Solid-phase bromination of hindered phenols

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The solid-phase bromination of a series of *tert*-butyl-substituted phenols with *N*-bromosuccinimide and dioxane dibromide afforded halogenated cyclohexadienones, quinobromides. Under the extrusion conditions, the latter underwent further transformations, mainly, debromination. A new reaction, dioxane dibromide catalyzed anhydroheterocyclization of 2,2′-dihydroxy-3,3′,5,5′-tetra-*tert*-butyldiphenyl to 2,4,6,8-tetra-*tert*-butyldibenzofuran, was discovered and the mechanism of this reaction was proposed.

Key words: hindered phenols; *N*-bromosuccinimide, dioxane dibromide; quinobromides; tetra-*tert*-butyldibenzofuran; solid phase.

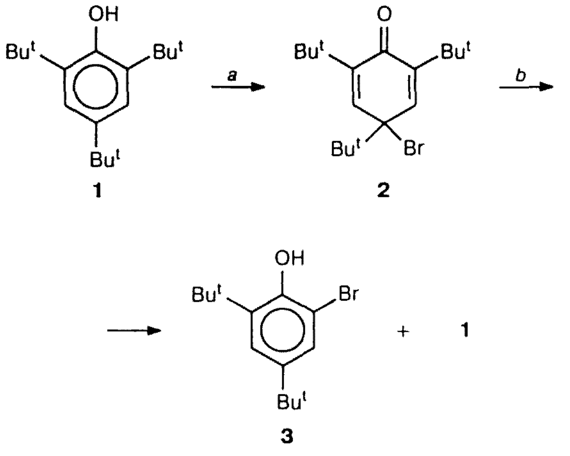
Halogenation of phenols is one of the key reactions in their functionalization and in the synthesis of different derivatives, including synthesis on an industrial scale. Therefore, the search for effective halogenating reagents suitable for ecologically safe technology is of interest. The solid-phase halogenation of phenols with Cl_2 and Br_2 in the absence of a solvent is rather promising in this respect.

The first studies of this process were carried out[1] using the chlorination of phenol in a PhOH—Cl_2(gas) heterophase system as an example. Data on the halogenation of ArOH derivatives in solid—gas (Cl_2 or Br_2 vapors) and in solid—liquid (Br_2) systems were obtained that allow one to conclude that the heterophase halogenation of ArOH proceeds through the formation of complexes with halogens and obeys topochemical reaction laws.[2] For alkyl-substituted ArOH, it was noted that *ipso*-attack with the formation of haloquinolide compounds is preferable.

In this work the solid-phase bromination of *tert*-butyl-substituted phenols with *N*-bromosuccinimide (NBS) and dioxane dibromide (DDB) has been studied. The reaction was carried out by three methods: trituration of binary mixtures of reagents, co-grinding in a high-speed mixer with a Z-shaped knife, and modified extrusion.[3] These methods are similar in the character of treatment: in all cases the material is subjected to pressure and deformation (shift or shear deformation). The difference is that the pressure in a mixer is created by impulse upon the impact of particles on a wall, while in trituration and extrusion the pressure acts continuously. In the latter case, the pressure can reach ~300 atm, therefore, extrusion is probably the harshest method among those considered for the stimulation of the solid-phase process. This is confirmed by the results of solid-phase bromination.

For example, the reaction of 2,4,6-tri-*tert*-butylphenol (1) with NBS or DDB in a mixer affords 4-bromo-2,4,6-tri-*tert*-butylcyclohexa-2,5-diene-1-one (2) in a practically quantitative yield whereas extrusion results in the formation of 6-bromo-2,4-di-*tert*-butylphenol (3) in a yield not higher than 20 %. The data[4] on the explosive transformation of solid quinobromide 2 under severe single-axial compression with the formation of phenols 1 and 3 allow one to propose that during extrusion halogenation, bromophenol 3 is formed from quinobromide 2, which is unstable under the extrusion conditions. In fact, when bromination of phenol 1 is carried out in two steps, first in a mixer and then in an extruder, intermediate quinobromide 2 is partially debrominated to phenol 1 and then transformed into bromophenol 3 as a result of isomerization and dealkylation (Scheme 1).

Scheme 1



Reagents and conditions: *a* — NBS, mixer; *b* — extruder.

