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> Dedicated to Full Member of the Russian Academy of Sciences I.P. Beletskaya on her jubilee

Oxidation of Iodo- and Bromo-Substituted Polymethylbenzenes in the System PbO₂-CF₃COOH-CH₂Cl₂

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Abstract—The oxidation of mono- and diiodo- and -bromo-substituted polymethylbenzenes (mesitylene and durene) in the system $PbO_2-CF_3COOH-CH_2Cl_2$ at room temperature (2–70 h) leads mainly to the formation of iodo- and bromobenzyl alcohols as result of oxidation of methyl group. The reaction involves intermediate formation of haloarene radical cations. ESR study of these radical cations made it possible to determine the structure of their singly occupied molecular orbitals a_2 or b_1 and interpret their reactivity.

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Iodo- and bromo-substituted arenes are important substrates in cross-coupling reactions such as Heck, Sonogashira, and Suzuki couplings [1–10]. Iodo- and bromoarenes are commonly synthesized by direct electrophilic halogenation of aromatic compounds. Another synthetic route to new haloarenes implies modification of side-chain substituents in arenes already containing halogen in the aromatic ring. The most efficient methods of modification of the benzylic position in alkyl substituents of arenes are halogenation [11–18], hydroxylation [19], and oxidation to carbonyl or carboxy group [20–30].

The goal of the present work was structural modification of methyl groups in mono- and diiodo- and bromopolymethylbenzenes (mesitylene and durene) via oxidation in the system PbO₂–CF₃COOH–CH₂Cl₂. Lead(IV) oxide (PbO₂) in strong acids (CF₃COOH, FSO₃H, HF, etc.) is known as a single-electron oxidant used to generate radical cations from arenes, alkenes [31, 32], and alkynes [33]. Lead(IV) oxide–strong acid systems are capable of oxidizing methyl groups in arenes and forming new carbon–carbon bonds via oxidative dimerization involving radical cations of organic compounds [31–33]. The oxidation of 1,4-diiodo- and 1,4-dibromotetramethylbenzenes **1a** and **1b** in PbO₂–CF₃COOH– CH₂Cl₂ at room temperature (70 h) afforded the corresponding benzyl alcohols **2a** and **2b** (Scheme 1). The oxidation of monohaloarenes **3a** and **3b** required a considerably shorter time (2 and 4 h, respectively). From iododurene **3a** we obtained two isomeric alcohols **4a** and **5a** as the major products, whereas the oxidation of bromodurene **3b** was more selective, and only one isomer **4b** was formed. The structure of **4a** and **5a** was confirmed by the NOESY spectra which showed correlations between the CH₂ protons and protons of the neighboring methyl group and aromatic proton (Fig. 1). In addition, a small amount of







diarylmethane **6a** was isolated in the oxidation of **3a** (Scheme 2).

The oxidation of 2-iodo- and 2-bromo-1,3,5-trimethylbenzenes **7a** and **7b** afforded benzyl alcohols **8a** and **8b** and benzaldehydes **9a** and **9b**, respectively (Scheme 3). The reaction selectively involved only one methyl group in the *para* position with respect to the halogen atom.

We then proceeded with a study aimed at generating and detecting by ESR spectroscopy radical cation intermediates in the above oxidative transformations. Radical cation $[2b]^+$ was generated by oxidation of dibromodurene 2b in PbO₂–FSO₃H at low temperature (-80°C). Its ESR spectrum (Fig. 2) consists of thirteen equidistant lines (tridecet) due to interaction of unpaired electron with twelve protons of the four methyl groups with a hyperfine coupling constant a_{Me}^{H} of 11.1 G (12H). This spectrum indicates that the singly occupied molecular orbital (SOMO) of radical cation [2b]⁺ is of a_2 type with localization of positive spin density on the aromatic carbon atoms bearing methyl groups (Fig. 2). The same character of SOMO a_2 should be typical of radical cations derived from durenes **1b**, **3a**, and **3b** (cf. the data on SOMO types reviewed in [31–33]). The observed positive spin density distribution in radical cations generated from haloarenes **1a**, **1b**, **3a**, and **3b** makes the methyl groups therein reactive sites, so that the oxidation involves the methyl group (Schemes 1, 2). We failed to record ESR spectra of primary radical cations generated from haloarenes **1b**, **3a**, **3b**, **7a**, and **7b** under analogous conditions (PbO₂–FSO₃H, –80°C) because of their high reactivity. Instead, only complex unresolved spectra of secondary radical cation intermediates were obtained.

