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DIRECT OXIDATION OF 4-METHYLPYRROLE-2-CARBOXYLATES WITH DDQ IN THE PRESENCE OF A GLYCOL (MS WORD STYLE "01 HET-TITLE")

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Abstract – Oxidation of 4-methylpyrrole-2-carboxylates with DDQ in the presence of a glycol proceeded smoothly on the methyl group at the C4 position regioselectively to afford the corresponding pyrrole-2,4-dicarboxylates directly. Direct oxidation of a methyl group of 2,4,6-trimethylphenol and 3-methyl-9*H*-carbazole into carboxylates was also demonstrated. (MS Word Style "04 Het-Abstract")

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a highly effective oxidant widely used in organic synthesis and its major functions include dehydrogenation, such as aromatization of hydroaromatic compounds, introduction of a double bond into carbonyl compounds, and oxidation of alcohols. Benzylic oxidation with DDQ in the presence of oxygen nucleophiles gives the corresponding oxygen-functionalized compounds. Furthermore, alternative oxidative cyclization and coupling reactions have been also reported.[1,2]

During our investigation on the syntheses of phytochromobilin (PΦB), phycocyanobilin (PCB), biliverdin (BV) and their analogs including sterically locked derivatives toward elucidation of the structure and function of phytochromes,[3] oxidative functionalization of pyrroles by the use of quinones was explored. In the case that DDQ was used as an oxidant, the α-position of the alkyl substituent at the C4 position was regioselectively oxidized in the presence of AcOH to afford 4-(1-acetoxyalkyl)pyrrole derivatives. In contrast, the corresponding 4-acylpyrroles were produced when MeOH was used instead of AcOH as a

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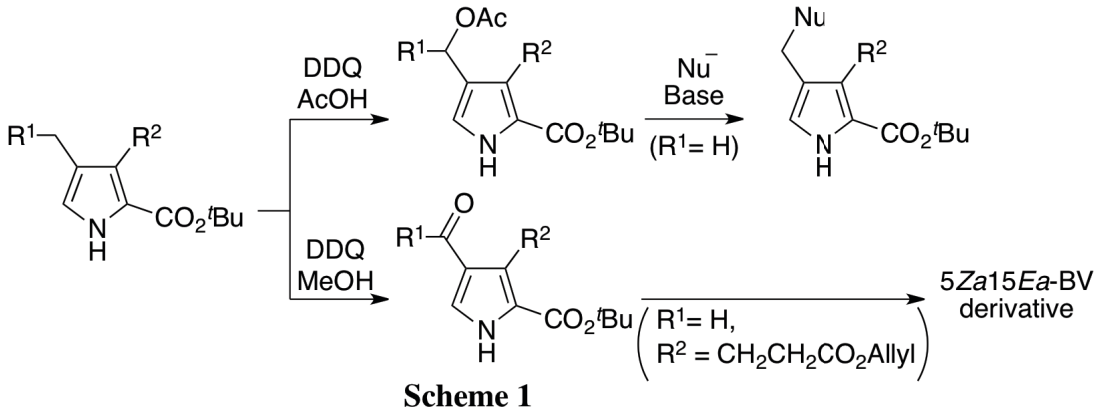
Dedicated with respect to Professor Eiichi Negishi on the occasion of his 77th birthday.

nucleophile (Scheme 1).[4] The oxidative transformation of 4-methylpyrrole-2-carboxylates with DDQ and MeOH was successfully applied to the convergent synthesis of sterically locked 5*Za*15*Ea*-BV derivative.[5,6] Herein we describe a regioselective direct oxidation of *t*-butyl 4-methylpyrrole-2-carboxylates with DDQ in the presence of a glycol as a nucleophile to afford the corresponding 2,4-dicarboxylates.



