Reactivity in solid phase. Transformations of 2,4-di-*tert*-butylphenol and its derivatives under elastic deformation conditions

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The solid-phase transformations of 2,4-di-*tert*-butylphenol (**1**) and its 6-bromo- (**5**) or 6-hydroxymethyl-substituted (**11**) derivatives were studied. The dependence of the behavior of compounds **1** and **5** in solid-phase processes on the composition of the medium was found. Oxidative coupling with the participation of atmospheric oxygen as an oxidant became possible at an excess of NaOH (or in NaOH/NaCl medium). The mechanism of oxidative debromocondensation of compound **5** that involves spontaneous dehalogenation of the haloquinolide intermediate and heterolysis of the C—Br bond with the elimination of Br^+ was proposed. It was concluded that the mechanism proposed is common to solid-phase dienone—phenol transformations. The dual reactivity of compound **11**, determined by the chemical hardness of the anion-catalyst, was discovered.

Key words: 2,4-di-*tert*-butylphenol, 6-bromo- and 6-hydroxymethyl-2,4-di-*tert*-butylphenols, oxidative coupling, heterocyclization; hydroxydibenzofuran, superoxide ion; solid phase; elastic deformation action.

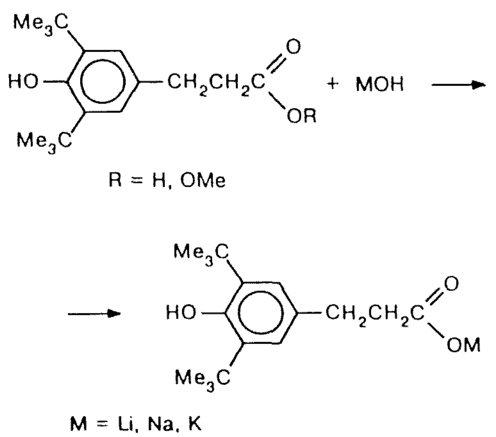
Among the peculiarities of solid-phase transformations under elastic deformation conditions are the low activity of atmospheric oxygen and the tendency of oxygen compounds for deoxygenation.[1] Therefore, the reactions of compounds sensitive to oxygen should preferably be carried out in the solid phase. The validity of such an approach is confirmed by examples from the chemistry of sterically hindered phenols. For example, we successfully carried out the solid-phase synthesis of alkali and alkaline-earth metal salts of 3-(4-hydroxy-3,5-di-*tert*-butylphenyl)propionic acid by elastic deformation action on binary mixtures of the acid with metal hydroxides, oxides, and carbonates.[2] The methyl ester of this acid was also used in the reactions with bases[3] (Scheme 1).

The protection against atmospheric oxygen is needed for similar syntheses of salts in solutions (alcohols, aqueous dioxane).[4]

The solid-phase synthesis of sodium 2,4-di-*tert*-butylphenoxide (**1**-Na) and *in situ* condensation of this compound with chloroacetic acid and benzoic anhydride (Scheme 2) are studied in this work.

The yields of the condensation products, 2,4-di-*tert*-butylphenoxyacetic acid (**2**) and 2,4-di-*tert*-butylphenylbenzoate (**3**), with respect to the reacted **1** reach 80 % at the degree of conversion of the initial phenol ~60 %. To achieve a higher degree of transformation of **1**, an excess of NaOH was used. However, in this case, in addition to product **2** (or **3**), the product of the oxidative coupling, 2,2′-dihydroxy-3,3′,5,5′-tetra-*tert*-butylbiphenyl (**4**), appeared in the reaction mixtures starting with the ratio NaOH : **1** ≥ 2, indicating the participation of atmospheric oxygen in this process. Since the implication of oxygen as an oxidant in a solid-phase process is the important problem, we studied the possi-