The fact that only the *para*-methyl group was oxidized in halomesitylenes **7a** and **7b** (Scheme 3) suggested a different type of SOMO of radical cations $[7a]^+$ and $[7b]^+$, namely b_1 (Fig. 3). In this case, the positive spin density in $[7a]^+$ and $[7b]^+$ is largely localized on the aromatic carbon atom in the *para* position with respect to the halogen atom, and the oxidation involves mainly the *para*-methyl group.

The main transformation paths and mechanisms of reactions with participation of radical cation intermediates have been considered in [31-34]. Taking



Fig. 1. Correlations in the ¹H–¹H NOESY spectra of compounds 4a, 4b, and 5a.



Fig. 2. ESR spectrum of radical cation $[2b]^+$ generated from dibromodurene 2b in the system PbO₂-FSO₃H at -80°C.

these data into account, the following scheme can be proposed for one-electron oxidation of haloarenes 1a, 1b, 3a, 3b, 7a, and 7b (Scheme 4). Deprotonation of initially formed radical cation A gives benzyl radical B which is oxidized to benzyl cation C. The latter can react along different paths. The reaction of C with nucleophile (trifluoroacetic acid or its anion) leads to benzyl trifluoroacetate D whose hydrolysis on treatment of the reaction mixture with aqueous alkali (see Experimental) yields benzyl alcohol 2, 4, 5, or 8 as final product (Scheme 4). Another reaction direction is electrophilic substitution in the initial arene with formation of diarylmethane 6 (see also Scheme 2). Ester **D** can also be oxidized to bis-trifluoroacetate **E** which undergoes hydrolysis to aldehyde 9 (Scheme 3). Deeper oxidation of the methyl groups in 1a, 1b, 3a, 3b, 7a, and 7b results in the formation of benzoic acids 10. When the reaction mixture is treated with aqueous alkali, alkali metal salts of acids 10 remain in solution, which reduces the overall yield of the isolated products. Therefore, the yields of 2, 4, 5, 6, 8, and 9 are moderate. All reactions were carried out using 1 equiv of PbO₂ (see Experimental). If smaller or

RUSSIAN JOURNAL OF ORGANIC CHEMISTRY Vol. 54 No. 3 2018

larger amount of the oxidant was added, the yields of benzyl alcohols were lower.

In summary, we were the first to study oxidation of (di)iodo- and (di)bromopolymethylbenzenes (halogenated mesitylenes and durenes) in the system PbO_2 - $CF_3COOH-CH_2Cl_2$. These reactions led to the formation of the corresponding halogenated benzyl alcohols which are promising substrates for various cross-coupling reactions. The oxidation involves intermediate formation of haloarene radical cations whose reactivity



Fig. 3. Structure of the singly occupied molecular orbital (SOMO) of radical cations $[7a]^{+}$ and $[7b]^{+}$ generated by one-electron oxidation of iodo- and bromomesitylenes **7a** and **7b**, respectively.





was rationalized by the character of their singly occupied molecular orbitals (a_2 or b_1), determined by ESR spectroscopy.

