Photochemical & Photobiological Sciences

Cite this: *Photochem. Photobiol. Sci.*, 2012, **11**, 616

www.rsc.org/pps

COMMUNICATION

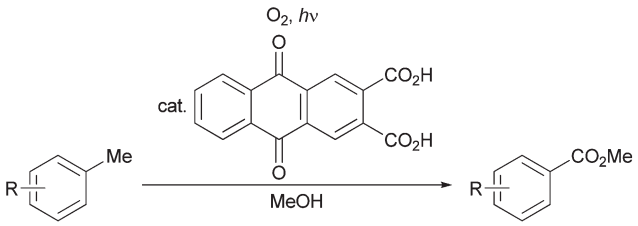
Direct aerobic photo-oxidative syntheses of aromatic methyl esters from methyl aromatics using anthraquinone-2,3-dicarboxylic acid as organophotocatalyst†

Norihiro Tada, Yuki Ikebata, Tomoya Nobuta, Shin-ichi Hirashima, Tsuyoshi Miura and Akichika Itoh*

Received 20th November 2011, Accepted 6th January 2012
DOI: 10.1039/c2pp05387j

This paper reports a useful method for facile direct syntheses of aromatic methyl esters from methyl aromatics by aerobic photo-oxidation using anthraquinone-2,3-dicarboxylic acid as an organophotocatalyst.

One of the most challenging research themes in modern organic synthesis is the development of a selective and direct oxidative synthetic protocol of hydrocarbons into synthetically useful multifunctional organic compounds using molecular oxygen under metal-free conditions.[1] Aromatic carboxylates are important structural motifs in organic synthesis as versatile compounds or intermediates such as liquid crystal polymers, cosmetics, pharmaceuticals, agrochemicals, and food additives. A general synthetic method of obtaining aromatic carboxylates has been achieved by oxidation of methyl aromatics to carboxylic acids with heavy metals such as Cr, Mn, and V,[1] followed by esterifications with alcohols.[2] In addition, oxidative esterifications of aldehydes[3] and acetals[4] have been developed. Furthermore, extensive efforts have been made to develop the direct oxidative esterification of alcohols, and a number of reactions have been reported in recent years.[5] Although these approaches provide efficient access to aromatic carboxylates, oxidized starting materials higher than methyl aromatics are required. Direct oxidative esterification of methyl aromatics is highly desirable but difficult to achieve because methyl aromatics are unreactive. In addition, alcohols used as solvents are oxidized more easily than methyl aromatics.



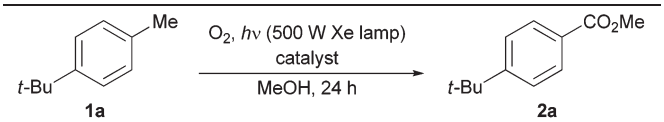
Scheme 1 Direct transformation of methyl aromatics to methyl carboxylates.

Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu 501-1196, Japan. E-mail: itoha@gifu-pu.ac.jp; Fax: (+81) 58-230-8108; Tel: (+81) 58-230-8108

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2pp05387j

We have previously reported that methyl groups at the aromatic nucleus are oxidized to the corresponding carboxylic acids in the presence of a catalytic amount of bromine source under an oxygen atmosphere and light irradiation.[6] In the course of our further study for extension of the application, we have recently determined that methyl aromatics are directly transformed to the corresponding methyl carboxylates with molecular oxygen in the

Table 1 Study of reaction conditions of direct aerobic photo-oxidative synthesis of methyl esters from methyl aromatics[a]