Scheme 1



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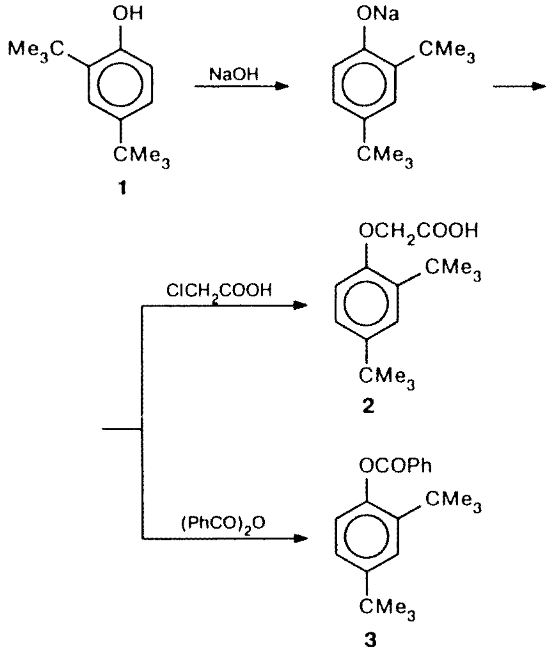
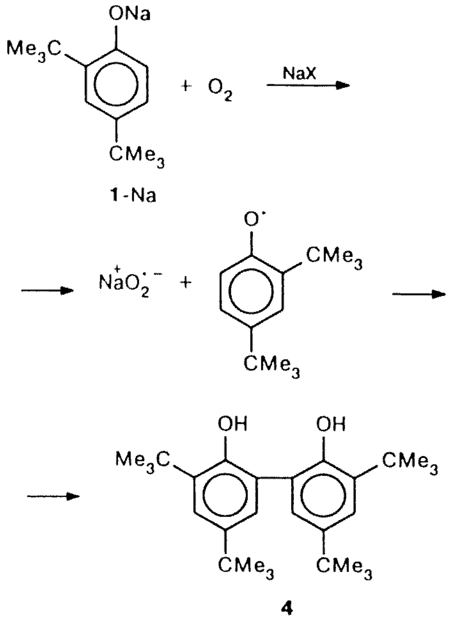
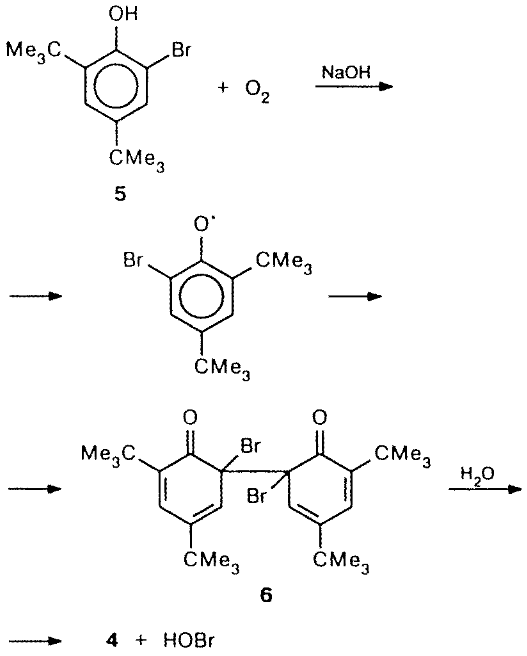
Scheme 2



Scheme 3



Scheme 4



bility of oxidation of **1** in relation to the amount of NaOH and found that compound **4** was formed in practically quantitative yield at NaOH : **1** ≥ 5. It was also found that when the excess of NaOH was changed to NaCl, the complete transformation of **1** into **4** occurred at **1**—NaOH—NaCl = 1 : 1 : *n* ($n \geq 4$).

