

Direct Aerobic Photo-Oxidative Synthesis of Aromatic Methyl Esters from Methyl Aromatics via Dimethyl Acetals

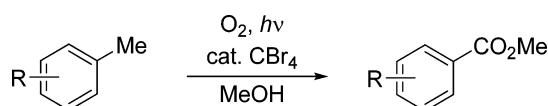
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ABSTRACT



A useful method for facile synthesis of aromatic methyl esters from methyl aromatics via dimethyl acetals by aerobic photo-oxidation using inexpensive and easily handled CBr_4 as catalyst is reported. This is the first example for direct preparation of the corresponding aromatic methyl esters from methyl aromatics.

Aromatic alkyl carboxylates have always attracted a great deal of interest in organic synthesis as versatile compounds or intermediates such as liquid crystal polymers, cosmetics, pharmaceuticals, agrochemicals, and food additives. One of the most general synthetic methods of aromatic esters from methyl aromatics has been achieved by oxidation of alkyl aromatics to carboxylic acids with heavy metals such as Cr, Mn, and V¹ followed by esterifications with alcohols.² In addition, oxidative esterifications of an aldehydes,³ alcohols,⁴ and acetals⁵ have also been developed.

Although a number of such efficient methods have been established, to the best of our knowledge, there has been no report on direct oxidative esterification from methyl aromatics. This is probably because methyl aromatics are unreactive and alcohols used as solvents are easily oxidized than methyl aromatics.

Due to an increasing demand for more environmentally benign synthesis, the development of a broadly applicable direct esterification method from methyl aromatics is highly desirable.

Recently, we reported aerobic photo-oxidation from methyl aromatics and primary alcohols to the corresponding carboxylic acids under mild conditions in the presence of a catalytic amount of bromine sources.⁶ In extending this aerobic photo-oxidation step, it occurred to us that the formation of dimethyl acetal in situ will make it possible to synthesize methyl esters from methyl aromatics in one pot (Scheme 1). Herein, we describe efficient direct transformation of methyl aromatics to methyl

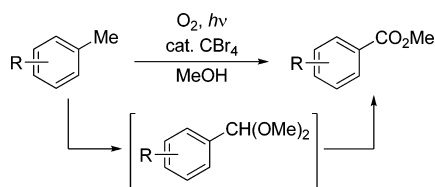
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Scheme 1. Direct Synthesis of Methyl Esters via Dimethyl Acetals



aryl carboxylates via dimethyl acetals under the aerobic photo-oxidation conditions.

To explore this approach, we selected 4-*tert*-butyltoluene (**1b**) as a test substrate for optimization of reaction conditions (Table 1). Although reaction conditions with various bromine sources

Table 1. Study of Reaction Conditions of Direct Aerobic Photo-Oxidative Synthesis of Methyl Esters from Methyl Aromatics^a

entry	bromine source (equiv)	time (h)	yield ^b (%)
1	Br ₂ (0.3)	10	19
2	48% aq HBr (0.3)	10	2
3	NBS (0.3)	10	7
4	LiBr (0.3)	10	NR ^c
5	NaBr (0.3)	10	NR ^c
6	KBr (0.3)	10	NR ^c
7	MgBr ₂ ·OEt ₂ (0.3)	10	3
8	Al Br ₃ (0.3)	10	16
9	TiBr ₄ (0.3)	10	14
10	ZrBr ₄ (0.3)	10	59
11	SmBr ₃ (0.3)	10	6
12	YbBr ₃ (0.3)	10	60
13	CBr ₄ (0.3)	10	90
14	CBr ₄ (0.3)	24	100 (99)
15 ^d	CBr ₄ (0.1)	24	100 (92)
16 ^d	-	24	NR ^c
17 ^{d,e}	CBr ₄ (0.1)	24	3
18 ^{d,f}	CBr ₄ (0.1)	24	NR ^c

^a A solution of 4-*tert*-butyltoluene (**1b**; 0.3 mmol) and bromine source in MeOH (5 mL) under an O₂ atmosphere was stirred and irradiated externally with four 22 W fluorescent lamps. ^b ¹H NMR analysis. Yield of isolated product in parentheses. ^c No reaction. ^d Used 1 mL of MeOH. ^e Under an Ar atmosphere. ^f In the dark.

were tried to accomplish the oxidative esterification, the yields of **2b** were unsatisfactory except for CBr₄ (entries 1–13). The excellent yield of **2b** was obtained by prolonging the reaction time to 24 h (entry 14). Further optimization using CBr₄ as catalyst led us to reduce the amount of catalyst to 0.1 equiv in 1 mL of MeOH (entry 15).⁷ It is noted that in all cases of light irradiation, CBr₄ and molecular oxygen were necessary for the direct oxidative esterification because the product **2b** was not obtained without them (entries 16–18).

