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Regioselective Oxidation of Pyrrole Derivatives with DDQ and Its Synthetic Application

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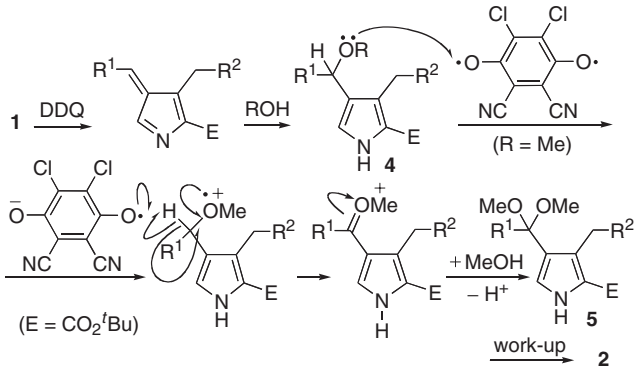
t-Butyl 4-alkyl-1*H*-pyrrole-2-carboxylates were oxidized with DDQ in the presence of MeOH at the α-position of the alkyl substituent at the C-4 position regioselectively to afford 4-acylpyrrole derivatives. On the other hand, treatment of the pyrroles with DDQ in the presence of AcOH furnished the corresponding 4-(1-acetoxyalkyl)pyrroles. The resulting 4-(acetoxymethyl)pyrrole reacted with various nucleophiles to afford the functionalized pyrrole derivatives in good yields.

We have been studying the total syntheses of natural and unnatural bilin chromophores of phytochromes,[1] and 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] During the course of syntheses of different types of locked chromophores, it was necessary to prepare various pyrroles that have arbitrary-length side chains and a wide variety of functional groups.[2] In the previous syntheses, the side chains and functional groups originated from aldehydes and/or nitro compounds through a modified Barton reaction. It would be ideal for the synthesis of locked chromophores if the various types of pyrroles could be available from a common pyrrole by simple manipulation. Herein we describe a regioselective oxidation of *t*-butyl 4-alkylpyrrole-2-carboxylates with DDQ[3] and its application toward the synthesis of various types of functionalized pyrroles.

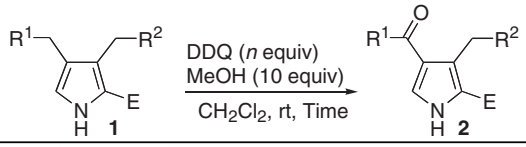
First, *t*-butyl 3-[2-(allyloxycarbonyl)ethyl]-4-methyl-1*H*-pyrrole-2-carboxylate (**1a**), which is a useful synthon for the B,C-ring components of bilin chromophores,[1] was treated with 1.2 equiv of DDQ in the presence of 10 equiv of MeOH.[4,5] The regioselectively oxidized product, 4-formylpyrrole **2a**, was obtained in 42% yield and 39% of unreacted **1a** was recovered,[6] while the expected 4-(methoxymethyl)pyrrole **4a** (R = Me, R^1 = H, R^2 = CH_2CO_2Allyl in Scheme 1) was not detected (Table 1, Entry 1). When 3.0 equiv of DDQ was used, **2a** was obtained in 77% yield (Entry 2). The oxidation of 3-ethyl-4-methylpyrrole-2-carboxylate **1b** also afforded the 4-formylpyrrole **2b** in good yield (Entry 3). In the case of 3,4-dimethylpyrrole **1c**, 4-formylpyrrole **2c**[7] was obtained in 25% yield accompanied by 52% of the dimerized by-product **3**. 3,4-Diethylpyrrole **1d** was oxidized regioselectively to give 4-acetylpyrrole **2d**[7] in poor yield (Entry 5). When the reaction was carried out at lower temperature, the reaction was sluggish but **2d** was obtained in improved yield (Entry 6). The 4-formylpyrrole **2a**–**2c** might be produced by further oxidation of the initially formed intermediate, 4-(methoxymethyl)pyrrole **4** (R = Me),[5] to **5** followed by hydrolysis (Scheme 1). During the oxidation of **1d**, formation of 4-(1-methoxyethyl)pyrrole **4d** (R, R^1, R^2 = Me), which was readily hydrolyzed to 4-(1-hydroxyethyl)pyrrole **4d** (R = H, R^1, R^2 = Me) in an attempt to isolate, was observed on TLC and gradually consumed during the progress of the reaction. This observation supports the stepwise oxidation mechanism via 4-(1-methoxyalkyl)pyrroles **4** as shown in Scheme 1. The oxidation of 4-methyl-2-tosylpyrrole derivative **1e**, possessing a tosyl group instead of an ester group, proceeded sluggishly to give 4-formyl-2-tosylpyrrole **2e** in low yield (Entry 7). In the case of 4-ethyl-2-tosylpyrrole derivative **1f**, **2f** was obtained in 54% yield (Entry 8).

Thus, if the electron density of the α-oxygen of the 4-alkyl group of intermediary pyrrole **4** is decreased, the second oxidation to **5** could be suppressed. Actually, when the oxidation of **1a** was carried out with 1.0 equiv of DDQ in the presence of AcOH (R = Ac in Scheme 1) instead of MeOH, 4-(acetoxymethyl)pyrrole **6a** was regioselectively obtained in 46% yield and 11% of **1a** was recovered (Table 2, Entry 1). When 1.5



Scheme 1.

