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# Benzylic Bromination–Acetoxylation of Toluenes by Bromide Ion Catalyzed Thermal Decomposition of Peroxydisulfate in Acetic Acid in the Presence of Acetate Ions

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Side-chain bromination and acetoxylation of alkylaromatics by halide ion induced decomposition of potassium peroxydisulfate in acetic acid have been studied by product analysis techniques. Catalytic amounts of lithium bromide in the presence of sodium acetate were found effective in promoting benzylic bromination, followed by conversion to the corresponding benzyl acetates by reaction with acetate. The reaction is interpreted to take place by a redox and free-radical chain mechanism involving bromine atoms ($\rho = -1.38$ vs. $\sigma^+$ for substituted toluenes). In competitive experiments, benzyl and 4-nitrobenzyl acetates were found less reactive than the corresponding toluenes in acetic acid with the couple $S_2O_8^{2-}/Br^-$ but more reactive in carbon tetrachloride with *N*-bromosuccinimide.

## Introduction

The peroxydisulfate oxidation of aromatics and alkenes in organic or mixed aqueous organic medium in the presence of transition-metal salts has attracted considerable attention as a convenient tool for the rapid functionalization of organic unsaturated substrates.[1,2] These reactions are understood to derive from the reaction of radical-cation intermediates initially formed through an electron-transfer process between the sulfate radical anion ($SO_4^{\bullet-}$) or metal salts in high oxidation states[3] and the unsaturated compound. Double-bond and allylic functionalization arise from nucleophile addition or side-chain proton abstraction or fragmentation, respectively. However, these oxidations are limited to electron-rich substrates. For instance, whereas toluenes substituted with electron-releasing groups are easily oxidized in acetic acid to the corresponding benzyl acetates, toluenes substituted with electron-withdrawing groups (i.e., $NO_2$) are quantitatively recovered.[4] This behavior has been ascribed to the low rate of interaction of $SO_4^{\bullet-}$ with these substrates ($k \leq 10^6$ $M^{-1}$ $s^{-1}$ at 25 °C for 4-nitrotoluene),[5] a rate similar to the oxidation of carboxylic acids[5] and higher than the oxidation of carboxylate ions.[5]

In order to overcome this limit and to extend the use of peroxydisulfate in organic medium, we attempted a different approach in which in the absence of any transition-metal cation the peroxydisulfate could oxidize anions, giving rise to radical species preferentially involved in the benzylic hydrogen atom abstraction. Halide ions were first analyzed. This choice was suggested by the well-known enhancement in reactivity of metal ions in high oxidation states (i.e., $Co^{3+}$, $Mn^{3+}$, $Ce^{4+}$, etc.)[6-8] toward the oxidation of alkylaromatics in the presence of alkaline halides. The origin of this effect has been ascribed either to the formation of a metal complex of higher oxidation potential that works via an electron-transfer mechanism or to a hydrogen atom abstraction reaction promoted by the halogen atom or by the metal halide species. Considerations based on standard monoelectronic redox potentials of these metal ions and halide ions[9] suggest that the formation of molecular halide, via the intermediate halide atom,[9] is thermodynamically possible. Peroxydisulfate ions, with a higher redox potential, no coordinating ability, and working by an electron-transfer mechanism, appear useful candidates to test the validity of this common intermediate. Moreover, the system peroxydisulfate–metal halide has been previously studied for the oxidation of carboxylic acids and amides and found effective in promoting hydrogen atom abstraction reactions.[10-17]

## Results and Discussion

Peroxydisulfate is unable to oxidize 4-nitrotoluene (**1a**) in acetic acid at 115 °C for 6 h, even in the presence of sodium acetate (Table I, entries 1 and 2). Conversely, when an equimolecular amount of lithium bromide is present in the system, benzylic bromination is easily obtained (Table I, entries 3 and 4) according to eq 1. Only minor amounts of the corresponding benzal bromide (**3a**),

