Synthesis of Cresotic Acids by Carboxylation of Cresols with Sodium Ethyl Carbonate

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Received May 12, 2015

Abstract—Carboxylation of *o*-cresol, *m*-cresol, and *p*-cresol with sodium ethyl carbonate (SEC) proceeds regioselectively with the formation of cresotic acids: 2-hydroxy-3-methylbenzoic acid, 2-hydroxy-4-methylbenzoic acid, and 2-hydroxy-5-methylbenzoic acid, respectively. Optimal conditions for conducting the process have been found to be as follows: the reactants ratio of [cresol] : [sodium ethyl carbonate] = (1.5-2) : 1, $T = 180-185^{\circ}$ C, $P_{CO_2} = 10$ atm, and t = 6-7 h. Simple and convenient methods for the synthesis of cresotic acids, which can be used for their industrial manufacturing, have been developed.

Keywords: cresotic acids; *o*-cresol, *m*-cresol, *p*-cresol, carboxylation, carbon dioxide, sodium ethyl carbonate **DOI:** 10.1134/S0965544116070161

Use of carbon dioxide as a source of carbon in organic synthesis is a challenging problem in current organic and petroleum chemistry [1]. The great interest stirred by this problem is manifested in the increasing rate of growth in the number of scientific publications devoted to this subject. It should be noted that the utilization of carbon dioxide in chemical synthesis is important for environmental protection as well, since it is one of the ways for reducing the emission of carbon dioxide, which is the main component of greenhouse gases, into the atmosphere [1, 2]. One of the most promising lines in the use carbon dioxide in organic synthesis is the preparation of carboxylic acids and their derivatives, organic compounds containing the carboxyl C(O)–O– or/and the amide C(O)– NH_2 group (carboxylic acids, esters, lactones, organic carbonates and carbamates, ureas, amides, etc.) [1, 3]. Currently, supercritical CO₂ is widely used as a medium for conducting chemical reactions, including its use as a reagent for the carboxylation of arenes [4].

The use of alkali metal salts of ethyl carbonate in the phenol carboxylation reaction was first reported by Jones [5]. Slow heating of a mixture of phenol with a suspension of sodium ethyl carbonate (SEC) in ethanol to 175° C with the simultaneous removal of the solvent and some unreacted phenol by distillation (under reduced pressure) and the subsequent treatment of the reaction mixture with water gave salicylic acid in a yield of 50%. When using potassium ethyl carbonate, a mixture of salicylic and *p*-hydroxybenzoic acids was obtained. Later, the use of alkali metal salts of alkyl carbonates as carboxylating agents in the carboxylation reaction of phenol and its derivatives (predominantly in the form of sodium and potassium phenolates) was reported in a series of works by Japanese researchers [6-8].

Earlier, we conducted guite detailed studies of the carboxylation reaction of hydroxyarenes (phenol and naphthols) with readily available CO_2 derivatives, namely, alkali metal salts of alkyl carbonates, and found that the reaction could be conducted without a solvent [9–11]. Optimal conditions for conducting the process were identified. The products of carboxylation of cresols, methyl-substituted phenolcarboxylic acids (cresotic acids), find a widespread application as photostabilizers, pharmaceuticals, and pesticides [12, 13]. Currently, the carboxylation of alkali metal cresylates with carbon dioxide under pressure (Kolbe-Schmitt reaction) is the main industrial method for the synthesis of cresotic acids. The method has a number of serious disadvantages, the main of which is the need for the preliminary synthesis of alkali metal cresylates. The production of cresylates is complicated by the labor-intensive technology of their preparation (water removal by vacuum distillation) and high hygroscopicity of dry alkali metal cresylates [14–16].

The aim of this work was to develop an improved method for the synthesis of cresotic acids via the carboxylation of *m*-cresol, *p*-cresol, and *o*-cresol with the sodium salt of ethyl carbonate.