Scheme 1

First, oxidation of *t*-butyl 3-[2-(allyloxycarbonyl)ethyl]-4-methyl-1*H*-pyrrole-2-carboxylate (**1A**), which is a useful synthon for the B- and C-ring components of bilin chromophores,[3] was examined by the use of 4.0 equiv of DDQ in the presence of 15 equiv of ethylene glycol (**2a**) in CH_2Cl_2 in order to trap the oxidation product as an acetal form. To our surprise, a desired 1,3-dioxolane **6Aa** was not obtained but the corresponding 2-hydroxyethyl ester **3Aa** was obtained in 50% yield (Table 1, Entry 1). The 2-hydroxyethyl ester **3Aa** might be produced as follows: Oxidation of **1A** with DDQ occurred at the C4 position to afford an intermediate **5Aa** via nucleophilic attack of the glycol **2a** to an intermediary azafulvene **4A**.[4] The second oxidation of **5Aa** with DDQ furnished **6Aa**, which was subjected to the third oxidation, followed by hydrolysis resulting in the formation of **3Aa** as shown in Scheme 2, since the acetal **6Aa** might be more easily oxidized by DDQ than **5Aa**. Then propylene glycol (**2b**) instead of ethylene glycol (**2a**) was used as a nucleophile for the present oxidation. The corresponding 3-hydroxypropyl ester **3Ab** was obtained in slightly enhanced chemical yield (Entry 2). The oxidation in the presence of 1,4-butanediol (**2d**) instead of ethylene glycol (**2a**) also proceeded to give the corresponding ester **3Ac**, but in lower yield along with the formation of aldehyde **8A** (Entry 11). The oxygen atom of the resulting ester carbonyl might be originated from H_2O. When the oxidation was carried out in the presence of 1 equiv of H_2O, the chemical yield was improved as expected (Entry 3). When the amount of H_2O was increased, the chemical yield was decreased (Entries 4 and 5) and the aldehyde **8A** was obtained (Entry 5). In the present oxidation, the production of a small amount of a dimeric compound **9** was often observed.[7] In order to suppress the production of the dimer, the pyrrole

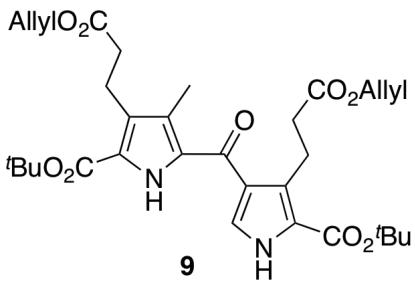


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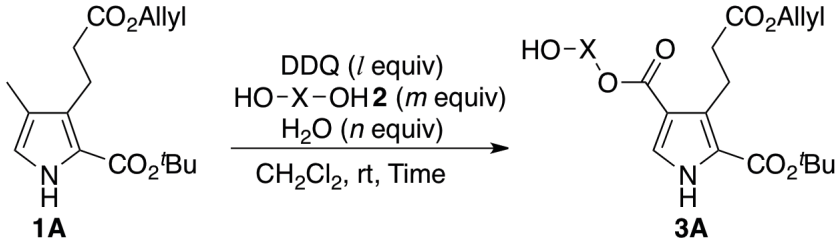
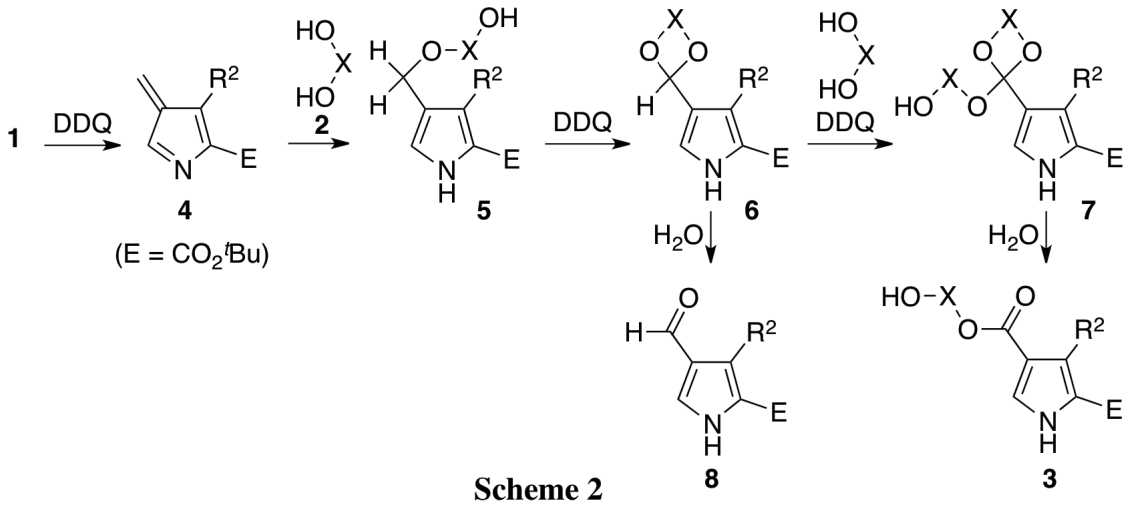
Table 1. Oxidation of 4-methylpyrrole-2-carboxylate **1A** with DDQ in the presence of a glycol



