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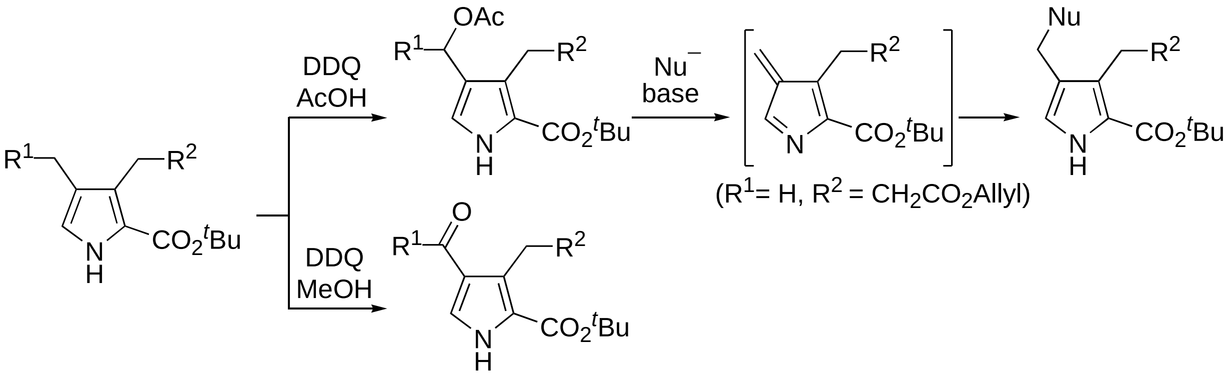
OXIDATION OF PYRROLE-2-CARBOXYLATES WITH *o*-CHLORANIL AND ITS SYNTHETIC APPLICATION

Ryo Sakata, Ryoji Iwamoto, Shuhei Fujinami, Yutaka Ukaji,* and Katsuhiko Inomata*

Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan; E-mail: inomata@se.kanazawa-u.ac.jp

Abstract – *t*-Butyl 3,4-dialkyl-1*H*-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.

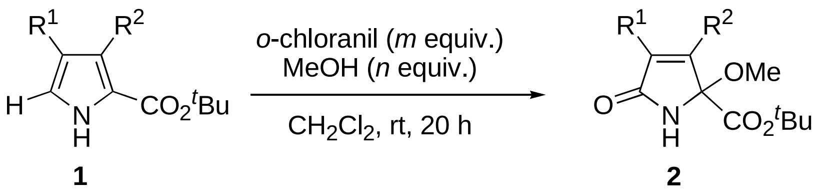
Toward elucidation of the structure and function of the linear tetrapyrrole (bilin) chromophores in phytochromes, we have succeeded in synthesizing phytochromobilin (PΦB), phycocyanobilin (PCB), modified PCBs, biliverdin (BV) and its analogs including sterically locked derivatives in free acid forms by developing efficient methods for the preparation of each pyrrole ring and a new coupling reaction between them.[1,2] In order to synthesize different types of locked chromophores, it was necessary to prepare various pyrrole and pyrrolinone derivatives bearing a wide variety of functional groups.[2] In our previous syntheses,[1] pyrrole rings with an electron withdrawing group were constructed by a modified Barton reaction starting from aldehydes, 1-nitroalkanes, and isonitrile compounds.[3] The produced tosyl- and ester-substituted pyrroles were converted into A- or D-ring and B- or C-ring, respectively. It would be ideal for the synthesis of the locked bilin chromophores if the various types of pyrroles and the related pyrrolinones could be available from a common pyrrole by a simple manipulation. Recently we have developed a regioselective oxidation of the α-position of the C-4 substituents on *t*-butyl pyrrole-2-carboxylates with DDQ and the subsequent substitution reaction via azafulvene intermediates (Scheme 1).[4] Herein we describe an oxidation of *t*-butyl pyrrole-2-carboxylates with *o*-chloranil and its application toward the synthesis of various types of functionalized pyrrolinone derivatives.



Scheme 1

First, *t*-butyl 3-(2-allyloxycarbonylethyl)-4-methyl-1*H*-pyrrole-2-carboxylate (**1a**), which is a useful synthon for the B- and C-ring components of bilin chromophores,[1] was treated with 3 equiv. of *p*-chloranil in the presence of 10 equiv. of MeOH in CH_2Cl_2. Although the reaction was carried out under refluxing for 5 d, oxidation did not proceeded and **1a** was recovered almost quantitatively. Since it is well-known that *o*-chloranil is a stronger electron acceptor than *p*-chloranil,[5] *o*-chloranil was then used as an oxidant.[6] When **1a** was treated with 3 equiv. of *o*-chloranil in the presence of 10 equiv. of MeOH in CH_2Cl_2 at rt for 20 h, the pyrrole ring was oxidized to give a 5-methoxypyrrolin-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



