{9}NO_{3}) [M+H]^+: 228.0655, found: 228.0658.

4.37. **Synthesis of 3-methylene-1-oxo-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole-10-carbaldehyde (93)**

A stirred solution of 3-formyl-1-prop-2-ynyl-1H-indole-2-carboxylic acid (92) (150 mg, 0.66 mmol) in chloroform (5 mL) was reacted with 3 mol % AuCl_{3} (6.0 mg) as described above to give the cyclization product 93. Orange plates (138 mg, 92%) from chloroform/n-hexane, m.p. 193-194 °C.
**1H NMR** (400 MHz, CDCl$_3$) $\delta$ 10.74 (s, 1H, CHO), 8.46 (d, $J = 8.5$ Hz, 1H), 7.54 – 7.48 (m, 1H), 7.43 – 7.37 (m, 2H), 5.21 (d, $J = 2.6$ Hz, 1H, C=CH), 4.96 (s, 2H, CH$_2$), 4.95 – 4.92 (m, 1H, C=CH).

**13C NMR** (100 MHz, CDCl$_3$) $\delta$ 187.7, 154.6, 147.2, 135.2, 127.6, 125.4, 125.1, 124.9, 124.3, 121.2, 110.0, 100.3, 42.4.

**IR** (ATR) 3034, 2848, 1735, 1648, 1535, 1471, 1426, 1310, 1251, 1206, 1158, 1109, 1043, 997, 866, 844, 746.

**HRMS** calcd for (C$_{13}$H$_9$NO$_3$) [M + H]$^+$: 228.0655; found: 228.0657.

**4.38. General procedure for TFA-catalyzed isomerization of methylene compounds**

To a stirred solution of cyclization product (2 mmol) in chloroform (5 mL) was added excess trifluoroacetic acid (15 mmol) at room temperature and the reaction was stirred for 1 d. After completion of the reaction, which was controlled by TLC, the solvent was evaporated under the reduced pressure. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine and dried over MgSO$_4$. Removal of the solvent gave the corresponding 1H-pyrrolo[2,1-c][1,4]oxazin-1-one derivatives.


A stirred solution of 3-methylene-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (62) (0.27 g, 1.8 mmol) in chloroform (5 mL) was treated with excess trifluoroacetic acid (15 mmol) at room temperature as described above to give 94. Colorless needles from chloroform/n-hexane, m.p. 95-97 °C (lit. m.p. 92-94 °C).$^{47}$

**1H NMR** (400 MHz, CDCl$_3$) $\delta$ 7.11 (bd, $J_{8,7} = 4.1$ Hz, 1H, H-8), 6.97 (dd, $J_{6,7} = 2.5$, $J_{6,8} = 1.5$ Hz, 1H, H-6), 6.75–6.71 (m, 1H, H-4), 6.43 (dd, $J_{7,8} = 4.1$, $J_{7,6} = 2.5$ Hz, 1H, H-7), 2.08 (d, $J = 1.1$ Hz, 3H, CH$_3$).

**13C NMR** (100 MHz, CDCl$_3$) $\delta$ 155.4, 141.0, 120.7, 116.5, 115.1, 112.8, 104.9, 16.7.
4.40. Synthesis of 3-ethyl-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (97)

A stirred solution of (3Z)-3-ethylidene-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (69) (70 mg, 0.43 mmol) in chloroform (5 mL) was reacted with trifluoroacetic acid as described above to give the isomerized product 97. The compound was purified by silica gel column chromatography eluting with n-hexane/EtOAc (3:1). Colorless viscous liquid (15 mg, 21%), crude yield 27%.

\[
\text{\textsuperscript{1}H NMR} \ (400 \text{ MHz, CDCl}_3) \delta 7.21 \text{ (bd, } J_{8,7} = 4.0, 1\text{H, H-8), 7.07 (dd, } J_{6,7} = 2.3 \text{ and } J_{6,8} = 1.4 \text{ Hz, 1H, H-6), 6.82 (bs, 1H, H-4), 6.53 (dd, } J_{7,8} = 4.0 \text{ Hz, } J_{7,6} = 2.3 \text{ Hz, 1H, H-7), 2.48 (q, } J = 7.3 \text{ Hz, 2H, CH}_2, 1.25 (t, } J = 7.3 \text{ Hz, 3H, CH}_3). 
\]

\[
\text{\textsuperscript{13}C NMR} \ (100 \text{ MHz, CDCl}_3) \delta 155.6, 146.0, 120.8, 116.7, 115.1, 112.8, 104.0, 24.2, 11.1. 
\]

\[
\text{IR (ATR)} \ 3121, 2970, 2922, 1717, 1691, 1531, 1485, 1458, 1378, 1344, 1213, 1090, 1072, 1036, 1014, 936, 728, 630.
\]