Entry	HO–X–OH	**2**	*l*	*m*	*n*	Time /h	**3A**	Yield of **3A** /%
1	HO–CH_2CH_2–OH	**a**	4.0	15	0	21	**Aa**	50
2	HO–$CH_2CH_2CH_2$–OH	**b**	4.0	15	0	15	**Ab**	52
3			4.0	15	1	19		65
4			4.0	15	5	22		63
5			4.0	15	10	20		55[a]
6[b]			4.0	15	1	16		71
7[c]			4.0	15	1	20		70
8[b]			4.5	15	1	15		68
9[b]			4.0	30	1	18		70
10[b]	HO–$CH_2C(Me)_2CH_2$–OH	**c**	4.0	15	1	15	**Ac**	67
11	HO–$CH_2CH_2CH_2CH_2$–OH	**d**	4.0	15	0	15	**Ad**	15[d]

[a]Aldehyde **8A** was also obtained in 12% yield. [b]A solution of pyrrole **1A** and H_2O in CH_2Cl_2 was slowly added to a mixture of DDQ and glycol **2** in CH_2Cl_2 in a period of 3 h. [c]A solution of pyrrole **1A** and H_2O in CH_2Cl_2 was slowly added to a mixture of DDQ and glycol **2** in CH_2Cl_2 in a period of 6 h. [d]Aldehyde **8A** was also obtained in 47% yield.



Scheme 2

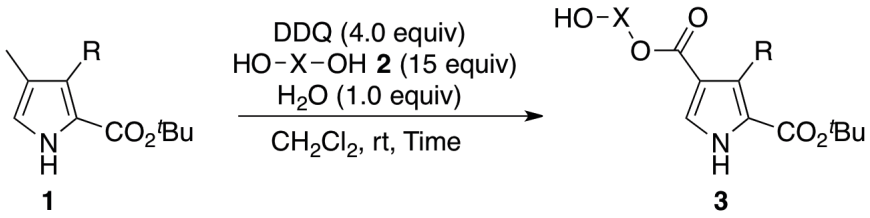
1A and H_2O were added to the mixture of glycol **2b** and DDQ in a period of 3 h to obtain the ester **3Ab** in enhanced 71% yield (Entry 6).[8] Slow addition of **1A** and H_2O in a longer period did not improve the yield any more (Entry 7). Furthermore, increase of the amount of DDQ or glycol was not so effective (Entries 8 and 9). The use of 2,2-dimethyl-1,3-propanediol (**2c**) as a glycol realized a similar result (Entry 10).

Next, the oxidation of other pyrroles with DDQ in the presence of a glycol was examined as listed in Table 2, together with the results of oxidation of **1A**. The reaction of *t*-butyl 3-ethyl-4-methyl-1*H*-pyrrole-2-carboxylate (**1B**) afforded esters **3Bb** and **3Bc** in 58% and 59% yields by the use of propylene glycol (**2b**) and 2,2-dimethyl-1,3-propanediol (**2c**), respectively (Entries 3 and 4). 3,4-Dimethyl-1*H*-pyrrole-2-carboxylate (**1C**) was oxidized regioselectively at the C4 methyl group (Entries 5 and 6). In this case, chemical yield was enhanced up to 71% by the use of 2,2-dimethyl-1,3-propanediol (**2c**) as a glycol. In the case of 3-phenyl-substituted pyrrole **1D** in the presence of **1b**, the reaction proceeded rather slowly to give the corresponding aldehyde **8D** as a major product, but the yield of an ester **3Db** was poor (Entry 7). In the oxidation using the glycol **2c** at 40 °C, reaction was still sluggish to give the ester **3Dc** in 27 % yield along with the aldehyde **8D** (6%) and an acetal **6Dc** (13%) (Entry 8).

