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Alkylation of Pyrocatechol in *tert*-Butyl Alcohol–Sulfuric Acid–Benzene

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Abstract—Alkylation of pyrocatechol with *tert*-butyl alcohol in benzene in the presence of sulfuric acid gave 3,5-di-*tert*-butylbenzene-1,2-diol in a higher yield than in analogous reaction with *tert*-butyl alcohol. This result was rationalized by reduction of inhibitory effect of liberated water, formation of heterogeneous system, and occurrence of the alkylation process in nonpolar organic phase. Intermediate products were identified and found to undergo intra- and intermolecular *tert*-butyl group transfer with formation of more stable 3,5-di-*tert*-butylbenzene-1,2-diol. The formation of *p*-di-*tert*-butylbenzene indicated participation of benzene in cross-alkylation processes.

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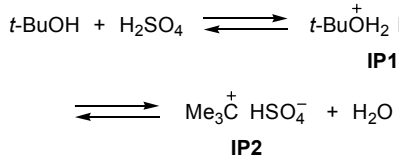
A procedure for the alkylation of pyrocatechols is based on their reaction with tertiary alcohols in the presence of protic acids. Most frequently, sulfuric and phosphoric acids are used, as well as polymeric sulfonic acids. Alcohol acts as reagent and solvent. These reactions are selective, and the only product is 3,5-di-*tert*-alkylbenzene-1,2-diol; however, the yield does not exceed 55–60% [1], presumably because of inhibitory effect of water liberated during the process (Scheme 1).

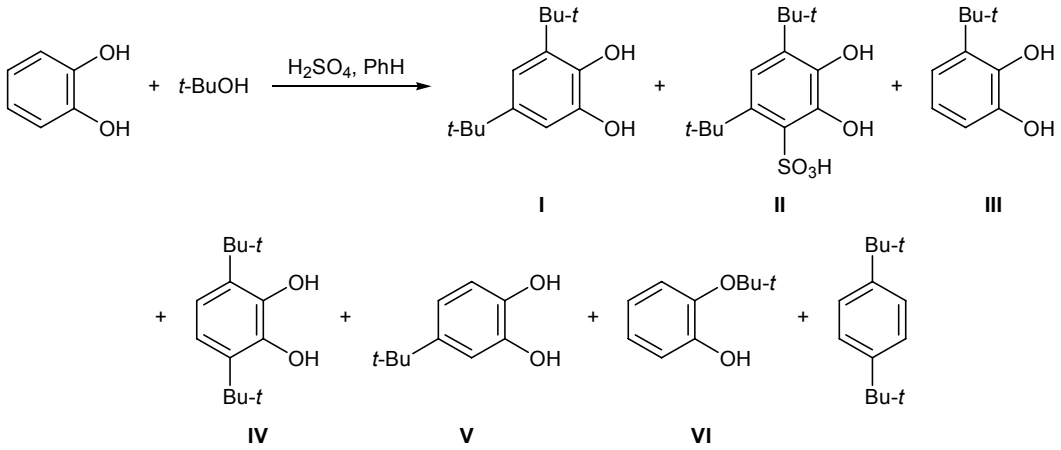
Scheme 1.



We examined the alkylation of pyrocatechol with *tert*-butyl alcohol in the presence of sulfuric acid and found that the yield of 3,5-di-*tert*-butylbenzene-1,2-diol (**I**) can be considerably increased (up to 90%) by carrying out the reaction in a mixture of *tert*-butyl alcohol with benzene. Presumably, the presence of benzene enhances hydrolytic stability of the alkylating agent generated by reaction of *t*-BuOH with H_2SO_4. Liberation of water in the binary system *t*-BuOH–benzene affects the state of phase equilibrium, products of reversible reaction are distributed over different phases (aqueous alcohol and benzene), and the equilibrium is displaced toward the products. Alkylation of the substrate occurs at the phase boundary, and inhibitory effect of water is weakened.

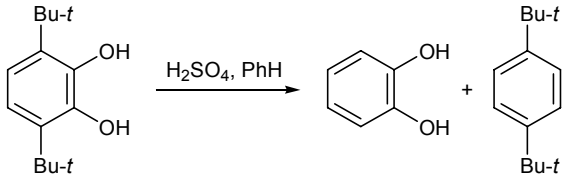
Specific feature of the process in mixed medium is generation *in situ* of a new acid catalyst, 4,6-di-*tert*-butyl-2,3-dihydroxybenzenesulfonic acid (**II**), as well as formation of a number of intermediate alkyl-substituted benzenediols **III**–**VI** and *p*-di-*tert*-butylbenzene (Scheme 2) which are capable of undergoing intra- and intermolecular alkyl group transfer. This was confirmed experimentally using 4-*tert*-butylbenzene-1,2-diol (**V**) and 3,6-di-*tert*-butylbenzene-1,2-diol (**IV**) as initial compounds. In both cases, the final product was 3,5-di-*tert*-butylbenzene-1,2-diol (**I**). Exchange of *tert*-butyl groups between different *tert*-butyl-substituted pyrocatechol derivatives was also revealed. For example, compound **I** was formed in a solution of benzenediols **II** and **V** in benzene in the absence of *tert*-butyl alcohol. Benzene also participates in the cross-alkylation process, as follows from the presence of *p*-di-*tert*-butylbenzene in the reaction mixtures. The ability of benzene to take up *tert*-butyl groups may be utilized for mild dealkylation of *tert*-butyl-substituted hydroxyaromatic compounds, which extends the potential of positional *tert*-butyl protection. Compounds **I**–**VI** underwent complete dealkylation by the action of

Scheme 2.



