Improved Synthesis of 3-Bromo-2,2-dimethyl-propanal, a Versatile Building Block for Compounds with two Geminal Methyl Groups on a Quaternary Center

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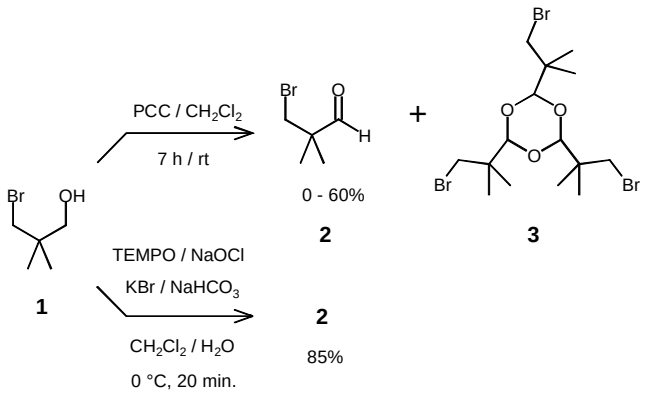
Abstract. A literature synthesis of 3-bromo-2,2-dimethyl-propanal (**2**) is reinvestigated since in our hands it gave very unreliable results. The ensuing decomposition reactions are studied (including X-ray structure of the trimer of **2**: 2,4,6-tris-(2-bromo-1,1-dimethyl-ethyl)-1,3,5-trioxane (**3**)), and a reliable method for the synthesis of **2** based on TEMPO catalyzed oxidation with NaOCl as co-oxidant is presented.

3-Bromo-2,2-dimethyl-propanal (**2**) is a well known compound [1–4]. Whereas Temnikova *et al*. [4] prepared **2** from the corresponding tosylate through Finkelstein reaction with KBr and described **2** as extremely unstable compound, Nerdel and coworkers [3] used the same method and did not mention any instability of **2**. The other authors [1, 2] obtained **2** by oxidation of 3-bromo-2,2-dimethyl-propanol (**1**) with pyridinium chlorochromate (PCC) and did not experience any difficulties. Interestingly, the four groups reported three different boiling points.

Wilt *et al*. [5, 6] prepared 3-chloro-2,2-dimethyl-propanal by oxidation of the corresponding alcohol with PCC without any problems.

For 3-iodo-2,2-dialkyl-propanals Nerdel *et al*. [7] found that they readily decompose with aqueous sodium hydroxide.

We needed **2** as building block for a compound with two geminal methyl groups on a quaternary carbon. Here, we wish to report our results concerning the synthesis and decomposition reactions of **2**. The synthesis of **2** according to [2] (Scheme 1) was very unreliable in our hands. Yields were in the range of 0% to 60%. One side product which could unequivocally be identified is the trimer **3** [8] of the aldehyde (Scheme 1).



Scheme 1 Oxidation of 3-bromo-2,2-dimethyl-propanol (**1**)

The trioxane **3** formed suitable crystals for X-ray analysis [9]. The corresponding ORTEP drawing is shown in Figure 1.

Next, we tried pyridinium dichromate PDC as oxidant. With PDC, decomposition of **2** did not occur during work up. Removing the pyridine from the crude product either by flash chromatography or by washing with dilute HCl without removing traces of acid, again resulted in decomposition of **2**.

In addition to the encountered difficulties, waste disposal of chromium containing reaction residues is problematic. To circumvent the observed difficulties we looked for other suitable oxidation methods. From the large number of available oxidizing agents (DMSO/$(COCl)_2$ [10], MnO_2 [11], Dess-Martin periodinane [12], TPAP/O_2 [13], TPAP/NMO [14], TEMPO/NaOCl [15–17], TEMPO/Diacetoxyiodobenzene [18]) the TEMPO catalyzed oxidation of primary alcohols to aldehydes with NaOCl as co-oxidant [16] was found very convenient (Scheme 1). It is cheap (advantage for large scale preparations), it uses mild conditions and is a very fast, high yielding reaction and waste disposal is no problem. During work up one carefully has to remove traces of acid by filtration of the organic extracts through basic alumina, otherwise, upon standing at room temperature **2** is converted more or less completely into the crystalline trimer **3**.

