A New Method for the Benzylic Oxidation of Alkylarenes Catalyzed by Hypervalent Iodine(III)

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Abstract: A convenient and simple procedure is described for the oxidation of the benzylic C–H moiety of alkylarenes to give the corresponding aryl ketones, using *tert*-butyl hydroperoxide and *m*-chloroperoxybenzoic acid in the presence of a catalytic amount of the hypervalent iodine reagent, (diacetoxyiodo)benzene. The reactions typically occur in good yields in 2,2,2-trifluoroethanol as the solvent and at room temperature.

Key words: benzylic oxidations, hypervalent iodine reagent, (diacetoxyiodo)benzene, ketones

The oxidation of benzylic C–H bonds to give the corresponding ketones is a well-known transformation in organic synthesis, and the resulting products represent important intermediates for the manufacture of high-value fine chemicals, agrochemicals and pharmaceuticals.[1] There are numerous methods available for benzylic oxidations, with the use of stoichiometric quantities of oxidants such as potassium permanganate or potassium dichromate being common approaches.[2] A number of additional oxidation catalysts have been described, but most of these involve toxic metals, such as chromium, cobalt, ruthenium, manganese, bismuth and rhodium, and their overall applicability is limited.[3] The use of hypervalent iodine reagents, which possess low toxicity and high stability, has been described as an improved process for benzylic oxidations, with the reagents themselves typically being applied in stoichiometric quantities.[4] In 2010, Zhao and Yeung reported a novel method for allylic oxidation using three equivalents of the hypervalent iodine reagent, (diacetoxyiodo)benzene (DIB) in combination with four equivalents of *tert*-butyl hydroperoxide (TBHP) in an ester solvent; two examples of benzylic oxidation were included in this publication.[5] Using this protocol, Zhao found that unactivated methylene groups could also be oxidized into ketones.[6]

The application of catalytic amounts of hypervalent iodine reagents has gained significant importance, with growing interest in the development of environmentally benign synthetic transformations.[7] In these reactions, a catalytic amount of an iodine-containing molecule together with a stoichiometric oxidant are used. The oxidant generates the hypervalent iodine reagent in situ, and after the oxidative transformation, the reduced iodine-containing molecule is reoxidized. Zhdankin and co-workers reported a facile benzylic C–H oxidation using Oxone® as the oxidant in the presence of catalytic amounts of iodobenzene (PhI) and ruthenium chloride ($RuCl_3$). The process involved two catalytic redox cycles, and the in situ generated, highly reactive hypervalent iodine(V) intermediate was responsible for the oxidation.[4e] To extend the scope of catalytic hypervalent iodine reagents in organic synthesis, we previously described a new and environmentally benign benzylic oxidation using iodobenzene as the catalyst and *m*-chloroperoxybenzoic acid (MCPBA) as the oxidant in the presence of potassium bromide in water.[8] In continuation of this work, we report herein a convenient and simple procedure for the oxidation of benzylic C–H groups of alkylarenes with *tert*-butyl hydroperoxide and *m*-chloroperoxybenzoic acid in the presence of a catalytic amount of (diacetoxyiodo)benzene.

At the outset of this work, ethylbenzene was chosen as a model substrate, and the benzylic oxidation reaction was investigated using (diacetoxyiodo)benzene (0.1 equiv), *tert*-butyl hydroperoxide (0.5 equiv) and different oxidants (2.0 equiv) in ethyl acetate at 60 °C for 18 hours. In each case, the expected product (acetophenone) was obtained in poor yield, with *m*-chloroperoxybenzoic acid proving to be the most effective oxidant (Table 1, entries 1–4). It became apparent that the yield was dependent on the amount of *tert*-butyl hydroperoxide utilized. The highest yield of 68% was obtained using three equivalents of this reagent at room temperature for 18 hours (Table 1, entries 5–8). The effect of the amount of *m*-chloroperoxybenzoic acid was also investigated, with two equivalents being the most suitable (Table 1, entries 7, 9 and 10). The solvent also influenced the reaction significantly: when (diacetoxyiodo)benzene (0.1 equiv), *tert*-butyl hydroperoxide (3.0 equiv) and *m*-chloroperoxybenzoic acid (2.0 equiv) were used for the benzylic oxidation of ethylbenzene in 2,2,2-trifluoroethanol (TFE) at room temperature over 18 hours, the reaction provided a near quantitative yield of acetophenone (Table 1, entry 14). The use of acetonitrile and acetone also led to the desired product in good yields, however, dichloromethane, tetrahydrofuran and cyclohexane resulted in poor yields (Table 1, entries 11–13, 15 and 16).

