

## Synthesis of Functionally Substituted Benzaldehydes

M. B. Gazizov<sup>a,\*</sup>, S. Yu. Ivanova<sup>a</sup>, Sh. N. Ibragimov<sup>a</sup>, R. A. Khairullin<sup>a</sup>, R. F. Karimova<sup>a</sup>,  
K. S. Gazizova<sup>a</sup>, and Corresponding Member of the RAS I. S. Antipin<sup>b</sup>

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**Abstract**—A new method of synthesis of functionally substituted benzaldehydes by catalytic debromomethoxylation of dibromomethylarenes with benzaldehyde dimethyl acetal has been suggested. Anhydrous zinc chloride has been used as a catalyst. Being soft Lewis acid, it formed no strong complex with aldehyde group and other functional groups. The initial acetal has been readily recovered by the treatment of benzaldehyde isolated from the reaction mixture with trimethyl orthoformate.

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We have recently shown [1, 2] that dihalomethylarenes react with methyl esters of P(IV) acids to form aromatic aldehydes and phosphorus acid anhydrides. However, the reaction requires high temperature (160–180°C) and expensive methyl esters of P(IV) acids. In recent decade, two promising methods have been proposed for the synthesis of aromatic monoaldehydes from dihalomethylarenes: heating of a mixture of the latter with a large excess of dimethyl sulfoxide [3] of pyridine [4] at 70–120°C for 1–18 h followed by treatment of reaction mixture with water. However, the isolation of individual aldehydes is a laborious process.

The aim of this work is to develop a new method for preparing functionally substituted aromatic aldehydes by the catalytic debromomethoxylation of dibromomethylarenes with benzaldehyde dimethyl acetal.

We propose for the first time to synthesize functionally substituted aromatic aldehydes by the catalytic debromomethoxylation of dibromomethylarenes **I** with benzaldehyde dimethyl acetal **II** (Scheme 1).

Zinc chloride was used as a catalyst, it is a soft Lewis acid, which forms no strong complex with aldehyde and other functional groups. We found in preliminary experiments that the reaction of compounds **I** and **II** without a catalyst occurs only at 220°C. When 10 mol % of ZnCl<sub>2</sub> is used, the reaction completes after 2 h at 50°C and after 1 h at 80°C. The reaction was conducted in isooctane or benzene or in the absence of a solvent. The reaction does not affect methoxycarbonyl and carbonyl groups (Scheme 2).

Acetal groups in dibromide **Ib** and 4-(dimethoxymethyl)benzaldehyde **IIIb** participate in debromomethoxylation to give terephthalic aldehyde **IIIa** as the major reaction product. Compound **IIIb** was detected only by <sup>1</sup>H NMR and chromatography. Moreover, since compound **Ib** contains both dibromomethyl and acetal groups, we expected the presence of intermolecular interaction between them. Indeed, the addition of catalytic amounts of ZnCl<sub>2</sub> to compound **Ib** caused the formation of terephthalic aldehyde **IIIa** in 96% yield.

In general case (Scheme 3), the reaction of tetrabromide **Ie** with benzaldehyde dimethyl acetal **II** depending on reagent ratio can result in formation of three aldehydes: monoaldehyde **Ia**, dialdehyde **IIIa**, and benzaldehyde **IV**, while tetrabromide **Ie** could react incompletely.

At the reagent ratio **Ie** : **II** = 1.0 : 2.1, the <sup>1</sup>H NMR spectrum of the reaction mixture showed no resonance signal at 6.61 ppm corresponding to the proton of the dibromomethyl group. We isolated terephthalic aldehyde **IIIa** in 90% yield.

With the aim to use this reaction for the preparation of 4-(dibromomethyl)benzaldehyde **Ia**—a promising heterofunctional compound for organic synthesis—synthesized by us for the first time [5], we reacted compounds **Ie** and **II** in different ratios.

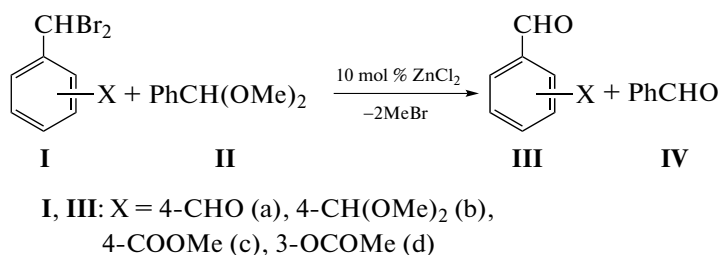
According to <sup>1</sup>H NMR, the reaction mixture contained no tetrabromide **Ie** at the 1.0 : 1.5 ratio. Compounds **Ia** and **IIIa** were isolated in individual state by column chromatography (benzene as an eluent, silica gel as a sorbent) in 11 and 64% yield, respectively.