1a 2a

Entry	Catalyst (equiv)	Yield[b] (%)
1	Rose bengal (0.1)	0
2	9,10-Dicyanoanthracene (0.1)	32
3	Anthracene (0.1)	27
4	Benzophenone (0.1)	1
5	AQN (0.1)	56
6	2-NH_2–AQN (0.1)	0
7	2-MeO–AQN (0.1)	40
8	2-*t*-Bu–AQN (0.1)	69
9	1-Cl–AQN (0.1)	87
10	2-Cl–AQN (0.1)	79
11	AQN-2-CO_2H (0.1)	65
12	AQN-2,7-diSO_3Na (0.1)	74
13	1,5-diCl–AQN (0.1)	77
14	2,3-diCl–AQN (0.1)	75
15	AQN-2,3-diCO_2Me (0.1)	85
16	AQN-2,3-diCO_2H (0.1)	91[c] (89)
17	AQN-2,3-diCO_2H (0.05)	69
18	AQN-2,3-diCO_2H (0.2)	59
19	AQN-2,3-diCO_2H (0.1)	65[d]
20	AQN-2,3-diCO_2H (0.1)	47[e]
21	—	0
22	AQN-2,3-diCO_2H (0.1)	0[f]
23	AQN-2,3-diCO_2H (0.1)	0[g]

[a] A solution of 4-*tert*-butyltoluene (**1a**, 0.3 mmol) and catalysts in MeOH (5 mL) under an O_2 atmosphere was stirred and irradiated externally with 500 W xenon lamp. [b] ^{1}H NMR yields. Number in parenthesis is isolated yield. [c] Anthraquinone-2,3-dicarboxylic acid (23% yield) was detected in crude by ^{1}H NMR. [d] This reaction was carried out with fluorescent lamp. [e] This reaction was carried out with 400 W Hg lamp. [f] This reaction was carried out in the dark. [g] This reaction was carried out under an Ar atmosphere.

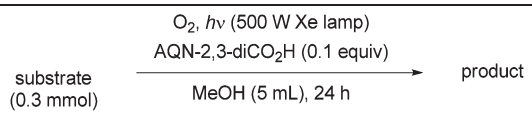
presence of CBr_4 under light irradiation (fluorescent lamp or xenon lamp).[7] This reaction is the only example of direct preparation of methyl carboxylates from methyl aromatics. Although this facile and efficient method is of interest in green chemistry through non-use of heavy metals, use of molecular oxygen, and inexpensive acquisition of reagents, the employment of CBr_4 as a bromine source poses a problem because of its toxicity. Furthermore, only methyl carboxylates were successfully obtained by this reaction, because other alcohols, such as ethanol or propanol used as solvent, are more easily oxidized than methanol.[8] These parameters are the driving forces of our further study on direct oxidative esterification with an organophotocatalyst.

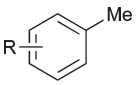
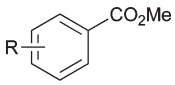
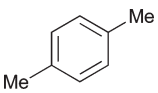
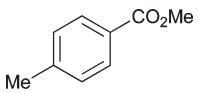
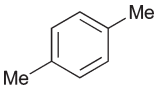
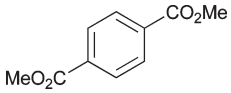
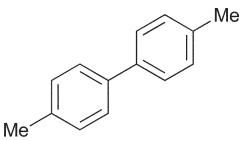
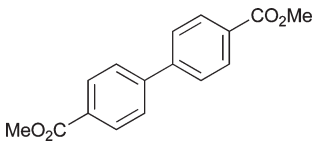
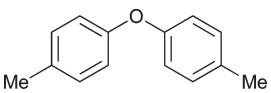
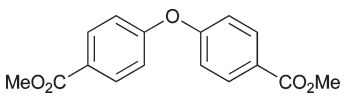
Anthraquinones (AQNs) are widely recognized as efficient electron and hydrogen atom acceptors and as oxidizers of organic compounds such as alcohols, amines, and alkenes.[9] We have recently developed a process for oxidation of methyl aromatics to carboxylic acid with 2-chloroanthraquinone as an organophotocatalyst under an air atmosphere and irradiation of VIS.[10,11] This reaction suggests that more efficient direct oxidative esterification are possible using AQN derivatives. Herein, we describe the efficient direct transformation of methyl aromatics to methyl carboxylates using anthraquinone-2,3-dicarboxylic acid as an organophotocatalyst under aerobic photo-oxidation conditions (Scheme 1).

