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Iron-Catalyzed Synthesis of Alkyl Esters of Benzoic Acid from Benzene and Its Derivatives with Use of CCl_4—Alcohol Reagent System †

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Abstract: The aim of this work is to develop a one-stage catalytic method for the preparation of alkyl esters of benzoic acid by the direct reaction of benzene and its derivatives with alcohols and halogenmethanes. We found that the reaction of benzene, phenol, and anisole with CCl4 and alcohol under the action of the $[Fe^0]$—acetylacetone catalyst leads to the formation of practically important esters of alkyl benzoates, as well as salicylic and p-hydroxybenzoic acids. The advantage of the developed method for the synthesis of esters of benzoic acid is the availability and low cost of the main starting reagents—benzene, phenol, anisole, CCl_4, alcohols and iron, cost reduction and simplification of technology, moderate reaction time (6 h), relatively low temperature, one-step process, possibility the use of this reaction in an industrial environment (scaling).

Keywords: benzene; phenol; anisole; esters of carboxylic acids; catalysis

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1. Introduction

The most important class of organic compounds are aromatic and heteroaromatic carboxylic acids. They are widely used in a wide variety of fields: in the food industry, perfumery, medicine, in the synthesis of polymers, dyes, corrosion inhibitors, preparations for agriculture and veterinary medicine. Esters of benzoic acid (methyl, ethyl, *n*-propyl, *n*-butyl and amyl), which have a characteristic odor, are widely used in the perfumery industry. Benzoic acid is used in medicine for the treatment of skin diseases externally as an antiseptic, antimicrobial and antifungal agent. The sodium salt of benzoic acid (sodium benzoate) is used as an expectorant and antipyretic agent. Benzoic acid and its sodium salt serve as food preservatives (E210, E211, E212, E213) [1,2].

The main industrially important method for the synthesis of aromatic carboxylic acids is the oxidation of alkyl-, alkenyl- and alkynylaromatic compounds [3,4].

The most promising and widely used methods for the synthesis of aromatic carboxylic acids include oxidative carbonylation and carboxylation of arenes with CO and CO_2 under the action of Co-, Pd-, Ru-, and Rh-containing catalysts [5–8].

At the same time, these methods for the synthesis of aromatic carboxylic acids are not universal; they have their own limitations. Carboxylation and carbonylation proceeds readily with haloarenes and with difficulty with other arene derivatives. In addition, CO and CO_2 are gaseous compounds, which creates great difficulties in the instrumentation of industrial processes and is a serious obstacle to widespread use in preparative practice. For these reasons, research is being carried out all over the world aimed at developing effective, alternative methods for the synthesis of aromatic carboxylic acids.

In view of the availability of benzene, methods of obtaining benzoic acid directly from benzene are of particular interest. Therefore, the aim of this work is to develop a one-stage method for the preparation of alkyl esters of benzoic acid by the direct reaction of benzene and its derivatives with alcohols and halogenmethanes under the action of a catalyst.

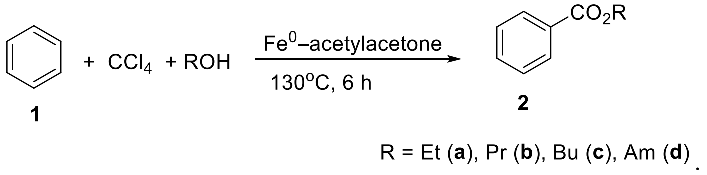
2. Results and Discussion

We carried out the synthesis of alkyl esters of benzoic acid from benzene and the corresponding alcohol using halogenmethane, in the presence of metallic iron as a catalyst.

The effect of temperature (from 100 °C to 180 °C), reaction time (1–12 h), various molar ratios of catalyst and reagents was studied. A wide range of metal complex catalysts based on Ni, Co, Cr, Fe were tested as a catalyst.

