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CERTAIN FEATURES OF THE ALKYLATION OF PHENOL BY BORNEOL AND ISOBORNEOL CATALYZED BY ALUMINUM ALKOXIDES

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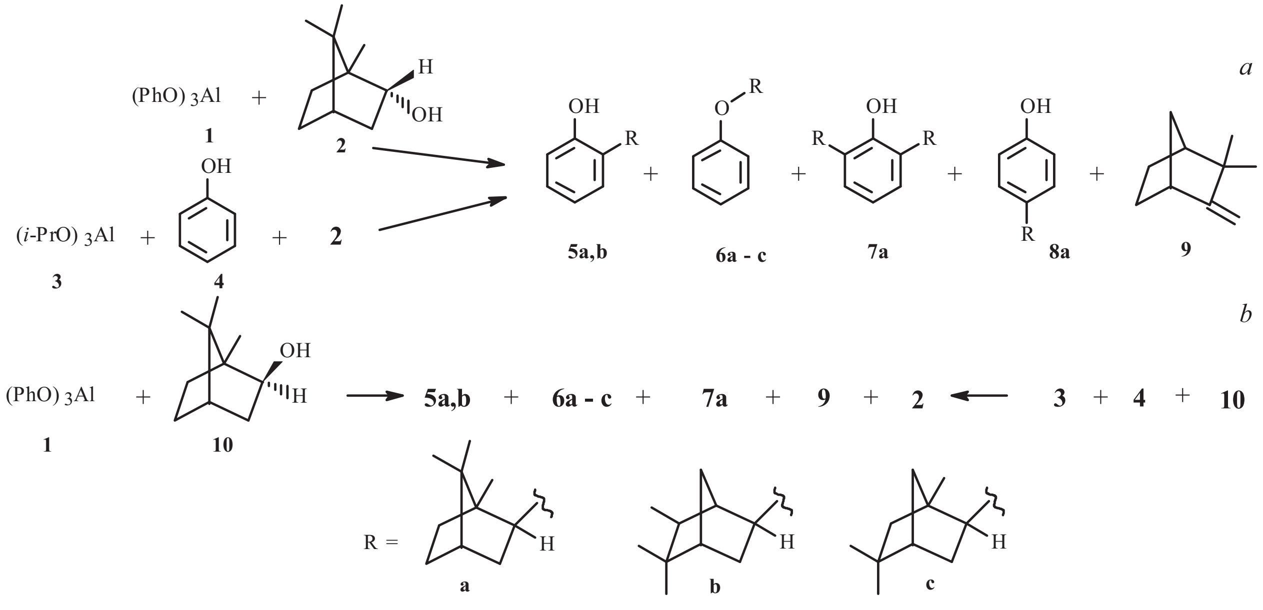
Phenol was alkylated by borneol and its stereoisomer isoborneol in the presence of aluminum phenolate and isopropylate. The reaction products were isolated and characterized. Certain features of the process were defined.

Keywords: phenol, borneol, isoborneol, organoaluminum catalysts, alkylation.

Many natural compounds can be regarded as the C-alkylation products of aromatic terpenes and are arbitrarily called aryl-substituted terpenes. Alkylaromatic compounds are synthesized biologically by direct alkylation of phenols by methyl or isoprene fragments [1, 2]. Alkylphenols are usually produced industrially by catalytic alkylation of phenols. The most common alkylation method is the Friedel–Crafts reaction, which is a convenient method for direct introduction of an alkyl group into an aromatic ring. Mainly halogen derivatives, olefins, alcohols, ethers, and esters are used as the alkylating agents. The catalysts can be either a Lewis acid ($AlCl_3$, $FeCl_3$, BF_3, $ZnCl_2$, $TiCl_4$) or a Bronsted acid (HF, H_2SO_4, H_3PO_4, ion-exchange resins, clays, zeolites, etc.). The introduction of a certain terpene fragment into a given position of phenol requires the development of selective procedures for carrying out the electrophilic substitution of phenols by terpenoids. This is especially important for terpenes that are characteristically unusually prone to various skeletal rearrangements.



