Synthesis of aromatic aldehyde acetals from (dibromomethyl)arenes

M. B. Gazizov, S. Yu. Ivanova, N. Yu. Bashkirtseva, O. D. Khairullina, R. A. Khairullin, and O. V. Gazizova*

Kazan National Research Technological University,
68 ul. Karl Marx, 420015 Kazan, Russian Federation.
Fax: +7 (843) 231 9505. E-mail: mukattisg@mail.ru

Zinc chloride-catalyzed double debromoalkoxylation of (dibromomethyl)arenes on treatment with trialkyl orthoformates resulted in the corresponding aromatic aldehyde acetals. On the first step, α-brominated ether is formed, which undergoes the second debromoalkoxylation producing acetal. This method is tolerated to ester functionalized derivatives.

Key words: acetals, trialkyl orthoformates, (dibromomethyl)arenes, debromoalkoxylation, zinc chloride, α-brominated ethers.

Acetals of aromatic aldehydes are widely used in the organic synthesis.[1,2] One of the known synthetic approaches towards acetals is the reaction of alkali metal alkoxides with organic geminal dihalides[3—9] resulting in conversion of the dihalomethyl group into the acetal function *via* a double dehaloalkoxylation. The main disadvantages of this method are the necessity of the preliminary preparation of alkali metal alkoxide and possibility of the transformations of other functional groups in the presence of very strong base, an alkoxide anion. More widely used synthetic approaches to acetals involve acetalization of aldehydes with alcohols, ortho esters, dimethyl sulfite, and tetraalkoxysilanes.[3,4,8—14]

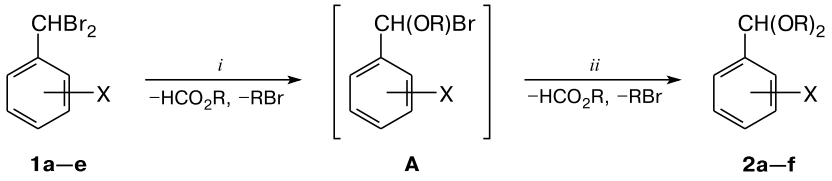
Earlier, we have described transformations of benzal chloride into benzaldehyde acetals *via* dechloroalkoxylation by using aprotic non-ionogenic trialkyl orthoformates instead of alkoxides.[15] However, this reaction occurs only at 225 °C and required 28 h to be completed. It is obvious that both the reaction temperature and the reaction time could be decreased by appropriate selection of the catalyst. The aim of the present work is the development of a new method for the catalytic double debromoalkoxylation of (dibromomethyl)arenes **1** into aromatic aldehyde acetals **2** with trialkyl orthoformates (Scheme 1).

Among Lewis acids (aluminum, iron, and zinc chlorides), zinc chloride is a reagent of choice for our reaction because being a mild Lewis acid it does not form stable complexes with the functional groups present in the starting material. When zinc chloride was used in the amount of 10 mol.%, the reaction was completed within 2 h at 80 °C.

We earlier have shown that α-chloro ethers undergo dechloroalkoxylation with trialkyl orthoformates at room temperature giving acetals.[16] We assume that in the studied reaction α-bromo ethers **A** are also initially formed (see Scheme 1), which then undergo the second debromoalkoxylation to give the corresponding acetal **2**. It is advisable to use 2.1—4.0 equiv. of ortho ester per each dibromomethyl group maintaining the excess of the ortho ester in the reaction mixture. This facilitates the reaction and prevents debromoalkylation of bromo ether **A** to the corresponding aldehyde.

Direction of the reaction of the previously synthesized in our group 4-(dibromomethyl)benzaldehyde (**1e**)[17,18] with trialkyl orthoformates depends on the reagent ratio.

