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Dual oxidation/bromination of alkylbenzenes

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In the presence of sodium bromide and Oxone, a range of alkylbenzene derivatives are brominated and/or oxidized with up to four C-H bonds being functionalized.

The development of new methods for the functionalization of simple inexpensive aromatic compounds is an important area of investigation. In particular, developing conditions that do not require the use of expensive, toxic or difficult to handle compounds is a worthwhile endeavor. For example, the halogenation of arenes is a ubiquitous chemical transformation for which there are many published procedures, however the use of elemental halogen or reagents such as *N*-halosuccinimide are often required.^{1,2} These reactants have disadvantages such as toxicity, corrosiveness, ease-of-use, relative high cost, low atom efficiency or supply issues.

We previously reported the use of sodium halides, in the presence of an oxidant, as electrophilic halogenating agents for the conversion of propargyl alcohols to α -iodoenones, α,α -dibromoketones and α,α -dichloroketones.³ We wished to extend this concept to the functionalization of simple alkylbenzenes. We envisaged that halogenation of the aromatic ring would occur with concomitant oxidation of the benzylic methylene to a ketone (Fig. 1).

We started our study with ethylbenzene **1** using our previously published conditions of sodium bromide with Oxone in the presence of trichloroacetic acid dissolved in a mixture of acetonitrile and water (Table 1).^{3a} Performing the reaction at room temperature in the dark led to very low conversion to α -bromoketone **3** (entry 1). Repeating the reaction in the light also led to low conversion of the starting material (entry 2). Heating the reaction mixture at 50 °C in the dark led to higher conversion and a mixture of products **2** and **3** (entry 3). However, when the reaction was repeated at 50 °C in the light conversion increased significantly and ketone **3** was isolated in 65% yield (entry 4). At this point, the requirement for the acid was evaluated and it was found that its removal led to no detriment in yield (entry 5). Small amounts of the *ortho*- and *meta*-bromination products were evident in the crude reaction mixtures but these could be removed by recrystallization. Lowering the number of equivalents of sodium bromide and oxidant led to lower yield.

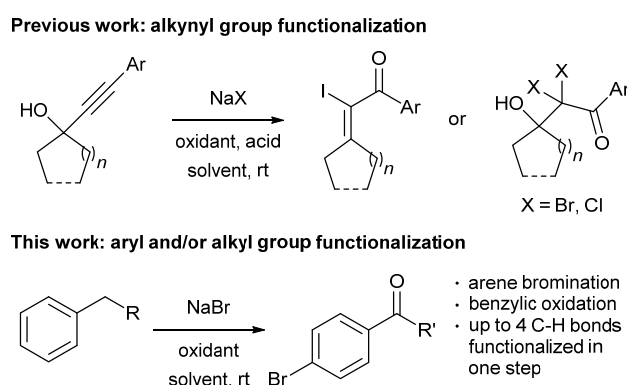
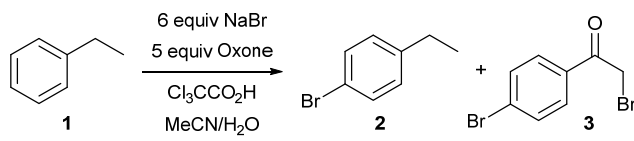


Fig. 1 Previous study of oxidative halogenation and this work

Table 1 Investigation of reaction conditions


Entry	Temperature (°C)	Conditions	Yield (%) ^a
1	20	in the dark	<5 (3)
2	20	in the light	6 (3)
3	50	in the dark	13 (2), 16 (3)
4	50	in the light	65 (3)
5	50	in the light	65 (3) ^b

^a Yield of isolated compound. ^b No Cl₃CCO₂H added.

With these reaction conditions in hand, we evaluated a range of substrates to explore this interesting reactivity profile. Benzylic oxidation and arene bromination are both known processes, with reports of these transformations using related conditions to ours,^{4,5} but performing both transformations simultaneously has not been reported. Subjecting *n*-propylbenzene **4** to the reaction conditions led to oxidation of the benzylic position and bromination of the ring, however bromination adjacent to the ketone did not occur (entry 2). In a similar fashion, *n*-butylbenzene **6** was converted in to ketone **7** with efficient conversion evident at room temperature. Cumene **8** has only one benzylic proton and cannot be converted to the ketone. Under the reaction conditions it was doubly brominated to provide compound **9** at room temperature (entry 4). Upon heating, elimination of HBr was observed. Isobutylbenzene **10** was converted to ketone **11** as expected (entry 5). With these results in hand, we turned our attention to substrates with aryl substituents to determine their effect on reactivity. Surprisingly, 4-chloro(ethylbenzene) **12** was oxidized to ketone **13** with bromination adjacent to the ketone not occurring unlike with ethylbenzene **1** (entry 6). The presence of a phenol shuts down the benzylic oxidation and double bromination of the ring occurs (entry 7). A nitro substituent shuts down all reactivity (entry 8) as does a ketone group (entry 9). Surprisingly, 2-ethylnaphthalene **18** is dibrominated without any benzylic oxidation (entry 10).