Thus, in the absence of tetrabromide **Ie**, terephthalic aldehyde **IIIa** is the major reaction product; i.e., the second dibromomethyl group of compound **Ie** is involved in the reaction to give target compound **Ia** in

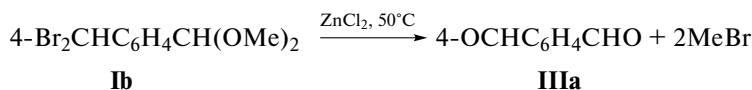
<sup>a</sup> Kazan State Technological University, Kazan, 420015 Tatarstan, Russia

<sup>b</sup> Kazan Federal University, Kazan, 420008 Tatarstan, Russia

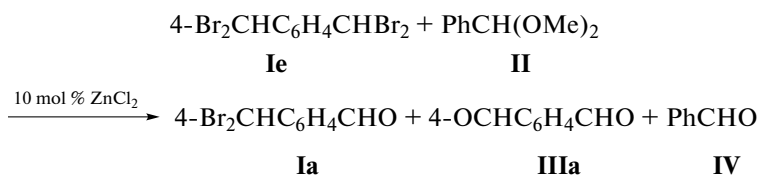
\*e-mail: mukattis@mail.ru



Scheme 1.



Scheme 2.



Scheme 3.

low yield. We isolated unchanged initial tetrabromide **Ie** in 18% yield at 1 : 1 ratio. The yields of individual compounds **Ia**, **IIIa**, and **IV** isolated by column chromatography toward reacted tetrabromide **Ie** were 23, 53, and 41%, respectively. Thus, the yield of target product **Ia** increased twofold at this ratio of the initial reagents. Initial acetal **II** was readily regenerated by the treatment of benzaldehyde formed in the reaction with trimethyl orthoformate.

Thus, we have developed for the first time the method of synthesis of functionalized aromatic aldehydes by catalytic debromomethoxylation of dibromomethylarenes with benzaldehyde dimethyl acetal.

## EXPERIMENTAL

<sup>1</sup>H NMR spectra were recorded on a Tesla BS 567 A and a Bruker AVANCE 400WB radiospectrometers operating at 100 and 400.13 MHz, respectively, in CDCl<sub>3</sub>. Chemical shifts are reported relative to tetramethylsilane using residual protons of the deuterated solvent as a reference.

**Reaction of 1,4-bis(dibromomethyl)benzene (Ie) with benzaldehyde dimethyl acetal (II).** Stage (a). Reagent ratio is 1.0 : 2.1. A mixture of 7 mmol of tetrabromide **Ie**, 15 mmol of acetal **II**, and 0.7 mmol of zinc chloride was heated at 50°C for 2 h. Extraction with isooctane afforded 5.97 mmol (84%) of compound **IIIa** as colorless crystals with mp 115–116°C

(mp 115–116°C [6]). Benzaldehyde **IV** (3.86 mmol, 28%) was isolated from the mother liquor.

Stage (b). A mixture of 7 mmol of tetrabromide **Ie**, 15 mmol of acetal **II**, and 0.7 mmol of zinc chloride in 5 mL of isooctane was heated at 50°C for 2.5 h. The isooctane solution was decanted, the residue was additionally extracted with 10 mL of isooctane. Compound **IIIa** (6.34 mmol, 89%) was isolated from the combined isooctane solutions. Benzaldehyde **IV** (4.05 mmol, 29%) was isolated from the mother liquor.

Stage (c). A mixture of 7 mmol of tetrabromide **Ie**, 15 mmol of acetal **II**, and 0.7 mmol of zinc chloride in 5 mL of isooctane was heated at 80°C for 1 h. Compound **IIIa** (6.42 mmol, 90%) was isolated from the isooctane solution. Benzaldehyde **IV** (3.77 mmol, 28%) was isolated from the mother liquor.

