

A simple synthetic protocol for oxidation of alkyl-arenes into ketones using a combination of HBr–H₂O₂

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This work is dedicated to my former Teacher Late Professor P. Sengupta, Department of Chemistry, Kalyani University, 741 235, India for his constant encouragement and moral support

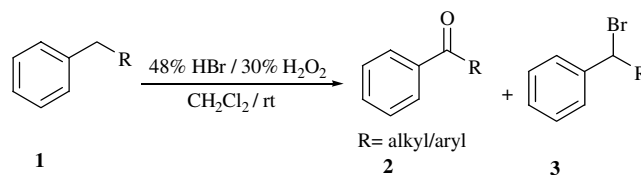
Abstract—A wide variety of alkyl- and cycloalkyl-arenes undergo benzylic C–H oxidation by employing a combination of 48% hydrogen bromide and 30% hydrogen peroxide in dichloromethane at room temperature. In addition, a chemoselective oxidation at the benzylic position is feasible by deactivating the aromatic ring using the same combination.

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The introduction of a carbonyl functionality mainly at the benzylic position from the corresponding alkyl-arenes is an important transformation in organic synthesis¹ because the product ketones can serve as valuable building blocks for the manufacture of speciality chemicals in pharmaceuticals and agrochemicals. In addition, aryl ketones are integral parts of various natural products.² Numerous methods have been developed for the oxidation of alkyl-arenes into the corresponding ketones.³ Most employ Cr(VI)⁴ or KMnO₄⁵ based reagents either in stoichiometric or excess quantities. In the last few years, other methods have been devised for introducing a carbonyl moiety at the benzylic position, for example, NaBiO₃/AcOH,⁶ Mn(III)salen complex/iodosobenzene,⁷ Gif reagent/picolinic acid,⁸ RuCl₂(PPh₃)₃-*t*-BuOOH,⁹ molybdenum(VI)-peroxo complex/H₂O₂,¹⁰ Cu(II) complex/H₂O₂,¹¹ NHTPPI/CuCl under an oxygen atmosphere,¹² and in situ generated Bi(0) as catalyst along with *tert*-butyl hydroperoxide and picolinic acid.¹³ Recently, Sudalai and co-workers reported the benzylic C–H oxidation¹⁴ of alkyl-arenes using a combination of NaIO₄/LiBr/H⁺. Though all these methods provide good yields, some have drawbacks such as lengthy work-up procedures, harsh reaction conditions¹³ and require absolutely dry⁹ and inert media. Thus, there is a need to develop an operationally simple, safe- and widely usable method. In continuation of our research

programme on the development of new synthetic methodologies,¹⁵ we were interested in developing a procedure for C–H oxidation that did not require any metal or metal-based reagents. Our idea was based on the following assumption: if the alkyl-arene undergoes bromination selectively at the benzylic position, it can slowly hydrolyze into the corresponding alcohol and finally it can be oxidized to a ketone. As a result, it might be possible to achieve a one-pot benzylic C–H oxidation if all three steps proceed in a sequential manner. In this Letter, we report an unprecedented, mild and simple synthetic protocol for the oxidation of alkyl- and cycloalkyl-arenes to their corresponding carbonyl compounds at room temperature using a combination of 48% HBr and 30% H₂O₂ as shown in Scheme 1.

Ethylbenzene was chosen as a model substrate to find optimal conditions (Table 1). We found that a (1: ≈ 0.9:5) substrate/hydrogen bromide/hydrogen peroxide ratio in dichloromethane (1 mL per mmol of



Scheme 1.

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Table 1. Optimization of the HBr–H₂O₂ catalyzed C–H oxidation of ethylbenzene^a

Run	48% HBr (mL/mmol)	30% H ₂ O ₂ (mL/mmol)	Ethylbenzene ^b (%)	Acetophenone ^b (%)	(1-Bromoethyl)benzene ^b (%)
1	0.2/1.72	0.6/5.0	28	13	59
2	0.2/1.72	1.2/10.0	25	61	14
3	0.2/1.72	1.8/15.0	8	46	46
4	0.5/4.30	3.0/25.0	5	80	15

^a All the reactions were carried out on 5 mmol scale.

^b The ratio of the products and starting material was determined from the ¹H NMR spectrum of the crude reaction mixture.

substrate) provided the best results. The percentage of conversion and ratio of acetophenone, (1-bromoethyl)benzene and unreacted ethylbenzene were determined from integration of the methyl signal in the ¹H NMR spectrum of the crude product. In ethylbenzene the methyl signal resonated at δ 0.89, for (1-bromoethyl)benzene at δ 2.07 and in acetophenone it appeared at δ 2.60.

