Synthesis of 4-bromocubane-1-carbaldehyde

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Oxidation of 4-bromo-1-hydroxymethylcubane and 1,4-bis(hydroxymethyl)cubane with the 2,2,6,6-tetramethylpiperidine-*N*-oxyl—trichloroisocyanuric acid—sodium bicarbonate system afforded the corresponding aldehydes. 4-Bromocubanecarbaldehyde was also obtained in high yield by reduction of 4-bromocubanecarboxylic acid and its methyl ester with bis(*N*-methylpiperazinyl)aluminum hydride.

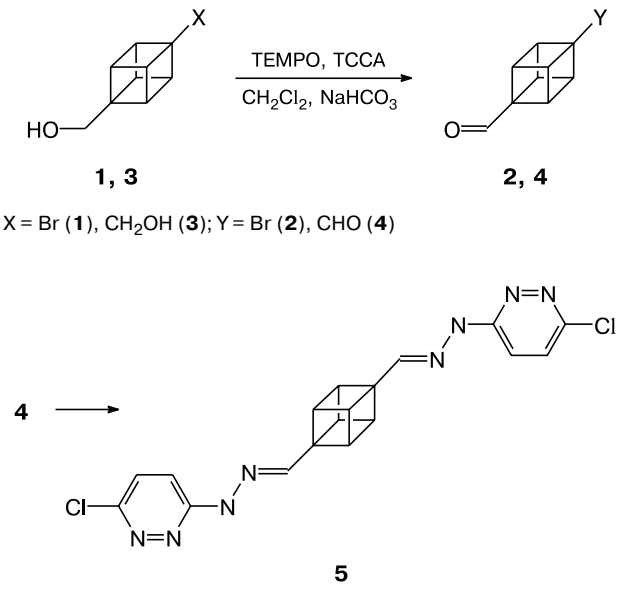
Key words: cubane derivatives, aldehydes, oxidation, reduction, TEMPO, aluminum hydrides, X-ray diffraction analysis.

Cubane derivatives find increasingly frequent use as pharmacologically active compounds.[1,2] For this reason, development of convenient methods for their syntheses has recently become a topical problem. There is considerable interest in cubanecarbaldehydes capable of various modification at the carbonyl group with the retention of the cubane framework. Earlier, such aldehydes have been synthesized by the Swern oxidation of appropriate alcohols with the DMSO—oxalyl chloride system.[3] Substantial drawbacks to this method include technological and ecological problems. In recent years, convenient oxidative systems involving 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) as a catalyst in combination with organic or inorganic oxidants have been widely employed for the transformation of alcohols into aldehydes.[4,5]

Here we studied for the first time the oxidation of 4-bromo-1-hydroxymethylcubane (**1**) into 4-bromocubane-1-carbaldehyde (**2**) and of 1,4-bis(hydroxymethyl)cubane (**3**) into cubane-1,4-dicarbaldehyde (**4**) with the TEMPO—trichloroisocyanuric acid (TCCA)—sodium bicarbonate system in CH_2Cl_2 at room temperature. The yield of monoaldehyde **2** was 71%. The oxidation of diol **3** gave a complex mixture of products from which dialdehyde **4** was isolated as chloropyridazine bishydrazone **5**. The low yield of dialdehyde **4** (5%) can be due to the poor solubility of the starting alcohol **3** in CH_2Cl_2.

Alternatively, aldehyde **2** was obtained by reduction of acid **6a** or its methyl ester **6b** with bis(*N*-methylpiperazinyl)aluminum hydride (**7**); earlier, this technique has been proposed for the reduction of carboxylic acids[7] or their esters[8] to the corresponding aldehydes (Scheme 2).

Scheme 1



Refluxing of acid **6a** or its ester **6b** with hydride **7** in THF at 65 °C for 9—12 h gave aldehyde **2** with an impurity of alcohol **1** (5—10%) (see Scheme 2). The yield of aldehyde **2** after crystallization from hexane was 87—92%.