HRMS calcld for (C\textsubscript{9}H\textsubscript{9}NO\textsubscript{2}) [M + H\textsuperscript{+}]: 164.0706; found: 164.0716.

4.41. Synthesis of 6,7-dibromo-3-methyl-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (98)

A stirred solution of 6,7-dibromo-3-methylene-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (74) (70 mg, 0.43 mmol) in chloroform (5 mL) was reacted with trifluoroacetic acid as described above to give the isomerized product 98. The compound was purified by silica gel column chromatography eluting with n-hexane/EtOAc (8:1). Pale yellow needles (25 mg, 42%), crude yield 54% from chloroform, m.p. 187-190 °C.

\[
\text{\textsuperscript{1}H NMR} \ (400 \text{ MHz, CDCl}_3) \delta 7.26 \text{ (s, 1H), 6.89 (bs, 1H), 2.20 (d, } J = 1.0 \text{ Hz, 3H, CH}_3). 
\]

\[
\text{\textsuperscript{13}C NMR} \ (100 \text{ MHz, CDCl}_3) \delta 153.3, 142.6, 117.7, 116.8, 105.0, 104.1, 103.2, 17.1. \text{IR (ATR)} \ 3119, 1732, 1685, 1440, 1391, 1378, 1350, 1298, 1220, 1179, 1128, 1065, 992, 818, 773, 731, 629, 545.
\]
HRMS calcd for (C₈H₅Br₂NO₂) [M - H]⁺: 303.8614; found: 303.8639.

4.42. Synthesis of 3-methyl-1H-[1,4]oxazino[4,3-a]indol-1-one (99)

A stirred solution of 3-methylene-3,4-dihydro-1H-indolo[2,1-c][1,4]oxazin-1-one (89a) (0.127 g, 0.63 mmol) in chloroform (5 mL) was reacted with trifluoroacetic acid as described above to give the isomerized product 99. Yellow plates (106 mg, 83%) from chloroform/n-hexane, m.p. 205-206 °C.

1H NMR (400 MHz, CDCl₃) δ 7.80 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.52 (s, 1H), 7.45 (ddd, J = 8.3, 7.0, and 1.0 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.09 (bs, 1H), 2.25 (d, J = 1.1 Hz, 3H, CH₃).

13C NMR (100 MHz, CDCl₃) δ 156.6, 138.8, 132.8, 127.4, 125.9, 123.2, 122.6, 120.3, 110.4, 107.7, 102.4, 16.9.

IR (ATR) 1732, 1559, 1539, 1458, 1406, 1351, 1328, 1248, 1166, 1135, 1069, 996, 809, 728.


4.43. Synthesis of 3-ethyl-1H-[1,4]oxazino[4,3-a]indol-1-one (100)

A stirred solution of (3Z)-3-ethylened-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one (89b) (120 mg, 0.56 mmol) in chloroform (5 mL) was reacted with trifluoroacetic acid as described above to give the isomerized product 100. Pale yellow solid (25 mg, 21%) from EtOAc (crude yield 37%), m.p. 96-98 °C.

1H NMR (400 MHz, CDCl₃) δ 7.84 (bd, J = 8.0 Hz, 1H), 7.60 (bd, J = 8.3 Hz, 1H), 7.55 (s, 1H), 7.48 (ddd, J = 8.3, 7.0, 0.9 Hz, 1H), 7.32 (ddd, J = 8.0, 7.0, 0.9 Hz, 1H), 7.11 (bs, 1H), 2.59 (dd, J = 1.0 and 7.5 Hz, 2H, CH₂), 1.33 (t, J = 7.5 Hz, 3H, CH₃).

