Direct synthesis of α-bromoketones from alkylarenes by aerobic visible light photooxidation†

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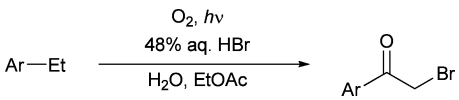
The direct synthesis of α-bromoketones from alkylarenes by aerobic photooxidation with hydrobromic acid is reported. The key success for this direct oxidative reaction is due to control of bromination with acetic acid and ethanol, which are generated *in situ* by solvolysis of ethyl acetate in the course of the reaction.

Introduction

The development of a selective and direct oxidative conversion of hydrocarbons into multifunctional organic compounds under metal-free conditions is a most challenging research theme in modern organic synthesis.[1] This is because the initial products, such as alcohol or carbonyl compounds, are usually more susceptible to oxidation than the starting materials.[2]

α-Bromoketones are one of the most important intermediates in the synthesis of a variety of bioactive compounds,[3] and have been generally synthesized from ketones,[4–8] alcohols,[9] olefins,[5a,10] and epoxides,[11] which are higher oxidized starting materials than alkylarenes. Although these approaches provide efficient access to α-bromoketones, the direct syntheses of α-bromoketones from alkylarenes, which are lower oxidized starting materials, require more drastic reaction conditions.[12] Recently, we have studied aerobic photooxidations under visible light irradiation with general purpose fluorescent lamps.[13] Molecular oxygen has received much attention as the ultimate oxidant, since it is photosynthesized by plants, produces little waste, is inexpensive and of larger atom efficiency than other oxidants. In the course of our further study, we found a direct oxidative synthesis step of α-bromoketones from alkylarenes under aerobic visible light irradiation conditions (Scheme 1). Herein, we report the detailed study of this reaction, including scope, limitation and mechanism.

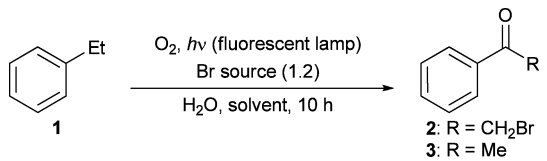


Scheme 1 Direct synthesis of α-bromoketones from alkylarenes.

Results and discussion

First, we optimized the reaction conditions for aerobic photooxidation of ethylbenzene (**1**) as a test substrate, and found that hydrobromic acid was the most effective reagent among the examination conditions. Table 1 shows the results for optimization of these reaction conditions, and water is found to play an important role for the progress of the reaction (entries 12 and 20–25). A lower yield of **2** and formation of benzoic acid, a by-product, were observed when xenon or Hg lamps were used instead of a fluorescent lamp (entries 26–28).[14] Both molecular oxygen

Table 1 Study of reaction conditions[a]



Entry	Br source	Solvent	H_2O/μL	Yield (%)[b] 2	3
1	LiBr	EtOAc	0	trace	14
2	NaBr	EtOAc	0	0	0
3	KBr	EtOAc	0	0	0
4	$MgBr_2$	EtOAc	0	0	13
5	$CaBr_2$	EtOAc	0	1	47
6	$AlBr_3$	EtOAc	0	0	0
7	$CoBr_2$	EtOAc	0	0	25
8	$SmBr_2$	EtOAc	0	3	47
9	NBS	EtOAc	0	6	trace
10	CBr_4	EtOAc	0	4	2
11	Br_2	EtOAc	0	21	13
12	48% aq. HBr	EtOAc	0	24	2
13	48% aq. HBr	CH_2Cl_2	0	17	44
14	48% aq. HBr	Benzene	0	8	59
15	48% aq. HBr	MeCN	0	8	0
16	48% aq. HBr	Hexane	0	6	16
17	48% aq. HBr	Acetone	0	0	0
18	48% aq. HBr	THF	0	0	1
19	48% aq. HBr	MeOH	0	0	0
20	48% aq. HBr	EtOAc	0	68	11
21	48% aq. HBr	EtOAc	50	73(68)	10
22	48% aq. HBr	EtOAc	100	71	14
23	48% aq. HBr	EtOAc	150	69	17
24	48% aq. HBr	EtOAc	200	52	33
25	48% aq. HBr	EtOAc	300	0	0
26[c,h]	48% aq. HBr	EtOAc	500	1	1
27[d,h]	48% aq. HBr	EtOAc	50	30	trace
28[e,h]	48% aq. HBr	EtOAc	50	4	1
29[f]	48% aq. HBr	EtOAc	50	3	2
30[g]	48% aq. HBr	EtOAc	50	0	0

