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Preparation of 2-(Phenylamino)benzoic Acid and 2-[(Carboxymethyl)(phenyl)amino]benzoic Acid via Ullmann Reaction under Microwave Irradiation

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Abstract—The optimal conditions of preparation of 2-(phenylamino)benzoic acid and 2-[(carboxymethyl)-(phenyl)amino]benzoic acid via Ullmann reaction under microwave irradiation have been determined.

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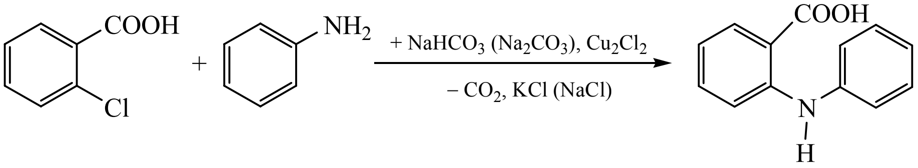
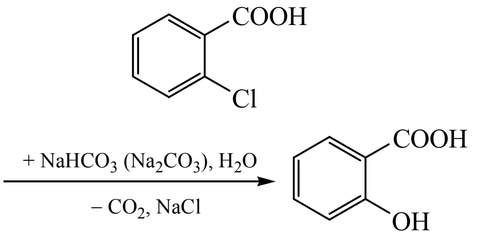
2-(Phenylamino)benzoic (*N*-phenylanthranilic) acid and 2-[(carboxymethyl)(phenyl)amino]benzoic acid are widely utilized in chemical, pharmaceutical, and electrochemical industries [1–3]. Thus, the development of more efficient methods of preparation of various 2-(phenylamino)benzoic acids is a topical task.

Synthesis under microwave irradiation is one of the promising modern approaches for the preparation of various organic compounds. In this work we determined the optimal conditions for 2-(phenylamino)benzoic and 2-[(carboxymethyl)(phenyl)amino]benzoic acids preparation via Ullmann reaction. The reaction was performed under microwave irradiation (400 W, 2450 MHz) using a MARS (Microwave Acceleration Reaction System, CEM Corporation) irradiation source.

2-(Phenylamino)benzoic acid was prepared from 2-chlorobenzoic acid and aniline in aqueous solution with copper(I) chloride as catalyst. Sodium carbonate or sodium hydrogen carbonate were used as hydrochloric acid acceptor.



One of the side reactions was that of salicylic acid formation.



The preparation was performed at various temperatures, the results are presented in Table 1.

The highest yield of target product (above 88%) was achieved when the reaction was run during 120 min with sodium hydrogen carbonate. The reaction mixture was a viscous syrupy mass, rapidly solidifying upon cooling. Increasing the reaction temperature did not improve the target product yield, thus 80–90°C was considered the optimal reaction temperature. Using of sodium carbonate as hydrochloric acid acceptor decreased the product yield noticeably.

When the same reaction was run under conditions of thermal heating, at equimolar ratio of aniline and 2-chlorobenzoic acid, with sodium hydrogen carbonate as base and with 20% of water in the mixture, somewhat lower yield was attained (81–82%) even though the reaction time was longer (180 min) [1].

Table 1. Preparation time, temperature conditions, and yield of 2-(phenylamino)benzoic acid in water

Run no.	Hydrochloric acid acceptor	Reaction conditions	Yield, % (g)
1	$NaHCO_3$	30–80°C (40 min) and 80°C (150 min)	83–85 (17.7–18.1)
2	$NaHCO_3$	30–80°C (40 min) и 90°C (80 min)	88–90 18.8–19.2)
3	$NaHCO_3$	30–80°C (40 min) and 100° C (80 min)	71–73 (15.1–15.6)
4	Na_2CO_3	30–80°C (40 min) and 90°C (80 min)	29–31 (6.2–6.6)

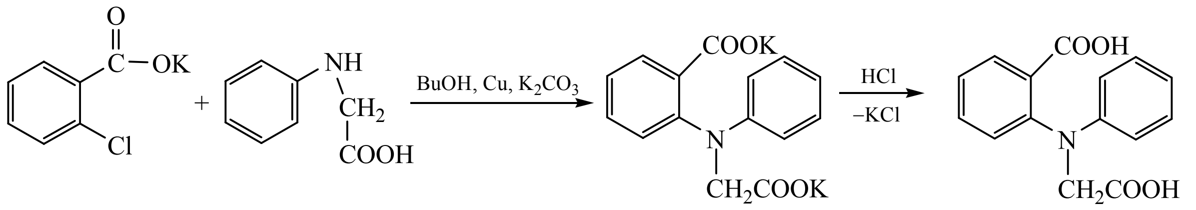
Quantitative determination of the target product accumulation was performed by thin layer chromatography. After the reaction reached its isothermal state, the reaction mixture was periodically sampled; the chromatograms obtained were analyzed using the Sorbfil visiodensitometer in Sorbfil 1.8 software, at 254 nm. The kinetic curves of 2-(phenylamino)benzoic acid formation were plotted according to the data obtained (Fig. 1).