In order to reveal the reaction mechanism of the present oxidation, the 1,3-dioxolane **6Aa** (Scheme 2) was treated with DDQ in the presence of ethylene glycol (**2a**): The oxidized ester **3Aa** was obtained in 63% yield accompanied with aldehyde **8A** (7%) (Eq. 1).[9] This fact supported that the ester was produced via oxidation of the intermediary acetal **6Aa**. Although the oxidation of the 3-phenyl substituted acetal **6Dc** with DDQ was also examined at 40 °C, the reaction was sluggish and the yield of ester **3Dc** was low (Eq. 2). The exact reason for the poor reactivity of the phenyl-substituted acetal **6Dc** toward DDQ oxidation is not yet clear, however, steric hindrance of phenyl group, which prevents the attack of DDQ to **6Dc**, might be a possible reason.

It is well known that DDQ oxidation of methyl group on aromatic ring in the presence of MeOH and/or H_2O gives the corresponding aldehydes.[1,2h,10] Thus, the present DDQ oxidation using a glycol as a nucleophile was applied to such substrates. 2,4,6-Trimethylphenol (mesitol) (**10**)[2h] was converted to an ester **11** in 77% yield regioselectively in the presence of glycol **2c** (Eq. 3). Carbazole compounds are intriguing because of containing pyrrole skeleton.[10c-e] 3-Methyl-9*H*-carbazole (**12)** was subjected to the present DDQ oxidation to afford the corresponding ester **13** in 66% yield (Eq. 4).

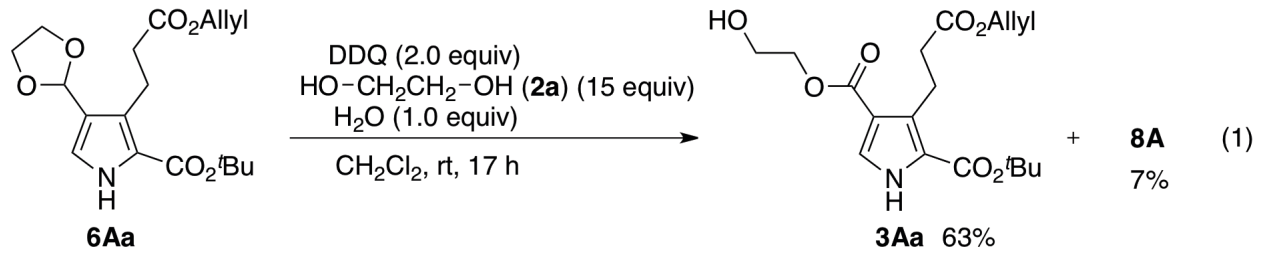
Table 2. Oxidation of 4-methylpyrrole-2-carboxylates **1** with DDQ in the presence of a glycol



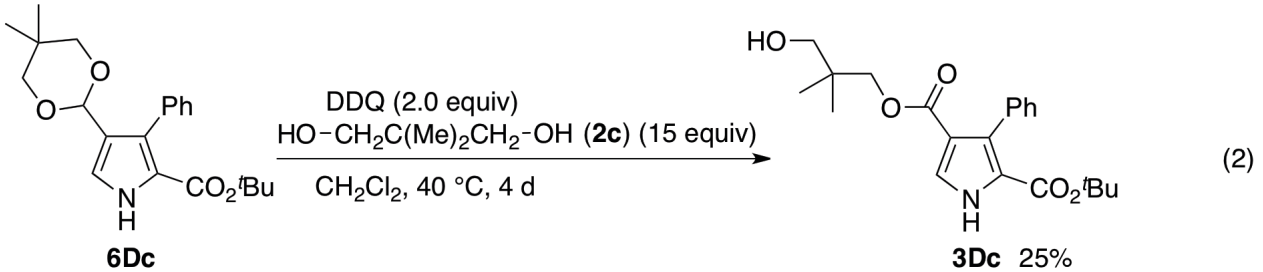
1 **3**

Entry	R	**1**	HO–X–OH	**2**	Time /h	**3**	Yield of **3** /%
1[a]	$CH_2CH_2CO_2Allyl$	**A**	HO–$CH_2CH_2CH_2$–OH	**b**	16	**Ab**	71
2[a]			HO–$CH_2C(Me)_2CH_2$–OH	**c**	15	**Ac**	67
3[a]	CH_2CH_3	**B**	HO–$CH_2CH_2CH_2$–OH	**b**	14	**Bb**	58
4[a]			HO–$CH_2C(Me)_2CH_2$–OH	**c**	14	**Bc**	59
5[a]	CH_3	**C**	HO–$CH_2CH_2CH_2$–OH	**b**	14	**Cb**	58
6[a]			HO–$CH_2C(Me)_2CH_2$–OH	**c**	14	**Cc**	71
7[b]	Ph	**D**	HO–$CH_2CH_2CH_2$–OH	**b**	15	**Db**	8[c]
8[d]			HO–$CH_2C(Me)_2CH_2$–OH	**c**	88[e]	**Dc**	27[f]