13C NMR (100 MHz, CDCl₃) δ 156.8, 143.9, 132.9, 127.5, 125.9, 123.3, 122.6, 110.4, 107.7, 101.5, 100.0, 24.4, 11.4.

IR (ATR) 2918, 1724, 1691, 1536, 1459, 1408, 1351, 1245, 1169, 1134, 1039, 1013, 806, 728.
HRMS calcd for (C_{13}H_{11}NO_{2}) [M + H]^+: 214.0863; found: 214.0873.

4.44. Reaction of 1-prop-2-ynyl-1H-pyrrole-2-carboxylic acid (59) with gold(I) in chloroform in the presence of ethanol. Formation of 1-(2-oxopropyl)-1H-pyrrole-2-carboxylic acid (102)

To a solution of 1-prop-2-ynyl-1H-pyrrole-2-carboxylic acid (59) (0.149 g, 1 mmol) in dry CHCl₃ (5 mL) was added 3 mol % 1,3-bis (2,6-di-isopropylphenyl)imidazole-2-ylidene gold(I) (18.6 mg), 5 mol % AgOTf (12.8 mg) and EtOH (1 mmol, 58 µL). The solution was stirred at room temperature for 1 d. After the completion of the reaction, controlled by TLC, the solvent was evaporated to give crude product. The \(^1\)H NMR spectral analysis of the residue revealed the formation of three products; 101, 102, and 62 in yields of 51%, 39%, and 10%, respectively. The \(^1\)H NMR spectral data of 101 were extracted from the spectrum of the mixture. The residue was chromatographed on silica gel eluting with n-hexane/EtOAc (5:1) to yield 102 as pale yellow needles (147 mg, 88%) from chloroform, m.p. 140-142 °C.

\(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.17 (dd, \(J_{3,4} = 4.0\) and \(J_{3,5} = 1.7\) Hz, 1H, H-3), 6.85 (dd, \(J_{5,4} = 2.6\) and \(J_{5,3} = 1.7\) Hz, 1H, H-5), 6.28 (dd, \(J_{4,3} = 4.0\) Hz, \(J_{4,5} = 2.6\) Hz, 1H, H-4), 5.06 (s, 2H, CH₂), 2.22 (s, 3H, CH₃).

\(^13\)C NMR (100 MHz, CDCl₃) \(\delta\) 202.4, 166.0, 130.8, 121.2, 120.5, 109.4, 58.4, 26.8.

IR (ATR) 2917, 2868, 2587, 1731, 1646, 1533, 1470, 1432, 1328, 1274, 1174, 1114, 1081, 927, 747, 605, 581, 547.

HRMS calcd for (C₈H₉NO₃) [M+Na]^+: 190.0475, found: 190.0471.

3-Ethoxy-3-methyl-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (101)

\(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.14 (dd, \(J_{3,4} = 4.0\) and \(J_{3,5} = 1.6\) Hz, 1H, H-3), 6.85 (dd, \(J_{5,4} = 2.6\) and \(J_{5,3} = 1.6\) Hz, 1H, H-5), 6.29 (dd, \(J_{4,3} = 4.0\) Hz, \(J_{4,5} = 2.5\) Hz, 1H, H-4), 4.17 (d, A-part of AB-system, \(^2J = 12.8\) Hz, 1H, NCH₂), 4.12 (d, B-part of AB-system, \(^2J = 12.8\) Hz, 1H, NCH₂), 3.81-3.67 (m, 2H, OCH₂), 1.67 (s, 3H, CH₃), 1.10 (t, \(J = 7.1\) Hz, 3H, CH₃).
4.45. Reaction of 1-prop-2-ynyl-1H-pyrrole-2-carboxylic acid (59) with gold(I) in chloroform

The reaction was carried out with 1 mol carboxylic acid 59 as described above. The \(^1\)H NMR spectral analysis of the reaction mixture indicated the sole formation of 94 and 62 in 83% and 17% yields, respectively.