EXPERIMENTAL

The chemical used were dry sodium ethyl carbonate, synthesized by reacting carbon dioxide with sodium ethoxide as described in [8, 9], and *meta*-, *para*-, and *ortho*-cresols (Sigma-Aldrich). The experiments were conducted in the solvent-free mode in a medium of gaseous CO_2 . The identity of synthesized cresotic acids was determined by the melting point and IR and NMR data. The IR spectra were recorded on a Mattson Satellite-FTIR Fourier-transform IR spectrometer in the frequency range of 4000–400 cm⁻¹ and the NMR spectra were recorded on a Bruker DPX 400 instrument operating at a frequency of 300 MHz. Tetramethylsilane was used as the standard.

Preparation of 2-Hydroxy-5-Methylbenzoic Acid

A glass reactor placed into a steel autoclave and equipped with a stirrer, electric heating, and carbon dioxide gas inlet (outlet) fittings, was loaded with 4.33 g (0.04 mol) of *p*-cresol and 2.24 g (0.02 mol) of sodium ethyl carbonate (reactants ratios was [*p*-cresol] : [sodium ethyl carbonate] = 2 : 1); the autoclave was pressurized; purged twice with CO₂ to remove air; and filled with CO₂ to a pressure of 10 atm; after which stirring and heating were switched on. The reaction mixture was heated to 185°C over 4 h (at a heating rate of 40°C/h) and held at this temperature and a CO₂ pressure of 10 atm for 3 h. After that, stirring and heating were stopped and the autoclave was cooled down to room temperature. The reaction mixture was treated with water. The obtained aqueous solution was extracted with ether to separate unreacted *p*-cresol. From the ether phase, 2.2 g of unreacted *p*-cresol was recovered. The product (2-hydroxy-5-methylbenzoic acid) was isolated by acidifying the aqueous phase with hydrochloric acid to afford 2.67 g (88.0%) of 2-hydroxy-5-methylbenzoic acid; the yield calculated on a *p*-cresol reacted basis was 97.3%. $T_{\rm m} = 149 - 150^{\circ}$ C.

2-Hydroxy-4-methylbenzoic acid (yield, 74.2%) and 2-hydroxy-3-methylbenzoic acid (yield, 38%) were also synthesized according to the above procedure by reacting sodium ethyl carbonate with *m*-cresol and *o*-cresol, respectively.

RESULTS AND DISCUSSION

There are no published data on the carboxylation of *o*-cresol, *p*-cresol, or *m*-cresol with alkali metal salts of alkyl carbonates. In this work, the carboxylation reaction of cresols with sodium ethyl carbonate was thoroughly studied using reagent grade *o*-cresol, *p*-cresol, and *m*-cresol (Sigma-Aldrich) (Scheme 1). It was found that sodium ethyl carbonate could be used for the carboxylation of cresols. The influence of the reaction conditions on the course of the process and the product yield was examined.



Scheme 1. Carboxylation of cresols with sodium ethyl carbonate.

It was found that under the test conditions, the carboxylation of *m*-cresol with sodium ethyl carbonate proceeded regioselectively at the *o*-position relative to the hydroxyl group with the exclusive formation of 2-hydroxy-4-methylbenzoic acid. The results of studying the effect of the reaction conditions for the carboxylation of *m*-cresol with sodium ethyl carbonate on the product yield are presented in Figs. 1–4. Since the reaction is conducted without introducing a foreign solvent, its role is played by *m*-cresol and, as the reaction proceeds further, by the ethanol released. The dependence of the yield of the product (2-hydroxy-4methylbenzoic acid) on the reaction temperature is nonmonotonic in character. With the increase in the temperature from 120 to 180° C, the product yield increases dramatically from 15.2 to 71.5%, but it drops to 64.8% during the further increase in temperature to 190° C (Fig. 1).

The optimum values of the CO_2 pressure and the reaction time are 10 atm and 7 h, respectively (Figs. 2, 3). Relatively cheap carbon dioxide is used as an inert gas. The optimum ratio of the reactants is

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Fig. 1. Effect of temperature on the yield of *m*-cresotic acid (α). *m*-Cresol : SEC = 2, $P_{CO_2} = 10$ atm, and t = 6 h.



