A new protocol for pyrrole synthesis by a combination of ring-closing metathesis and \textit{in situ} oxidative aromatization

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Abstract
A new and straightforward protocol for pyrrole synthesis is developed by a unique one-pot combination of ring-closing metathesis and \textit{in situ} oxidative aromatization by a quinone.

\textbf{Keywords:} Pyrrole synthesis, ring-closing metathesis, oxidative aromatization, transfer hydrogenation

Introduction
The occurrence of the pyrrole nucleus in many natural and synthetic biologically active compounds continues to contribute to the development of new synthetic methodologies towards this important heterocycle.$^1$ Recently we reported on the development of a new catalytic tandem comprising the second generation Grubbs’ catalyst and RuCl$_3 \times$ H$_2$O.$^2$ This catalytic couple is able to convert diallylamines 1 into the corresponding pyrroles 2 (Scheme 1). A weak point of this method is the long reaction time (over 12h for complete conversion). In this paper we report an improved methodology using a strong hydrogen acceptor (tetrachloro-1,4-benzoquinone) to speed up the aromatization process.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme1.png}
\end{center}

\textit{Scheme 1.} Pyrrole synthesis using the second generation Grubbs’ catalyst in combination with RuCl$_3 \times$ H$_2$O.
Results and Discussion

In an effort to speed up the dehydrogenation process, the possibility of adding a strong hydrogen acceptor was explored. As a first choice, 1 equivalent of DDQ 3 (Figure 1) was added to the reaction mixture since it is known that pyrrolines can be converted to the corresponding pyrroles by DDQ. Analyzing our first results, no ring-closing metathesis could be observed, suggesting that the second generation Grubbs’ catalyst and DDQ are incompatible. Literature study however, revealed that a combination of ring-closing metathesis and oxidative aromatization was recently reported as a new protocol for benzoannulation. Although this is a one-pot reaction, the DDQ was added after metathesis, thus avoiding catalyst inactivation. In a quest for quinones which do not react with the second generation Grubbs’ catalyst, our attention turned to tetramethyl-1,4-benzoquinone 4 (duroquinone) and tetrachloro-1,4-benzoquinone 5 (chloranil) as strong hydrogen acceptors (Figure 1). These quinones have been evaluated before as hydrogen acceptor in combination with RuCl3 × H2O.

![Figure 1](image_url)

Figure 1. The evaluated different hydrogen acceptors: DDQ (3), duroquinone (4) and chloranil (5).

Upon evaluation of 4, we were pleased to find that ring-closing metathesis was not inhibited, however, the rate of aromatization was not significantly influenced. Finally, adding tetrachloro-1,4-benzoquinone together with the second generation Grubbs’ catalyst resulted in the complete conversion of the diallylamine to the corresponding pyrrole within 2 hours. It was even observed that RuCl3 × H2O is not necessary in this conversion. This might suggest that either the metathesis catalyst, or decomposition compounds thereof, catalyze the hydrogen transfer or that hydrogen is directly transferred from donor to acceptor. A possible mechanism for this reaction sequence (in accordance to the mechanism of the reaction of Hantzsch esters to pyridines) is outlined in Scheme 2. After ring-closing metathesis, the electron lone pair on N of the intermediate 3-pyrroline 6 initiates the aromatization by expelling a hydride which immediately reacts with 5. This assumption is consistent with the observation that diallylamines with strong electron-withdrawing groups on N do not aromatize. Possibly both donor and acceptor are coordinated to the transition metal center in this step, thus facilitating the H-transfer. In the next step, the intermediate iminium-ion 7 loses another proton and aromatizes to the pyrrole 2. In a final step, a proton-shift converts 9 to hydroquinone 10.
Scheme 2. Proposed mechanism for ring-closing metathesis with *in situ* oxidative aromatization.

Following this methodology, a number of pyrroles were synthesized with very high conversion compared to the RuCl₃ system published before (Table 1).