4.46. Reaction of 1-prop-2-ynyl-1H-pyrrole-2-carboxylic acid (59) with gold(I) in the presence of CD\(_3\)OD

A solution of 1-prop-2-ynyl-1H-pyrrole-2-carboxylic acid (59) (1 mmol) and CD\(_3\)OD in dry CHCl\(_3\) (5 mL) was reacted with 3 mol % 1,3-bis(2,6-di-isopropylphenyl)imidazole-2-ylidene gold(I) (18.6 mg), 5 mol % AgOTf (12.8 mg) as described above. The \(^1\)H NMR spectral analysis of the residue revealed the formation of three products; 103a/103b, and 104a/104b in yields of 65% and 35%, respectively. The \(^1\)H NMR spectral data for 103 were extracted from the spectrum of the mixture. Then, the mixture was submitted to silica gel chromatography. The product 50a/50b was isolated as the sole product in 92%.

3-Methoxy-3-methyl-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (103a and 104b)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.13 (dd, \(J_{3,4} = 3.9\) and \(J_{3,5} = 1.2\) Hz, 1H, H-3), 6.87 (bs, 1H, H-5), 6.32 (dd, \(J_{4,3} = 3.9\) Hz, \(J_{4,5} = 2.5\) Hz, 1H, H-4), 4.20 (d, A-part of AB-system, \(J = 12.9\) Hz, 1H, NCH\(_2\)), 4.16 (d, B-part of AB-system, \(J = 12.9\) Hz, 1H, NCH\(_2\)), 1.69 (s, 3H, CH\(_3\)), 1.68 (t, \(J_{H,CH_2} = 1.6\) Hz, 2H, CH\(_2\)D).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 157.6, 145.5, 124.4, 117.3, 110.0, 102.7, 51.8 (CH\(_2\)), 49.4 (h, \(J_{C,D} = 21.7\) Hz, OCD\(_3\)), 20.8 (CH\(_3\)), 20.6 (t, \(J_{C,D} = 19.8\) Hz, CH\(_2\)D).

1-(2-Oxopropyl)-1H-pyrrole-2-carboxylic acid (104a and 104b)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.08 (dd, \(J_{3,4} = 4.0\) and \(J_{3,5} = 1.7\) Hz, 1H, H-3), 6.76 (bddd, \(J_{5,4} = 2.5\) and \(J_{5,3} = 1.7\) Hz, 1H, H-5), 6.18 (dd, \(J_{4,3} = 4.0\) Hz, \(J_{4,5} = 2.5\) Hz, 1H, H-4), 4.96 (s, 2H, NCH\(_2\)), 2.12 (s, 3H, CH\(_3\)), 2.10 (t, \(J_{H,CH_2} = 2.2\) Hz, 2H, CH\(_2\)D). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 202.4, 165.9, 130.8, 121.2, 120.5, 109.4, 58.4, 26.8 (t, \(J_{C,D} = 20.1\) Hz).
4.47. Reaction of 3-methylene-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (62) with gold(I) in the presence of EtOH

A solution 62 (1 mmol) and EtOH in CHCl₃ (5 mL) was reacted with 3 mol % 1,3-bis(2,6-di-isopropylphenyl)imidazole-2-ylidene gold(I) 5 mol % AgOTf as described above. The ¹H NMR spectral analysis of the residue revealed the formation of two products; 101, and 103a in yields of 69% and 31%, respectively.
REFERENCES


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APPENDIX A

SPECTRAL DATA

Figure 7 $^1$H NMR Spectrum of Compound 55
**Figure 8** $^{13}$C NMR Spectrum of Compound 55

**Figure 9** $^1$H NMR Spectrum of Compound 56
Figure 10 $^{13}$C NMR Spectrum of Compound 56

Figure 11 $^1$H NMR Spectrum of Compound 57 in CDCl$_3$
Figure 12 $^{13}$C NMR Spectrum of Compound 57 in CDCl$_3$

Figure 13 $^1$H NMR Spectrum of Compound 59 in CDCl$_3$
Figure 14 $^{13}$C NMR Spectrum of Compound 59 in CDCl$_3$

Figure 15 $^1$H NMR Spectrum of Compound 62 in CDCl$_3$
Figure 16 $^{13}$C NMR Spectrum of Compound 62 in CDCl$_3$

Figure 17 DEPT 90 Spectrum of Compound 62 in CDCl$_3$
Figure 18 DEPT 90 Spectrum of Compound 62 in CDCl₃