Fig. 3. Effect of the reaction time (*t*, h) on the yield of *m*-cresotic acid. *m*-Cresol : SEC = 2, $T = 180^{\circ}$ C, and $P_{CO_2} = 10$.

[m-cresol]: [sodium ethyl carbonate] = 1.5:1 (Fig. 4). It should be noted that an increase in the yield of salicylic acid during the carboxylation of phenol with sodium ethyl carbonate in the case of an excess amount of the substrate (phenol) used was reported in [9]. Under the optimum conditions found in this study for the *m*-cresol carboxylation reaction with sodium ethyl carbonate, the yield of 2-hydroxy-4-methylben-zoic acid is 74.2% and the yield calculated on a reacted *m*-cresol basis is 91.0%.

The nonmonotonic pattern of curves in Figs. 1–4 can be associated with the following. The decrease in the yield with the increase in the temperature (Fig. 1) and the reaction time (Fig. 3) above optimum values can be due to side reactions (decarboxylation and tar formation). It can be assumed that at a pressure of car-



Fig. 2. Effect of CO₂ pressure on the yield of *m*-cresotic acid (α). *m*-Cresol : SEC = 2, *T* = 180°C, and *t* = 6 h.



Fig. 4. Yield of *m*-cresotic acid (α) depending on the initial molar ratio of *m*-cresol to sodium ethyl carbonate (*n*). *T* = 160°C, *P*_{CO2} = 10 atm, and *t* = 6 h.

bon dioxide above the optimum value, the properties of the medium change as a result of its high solubility (Fig. 2). Ethanol, which acts as a cosolvent, is released during the reaction. It is likely that the maximum in the yield (Fig. 4) in the case of the increase in the *m*-cresol/SEC ratio is due to the shortage of ethanol for the creation of the optimum composition of the medium.

It has been found that sodium ethyl carbonate can be used as a carboxylating agent in the carboxylation reaction of *o*-cresol and *p*-cresol. The carboxylation of *p*-cresol with sodium ethyl carbonate was found to proceeded regioselectively with the formation of 2-hydroxy-5-methylbenzoic acid. The effect of the reaction conditions on the product yield was investigated (Table 1). Under the optimum reaction condi-

Run no.	Reaction conditions				Viald of 2 bydrowy 5
	Reactant ratio [p-cresol] : [sodium ethyl carbonate]	<i>T</i> , °C	P _{CO2} , atm	time, h	methylbenzoic acid, wt %
1	1:1	185	10	7	53.7
2	2:1	185	10	7	88.1
3	3:1	185	10	7	74.3
4	2:1	150	10	7	48.8
5	2:1	170	10	7	72.4
6	2:1	180	10	7	80.0
8	2:1	195	10	7	80.5
9	2:1	185	8	7	38.6
11	2:1	185	12	7	74.4
12	2:1	185	10	5	70.3
13	2:1	185	10	6	72.3
15	2:1	185	10	8	75.0

Carboxylation of *p*-cresol with sodium ethyl carbonate

tions ([*p*-cresol] : [sodium ethyl carbonate] = 2 : 1, $T = 185^{\circ}$ C, $P_{CO_2} = 10$ atm, and t = 7 h), the yield of 2-hydroxy-5-methylbenzoic acid reached 88.1% and the yield calculated on the reacted *p*-cresol basis was 97.3%.

It was found that the *o*-cresol carboxylation reaction with sodium ethyl carbonate also proceeded selectively with the exclusive formation of 2-hydroxy-3-methylbenzoic acid. It should be noted that in the case of *o*-cresol, the reaction proceeds with a substantially lower yield of the product as compared to *p*-cresol and *m*-cresol. In *o*-cresol carboxylation under the optimum conditions found for the reaction of *p*-cresol with sodium ethyl carbonate ([*o*-cresol] : [sodium ethyl carbonate] = 2 : 1, $T = 185^{\circ}$ C, $P_{CO_2} =$ 10 atm, t = 7 h), the yield of the product (2-hydroxy-3-methylbenzoic acid) is 38.0% and the yield calculated on the reacted *o*-cresol basis is 90.1%.

