High atomic yield bromine-less benzylic bromination

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A two-phase mixture (sodium bromide, aqueous hydrogen peroxide/carbon tetrachloride or chloroform) under visible light provides a simple and convenient system for benzylic bromination of toluenes. A high atomic yield for bromine atoms is attained. Substitution of the chlorinated solvents by other more environmentally benign organic solvents has been attempted and good results are obtained for methyl pivalate.

Introduction

Molecular bromine in preparative chemistry is a serious cause of concern, due to its toxicity and corroding properties. In order to circumvent this drawback, generation of bromine *in situ* by oxidation of hydrogen bromide or an alkali-metal bromide by potassium permanganate, sodium bromate, hydrogen peroxide, or other reagents has been performed as far back as in the 19th century, although these methods have not found general application.[1–3]

Further, some of the most significant synthetic reactions of molecular bromine, namely the bromination of aromatic nuclei, ketones, carboxylic acids or allylic or benzylic sites occur under low atomic yield for bromine. Indeed, only one out of two bromine atoms of molecular bromine becomes part of the product, the other atom becomes the corroding hydrogen bromide, a substance which must be neutralized before it is discarded.[4] Brominations may thus be qualified as environmentally unfriendly reactions.[5]

The Wohl–Ziegler method of bromination with the easy to handle NBS has become for many years the reagent of choice for allylic and benzylic brominations.[6,7] Direct use of molecular bromine in the laboratory is avoided and no hydrogen bromide is generated. However, the atomic yield is still poor and succinimide is obtained as a concomitant product which, although not harmful, must be either disposed or recycled to NBS, and very frequently complicates cristallizations for isolation and purification of products.

Combined bromide–hydrogen peroxide systems have been used recently for addition to unsaturated double or triple bonds,[8–10] aromatic electrophilic substitution,[8,9,11] synthesis of amine tribromides,[12] or for oxidation of alcohols, aldehydes,[9] or sulfides.[13–15] Aromatic side-chain halogenations in the presence of metal oxide catalysts have been reported as well.[16,17] Interestingly, significant improvements of both electrophilic aromatic and photochemical side-chain brominations by bromine in the presence of zeolites have been recently described.[18]

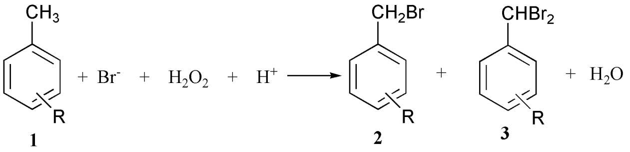
In the course of our studies for the synthesis of some benzyl ether dendritic and polymeric structures,[19] we wished to improve the benzylic bromination of protected methylphenols. Although bromination of 4-methylbenzoyloxybenzene **1a** with NBS occurred satisfactorily in general terms, we needed a procedure more suitable for a multigram scale. On the other hand, the urgent need for development of safe and environmentally benign methods encouraged us to search for the possibility of a convenient benzylic bromination through oxidative generation of bromine *in situ*. Use of hydrogen peroxide seemed very convenient in the view of the above precedents and because water is the only concomitant product (eqn. (1)–(3)).

$$2\ \mathrm{Br}^- + \mathrm{H_2O_2} + 2\ \mathrm{H}^+ = \mathrm{Br_2} + 2\ \mathrm{H_2O} \qquad (1)$$

$$\mathrm{ArCH_3} + \mathrm{Br_2} = \mathrm{ArCH_2Br} + \mathrm{Br}^- + \mathrm{H}^+ \qquad (2)$$

$$\mathrm{ArCH_3} + \mathrm{Br}^- + \mathrm{H_2O_2} + \mathrm{H}^+ = \mathrm{ArCH_2Br} + 2\ \mathrm{H_2O} \qquad (3)$$

Further, when the substitution reaction is taken into account, the whole conversion should be possible by consuming a single mole of bromide and one mole of acid. The photochemical bromination of a number of substituted toluenes by a bromide–hydrogen peroxide reagent under acidic conditions was thus studied (Scheme 1). The reactions were carried out initially in carbon tetrachloride, the solvent commonly used up now for molecular bromine or NBS brominations. Other chlorinated solvents and other non-chlorinated solvents were then assayed.



1a: **R =** ***p*-C$_6$H$_5$CO$_2$;**
1b: **R =** ***p*-Cl; 1c: R =** ***m*-Cl; 1d: R = H; 1e: R =** ***p*-NO$_2$;**
1f: **R =** ***p*-MeO$_2$C; 1g: R =** ***p*-HO**

Scheme 1

Green Context

The use of bromine is fraught with problems of handling and the low atom efficiency of substitution reactions (50% maximum with bromide by-poduct). For these reasons work has been carried out using bromide and an oxidant to generate bromine (or electrophilic Br species) for electrophilic aromatic brominations. Here, bromide is used in conjunction with light to carry out side-chain brominations of benzylic systems, extending the concept to radical-type reactions. Importantly, a non-halogenated solvent has also been found for these reactions which typically use CCl$_4$ or CHCl$_3$. ***DJM***