Entry	R[1]	R[2]	1	*m*	*n*	Yield/%
1[a]	CH_3	$(CH_2)_2CO_2$Allyl	**a**	3	10	51
2[a]				3	5	58
3[a]				3	3	58
4[a]				3	2	61
5[a]				2	2	27
6[a]				4	2	57
7[a]	CH_3	CH_3CH_2	**b**	3	2	80
8[a]	CH_3	CH_3	**c**	3	2	82
9[b]	CH_3CH_2	CH_3CH_2	**d**	3	2	78

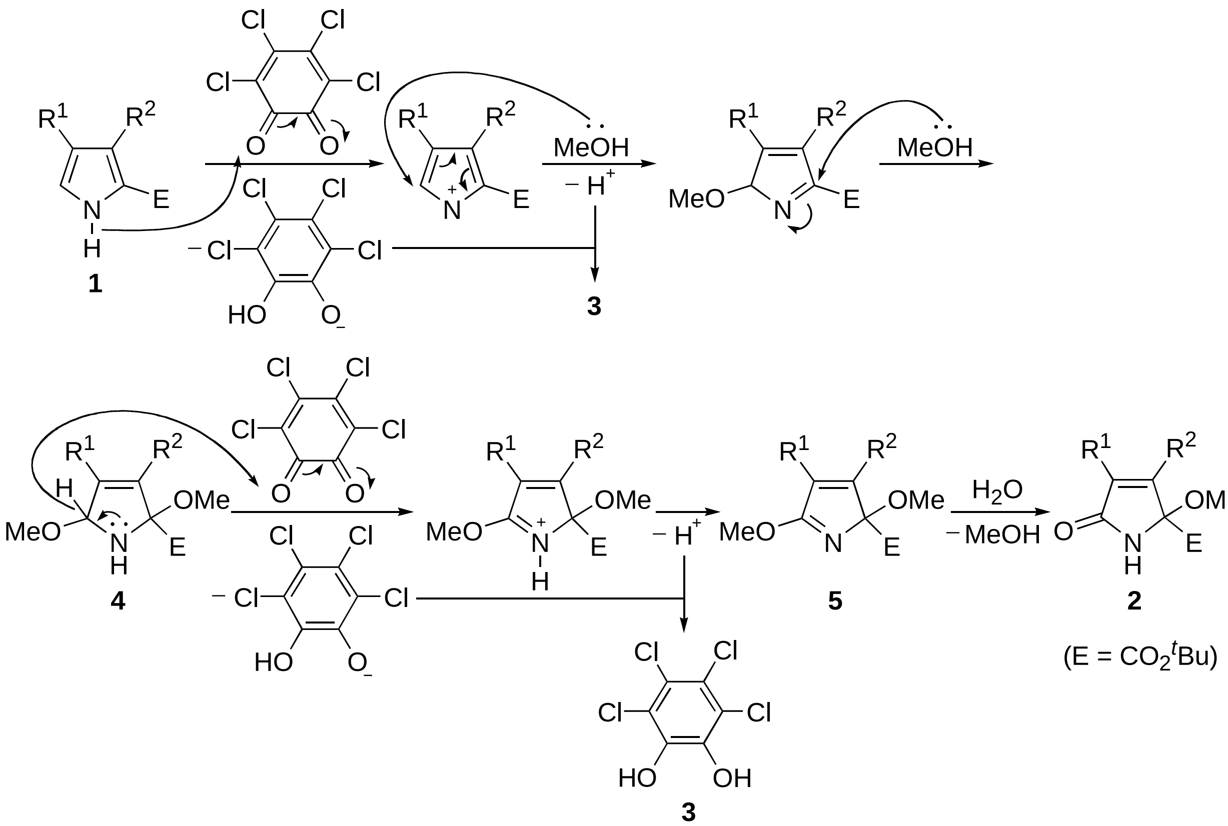
[a]Reaction was carried out on a 0.3 mmol scale of **1** in 15 ml of CH_2Cl_2.
[b]Reaction was carried out on a 3.0 mmol scale of **1** in 150 ml of CH_2Cl_2.

The oxidation of other pyrroles with *o*-chloranil was examined. *t*-Butyl 3-ethyl-4-methyl-1*H*-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).[7]