Using optimized reaction conditions,¹⁶ *n*-butylbenzene (Table 2, entry **b**) was converted into the desired ketone **2b** in 45% yield along with brominated product **3b** in 42% yield with an overall 60% conversion. Interestingly, we found that brominated products **3b** and **3l** could be oxidized to the desired ketones **2b** and **2l** in 75% and 80% yields when they were treated independently with the HBr–H₂O₂ combination under identical reaction conditions. With, *n*-hexylbenzene we observed only 42% conversion as shown in Table 2. From this observation, we can conclude that the present protocol is not suitable for a long chain alkyl-arenes due to slow hydrolysis of the intermediate bromide or incomplete benzylic bromination. However, on substitution of the aromatic ring of the *n*-hexylbenzene by nitration (Table 2, entry **d**), it was possible to achieve oxidation in 70% yield. Following the same procedure, alkyl- and cycloalkyl-arenes (Table 2, entries **e–g**) underwent selective oxidation smoothly at the benzylic position in good yields.

Next, we were keen to investigate whether the same method could be applied to a substrate containing a non-activated hydroxyl group. 3-Phenyl-1-propanol (Table 2, entry **h**) underwent benzylic oxidation to give the desired ketone **2h** without affecting the hydroxyl

group. On the other hand, when the oxidation was tried with 4-phenylbutanol, we obtained an inseparable mixture of products instead of the desired ketone. Hydroxyl protected substrates (Table 2, entries **i–m**) underwent oxidation smoothly to the corresponding products **2i–m** in good yields under similar reaction conditions. From these results, it is clear that benzylic C–H oxidation occurs without affecting protecting groups such as acetate or benzoate. In addition, oxidized product **2l** can be easily hydrolyzed on treatment with 0.1 M NaOMe in methanol in good yield. Thus a carbonyl group can be introduced in the presence of a masked hydroxyl group.

We noted¹⁷ that the combination of HBr and H₂O₂ can be used for ring bromination of alkyl-arenes in the presence of tetrabutylammonium bromide as an additive. Moreover, using a combination of HBr and *tert*-butylhydroperoxide (70%), it is possible to achieve ring bromination of various electron-rich aromatic substrates.¹⁸ From these results, it is apparent that this reagent combination can react by either a radical pathway to provide side-chain brominated products or aromatic electrophilic substitution products depending on the substrates as well as the reaction conditions. Thus, we were interested in studying whether benzylic C–H oxidation was possible for a substrate containing an electron-rich substituent. We chose 4-ethylphenol and 4-ethylaniline as substrates for this study and the results are summarized in Table 3. If an electron-donating group such as –OH or –NHAc (Table 3, entries **4a** and **4c**) was present on the aromatic ring, then aromatic ring bromination occurred instead of benzylic C–H oxidation. However, on substitution of the aromatic ring either by hydroxyl

Table 2. Benzylic C–H oxidation of alkyl-arenes using a combination of 48% HBr and 30% H₂O₂ under biphasic conditions at room temperature

Entry	Substrate 1	Time (h)	Product ^a 2	Conversion	Ratio ^b 2:3	Yield ^c (%)
a	Ethylbenzene	12	Acetophenone	95	84:16	75
b	<i>n</i> -Butylbenzene	20	Butyrophenone	60	50:50	45 ^d
c	<i>n</i> -Hexylbenzene	30	Hexanophenone	42	30:70	30 ^d
d	4-Nitro- <i>n</i> -hexylbenzene	28	4-Nitro- <i>n</i> -hexanophenone	95	90:10	70
e	4-Ethylbiphenyl	12	4-Acetylbiphenyl	100	100:0	85
f	Diphenylmethane	12	Benzophenone	100	100:0	91
g	1,2,3,4-Tetrahydronaphthalene	20	α -Tetralone	70	100:0	90 ^d
h	3-Phenyl-1-propanol	12	2-Benzoyl ethanol	100	100:0	72
i	2-Phenylethyl acetate	24	Benzoylmethyl acetate	100	100:0	72
j	3-Phenylpropyl acetate	25	2-Benzoyl ethyl acetate	100	100:0	88
k	4-Phenylbutyl acetate	30	3-Benzoyl propyl acetate	100	100:0	88
l	5-Phenylpentyl acetate	30	4-Benzoyl butyl acetate	100	45:55	40
m	4-Phenylbutyl benzoate	20	3-Benzoyl propyl benzoate	100	90:10	71

^a All the products were characterized by spectroscopic analysis, known compounds were compared with authentic data.

^b Ratio was determined from the ¹H NMR spectrum.

^c Isolated yield.

^d Yields based on starting material recovery.