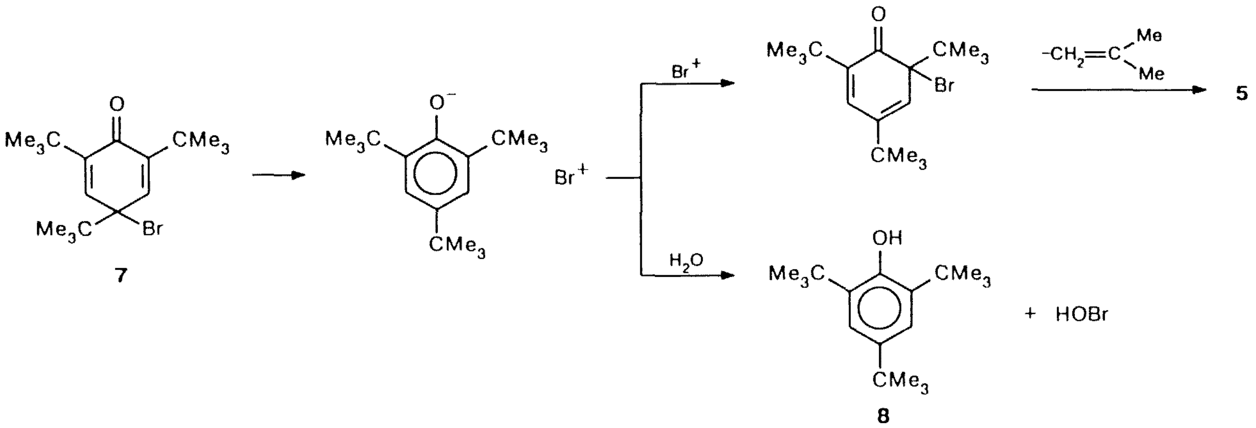
Without detailed consideration of the mechanism of the oxidation one may assume that an inorganic ionic medium favors the formation of the ionic intermediate. In our opinion, the superoxide mechanism where NaX molecules serve two functions (as the anionic catalyst and as a bridge for the electron transfer) is the most probable (Scheme 3).

In liquid-phase processes, oxidative coupling is typical of phenols without a substituent in at least one of the *ortho-para*-positions of the ring; however, under elastic deformation conditions in solid NaOH medium, debromocondensation of trisubstituted 6-bromo-2,4-di-*tert*-butylphenol (**5**) resulted also in its transformation into **4**. In this case, *ortho*-quinolide **6**, which is spontaneously transformed into **4**, should be the intermediate (Scheme 4).

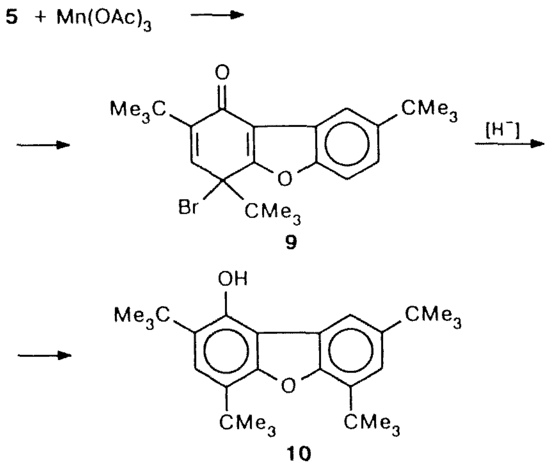
Spontaneous dehalogenation of a haloquinolide compound has been observed by us earlier in the solid-phase transformation of 4-bromo-2,4,6-tri-*tert*-butylcyclohexa-2,5-diene-one (**7**).[5] The formation of tri-*tert*-butylphenol **8** along with bromophenol **5** can be explained within the framework of the scheme that involves heterolysis of the C—Br bond (Scheme 5).

The similar behavior of quinobromides **6** and **7** in solid-phase transformations allows one to predict the reactivity of analogous quinolide compounds, in which one of the geminal substituents is capable of elimination as a cation. Elastic deformation action upon such substances can be used as a new method for stimulation of dienone—phenol transformations, which are widespread in the chemistry of phenols. In some cases, this method appears to be more rational than a similar liquid-phase process. For example, the bromoquinolide—phenol trans-