To explore this approach, we selected 4-*tert*-butyltoluene (**1a**) as a test substrate for optimization of reaction conditions (Table 1).‡ Although various photosensitizers were used for realizing oxidative esterification, only the yields of **2a** using AQN were satisfactory (entries 1–5). Among the examined AQN derivatives, anthraquinone-2,3-dicarboxylic acid gave the best result (entries 5–16). It is noted that a lower yield of **2a** was observed when fluorescent or high-pressure mercury lamps were used instead of a xenon lamp (entries 19 and 20).[12] Anthraquinone-2,3-dicarboxylic acid, light irradiation, and molecular oxygen were necessary for direct oxidative esterification to obtain product **2a** (entries 21–23).

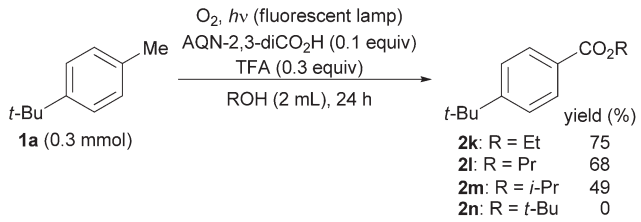
The results of oxidative esterification of various methyl aromatics are summarized in Table 2. The electron-rich and neutral methyl aromatics were good substrates for oxidative esterification to afford the corresponding methyl carboxylates in high yields (entries 1–4); however, the electron-deficient methyl aromatics with the cyano group were poor substrates (entry 6). Steric hindrance of 2-bromotoluene (**1g**) led to low yields of methyl 2-bromobenzoate (**2g**) (entry 7). Interestingly, methyl 4-methylbenzoate (**2ha**) was obtained from *p*-xylene in moderate yields in the optimized condition, and dimethyl terephthalate (**2hb**) was obtained in moderate yields in the presence of anthraquinone-2,3-diCO_2H (0.2 equiv) for 48 h (entries 8 and 9). 4,4′-Dimethylbiphenyl (**1i**) and 4,4′-oxybis(methylbenzene) (**1j**) afforded high yields of corresponding dimethyl esters **2i** and **2j**, which were good intermediates for high-performance materials (entries 10 and 11).

Table 2 Direct aerobic photo-oxidative synthesis of methyl esters from methyl aromatics[a]



Entry	Substrate		Product		Yield[b] (%)
1		**1b**: R = *p*-OMe		**2b**	86
2		**1a**: R = *p*-*t*-Bu		**2a**	89
3		**1c**: R = *p*-Ph		**2c**	72
4		**1d**: R = *p*-Br		**2d**	80
5[c]		**1e**: R = *p*-Cl		**2e**	52
6		**1f**: R = *p*-CN		**2f**	0
7		**1g**: R = *o*-Br		**2g**	4
8		**1h**		**2ha**	49
9[c,d]		**1h**		**2hb**	46
10[c,e]		**1i**		**2i**	87
11[c,e]		**1j**		**2j**	80

[a] A solution of substrate (0.3 mmol) and AQN-2,3-diCO_2H (0.1 equiv) in MeOH (5 mL) under an O_2 atmosphere was stirred and irradiated externally with 500 W xenon lamp for 24 h. [b] Isolated yields. [c] This reaction was carried out for 48 h. [d] This reaction was carried out with AQN-2,3-diCO_2H (0.2 equiv). [e] This reaction was carried out with AQN-2,3-diCO_2H (0.3 equiv).

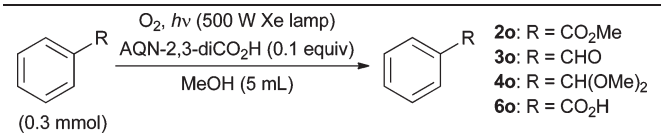


Scheme 2 Direct aerobic photooxidation synthesis of alkyl esters from methyl aromatics.

