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LETTERS TO THE EDITOR

New Synthetic Method for Preparation of Functionally Substituted Benzenecarbaldehyde Acetals

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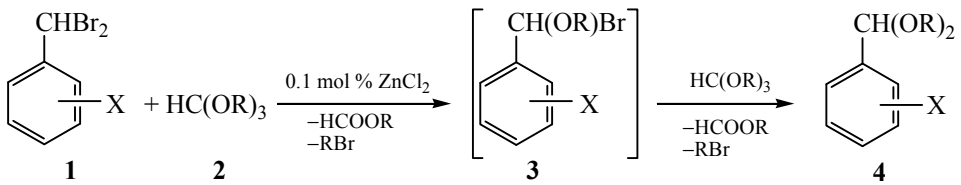
One of the methods of acetals synthesis is the reaction of readily available organic *gem*-halides with alkali metals alcoholates resulting in di(dehaloalkoxylation) [1–8]. Often *gem*-dichlorides [3–7] are used in this reaction, while it is much less likely to use *gem*-dibromides [8–10]. The main disadvantages of this method are the necessity of preparation of alkali metal alkoxide and the attack of alkoxide anion being a strong base on the available functional groups. In this regard, the method is inferior to modern methods of the synthesis of acetals from aldehydes using alcohols, orthoesters, dimethylsulfite, tetraalkoxysilanes [1, 2], including phthalaldehyde acetals [9–15].

Previously, we used an easily accessible aprotic nonionic agent trialkyl orthoformate instead of alcoholate for benzylidene chloride di(dechloroalkoxylation) [16]. However, the reaction proceeded only at 225°C for 28 h. To develop this approach we performed catalytic di(debromoalkoxylation) of functionally substituted dibromomethylarenes **1** with trialkyl orthoformate **2**. Zinc chloride was used as a catalyst, which did not form a strong complex with the available functional groups in the substrate molecule. The reaction was complete in 2 hours at 80°C when using 0.1 mol % of $ZnCl_2$ (Scheme 1).

In the case of benzaldehyde dimethyl acetal intermediate α-bromoester cleaved methylbromide to form the corresponding aldehydes [17]. Unlike $C_6H_5(OMe)_2$ orthoester **2** was able to re-debromoalkoxylate bromoester **3** to give acetal **4**; an excess of orthoester (2.1–4.0 equivalents per dibromomethyl group) was used. It favoured debromoalkoxylation of bromoester **3** and prevented the aldehydes formation.

Reaction of 1-(dibromomethyl)-4-(dimethoxymethyl)benzene (1a) with trimethyl orthoformate (2). A mixture of 1.61 g (0.005 mol) of compound **1a**, 2.12 g (0.020 mol) of trimethyl orthoformate **2,** and 0.07 g (0.0005 mol) of zinc chloride was heated at 80°C for 2 h. Next, an excess of orthoester was removed in a vacuum to obtain 1.11 g (98%) of 1,4-bis(di-

Scheme 1.



1 **2** **3** **4**

1, X = 4-CH(OMe)$_2$ (**a**), 4-COOMe (**b**), 3-OCOMe (**c**), 4-CHBr$_2$ (**d**); **4**, X = 4-CH(OMe)$_2$, R = Me (**a**); X = 4-CH(OEt)$_2$, R = Et (**b**); X = 4-COOMe, R = Me (**c**); X = 4-COOMe, R = Et (**d**); X = 3-OCOMe, R = Me (**e**).

methoxymethyl)benzene **4a** as colorless crystals melting at 53°C (mp 53°C [13]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.13 s (12H, OMe), 5.23 s (2H, CHO_2), 7.26 s (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 52.1 (OMe), 102.4 (CHO_2), 126.6 (CH_{Ar}), 138.1 (C_{Ar}).

Reaction of methyl 4-(dibromomethyl)benzenecarboxylate (1b) with trimethyl orthoformate (2) (a ratio of 1 : 4). A mixture of 0.63 g (0.002 mol) of compound **1b**, 0.85 g (0.008 mol) of trimethyl orthoformate, and 0.03 g (0.0002 mol) of zinc chloride was heated at 80°C for 2 h. Extraction with isooctane provided methyl 4-(dimethoxymethyl)benzenecarboxylate **4c** as a colorless oil [9–11]. Yield 0.34 g (81%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.21 s (6H, OMe), 3.84 s (3H, COOMe), 5.35 s (1H, CHO_2), 7.43 and 7.94 d (4H, C_6H_4, $^3J_{HH}$ = 8.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 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)benzenecarboxylate (1b) with triethyl orthoformate (2) (a ratio of 1.0 : 2.6). A mixture of 1.5 g (0.0049 mol) of compound **1b**, 1.9 g (0.0128 mol) of triethyl orthoformate **2,** and 0.07 g (0.00049 mol) of zinc chloride was heated at 80°C for 4 h. Extraction with isooctane provided 0.87 g of a mixture of methyl 4-(diethoxymethyl)benzenecarboxylate **4d** and ethyl 4-(diethoxymethyl)benzenecarboxylate **4e** in a ratio of 1.7 : 1.0. Attempts to isolate compounds in pure state failed.