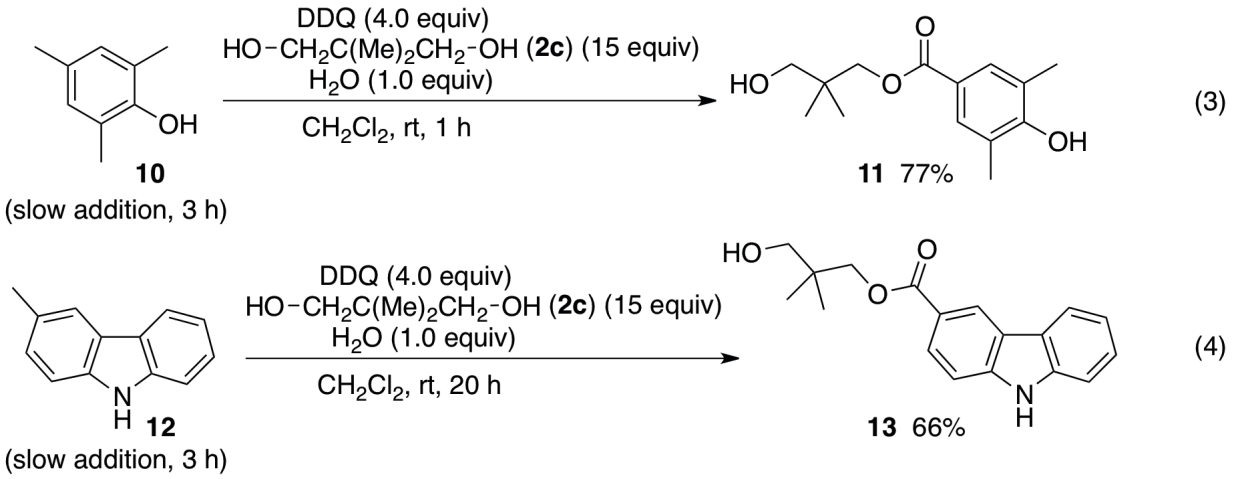
[a]A solution of pyrrole **1** and H_2O in CH_2Cl_2 was slowly added to a mixture of DDQ and glycol **2** in CH_2Cl_2 in a period of 3 h. [b]A solution of pyrrole **1** in CH_2Cl_2 was added (without addition of H_2O) all at once to a mixture of DDQ and glycol **2** in CH_2Cl_2. [c]Aldehyde **8D** was also obtained in 43% yield. [d]A solution of pyrrole **1** in CH_2Cl_2 was slowly added (without addition of H_2O) to a mixture of DDQ and glycol **2** in CH_2Cl_2 in a period of 3 h. [e]Reaction was carried out at rt for 20 h and at 40 °C for 68 h. [f]Aldehyde **8D** and acetal **6Dc** were also obtained in 6% and 13% yields, respectively.



6Aa **3Aa** 63% (1)



6Dc **3Dc** 25% (2)



As described above, the regioselective oxidation of *t*-butyl 4-methyl-1*H*-pyrrole-2-carboxylate was achieved with DDQ in the presence of a glycol to give the corresponding pyrrole-2,4-dicarboxylates.[11] This method could be also applied to the DDQ oxidation of methyl groups attached to aromatic rings into the corresponding esters. The direct oxidation of methylarenes to the carboxylic acids and its derivatives is very important, since such carbonyl derivatives are versatile building blocks in the synthesis of pharmaceutical chemicals. A variety of oxometal oxidants have been employed for such oxidative processes.[12] The present reaction would provide an efficient method for metal-free oxidation to produce useful carboxylic acid derivatives.