It was found that when benzene reacts with carbon tetrachloride and aliphatic alcohols (ethanol, *n*-propanol, *n*-butanol, *n*-pentanol) in the presence of metallic iron and acetylacetone at a temperature of 130–150 °C for 4–8 h at a molar ratio [Fe^0 (met.)]:[acetylacetone]:[benzene]:[CCl_4]:[alcohol] = 2–20:1–10:20:20–400:20–400, benzoic acid ester is formed (Scheme 1). The optimal conditions for the reaction and the concentration of the catalyst and reagents were developed by the example of the reaction of benzene with ethanol, CCl_4 in the presence of Fe^0 (met.). The following ligands were tested: pyridine, acetylacetone, triphenylphosphine, triethylamine. The best catalyst is metallic iron with acetylacetone as an additive.

Optimal ratios of catalyst and reagents were founds: [Fe^0 (met.)]:[acetylacetone]:[benzene]:[CCl_4]:[alcohol] = 10:1:20:200:200. At a temperature of 130 °C and the duration of the reaction for 6 h, the yield of benzoic acid esters is 30–50% (ethyl benzoate **2a**—42%, propyl benzoate **2b**—50%, butyl benzoate **2c**—32%, and amyl benzoate **2d**—30%). The reaction by-products are HCl and ROR. The synthesis proceeds best in an argon atmosphere. When using a catalyst concentration below 10 mol%, the yield of alkyl esters of benzoic acid is noticeably lower.



Scheme 1. The synthesis benzoic acid ester from benzene under the action of CCl_4, alcohols and Fe^0 –acetylacetone reagent system.

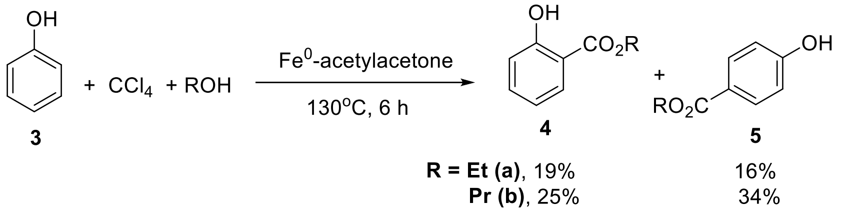
Further, in order to study the reaction mechanism, we studied the kinetics of the process of obtaining ethyl ester of benzoic acid **2b** by gas chromatography. In particular, it was found that in the first 3 hours there was an insignificant consumption of metallic iron, however, 6 hours after the start of the reaction, the iron is almost completely consumed, passing into solution in the form of a salt.

Qualitative reactions to Fe^{2+} and Fe^{3+} proved the presence of mainly Fe^{3+} in the samples, and titration showed the presence of HCl in the reaction mixture in an amount of 4.1 mol/L.

The elemental composition of the catalyst isolated after the reaction was determined using chemical analysis: C, 38.27%; H, 3.15%; O, 8.43%; Cl, 36.15%; Fe, 14.0%. Based on the data obtained, the following elemental composition of the precipitate was determined [$Fe(C_{10}H_{14}O_4Cl$], which can be represented as a binary mixture of iron compounds [$FeCl_3$:$Fe(acac)_3$] (1:3).

It was found that a binary mixture $FeCl_3$: $Fe(acac)_3$ (1:3) catalyzes the reaction in a manner analogous to metallic iron activated by acetylacetone. Separately, $FeCl_3$ and $Fe(acac)_3$ exhibit weak catalytic activity in the studied reaction (yield **2a** < 5%).

Under the developed conditions, we tried to introduce an ester group into phenol and anisole molecules. On the basis of the developed method for the preparation of alkyl esters of benzoic acid **2a–d**, we succeeded in introducing an ester group into the molecule of phenol **3** with the formation of two products: ethyl ester of salicylic acid **4a** and ethyl ester of *p*-hydroxybenzoic acid **5a** (Scheme 2).

