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Free radical bromination by the H_2O_2–HBr system on water

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Abstract—An aqueous solution of hydrogen peroxide and hydrogen bromide illuminated by a 40 W incandescent light bulb serves as a source of bromine radicals. Various substituted toluenes (H, Me, *t*Bu, Br, COOEt, COPh, NO_2) were brominated at the benzyl position. This haloperoxidase-like system for benzylic bromination does not require the presence of metal ions or an organic solvent for efficient conversion of methyl-arenes to benzyl bromides.

Nature solved the problem of halogenations by creating *haloperoxidases* enzymes. Their active site contains ferrous or vanadium ions that convert halide ions, with hydrogen peroxide under acidic conditions, into hypohalous acid that serves as the halogenating agent.[1] These biogenic reactions proceed in aqueous medium while artificial (chemical) ones occur in organic solvents. Water is the most desirable and preferred substitute for volatile organic compounds (VOCs) due to cost, safety and environmental concerns. Yet, until recently its use was avoided as a medium for organic reactions due to the low solubility of organic compounds in aqueous medium resulting in low reaction rates and low yields.[2] Nevertheless, recent reports have shown that reactions can be accelerated by adding water despite the non-solubility of the reactants.[3–5] Furthermore, water is suitable for radical reactions since its strong OH bonds make hydrogen abstraction by radicals unlikely.[6]

Traditionally, radical bromination at benzylic positions is performed with *N*-bromosuccinimide (NBS) in boiling carbon tetrachloride with the addition of a radical initiator—this method is known as Wohl–Ziegler bromination.[7] With respect to green chemistry, there is a pressing need to find a method for free-radical benzyl bromination of less environmental impact.[8] So far, research has focused on using NBS and on reducing the amounts of VOCs and their substitution for non-chlorinated solvents,[9] ionic liquids[10] and water.[11] Even solvent-free reactions have been investigated.[10,12] Water has been used as a solvent for free-radical bromination of methyl substituted benzenes with molecular bromine.[13] The main drawback of the process was selectivity for benzyl bromination due to dibromination and electrophilic bromination. More efficient methods for free-radical bromination were developed that involve in situ generation of bromine by reducing $NaBrO_3$ with $NaHSO_3$[14] or by oxidizing a bromide salt with H_2O_2.[15,16] The latter method was performed with H_2O_2/NaBr in the presence of an excess of sulfuric acid in a chlorinated solvent.[16]

In order to obtain a 'greener' reaction protocol for benzyl bromination we imitated the action of *haloperoxidases* enzymes by using hydrogen peroxide as the oxidant, hydrogen bromide as the halogen atom source, water as the reaction medium and visible light as the radical chain process initiator. In several studies, metal ions were used to achieve *haloperoxidase*-like bromination,[17–19] however, we were interested to see if metal ions were dispensable in this free-radical bromination.

We have achieved an effective, visible-light induced free radical bromination of methyl benzenes using H_2O_2 and HBr in water at ambient temperature. The procedure allows the easy isolation of products since the only by-product of the reaction is water (Eq. 1).

$$ArCH_3 + H_2O_2 + HBr \rightarrow ArCH_2Br + 2H_2O \qquad (1)$$

Keywords: Halogenation; Bromination; Benzyl bromination; Radicals; Water; Haloperoxidase; Hydrogen peroxide; Green chemistry.

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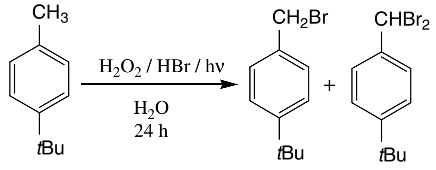
We initially wanted to define the best conditions for visible-light induced radical bromination with aqueous H_2O_2 and HBr in water, so we performed a series of reactions with 4-*tert*-butyltoluene **1** as a model substrate. The method involved adding 1 mmol of substrate **1** to a 1.2 mL aqueous solution of 1 mmol of H_2O_2 and 1 mmol of HBr (3 wt% H_2O and 7 wt% HBr). First, ambient light was used as an activator and bromination occurred at the benzyl position with the formation of benzyl bromide **2a** in 58% yield (Table 1, entry 1). Needless to say that reaction in the dark produced only a trace amount of **2a**. Having discovered that ambient light was a sufficient activator, we placed an incandescent light bulb (40 W) 10 cm from the flask to ensure a constant source of light. When we stirred the reaction mixture for 24 h at room temperature under irradiation with 40 W light bulb we observed 65% conversion into benzyl bromide **2a** (Table 1, entry 2). Reducing the amount of water to 0.8 mL increased the yield of benzyl bromide **2a** to 70% (entry 3). When an excess of H_2O_2 was used the reaction proceeded with 77% conversion (entry 5), while adding more H_2O_2 (2 equiv) gave even higher conversion (entry 6). We obtained the best yield of bromide **2a** with 2 equiv of H_2O_2 and 10% excess of HBr (entry 7). In our experiments, 4-*tert*-butyltoluene **1** was converted into benzyl bromide **2a**, selectively, without the formation of dibrominated product **2b**, except when adding a large excess of HBr (1.5 equiv) (entry 8).