**Table 1.** Synthesis of different pyrroles by a combination of second generation Grubbs’ catalyst and tetrachloro-1,4-benzoquinone starting from diallylamines of type 1

<table>
<thead>
<tr>
<th>Entry No.</th>
<th>R¹</th>
<th>R²</th>
<th>Conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>H</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>CH₃</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>CH₂morpholine</td>
<td>90&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>CH₂COOMe</td>
<td>H</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>CH₂P(O)(OEt)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>o-methoxyPh</td>
<td>H</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>Cl</td>
<td>0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by the <sup>1</sup>H-NMR spectrum of the crude reaction mixture. <sup>b</sup>The pyrrole broke down on the silica column during purification. <sup>c</sup>Only dimer could be isolated.

The yields of the purification of the pyrroles were previously described and a significant drop in yield is observed during flash chromatography (usually around 20%).<sup>2</sup>

For the moment the main weakness of this methodology is the activity of the metathesis catalyst. Highly substituted pyrroles for example are for the moment still out of reach. This is exemplified by entry 7 where the attempted synthesis of a 3-chloro substituted pyrrole failed, only dimer could be isolated from the reaction mixture.

**Conclusions**

The combination of the second generation Grubbs’ catalyst and chloranil (tetrachloro-1,4-benzoquinone) provides an easy way to convert diallylamines to the corresponding pyrroles. It
also proves that ring-closing metathesis can be performed in the presence of a quinone which opens the way to the one-pot synthesis of other aromatic systems.

**Experimental Section**

**General Procedures.** All $^1$H-NMR, $^{13}$C-NMR and $^{31}$P-NMR spectra were recorded on a JEOL JNM-ECP 300-spectrometer. The purity was checked by quantitative GC analysis (Agilent 6890 Series. Phase EC-5, length 30m, ID 0.25mm, film thickness 0.25µm, carrier gas N$_2$, detector gas H$_2$). All mass spectra were recorded by GC-MS coupling. A Hewlett-Packard 6890 GC Plus (carrier gas He, 1.2 ml min$^{-1}$) was used coupled with a HP 5973 MSD (Mass Selective Detector-Quadrupole type, ionization EI 70eV), equipped with a CIS-4 PTV (Programmed Temperature Vaporization) injector (Gertsel), and a HP5-MS capillary column (30 x 0.25mm i.d.; coating thickness 0.25 µm).

**General procedure for pyrrole synthesis**

In a dry reaction tube, 50 mg of diallylamine is weighed and dissolved in 1,2-dichloroethane (0.05 M). To this solution, 5 mol% of Grubbs’ second generation catalyst and 0.75 equivalents of tetrachloro-1,4-benzoquinone are added. The reaction tube is sealed and placed in an oil bath at 70-75°C. After 1 h, the tube is removed from the oil bath, opened and 5 mol% of Grubbs’ second generation catalyst and 0.75 equivalents of tetrachloro-1,4-benzoquinone are added for a second time. The tube is sealed and placed back in the oil bath for an additional hour. Afterwards the solvent is removed in vacuo and a $^1$H-NMR spectrum is taken to check the conversion. The crude pyrrole is coated on silica-gel and purified by flash-chromatography (with an appropriate mixture of hexanes-ethyl acetate).

**1-Benzyl-$^1$H-pyrrole** entry 1.

$^1$H NMR (300 MHz, CDCl$_3$) δ: 5.07 (2H, s, CH$_2$Ph), 6.19 (2H, t, J= 2.1 Hz, HCCH), 6.69 (2H, t, J= 2.1 Hz, HCNCH), 7.09-7.40 (5H, m, Ph). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 53.41 (CH$_2$Ph), 108.58 (HCCH), 121.25 (HCNCH), 127.09 (CH$_{arom}$), 127.73 (CH$_{arom}$), 128.81 (CH$_{arom}$), 138.26 (C$_{arom}$). IR (cm$^{-1}$) $v_{max}$: 1683 (br). MS: m/z (%): 157 (M$^+$, 65), 91 (100), 65 (13).

