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Arene oxidation with malonoyl peroxides

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Supporting Information Placeholder

ABSTRACT: Malonoyl peroxide 7, prepared in a single step from the commercially available diacid, is an effective reagent for the oxidation of aromatics. Reaction of an arene with peroxide 7 at room temperature leads to the corresponding protected phenol which can be unmasked by aminolysis. An ionic mechanism consistent with the experimental findings and supported by isotopic labeling, Hammett analysis, EPR investigations and reactivity profile studies is proposed.

The oxidation and functionalization of hydrocarbons is a central facet of the chemical industry for the production of high-tonnage commodities and the preparation of high-value pharmaceuticals, agrochemicals and fine chemicals. Therefore, methods for selective oxidation of C—H bonds are of great importance.1 Phenols represent a key class of oxidized hydrocarbon.2 While there are a small number of reports in which arenes are oxidized to the respective phenols using peroxides and strong acids as additives,3 the oxidation of aromatic C—H bonds still presents a synthetic challenge specifically with respect to avoiding over oxidation.

Scheme 1. C—H Oxidation Using Phthaloyl Peroxide

A recent report from the laboratories of Houx and Siegel described a metal-free oxidation of aromatic carbon-hydrogen bonds which was proposed to proceed through an intriguing reverse-rebound mechanism (Scheme 1).4 Reaction of mesitylene 2 with 1.3 equiv of phthaloyl peroxide 1 in hexafluoroisopropanol (HFIP) followed by basic solvolysis gave the phenol 3 (97%).

The method outlined in Scheme 1 represents a significant advance in arene oxidation. The proposed mechanistic pathway for the transformation suggested homolytic fission of the weak oxygen—oxygen bond leading to diradical 4. Addition of this radical to the arene gives 5 which through H-atom abstraction provides the observed product 6. Ester hydrolysis leads to the phenol 3 (97%, two steps). The procedure has wide functional group tolerance and arene oxidation did not prove problematic. We believed two fundamental opportunities existed for development of this procedure: First, phthaloyl peroxide 1 is known to be very shock sensitive and explodes violently when heated, representing a significant hazard.5,6 Second, the proposed reverse-rebound mechanism leading to 6 was based upon theoretical studies. Provision of experimental evidence to support this pathway would be of great importance to the understanding and development of this procedure.

In recent years we have been interested in the chemistry of cyclic diacylperoxides and have shown that malonoyl peroxide 7,7 and related derivatives,8 are effective for the syn-dihydroxylation of alkenes.9 This reagent provides significant advantages over phthaloyl peroxide 1 within the syn-dihydroxylation reaction in terms of yield, selectivity, reaction rate, substrate scope and operating temperature.10,11 Given our experience in understanding the mechanism of reactions involving the peroxide 7,12 together with the specific advantages provided in alkene dihydroxylation we elected to investigate the reactivity of 7 in the oxidation of arenes. Within this report we show that 7 reacts with arenes in the presence of a hydrogen bond donor to give the corresponding functionalized aromatic and present data consistent with the arene and peroxide reacting through an ionic pathway.
As a starting point to our investigations we reacted mesitylene 2 with malonyl peroxide 7 under the conditions reported by Houk and Siegel (0.07 M, 40 °C).\(^2\) Reaction of mesitylene 2 with 1.3 equiv of peroxide 7 in HFIP gave the adduct 8 (94%, 20 h). More conveniently, this reaction could be performed at room temperature (25 °C) rather than 40 °C without compromise in yield (8, 98%) (Scheme 2). Cleavage of the ester (MeNH₂, EtOH, 25 °C, 1 h) gave the corresponding phenol 3 (92% over two steps). Delighted by these excellent preliminary results and given the distinct advantages of malonyl peroxide 7 over phthaloyl peroxide 1 outlined above we examined this transformation further.

**Scheme 2. Malonyl Peroxide Mediated Oxidation of Mesitylene**

\[
\begin{align*}
\text{O} & \quad + \\
\text{HFIP (0.07 M)} & \quad 25 \degree \text{C} \\
\text{7 (1.3 equiv)} & \quad \text{2} \\
\text{8 (98%)} &
\end{align*}
\]

Brief optimization of the reaction conditions showed that transformations could be performed at room temperature and considerably higher concentration (0.5 M) than those reported previously (0.07 M) (see Supporting Information).

