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LOW-MOLECULAR-WEIGHT COMPOUNDS

Alkylation of *p*-Cresol with Camphene in the Presence of Aluminum-Containing Catalysts

I. Yu. Chukicheva[1], I. V. Fedorova, O. A. Shumova, and A. V. Kutchin

Institute of Chemistry, Komi Research Center, Ural Branch of Russian Academy of Sciences, ul. Pervomaiskaya 48, Syktyvkar 167982, Russia

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Abstract—Alkylation of *p*-cresol with camphene was studied in the presence of aluminum-based catalysts $(i\text{-PrO})_3Al$, AlH_3, $AlCl_3$, $(i\text{-Bu})_2AlH$, $EtAlCl_2$, and $LiAlH_4$. Aluminum isopropylate was a selective catalyst for the preparation of *ortho*-isobornylphenol, its activity being close to that of aluminum phenolate.

Keywords: alkylation, camphene, cresol, terpenophenols

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INTRODUCTION

Certain aluminum-containing homogeneous catalysts, primarily aluminum phenolate, manifest high selectivity in phenol *ortho*-alkylation reactions. The use of aluminum-derived catalysts for phenol alkylation has been described in many publications. The most common are aluminum phenoxides [1, 2], isobutelene fractions, 2-substituted alkenes as olefins [3–5]. The reaction is normally highly regioselective and results in high product yields. As was reported, aluminum-containing compounds interact smoothly with phenols to give mixed aluminum phenoxides [6].

The use as alkylating reagents of terpene-derived compounds characterized by the tendency toward various backbone rearrangements make these reactions very peculiar and single terpenophenols out from the entire class of alkylphenols.

Earlier we found that alkylation of *p*-cresol with camphene in the presence of aluminum cresolate led to *ortho*-isobornylphenols in high yields (84%) [7]. It seemed important to compare the effect of various aluminum-derived compounds for phenol alkylation. In addition, we set a task of developing a convenient and effective method to synthesize 2,6-diisobornyl-4-methylphenol, which manifests a wide spectrum of pharmacological activity [8, 9].

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on Bruker AM-300 spectrometers (working frequencies 75 and 300 MHz, respectively) in $CDCl_3$. As an internal standard, chloroform resonances (for δ_H, 7.26 ppm, and δ_C, 77.00 ppm) were used. Resonances were ascribed using ^{13}C NMR spectra in the JMOD mode and, occasionally, two-dimensional NMR spectra (COSY and HETCORR).

To purify the initial terpenophenols and analyze volatile products, gas chromotography on a Shimadzu GC-2010AF chromatograph equipped with a flame ionization detector was performed using an SLB™-5ms column (Supelco) (60 m × 0.25 mm, 0.5 μm; phase: poly{5% diphenyl/95% dimethylsiloxane}; temperature: 135–255 and 85–250°C; heating: 6°C/min) and helium as the carrier gas.

Thin-layer chromatography was carried out on Sorbfil plates eluted with hexane, 5 : 1 hexane–ether, and 3 : 1 hexane–ether. The products were separated by column chromatography on silica gel (70/230 μm, Alfa Aesar).

Alkylation of *p*-cresol with camphene (general procedure). Initial *p*-cresol **1** and camphene **2** were taken at a 2 : 1 mol/mol ratio in all the experiments.

Calculated amounts of *p*-cresol **1**, camphene **2**, and the catalyst were heated at the given temperature in a two-head flask with a thermometer and a reflux condenser. The reaction was performed until a complete conversion of starting *p*-cresol **1** (GC and TLC monitoring) was achieved. The reaction mixture was cooled, dissolved in ether, and washed twice with HCl solution in order to disintegrate the catalyst. The ether extract was washed with 5% NaOH for removal of the unreacted *p*-cresol and then with water to neutral pH. The organic extract was dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The product mixture was separated by column chromatography on silica gel (70/230 μm) eluted with a petroleum ether–ether mixture by increasing the portion of ether.

In the case of $LiAlH_4$ as a catalyst, the reaction did not proceed according to GC and TLC data.

[1] Corresponding author: e-mail: chukicheva-iy@chemi.komisc.ru.

