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Moving of the tetramethylbutanediyl substituent over the catecholcarbaldehyde core

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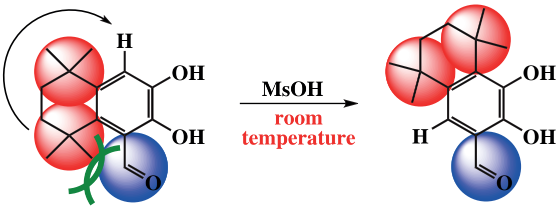
1,1,4,4-Tetramethylbutane-1,4-diyl substituent fused to positions 5,6 of 2,3-dihydroxybezaldehyde (‘catecholcarbaldehyde’) upon the action of acids readily moves to positions 3,4 to afford less strained isomer, with the optimum reagent being neat methanesulfonic acid acting at room temperature. The same compound was prepared in four steps from 3,4-(1,1,4,4-tetramethylbutane-1,4-diyl)phenol; the intermediates were the mixtures of 3,4- and 4,5-fused *o*-benzoquinones/catechols whereas the last step involved the abovementioned substituent moving.



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Catechols and *o*-quinones have been the objects of interest due to their ability to transform into each other in the course of oxidation/reduction processes.[1,2] These compounds are used as anti/prooxidants,[3–6] metal extractants,[7–9] redox-active ligands,[10–12] initiators/inhibitors of radical processes,[13–15] and dyes.[16,17] Bulky alkyl substituents without mobile hydrogen atoms are traditionally used to stabilize the oxidized forms of catechol. To date, the most common and best studied are 3,5- and 3,6-di-*tert*-butylcatechols/*o*-benzoquinones[18,19] (Figure 1). In comparison with 3,5- and 3,6-disubstituted derivatives, catechols/*o*-quinones containing 4- and 5-positioined *tert*-alkyl substituents are less known,[20–22] whereas 3,4-di-*tert*-alkyl-substituted catechols and *o*-quinones are studied even scarcely.[23–26] It is worth noting that catecholcarbaldehydes are convenient starting compounds for modification of catechols/quinones. Among the spatially shielded catecholcarbaldehydes, the greatest attention has been paid to the derivative of 3,5-di-*tert*-butylcatechol[27–33] bearing two *tert*-butyl groups in the *meta* position. Apparently, analogs with two separate *ortho*-positioned *tert*-alkyl groups are less available due to steric hindrance. However, such a substitution pattern can be readily accessed by moving to 1,1,4,4-tetramethylbutane-1,4-diyl (TMB) fusing substituent thus affording a series of 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalenes (see Figure 1).

In our previous work,[34] we discovered the rearrangement of 3,4,5-substituted catechol into its 3,4,6-regioisomer, when the TMB fusing substituent moved from positions 4 and 5 to positions 3 and 4 thus affording less strained product. In this work, the analogous approach was used to convert 2,3-dihydroxybezaldehyde with 5,6-positioned TMB (2,3-dihydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-1-carbaldehyde **1**) into its regioisomer with 3,4-positioned TMB (3,4-dihydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde **2**, Scheme 1). Compound **2** seems to be a promising building block for the synthesis of various 3,4,6-substituted catechols/quinones. In the previous work,[34] the regioisomerization was carried out in acetic acid in the presence of a strong acid (HBr) at 120 °C. Herein catecholaldehyde **1** also underwent the transformation under similar conditions, however, along with the target isomer **2**, the deformylation product, catechol **3**, was also formed (1 : 1 ratio, Table 1, entry 1 and Scheme 1).