Scheme 5



Scheme 6

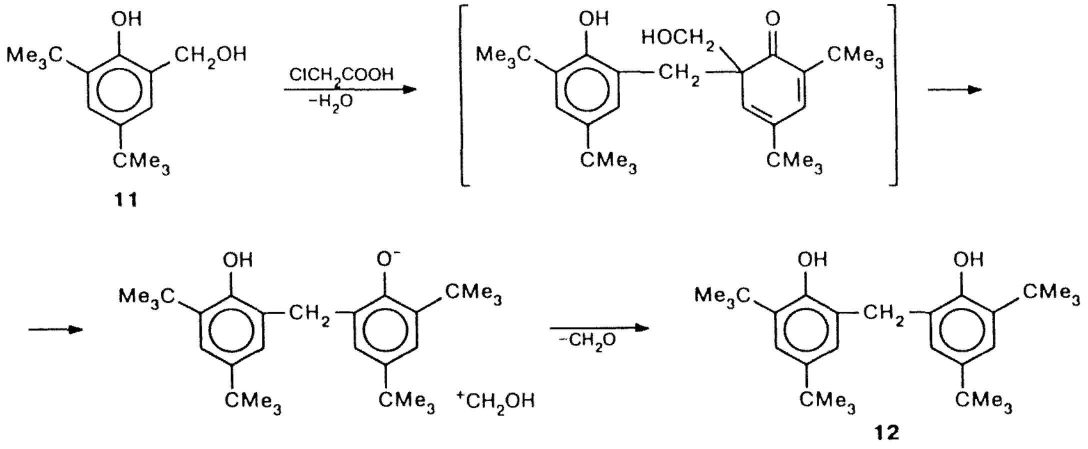


formation is one of the key steps in the synthesis of hydroxydibenzofuran by the oxidative heterocyclization of **5** under the action of Mn(OAc)$_3$ and a special reducing agent[6] (Scheme 6).

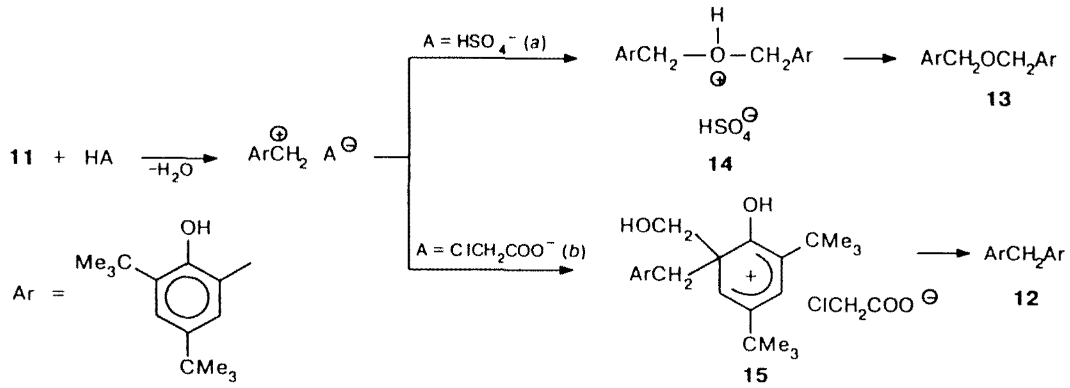
We carried out the solid-phase reaction of **5** with Mn(OAc)$_3$ and found that the transformation of 4-bromo-1-oxo-2,4,6,8-tetra-*tert*-butyldihydrodibenzofuran (**9**) to 1-hydroxy-2,4,6,8-tetra-*tert*-butyldibenzofuran (**10**) proceeds spontaneously and **10** is the direct product of the transformation formed in ~80 % yield. Traces of compound **9** were registered chromatographically, indicating its participation in the process. Thus, bromoquinolide **9** (the intermediate in the liquid-phase synthesis) appeared to be the unstable intermediate in the solid-phase process, and the transformation of bromophenol **5** to target **10** is reduced by one step.

Another example of the solid-phase dienone—phenol transformation with a similar heterolysis of the C—X bond of a quinolide compound is the chloroacetic acid-catalyzed condensation of 2-hydroxy-3,5-di-*tert*-butylbenzyl alcohol (**11**) with the formation of 2,2'-dihydroxy-3,3',5,5'-tetra-*tert*-butyldiphenylmethane (**12**). Any variant of the mechanism of the transformation of **11** to **12** should involve the intermediate formation and dehydroxymethylation of the quinolide structure (Scheme 7).