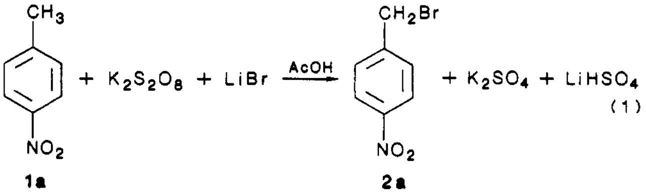

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**Table I. Benzylic Oxidation of 4-Nitrotoluene (1a, 14.8 mmol) by Potassium Peroxydisulfate and Halide Ion ($CH_3COOH$, 115 °C, 6 h)**

| entry | $K_2S_2O_8$, mmol | LiBr, mmol | AcONa, mmol | AcOH, mL | products, % yield: 1a, % conv | 2a | 3a | 4a + 5a | 6a |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 14.8 | | | 40 | | | | | |
| 2 | 14.8 | | 60 | 40 | 2 | tr | | | |
| 3 | 14.8 | 14.7 | | 40 | 59 | 51 | 1 | 3 | 4 |
| 4 | 14.8 | 14.7 | | 20 | 51 | 39 | 1 | | 11 |
| 5[a] | | | | 20 | 50 | 40 | 1 | | 7 |
| 6[b] | 14.8 | 14.7 | 60 | 20 | 44 | 1 | 2 | | 40 |
| 7[a,b] | | | 60 | 20 | 41 | 1 | 4 | 3 | 32 |
| 8 | 14.8 | 1.8 | 60 | 20 | 42 | 1 | 2 | 1 | 38 |
| 9 | 14.8 | 1.8 | 60 | 40 | 48 | 1 | 5 | 16 | 26 |
| 10 | 26.0 | 1.8 | 60 | 40 | 63 | | 1 | 28 | 33 |
| 11[c] | 26.0 | | 60 | 40 | 48 | | 4 | 39 | 1 |
| 12[d] | 26.0 | | 60 | 40 | 34 | | 6 | 24 | 1 |

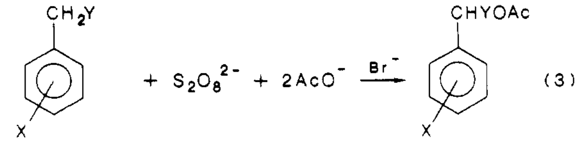
[a] Experiments carried out with $Br_2$ (14.8 mmol) without $K_2S_2O_8$. [b] Sodium acetate added after 6 h of reaction and then the mixture refluxed for 2 h. [c] Experiment carried out in the presence of NaCl (1.8 mmol). [d] Experiment carried out in the presence of NaI (1.8 mmol).

benzotribromide (**4a**), and benzoic acid (**5a**) are detected. Very similar results are obtained when molecular bromine is used instead of the couple $K_2S_2O_8/Br^-$ under similar conditions (Table 1, entry 5). The conversion of the substrate **1a** is limited in both experiments owing to the competitive bromination of the solvent to give bromoacetic acid (37% and 42% yields, respectively). In both experiments low amounts of benzyl acetate (**6a**) and acetoxyacetic acid are formed, due to the solvolysis of the corresponding bromides. This reaction become more important with the time and the dilution of the system (Table I, entry 4 vs. 3). Practically quantitative conversion of the brominated compounds into the corresponding acetates is obtained by adding an excess of sodium acetate to the final solution (eq 2) and heating the resulting mixture 2 h further (Table I, entry 6).

$$XCH_2Br + AcONa \xrightarrow{AcOH} XCH_2OAc + NaBr \quad (2)$$

$$X = 4\text{-}(NO_2)C_6H_4;\ COOH$$

This result suggests to us the possible use of catalytic amounts of lithium bromide in the presence of sodium acetate for the one-step side-chain acetoxylation of alkylaromatics by peroxydisulfate (eq 3).