[a] Conditions: **1** (0.3 mmol)/48% aq. HBr (1.2 equiv.)/H_2O/solvent/*hν* (fluorescent lamp)/room temperature/O_2 balloon. [b] ^1H NMR yields. Numbers in parenthesis is isolated yield. [c] Xenon lamp (500 W). [d] UV lamp (100 W). [e] UV lamp (400 W). [f] Ar balloon. [g] In the dark. [h] Yield of benzoic acid **4**: 54% (entry 26), 17% (entry 27), and 36% (entry 28).

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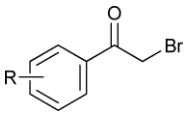
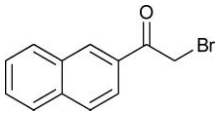
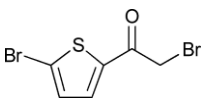
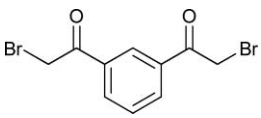
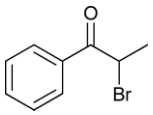
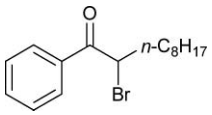
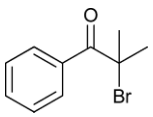
Table 2 Direct synthesis of α-bromoketones[a]

substrate → (O_2, $h\nu$ (fluorescent lamp), 48% aq. HBr (equiv), H_2O, EtOAc) → product

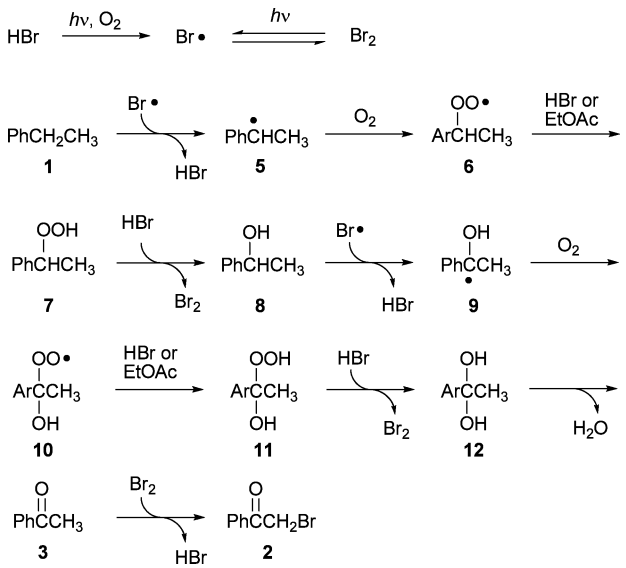
Entry	Product	HBr (equiv.)	H_2O (μL)	Time/h	Yield[b]
1		1.2	150	10	0[c]
2		1.2	150	10	76
3		1.5	170	10	76
4		1.5	100	10	72
5		1.5	100	10	66
6		2.0	100	24	61
7		2.0	100	24	66
8		2.0	100	24	45
9		2.0	200	24	60
10[d]		3.0	50	24	40
11[e]		3.0	200	24	50
12		1.5	50	10	61
13		1.5	50	10	63
14		3.0	0	24	57
15		2.0	100	10	45

[a] Conditions: substrate (0.3 mmol)/48% aq. HBr/H_2O–EtOAc/$h\nu$(fluorescent lamp)/room temperature/O_2 balloon. [b] Isolated yields. [c] *p*-Ethylanisole (74%) was recovered. 4-Methoxyphenol (4%) was obtained. [d] Substrate: 2-ethylthiophene. [e] Substrate: 1,3-diethylbenzene.

and visible light irradiation are necessary for this transformation, since **2** cannot be satisfactorily obtained without them (entries 29 and 30).