EXPERIMENTAL

The ¹H and ¹³C NMR spectra were recorded at room temperature on a Bruker AM-500 spectrometer at 500 and 125 MHz, respectively, using CDCl₃ as solvent and reference (CHCl₃, δ 7.26 ppm; CDCl₃, $\delta_{\rm C}$ 77.0 ppm). GC/MS analysis was performed on an Agilent Technologies G2570A 6850 GC/MSD instrument (HP-5MS capillary column, $3 \text{ m} \times 0.25 \text{ mm}$, film thickness 0.25 µm). The high-resolution mass spectra were obtained on a Varian 902-MS MALDI mass spectrometer. The ESR spectra of radical cations in the system PbO₂-FSO₃H were recorded at -80°C on a Bruker ELEXSYS E580 spectrometer. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates. The product mixtures were separated by column chromatography on silica gel (Chemapol, 40–100 µm) using petroleum ether–ethyl acetate as eluent.

General procedure for the oxidation of haloarenes 1a, 1b, 3a, 3b, 7a, and 7b in the system PbO₂–CF₃CO₂H–CH₂Cl₂. Compound 1a, 1b, 3a, 3b, 7a, or 7b, 0.57 mmol, was added with vigorous stirring at 20°C to a solution of 0.2 mL (2.6 mmol) of trifluoroacetic acid in 3 mL of methylene chloride, 136 mg (0.57 mmol) of lead(IV) oxide was then added, and the mixture was stirred for 2–70 h. When the reaction was complete, the mixture was treated with water (50 mL) and extracted with chloroform (3× 50 mL). The combined extracts were washed with water, a saturated aqueous solution of NaHCO₃, and water again and dried over Na₂SO₄, and the solvent was distilled off. The residue was subjected to silica gel column chromatography using petroleum etherethyl acetate as eluent. Given below are the yields of the isolated compounds.

(2,5-Diiodo-3,4,6-trimethylphenyl)methanol (2a). Yield 35%, colorless crystals, mp 152–154°C. ¹H NMR spectrum, δ , ppm: 1.94 s (1H, OH), 2.62 s (3H, CH₃), 2.64 s (3H, CH₃), 2.73 s (3H, CH₃), 5.01 s (2H, CH₂). ¹³C NMR spectrum, $\delta_{\rm C}$, ppm: 28.6 (CH₃), 29.4 (CH₃), 29.9 (CH₃), 70.3 (CH₂), 111.4, 113.1, 138.3, 139.2, 139.8, 140.8. Mass spectrum: *m*/*z* 402 [*M*]⁺. HRMS: found: 402.9059; calculated for C₁₀H₁₃I₂O: [*M* + H]⁺ 402.9050.

(2,5-Dibromo-3,4,6-trimethylphenyl)methanol (2b). Yield 30%, colorless crystals, mp 179–181°C. ¹H NMR spectrum, δ , ppm: 1.89 s (1H, OH), 2.49 s (3H, CH₃), 2.50 s (3H, CH₃), 2.60 s (3H, CH₃), 4.94 s (2H, CH₂). ¹³C NMR spectrum, $\delta_{\rm C}$, ppm: 21.3 (CH₃), 22.0 (CH₃), 22.4 (CH₃), 64.2 (CH₂), 127.9, 129.0, 135.5, 136.5, 136.7, 138.1. Mass spectrum: *m*/*z* 306 [*M*]⁺. HRMS: found: 306.9321; calculated for C₁₀H₁₃Br₂O: [*M* + H]⁺ 306.9328.

(2-Iodo-3,4,6-trimethylphenyl)methanol (4a). Yield 15%, colorless crystals, mp 86–88°C. ¹H NMR spectrum, δ , ppm: 1.66 s (1H, OH), 2.33 s (3H, CH₃), 2.44 s (3H, CH₃), 2.45 s (3H, CH₃), 4.88 s (2H, CH₂), 6.94 s (1H, H_{arom}). Mass spectrum: *m*/*z* 276 [*M*]⁺. HRMS: found: 277.0076; calculated for C₁₀H₁₄IO: [*M* + H]⁺ 277.0084.