Having established optimized conditions, the catalytic benzylic oxidation of a series of alkylarenes **1** into the corresponding carbonyl compounds **2** was investigated (Scheme 1), and the results are summarized in Table 2.

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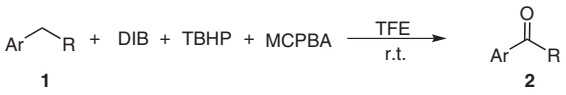


Scheme 1 Benzylic oxidation

As shown in Table 2, this benzylic oxidation reaction was compatible with various cyclic alkylarenes **1a–f** and provided the corresponding ketones in good to excellent yields (Table 2, entries 1–6). With linear alkylbenzenes **1g–j**, the size of the group on the benzene ring influenced the yield: as its size increased, the yield decreased (Table 2, entries 7–10). Compared with ethylbenzene, it was strange that 1-ethyl-4-methoxybenzene (**1k**), which has an electron-donating group, afforded the corresponding product in moderate yield, while the *p*-nitro derivative **1l**, having an electron-withdrawing group only led to a poor yield of product (Table 2, entries 11 and 12). Two diarylmethanes (**1m**,**n**) were also subjected to this oxidation reaction, however, both these substrates showed poor reactivity leading to low yields of the expected products (Table 2, entries 13 and 14).

A plausible mechanism for the present reaction is shown in Scheme 2.[5] Initially, the hypervalent iodine reagent, (diacetoxyiodo)benzene, undergoes transformation into the unstable species PhI(OO*t*-Bu)$_2$. This is converted into the reactive *tert*-butylperoxy radical (*t*-BuOO•), which then initiates the benzylic oxidation reaction with ethylbenzene. The reduced by-product, iodobenzene is reoxidized into the hypervalent iodine reagent by *m*-chloroperoxybenzoic to complete the catalytic cycle.

Table 1 Optimization of the Catalytic Benzylic Oxidation of Ethylbenzene

Entry	Oxidant (equiv)	TBHP (equiv)	Solvent	Yield (%)[a]
1	MCPBA (2.0)	0.5	EtOAc	40[b]
2	Oxone® (2.0)	0.5	EtOAc	20[b]
3	$NaBO_3$ (2.0)	0.5	EtOAc	15[b]
4	$Na_2S_2O_8$ (2.0)	0.5	EtOAc	17[b]
5	MCPBA (2.0)	1.2	EtOAc	37
6	MCPBA (2.0)	2.0	EtOAc	57
7	MCPBA (2.0)	3.0	EtOAc	68
8	MCPBA (2.0)	4.0	EtOAc	62
9	MCPBA (1.5)	3.0	EtOAc	49
10	MCPBA (2.5)	3.0	EtOAc	50
11	MCPBA (2.0)	3.0	CH_2Cl_2	23
12	MCPBA (2.0)	3.0	MeCN	83
13	MCPBA (2.0)	3.0	THF	18
14	**MCPBA (2.0)**	**3.0**	**TFE**	**96**
15	MCPBA (2.0)	3.0	acetone	76
16	MCPBA (2.0)	3.0	cyclohexane	21

[a] Yield of isolated product.
[b] Reaction was carried out at 60 °C.