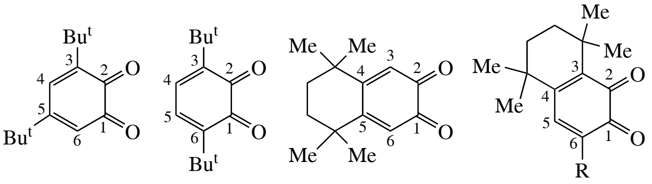
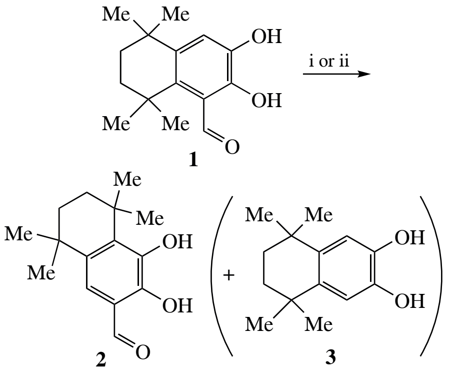


Figure 1 Spatially shielded *o*-quinones.

We optimized the conditions of the **1** → **2** isomerization testing five different acids (TsOH, HBr, H_2SO_4, $HClO_4$, and methanesulfonic acid MsOH) with the use of acetic acid as a solvent and in the temperature range of 25–120 °C for 24 h. The reaction of catecholcarbaldehyde **1** with HBr gave different



Scheme 1 *Reagents and conditions*: i, H$^+$, AcOH, 25–120 °C; ii, MsOH, room temperature.

Table 1 Reaction conditions of catecholaldehyde isomerization **1** to **2**.

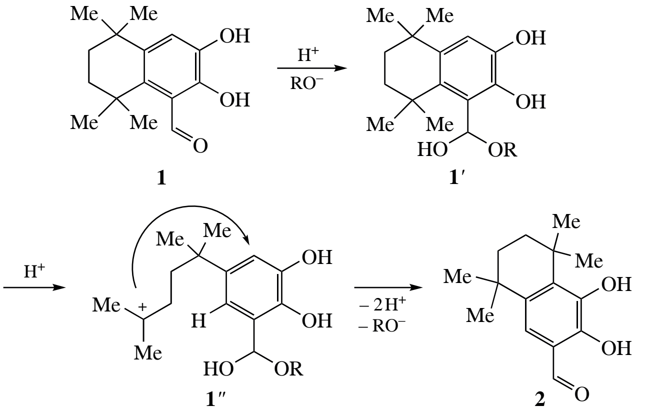
Entry	Acidic system^a	T/°C	Conversion of **1** (%)^a	Yield of products (%)^b	
				2	**3**
1	HBr/AcOH	120	~100	50	50
2	HBr/AcOH	70	44	34	10
3	HBr/AcOH	40	0	0	0
4	TsOH/AcOH	70	12	10	2
5	H_2SO_4/AcOH	70	~100	95	5
6	H_2SO_4/AcOH	40	13	13	0
7	$HClO_4$/AcOH	70	~100	97	3
8	$HClO_4$/AcOH	40	6	6	0
9	$HClO_4$	70	~100	–	–
10	MsOH	40	~100	60	18
11	MsOH/AcOH	40	1	1	0
12	MsOH	25	~100	98	2

[a] The volume ratio of acid : AcOH was 1 : 10 (ml). [b] From ^{1}H NMR data (the peaks in the aromatic part were used).