$$+ S_2O_8^{2-} + 2AcO^- \xrightarrow{Br^-} \quad (3)$$

**6** + $2SO_4^{2-}$ + AcOH

**1a**: $X = 4\text{-}NO_2, Y = H$
**b**: $X = 3\text{-}NO_2, Y = H$
**c**: $X = 2\text{-}NO_2, Y = H$
**d**: $X = 4\text{-}Cl, Y = H$
**e**: $X = 4\text{-}CH_3, Y = H$
**f**: $X = 4\text{-}COOCH_3, Y = H$
**g**: $X = 3\text{-}OC_6H_5, Y = H$
**h**: $X = H, Y = H$
**i**: $X = 3\text{-}COC_6H_5, Y = H$
**l**: $X = H, Y = CH_3$
**m**: fluorene

The best yield (38%) and selectivity (90%) in monoacetoxylation of **1a** are obtained by using a 12% molar amount of lithium bromide, a saturated solution of sodium acetate in acetic acid, and moderate conversion (Table I, entry 8).

Sodium chloride and iodide, used instead of lithium bromide, also catalyze the decomposition of peroxydisulfate with oxidation of 4-nitrotoluene; however, only a trace of benzyl acetate is formed and the main product is 4-nitrobenzoic acid (Table I, entries 11 and 12).

The best conditions found under $Br^-$ catalysis for compound **1a** were extended to other substituted toluenes or alkylbenzenes (**1b**–**1m**). Side-chain monoacetoxylation was found in good yield and selectivity (>70%) except with 2-nitro-, 3-nitro-, and 4-chlorotoluenes. Nuclear substitution was found only with fluorene (low yield). Nuclear bromination was conversely never observed. Variable amounts of benzylic diacetates (examined as the corresponding aldehydes or ketones) and carboxylic acids are always present. The contribution of oxidative decarboxylation with $CO_2$ evolution was in all cases very low (<2%).

**Table II. Benzylic Bromination–Acetoxylation of Toluenes and Some Alkylbenzenes (1a–1m) by LiBr-Catalyzed Peroxydisulfate Decomposition[a]**

| aromatic substrate | % conv | products, % yield: 6 | 3 | 5 | 6,[b] % selectivity |
|---|---|---|---|---|---|
| **1a** | 41 | 38 | 3 | tr | 93 |
| **1b** | 44 | 25 | 9 | 8 | 57 |
| **1c** | 34 | 17 | 7 | 8 | 50 |
| **1d** | 74 | 63 | 17 | 5 | 63 |
| **1e** | 49 | 40 | 4 | 5 | 82 |
| **1f** | 65 | 46 | 9 | 8 | 71 |
| **1g** | 50 | 39 | 8 | 2 | 78 |
| **1h** | 76 | 57 | 11 | 8 | 74 |
| **1i** | 52 | 44 | 6 | 2 | 85 |
| **1l** | 74 | 62 | 11 | | 84 |
| **1m**[c] | 61 | 48 | 8 | | 78 |

[a] Reaction conditions: LiBr (1.8 mmol), AcONa (60 mmol), $K_2S_2O_8$ (14.8 mmol), aromatic substrate (14.6 mmol) in acetic acid (20 mL) at 113 °C for 6 h. [b] Yield on converted 1. [c] Two different nuclear acetates (3% yield) were also detected.

The results with toluenes substituted with electron-releasing groups parallel those obtained with the couple $S_2O_8^{2-}/Cu^{2+}$, even if the latter is unable to oxidize strongly electron-deficient substrates.

The yields reported in Table II are roughly correlated with the donor power of substituents. Since the only competitive process found was the solvent oxidation, we examined the substituent effect on the yield of benzyl acetates formed in competitive experiments. A very good Hammett plot (vs $\sigma^+$)[11] was obtained with a deduced $\rho$ value of $-1.38 \pm 0.03$ (Table III).