Table 2 Catalytic Benzylic Oxidation of Alkylarenes

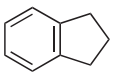
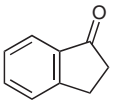
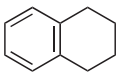
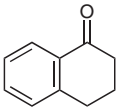
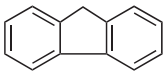
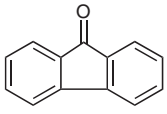
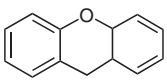
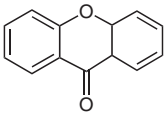
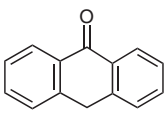
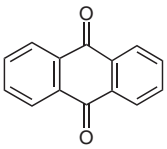
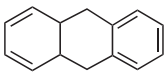
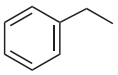
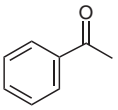
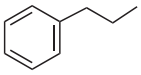
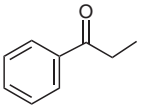
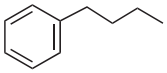
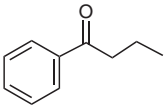
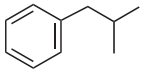
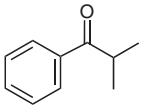
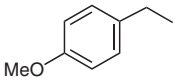
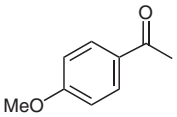
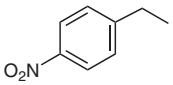
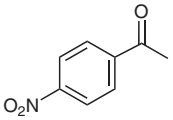
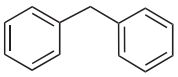
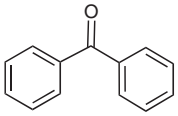
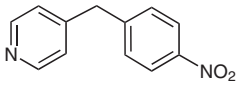
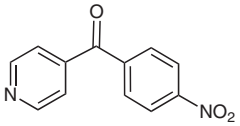
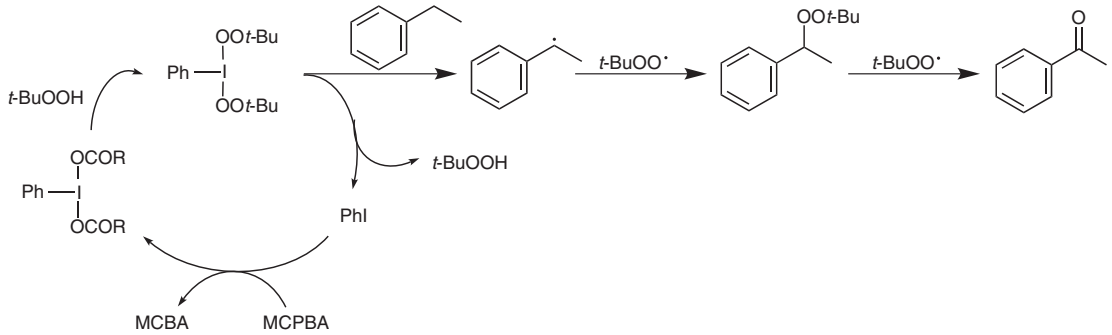
Entry	Substrate	Product	Time (h)	Yield (%)[a]
1	**1a** 	**2a** 	10	92
2	**1b** 	**2b** 	10	95
3	**1c** 	**2c** 	9	86[b]
4	**1d** 	**2d** 	9	99
5	**1e** 	**2e** 	9	97

Table 2 Catalytic Benzylic Oxidation of Alkylarenes (continued)

Entry	Substrate	Product	Time (h)	Yield (%)[a]
6	**1f** 	**2e**	9	99
7	**1g** 	**2g** 	12	93
8	**1h** 	**2h** 	12	62
9	**1i** 	**2i** 	12	47
10	**1j** 	**2j** 	12	40
11	**1k** 	**2k** 	11	63
12	**1l** 	**2l** 	10	11
13	**1m** 	**2m** 	9	38[b]
14	**1n** 	**2n** 	9	11[b]

[a] Yield of isolated product.
[b] EtOAc was used as the solvent.



Scheme 2 A plausible reaction mechanism for the catalytic benzylic oxidation of alkylarenes

In summary, we have developed a novel and efficient method for the oxidation of the benzylic C–H moiety of alkylarenes with *tert*-butyl hydroperoxide and *m*-chloroperoxybenzoic acid in the presence of a catalytic amount of (diacetoxyiodo)benzene in 2,2,2-trifluoroethanol at room temperature. The corresponding aryl ketones were obtained typically in good yields. This method has the advantages of mild reaction conditions and a simple experimental procedure. Furthermore, the scope of hypervalent iodine reagents in organic synthesis has been extended via this approach.

The alkylarenes, *m*-chloroperoxybenzoic acid, *tert*-butyl hydroperoxide and (diacetoxyiodo)benzene were commercially available. Petroleum ether (PE) refers to the fraction boiling in the 60–90 °C range. Melting points were measured with an XT-4 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III (500M) spectrometer.

Benzylic Oxidation; General Procedure

To a soln of alkylarene **1** (1.0 mmol) in TFE (5 mL) were added MCPBA (2.0 mmol), DIB (0.1 mmol) and TBHP (3.0 mmol). The resulting mixture was stirred at r.t. for ca. 10 h (see Table 2). After completion of the reaction, the solvent was evaporated under reduced pressure and then H_2O (5 mL), sat. aq $Na_2S_2O_3$ (2 mL) and sat. aq Na_2CO_3 (2 mL) were added. The mixture was extracted with CH_2Cl_2 (2 × 10 mL), then the combined organic extract was washed with brine (10 mL), dried over anhyd $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified on a silica gel plate (PE–EtOAc, 20:1 or 10:1) to provide the corresponding ketone **2**.

Indan-1-one (2a)

Yield: 121 mg (92%); yellow solid; mp 42–44 °C (Lit.[9] 41–42 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 10.0 Hz, 1 H), 7.59–7.56 (m, 1 H), 7.48–7.47 (m, 1 H), 7.38–7.34 (m, 1 H), 3.13 (t, *J* = 10.0 Hz, 2 H), 2.69–2.67 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.0, 155.1, 137.1, 134.6, 127.3, 126.7, 123.7, 36.2, 25.8.