The optimum reaction conditions (1 mmol of substrate and 0.8 mL solution of 2 mmol of H_2O_2 and 1.1 mmol of HBr) were used for free-radical bromination of various methyl benzene derivatives and after reaction, organic products could be obtained by simple phase separation, while in small scale experiments, extraction with the appropriate organic solvent had to be applied.[20]

Table 1. Visible-light induced free-radical bromination of 4-*tert*-butyltoluene **1** with H_2O_2/HBr on water[a]



1 **2a** **2b**

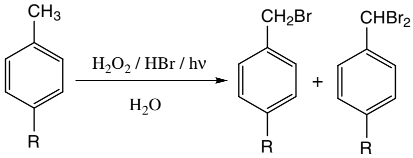
Entry	*n* (mmol **1**:H_2O_2:HBr]	Volume (mL]	Distribution[b]
			1:**2a**:**2b**
1[c]	1:1:1	1.2	42:58: —
2	1:1:1	1.2	35:65:—
3	1:1:1	0.8	30:70:—
4	1:1.5:1	1.2	25:75:—
5	1:1.5:1	0.8	23:77:—
6	1:2:1	0.8	15:85:—
7	1:2:1.1	0.8	9:91:—
8	1:2:1.5	0.8	—:78:22

[a] Typical reaction conditions: 1 mmol of **1** was added to the solution of H_2O_2 and HBr in water.

[b] Conversion and distribution of products were determined by ^{1}H NMR spectroscopy.

[c] Reaction proceeded with ambient light for a period of 15 h.

Table 2. Visible-light induced free-radical bromination of *para*-substituted toluenes with H_2O_2/HBr on water



Substrate	Time (h)	Yield[a] (%)
1: R = *t*Bu	24	**2a**: 91 (80)
3: R = H	10	**4a**: 89 (81), **4b**: 7 (4)
5: R = Br[b]	28	**6a**: 85 (77)
7: R = COOEt[b]	32	**8a**: 84 (71), **8b**: 6 (4)
9: R = COPh[b]	66	**10a**: 93 (90)
11: R = NO_2[b]	66	**12a**: 91 (90)

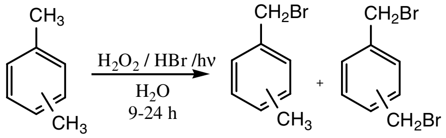
[a] Yields were determined by ^{1}H NMR spectroscopy and are based on starting compound; yields in parentheses refer to isolated yields.

[b] Aqueous solution of H_2O_2 was added slowly and the reaction mixture was irradiated with a 125 W high pressure mercury lamp.

4-*tert*-Butyltoluene **1**, toluene **3** and 4-bromotoluene **5** were converted into their corresponding benzyl bromides in high yields (Table 2). In the case of toluene **3**, dibromide **4b** was also formed in a small amount. Under the same conditions deactivated alkyl benzenes (ethyl 4-methylbenzoate **7**, 4-methylbenzophenone **9** and 4-nitrotoluene **11**) produced lower quantities of benzyl bromides. It is well known that hydrogen peroxide decomposes in the presence of hydrogen bromide. Therefore, we could anticipate that less reactive substrates with electron-withdrawing groups lead to lower yields due to decomposition of hydrogen peroxide during the reaction. We repeated the experiments with **7**, **9** and **11**, but this time slowly adding the aqueous solution of H_2O_2 to the reaction mixture irradiated with a 125 W high pressure mercury lamp ('solar' light). On this occasion the benzyl bromides were obtained in high yields.

Visible-light-induced bromination of xylenes **12**, **14** and **16** gave interesting results (Scheme 1, yields were determined by ^{1}H NMR and are based on starting compound, yields in parentheses refer to isolated yields). Contrary to published results on bromination with bromine,[13] the major products were monobrominated with the best selectivity found in the case of *ortho*-xylene **12** and the worse with the *para*-isomer **16**.

In summary, visible-light induced free-radical bromination of various substituted methyl benzenes with aque-



o-xylene **12**	**13a:** 88 (80)	**13b:** 10 (6)
m-xylene **14**	**15a:** 78 (73)	**15b:** 13 (11)
p-xylene **16**	**17a:** 65 (62)	**17b:** 19 (10)

Scheme 1.

ous H_2O_2 and HBr on water is an efficient and selective method for bromination at the benzylic position. The method also has a lower impact on the environment since bromine is generated in situ from H_2O_2 and HBr and the use of H_2O_2 as an oxidant gives water as the only by-product. The method obviates the use of a metal catalyst for HBr oxidation.

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20. Typical experiment on 1 mmol scale: Methyl benzene (1 mmol) was added to 0.8 mL aqueous solution of 2 mmol of H_2O_2 and 1.1 mmol of HBr. The reaction mixture was stirred at 500 rpm at room temperature under irradiation with a 40 W incandescent light bulb for 24 h. Then the reaction mixture was transferred into a separating funnel, into which 10 mL of water and 2 mL of 0.01 M $NaHSO_3$ were added. The crude product was extracted using 3 × 5 mL CH_2Cl_2 and the combined organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude reaction product was analyzed by ^1H NMR spectroscopy, isolated by column chromatography (SiO_2, appropriate mixture of hexane/ethyl acetate) and identified on the basis of comparison with the literature data.