ACKNOWLEDGEMENTS

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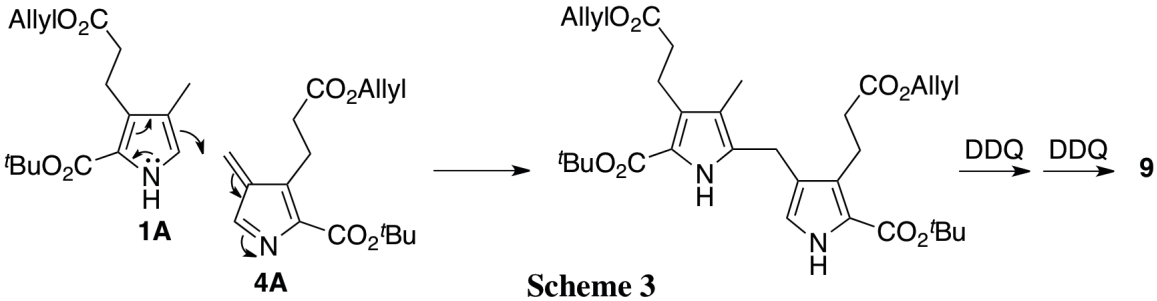
REFERENCES AND NOTES

1. D. Walker and J. D. Hiebert, *Chem. Rev.*, 1967, **67**, 153; A. B. Turner, 'Synthetic Reagents,' Vol. 3, ed. by J. S. Pizey, Halstead-Wiley, New York, 1977, 193; D. R. Buckle and I. L. Pinto, 'Comprehensive Organic Synthesis,' Vol. 7, ed. by B. M. Trost and I. Fleming, Pergamon Press, New York, 1991, pp.135–139.
2. Examples of oxidation reaction using DDQ. Aromatization: a) P. P. Fu and R. G. Harvey *Chem. Rev.*, 1978, **78**, 317; b) U. Kämpfen and A. Eschenmoser, *Tetrahedron Lett.*, 1985, **26**, 5899. Benzylic oxidation: c) H. Lee and R. G. Harvey, *J. Org. Chem.*, 1983, **48**, 749; d) T. Ishiguro, H. Mizuguchi, K. Tomioka, and K. Koga, *Chem. Pharm. Bull.*, 1985, **33**, 609; e) E. J. Corey and Y. B. Xiang, *Tetrahedron Lett.*, 1987, **28**, 5403. Oxidation of alcohol: f) H.-D. Becker, A. Björk, and E.

Adler, *J. Org. Chem.*, 1980, **45**, 1596; g) L. Wang, J. Li, H. Yang, Y. Lv, and S. Gao, *J. Org. Chem.*, 2012, **77**, 790. Oxidative coupling and cyclization reaction: h) H.-D. Becker, *J. Org. Chem.*, 1965, **30**, 982; i) Y. Zhang and C.-J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 4242; j) L. Liu and P. E. Floreancig, *Org. Lett.*, 2010, **12**, 4686.

3. H. Khawn, L.-Y. Chen, H. Kinoshita, and K. Inomata, *Chem. Lett.*, 2008, **37**, 198; K. Inomata, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 25; L.-Y. Chen, H. Kinoshita, and K. Inomata, *Chem. Lett.*, 2009, **38**, 602; K. Inomata, H. Khawn, L.-Y. Chen, H. Kinoshita, B. Zienicke, I. Molina, and T. Lamparter, *Biochemistry*, 2009, **48**, 2817; K. Nishiyama, A. Kamiya, M. A. S. Hammam, H. Kinoshita, S. Fujinami, Y. Ukaji, and K. Inomata, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 1309; R. Yang, K. Nishiyama, A. Kamiya, Y. Ukaji, K. Inomata, and T. Lamparter, *Plant Cell*, 2012, **24**, 1936 and references cited therein.
4. R. Iwamoto, Y. Ukaji, and K. Inomata, *Chem. Lett.*, 2010, **39**, 176.
5. L.-Y. Chen, R. Iwamoto, Y. Ukaji, and K. Inomata, *Chem. Lett.*, 2011, **40**, 632.
6. Related oxidation reaction using *o*-chloranil: R. Sakata, R. Iwamoto, S. Fujinami, Y. Ukaji, and K. Inomata, *Heterocycles*, 2011, **82**, 1157.
7. The dimeric compound **9** might be formed by Friedel-Crafts-type reaction of the azafulvene **4A** with unreacted **1A** followed by further oxidation with DDQ as shown in Scheme 3.