In order to probe the mechanism of this process, we subjected acetophenone **20** to the reaction conditions. Approximately 12% α -bromination was observed but no ring bromination was evident (Scheme 1). This suggests that bromination of the aromatic ring must occur before the benzylic site oxidation. We can also propose that α -ketone bromination is possible under these conditions, but that it is slow. Therefore, an alternative mechanistic pathway must be in operation here. In a second reaction, we subjected 1'-bromoethylbenzene **22** to the reaction conditions and observed complete conversion with approximately a 2:1 ratio of acetophenone **20** and bromide **21**.⁶

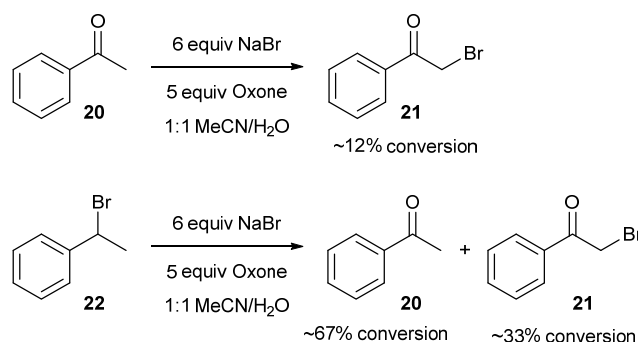
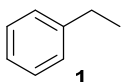
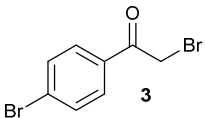
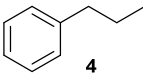
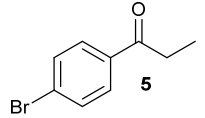
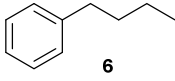
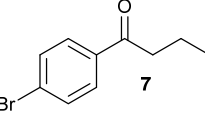
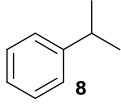
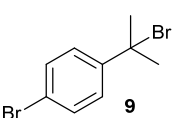
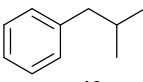
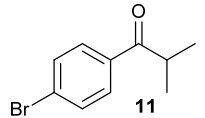
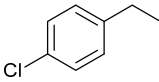
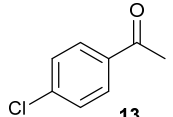
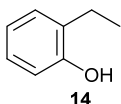
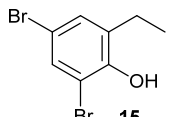
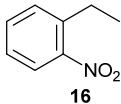
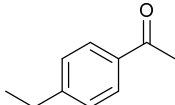
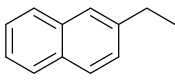
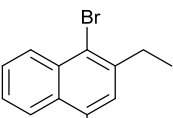
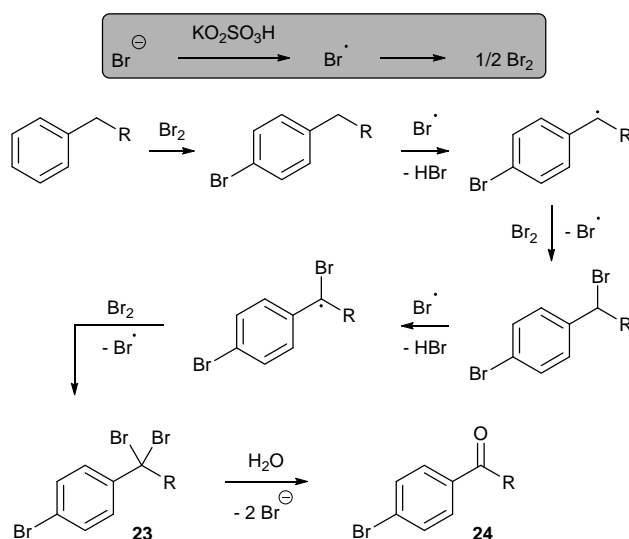
**Scheme 1** Reactions to probe mechanistic features.

Table 2 Scope of alkylbenzene oxidative bromination^a

Entry	Arene	Product	Yield ^b (%)
1			65
2			86
3			63 ^c
4			57 ^c
5			30
6			73 ^c
7			74
8		no reaction	-
9		no reaction	-
10			32 ^c

^a Reaction conditions: NaBr (6 equiv), Oxone (5 equiv), 1:1 MeCN/H₂O, 50 °C (or room temperature where indicated), in the light. ^b Yield of isolated compound. ^c Reaction performed at room temperature.

The mechanism of this process is proposed to initiate by the oxidation of bromide.⁷ This is a complicated process but bromine radical and elemental bromine will be generated with light (Scheme 2). Bromination of the arene by bromine takes place first, if possible, followed by benzylic hydrogen atom abstraction. This can combine with bromine (or another bromine radical) to generate the benzyl bromide. A second hydrogen abstraction then occurs followed by coupling with bromine (or another bromine radical). Finally, dibromide **23** is converted to the ketone **24** by displacement with water.



Scheme 2 Postulated reaction mechanism

Conclusions

In summary, we have shown that in the presence of the inexpensive oxidant Oxone, NaBr can be used to functionalize a range of simple alkylbenzenes with up to four C-H bonds being replaced. These conditions provide a greener access into functionalized aromatic compounds. The reactions are easy to carry out, use reagents with relatively low toxicity and generally lead to the installation of more than one functional group in one operation. This simple and environmentally friendly procedure to rapidly functionalize simple aromatics should find applicability in synthesis.

Acknowledgements

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Notes and references

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