3,4-Dihydronaphthalen-1(2*H*)-one (2b)[8]

Yield: 139 mg (95%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 5.0 Hz, 1 H), 7.50–7.48 (m, 1 H), 7.32–7.24 (m, 2 H), 2.97 (t, *J* = 10.0 Hz, 2 H), 2.66 (t, *J* = 10.0 Hz, 2 H), 2.17–2.12 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.3, 144.4, 133.3, 132.6, 128.7, 127.1, 126.6, 39.1, 29.7, 23.3.

Fluoren-9-one (2c)

Yield: 155 mg (86%); yellow solid; mp 84–86 °C (Lit.[10] 82–83 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 5.0 Hz, 2 H), 7.55–7.48 (m, 4 H), 7.32–7.28 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.9, 144.5, 134.7, 134.2, 129.1, 124.3, 120.3.

Xanthen-9-one (2d)

Yield: 194 mg (99%); yellow solid; mp 173–175 °C (Lit.[11] 172–173 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 5.0 Hz, 2 H), 7.75–7.72 (m, 2 H), 7.51 (d, *J* = 5.0 Hz, 2 H), 7.41–7.38 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.2, 156.2, 134.8, 126.7, 123.9, 121.9, 117.9.

Anthraquinone (2e)

Yield: 202 mg (97%); white solid; mp 279–281 °C (Lit.[12] 284–285 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.35–8.32 (m, 4 H), 7.84–7.81 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 183.2, 134.1, 133.6, 127.3.

Acetophenone (2g)[3g]

Yield: 111 mg (93%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 5.0 Hz, 2 H), 7.29–7.26 (m, 1 H), 7.18–7.15 (m, 2 H), 2.28 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.4, 136.9, 132.8, 128.3, 128.1, 26.2.

1-Phenylpropan-1-one (2h)[4f]

Yield: 83 mg (62%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 10.0 Hz, 2 H), 7.30–7.27 (m, 1 H), 7.21–7.18 (m, 2 H), 2.71 (q, *J* = 10.0 Hz, 2 H), 0.98 (t, *J* = 10.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.0, 136.7, 132.6, 128.3, 127.7, 31.4, 7.9.

1-Phenylbutan-1-one (2i)[3g]

Yield: 70 mg (47%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 5.0 Hz, 2 H), 7.56–7.53 (m, 1 H), 7.47–7.41 (m, 2 H), 2.95 (t, *J* = 10.0 Hz, 2 H), 1.81–1.74 (m, 2 H), 1.01 (t, *J* = 10.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.4, 137.1, 132.8, 128.5, 128.0, 40.5, 17.8, 13.9.

2-Methyl-1-phenylpropan-1-one (2j)[13]

Yield: 59 mg (40%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 5.0 Hz, 2 H), 7.58–7.55 (m, 1 H), 7.50–7.47 (m, 2 H), 3.61–3.55 (m, 1 H), 1.24 (d, *J* = 5.0 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.5, 136.3, 132.8, 128.6, 128.3, 35.4, 19.2.

1-(4-Methoxyphenyl)ethanone (2k)

Yield: 95 mg (63%); white solid; mp 34–36 °C (Lit.[14] 37–39 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 10.0 Hz, 2 H), 6.94 (d, *J* = 5.0 Hz, 2 H), 3.87 (s, 3 H), 2.56 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.7, 163.5, 130.6, 130.4, 113.7, 55.4, 26.3.

1-(4-Nitrophenyl)ethanone (2l)

Yield: 18 mg (11%); white solid; mp 47–49 °C (Lit.[15] 49 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 10.0 Hz, 2 H), 8.12 (d, *J* = 10.0 Hz, 2 H), 2.69 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3, 150.4, 141.4, 129.3, 123.9, 26.9.

Benzophenone (2m)

Yield: 69 mg (38%); white solid; mp 46–47 °C (Lit.[3g] 46–48 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 10.0 Hz, 4 H), 7.61–7.58 (m, 2 H), 7.51–7.47 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.7, 137.6, 132.4, 130.1, 128.3.

(4-Nitrophenyl)(pyridin-4-yl)methanone (2n)

Yield: 25 mg (11%); white solid; mp 125–126 °C (Lit.[16] 121–122 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.89 (d, *J* = 10.0 Hz, 2 H), 8.39 (d, *J* = 10.0 Hz, 2 H), 8.00 (d, *J* = 5.0 Hz, 2 H), 7.61 (d, *J* = 5.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.5, 150.8, 150.5, 142.8, 140.8, 130.9, 123.9, 122.6.

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