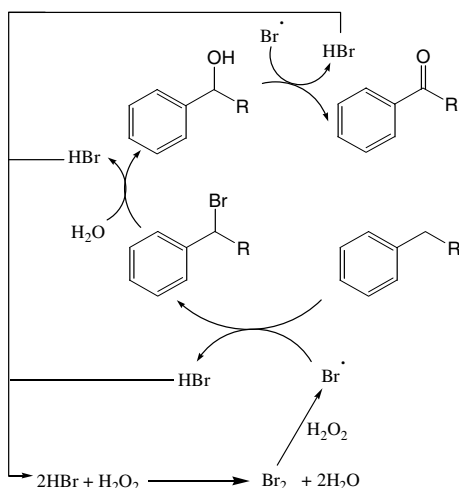
Table 3. Competing ring bromination versus benzylic C–H oxidation using the HBr/H₂O₂ combination

Entry	Substrate 4	Time (h)	Product ^a 5	Yield ^b (%)
a		3		76 ^c
b		8		72
c		3		71
d		15		70

^a All the products were characterized by spectroscopic analysis.

^b Isolated yield.

^c Yield based on starting material recovery.

**Scheme 2.** A plausible mechanism for the benzylic C–H oxidation.

protection (entry **4b**) or by nitration (entry **3d**), it was possible to achieve benzylic C–H oxidation over ring bromination.

A mechanism portraying the probable sequence of events is shown in **Scheme 2**. Hydrobromic acid reacts with aqueous hydrogen peroxide to liberate molecular bromine in solution which can generate bromine radicals in the presence of hydrogen peroxide. Radical bromination at the benzylic position of the alkyl-arene occurs with the product undergoing slow hydrolysis to the corresponding alcohol, which is ultimately oxidized to the ketones.

The efficiency and generality of the present method can be realized by comparing our results with those of some recently reported procedures (**Table 4**). The results are compared with respect to the reaction times, reaction conditions, mol % of the catalysts and yields.

In conclusion, we have devised a new and useful synthetic protocol for the oxidation of various alkyl- and cycloalkyl-arenes to the corresponding carbonyl compounds using a combination of 48% aqueous HBr and 30% H₂O₂ in dichloromethane–water biphasic system at room temperature. A carbonyl group can also be installed at the benzylic position in the presence of a non-activated primary hydroxyl group. The significant

Table 4. Comparison of the results of C–H oxidation of ethylbenzene to acetophenone with other catalysts

Entry	Oxidant (equiv)	Catalyst (equiv)	Solvent	Reaction conditions/time (h)	Yield (%)
1	—	KMnO ₄ /Al ₂ O ₃ (1:4) (3.2 g per mmol)	CH ₂ Cl ₂	rt/141	58 ⁵
2	PhI = O (3 equiv)	Mn(III) salen complex (0.15 equiv)	CH ₃ CN	0 °C/3	60 ⁷
3	<i>t</i> -BuOOH (3 equiv)	Fe(III) compound (0.02 equiv) and 2-picolinic acid (0.05 equiv)	CH ₃ CN and C ₅ H ₅ N	rt/10	84 ⁷
4	<i>t</i> -BuOOH (4 equiv)	RuCl ₂ (PPh ₃) ₃ (0.01)	Dry C ₆ H ₆	20 °C under argon/2	91 ⁹ total conversion is 58%
5	H ₂ O ₂ (40 equiv)	Mo(VI) peroxo complex (0.05)	CH ₃ CN	80 °C under O ₂ /15	7 ¹⁰
6	H ₂ O ₂ (10 equiv)	Cu(II) salen–H ₄ complex	CH ₃ CN	80 °C/5	86 ¹¹
7	H ₂ O ₂ (5 equiv)	HBr (0.9)	CH ₂ Cl ₂	rt/12	75

features of the present method include the ease of operation, high efficiency and mild conditions.

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16. *Typical experimental procedure*: To a stirred solution of alkyl-arene (5 mmol) and aq 48% HBr (0.5 mL, 4.30 mmol) in 5 mL of dichloromethane was added 30% H₂O₂ (3 mL, 25 mmol) at room temperature. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion, saturated aqueous sodium metabisulfite solution (2 mL) was added and the reaction mixture was extracted with dichloromethane (2 × 20 mL). The combined organic extract was washed with water then brine (1 × 10 mL) and dried over anhydrous sodium sulfate. The organic layer was concentrated on a rotavapour and the crude residue was passed through a silica gel column to obtain the pure products. *2-Benzoyl ethanol 2i*: ¹H NMR (CDCl₃, 400 MHz): 2.33 (br s, 1H, D₂O exchangeable), 3.23 (t, *J* = 5.6 Hz, 2H), 4.02 (t, *J* = 5.6 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.54–7.58 (m, 1H), 7.94 (d, *J* = 7.6 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): 40.5, 58.1, 127.9 (2C), 128.5 (2C), 133.4, 136.5, 200.1; IR (neat): 3411 (OH), 1685 (CO) cm⁻¹; Anal. Calcd. for C₉H₁₀O₂ (150.18): C, 71.98; H, 6.71. Found: C, 71.72; H, 6.79.
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