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Results and discussion

For comparison purposes, brominations of 4-benzoyloxytoluene **1a** with NBS and with molecular bromine in carbon tetrachloride were carried out first. Thus, bromination with one equivalent of NBS in the presence of benzoyl peroxide, ilumination with visible light and heating under reflux, according to the typical procedure, gave a 84 : 16 mixture of mono- and di-bromination compounds, **2a** and **3a**, with the starting material left as a trace amount. With a slight excess (1.1 molar equivalents) of bromine relative to the substituted toluene **1a**, the red colour of the solution faded in less than 10 min and the resulting mixture (91% isolated crude yield) contained compounds **2a** (72%) and **3a** (25%), and a very small amount of the starting toluene **1a** (3%). When the bromination was carried out with slightly more than half an equivalent (0.55) of bromine in the presence of hydrogen peroxide (1.5 equivalents), progress of the reaction was much slower, a red to orange colour change being observed after 8 h. Quenching of the reaction after 20 h gave a crude mixture (85%) of compounds **1a**, **2a** and **3a** in a ratio 18, 74 and 8%, respectively. The introduction of a second atom of bromine is in keeping with the results of Smith *et al.* on the bromination of ethyl 4-methylbenzoate,[18] and is probably due to the rate constants for the dissociation of the C–H bonds of the starting toluene and of the monobromo derivative **1** being of a similar order.

Brominations with the bromide–hydrogen peroxide system were carried out at room temperature in an open vessel provided with a cooling condenser and under illumination with an incandescent light bulb. Sodium (occasionally potassium) bromide, hydrochloric or sulfuric acid and 30% aqueous hydrogen peroxide, the concentration of which was determined volumetrically with $KMnO_4$, were employed. On mixing of the reagents and the toluene **1**, a red colour developed, which slowly faded in *ca.* 4–6 h. However, no systematic control of the reaction time was conducted, as most experiments were carried out overnight (20 h). The simple work-up procedure for most toluenes **1** consisted in thorough removal of peroxides from the organic layer by aqueous sodium hydrogensulfite and evaporation of the solvent to give a crude material, whose composition was established by ^1H NMR spectroscopy. Work-up for bromination of toluene **1d** differed in that evaporation of the solvent was not carried out, as remaining unreacted toluene might be partly evaporated along with the solvent. Only the starting material **1**, and the mono- and di-bromo compounds **2** and **3** (Scheme 1) were found in the crude mixtures.

Study of the effect of conditions were carried out with 4-benzoyloxytoluene **1a** as substrate, due to the easy isolation of the resulting reaction mixture. It had been ascertained previously that no substitution reaction took place in the absence of photochemical activation and that the alkali-metal bromide could be added either as a solid or previously dissolved in the aqueous acid with no significant change in the results. Similarly, changes in the concentration or nature of the acid, the cation (Na or K) of the bromide salt, or the order of addition of reagents had no effect.

A rough estimation of the efficiency of the bromination is given by the bromination yield (Table 1). This is obtained here by summing the amounts of bromine found in the reaction mixture, as given by the product ratios for the mono- and di-brominated compounds **2** and **3**, corrected by the crude yield. Good bromination yields were obtained with only a slight excess (1.1) of bromide salt. According to eqns. (1)–(3) bromination could be complete with one molar equivalent of acid, but the reaction became slower and afforded much lower halogenation (Table 1, entry 5) on use of 1.1 equivalents of acid. A large excess of acid seems thus to have a beneficial effect and most brominations were carried out in the presence of 3 equivalents of acid. The amount of hydrogen peroxide could be reduced to 1.1 equivalents without a significant detriment on bromination yields. However, most experiments were carried out with a larger excess of hydrogen peroxide.

Chloroform as solvent gave a satisfactory result (Table 1, entry 10), but poor bromination yields were obtained with methylene dichloride (entry 9).

The general applicability of this procedure was confirmed when bromination of other substituted toluenes **1b**–**g** was assayed (Table 2). No significant differences were observed in proportions of the mixtures resulting as function of the electron-donating or electron-withdrawing character of the substituents in toluenes **1b**–**f**, although crude yields for the chloro compounds **1b** and **1c** were lower and thus, bromination yields were also low. For *p*-cresol **1g** side-chain bromination did not occur to a significant extent, electrophilic aromatic substitution instead being observed. This finding is in keeping with earlier results of oxybromination of strongly activated benzenes.[8–10] Methylene dichloride and chloroform were also assayed for *p*-nitro- and *p*-methoxycarbonyl toluenes **1e** and **1f**.