The synthesized compounds were identified by matching a physicochemical constant (T_m) , by the absence of melting point depression for a mixed sample of the products with authentic reagent-grade samples of 2-hydroxy-3-benzoic acid, 2-hydroxy-4-benzoic acid, and 2-hydroxy-5-benzoic acid, as well as by the IR and NMR data. In the IR spectra of all the synthesized compounds exhibit the band at 1620–1660 cm⁻¹ (carboxyl group) and a broad diffuse band at 2300–3500 cm⁻¹ (due to hydrogen-bonded hydroxyl groups). In the ¹H NMR spectrum of 2-

hydroxy-3-methylbenzoic acid, the protons of the aromatic ring in the 4- and 6-positions appear as doublets at 7.36 and 7.78 ppm, respectively, and the proton in the 7-position, gives a triplet at 6.68 ppm. The methyl group produces a singlet at 2.3 ppm. The carboxyl and hydroxyl protons appear as a broadened signal at 10.6 ppm because of a strong hydrogen bond.

In summary, it has been shown that sodium ethyl carbonate can be used as a carboxylating agent in the carboxylation reaction of cresols. It has been found that the carboxylation of *o*-cresol, *m*-cresol, or *p*-cresol proceeds regioselectively with the formation of 2-hydroxy-3-metheylbenzoic acid, 2-hydroxy-4-metheylbenzoic acid, or 2-hydroxy-5-metheylbenzoic acid, respectively. Optimum conditions for conducting this reaction have been found. The developed simple and convenient methods for the synthesis of cresotic acids can be used for their industrial manufacturing.

REFERENCES

- 1. Carbon dioxide as a Source of Carbon: Biochemical and Chemical Uses, Ed. by M. Aresta and G. Forti (D. Reidel, Dordrecht, 1987).
- 2. Organic and Bio-organic Chemistry of Carbon Dioxide, Ed. by S. Inoue and N. Yamazaki (Kodansha, Tokyo, 1982).
- 3. Kh. A. Suerbaev, Eur. Chem.-Technol. J. 12, 105 (2010).

- 4. A. V. Shlyakhtin, S. Z. Vatsadze, D. P. Krut'ko, et al., Sverkhkrit. Flyuidy: Teor. Prakt. 71, 21 (2012).
- 5. I. J. Jones, Chem. Ind., 1245 (1958).
- I. Hirao, T. Kondo, and T. Kito, Kogyo Kagaku Zasshi 72, 692 (1969).
- T. Kito, T. Kondo, H. Ago, et al., Kogyo Kagaku Zasshi 73, 742 (1970).
- 8. T. Kito and I. Hirao, Bull. Chem. Soc. Jpn. 44, 3123 (1971).
- 9. Kh. A. Suerbaev, O. E. Mikhnenko, G. B. Akhmetova, et al., Pet. Chem. **45**, 41 (2005).
- Kh. A. Suerbaev, O. E. Mikhnenko, G. B. Akhmetova, et al., Pet. Chem. 45, 335 (2005).

- 11. Kh. A. Suerbaev, E. G. Chepaikin, F. M. Kanapieva, and G. Zh. Seitenova, Pet. Chem. 49, 265 (2009).
- 12. D. E. Hyams, A. N. Howard, I. E. Evans, and H. H. Davison, Diabetologia 7, 94 (1971).
- 13. L. G. Shakirov, P. M. Zobov, and A. Z. Bikkulov, Zh. Prikl. Khim. **58**, 872 (1985).
- 14. A. S. Lindsey and M. Jeskey, Chem. Rev. 57, 583 (1957).
- 15. L. G. Shakirov, P. M. Zobov, and A. Z. Bikkulov, Zh. Prikl. Khim. 58, 963 (1985).
- V. N. Khlebnikov, L. G. Shakirov, O. E. Kuznetsov, and A. Z. Bikkulov, Zh. Prikl. Khim. 62, 626 (1989).

Translated by E. Boltukhina