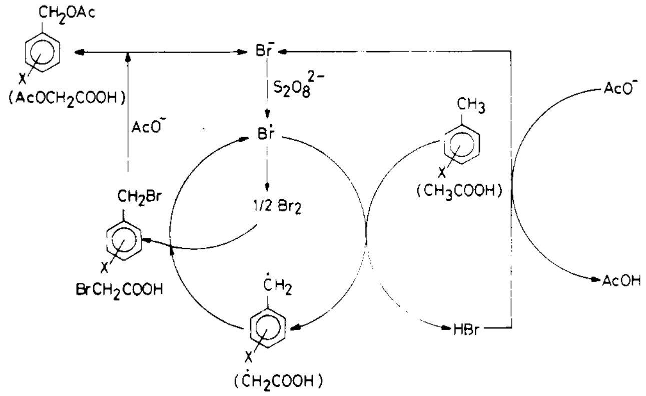
This value is very close to the known one for side-chain bromination or acetoxylation by different oxidant couples (Table III). Taking into consideration the different radical sources, temperature, and solvents used, with the exception of the system $Br_2$ in nitrobenzene, the restricted range of $\rho$ values strongly indicates that a common mechanism involving the electrophilic bromine radical operated in all systems containing brominating species.

We suggest the redox and free-radical chain process summarized in Scheme I to explain the results obtained both in the absence and in the presence of sodium acetate.

**Table III. $\rho$ Values (vs. $\sigma^+$) of Hammett Correlations in Benzylic Brominations or Acetoxylations of Substituted Toluenes**

| source | solvent | $T$, °C | $\rho$ ($\sigma^+$) | correln coeff | ref |
|---|---|---|---|---|---|
| NBS | $C_6H_6$ | 80 | −1.46 | 0.996 | 12 |
| NBS | $CCl_4$ | 80 | −1.81 | 0.977 | 13 |
| | | | −1.38 | 0.977 | 14 |
| $Br_2$ | $CCl_4$ | 80 | −1.36 | 0.996 | 12 |
| $Br_2$/NBS | $C_6H_6$ | 80 | −1.66 | 0.989 | 15 |
| $Br_2$/NBS | $BrC_6H_5$ | 80 | −1.64 | 0.981 | 15 |
| $Br_2$/NBS | $NO_2C_6H_5$ | 80 | −0.334 | 0.998 | 15 |
| $Br_2/h\nu$ | AcOH | 70 | −1.82 | | 7b |
| $Mn(OAc)_3$/KBr | AcOH | 70 | −1.81 | | 7b |
| $Co(OAc)_3$ | AcOH | 65 | −2.4 | | 16 |
| $Co(OAc)_3$/LiCl | AcOH | 65 | −1.35 | 0.97 | 16 |
| $S_2O_8^{2-}/Cu^{2+}$ | AcOH | 110 | −1.9 | 0.97 | 2b |
| $S_2O_8^{2-}/Br^-$ | AcOH | 113 | −1.38 ± 0.03 | 0.999 | this work |

**Scheme I. Proposed Mechanism: Redox and Free-Radical Chain Process Involving Br•**



Under this hypothesis, fast reactions and good yields are obtained if the oxidant system is able to provide steady concentrations of Br• radical and molecular bromine in order to maintain an efficient radical chain. In our system, the nucleophilic substitution of the benzyl bromide appears to be the limiting step of the overall process. Low temperatures and dilution of the reaction mixture were in fact found to reduce the rate and the yield of monosubstitution products.

## Experimental Section

Starting and reference materials either were commercial samples or were synthesized by standard methods; their purities were checked by GC or NMR analyses, and they were used at a purity higher than 98%. The products of all reactions were identified on the basis of GC–MS spectral data, $^1$H NMR, and GC coinjection with authentic samples. All acids were analyzed as methyl ester via diazomethane.

$^1$H NMR spectra were taken on a 60-MHz Hitachi Perkin-Elmer R-24B instrument. Mass spectra were recorded on a GC–MS system Varian MAT 112 S equipped with a column (2 m × 0.6 cm) of 10% UCC W 982 on Chromsorb W (80–100 mesh). GC analyses were performed on (a) a Carlo Erba HRGC 5300 gas chromatograph equipped with flame-ionization detector and glass column (2 m × 0.4 cm) packed with 10% UCC W 982 on Chromosorb W (80–100 mesh) and (b) a DANI 6500 HR instrument equipped with flame-ionization detector and OV 101 (25 m × 0.22 mm) or Carbowax 20 M fused silica capillary column.