Scheme 7



Scheme 8



It is interesting to note that the transformation of **11** to **12** appeared to be a typical solid-phase process and we failed to carry out this transformation in solution using solvents of different nature (CH_2Cl_2, benzene, ether, acetone, MeOH). When $ClCH_2CO_2H$ was replaced by H_2SO_4 in CH_2Cl_2, anhydrodimerization, usual for benzyl alcohols, with the formation of 2,2′-dihydroxy-3,3′,5,5′-tetra-*tert*-butyldibenzyl ether (**13**) was observed. Such a transformation has been observed by us earlier in the solid-phase too for the reaction catalyzed by $Na_2SO_4 \cdot SO_3$.[7] Thus, alcohol **11** exhibits dual reactivity in solid-phase transformations and can undergo two types of transformations depending on the nature of the acid-catalyst with the formation of new C—O or C—C bonds as the result of O- or C-benzylation (Scheme 8).

The two directions of the transformations observed correspond to different chemical hardnesses of the anion A: hard HSO_4^- (*a*) accompanies the hard intermediate oxonium ion **14** (*O*-benzylation) and the softer $ClCH_2COO^-$ anion (*b*) accompanies the soft arenonium ion **15** (*C*-benzylation).

Experimental

Condensation of 2,4-di-*tert*-butylphenol (1) with chloroacetic acid and benzoic anhydride. Equimolar amounts of **1**, NaOH, and $ClCH_2COOH$ or $(PhCO)_2O$ were triturated in a mortar for 10 min at room temperature. The reaction mixture was analyzed by TLC. The reaction mixture was treated with water acidified with HCl and ether, and the solvent was distilled off. 2,4-Di-*tert*-butylphenoxyacetic acid (**2**) in 80 % yield with respect to the reacted **1** was isolated from the crystallized oil, m.p. 178—179 °C (hexane—$CHCl_3$). Found (%): C, 72.39; H, 9.33. $C_{16}H_{24}O_3$. Calculated (%): C, 72.69; H, 9.15. ^1H NMR ($CDCl_3$), δ: 1.29 and 1.58 (both s, 18 H, Me_3C); 4.10 (s, 2 H, CH_2); 6.36 (d, 1 H, Ph, J = 8.5 Hz); 7.04 (dd, 1 H, Ph, J = 2.4 and 8.5 Hz); 7.52 (d, 1 H, J = 2.4 Hz). 2,4-Di-*tert*-butylphenylbenzoate (**3**) was obtained by a similar procedure, m.p. 110—111 °C (hexane). Found (%): C, 80.89; H, 8.51. $C_{21}H_{26}O_2$. Calculated (%): C, 81.20; H, 8.44. The structure of **3** was confirmed by its hydrolysis to **1** and PhCOOH. With an excess of alkali (NaOH : **1** ≥ 2), in addition to **2** (or **3**), tetra-*tert*-butylbisphenol (**4**) in ~40—95 % yield (depending on the amount of the alkali) was isolated, m.p. 208—209 °C (from MeOH), identical to the previously described one.[8]

Debromocondensation of 6-bromo-2,4-di-*tert*-butylphenol (5) under elastic deformation conditions. ***A.*** A mixture of **5** (0.14 g, 0.5 mmol) and NaOH (0.04 g, 1 mmol) was triturated in a mortar for 10—15 min and then treated as described above to yield 0.02 g (45 %) of **4**.

B. A mechanical mixture of **5** (2.8 g, 10 mmol) and $Mn(OAc)_3$ was passed through a worm device over 10 min at room temperature.[2] The product was treated with water and ether, the solvent was distilled off, and 1-hydroxy-2,4,6,8-tetra-*tert*-butyldibenzofuran (**10**) (1.6 g, 79 %) was isolated from the crystallized mass, m.p. 219—220 °C (hexane).[6]

Acid-catalyzed condensation of 2-hydroxy-3,5-di-*tert*-butylbenzyl alcohol (11). A mixture of **11** (2.3 g, 10 mmol) and $ClCH_2CO_2H$ (1.9 g, 20 mmol) was treated by the known procedure.[9] The reaction mixture was treated with ether and washed with water, and the solvent was evaporated to yield 1.7 g (83 %) of **12**, m.p. 149—150 °C (hexane).[9]

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