Stage (d). Ratio 1.0 : 1.5. A mixture of 7 mmol of tetrabromide **Ie**, 11 mmol of acetal **II**, and 0.7 mmol of zinc chloride in 5 mL of isooctane was heated at 80°C for 1 h. Compound **IIIa** (3.73 mmol, 53%) was isolated from the isooctane solution. Benzaldehyde **IV** (6.22 mmol, 55%), compound **Ia** (0.79 mmol, 11%), and additional compound **IIIa** (0.82 mmol, 11%) were isolated from the residue by column chromatography (benzene as an eluent, silica gel as a sorbent).

Stage (e). Ratio 1 : 1. A mixture of 7 mmol of tetrabromide **Ie**, 7 mmol of acetal **II**, and 0.7 mmol of zinc chloride in 10 mL of benzene was heated at 80°C for 1 h.

The solution was concentrated in a vacuum and subjected to column chromatography (benzene as an eluent, silica gel as a sorbent) to give 1.33 mmol (23%) of compound **Ia** and 3.13 mmol (53%) of compound **IIIa**, whose yields were calculated toward reacted tetrabromide **Ie**, and 2.83 mmol (41%) of compound **IV**.

**Reaction of 4-(dibromomethyl)benzaldehyde (Ia) with acetal II.** A mixture of 3.6 mmol of compound **Ia**, 3.8 mmol of acetal **II**, and 0.36 mmol of zinc chloride in 5 mL of isooctane was heated at 80°C for 1 h. Compound **IIIa** (2.99 mmol, 83%) was isolated from the isooctane solution. Benzaldehyde **IV** (1.98 mmol, 55%) was obtained from the mother liquor.

**Reaction of 1-(dibromomethyl)-4-(dimethoxymethyl)benzene (Ib) with acetal II.** A mixture of 3.1 mmol of compound **Ib**, 3.3 mmol of acetal **II**, and 0.31 mmol of zinc chloride was heated at 50°C for 1.5 h. Compound **IIIa** (1.12 mmol, 36%) was isolated by extraction with isooctane. Fractions containing 0.94 mmol (30%) of benzaldehyde **IV**, 0.45 mmol (15%) of dialdehyde **IIIa**, and a fraction composed of compounds **II** and **IIIb** identified by chromatography on a Sorbfil PTLC-AF-A-UV high-performance plate (Labtekh, Russia, benzene as an eluent) were isolated from the mother liquor by chromatography (benzene : diethyl ether = 19 : 1 as an eluent, silica gel as a sorbent).

**Transformation of 1-(dibromomethyl)-4-(dimethoxymethyl)benzene (I) in dialdehyde (IIIa) under the action of catalytic amounts of zinc chloride.** A mixture of 3.4 mmol of compound **Ib** and 0.34 mmol of zinc chloride was heated at 50°C for 1 h. Compound **IIIa** (3.28 mmol, 96%) was isolated by extraction with isooctane.

**Methyl 4-formylbenzoate (IIIc).** A mixture of 3.2 mmol of compound **Ic**, 3.4 mmol of acetal **II**, and 0.32 mmol of zinc chloride was heated at 50°C for 2 h and at 80°C for 2 h. Compound **IIIc** (2.62 mmol, 82%) was isolated by extraction with isooctane, mp 59–61°C (mp 63–65°C [7]). <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm): 3.97 (s, 3H, OCH<sub>3</sub>), 7.94 d and 8.19 d (4H, C<sub>6</sub>H<sub>4</sub>, <sup>3</sup>J<sub>HH</sub> 8.4 Hz), 10.10 (s, 1H, CHO). Benzaldehyde **IV** (0.94 mmol, 29%) was isolated from the mother liquor.

**3-Formylphenyl acetate (IIIId).** A mixture of 6.5 mmol of compound **Id**, 6.8 mmol of acetal **II**, and 0.65 mmol of zinc chloride was heated at 80°C for 2 h. Column chromatography (benzene : diethyl ether = 19 : 1 as an eluent, silica gel as a sorbent) afforded 2.01 mmol (30%) of compound **IIIId** as an oil [8] and 1.89 mmol (29%) of benzaldehyde **IV**. <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm): 2.42 (s, 3H, CH<sub>3</sub>), 7.47–8.13 (m, 4H, C<sub>6</sub>H<sub>4</sub>), 10.08 (s, 1H, CHO).

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