Table 2. Preparation time, temperature conditions, and yield of 2-((carboxymethyl)(phenyl)amino)benzoic acid in *n*-butanol

Run no.	Reaction conditions	Yield, % (g)
1	90°C (420 min)	63–64 (17.1–17.4)
2	90°C (60 min) and 100°C (180 min)	77–78 (20.9–21.1)
3	90°C (60 min) and 110°C (180 min)	72–73 (19.5–19.8)
4	90°C (60 min) and 100°C (100 min)	68–70 (18.4–19.0)

From Fig. 1 it is seen that in the initial stage of the reaction the kinetics did not depend on temperature. The decay of the product yield was noticeable at 100°C (as compared with the reaction at the optimal conditions), likely due to the side reactions of decarboxylation and salicylic acid formation.

2-((Carboxymethyl)(phenyl)amino)benzoic acid was prepared from 2-chlorobenzoic acid and *N*-phenylglycine with potassium carbonate as hydrochloric acid acceptor and copper(I) chloride as catalyst, in *n*-butanol containing less that 20% of water.



Higher concentrations of water were to be avoided, as in this case the reaction system was not homogeneous.

2-[(Carboxymethyl)(phenyl)amino]benzoic acid preparation was performed at various temperatures, the results are presented in Table 2.

The highest yield of 2-[(carboxymethyl)(phenyl)-amino]benzoic acid (more than 77%) was obtained at the reaction time of 240 min: first, the mixture was incubated at 90°C during 60 min, then the temperature was increased to 100°C and the reaction was run for another 180 min. At this reaction temperature range the side product concentration was minimal; further

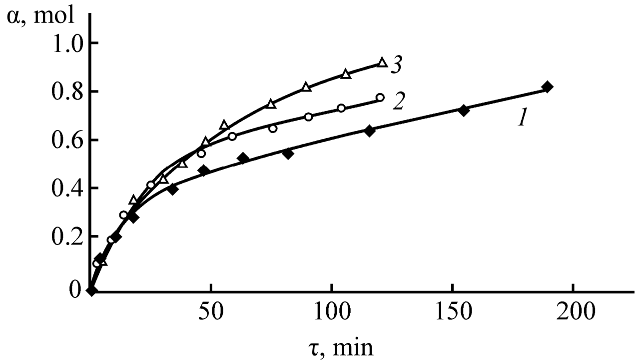


Fig. 1. Kinetic curves of 2-(phenylamino)benzoic acid accumulation at various temperatures, °C: (*1*) 80, (*2*) 100, and (*3*) 90.

increase in the reaction temperature did not lead to higher target product yield.

Under thermal heating, other conditions being the same, the 2-[(carboxymethyl)(phenyl)amino]benzoic acid preparation took no less than 6 hours.

It should be noted that the prepared product should have been dried at 90°C with the forced air circulation, as in the humid environment 2-[(carboxymethyl)(phenyl)amino]benzoic acid turned green.

To compare the two reported syntheses, 2-[(carboxymethyl)(phenyl)amino]benzoic acid was also prepared in the aqueous medium, in the absence of organic co-solvents.

In the absence of *n*-butanol, other conditions being the same (reagents ratio and concentrations, timing, irradiation power, etc), 2-[(carboxymethyl)(phenyl)amino]benzoic acid yield did not exceed 63%, thus it was not rational to prepare 2-[(carboxymethyl)(phenyl)amino]benzoic acid in the aqueous medium. With potassium carbonate changed to Na_2CO_3 or $NaHCO_3$, the target product was obtained in the form of yellow oily uncrystallizable substance, and it was not possible to separate the pure target product from it; thus, this synthesis in the presence of sodium (hydrogen) carbonate was not of practical interest.

The kinetics of 2-[(carboxymethyl)(phenyl)amino] benzoic acid formation was studied as described above for 2-(phenylamino)benzoic acid synthesis. The results obtained are shown in Fig. 2.

Similarly to the discussed above, the rate of 2-[(carboxymethyl)(phenyl)amino]benzoic acid formation in the initial stage was not sensitive to the reaction temperature. At higher conversion, the target product yield first increased with increasing temperature (Fig. 2, curves *1*, *3*), further the temperature increase led to lower target product yield (Fig. 2, curves *2*, *3*), likely due to the side reactions enhancement.