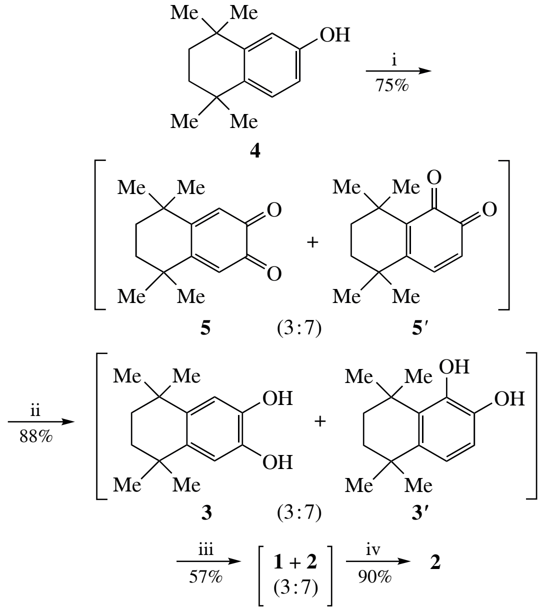
results depending on the temperature. The target product was not formed at 40 °C whereas a mixture of three compounds (aldehyde **1**, aldehyde **2**, and catechol **3**) was observed at 70 °C, but conversion of **1** was 34% (see Table 1, entries 2, 3). The use of TsOH at 70 °C gave only 10% of catecholcarbaldehyde **2** with 2% of **3** when the main component was unreacted aldehyde **1** (entry 4). The use of sulfuric acid at 40 °C led to a mixture in which the content of the target aldehyde **2** was 13% (entry 6). The result was significantly improved by carrying out the reaction at 70 °C when the yield of aldehyde **2** reached 95% (entry 5). Almost identical results were obtained in the presence of $HClO_4$ (the yield of compound **2** at 70 °C was 97%, entry 7). When methanesulfonic acid (MsOH) together with acetic acid were employed at 40 °C, the formation of aldehyde **2** in trace amounts (1%, entry 11) was observed. However, the use of MsOH as a solvent at room temperature allows one to obtain catecholaldehyde **2** with a yield of 98% (entry 12). Carrying out the reaction at temperatures higher than ambient was accompanied by the formation of resinification products (entry 10).

The proposed mechanism for the conversion of catecholcarbaldehyde **1** to its isomer **2** is shown in Scheme 2. Probably, the first step involves protonation of the aldehyde group to form hemiacetal species **1′**. The next step is *ipso*-substitution of one part of the TMB fragment (species **1″**). The final step involves alkylation at the free position *ortho* to hydroxy group to form compound **2**. According to the DFT calculations, the energy of molecule **2** (E = –809.066055 Hartree) is lower than the energy of molecule **1** (E = –809.055406 Hartree) by 6.68 kcal mol^{-1}.

Taking this transformation into account, an alternative four-step scalable synthesis for preparing catecholcarbaldehyde **2** from known 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ol **4** was proposed (Scheme 3). In the first step, phenol **4** was oxidized with 2-iodoxybenzoic acid (IBX) to afford a mixture of *o*-quinones **5** and **5′**. Treatment of the resulting mixture with hydrazine hydrate in methanol yields a mixture of catechols **3** and **3′**. Formylation of this catechol mixture with hexamethylenetetramine under the Duff reaction conditions gives a mixture of catecholcarbaldehydes **1** and **2**. Treatment of the resulting mixture with methanesulfonic acid yields individual catecholaldehyde **2**. In the obtained mixtures at steps i–iii, the ratios of 3,4-TMB-fused catechols to 4,5-isomers (**5**/**5′**, **3**/**3′**, **1**/**2**) was 3 : 7. Thus, this approach does not require preparative isolation of quinone **5′** and catechol **3′** (it is of note that unlike 4,5-di-*tert*-alkyl-substituted catechol **3**, catechol **3′** is less accessible). All new compounds were isolated and characterized by a set of spectral methods.



Scheme 2



Scheme 3 *Reagents and conditions*: i, IBX, $CHCl_3$–MeOH, room temperature; ii, $N_2H_4 \cdot H_2O$, MeOH, room temperature; iii, $(CH_2)_6N_4$, AcOH, 120 °C; iv, MsOH, room temperature.

To conclude, the synthesis of 2,3-dihydroxybenzaldehyde bearing 4,5-fusing 1,1,4,4-tetramethylbutane-1,4-diyl substituent (compound **2**) based on the moving of this substituent from positions 5,6 is presented. The reaction would proceed due to lesser strain in the product, the optimum conditions being the use of methanesulfonic acid as a solvent and acidic reagent at room temperature. This opens up prospects for using compound **2** as a precursor for the production of a wide range of new biologically active compounds, redox-active ligands, extractants, *etc*.

The work was carried out within the framework of a state assignment using the equipment of the Analytical Center of the G. A. Razuvaev Institute of Organometallic Chemistry of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7838.

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