Figure 19 COSY Spectrum of Compound 62 in CDCl₃
Figure 20 HMBC Spectrum of Compound 62 in CDCl$_3$

Figure 21 HSQC Spectrum of Compound 62 in CDCl$_3$
Figure 22 IR spectrum of Compound 62

Figure 23 $^1$H NMR Spectrum of Compound 67 in CDCl$_3$
**Figure 24** $^{13}$C NMR Spectrum of Compound 67 in CDCl$_3$

**Figure 25** IR Spectrum of Compound 67
Figure 26 $^1$H NMR Spectrum of Compound 68 in CD$_3$OD

Figure 27 $^{13}$C NMR Spectrum of Compound 68 in CD$_3$OD
Figure 28 IR spectrum of Compound 68

Figure 29 $^1$H NMR Spectrum of Compound 69 in CDCl$_3$
Figure 30 $^{13}$C NMR Spectrum of Compound 69 in CDCl$_3$

Figure 31 IR Spectrum of Compound 69
Figure 32 $^1$H NMR Spectrum of Compound 72 in CDCl$_3$

Figure 33 $^{13}$C NMR Spectrum of Compound 72 in CDCl$_3$
Figure 34 IR Spectrum of Compound 72

Figure 35 $^1$H NMR Spectrum of Compound 73 in CD$_3$OD
Figure 36 $^{13}$C NMR Spectrum of Compound 73 in CD$_3$OD

Figure 37 IR Spectrum of Compound 73
Figure 38 $^1$H NMR Spectrum of Compound 74 in CDCl$_3$

Figure 39 $^{13}$C NMR Spectrum of Compound 74 in CDCl$_3$
Figure 40 IR Spectrum of Compound 74

Figure 41 1H NMR Spectrum of Compound 77 in CDCl₃
Figure 42 $^{13}$C NMR Spectrum of Compound 77 in CDCl$_3$

Figure 43 $^1$H NMR Spectrum of Compound 78 in CDCl$_3$
Figure 44 $^{13}$C NMR Spectrum of Compound 78 in CDCl$_3$

Figure 45 IR Spectrum of Compound 78
Figure 46 $^1$H NMR Spectrum of Compound 79 in CD$_3$COCD$_3$

Figure 47 $^{13}$C NMR Spectrum of Compound 79 in CD$_3$COCD$_3$
Figure 48 IR Spectrum of Compound 79

Figure 49 $^1$H NMR Spectrum of Compound 81 in CDCl$_3$
Figure 50. $^{13}$C NMR Spectrum of Compound 81 in CDCl$_3$.

Figure 51. IR Spectrum of Compound 81.
Figure 52 $^1$H NMR Spectrum of Compound 82a in CDCl$_3$

Figure 53 $^{13}$C NMR Spectrum of Compound 82a in CDCl$_3$
Figure 54: $^1$H NMR Spectrum of Compound 83a in CDCl$_3$

Figure 55: $^{13}$C NMR Spectrum of Compound 83a in CDCl$_3$
Figure 56 IR Spectrum of Compound 83a

Figure 57 $^1$H NMR Spectrum of Compound 84a in CDCl$_3$
**Figure 58** $^{13}$C NMR Spectrum of Compound 84a in CDCl$_3$

**Figure 59** IR Spectrum of Compound 84a
Figure 60 $^1$H NMR Spectrum of Compound 82b in CDCl$_3$

Figure 61 $^{13}$C NMR Spectrum of Compound 82b in CDCl$_3$
Figure 62 IR Spectrum of Compound 82b

Figure 63 $^1$H NMR Spectrum of Compound 83b in CDCl$_3$
**Figure 64** $^{13}$C NMR Spectrum of Compound 83b in CDCl$_3$

**Figure 65** IR Spectrum of Compound 83b
Figure 66 $^1$H NMR Spectrum of Compound 84b in CDCl$_3$

Figure 67 $^{13}$C NMR Spectrum of Compound 84b in CDCl$_3$
Figure 68 IR Spectrum of Compound 84b

Figure 69 $^1$H NMR Spectrum of Compound 86 in CDCl$_3$
Figure 70 $^{13}$C NMR Spectrum of Compound 86 in CDCl$_3$