**1-Benzyl-3-methyl-$^1$H-pyrrole** entry 2.

$^1$H NMR (300 MHz, CDCl$_3$) δ: 2.10 (3H, s, CH$_3$), 4.98 (2H, s, CH$_2$Ph), 6.00 (1H, s, CH), 6.44 (1H, s, CH), 6.58 (1H, s, CH), 7.21-7.36 (5H, m, Ph). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 12.09 (CH$_3$), 53.34 (CH$_2$Ph), 109.74 (HC), 116.29 (C$_q$pyrrole), 119.25 (HCN), 121.10 (HCN), 127.15 (CH$_{arom}$), 127.65 (CH$_{arom}$), 128.78 (CH$_{arom}$), 138.51 (C$_{arom}$). IR (cm$^{-1}$) $v_{max}$: 1498, 1454). MS: m/z (%): 171 (M$^+$, 74), 170 (18), 92 (10), 91 (100), 65 (13).

**Methyl $^1$H-pyrrol-1-yl acetate** entry 4.

$^1$H NMR (300 MHz, CDCl$_3$) δ: 3.76 (3H, s, COOMe), 4.65 (2H, s, CH$_2$), 6.21 (2H, t, J= 2.1 Hz, HCCH), 6.67 (2H, t, J= 2.1 Hz, HCNCH). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 50.81 (CH$_3$), 52.62 (CH$_2$), 109.22 (HC), 121.88 (HCN), 169.33 (C=O). IR (cm$^{-1}$) $v_{max}$: 1755 (br, C=O). MS: m/z (%): 139 (M$^+$, 60), 80 (100), 53 (17).
Diethyl 1H-pyrrol-1-ylmethylphosphonate\(^\text{10}\) (entry 5). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 1.26 (3H, d, J= 6.6 Hz, CH\(_3\)), 1.27 (3H, d, J= 6.6 Hz, CH\(_3\)), 3.96-4.09 (4H, m, P(O)(OCH\(_2\)CH\(_3\))\(_2\)), 4.26 (2H, d, J= 11.6 Hz, NCH\(_2\)P), 6.17 (2H, dt, J= 0.8 Hz, J= 2.2 Hz, HCCH), 6.72 (2H, dt, J= 0.6 Hz, J= 2.2 Hz, HCNCH). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 16.49 (d, J= 5.8 Hz, CH\(_3\)), 45.93 (d, J= 158.1 Hz, NCH\(_2\)P), 62.88 (d, J= 6.9 Hz, P(O)(OCH\(_2\)CH\(_3\))\(_2\)), 109.12 (HCCH), 121.97 (HCNCH). \(^{31}\)P NMR (109 MHz, CDCl\(_3\)) \(\delta\): 19.99. IR (cm\(^{-1}\)) \(\nu\)\(_{\text{max}}\): 1497. MS: m/z (%): 217 (M\(^+\), 54), 202 (17), 174 (13), 107 (29), 81 (33), 80 (100), 53 (15).

1-(2-Methoxyphenyl)1H-pyrrole\(^\text{11}\) (entry 6). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 3.83 (3H, s, CH\(_3\)), 6.31 (2H, t, J= 2.2 Hz, HCCH), 6.98 (2H, t, J= 2.2 Hz, HCNCH), 6.99-7.04 (2H, m, CH\(_\text{arom.}\)), 7.22-7.30 (2H, m, CH\(_\text{arom.}\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 55.91 (OCH\(_3\)), 108.86 (HCCH), 112.41 (CH\(_\text{arom.}\)), 121.01 (CH\(_\text{arom.}\)), 122.17 (HCNCH), 125.86 (CH\(_\text{arom.}\)), 127.56 (CH\(_\text{arom.}\)), 130.38 (CH\(_\text{arom.}\)), 132.83 (CH\(_\text{arom.}\)). IR (cm\(^{-1}\)) \(\nu\)\(_{\text{max}}\): 1512, 1598. MS: m/z (%): 173 (M\(^+\), 100), 172 (46), 158 (13), 144 (14), 130 (13), 115 (15), 77 (14). Commercially available (Ambinter Screening Library).

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