Table 2 shows the scope and limitations of the direct synthesis of α-bromoketones from various alkylarenes under the optimized reaction conditions as mentioned above. Ethylbenzenes, that possess an electron withdrawing group at the *para* position were converted to their corresponding α-bromoketones in high yields (entries 2–7), but *p*-ethylanisole, which possesses an electron-donating group, produced only 4-methoxyphenol, which was assumed to be produced by decomposition of 1-(4-methoxyphenyl)ethyl hydroperoxide, in 4% yield (entry 1).[15] A sterically demanding *ortho*-substituted substrate provided the corresponding α-bromoketones in moderate yield (entry 8). We noted that 2-ethylthiophene was directly converted to the 2-bromo-1-(5-bromo-2-thienyl)ethanone (entry 10), and also *m*-bis(bromoacetyl)benzene was directly synthesized from 1,3-diethylbenzene (entry 11). Furthermore, α-substituted α-bromoketones were obtained from the corresponding alkylbenzenes in good yields (entries 12–15).

A plausible reaction mechanism is shown in Scheme 2. The initial aerobic oxidation of ethylbenzene **1** to acetophenone **3** probably involves the following path: (1) generation of bromine radical by both aerobic photooxidation of hydrogen bromide and homolysis of bromine under visible light irradiation, (2) formation of benzyl radical species **5**, which traps molecular oxygen to produce **6**, (3) formation of hydroperoxide **7** by abstraction of hydrogen from hydrogen bromide or ethyl acetate,[16] (4) formation of alcohol **8** by reduction of **7**, and (5) production of acetophenone **3** from alcohol **8** through the same oxidation path.[17] Finally, **2** was produced by bromination with bromine, which is accelerated by hydrogen bromide or photoirradiation.[18]

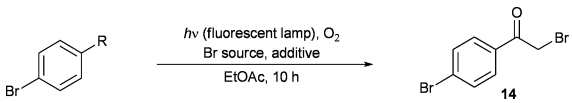


Scheme 2 Plausible mechanism.

The effect of additive water in the aerobic photooxidation is interesting, and the time course for direct synthesis of 2,4′-dibromoacetophenone (**14**) reveals a gradual hydrolysis of the ethyl acetate to acetic acid and ethanol (Fig. 1). After hydrolysis of ethyl acetate, a component of ethanol remaining was further oxidized to acetic acid at a late stage of the reaction.

Then, we investigated the influence of additives (Table 3). The aerobic photooxidation of **13** in the absence of water produced 2,4′-dibromoacetophenone (**14**) (44%) with α-ketoester (36%), which is obtained by over-oxidation of **14**. However, the aerobic photooxidation of **13** in the presence of water resulted in 2,4′-dibromoacetophenone (**14**) (72%) with α-ketoester (6%).

Table 3 Effect of additives[a]



Additive	R: Et [b]	OOH [b]	O [c]	O, Br [c]
—	44[d]	41	74	13
AcOH (5.6 mmol) EtOH (5.6 mmol)	0[f]	73	56	62
H_2O (100 μL, 5.6 mmol)	72[e]	79	48	78

[a] Conditions: substrate (0.3 mmol)/Br source/additive (5.6 mmol)/EtOAc (5 mL)/*hν* (fluorescent lamp)/room temperature/O_2 balloon. ^{1}H NMR yields (%) of 2,4′-dibromoacetophenone (**14**). [b] Br source is aq. HBr (1.5 equiv.). [c] Br source is Br_2 (0.75 equiv.). [d] Yield of α-ketoester (36%). [e] Yield of α-ketoester (6%). [f] SM (68%) was recovered.