Scheme 1



1a—e **A** **2a—f**

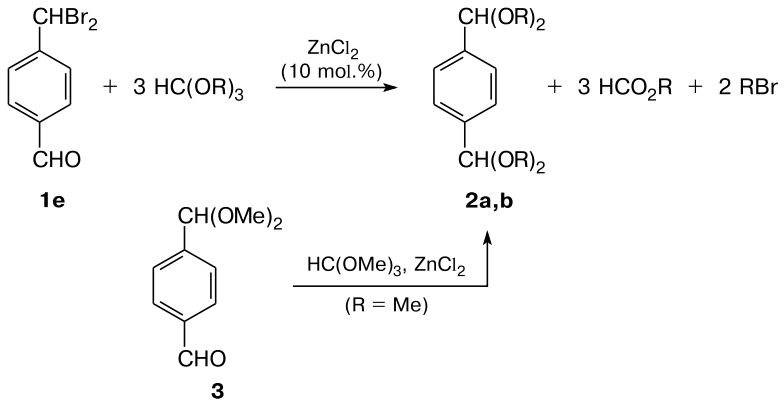
1: X = 4-CH(OMe)$_2$ (**a**), 4-CO$_2$Me (**b**), 3-OAc (**c**), 4-CHBr$_2$ (**d**), 4-CHO (**e**)
2: X = 4-CH(OMe)$_2$, R = Me (**a**); X = 4-CH(OEt)$_2$, R = Et (**b**); X = 4-CO$_2$Me, R = Me (**c**); X = 4-CO$_2$Me, R = Et (**d**); X = 4-CO$_2$Et, R = Et (**e**); X = 3-OAc, R = Me (**f**)

Reagents and conditions: *i*. HC(OR)$_3$, ZnCl$_2$ (10 mol.%), 80 °C, 2 h; *ii*. HC(OR)$_3$.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1230—1233, July, 2017.

1066-5285/17/6607-1230

Scheme 2



At **1e** : $HC(OR)_3$ = 1 : 4, the identical acetal groups are formed from aldehyde and dibromomethyl moieties and terephthaldehyde diacetals **2a** and **2b** were obtained in high yields (see Schemes 1 and 2). According to ^1H NMR spectroscopy, the reaction takes place even at room temperature and completes within 24 and 48 h for the methyl and ethyl derivatives, respectively. After this reaction time, ^1H NMR spectra contain the proton signals of diacetals **2a** and **2b**, alkyl formate (intensity ratio of 1 : 1), and ortho ester used in an excess. When alkyl formate and ortho ester were removed, ^1H NMR spectra show only the signals from diacetal **2**. Compound **2a** was also synthesized by alternative procedure reacting terephthaldehyde monoacetal **3** with trimethyl orthoformate in the presence of $ZnCl_2$ (see Scheme 2).

A tentative mechanism of the catalytic reaction is given on Scheme 3. The reaction starts from the formation of the electron donor-acceptor complex **B**, which transforms into either the contact (**C**) or separated (**D**) ion pair. O-Nucleophilic trialkyl orthoformate attacks the carbocation reaction center of these ion pairs with the release of zinc chloride and formation of a new ion pair **E**, which further decomposes to give α-bromo ether **A** (see Scheme 1) and bromoformaldehyde acetal (**F**). Compound **F** readily transforms into alkyl formate and alkyl bromide.

In summary, we first used $ZnCl_2$ to catalyze the reaction of (dibromomethyl)arenes **1** with trialkyl orthoformates **2**. This catalyst serves to decrease the reaction temperature from 220 to 80 °C and reduce the reaction time from 28 to 2 h. The developed procedure represents efficient synthetic approach towards aromatic aldehyde acetals including those bearing the additional functional groups.

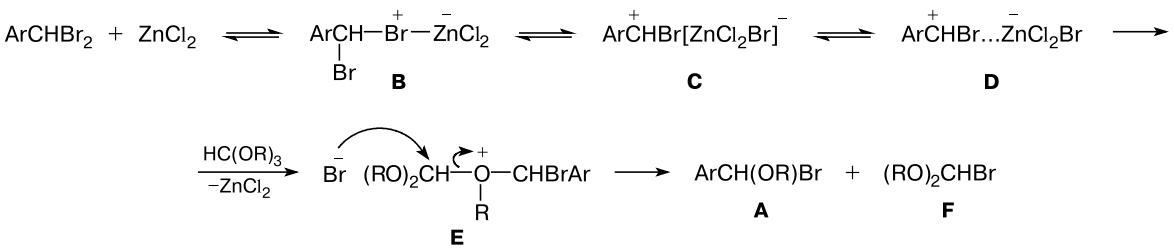
Experimental

^1H and ^{13}C NMR spectra were recorded on Tesla BS-567A (working frequency of 100 MHz) and AVANCE 400WB instruments (working frequencies of 400.13 (^1H) and 100.61 MHz (^{13}C)) in $CDCl_3$. Chemical shifts were measured in the δ scale relative to residual solvent signal (^1H) and the carbon atom of the solvent (^{13}C) and referred to Me_4Si.