The results of oxidation of various methyl aromatics under the optimized reaction conditions are summarized in Table 2. The methyl aromatics with an electron-donating group were good substrates that offer the corresponding methyl

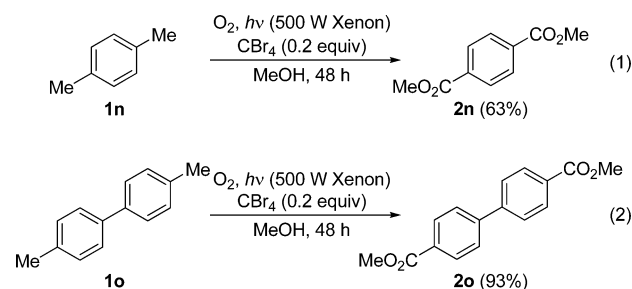
Table 2. Direct Aerobic Photo-Oxidative Synthesis of Methyl Esters from Methyl Aromatics^a

entry	Ar	light source ^b	time (h)	yield (%) ^c
1	Ph (1a)	fluorescent lamp	24	71 (2a)
2	4- <i>t</i> -BuC ₆ H ₄ (1b)	fluorescent lamp	24	92 (2b)
3	4-PhC ₆ H ₄ (1c)	fluorescent lamp	24	89 (2c)
4	4-BzC ₆ H ₄ (1d)	fluorescent lamp	24	70 (2d)
5	4-BrC ₆ H ₄ (1e)	xenon lamp	24	80 (2e) ^e
6	3-BrC ₆ H ₄ (1f)	xenon lamp	24	54 (2f)
7	2-BrC ₆ H ₄ (1g)	xenon lamp	24	34 (2g)
8	4-ClC ₆ H ₄ (1h)	xenon lamp	24	78 (2h) ^e
9	4-NCC ₆ H ₄ (1i)	xenon lamp	48	53 (2i) ^e
10	4-NO ₂ C ₆ H ₄ (1j)	xenon lamp	48	22 (2j) ^e
11	1-naphthyl (1k)	xenon lamp	48	57 (2k) ^e
12	2-naphthyl (1l)	xenon lamp	48	78 (2l) ^e
13	2-pyridyl (1m)	xenon lamp	48	2 ^d (2m)

^a A solution of substrate (0.3 mmol) and CBr₄ (0.1 equiv) in MeOH (1 mL) under an O₂ atmosphere was stirred and irradiated externally with the indicated lamp. ^b Fluorescent lamp: four 22 W lamps. Xenon lamp: 500 W lamp. ^c Yield of isolated product. ^d ¹H NMR analysis. ^e **2e** (57%), **2h** (66%), **2i** (32%), **2j** (12%), **2k** (12%), and **2l** (55%) were obtained under fluorescent lamp irradiation.

carboxylates in high yields (entries 2 and 3). However, the methyl aromatics with electron-withdrawing substituents, such as halogen, CN, and NO₂, afford the corresponding methyl benzoates in lower yields under irradiation of 500 W xenon lamp (entries 5–10). The reaction of 2-bromotoluene (**1g**) gave methyl 2-bromobenzoate in low yield due to its steric hindrance (entry 7). Furthermore, 1-methyl- (**1k**) and 2-methylnaphthalene (**1l**) were oxidized to the corresponding methyl esters in moderate to good yields, respectively (entries 11 and 12). Unfortunately, 2-picoline (**1m**) seems to be a poor substrate, presumably due to the basic nitrogen of pyridine ring, which reacted with HBr, generated in situ (entry 13). Dimethyl terephthalate (**2n**) was easily obtained in good yield from *p*-xylene (**1n**) under mildly aerobic photo-oxidative conditions (Scheme 2, eq 1).⁸

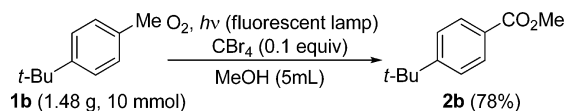
Scheme 2. Direct Aerobic Photo-Oxidative Synthesis of Methyl Esters from Methyl Aromatics



Interestingly, 4,4'-dimethylbiphenyl (**1o**) also afforded the corresponding dimethyl ester **2o**, which is a good intermediate for high-performance materials in excellent yield (Scheme 2, eq 2).