Scheme 3

8. Slow addition procedure was also effective even in the case of ethylene glycol (**2a**) and 1,4-butanediol (**2d**) to give the corresponding esters **3Aa** and **3Ad** in 57% and 62% yields accompanied with the aldehyde **8A** in 7% and 17% yields, respectively.
9. It was reported that 1,3-dioxolanes and 1,3-dioxanes with an aromatic group at C2 position, especially with an electron-donating *p*-methoxyphenyl group, were oxidized by DDQ into the corresponding carboxylates and their equivalents, for example: a) J.-I. Iwamura, N. Iwamoto, and N. Hirao, *Nippon Kagaku Kaishi*, 1977, 1009; b) K. Nakayama and J. D. Rainier, *Tetrahedron*, 1990, **46**, 4165; c) B. Wünsch and S. Nerdinger, *Eur. J. Org. Chem.*, 1999, 503; d) H. Tanabe, X. He, P. Kothandaraman, and M. Yamane, *Synlett*, 2010, 1190.
10. Recent examples of DDQ oxidation of methyl groups attached to aromatic rings to the corresponding

aldehydes: a) J. H. P. Utley and G. G. Rozenberg, *Tetrahedron*, 2002, **58**, 5251; b) S. Nandi, K. Panda, J. R. Suresh, H. Ila, and H. Junjappa, *Tetrahedron*, 2004, **60**, 3663; c) R. Forke, M. P. Krahl, F. Däbritz, A. Jäger, and H.-J. Knölker, *Synlett*, 2008, 1870; d) M. Schmidt and H.-J. Knölker, *Synlett*, 2009, 2421; e) R. Bautista, P. Bernal, L. E. Montiel, F. Delgado, and J. Tamariz, *Synthesis*, 2011, 929.

11. A representative procedure for the oxidation of **1A** (Table 1, Entry 6): To a solution of DDQ (454 mg, 2.0 mmol) and 1,3-propanediol (571 mg, 7.5 mmol) in CH_2Cl_2 (9 mL) was slowly added a solution of **1A** (147 mg, 0.5 mmol) and H_2O (9 mg, 0.5 mmol) in CH_2Cl_2 (6 mL) in a period of 3 h at rt under a nitrogen atmosphere. After stirring for another 16 h at rt, the reaction mixture was quenched by the addition of an aqueous solution containing ascorbic acid (0.7%), citric acid (1.3%), and sodium hydroxide (0.9%). The mixture was extracted with ether and the combined extracts were washed with brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was separated by TLC on SiO_2, which was pretreated with hexane/Et_3N (100/1, v/v), (hexane/AcOEt = 2/1, v/v) to afford **3Ab** (136 mg, 71%) as an oil. **3Ab**: IR (neat) 3308, 2976, 1734, 1716, 1697, 1557, 1541, 1507, 1457, 1417, 1369, 1288, 1141, 1050, 943, 840, 786, 757 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 9H), 1.93–1.99 (m, 2H), 2.54 (br, 1H), 2.60 (t, 2H, J = 8.3 Hz), 3.40 (t, 2H, J = 8.3 Hz), 3.71–3.79 (m, 2H), 4.40 (t, 2H, J = 6.0 Hz), 4.59 (d, 2H, J = 6.0 Hz), 5.22 (d, 1H, J = 10.6 Hz), 5.30 (d, 1H, J = 17.0 Hz), 5.86–5.97 (m, 1H), 7.48 (d, 1H, J = 3.6 Hz), 9.87 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 28.2, 31.8, 35.2, 59.0, 60.6, 64.9, 82.0, 115.7, 118.0, 122.1, 127.2, 130.5, 132.1, 161.0, 164.7, 172.8. HRMS (FAB^+) (M^+ + H), Found: *m/z* 382.1864. Calcd for $C_{19}H_{28}NO_7$: 382.1866.
12. R. A. Sheldon and J. K. Kochi, 'Metal-Catalyzed Oxidations of Organic Compounds,' Academic Press, New York, 1981, Chap. 10; A. H. Haines, 'Methods for the Oxidation of Organic Compounds,' Academic Press, London, 1985, Chap. 2.5.