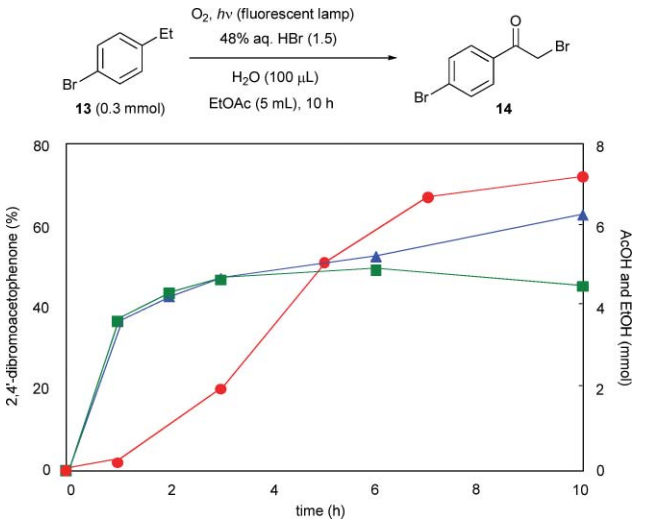


Fig. 1 Time course for direct synthesis of 2,4′-dibromoacetophenone (determined by ^{1}H NMR analyses). Reaction conditions: Table 2, entry 4. (a) (●) 2,4′-dibromoacetophenone (%). (b) (▲) AcOH (mmol). (c) (■) EtOH (mmol).

In contrast, in the presence of acetic acid and ethanol instead of water the reaction did not proceed, and **13** (68%) was recovered unchanged. It indicates that acetic acid and ethanol inhibited this oxidation at the early stage. Although **14** was recovered in 62% and 78% yields in the presence of acetic acid/ethanol and water, respectively, only 13% of **14** was recovered without additives. These results indicate that acetic acid and ethanol, that controlled the bromination of ketones and α-bromoketones, were not found in the early stage of this reaction; and in the late stage they were generated by hydrolysis of ethyl acetate. Both acetic acid and ethanol play an important role in the selective synthesis of α-bromoketones.

Conclusions

In conclusion, we have developed a direct synthesis method for α-bromoketones from alkylarenes by aerobic photooxidation with hydrobromic acid. The key success for this direct oxidative reaction is due to the control of bromination with acetic acid and ethanol, which are generated *in situ* by solvolysis of ethyl acetate in the course of the reaction. Further studies and additional applications are now in progress in our laboratory.

Experimental

General experimental

All dry solvents were obtained from Kanto Kagaku Co., Ltd. Other chemicals used were of reagent grade and were obtained from Aldrich Chemical Co., Tokyo Kasei Kogyo Co., Ltd. and Wako Pure Chemical Industries, Ltd. ^{1}H NMR and ^{13}C NMR spectra were obtained on a JEOL AL 400 spectrometer or JEOL EX 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts (δ) are reported in parts per million (ppm) downfield from internal Me_4Si. Mass spectra (MS) were obtained on a JEOL JMS-SX102A instrument. Preparative thin-layer chromatography (TLC) was carried out on precoated plates of silica gel (MERCK, silica gel F-254).

Typical experimental procedure

A typical example (Table 1, entry 21). A dry EtOAc solution (5 mL) of ethylbenzene (**1**) (31.8 mg, 0.3 mmol), H_2O (100 μL), and 48% aq. HBr (40.7 μL, 0.36 mmol) in a Pyrex test tube equipped with an O_2 balloon was stirred and irradiated with four 22 W fluorescent lamps, which were set up at a distance of 65 mm, for 10 h. The temperature of the final stage of this reaction was about 40 °C. The reaction mixture was concentrated under reduced pressure, and the pure product was obtained by preparative TLC. All products are known compounds. Products were characterized by comparison with authentic samples.

*2-Bromoacetophenone (phenacyl bromide) (**2**)*[19]. Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 4.46 (s, 2H); MS m/z 198 (M^+), 105.

2-Bromo-4′-phenylacetophenone (Table 2, entry 2)[19]. Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 7.8 Hz, 2H), 7.48 (t, J = 7.8 Hz, 2H), 7.42 (t, J = 7.8 Hz, 1H); MS m/z 274 (M^+), 181, 152.