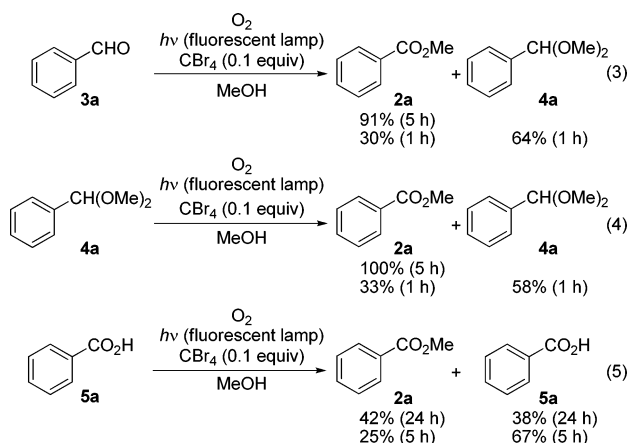
We also attempted the gram-scale synthesis of methyl ester under the optimized conditions mentioned above. Although, in general, photoreaction is difficult at high concentration, fortunately, methyl ester **2b** was obtained in good yield even at 10 mmol scale (30 w/v %) (Scheme 3).

Scheme 3. Gram-Scale Synthesis of Methyl Esters



During this process, a small amount of 4-*tert*-butylbenzaldehyde (**3b**) was detected.⁹ In order to examine the intermediate of this reaction, benzaldehyde (**3a**) was subjected to similar aerobic photo-oxidation conditions for 5 h to obtain **2a** in 91% yield. We also found that dimethyl acetal **4a** was formed from aldehyde **3a** in situ (Scheme 4, eq 3).

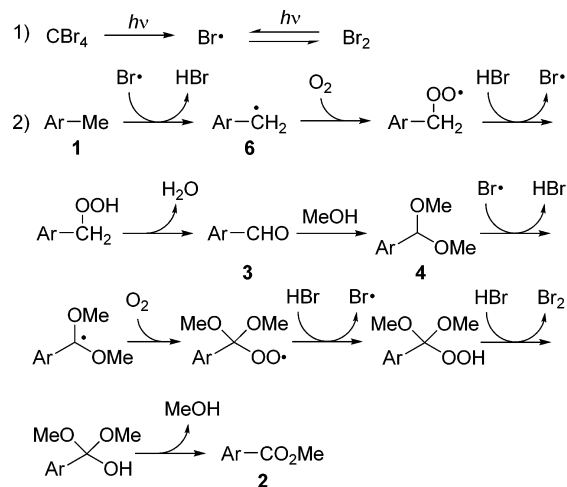
Scheme 4. Study of Reaction Intermediates



Moreover, **4a** was transformed to **2a** under the same reaction conditions (Scheme 4, eq 4). These results suggest that the reaction proceeds through the aldehyde **3** and dimethyl acetal **4** as intermediates. In addition, esterification of carboxylic acid **5a** was slow under these conditions, and methyl ester **2a** was obtained in 42% yield with recovery of **5a** (38%) even after 24 h (Scheme 4, eq 5).

On the basis of our previous studies in related reactions⁶ and the results mentioned above, a plausible mechanistic pathway is shown in Scheme 5. The first step involves abstraction of hydrogen radical from methyl aromatics with bromine radical, generated from CBr_4 under light irradiation, to produce the radical species **6**. Molecular oxygen is trapped with **6**, followed by dehydration to afford aldehyde **3**, which is transformed to dimethyl acetal **4** under the reaction

Scheme 5. Plausible Path of the Aerobic Photo-Oxidation of Methyl Aromatics



conditions in methanol. Acetal **4** is oxidized to methyl ester **2** under aerobic photo-oxidative conditions.

In conclusion, we report a useful method for facile synthesis of aromatic methyl carboxylates from methyl aromatics via dimethyl acetal by aerobic photo-oxidation using inexpensive and easily handled CBr_4 as catalyst. This is the first example for direct preparation of the corresponding methyl esters from methyl aromatics.

Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(7) Ethyl 4-*tert*-butylbenzoate was obtained only in 1% yield when ethanol was used as solvent with recovery of 4-*tert*-butyltoluene (62%) under the optimal conditions.

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(9) 4-*tert*-Butylbenzaldehyde (**3b**) was obtained in 8% yield for 4 h under the optimal conditions (**2b** and **1b** were obtained in 22% and 63% yields, respectively).