Here is a detailed description of the reaction:

\[
\begin{align*}
\text{R} & \quad + \\
\text{HFIP (0.5 M)} & \quad 25 \degree \text{C} \\
\text{7 (2 equiv)} & \quad \text{2} \\
\end{align*}
\]

**Figure 1. Arene oxidation with malonyl peroxide 7**

Houk and Siegel showed their transformation to have broad functional group tolerance, describing the oxidation of over 50 substrates\(^2\). Direct comparison of the reaction using malonyl peroxide 7 to those obtained for phthaloyl peroxide 1 on a selection of these substrates showed the transformation to proceed with similar yield and selectivity (Figure 1). Functional group tolerance mirrored that obtained with phthaloyl peroxide, which bodes well for further reaction development. We therefore believe that malonyl peroxide 7 represents an effective alternative to the explosive phthaloyl peroxide 1 in the oxidation of arenes.

In order to understand the reaction further a series of experiments were undertaken to probe the mechanistic course of the process. The reverse-rebound mechanism proposed for the reaction of phthaloyl peroxide 1 was based upon theoretical calculations.\(^7\) We sought to obtain experimental data using malonyl peroxide 7 to underpin knowledge of this transformation. An analogous reverse-rebound mechanism with peroxide 7 would involve homolytic cleavage of the peroxide bond to give the diradical species 17 which on addition to the arene would give the intermediate 18. Rearomatization of 18 through H-atom abstraction would lead to the observed product 8 (Scheme 3). In addition to this reverse-rebound mechanism we also considered an ionic pathway based on the established reactivity of 7 with alkenes.\(^10\) Thus, nucleophilic attack of the electron rich arene 2 on the weak peroxide bond would lead to intermediate 19, which upon rearomatization would give 8.

**Scheme 3. Potential Mechanistic Course of Reaction**

Based upon reactivity patterns an ionic process appeared plausible: the reaction required electron rich aromatics to proceed, with electron donating groups directing the addition of the peroxide to the ortho/para positions. Interestingly, aromatic substrates containing electron withdrawing groups proved unreactive within this transformation. For example, acetophenone, benzoic acid, methyl benzoate, and benzonitrile all proved to be unreactive to peroxide 7 under the optimized reaction conditions (7, 2 equiv, HFIP 0.5 M, 25 °C). Conducting the reaction of mesitylene 2 and malonyl peroxide 7 in HFIP (i) in the presence of light and air; (ii) exposed to light under an argon atmosphere; (iii) in the dark in an aerobic environment; and (iv) in the dark under an inert atmosphere showed no significant differences in outcome with reactions giving the product 8 (90-92% yield) after 6 h. In addition, conducting the reaction at 4 °C, in the dark under an argon atmosphere gave the product (83% yield) after 24 h. Combined these observations show the reaction to proceed under very mild conditions and did not rule out an ionic pathway.

Further investigations were carried out using\(^1^8\)O isotopically labelled malonyl peroxide 20 as a mechanistic probe, which was prepared from cyclopropane-1,1-dicarboxylic acid (see Supporting Information for full details). Treatment of mesitylene 2
with 1.35 equiv of malonyl peroxide 20 (25 °C, 16 h) gave the ester 21 with two labels incorporated in the structure (Scheme 4). Mass spectrometric analysis was consistent with incorporation of one label in the carboxylic acid terminus of the molecule, and a second label in the carbonyl oxygen atom of the ester. No labelled oxygen was observed in the newly formed carbon—oxygen bond. To corroborate this finding, a sample of 21 was treated with methyamine and the crude reaction mixture was analyzed by GCMS. The observed products were 2,4,6-trimethylphenol 3, amides 22 and 24 containing either one or two ^18O labels, and amide 23 resulting from decarboxylation. These findings show that no scrambling of the ^18O label from the peroxide 20 is observed during the course of reaction and are consistent with addition of an arene nucleophile to the weak O—O peroxide bond.