Non-chlorinated solvents were examined with substrate **1a** in the hope of improving the environmental aspects of the procedure (Table 3). Hexane was not convenient due to the low solubility of the substrate **1a**. Benzene gave fairly good results, but esters, namely ethyl and isopropyl acetate or methyl isobutyrate, or *tert*-butyl methyl ether gave poor conversions. Methyl pivalate gave a satisfactory bromination yield, although halogenation products were accompanied by 4-benzoyloxybenzoic acid, which might result from substitution and oxidation of monobrominated **2a** or from hydrolysis of **3a** and oxidation of the resulting benzaldehyde. Higher solubility of water in this solvent is probably the origin of this exceptional behaviour. A similar very small amount of carboxylic acid was observed in the halogenation of *p*-nitrotoluene **1e** in carbon tetrachloride.

In conclusion, we have found a very simple method for side-chain bromination of methylbenzenes which should be easily scaled-up.

Table 1 Conditions and results (^1H NMR) for bromide/hydrogen peroxide benzylic bromination of toluene **1a** (0.25 M) in chlorinated solvents

	Reagents[a]					Product ratio			
Run	H_2O_2	NaBr	H^+	Solvent	Crude yield	**1**	**2**	**3**	Bromination yield[b]
1	3	1.5	3[c]	CCl_4	95	2.5	80.5	17	108.7
2	3	1.1[d]	3	CCl_4	94	6	84	10	97.7
3	3	1.1	2	CCl_4	91	16	76	8	83.7
4	3	1.1	1.5	CCl_4	89	15	77	8	81.9
5	3	1.1	1.1[c]	CCl_4	87	29	71	tr	61.8
6	2	1.1	3	CCl_4	89	16.5	78	5.5	79.2
7	1.5	1.1	3	CCl_4	91	20.2	74.3	5.5	77.6
8	1.1	1.1	3	CCl_4	88	16	76	8	81
9	1.5	1.1	3	CH_2Cl_2	86	37	63	tr.	54.2
10	1.5	1.1	3	$CHCl_3$	93	15.5	79.5	5	83.2

[a] Molar ratio relative to **1**. [b] Bromination yield; estimated: (crude yield/100)[ratio **2** + (2 × ratio **3**)]. [c] 2 M HCl; other runs, conc. H_2SO_4. [d] KBr.

Table 2 Bromide/hydrogen peroxide benzylic bromination of toluenes **1b**–**f** (0.25 M) in chlorinated solvents[a]

Run	1	Solvent	Crude yield	Product ratio 1	2	3	Bromination yield[b]
1	**1b**	CCl_4	62	13.5	79.5	7	58
2	**1c**	CCl_4	60	16	74.5	9.5	56
3	**1d**	CCl_4		14.5	79.5	5	
4	**1e**	CCl_4	82	14	79	7	76.2
5	**1e**	CH_2Cl_2	92	12.5	80.5	7	86.9
6	**1e**	$CHCl_3$	93	13	78	8.7	88.7
7	**1f**	CCl_4	63	15	78	7	57.9
8	**1f**	CH_2Cl_2	76	57	43	tr.	32.7
9	**1f**	$CHCl_3$	99	13	87	tr.	86.1

[a] Conditions for all runs: 3 equivalents of 30% H_2O_2, 1.1 equivalent of NaBr, 3 equivalents of conc. H_2SO_4. [b] Bromination yield; estimated: (crude yield/100)[ratio **2** + (2 × ratio **3**)].

Table 3 Conditions and results (^{1}H NMR) for bromide/hydrogen peroxide benzylic bromination of toluene **1a** (0.25 M) in non-halogenated solvents

Run[a]	Solvent	Crude yield	Product ratio 1	2	3	Bromination yield
1	Hexane–ethyl acetate	85	63	37	—	31.5
2	Benzene	91	21	74	5	76.5
3	Ethyl acetate	76	66.5	33.5	—	25.5
4	Isopropyl acetate	84	20.4	79.6	tr	66.8
5	Methyl isobutyrate	97	67	33	—	32
6	Methyl pivalate	84	11	84	5	79
7	Methyl pivalate	78	5.7	85.7	8.6	80
8	*tert*-Butyl methyl ether	89	58	42	tr.	30

[a] Conditions for all runs: 3 equivalents of 30% H_2O_2, 1.1 equivalent of NaBr, 3 equivalents of conc. H_2SO_4.

Experimental

4-Benzoyloxybenzyl bromide 1a

A mixture of 4-benzoyloxytoluene (2.12 g; 10 mmol), sodium bromide (1.13 g; 11 mmol), 30 % hydrogen peroxide (1.70 mL; 15 mmol), conc. sulfuric acid (1 mL; 15 mmol) and chloroform (40 mL) was stirred in a 100 mL round bottomed flask provided with a reflux condenser and under illumination with a 100 W incandescent lamp. The mixture became red and the colour slowly faded in 2.25 h. The mixture was washed with 40% sodium hydrogensulfite (2 × 10 mL), until a negative starch-iodide test for peroxides, and water and dried. Evaporation of the solvent gave a crude mixture as an oil which solidified (2.71 g; 93%). The ^{1}H NMR spectrum of a sample was run. Crystallization from hexane–benzene gave the title compound as colourless prisms (2.11 g; 73%), mp 110–111 °C (lit.,[20] 108–111 °C).

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