Scheme 1

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TABLE 1. Alkylation of Phenol by Borneol

Reaction conditions	Reaction products, %					
	5a	**5b**	**6a–c**	**7a**	**8a**	**9**
Borneol– $(\text{PhO})_3\text{Al}$ (1:1)						
110–120°C, 9 h	38	–	12	38	–	13
170–180°C, 7 h	40	8	13	–	–	38
Borneol–phenol– $(i\text{-PrO})_3\text{Al}$ (1:1:1)						
110–120°C, 9 h	–	–	–	–	–	–
170–180°C, 10 h	34	5	2	–	37	13

TABLE 2. Alkylation of Phenol by Isoborneol

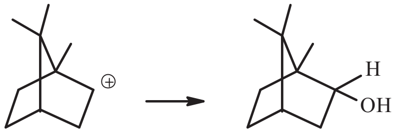
Reagent ratio and reaction conditions	Reaction products, %						
	5a	**5b**	**6a–c**	**7a**	**7b**	**9**	**2**
$(\text{PhO})_3\text{Al}$–isoborneol (1:1), 160°C, 2 h	58	15	3	22	2	–	–
$(\text{PhO})_3\text{Al}$–isoborneol (1:2), 160°C, 2 h	49	28	1	13	9	–	–
$(\text{PhO})_3\text{Al}$–isoborneol (2:1), 160°C, 2 h	58	17	–	14	3	–	–
Phenol–isoborneol– $(i\text{-PrO})_3\text{Al}$ (1:1:1), 135°C, 5 h	4	1	4	–	–	76	–
Phenol–isoborneol– $(i\text{-PrO})_3\text{Al}$ (1:2:1), 160°C, 5 h	–	–	1	–	–	99	–
Phenol–isoborneol– $(i\text{-PrO})_3\text{Al}$ (2:1:1), 110°C, 7.5 h	11	3	18	–	–	37	15
Phenol–isoborneol– $(i\text{-PrO})_3\text{Al}$ (1:1:0.1), 160°C, 15 h	–	–	10	–	–	90	–

It was shown in prior studies on the alkylation of phenols by camphene that organoaluminum homogeneous catalysts, in particular aluminum phenolate $(\text{PhO})_3\text{Al}$, exhibits high *ortho*-selectivity in alkylation reactions [3, 4]. Herein we present results for the alkylation of phenol (**4**) and aluminum phenolate (**1**) by the bicyclic terpene alcohols borneol (**2**) and isoborneol (**10**) in the presence of stoichiometric and catalytic amounts of organoaluminum compounds [aluminum phenolate and aluminum isopropoxide (**3**)]. The reaction mixture included products of *O*- and *C*-alkylation (Scheme 1a and 1b).

The principal products from the reaction of aluminum phenolate–borneol and phenol–borneol–$(i\text{-PrO})_3\text{Al}$ (equimolar amounts) were mono- and dialkylated phenols with the isobornyl moiety **5a** and **7a**. Regardless of the reaction temperature (Table 1), ethers **6a**–**c** were isolated as side products. The use of catalytic amounts of the organoaluminum compounds was insufficient to alkylate phenol with borneol. The reaction did not occur under such conditions. Phenol was alkylated by borneol in the presence of aluminum isopropoxide after formation of mixed alkoxy-phenoxy aluminum compounds that reacted further. The reaction mixture had to be heated to 170–180°C in order for the mixed alkoxy-phenoxy species to form and react for the phenol–$(i\text{-PrO})_3\text{Al}$ reaction. Otherwise, the reaction did not occur (Table 1). However, this temperature range led to dehydration of starting borneol to form camphene (**9**). Furthermore, increasing the temperature caused dealkylation because the amount of dialkylated **7a** that was formed at 110–120°C decreased. Also, carrying out the reaction in the presence of $(i\text{-PrO})_3\text{Al}$ caused the formation of a significant amount of *para*-substituted phenol **8a**. This was not observed if aluminum phenolate was used. This was explained by the high temperature of the reaction mixture in the presence of free phenol, which is a proton donor and activates camphene to facilitate the formation of carbonium ions. As a result, *para*-substitution of the aromatic ring in addition to *ortho*-alkylation occurs.