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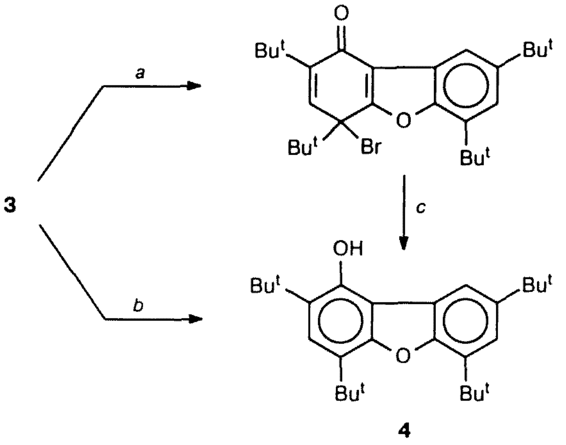
The **2** → **1** reverse reaction makes extrusion bromination a "degenerate" process with an "idle" consumption of the brominating reagent. However, this debromination of quinobromide under the extrusion conditions can be used as a rational synthetic technique. For example, oxidative heterocyclization of bromophenol **3** carried out under the extrusion conditions allows one to remove one step from the synthesis of substituted hydroxydibenzofuran **4** as compared with the liquid-phase process in which debromination of the quinobromide requires the application of a reducing agent (Pr^iOH)[5] (Scheme 2).

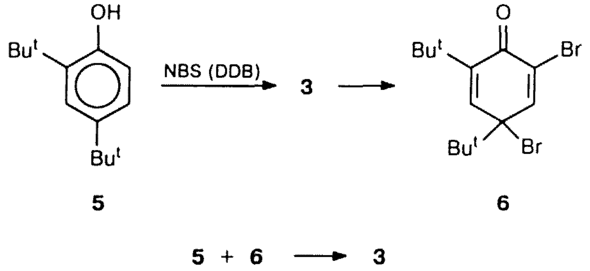
Scheme 2



Reagents and conditions: *a* — Mn^{III}—AcOH; *b* — Mn^{III}, extruder; *c* — Pr^iOH.

The more drastic character of the extrusion process is also revealed in the bromination of 2,4-di-*tert*-butylphenol (**5**). Bromophenol **3** is formed rapidly and in a quantitative yield under extrusion conditions, whereas the quantitative formation of compound **3** needs a prolonged time if the process is carried out in a mixer or through trituration, and another product, 4,6-dibromo-2,4-di-*tert*-butylcyclohexa-2,5-diene-1-one (**6**) predominates in the intermediate steps of the transformation of the initial **5**. Quinobromide **6** can be isolated from its mixture with compounds **5** and **3** if the process is interrupted before the conversion of **5** ceases. The directed synthesis of quinobromide **6** can be carried out by the reaction of bromophenol **3** with NBS (DDB) or phenol **5** with 2 equiv. of NBS (or DDB). In the presence of an excess of phenol **5**, quinobromide **6** is gradually debrominated to bromophenol **3**, and an equimolar mixture of phenol **5** and quinobromide **6** is transformed quantitatively into **3** through treatment in a mixer or by prolonged trituration. These data allow one to describe the bromination of phenol **5** in a mixer as a complex process in which the formation of a new brominating reagent, *i.e.*, quinobromide **6**, and its further debromination take place. Hence, the target product can be formed in two ways, *i.e.*, in the reaction of the initial phenol **5** with NBS (DDB) or in the reaction with quinobromide **6** (Scheme 3).

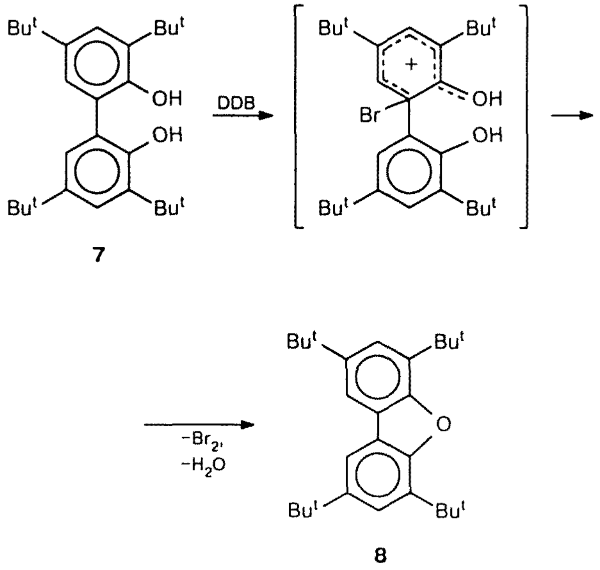
Scheme 3



Thus, using the halogenation of ArOH as an example we have shown that the formation of quinohalides followed by their further transformations, which depend substantially on the reaction conditions, are typical of solid-phase processes.