Table 1. Oxidation of *t*-butyl 1*H*-pyrrole-2-carboxylates **1** with DDQ in the presence of MeOH



Entry	R^1	R^2	E		*n*	Time	**2**/%
1	H	CH_2CO_2Allyl	$CO_2{}^tBu$	**a**	1.2	43 h	42
2					3.0	43 h	77
3	H	CH_3	$CO_2{}^tBu$	**b**	3.0	9 h	72
4	H	H	$CO_2{}^tBu$	**c**	3.0	7 h	25[a]
5	CH_3	CH_3	$CO_2{}^tBu$	**d**	3.0	2 h	14
6[b]					3.0	4 d	66
7	H	CH_3	Ts	**e**	3.0	4 d	25
8	CH_3	H	Ts	**f**	3.0	47 h	54

[a]By-product **3** was obtained in 52% yield. [b]The reaction was carried out at −20 °C for 3 d and at −10 °C for 1 d.

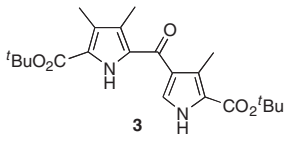
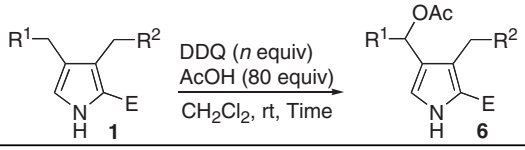


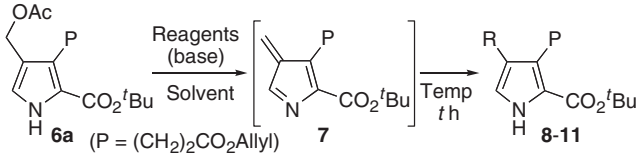
Table 2. Oxidation of *t*-butyl 1*H*-pyrrole-2-carboxylates **1** with DDQ in the presence of AcOH



Entry	R^1	R^2	E		*n*	Time	**6**/%
1[a]	H	CH_2CO_2Allyl	$CO_2{}^tBu$	**a**	1.0	43 h	46
2					1.5	41 h	80
3	H	CH_3	$CO_2{}^tBu$	**b**	1.5	43 h	67
4	H	H	$CO_2{}^tBu$	**c**	1.5	19 h	59
5	CH_3	CH_3	$CO_2{}^tBu$	**d**	1.5	2 h	95
6	H	CH_3	Ts	**e**	1.5	9 d	—
7	CH_3	H	Ts	**f**	1.5	63 h	69

[a]The reaction was carried out by using 10 equiv of AcOH.

Table 3. Substitution reaction of **6a**



Entry	Reagents (equiv)	Solvent Temp	*t*/h	R		Yield/%
1	DBU (1.1) TsNa (2.0)	DMF rt	1	$TsCH_2$	**8**	58
2	DBU (1.1) TsNa (2.0) $^nBu_4NBr$ (0.2)	DMF rt	1			82
3	DBU (2.0) CH_3NO_2 (1.4)	THF rt	43	$O_2NCH_2CH_2$	**9**	61
4	DBU (1.4) CH_3NO_2 (excess)	CH_3NO_2 rt	1.5			84
5	^{n}BuMgBr (2.0)	CH_2Cl_2 0 °C	1	$^n BuCH_2$	**10**	71
6	^{n}BuMgBr (3.0)	CH_2Cl_2 −78 °C	2.5			81
7	DBU (1.1) $^nBu_3P$ (2.2) PhCHO (10)	THF reflux	16	PhCH=CH	**11**	86 (E/Z = 75/25)

equiv of DDQ was used in the presence of large excess amount (80 equiv) of AcOH, the oxidation more readily proceeded to afford **6a** in 80% yield (Entry 2). 3-Ethyl-4-methylpyrrole **1b** and 3,4-dimethylpyrrole **1c** were also regioselectively oxidized to give the corresponding 4-(acetoxymethyl)pyrroles **6b** and **6c**[7] (Entries 3 and 4). The oxidation of 3,4-diethylpyrrole **1d** proceeded quite fast to afford 4-(1-acetoxyethyl)pyrrole **6d**[7] regioselectively in excellent yield (Entry 5). 4-Methyl-2-tosylpyrrole **1e** was not oxidized (Entry 6), but 4-ethyl-2-tosylpyrrole **1f** was slowly oxidized to furnish **6f** (Entry 7).

The oxidized pyrroles obtained above are versatile synthetic intermediates for further transformation. For example, 2-azafulvene **7** could be generated from the 4-(acetoxymethyl)-pyrrole **6a** by treating with a base, and it was further converted to the functionalized pyrroles by reaction with a nucleophile. As shown in Table 3, acetoxy group in **6a** was substituted with a tosyl group by treating with sodium *p*-toluenesulfinate (TsNa) in the presence of DBU (Entry 1). Quaternary ammonium salt promoted the substitution to give **8** in enhanced chemical yields (Entry 2). Introduction of a nitromethyl group was also possible by treating with nitromethane and DBU (Entry 3). By the use of nitromethane as a solvent, 4-(2-nitroethyl)pyrrole **9** was obtained in good yield (Entry 4). The reaction with the Grignard reagent afforded an alkylated pyrrole **10** (Entries 5 and 6). Furthermore, Wittig-type olefination was achieved by treating with n-Bu_3P and benzaldehyde to give olefin **11** in good yield (Entry 7).[1,8]

As described above, the regioselective oxidation of *t*-butyl 4-alkyl-1*H*-pyrrole-2-carboxylate was achieved with DDQ to give the corresponding 4-acyl- or 4-(1-acetoxyalkyl)pyrroles, respectively, depending on the used nucleophiles.[9] Further substitution reaction of the obtained 4-(acetoxymethyl)pyrrole via the azafulvene intermediate was realized to afford functionalized pyrroles. The present methods would be useful for the preparation of various types of pyrroles and could be applied especially to the synthesis of locked bilin chromophores of phytochromes.[1]

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