OXIDATION OF PYRROLE-2-CARBOXYLATES WITH o-CHLORANIL
AND ITS SYNTHETIC APPLICATION

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Abstract – t-Butyl 3,4-dialkyl-1H-pyrrole-2-carboxylates were oxidized with o-chloranil in the presence of MeOH to afford the corresponding 5-methoxypyrrolin-2-one derivatives. The resulting 5-methoxypyrrolin-2-one was reacted with various nucleophiles under acidic conditions to afford the functionalized pyrrolinone derivatives in good yields.
First, \( t \)-butyl 3-(2-allyloxy carbonyl ethyl)-4-methyl-1\( H \)-pyrrole-2-carboxylate (1a), which is a useful synthon for the B- and C-ring components of bilin chromophores, was treated with 3 equiv. of \( p \)-chloranil in the presence of 10 equiv. of MeOH in CH\(_2\)Cl\(_2\). Although the reaction was carried out under refluxing for 5 d, oxidation did not proceed and 1a was recovered almost quantitatively. Since it is well-known that \( o \)-chloranil is a stronger electron acceptor than \( p \)-chloranil, o-chloranil was then used as an oxidant. When 1a was treated with 3 equiv. of \( o \)-chloranil in the presence of 10 equiv. of MeOH in CH\(_2\)Cl\(_2\) at rt for 20 h, the pyrrole ring was oxidized to give a 5-methoxypyrrolino-2-one derivative 2a in 51\% yield (Table 1, Entry 1). Decreasing the amount of MeOH slightly improved the chemical yield (Entries 2–4). In the presence of 2 equiv. of MeOH, the pyrrolinone 2a was obtained in enhanced 61\% yield (Entry 4). Variation of the amount of \( o \)-chloranil to 2 or 4 equiv. did not improve the chemical yield (Entries 5 and 6).

**Table 1. Oxidation of \( t \)-butyl pyrrole-2-carboxylates 1 with \( o \)-chloranil**

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>1</th>
<th>( m )</th>
<th>( n )</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>CH(_3)</td>
<td>((CH_2)_2CO_2)Allyl</td>
<td>a</td>
<td>3</td>
<td>10</td>
<td>51</td>
</tr>
<tr>
<td>2(^a)</td>
<td>3</td>
<td>5</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3(^a)</td>
<td>3</td>
<td>3</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4(^a)</td>
<td>3</td>
<td>2</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5(^a)</td>
<td>2</td>
<td>2</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6(^a)</td>
<td>4</td>
<td>2</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7(^a)</td>
<td>CH(_3)</td>
<td>CH(_3)CH(_2)</td>
<td>b</td>
<td>3</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>8(^a)</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>c</td>
<td>3</td>
<td>2</td>
<td>82</td>
</tr>
<tr>
<td>9(^b)</td>
<td>CH(_2)CH(_3)</td>
<td>CH(_2)CH(_3)</td>
<td>d</td>
<td>3</td>
<td>2</td>
<td>78</td>
</tr>
</tbody>
</table>

\(^a\)Reaction was carried out on a 0.3 mmol scale of 1 in 15 ml of CH\(_2\)Cl\(_2\).

\(^b\)Reaction was carried out on a 3.0 mmol scale of 1 in 150 ml of CH\(_2\)Cl\(_2\).
The oxidation of other pyrroles with o-chloranil was examined. t-Butyl 3-ethyl-4-methyl-1H-pyrrole-2-carboxylate (1b) afforded the pyrrolinone 2b in 80% yield (Entry 7). In the cases of 3,4-dimethylpyrrole 1c and 3,4-diethylpyrrole 1d, the oxidation also proceeded smoothly to give the corresponding 5-methoxypyrrolin-2-ones 2c and 2d in high yields (Entries 8 and 9). In order to gain an insight into how the reaction proceeds, the oxidation of 1d was monitored by 1H and 13C NMR in CDCl₃. In 1H NMR spectra, the generation of 2d was confirmed after 2 h and the most of 1d was converted into 2d after 20 h. However, any other substrates were not clearly detected especially in the region of aliphatic protons. In 13C NMR at 20 h, the signals assigned to 2d and 3,4,5,6-tetrachlorocatechol (3) were confirmed and o-chloranil scarcely remained. Two or three kinds of unknown aromatic compounds were further observed downfield below 100 ppm. In the upfield region around 0–20 ppm, two sets of ethyl group corresponding to 2d were mainly observed accompanied with a few small peaks. Ultimately, any useful information about reaction intermediates was not acquired based on the NMR observation.