The solid-phase reaction of 2,2′-dihydroxy-3,3′,5,5′-tetra-*tert*-butyldiphenyl (**7**) with DDB, which unexpectedly affords 2,4,6,8-tetra-*tert*-butyldibenzofuran (**8**), deserves special examination. The mechanism of this heterocyclization probably involves the formation and dehydroxyhalogenation of the intermediate quinobromide (Scheme 4).

Scheme 4



This reaction illustrates also the tendency for the formation of haloquinolide compounds and their increased lability typical of solid-phase processes.

Experimental

Compounds **3**, **7**, and DDB were synthesized by the known procedures (see Refs. 7, 10, and 11, respectively); the other initial reagents (**1**, **5**, and NBS) were purchased from Aldrich Chemical.

Solid-phase reactions were carried out in a L'vov Koncern-Elektron· EKMU-500 mixer (model 2) and in an extruder described previously.[3]

NMR spectra were recorded on a Bruker WM-400 instrument in $CDCl_3$; UV spectra were obtained on a Specord-UV-Vis spectrophotometer.

Reaction of 2,4,6-tri-*tert*-butylphenol (1) with DDB or NBS. ***A.*** A mixture of compound **1** (5.2 g, 20 mmol) and NBS (3.6 g, 20 mmol) was triturated in a mixer for 10 min, then the reaction mixture was extracted with hexane (~100 mL), and the extract was cooled with dry ice (15 min) to give 6.1 g (91 %) of 4-bromo-2,5,6-tri-*tert*-butylcyclohexa-2,5-diene-1-one[6] (**2**) as pale-yellow crystals, m.p. 80—81 °C (from hexane). UV, λ_{max}/nm: 245.

B. A mixture of compound **1** (0.26 g, 1 mmol) and NBS (0.18 g, 1 mmol) was triturated in an agate mortar until compound **1** disappeared (TLC analysis, ~10—12 min). The reaction mixture was then extracted with hexane. The formation of compound **2** was monitored by UV spectroscopy (λ_{max} = 245 nm).

C. A mixture of compound **1** (5.2 g, 20 mmol) and NBS (3.6 g, 20 mmol) was passed through the extruder for 10 min. The reaction mixture was then extracted with hexane to isolate 1.1 g (20 %) of 6-bromo-2,4-di-*tert*-butylphenol[7] (**3**), m.p. 57—58 °C (from MeOH), and 3.9 g (~75 %) of compound **1**,[8] m.p. 135—136 °C (from hexane).

D. A mixture of the same amounts of compound **1** and NBS was first treated in a mixer until the disappearance of initial **1**, then the reaction mixture was passed through the extruder, analyzed by TLC, and compounds **1** and **3** were separated in preparative amounts.

Reaction of bromophenol 3 with $Mn(OAc)_3$. A mixture of bromophenol **3** (4.2 g, 15 mmol) and $Mn(OAc)_3$ (4 g, 15 mmol) was passed through the extruder for 10 min. The reaction mixture was then treated sequentially with ether and water and the ether solution was evaporated to afford 2.1 g (70 %) of 1-hydroxy-2,4,6,8-tetra-*tert*-butyldibenzofuran[9] (**4**), m.p. 213—214 °C (from MeOH).

Reaction of 2,4-di-*tert*-butylphenol (5) with NBS (DDB). ***A.*** A mixture of compound **5** (2 g, 10 mmol) and NBS (1.8 g, 10 mmol) was passed through the extruder and then treated similarly to the previous experiment to afford 2.5 g (91 %) of bromophenol **3**.

B. A mixture of phenol **5** (0.2 g, 1 mmol) and NBS (0.36 g, 2 mmol) was triturated in an agate mortar. The reaction mixture was then treated sequentially with water and ether and the ether solution was evaporated to give 4,6-dibromo-2,4-di-*tert*-butylcyclohexa-2,5-diene-1-one (**6**) as pale-yellow crystals, m.p. 100—101 °C (from MeOH). Found (%): C, 46.12; H, 5.63. $C_{14}H_{20}OBr_2$. Calculated (%): C, 46.17; H, 5.53. UV, λ_{max}/nm: 255. ^1H NMR ($CDCl_3$), δ: 1.17, 1.26 (both s, 18 H, Me_3C); 7.03, 7.58 (both d, 1 H, Ph, J = 2.8 Hz).

Reaction of 2,2′-dihydroxy-3,3′,5,5′-tetra-*tert*-butyldiphenyl (7) with DDB. A mixture of compound **7** (0.1 g, 0.25 mmol) and DDB (0.12 g, 0.5 mmol) was triturated in an agate mortar for 5 min to obtain 0.09 g (99 %) of the colorless product, 2,4,6,8-tetra-*tert*-butyldibenzofuran[10] (**8**) in an individual form, m.p. 208—209 °C (from MeOH).

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