2,4′-Dibromoacetophenone (Table 2, entry 4)[19]. Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 4.40 (s, 2H); MS m/z 278 (M^+), 200, 183, 169, 155.

2-Bromo-4′-chloroacetophenone (Table 2, entry 5)[19]. Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 4.41 (s, 2H); MS m/z 234 (M^+), 184, 169, 139, 125, 111, 75.

2-Bromo-4′-cyanoacetophenone (Table 2, entry 6)[20]. colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 8.6 Hz, 2H), 4.43 (s, 2H); MS m/z 223 (M^+), 130, 116, 102.

2-Bromo-4′-nitroacetophenone (Table 2, entry 7)[19]. Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 9.0 Hz, 2H), 8.16 (d, J = 9.0 Hz, 2H), 4.46 (s, 2H); MS m/z 243 (M^+), 150, 120, 104.

2,2′-Dibromoacetophenone (Table 2, entry 8)[21]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.7, 1.6 Hz, 1H), 7.48

(dd, J = 7.7, 1.6 Hz, 1H), 7.41 (td, J = 7.7, 1.6 Hz, 1H), 7.35 (td, J = 7.7, 1.6 Hz, 1H), 4.49 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.84, 138.63, 133.72, 132.51, 129.75, 127.58, 119.11, 33.88; MS m/z 278 (M^+), 183, 169, 155.

2-Bromo-2′-acetonaphthone (Table 2, entry 9)[19]. Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.03 (dd, J = 8.8, 2.0 Hz, 1H), 7.98 (dd, J = 8.4, 0.6 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.67–7.61 (m, 1H), 7.61–7.54 (m, 1H), 4.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 136.6, 133.1, 132.0, 131.6, 130.4, 129.7, 129.5, 128.5, 127.8, 124.8, 31.7; MS m/z 248 (M^+), 158, 141, 127, 115, 101, 77.

2-Bromo-1-(5-bromo-2-thienyl)ethanone (Table 2, entry 10)[22]. Colorless leaflets (recrystallized from dichloromethane–hexane); mp 91–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 4.0 Hz, 1H), 7.15 (d, J = 4.0 Hz, 1H), 4.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 142.4, 134.0, 131.8, 124.7, 29.9; MS m/z 284 (M^+), 189, 175, 111. Anal. Calcd for $C_6H_4Br_2OS$: C, 25.38; H, 1.42. Found: C, 25.78; H, 1.60.

m-*Bis(bromoacetyl)benzene (Table 2, entry 11)*[23]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (t, J = 1.7 Hz, 1H), 8.23 (dd, J = 7.7, 1.7 Hz, 2H), 7.67 (t, J = 7.7 Hz, 1H), 4.49 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 134.8, 134.1, 129.9, 129.5, 30.6; MS m/z 320 (M^+), 225, 147, 118.

2-Bromopropiophenone (Table 2, entry 12)[24]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.4 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.4 Hz, 2H), 5.30 (q, J = 6.4 Hz, 1H), 1.91 (d, J = 6.4 Hz, 3H); MS m/z 212 (M^+), 105, 77.

2-Bromo-1-phenyl-1-decanone (Table 2, entry 13)[25]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.4 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.4 Hz, 2H), 5.13 (t, J = 7.2 Hz, 1H), 2.28–2.03 (m, 2H), 1.60–1.10 (m, 12H), 0.88 (t, J = 7.0 Hz, 3H); MS m/z 310 (M^+), 231, 198, 120, 105, 77.

2-Bromoisobutyrophenone (Table 2, entry 14)[26]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.4 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 2.04 (s, 6H); MS m/z 226 (M^+), 105, 77.

2-Bromo-2-phenylacetophenone (Table 2, entry 15)[27]. Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.96 (m, 2H), 7.59–7.50 (m, 3H), 7.48–7.42 (m, 2H), 7.40–7.29 (m, 3H), 6.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 135.9, 134.1, 133.7, 129.1, 129.0, 128.8, 51.0; MS m/z 195 [(M-Br)$^+$], 105, 77.

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