According to the X-ray diffraction data, structure **2** consists of two crystallographically independent molecules (Fig. 1). One molecule has the symmetry *m* (see Fig. 1, *a*), while the other has the symmetry 2/*m* (see Fig. 1, *b*). Both the molecules are disordered, the aldehyde group and the

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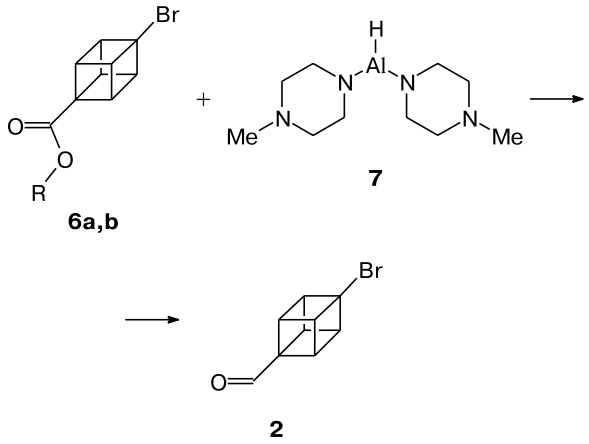
Scheme 2



R = H (**6a**), Me (**6b**) **Conditions:** THF, 65 °C, 9—12 h.

Br substituents being interchanged in either (at the C(1), C(6), and C(7) atoms of cubane).

Thus, our study made 4-bromocubane-1-carbaldehyde synthetically more accessible.

Experimental

The starting 4-bromo-1-hydroxymethylcubane (**1**), 1,4-bis(hydroxymethyl)cubane (**3**), 4-bromocubanecarboxylic acid (**6a**), and methyl 4-bromocubanecarboxylate (**6b**) were prepared according to known procedures.[6,10,11] Hydride **7** was synthesized as described earlier.[7] Solvents were purified according to standard procedures. Solutions of hydride **7** were prepared and used to reduce acid **6a** or ester **6b** under argon.[12]

The IR spectra of the compounds obtained were recorded on a Specord M-82 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker WM-250 and Bruker AM-300 instruments with Me_4Si as the internal standard. TLC was carried out on Silufol UV-254 plates with hexane—acetone (10 : 1) as an eluent.

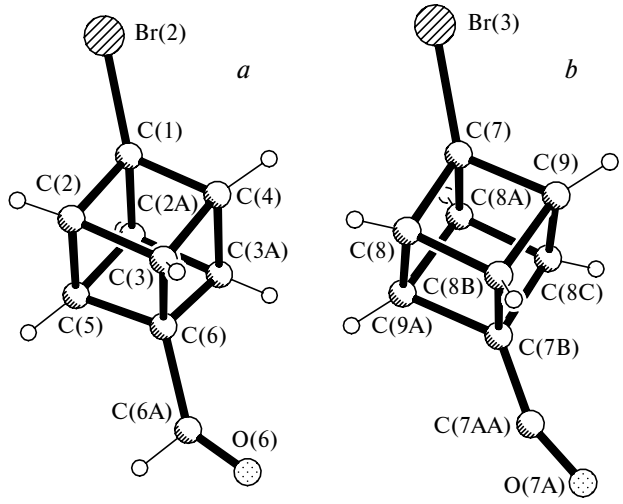


Fig. 1. Structure of 4-bromocubane-1-carbaldehyde (**2**).

Synthesis of 4-bromocubane-1-carbaldehyde (2) by the oxidation of alcohol 1. Alcohol **1** was oxidized according to a modified procedure[9] using solid $NaHCO_3$ instead of its aqueous solution. 4-Bromo-1-hydroxymethylcubane (140 mg, 0.62 mmol) was added at room temperature to a stirred mixture of trichloroisocyanuric acid (127 mg, 0.55 mmol), TEMPO (10 mg, 0.064 mmol), and $NaHCO_3$ (100 mg, 1.2 mmol) in CH_2Cl_2 (7 mL). The reaction was continued until the starting alcohol disappeared (TLC data). The reaction mixture was filtered and the residue was washed with CH_2Cl_2. The combined solution was washed with water, dried with Na_2SO_4, passed through a 2 cm column with silica gel, and concentrated. The product from the residue was extracted with boiling hexane and the solvent was removed *in vacuo*. The yield of 4-bromocubane-1-carbaldehyde was 100 mg (71%), m.p. 139—140 °C. ^{1}H NMR ($CDCl_3$), δ: 4.28—4.47 (m, 6 H, CH_{cub}); 9.77 (s, 1 H, CHO). ^{13}C NMR ($CDCl_3$), δ: 196.8 (CO); 62.3 (C(1)); 53.9 (C(7), C(5), C(3)); 46.0 (C(2), C(6), C(8)); 45.3 (C(4)). IR (KBr), ν/cm^{-1}: 2995, 2931, 2809, 2709, 1692, 1380, 1292, 1205, 1035, 930, 837, 806.