We also attempted to synthesis of ethyl esters under the optimized condition mentioned above. However, ethyl carboxylate **2k** was obtained only in 20% yield in the presence of ethanol as a solvent. Thus, we further searched more suitable reaction conditions, and found that use of fluorescent lamp instead of xenon lamp and addition of trifluoroacetic acid improved the product yield up to 75% yield (Scheme 2). Furthermore, propyl carboxylate **2l** and iso-propyl carboxylate **2m** were also obtained in good and moderate yields, respectively. These reactions are the first examples of the direct synthesis of ethyl, propyl, and iso-propyl esters from methyl aromatics.[13] However, *tert*-butyl carboxylate **2n** was not obtained at all.

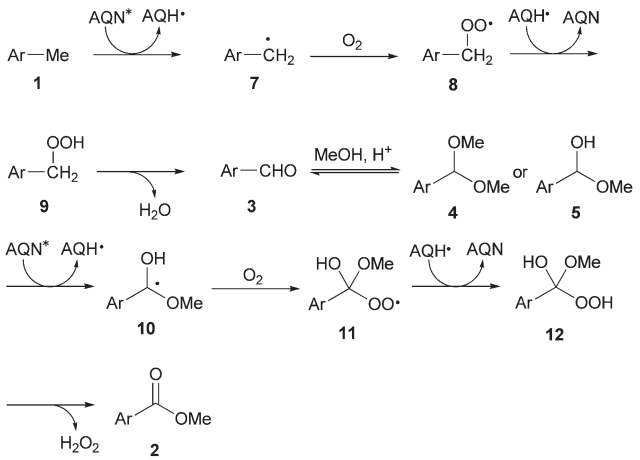
During this process, a small amount of aldehyde **3** was detected by ^{1}H NMR analysis. To determine the intermediate of this reaction, benzaldehyde **3o** was subjected to similar aerobic photo-oxidation conditions for 24 h, and **2o** was obtained in 90% yield (Table 3, entry 2). In addition, we determined that dimethyl acetal **4o** was formed from aldehyde **3o** *in situ* (entry 1) and **4o** was transformed to **2o** under a similar reaction condition (entries 3 and 4). These results suggest that the reaction proceeds through aldehyde **3** and dimethyl acetal **4** or hemiacetal **5** as intermediates. It is noted that esterification of benzoic acid (**6o**) did not proceed under the reaction conditions and **6o** was recovered in quantitative yields (entry 5). In addition, *m*-chloroperbenzoic acid was reduced to *m*-chlorobenzoic acid in 97% yield, and methyl ester was not obtained. Furthermore, esterification of benzoic acid (**6o**) proceeded only in 1% yield even in the presence of trifluoroacetic acid in ethanol irradiated with fluorescent lamp (entry 6). This result suggests that trifluoroacetic acid mainly works for the formation of acetal or hemiacetal from benzaldehyde (**3o**).

Table 3 Study of reaction intermediates



			Yield[a] (%)			
Entry	Substrate	Time (h)	**2o**	**3o**	**4o**	**6o**
1	**3o**	5	38	10	42	0
2	**3o**	24	90	1	2	0
3	**4o**	5	48	2	39	0
4	**4o**	24	81	2	2	0
5	**6o**	24	0	0	0	quant
6[b]	**6o**	24	1[c]	0	0	98
7	*m*CPBA	24	0	0	0	97[d]

[a] ^{1}H NMR yields. [b] Reaction was carried out in the presence of TFA (0.3 equiv) in EtOH (2 mL) irradiated externally with fluorescent lamp. [c] Ethyl benzoate (1% yield) was obtained. [d] *m*-Chlorobenzoic acid (97% yield) was obtained.



Scheme 3 Plausible path of the aerobic photooxidative synthesis of alkyl carboxylates.

A plausible mechanistic pathway based on the aforementioned results is shown in Scheme 3. Excited AQN, which absorbs light, abstracts the hydrogen radical at the benzylic position to produce benzyl radical **7**,[14] which traps molecular oxygen to give peroxy radical **8**. Aldehyde **3** is formed *via* peroxyradical **8** and hydroperoxide **9**. Acetal **4** or hemiacetal **5**, which are formed by the addition of alcohols to aldehydes **3** in acidic conditions, are transformed to benzyl radical **10** through the absorption of the hydrogen radical by excited AQN, and **10** traps molecular oxygen to give methyl ester **2** through peroxyradical **11** and hydroxyperoxide **12**.