(2-Bromo-3,4,6-trimethylphenyl)methanol (4b). Yield 35%, colorless crystals, mp 75–77°C. ¹H NMR spectrum, δ , ppm: 1.69 s (1H, OH), 2.29 s (3H, CH₃), 2.36 s (3H, CH₃), 2.42 s (3H, CH₃), 4.84 s (2H, CH₂), 6.95 s (1H, H_{arom}). ¹³C NMR spectrum, δ_{C} , ppm: 19.7 (CH₃), 19.9 (CH₃), 21.2 (CH₃), 69.9 (CH₂), 128.9, 131.2, 134.4, 135.5, 135.9, 137.9 (C_{arom}). Mass spectrum: *m/z* 228 [*M*]⁺. Calculated: *M* 228.0. (3-Iodo-3,4,5-trimethylphenyl)methanol (5a). Yield 23%, colorless crystals, mp 80–82°C. ¹H NMR spectrum, δ , ppm: 1.55 s (1H, OH), 2.35 s (3H, CH₃), 2.48 s (3H, CH₃), 2.51 s (3H, CH₃), 4.69 s (2H, CH₂), 7.09 s (1H, H_{arom}). Mass spectrum: *m*/*z* 276 [*M*]⁺. HRMS: found: 277.0081; calculated for C₁₀H₁₄IO: [*M* + H]⁺ 277.0084.

1-Iodo-4-[(2-iodo-3,4,6-trimethylphenyl)methyl]-2,3,5,6-tetramethylbenzene (6a). Yield 5%, colorless crystals, mp 110–112°C. ¹H NMR spectrum, δ, ppm: 2.15 s (6H, CH₃), 2.17 s (3H, CH₃), 2.44 s (3H, CH₃), 2.57 s (6H, CH₃), 2.62 s (3H, CH₃), 3.93 s (2H, CH₂), 6.23 s (1H, H_{arom}). Mass spectrum: m/z 518 $[M]^+$. HRMS: found: 519.0048; calculated for C₂₀H₂₅I₂: $[M + H]^+$ 519.004.

(4-Iodo-3,5-dimethylphenyl)methanol (8a). Yield 15%, yellow crystals, mp 71–72°C [35]. ¹H NMR spectrum, δ , ppm: 1.70 s (1H, OH), 2.48 s (6H, CH₃), 4.60 s (2H, CH₂), 7.06 s (1H, H_{arom}). ¹³C NMR spectrum, δ_{C} , ppm: 29.6 (CH₃), 64.6 (CH₂), 107.0, 125.5, 140.3, 142.3. Mass spectrum: m/z 262 $[M]^+$. Calculated: M 262.1.

(4-Bromo-3,5-dimethylphenyl)methanol (8b). Yield 10%, colorless crystals, mp 80–82°C [36, 37]. ¹H NMR spectrum, δ , ppm: 1.76 s (1H, OH), 2.41 s (6H, CH₃), 4.59 s (2H, CH₂), 7.07 s (1H, H_{arom}). ¹³C NMR spectrum, δ_C , ppm: 23.8 (CH₃), 64.7 (CH₂), 126.5, 126.8, 138.5, 139.2. Mass spectrum: *m*/*z* 214 [*M*]⁺. Calculated: *M* 214.0.

4-Iodo-3,5-dimethylbenzaldehyde (9a). Yield 17%, yellow crystals, mp 65–67°C [38]. ¹H NMR spectrum, δ , ppm: 2.55 s (6H, CH₃), 7.51 s (2H, H_{arom}), 9.93 s (1H, CHO). Mass spectrum: m/z 260 $[M]^+$. Calculated: M 260.0.

4-Bromo-3,5-dimethylbenzaldehyde (9b). Yield 12%, colorless crystals, mp 67–69°C [39]. ¹H NMR spectrum, δ , ppm: 2.49 s (6H, CH₃), 7.56 s (2H, H_{arom}), 9.93 s (1H, CHO). Mass spectrum: *m/z* 212 [*M*]⁺. Calculated: *M* 212.0.

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RUSSIAN JOURNAL OF ORGANIC CHEMISTRY Vol. 54 No. 3 2018

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