Phenol was also not alkylated by isoborneol in the presence of catalytic amounts of the organoaluminum compounds. The reaction of aluminum phenolate with isoborneol occurred at a lower temperature (160°C, 2 h) than the reaction with borneol (Table 2, Scheme 1b). The principal product was phenol **5a** in higher yield (58%) than for alkylation by borneol. This was explained by the fact that the hydroxyl in isoborneol is situated in the *exo*-position and is sterically more available and, therefore, more reactive.

Alkylation of aluminum phenolate by isoborneol afforded more mono- and dialkylated phenols with the isocamphyl structure for the terpene (**5b** and **7b**) than that by borneol. Carrying out the reaction using both stoichiometric and catalytic amounts of $(i\text{-PrO})_3\text{Al}$ led to dehydration of borneol, as a result of which camphene (**9**) was formed in almost quantitative yield. Alkylation products were not formed if the reaction time was increased. Dehydration of the starting alcohol was probably accompanied by deactivation of the catalyst. Carrying out the reaction with an excess of phenol in the presence of aluminum isopropoxide afforded borneol (**2**), which was formed by hydration of carbonium ion **11** [1].



11 **2**

Thus, characterization of the alkylation products led to the conclusion that the reaction occurred in the coordination sphere of the organoaluminum compounds. The structure of the alcohol affected the ability to coordinate to the organoaluminum compound and then the reaction with the aromatic ring. The reaction temperature and nature of the organoaluminum compound also influenced the composition of the product mixture.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature on a Bruker Avance II 300 spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C. The internal standards were the $CDCl_3$ resonances (δ_H 7.26 ppm; δ_C 77.00). Resonances were assigned using ^{13}C NMR spectra recorded in JMOD mode. IR spectra were recorded in KBr pellets for solids and as thin layers for liquids on a Shimadzu IR Prestige 21 IR-Fourier spectrometer. The purity of the starting reagents and the course of their conversion were monitored by GC on a Shimadzu GC-2010AF chromatograph using an HP-1 capillary column (60 m × 0.25 mm × 0.25 μm, 100–240°C, 6°C/min) and a flame-ionization detector (He carrier gas). TLC was performed on Sorbfil plates. Compounds were detected using $KMnO_4$ solution (15 g $KMnO_4$, 300 mL H_2O, 0.5 mL conc. H_2SO_4). Products were separated by column chromatography over silica gel (Alfa Aesar 70/230 μ).

Alkylation of Aluminum Phenolate by Borneol and Isoborneol. A two-necked flask (100-mL) equipped with a thermometer and reflux condenser was charged with phenol (3.6 g, 39 mmol) and heated to 160°C. Aluminum turnings (0.35 g, 13 mmol) were added in small portions. After the Al was completely dissolved in the phenol, the solution was cooled to 40°C, treated with isoborneol (borneol) (2.00 g, 13 mmol) (Tables 1 and 2 give the reagent ratios). The reagents were added simultaneously for $(i\text{-PrO})_3Al$. The course of the reactions was followed by GC and TLC. When the reaction was finished, the mixture was cooled, diluted with Et_2O, treated with HCl solution (50%) to decompose the aluminum alkoxide, and washed with NaOH solution (5%) and H_2O until neutral. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated.

Catalytic Alkylation of Phenol by Borneol and Isoborneol. A two-necked flask (100-mL) equipped with a thermometer and reflux condenser was charged with phenol (1.22 g, 13 mmol) and isoborneol (borneol) (2.00 g, 13 mmol), heated to 160°C, and treated with catalyst [10 mass%, $(i\text{-PrO})_3Al$ or $(PhO)_3Al$]. The course of the reactions was followed by GC and TLC (petroleum ether:Et_2O, 3:1). The reaction mixture was worked up and the reaction products were separated by the standard method given above.

Spectral and physicochemical properties of the isolated products agreed with those published [5, 6].

ACKNOWLEDGMENT

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