1,4-Bis(dimethoxymethyl)benzene (2a). ***A***. A mixture of 1-dibromomethyl-4-(dimethoxymethyl)benzene (**1a**) (1.61 g, 5 mmol), trimethyl orthoformate (2.12 g, 20 mmol), and zinc chloride (0.07 g, 0.5 mmol) was heated at 80 °C for 2 h. The excess ortho ester was removed *in vacuo* and the residue was extracted with hot isooctane to give 1.11 g (98%) of compound **2a**, colorless crystals, m.p. 53 °C (*cf.* Ref. 12: m.p. 53 °C). ^1H NMR ($CDCl_3$), δ: 3.13 (s, 12 H, OMe); 5.23 (s, 2 H, CHO_2); 7.26 (s, 4 H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ: 52.1 (OMe); 102.4 (CHO_2); 126.6 (CH_{Ar}); 138.1 (C_{Ar}).

B. A mixture of 1,4-bis(dibromomethyl)benzene (15.00 g, 35.5 mmol) (**1d**), trimethyl orthoformate (15.82 g, 149.1 mmol), and zinc chloride (0.48 g, 3.55 mmol) was heated at 80 °C for 2 h. Vacuum distillation of the reaction mixture afforded 6.05 g

Scheme 3



(76%) of compound **2a**, colorless crystals, m.p. 53 °C (*cf.* Ref. 12: m.p. 53 °C), b.p. 107 °C (0.1 Torr) (*cf.* Ref. 12: b.p. 138—139 °C (9 Torr)). The samples obtained by methods ***A*** and ***B*** are identical.

C. A mixture of 4-(dibromomethyl)benzaldehyde (**1e**) (1.00 g, 3.6 mmol), $CH(OMe)_3$ (1.53 g, 14.4 mmol), and zinc chloride (0.05 g, 0.36 mmol) was heated at 80 °C for 2 h. The volatiles were removed *in vacuo* and the residue was extracted with hot isooctane to give 0.80 g (99%) of compound **2a**, colorless crystals. The physicochemical properties of the sample are coincide with those given above.

D. A mixture of compound **1e** (0.25 g, 0.9 mmol), $CH(OMe)_3$ (0.38 g, 3.6 mmol), and zinc chloride (0.01 g, 0.09 mmol) was kept at room temperature for 24 h. ^{1}H NMR spectrum of the reaction mixture ($CDCl_3$), δ: 3.26 (s, OMe acetal and ortho ester); 4.89 (s, 1 H, CHO_3); 5.38 (s, 2 H, CHO_2); 7.39 (s, 4 H, C_6H_4); 3.71 (s, 3 H, OMe); 8.01 (s, 1 H, HC(O)O). Removal of the volatiles *in vacuo* afforded 0.19 g (95%) of diacetal **2a**, colorless crystals. The sample was identical to the products obtained by the other methods.

E. Independent synthesis. A mixture of 4-(dimethoxymethyl)-benzaldehyde (**3**) (0.32 g, 1.8 mmol), $CH(OMe)_3$ (0.38 g, 3.6 mmol), and zinc chloride (0.02 g, 0.18 mmol) was heated at 80 °C for 2 h. The volatiles were removed *in vacuo* and the residue was extracted with hot isooctane to give 0.40 g (98%) of compound **2a**, colorless crystals. Physicochemical and spectral properties of the sample are identical with those given above.

1,4-Bis(diethoxymethyl)benzene (2b). ***A.*** A mixture of 1,4-bis-(dibromomethyl)benzene (**1d**) (15.00 g, 35.5 mmol), triethyl orthoformate (22.10 g, 149.1 mmol), and zinc chloride (0.48 g, 3.55 mmol) was heated at 80 °C for 4.5 h. Vacuum distillation of the reaction mixture afforded 6.80 g (68%) of compound **2b**, colorless liquid, b.p. 119—120 °C (0.1 Torr) (*cf.* Ref. 11: b.p. 107—108 °C (0.001 Torr)). ^{1}H NMR ($CDCl_3$), δ: 1.17 (t, 12 H, $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.0 Hz); 3.49 (q, 8 H, OCH_2, $^3J_{H,H}$ = 7.0 Hz); 5.44 (s, 2 H, CHO_2); 7.37 (s, 4 H, C_6H_4).

B. A mixture of 4-(dibromomethyl)benzaldehyde (**1e**) (1.00 g, 3.6 mmol), triethyl orthoformate (2.13 g, 14.4 mmol), and zinc chloride (0.05 g, 0.36 mmol) was heated at 80 °C for 2 h. Removal of the volatiles *in vacuo* and extraction of the residue with hot isooctane afforded 0.99 g (98%) of 1,4-bis(diethoxymethyl)benzene (**2b**), colorless liquid. The samples obtained by methods ***A*** and ***B*** are identical.