Reaction of 3-(dibromomethyl)phenylacetate (1c) with trimethyl orthoformate (2). A mixture of 2.48 g (0.008 mol) of compound **1c**, 3.40 g (0.032 mol) of trimethyl orthoformate **2,** and 0.1 g (0.0008 mol) of zinc chloride was heated at 50°C for 1 h. Due to the presence of a weak signal of aldehyde proton (10.03 ppm) in the ^{1}H NMR spectrum of the reaction mixture, 2.55 g (0.024 mol) of compound **2** was added and heating was continued for 2 h. After the excess orthoester was removed in a vacuum, the residue was treated with isooctane to obtain 0.5 g (30%) of 3-(dimethoxymethyl)phenyl acetate **4e** as colorless oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.35 s (3H, COMe), 3.38 s (6H, OMe), 5.51 s (1H, CHO_2), 7.12–7.46 m (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 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.

Reaction of 1,4-bis(dibromomethyl)benzene (1d) with trialkyl orthoformates (a ratio of 1.0 : 4.2). *a*. A mixture of 15 g (0.0355 mol) of tetrabromide **1d**, 15.82 g (0.1491 mol) of compound **2,** and 0.48 g (0.00355 mol) of zinc chloride was heated at 80°C for 2 h. The reaction mixture was distilled in a high vacuum to give 6.05 g (76%) of compound **4a** as colorless crystals melting at 53°C (mp 53°C [13]) and bp 107°C (0.1 mmHg) {bp 105–110°C (1.0 mmHg) [11], bp 138–139°C (9 mmHg) [13]}. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 t (12H, $OCH_2\underline{Me}$, $^3J_{HH}$ = 7.0 Hz), 3.49 q (8H, OCH_2, $^3J_{HH}$ = 7.0 Hz), 5.44 s (2H, CHO_2), 7.37 s (4H, C_6H_4).

b. A mixture of 15 g (0.0355 mol) of tetrabromide **1d**, 1.22 g (0.1491 mol) of compound **2,** and 0.48 g (0.00355 mol) of zinc chloride was heated at 80°C for 4.5 h. The reaction mixture was distilled in a high vacuum to give 6.8 g (68%) of 1,4-bis(diethoxymethyl)benzene **4b** as colorless liquid, bp 119–120°C (0.1 mmHg) {bp 107–108°C (0.001 mmHg) [12]}. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 t (12H, $OCH_2\underline{Me}$, $^3J_{HH}$ = 7.0 Hz), 3.49 q (8H, OCH_2, $^3J_{HH}$ = 7.0 Hz), 5.44 s (2H, CHO_2), 7.37 s (4H, C_6H_4).

^{1}H NMR spectra were registered on an AVANCE 400WB (400.13) spectrometer in $CDCl_3$, internal reference TMS.

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REFERENCES

1. March, J., *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*, New York: John Wiley and Sons, 1992, p. 387.
2. Yanovskaya, L.A., Yufit, S.S., and Kucherov, V.F., *Khimiya atsetalei* (Chemistry of Acetals), Moscow: Nauka, 1975.
3. Monral, E. and Hand, C.R., *J. Am. Chem. Soc*., 1950, vol. 72, p. 5345.
4. Moffett, R.B., *Org. Synth. Coll*., 1963, vol. 4, p. 427.
5. Schank, K., *Chem. Ber*., 1967, vol. 100, p. 2292.
6. Chastrette, M., *Ann. Chim*., 1962, vol. 7, p. 643.
7. Cavallini, G., *J. Med. Chem*., 1964, vol. 7, p. 255.
8. Kober, E. and Grundmann, C., *J. Am. Chem. Soc*., 1958, vol. 80, p. 5547.

9. Clerici, A., Pastori, N., and Porta, O., *Tetrahedron*, 1998, vol. 54, p. 15679. doi 10.1016/S0040-4020(98)00982-X
10. Nao, H., Kiyoshi, K., Tsuneo, S., and Hisashi, S., *Synlett*, 2004, no. 6, p. 1074. doi 10.1055/s-2004-820038
11. Wiles, C., Watts, P., and Haswell, S.J., *Tetrahedron*, 2005, vol. 61, p. 5209. doi 10.1016/j.tet.2005.03.082
12. Crosby, I.T., Pietersz, G.A., and Ripper, J.A., *Aust. J. Chem*., 2008, vol. 61, p. 138. doi 10.1071/CH07404
13. Krishtal, G.V., Zhdankina, G.M., and Serebryakov, E.P., *Russ.Chem. Bull.*, 1993, no. 5, p. 866.
14. Ehrlichmann, W., and Friedrich, K., *Chem. Ber*., 1961, vol. 94, p. 2217.
15. Schmitz, E., *Chem. Ber*., 1958, vol. 91, p. 410.
16. Gazizov, M.B., Gazizov, K.M., Pudovik, M.A., Mukhamadiev, A.A., Karimova, R.F., Sadykova, A.I., and Sinyashin, O.G., *Doklady Akad. Nauk*, 2001, vol. 381, no. 2, p. 207.
17. Gazizov, M.B., Ivanova, S.Yu., Ibragimov, Sh.N., Bagauva, L.R., Khairullin, R.A., and Medvedeva, K.A., *Russ. J. Gen. Chem.*, 2016, vol. 86, no. 9, p. 2129. doi 10.1134/S1070363216090267