Conditions and products of *p*-cresol alkylation with camphene in the presence of aluminum-based catalysts

Reaction conditions	Conversion of *p*-cresol, %	Reaction prodicts, %										
		3(a)	**3(b)**	**3(c)**	**4(a)**	**4(b)**	**4(c)**	**4(d)**	**5(a)**	**5(b)**	**5(c)**	*
$(i\text{-PrO})_3Al$												
180°C, 7 h	99	–	–	–	26	3	–	–	52	10	7	–
$AlCl_3$												
150°C, 15 h	99	–	–	–	11	12	4	–	29	26	18	–
AlH_3												
140°C, 6 h	91	51	–	–	40	4	–	–	5	–	–	–
$(i\text{-Bu})_2AlH$												
100°C, 12 h	100	42	3	3	44	2	4	–	–	–	–	–
$(4\text{-MePhO})_3Al + EtAlCl_2$												
150°C, 3 h ($EtAlCl_2$—0.2%)	98	1	–	–	15	10	–	5	28	10	6	16
150°C, 3 h ($EtAlCl_2$—1%)	92	25	–	–	24	3	–	1	18	5	–	26

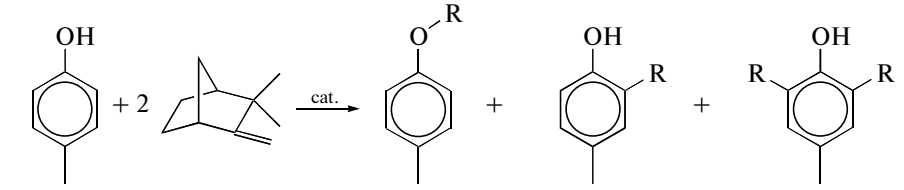
* Resinification products.

Ethyldichloroaluminum $EtAlCl_2$ (A1, 1 and 0.2%) was used as a cocatalyst for aluminum cresolate ($4\text{-}CH_3PhO)_3Al$).

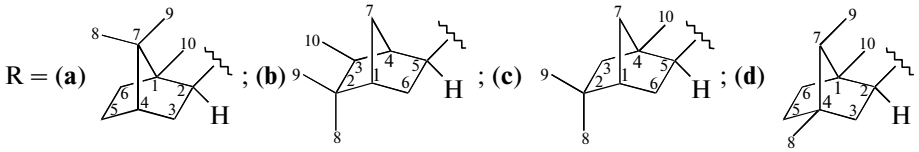
Alkylation conditions and product yields are shown in the table. Spectral characteristic of isolated terpenophenols (**3**–**5**) corresponded to published data [10].

RESULTS AND DISCUSSION

In this work, we reported studies of alkylation of *p*-cresol **1** with camphene **2** in the presence of aluminum-based compounds at varied temperatures (Scheme 1 and table).



1 **2** **3(a–c)** **4(a–d)** **5(a–c)**



The coupling of *p*-cresol **1** and camphene **2** in the presence of aluminum isopropylate performed at 180°C resulted in 69% of dialkylated products (table). 2,6-Diisobornyl-4-methylphenol **5(a)** was isolated as a major product in a yield of 52%. The yield of 2-isobornyl-4-methylphenol **4(a)** was 26%.

When $(i\text{-PrO})_3Al$ was used, a mixed alkoxide of isopropylate and phenolate $(i\text{-PrO})_{3-n}Al(PhO)_n$ were first formed, and then the latter was involved in the alkylation reaction as a catalyst.

Lewis acid $AlCl_3$ and aluminum organic compounds are more active catalysts providing decreased reaction temperatures. Although nearly complete conversion was achieved, the selectivity in the case of 2,6-diisobornyl-4-methylphenol was rather low. Particularly, in the presence of $AlCl_3$ as a catalyst, a mixture of monoalkyl-**4** and dialkyl **5** products bearing isobornyl (**a**), isocamphyl (**b**), and isofenchyl (**c**) substituents was formed. Release of HCl also supported the reduction in the reaction selectivity. The presence of H^+ resulted in intensification of side reactions.

When pyridine or triethylamine were added to the reaction mixture with the goal of restraining hydrochloric acid, alkylation did not proceed. We can assume that the nitrogen atom coordinated to the aluminum atom and prevented phenol alkylation with camphene within the organized coordination sphere of aluminum [6].

In the presence of hydrides AlH_3 and $(i\text{-Bu})_2AlH$, the initial phenol interacted with the hydrids to give a mixed complex, for example, $(i\text{-Bu})_{2-n}Al(PhO)_n$, which served as a catalyst. The use of aluminum hydrides resulted in a reduction in the reaction temperature to 100°C. The major products under these conditions were phenylbornyl ester **3(a)** and 2-isobornyl-4-methylphenol **4(a)** at a 1 : 1 ratio.

It is noteworthy that the selectivity of the process decreased if ethyldichloroaluminum was added to aluminum cresolate as a cocatalyst at 150°C and a set of O- and C-alkylation products with varied structures of the terpenoid substituent was formed. Also, the formation of considerable amounts of resinification products was observed.

When aluminum cresolate immobilized on aluminum oxide was used as a catalytic system, alkylation of *p*-cresol with camphene did not proceed.

CONCLUSIONS

Alkylation of *p*-cresol with camphene was studied in the presence of aluminum-based catalysts $(i\text{-PrO})_3Al$, AlH_3, $AlCl_3$, $(i\text{-Bu})_2AlH$, $EtAlCl_2$, and $LiAlH_4$. Aluminum phenolate was found to be the most selective catalyst among the tested compounds.

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