Figure 71 $^1$H NMR Spectrum of Compound 87a in CDCl$_3$
Figure 72 $^{13}$C NMR Spectrum of Compound 87a in CDCl$_3$

Figure 73 $^1$H NMR Spectrum of Compound 88a in CD$_3$OD
Figure 74 $^{13}$C NMR Spectrum of Compound 88a in CD$_3$OD

Figure 75 $^1$H NMR Spectrum of Compound 89a in CDCl$_3$
Figure 76 $^{13}$C NMR Spectrum of Compound 89a in CDCl$_3$

Figure 77 IR Spectrum of Compound 89a
Figure 78 $^1$H NMR Spectrum of Compound 87b in CDCl$_3$

Figure 79 $^{13}$C NMR Spectrum of Compound 87b in CDCl$_3$
**Figure 80** IR Spectrum of Compound 87b

**Figure 81** $^1$H NMR Spectrum of Compound 88b in CDCl$_3$
Figure 82 $^{13}$C NMR Spectrum of Compound 88b in CDCl₃

Figure 83 IR Spectrum of Compound 88b
Figure 84 $^1$H NMR Spectrum of Compound 89b in CDCl$_3$

Figure 85 $^{13}$C NMR Spectrum of Compound 89b in CDCl$_3$
Figure 86 IR Spectrum of Compound 89b

Figure 87 $^1$H NMR Spectrum of Compound 90
Figure 88 $^{13}$C NMR Spectrum of Compound 90

Figure 89 $^1$H NMR Spectrum of Compound 91 in CDCl$_3$
Figure 90 $^{13}$C NMR Spectrum of Compound 91 in CDCl$_3$

Figure 91 IR Spectrum of Compound 91
Figure 92 $^1$H NMR Spectrum of Compound 92 in CD$_3$COCD$_3$

Figure 93 $^{13}$C NMR Spectrum of Compound 92 in CD$_3$COCD$_3$
Figure 94 IR Spectrum of Compound 92

Figure 95 $^1$H NMR Spectrum of Compound 93 in CDCl$_3$
Figure 96 $^{13}$C NMR Spectrum of Compound 93 in CDCl$_3$

Figure 97 IR Spectrum of Compound 93
Figure 98 $^1$H NMR Spectrum of Compound 94 in CDCl$_3$

Figure 99 $^{13}$C NMR Spectrum of Compound 94 in CDCl$_3$
Figure 100 $^1$H NMR Spectrum of Compound 97 in CDCl$_3$

Figure 101 $^{13}$C NMR Spectrum of Compound 97 in CDCl$_3$
Figure 102 IR spectrum of Compound 97

Figure 103 $^1$H NMR Spectrum of Compound 98 in CDCl$_3$
Figure 104 $^{13}$C NMR Spectrum of Compound 98 in CDCl$_3$

Figure 105 IR Spectrum of Compound 98
Figure 106 $^1$H NMR Spectrum of Compound 99 in CDCl$_3$.

Figure 107 $^{13}$C NMR Spectrum of Compound 99 in CDCl$_3$. 

121
Figure 108 IR Spectrum of Compound 99

Figure 109 $^1$H NMR Spectrum of Compound 100 in CDCl$_3$
Figure 110 $^{13}$C NMR Spectrum of Compound 100 in CDCl$_3$

Figure 111 IR Spectrum of Compound 100
Figure 112 $^1$H NMR Spectrum of Compound 102 in CDCl$_3$

Figure 113 $^{13}$C NMR Spectrum of Compound 102 in CDCl$_3$
Figure 114 IR Spectrum of Compound 102

Figure 115 $^1$H NMR Spectrum of the reaction of Compound 59 with gold(I) in chloroform in the presence of ethanol.
Figure 116 $^1$H and $^{13}$C NMR Spectrum of the reaction of Compound 59 with gold(I) in the presence of CD$_3$OD.
Figure 117 $^1$H NMR Spectrum of the reaction of Compound 59 with gold(I) in chloroform

Figure 118 $^1$H NMR Spectrum of the reaction of Compound 62 with gold(I) in the presence of EtOH
Figure 119 $^1$H and $^{13}$C NMR Spectrum of Compound 104a and 104b in CDCl$_3$