C. A mixture of 4-(dibromomethyl)benzaldehyde **1e** (0.25 g, 0.9 mmol), $CH(OEt)_3$ (0.53 g, 3.6 mmol), and zinc chloride (0.01 g, 0.09 mmol) was kept at room temperature for 24 h. ^{1}H NMR ($CDCl_3$) spectrum of the reaction mixture contained resonances for the protons of the starting compound at δ 6.71 (s, 1 H, $CHBr_2$) and 9.94 (s, 1 H, CHO). These signals disappeared 24 h after the additional reaction time and ^{1}H NMR spectrum showed signals of diacetal **2b** at δ 5.40 (s, 2 H, 2 CHO_2) and 7.34 (s, 4 H, C_6H_4), ethyl formate at δ 4.09 (q, 2 H, OCH_2, $^3J_{H,H}$ = 7.0 Hz) and 7.91 (s, 1 H, HC(O)O), and excess $CH(OEt)_3$ at δ 5.01 (s, 1 H, CHO_3); the signals of the ethoxy groups of diacetal and ortho ester overlapped. Removal of the volatiles *in vacuo* afforded diacetal **2b**, colorless liquid. Physicochemical and spectral properties of the sample are identical with those given above.

Methyl 4-(dimethoxymethyl)benzoate (2c). A mixture of methyl 4-(dibromomethyl)benzoate (**1b**) (0.63 g, 2 mmol), trimethyl orthoformate (0.85 g, 8 mmol), and zinc chloride (0.03 g, 0.2 mmol) was heated at 80 °C for 2 h. Extraction of the reaction mixture with isooctane afforded 0.34 g (81%) of compound **2c**, colorless oil (*cf.* Ref. 8, 10). ^{1}H NMR ($CDCl_3$), δ: 3.21 (s, 6 H, OMe); 3.84 (s, 3 H, COOMe); 5.35 (s, 1 H, CHO_2); 7.43, 7.94 (both s, 2 H each, C_6H_4, $^3J_{H,H}$ = 8.2 Hz). ^{13}C NMR ($CDCl_3$), δ: 51.9 (COOMe); 52.2 (OMe); 101.8 (CHO_2); 126.8, 127.0, 129.5, 129.5 (CH_{Ar}); 130.1, 142.8 (C_{Ar}); 166.3 (CO).

Reaction of methyl 4-(dibromomethyl)benzoate (1b) with triethyl orthoformate. A mixture of compound **1b** (1.50 g, 4.9 mmol), triethyl orthoformate (1.90 g, 12.8 mmol), and zinc chloride (0.07 g, 0.49 mmol) was heated at 80 °C for 4 h. Extraction of the reaction mixture with isooctane afforded 0.87 g of an inseparable mixture of methyl 4-(diethoxymethyl)benzoate (**2d**) and ethyl 4-(diethoxymethyl)benzenecarboxylate (**2e**) in a ratio of 1.7 : 1.0.

3-(Dimethoxymethyl)phenyl acetate (2f). A mixture of 3-(dibromomethyl)phenyl acetate (**1d**) (2.48 g, 8 mmol), trimethyl orthoformate (3.40 g, 32 mmol), and zinc chloride (0.10 g, 0.8 mmol) was heated at 50 °C for 1 h. ^{1}H NMR spectrum contained weak signal of the aldehyde group (δ 10.03), therefore $CH(OMe)_3$ (2.55 g, 24 mmol) was additionally added and heating at 50 °C was continued for 2 h. Removal of the volatiles *in vacuo* and extraction of the residue with isooctane afforded 0.50 g (30%) of compound **2f**, colorless oil. ^{1}H NMR ($CDCl_3$), δ: 2.35 (s, 3 H, COMe); 3.38 (s, 6 H, OMe); 5.51 (s, 1 H, CHO_2); 7.12—7.46 (m, 4 H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ: 20.9 (COMe); 52.0 (OMe); 101.6 (CHO_2); 120.2, 121.5, 124.1, 127.1, 127.5, 129.9, 139.8 (C_6H_4); 168.7 (CO). Found (%): C, 62.63; H, 6.59. $C_{11}H_{14}O_4$. Calculated (%): C, 62.86; H, 6.67.

This work was financially supported by the Ministry of Education and Science of the Russian Federation (Project No. 4.5348.2017/8.9 in the framework of the basic part of the State Assignment).

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Received May 4, 2017