Although the precise reaction mechanism is not yet clear, radical mechanism might be ruled out: Addition of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) (3 equiv.) in the reaction of 1d as a radical inhibitor did not affect the oxidation resulting in the formation of 2d in 79% yield, while TEMPO itself could not oxidize 1d. Based on the facts described above, a possible mechanism is proposed as shown in Scheme 2. The hydride abstraction from pyrrole by o-chloranil followed by nucleophilic addition of 2 equiv. of MeOH affords 4. Further oxidation of 4 by o-chloranil resulted in the formation of 5, which is hydrolyzed to afford 2. Although H₂O was not added into the reaction mixture on purpose to hydrolyze 5, irrupting moisture might be sufficient.

The oxidized pyrrolinones 2 obtained above are versatile synthetic intermediates (Scheme 3). For example, methoxy group in 2d was substituted with a tosyl group by treating with p-toluenesulfinic acid (TsH) in the presence of AcOH to give 6. The t-butoxycarbonyl group was directly removed by treating with excess amount of TsH to afford 7, which was employed to the Wittig-like coupling reaction developed by us with 8 to give the coupling product 9. A series of transformations from 1d to 9 means that AB- and CD-ring components of bilin chromophores could be synthesized from ester-substituted pyrroles without preparation of tosyl pyrroles, which were required in our previous methods. Direct C-C bond formation was examined by the treatment with allytrimethylsilane in the presence of trifluoroacetic acid. To our surprise, an envisaged allylated pyrrolinone 11 was not produced but a reduced pyrrole 10 was isolated in 74% yield. This unprecedented transformation might be a useful method for the reduction at congested carbon center.
Scheme 2

Scheme 3
As described above, the mild oxidation of \( t \)-butyl 3,4-dialkyl-1\( H \)-pyrrole-2-carboxylates was achieved with \( o \)-chloranil in the presence of MeOH to give the corresponding 5-methoxypyrrolin-2-one derivatives in good yields. Further transformation of the oxidized products to other synthetically useful derivatives was also performed. The present methods would be useful for the preparation of various types of pyrrolinones and applicable to the synthesis of bilin chromophores of phytochromes including their sterically locked derivatives.\(^1\)\(^2\)

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Dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday.

REFERENCES AND NOTES

7. A representative procedure for the oxidation of 1d (Table 1, Entry 9): To a solution of \( o \)-chloranil (2.22 g, 9 mmol) in CH\(_2\)Cl\(_2\) (120 mL), MeOH (0.24 mL, 6 mmol) and a solution of 1d (670 mg, 3 mmol) in CH\(_2\)Cl\(_2\) (30 mL) were successively added at rt under a nitrogen atmosphere. After stirring for 20 h at rt, the reaction mixture was passed through basic aluminium oxide (Merck 1076) to
remove the catechol 3 and the solvent was evaporated under reduced pressure. The residue was separated by flash column chromatography (basic aluminium oxide (Merck 1076), hexane/AcOEt = 2/1, v/v) to give 2d (641 mg, 78% yield) as an oil. IR (neat) 3225, 3092, 2976, 2937, 2878, 1736, 1709, 1460, 1394, 1369, 1287, 1256, 1161, 1117, 1061, 1002, 844, 824, 788 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) \(\delta = 1.11\) (t, 3H, \(J = 7.3\) Hz), 1.16 (t, 3H, \(J = 7.8\) Hz), 1.46 (s, 9H), 2.31 (q, 2H, \(J = 7.3\) Hz), 2.36 (q, 2H, \(J = 7.8\) Hz), 3.17 (s, 3H), 6.24 (br, 1H) ppm. \(^13\)C NMR (CDCl\(_3\)) \(\delta = 12.1, 12.8, 16.4, 18.1, 27.2, 50.0, 82.7, 91.2, 137.2, 152.1, 166.4, 173.9\) ppm. HRMS (FAB\(^+\)) (M\(^+\) + 1). Found: \(m/z\) 270.17018. Calcd for C\(_{14}\)H\(_{24}\)NO\(_4\): 270.17053.