Thus, in this work, the optimal conditions of preparation of 2-(phenylamino)benzoic acid and 2-[(carboxymethyl)(phenyl)amino]benzoic acid via Ullmann reaction under microwave irradiation were found. Performing the reactions under the selected conditions led to higher yield and purity of the products as compared to those under conventional thermal heating; in the case of 2-(phenylamino)benzoic acid preparation the process was also more environmentally friendly that the conventional one [4].

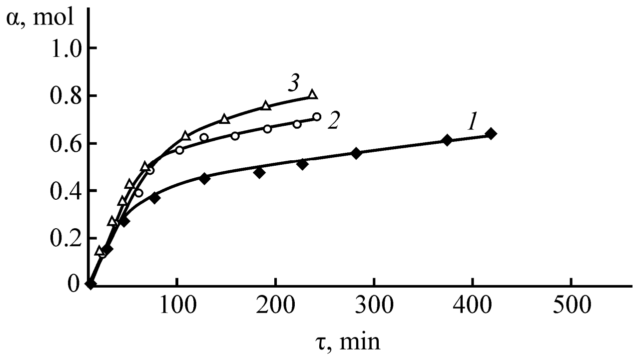


Fig. 2. Kinetic curves of 2-[(carboxymethyl)(phenyl)amino]-benzoic acid accumulation at various temperatures, °C: (*1*) 90, (*2*) 110, and (*3*) 100.

EXPERIMENTAL

The initial and final products purity was checked by thin layer chromatography using the high-efficiency Sorbfil plates (PTSKh-AF-V-UF). Chromatograms were analyzed using Sorbfil densitometer and Sorbfil 1.8 software. The following eluents were used: benzene–acetic acid 10:0.8 in the case of 2-(phenylamino)benzoic acid and toluene–ethanol–acetic acid 10:7:0.1 in the case of 2-[(carboxymethyl)(phenyl)amino]benzoic acid.

Composition and structure of the products were confirmed by thin layer chromatography (comparison with standard samples) and IR spectroscopy (IR-200 Nicolet, KBr), as well as by determination of some physicochemical constants.

2-[(Carboxymethyl)(phenyl)amino]benzoic acid. 15.6 g (0.1 mol) of 2-chlorobenzoic acid was added in several portions to 11.5 ml of cold aqueous potassium hydroxide (35 wt.%), and the mixture was stirred at the highest stirring rate in MARS during 20 min at 45°C. Then, 0.5 g of Cu_2Cl_2, 9.2 ml (0.1 mol) of aniline, and 9.24 g (0.1 mol) of $NaHCO_3$ or 5.3 g (0.6 mol) of Na_2CO_3 were added. The temperature was raised from 30°C to 80°C within 40 min, further temperature program was set according to the data given in Table 1.

After the reaction was completed, 10 ml of aqueous potassium hydroxide (10 wt.%) was added to the reactor. The mixture was boiled with activated carbon, and filtered. The filtrate was acidified with hydrochloric acid. The precipitated product was filtered off and washed with hot water. Mp 181–182°C (technical product), 182–183°C (glacial acetic acid) (mp 183–184°C [6]). IR spectrum, ν, cm^{-1}: 3340 (N–H); 3300–

2500 (O–H, C–H), 1659 (C=O), 1591 (C_{Ar}–C_{Ar}), 1262 (C–O) [5].

2-[(Carboxymethyl)(phenyl)amino]benzoic acid. 15.1 g (0.1 mol) of *N*-phenylglycine, 20.7 g (0.15 mol) of K_2CO_3, and 1.6 g (0.1 mol) of 2-chlorobenzoic acid were added (under stirring) to 47 ml of butanol or 15 ml of aqueous potassium hydroxide (45 wt.%). The reaction mixture was heated up to 90°C within 30 min, and then 0.3 g of Cu_2Cl_2 was added. The temperature program was set according to the data given in Table 2. After the reaction was completed, the reaction mixture was cooled to 80°C, and 40 ml of aqueous potassium hydroxide (5 wt %) and 70 ml of water were added. In the case of butanol reaction medium, it was then distilled off; the residue was boiled with activated carbon and filtered. The filtrate was heated to 70°C and poured in small portions into the hydrochloric acid solution, preheated to 70°C. White crystals precipitated, the product was filtered off, washed with hot water (80–90°C) till coloring with $FeCl_3$ disappeared (that is, till negative salicylic acid test). Mp 161–162°C (technical product), 164–165°C (glacial acetic acid) (mp 165–167°C [7]). IR spectrum, ν, cm^{-1}: 3300–2400 (C–H, O–H), 1707 (C=O), 1674 ($C=O_{Ar}$), 1597–1497 (C_{Ar}–C_{Ar}), 1350 (C–N), 1255–1233 (C–O) [5].

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