Synthesis of cubane-1,4-dicarbaldehyde 4. The reaction mixture obtained in the oxidation of diol **3** (164 mg, 1 mmol) as described above (with twice as much the amounts of the oxidant, the catalyst, and the base as in the oxidation of monoalcohol **1**) was passed through a 2-cm column with silica gel and concentrated. The residue was dissolved in ethanol (10 mL) and (6-chloropyridazin-3-yl)hydrazine (144 mg, 1 mmol) was added. The yield of bishydrazone (**5**) was 21 mg (5% with respect to the starting diol), decomp. at 260 °C. Found (%): C, 52.3; H, 3.4; N, 27.0. $C_{18}H_{14}Cl_2N_8$. Calculated (%): C, 52.3; H, 3.4; N, 27.1. ^{1}H NMR (DMSO-d_6), δ: 11.40 (s, 1 H, CH=N); 7.62 (s, 1 H, NH); 7.56, 7.45 (both d, 1 H each, CH, J = 9.0 Hz); 4.12 (s, 6 H, CH_{cub}). ^{13}C NMR ($CDCl_3$), δ: 158.74 (HC=N—N); 143.56, 129.63, 115.26 (C and CH of pyridazine), 57.44 ($C_{quat.\ cub}$); 45.73 (CH_{cub}). IR (KBr), ν/cm^{-1}: 2990, 2917, 2863, 1603, 1523, 1407, 1382, 1274, 1199, 1130, 1065, 962, 834.

Synthesis of 4-bromocubane-1-carbaldehyde (2) by the reduction of methyl 4-bromocubane-1-carboxylate (6b) with bis(*N*-methylpiperazinyl)aluminum hydride (7). A solution of ester **6b** (243 mg, 1.01 mmol) in anhydrous THF (15 mL) was added dropwise for 5 min to a stirred (and cooled on an ice bath) solution of hydride **7** (664 mg, 2.8 mmol) in THF (10 mL).[7] The reaction mixture was refluxed for 9 h and treated with water (0.16 mL) at 0—5 °C. Then it was heated to 70 °C for 5 min, cooled to room temperature, and filtered. The filter cake was washed with THF (2×5 mL) and ether (10 mL). The filtrate was concentrated *in vacuo*. Ether (60 mL) was added and the solution was successively washed with brine (12 mL), 2 *M* NaOH (2×6 mL), 2 *M* HCl (2×9.5 mL), and a solution of NaCl (6 mL). The colorless ethereal solution was dried with Na_2SO_4 and concentrated *in vacuo* to give a product (209 mg) with m.p. 135.5—138.0 °C. Recrystallization from hexane gave aldehyde **2** (196 mg, 92%), m.p. 136.5—140.0 °C. Its spectroscopic characteristics were identical with those of the aldehyde obtained by oxidation.

Reduction of 4-bromocubane-1-carboxylic acid (6a) with bis(*N*-methylpiperazinyl)aluminum hydride (7). A solution of acid **6a** (140 mg, 0.617 mmol) in anhydrous THF (10 mL) was added to a stirred (and cooled on an ice bath) solution of

Table 1. Crystallographic parameters and a summary of data collection for compound **2**

Parameter	Value
Molecular formula	C_9H_7BrO
Molecular mass	211.06
Space group	*C*2/*m*
a/Å	33.716(7)
b/Å	6.4550(10)
c/Å	5.3110(10)
β/deg	98.08(3)
V/Å^3	1144.4(4)
Z	6
ρ_{calc}/g cm^{-3}	1.837
μ/mm^{-1}	5.317
Radiation	Mo-*K*α (λ = 0.71073 Å)
Number of measured reflections	1756
Number of reflections with $I > 2\sigma$	363
R_1	0.1077
wR_2	0.2842

hydride **7** (390 mg, 1.73 mmol) in THF (6 mL). The reaction mixture was refluxed for 12 h and then treated as described above. The yield of compound **2** was 114 mg (87.5%), m.p. 137.6—140.0 °C.

X-ray diffraction experiment was carried out on an Enraf Nonius CAD-4 automatic diffractometer (graphite monochromator, 293 °C, ω-scan mode). Crystals for X-ray diffraction analysis were grown from a dilute solution of aldehyde **2** in hexane. Crystallographic parameters and a summary of structure refinement for aldehyde **2** are given in Table 1. Structure **2** was solved by the direct methods and refined in the full-matrix anisotropic approximation for Br atoms; all the other atoms were refined isotropically. The calculations were performed with the SHELX97 program package.[13,14] The main geometrical parameters of the compounds studied are close to standard values. Crystallographic data for compound **2** have been deposited with the Cambridge Crystallographic Data Center and can be made available upon request to the authors.

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