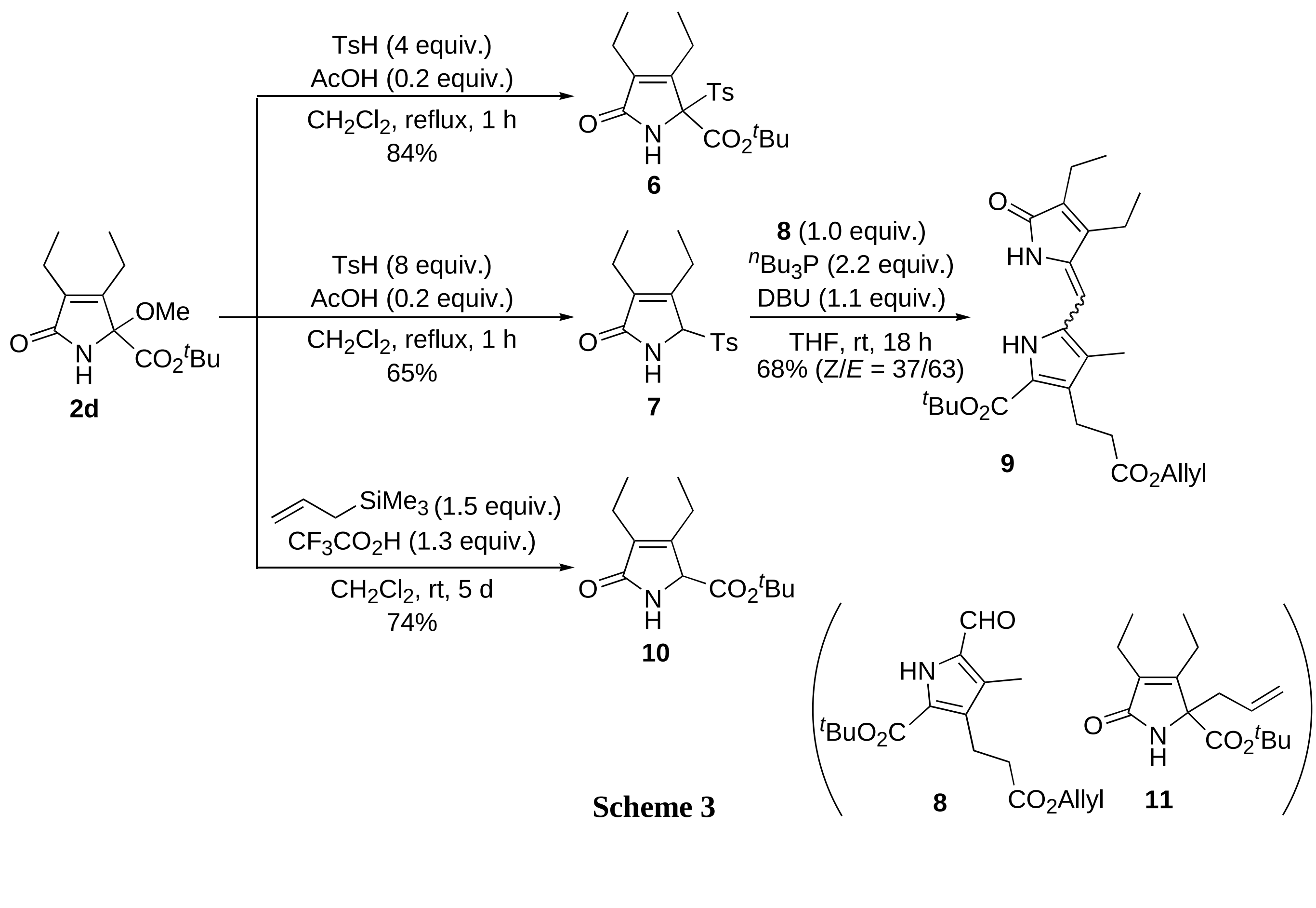
In order to gain an insight into how the reaction proceeds, the oxidation of **1d** was monitored by ^{1}H and ^{13}C NMR in $CDCl_3$.[8] In ^{1}H NMR spectra, the generation of **2d** was confirmed after 2 h and the most of **1d** was converted into **2d** after 20 h. However, any other substrates were not clearly detected especially in the region of aliphatic protons. In ^{13}C NMR at 20 h, the signals assigned to **2d** and 3,4,5,6-tetrachlorocatechol (**3**)[9] 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 H_2O was not added into the reaction mixture on purpose to hydrolyze **5**, irrupting moisture might be sufficient.[10]

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**.[11] 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**.[1,12] 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.[1] Direct C-C bond formation was examined by the treatment with allytrimethylsilane in the presence of trifluoroacetic acid.[13] To our surprise, an envisaged allylated pyrrolinone **11** was not produced but a reduced pyrroline **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.

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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_2Cl_2 (120 mL), MeOH (0.24 mL, 6 mmol) and a solution of **1d** (670 mg, 3 mmol) in CH_2Cl_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 ($CDCl_3$) δ = 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 ($CDCl_3$) δ = 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.
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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, 2935, 1733, 1713, 1455, 1370, 1255, 1170, 1112, 1079, 996, 840, 759 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 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, 1651, 1596, 1455, 1369, 1251, 1165, 1083, 1001, 844, 812 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 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: $C_{20}H_{27}NO_5S$, *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, β = 101.364°, Z = 8. D_{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.
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13. Allylation using allytrimethylsilane in the presence of $BF_3 \cdot OEt_2$ (2 equiv.) in CH_2Cl_2 at rt gave a complicated reaction mixture. Related allylation: see, X. Liu and J. K. Snyder, *J. Org. Chem*., 2008, **73**, 2935.