H_2SO_4 in benzene with formation of an equivalent amount of *p*-di-*tert*-butylbenzene (Scheme 3).

Scheme 3.



In addition, intermediate isomerization and partial dealkylation products, namely compounds **I**, **III**, and **V**, are formed. The composition of the reaction mixture and its variation during the process were monitored by TLC using authentic samples. Compounds **I**–**VI** are characterized by clearly different R_f values and colors of spots developing on exposure of chromatograms to air [2]. It was especially interesting that we succeeded in detecting in the reaction mixtures *ortho*-substituted pyrocatechols **III** and **IV**; formation of the latter in protic medium was not reported previously. Compounds **III** and **IV** were synthesized by alkylation of pyrocatechol with isobutylene catalyzed by titanium bis-pyrocatechol complex [3]. Here, the selectivity of *ortho*-alkylation is ensured by coordination of the substrate and alkylating agent to the metal ion. The process may be regarded as intracomplex transfer of the substituting group.

Selective *ortho*-substitution in the series of hydroxyaromatic compounds is also possible as a result of intramolecular rearrangements of compounds substituted at the hydroxy group with migration of the substituent into the *ortho* position of the ring (e.g., Fries and Claisen rearrangements). It is naturally to presume that in our case *ortho*-substituted pyrocatechols **III** and **IV** are formed via rearrangement of ether **VI** with migration of *tert*-butyl group from the oxygen atom to the nearest position in the benzene ring rather than by direct alkylation.

Compounds **III** and **IV** were not detected in the alkylation carried out in *tert*-butyl alcohol; their possible precursor, ether **VI**, was not detected as well. The observed differences may be related to different structures of ion pairs formed by reaction of *t*-BuOH with H_2SO_4 in *t*-BuOH (water-separated ion pair **IP1**) and in benzene (dehydrated ion pair **IP2**; see Scheme 1). Ion pair **IP2** is a harder electrophile which is capable of reacting at the oxygen atom of the hydroxy group as a harder nucleophilic center of pyrocatechol.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WH-250 spectrometer (250 MHz) from solutions in $CDCl_3$ using tetramethylsilane as internal reference. Thin-layer chromatography was performed on Silufol UV-254 plates using hexane–diethyl ether (15 : 1) as eluent.

Pyrocatechol was purified by vacuum sublimation. Commercially available benzenediols **I** and **V** and *p*-di-*tert*-butylbenzene were used as reference compounds. Pyrocatechols **III** and **IV** were synthesized by alkylation of pyrocatechol with isobutylene catalyzed by titanium bis-pyrocatechol complex according to the procedure described in [2].

Alkylation of pyrocatechol in the system *t*-BuOH–H_2SO_4–benzene. Concentrated sulfuric acid, 10 ml, was added to a solution of 30 g (0.27 mol) of pyrocatechol in a mixture of 80 ml of *tert*-butyl alcohol and 100 ml of benzene, and the mixture was

stirred for 3 h. Samples were withdrawn during the process for TLC analysis. The reaction mixture initially contained compounds **I** (dark red), **III** (black), **V** (light violet), and **IV** (green–brown), which were identified by R_f values and color of spots on the chromatograms. Pyrocatechol **II** was not reported previously, and its isolation and identification are described below. As the reaction progressed, *p*-di-*tert*-butylbenzene appeared in the reaction mixture, while compounds **III**–**V** disappeared. When the reaction was complete, the mixture contained only *p*-di-*tert*-butylbenzene and compounds **I** and **II**. A crystalline product separated from the solution and was filtered off, washed with water, and dried. The filtrate was extracted with diethyl ether, the extract was dried over Na_2SO_4 and evaporated, and the residue was combined with the crystalline product and dissolved in boiling hexane. By slow cooling of the solution we succeeded in separating compounds **II** [precipitated first, 4.5 g (5.6%)] and **I** [57 g (92%)], mp 99–100°C [3].

4,6-Di-*tert*-butyl-2,3-dihydroxybenzenesulfonic acid (II) was identified as 2,4-di-*tert*-butyl-5,6-dioxocyclohexa-1,3-diene-1-sulfonic acid which was obtained by oxidation of **II** with silver oxide in benzene. Silver oxide, 7 g (30 mmol), was added to 3.02 g (10 mmol) of compound **II** in 50 ml of benzene. The mixture was stirred for 1 h and filtered, the filtrate was evaporated, and the residue was recrystallized from hexane–benzene (5:1). Yield 2.9 g (96%), dark orange crystals, mp 121°C. ^{1}H NMR spectrum, δ, ppm: 1.26 s (9H, *t*-Bu), 1.50 s (9H, *t*-Bu), 7.16 s (1H). Found, %: C 55.81; H 6.54. $C_{14}H_{20}O_5S$. Calculated, %: C 56.00; H 6.67.

Alkylation of benzenediols IV and V in *t*-BuOH–H_2SO_4–benzene was carried out in a similar way. The results were identical to those obtained in the reaction with unsubstituted pyrocatechol. Yield of **I** ~90%.

Dealkylation of compounds I and IV. Concentrated sulfuric acid, 1 ml, was added to a solution of 1.1 g (5 mmol) of compound **I** in 50 ml of benzene. The mixture was stirred for 1 h, washed with water, dried over Na_2SO_4, and evaporated, and the residue was recrystallized from hexane to isolate 0.88 g (93%) of *p*-di-*tert*-butylbenzene with mp 77–78°C. ^{1}H NMR spectrum, δ, ppm: 1.30 s (9H, *t*-Bu), 5.80 s (2H, H_{arom}).

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