8. It was confirmed that the oxidation of 1d proceeded in CHCl\(_3\) under the same conditions as those of Entry 9 in Table 1 except the solvent and the scale (0.3 mmol scale of 1d in 15 ml of CHCl\(_3\)) to give 2d in 74% yield.


10. A control experiment of oxidation starting from 1a in the presence of MS 3A corresponding to Entry 4 in Table 1 afforded 2a in 23% yield accompanied with 20% of 5a and 30% of 1a was recovered. This fact might support the mechanism shown in Scheme 2. 2a: An oil. IR (neat) 3325, 2979, 1677, 1596, 1455, 1369, 1251, 1165, 1083, 1001, 844, 812 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) \(\delta = 1.48\) (s, 9H), 1.88 (s, 3H), 2.55 – 2.77 (m, 4H), 3.18 (s, 3H), 4.56 (d, 2H, \(J = 5.9\) Hz), 5.20 (dd, 1H, \(J = 10.5, 1.5\) Hz), 5.28 (dd, 1H, \(J = 17.4, 1.5\) Hz), 5.90 (ddt, 1H, \(J = 17.4, 10.5, 5.9\) Hz), 6.47 (br, 1H) ppm. HRMS (FAB\(^+\)) (M\(^+\) + 1). Found: \(m/z\) 340.17542. Calcd for C\(_{17}\)H\(_{26}\)NO\(_6\): 340.17601.

5a: An oil. IR (neat) 2979, 2944, 1737, 1677, 1596, 1455, 1369, 1251, 1165, 1083, 1001, 844, 812 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) \(\delta = 1.45\) (s, 9H), 1.83 (s, 3H), 2.53 – 2.72 (m, 4H), 3.26 (s, 3H), 3.98 (s, 3H), 4.58 (d, 2H, \(J = 6.0\) Hz), 5.24 (dd, 1H, \(J = 10.2, 1.6\) Hz), 5.31 (dd, 1H, \(J = 17.2, 1.6\) Hz), 5.93 (ddt, 1H, \(J = 17.2, 10.2, 6.0\) Hz) ppm. HRMS (FAB\(^+\)) (M\(^+\) + 1). Found: \(m/z\) 354.19234. Calcd for C\(_{18}\)H\(_{28}\)NO\(_6\): 354.19166.

11. The structure of 5-tosylpyrrolin-2-one 6 was determined by X-ray crystallographic analysis of its single crystal: Single crystals of 6 were obtained by recrystallization from toluene/hexane. Crystal data: C\(_{20}\)H\(_{27}\)NO\(_5\)S, FW. 393.50, monoclinic, P2\(_1\)/a, \(a = 20.010(2), b = 8.5655(8), c = 24.084(3)\) Å, \(V = 4047.0(7)\) Å\(^3\), \(\beta = 101.364^\circ\), \(Z = 8\). \(D_{\text{calc}} = 1.292\) g/cm\(^3\). \(R = 0.049\) (\(R_w = 0.058\)) for 5245 reflections with \(I > 3.00\sigma(I)\) and 487 variable parameters.