**Benzylic Acetoxylation of Toluenes with Peroxydisulfate.** These reactions were carried out according to the general procedure exemplified for the case of 4-nitrotoluene (**1a**).

**4-Nitrobenzyl Acetate (6a).** A solution of potassium peroxydisulfate (14.8 mmol), lithium bromide (1.8 mmol), 4-nitrotoluene (14.6 mmol), and sodium acetate (60 mmol) in acetic acid (20 mL) was heated in a closed vessel at 115 °C for 6 h. The mixture was cooled, diluted with diethyl ether, and filtered. The organic solution, after addition of methyl benzoate as internal standard, was analyzed by GC on the Carlo Erba instrument giving the following results: **1a**, conversion 41%; **6a**, yield 38%.

Acetoxyacetic acid (30%) was identified and quantitatively determined by treatment of the organic solution with diazomethane in excess and by GC–MS analysis. In a parallel experiment, the crude reaction mixture was evaporated under vacuum; the residue was added to 0.2 N HCl solution and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution and water. The alkaline solution was acidified with concentrated HCl to recover the benzoic acid eventually formed. The dried organic phase was evaporated under vacuum to constant weight. The residue was analyzed by $^1$H NMR, and the reaction products were isolated by column chromatography. In all experiments, the GC and NMR analyses matched at 3–5% precision. With toluene, ethylbenzene, and chlorobenzene only GC analyses were carried out.

**Competition Experiments. (1) Between Substituted Toluenes with $K_2S_2O_8$.** Toluene and a substituted toluene (15 mmol) were injected, under nitrogen, through a rubber septum in a closed flask (50 mL) equipped with magnetic bar and containing $K_2S_2O_8$ (1.5 mmol), AcONa (60 mmol), LiBr (0.6 mmol), and acetic acid (20 mL). The system was kept at 116 ± 1 °C for 6 h.

The mixture was cooled at 0 °C and after addition of 4-methoxy- or 4-chlorobenzyl acetate (0.7 mmol) was diluted with diethyl ether (50 mL); the solid was allowed to separate, and then the cooled solution was analyzed by GC on the DANI instrument. The calculated logs of the relative rate constants (log ($K_X/K_H$)) were as follows: −1.14 (X = $p$-$NO_2$), −0.50 (X = $m$-Cl), −0.21 (X = $p$-Cl), +0.12 (X = $m$-$CH_3$), +0.41 (X = $p$-$CH_3$), +1.04 (X = $p$-$OCH_3$). The data plotted vs. $\sigma^+$ gave a $\rho$ value of −1.38 ± 0.03 as reported in Table III.

**(2) Between 1a and 6a with $K_2S_2O_8$.** The previous conditions were used also with 4-nitrotoluene and 4-nitrobenzyl acetate. After the workup reported in the general procedure, the following product distribution was obtained: **1a**, 35%; **6a**, 43.3%; **3a**, 17%; **4a**, 5%.

**(3) Between 1a and 6a by $Br_2$.** 4-Nitrotoluene (7.3 mmol), 4-nitrobenzyl acetate (7.3 mmol), and sodium acetate (60 mmol) were added to a solution of bromine (0.86 mL, 14.8 mmol) in acetic acid. The mixture was heated at 115 °C for 6 h. After the workup reported in the general procedure, the following product distribution was obtained: **1a**, 35%; **6a**, 51%; **3a**, 11.4%; **4a**, 2.8%.

**Registry No.** **1a**, 99-99-0; **1b**, 99-08-1; **1c**, 88-72-2; **1d**, 106-43-4; **1e**, 106-42-3; **1f**, 99-75-2; **1g**, 3586-14-9; **1h**, 108-88-3; **1i**, 643-65-2; **1l**, 100-41-4; **1m**, 86-73-7; LiBr, 7550-35-8.