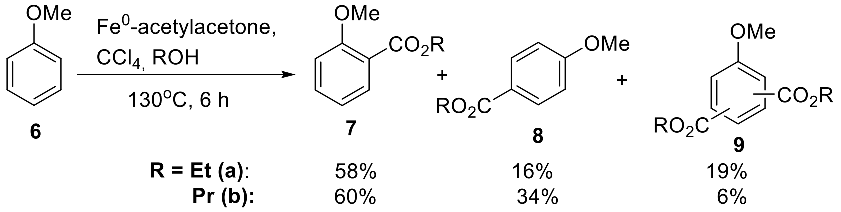


Scheme 2. The reaction of phenol with CCl_4, alcohols and Fe^0—acetylacetone reagent system.

Despite the complete conversion of phenol **3**, the overall yield of esters **4a** and **5a** did not exceed 35%. The low yield of esters **4** and **5** is due to the oxidation of the hydroxyl group of phenol with the formation of hydroquinone and quinone, followed by their condensation.

When ethanol was replaced with propanol, the yields of propyl ester of salicylic **4b** and *p*-hydroxybenzoic **5b** acids were 25% and 34%, respectively.

Therefore, in order to avoid oxidation reactions of the OH group, we involved anisole **6** into the reaction under similar conditions. Reaction of anisole **6** with CCl_4 and ROH in the presence of Fe^0—acetylacetone reagent system gave alkyl esters of 2-methoxybenzoic acids **7a**,**b** and 4-methoxybenzoic acids **8a**,**b** (Scheme 3).The process was complicated by the formation of the product **9a**,**b**.



Scheme 3. The reaction of anisole with CCl_4, alcohols and Fe^0—acetylacetone reagent system.

Further, we tried to introduce an ester group into other functionally substituted arenes. However, the attempt was unsuccessful for benzoic acid, benzonitrile, and benzamide: in all three cases, the reaction product was ethyl benzoate **2a**. For toluene, xylenes, and benzyl chloride, the yields of the corresponding esters turned out to be low due to the formation of by-products by chlorination of methyl-substituted arene at the methyl group with CCl_4 and subsequent Friedel-Crafts alkylation with the formation of diarylmethanes [9].

3. Conclusions

The reaction of benzene, phenol and anisole with carbon tetrachloride and alcohol under the action of the Fe^0—acetylacetone reagent system leads to the formation of practically important esters of alkyl benzoates, as well as salicylic and *p*-hydroxybenzoic acids. The advantage of the developed method for the synthesis of esters of benzoic acid is the availability and low cost of the main starting reagents - benzene, phenol, anisole, CCl_4, alcohols and metallic iron, cost reduction and simplification of technology, moderate reaction time (6 h), relatively low temperature, one-stage process, the possibility of using this reaction in an industrial environment (scaling).

4. Experimental Part

Commercially available reagents were used. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400 spectrometer (100.62 MHz for ^{13}C and 400.13 MHz for ^1H). When recording the ^1H and ^{13}C NMR spectra, $SiMe_4$ and $CDCl_3$ were used as an internal standards, respectively. Mass spectra were measured using Finnigan 4021 instrument with an ionizing electron energy of 70 eV and an ionization chamber temperature of 200 ° C. The elemental analysis of the samples was determined on Carlo Erba elemental analyzer, model 1106.

Preparation of benzoic acid propyl ester 2b.

The reactions were carried out in a glass ampoule (V = 10 mL) placed in a stainless steel microautoclave (V = 17 mL) with constant stirring and controlled heating.

Metallic iron (56 mg, 1 mmol), acetylacetone (10 mg, 0.1 mmol), benzene (156 mg, 2 mmol), carbon tetrachloride (3080 mg, 20 mmol) and *n*-propyl alcohol (1200 mg, 20 mmol) were loaded into an ampoule under argon. The sealed ampoule was placed in an autoclave, the autoclave was sealed and heated at 130 °C for 6 hours with constant stirring. After the completion of the reaction, the autoclave was cooled to 20 °C, the ampoule was opened, the reaction mixture was neutralized with Na_2CO_3, boiled with coal in petroleum ether for 10–15 min and filtered through a paper filter. The solvent was distilled off, the residue was distilled in a vacuum. Yield **2b** was 328 mg (50%).

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