Conclusions

In conclusion, we reported a useful method for facile synthesis of aromatic methyl carboxylates from methyl aromatics by aerobic photo-oxidation using anthraquinone-2,3-dicarboxylic acid as an organophotocatalyst. This synthetic protocol is the first example for the direct synthesis of the corresponding ethyl, propyl, and iso-propyl esters from methyl aromatics.

Notes and references

‡ The following is a typical procedure for direct esterification (Table 1, entry 16). A solution of 4-*tert*-butyltoluene (**1a**, 0.3 mmol) and anthraquinone-2,3-dicarboxylic acid (0.03 mmol) in dry MeOH (5 mL) in a pyrex test tube, purged with an O_2 balloon, was stirred and irradiated externally with a 500 W xenon lamp for 24 h. The reaction mixture was concentrated *in vacuo*, and purification of the crude product by PTLC (toluene) provided methyl 4-*tert*-butylbenzoate (51.4 mg, 89%).

1 *Comprehensive Organic Transformations*, ed. R. C. Larock, Wiley-VCH, New York, 2nd edn, 1999, p. 1625; *March's Advanced Organic Chemistry*, ed. M. B. Smith and J. March, John Wiley & Sons, Inc., Hoboken, 6th edn, 2007, p. 1745.

2 *Greene's Protective Groups in Organic Synthesis*, ed. P. G. M. Wutz and T. W. Greene, John Wiley & Sons, Inc., Hoboken, 4th edn, 2006, pp. 538–543.

3 *Comprehensive Organic Transformations*, ed. R. C. Larock, Wiley-VCH, New York, 2nd edn, 1999, p. 1656; *March's Advanced Organic Chemistry*, ed. M. B. Smith and J. March, John Wiley & Sons, Inc., Hoboken, 6th edn, 2007, p. 1769.

4 M. Miura, M. Nojima and S. Kusabayashi, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2909–2913; K. G. Brinkhaus, E. Steckhan and D. Degner, *Tetrahedron*, 1986, **42**, 553–560; R. Curci, L. D'Accolti, M. Fiorentino, C. Fusco, W. Adam, M. E. González-Nunez and R. Mello, *Tetrahedron Lett.*, 1992, **33**, 4225–4228; B. A. Marples, J. P. Muxworthy and K. H. Baggaley, *Synlett*, 1992, 646; T. Sueda, S. Fukuda and M. Ochiai, *Org. Lett.*, 2001, **3**, 2387–2390; B. Karimi and J. Rajabi, *Synthesis*, 2003, 2373–2377; B. Karimi and J. Rajabi, *J. Mol. Catal. A: Chem.*, 2005, **226**, 165–169.