Scheme 4. Reaction of Mesitylene with Isotopically Labelled Peroxide 20

3

The data assembled at this stage were consistent with an ionic interaction between the aromatic substrate and the peroxide 7. To gain further evidence for the formation of a carbonation intermediate, a Hammett analysis was conducted on the arene oxidation. Monosubstituted mesitylene derivatives were reacted with 1 equiv of malonyl peroxide 7 (Figure 3), monitoring peroxide consumption against an internal standard by ^1H NMR spectroscopy. Determination of the initial rates provided a linear Hammett plot based on literature σ meta values:14

\[ \text{R = Me, H, OMe, F, Br} \]

\[ \text{7 (1.0 equiv)} \]

\[ \text{HFIP (0.1 M), 25 °C} \]

\[ \log k_b(K_b) \]

\[ \sigma_{meta} \]

\[ \rho = -2.7 \]

\[ \gamma = -2.69 \pm 0.0089 \]

\[ R^2 = 0.9995 \]

\[ R = Me (28) \]

\[ R = H (8) \]

\[ R = OMe (29) \]

\[ R = F (30) \]

\[ R = Br (14) \]

Figure 3. Hammett analysis of arene oxidation with peroxide 7

The Hammett plot (Figure 3) showed an excellent linear relationship for both electron withdrawing and donating substituents in the meta-position indicating that the same mechanism is in operation with each substrate examined. The gradient of the line, ρ, gave a moderate negative value of -2.7 indicating a considerable buildup of positive charge during the transition state of the reaction, consistent with an aryl carbocation intermediate (e.g. 19). As expected, reactions of substrates with a meta-electron donating substituent (e.g. 28) proceeded at a significantly faster rate than those containing a meta-electron-withdrawing group (e.g. 14 and 30).

To probe further the possibility of the reaction proceeding through the diradical intermediate 17 we examined the homolytic bond cleavage of peroxide 7 through DFT calculations \((\text{U})\text{B3LYP/6-31+G(d)})\). Of importance was the use of trifluoroethanol as the solvent in a CPCM, providing a more accurate reflection of the reaction medium when compared to the previous approaches to modeling this class of transformation.2 A transition state \(\text{TS1 (29.7 kcal mol}^{-1})\) to form the diradical species 17 \((24.8 \text{ kcal mol}^{-1})\) from peroxide 7 was found (Figure 4), a particularly high barrier for a reaction that proceeds readily at 4 °C.

Figure 2. Potential scrambling of labels on formation of diradical
Figure 4. Peroxide homolytic cleavage (kcal mol⁻¹)

The potential of 17 being present within the reaction mixture was also examined using electron paramagnetic resonance (EPR) spectroscopy experiments using 5,5-dimethyl-1-pyrroline-N-oxide (DMPO), a spin trap used in EPR spectroscopy for the detection of oxygen based radicals. DMPO was inert to the peroxide 7 in HFIP, as shown by control experiments. Mixtures of mesitylene 2 and malonyl peroxide 7 in both the presence and absence of DMPO were analyzed by EPR spectroscopy. In each of these experiments no radicals were detected providing further evidence in support of an ionic pathway.

In summary, reaction of an aren with malonyl peroxide 7 at room temperature in the presence of a hydrogen bond donor leads to the corresponding functionalized aromatic. Experimental findings supported by isotopic labeling, Hammett analysis, EPR studies and reactivity profile studies support an ionic reaction pathway. The importance of the phenol functional group in imparting unique structural, physical and electronic properties within molecules suggests this simple, effective and high yielding method for the oxidation of aromatics will provide a useful route for the late stage aromatic functionalization. Given the specific advantages of malonyl peroxide 7 over phthaloyl peroxide 1, it is expected that this methodology will be of great use in the introduction of the phenol functionality.

ASSOCIATED CONTENT

Supporting Information

Analytical data, experimental procedures and NMR spectra for all compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

The authors thank the EPSRC and University of Strathclyde for financial support and the EPSRC Mass Spectrometry Service, Swansea for high-resolution spectra.

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