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Experimental

3-Bromo-2,2-dimethyl-propanol (**1**) is prepared according to [19]. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruk-

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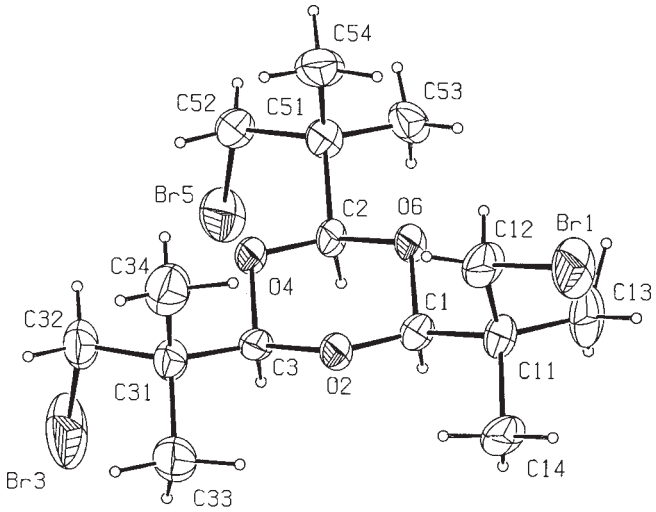

Fig. 1 ORTEP drawing of the X-ray structure of 2,4,6-tris(2-bromo-1,1-dimethyl-ethyl)-1,3,5-trioxane (**3**)

er AMX 360. Chemical shifts are reported relative to tetramethylsilane as internal standard. $CDCl_3$ was used as solvent. Mass spectra were obtained from a Finnigan MAT 8200 in EI mode.

3-Bromo-2,2-dimethyl-propanal (**2**)

16.7 g (0.1 mol) of 3-bromo-2,2-dimethyl-propanol (**1**) are dissolved in 65 ml of dichloromethane. 0,78 g (5 mmol) of TEMPO and a solution of 1.2 g (10 mmol) KBr in 5 ml water are added, and the resulting mixture is cooled below 0 °C under vigorous stirring. A mixture of 61 ml of 1.8M aqueous NaOCl, 47 ml of water and 3.4 g (40 mmol) of $NaHCO_3$ is added under vigorous stirring in such a way, that the temperature does not exceed 10 °C. Stirring is continued until the alcohol is consumed (10–20 min.). The phases are separated, and the aqueous phase is extracted three times with 20 ml of diethyl ether. The combined organic phases are washed with 40 ml of 10% HCl, which contains 1.3 g (8 mmol) of KI. The brown organic phase is washed twice with 20 ml of saturated aqueous $Na_2S_2O_3$, with 20 ml of saturated aqueous $NaHCO_3$ and with 20 ml of brine. After drying with $MgSO_4$ the organic phase is filtered through a short pad of basic alumina. The solvent is removed at normal pressure, and Kugelrohr distillation at atmospheric pressure affords 14.0 g of pure **2** (85%), which is best stored in the refrigerator under nitrogen. Compound **2** prepared in this way is stable for more than one year. *b.p.* 130–135 °C/760 Torr (Lit. [1]: *b.p.* 49–50 °C/13 Torr; lit. [2]: *b.p.* 62–63 °C/22 Torr; lit. [3]: *b.p.* 60–70 °C/80 Torr; lit. [4]: *b.p.* 73 °C/0.5 Torr. ^{1}H NMR (360 MHz): δ/ppm = 1.19 (s, 6H), 3.43 (s, 2H), 9.45 (s, 1H). ^{13}C NMR (90.3 MHz): δ/ppm = 202.8 (CHO), 46.7 (C), 38.4 (CH_2), 21.0 (CH_3). MS (EI, 70 eV): *m/z* (%) = 166 (M^+ (^{81}Br), 10%); 164 (M^+ (^{79}Br), 10%); 137 (M^+–CHO, 71%); 135 (M^+–CHO, 74%); 109 (10%); 107 (11%); 56 (100%); 55 (96%); 41 (65%); 39 (40%).

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[8] 2,4,6-Tris-(2-bromo-1,1-dimethyl-ethyl)-1,3,5-trioxane (**3**): ^{1}H NMR (360 MHz): δ/ppm = 4.74 (s, 3H) 3.35 (s, 6H), 1.04 (s, 18 H). ^{13}C NMR (90.3 MHz): δ/ppm = 103.2 (O–CH–O), 41.4 (CH_2), 39.0 (C), 20.9 (CH_3). *m.p.* 84–84.5 °C.
[9] Compound **3** crystallizes in space group P21/c with a = 9.0759(2) Å, b = 18.2951(2) Å, c = 12.2335(2) Å, $\alpha = \gamma$ = 90°, β = 104.099(5)°, V = 1970.1(3) Å^3, D_{calc} = 1.669 g/cm^3 for Z = 4. Least-squares refinement based on 2854 reflections ($I > 2.0\,\sigma(I)$) converged to a final R_1 = 8.63% and wR_2 = 24.14%. The crystallographic data were deposited as supplementary publication no. CCDC-125446 at Cambridge Crystallographic Data Centre. Copies free of charge can be obtained from CCDC, 12 Union Road, Cambridge, CB21EZ, GB (e-mail: deposit@ccdc.cam.ac.uk).
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[18] A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, J. Org. Chem. **1997**, *62*, 6974. Synthesis of **2** with TEMPO/diacetoxyiodobenzene at 0 °C to room temperature works well in large scale when the crude reaction mixture is distilled through a vigreux column to achieve separation of iodobenzene, but small amounts of **3** are formed since the reaction mixture becomes acidic during reaction.
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