5 H. Tohma, T. Maegawa and Y. Kita, *Synlett*, 2003, 723–725; J. S. Foot, H. Kanno, G. M. P. Giblin and R. J. K. Taylor, *Synthesis*, 2003, 1055–1064; G. A. Hiegel and C. B. Gilley, *Synth. Commun.*, 2003, **33**, 2003–2009; N. Mori and H. Togo, *Synlett*, 2004, 880–882; N. N. Karade, G. B. Tiwari and D. B. Huple, *Synlett*, 2005, 2039–2042; N. Mori and H. Togo, *Tetrahedron*, 2005, **61**, 5915–5925; T. M. A. Shaikh, L. Emmanuvel and A. Sudalai, *Synth. Commun.*, 2007, **37**, 2641–2646; N. A. Owston, A. J. Parker and J. M. J. Williams, *Chem. Commun.*, 2008, 624–625; F.-Z. Su, J. Ni, H. Sao, Y. Cao, H.-Y. He and K.-N. Fan, *Chem.–Eur. J.*, 2008, **14**, 7131–7135; I. S. Nielsen, E. Taarning, K. Egeblad, R. Madsen and C. H. Christensen, *Catal. Lett.*, 2007, **116**, 35–40; X.-L. Liu, S.-Y. Lin, S.-R. Sheng, M.-H. Wei and B. Gong, *J. Chin. Chem. Soc. (Taipei)*, 2007, **54**, 1119–1122; S. K. Klitgaard, A. T. DeLa Riva, S. Helveg, R. M. Werchmeister and C. H. Christensen, *Catal. Lett.*, 2008, **126**, 213–217; N. A. Owston, T. D. Nixon, A. J. Parker, M. K. Whittlesey and J. M. J. Williams, *Synthesis*, 2009, 1578–1581; K. R. Reddy, M. Venkateshwar, C. U. Maheswari and S. Prashanthi, *Synth. Commun.*, 2009, **40**, 186–195; H. Miyamura, T. Yasukawa and S. Kobayashi, *Green Chem.*, 2010, **12**, 776–778; K. Kaizuka, H. Miyamura and S. Kobayashi, *J. Am. Chem. Soc.*, 2010, **132**, 15096–15098; F. Luo, C. Pan, J. Cheng and F. Chen, *Tetrahedron*, 2011, **67**, 5878–5882; N. Yamamoto, Y. Obora and Y. Ishii, *J. Org. Chem.*, 2011, **76**, 2937–2941; C. Liu, J. Wang, L. Meng, Y. Deng, Y. Li and A. Lei, *Angew. Chem., Int. Ed.*, 2011, **50**, 5144–5148; S. Gowrisankar, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 5139–5143.

6 A. Itoh, S. Hashimoto, T. Kodama and Y. Masaki, *Synlett*, 2005, 2107–2109; A. Itoh, S. Hashimoto and Y. Masaki, *Synlett*, 2005, 2639–2640; S. Hirashima and A. Itoh, *Synthesis*, 2006, 1757–1759; S. Hirashima, S. Hashimoto, Y. Masaki and A. Itoh, *Tetrahedron*, 2006, **62**, 7887–7891; S. Hirashima and A. Itoh, *Photochem. Photobiol. Sci.*, 2007, **6**, 521–524; S. Hirashima and A. Itoh, *Green Chem.*, 2007, **9**, 318–320; S. Hirashima and A. Itoh, *J. Synth. Org. Chem. Jpn.*, 2008, **66**, 748–756.

7 S. Hirashima, T. Nobuta, N. Tada, T. Miura and A. Itoh, *Org. Lett.*, 2010, **12**, 3645–3647.

8 When the oxidative esterification of 4-tert-butyltoluene (**1a**) was carried out using CBr_4 (0.1 equiv) in EtOH (1 mL) under molecular oxygen irradiated with fluorescent lamps for 24 h, ethyl benzoate (**2l**) was obtained only in 1% yield with recovered starting material in 72% yield.

9 H. Görner, *Photochem. Photobiol.*, 2003, **77**, 171–179; Y. Hou, L. A. Huck and P. Wan, *Photochem. Photobiol. Sci.*, 2009, **8**, 1408–1415.

10 N. Tada, K. Hattori, T. Nobuta, T. Miura and A. Itoh, *Green Chem.*, 2011, **13**, 1669–1671.

11 Aerobic photo-oxidation of toluenes to aldehydes catalyzed by organophotocatalyst have been reported, see: K. Ohkubo and S. Fukuzumi, *Org. Lett.*, 2000, **2**, 3647–3650; K. Ohkubo, K. Suga, K. Morikawa and S. Fukuzumi, *J. Am. Chem. Soc.*, 2003, **125**, 12850–12859.

12 Anthraquinone derivatives absorb visible light, see: UV-vis spectra of anthraquinone derivatives in supporting information.

13 When the oxidative esterification of 4-*tert*-butyltoluene (**1a**) was carried out using CBr_4 (0.1 equiv), EtOH (2 mL) in the presence of CF_2CO_2H (0.3 equiv) under molecular oxygen irradiated with fluorescent lamps for 24 h, ethyl benzoate (**2l**) was obtained only in 2% yield with recovered starting material in 69% yield.

14 Primary electron transfer from the toluene derivatives to AQN* is not excluded.