Use of Ultrasound in the Synthesis of 2-(Alkylamino)benzoic Acids in Water

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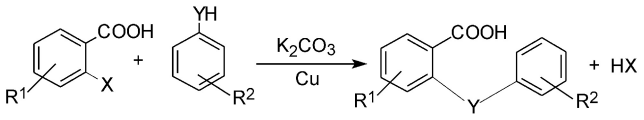
Abstract: The synthesis of substituted 2-(alkylamino)benzoic acids using the Ullmann condensation with water as the solvent and utilizing ultrasound irradiation was achieved with high yields in a short reaction time.

Key words: Ullmann condensation, copper, catalysis, ultrasound, 2-(alkylamino)benzoic acids

There is high demand for new methods to facilitate syntheses using the classical copper-mediated Ullmann condensation of aryl derivatives, which are present as structural motifs in a wide range of molecules with numerous and important applications. However, the harsh reaction conditions needed to effect these transformations, usually only in moderate yields, led to severe limitations in the general use of this reaction, especially on a large scale.[1] Some advances in the use of ultrasounds,[2] and microwave[3] enhancing reaction rates have been reported, however, these have not resulted in widespread popularity or use. Recently, several reviews on synthetic methods for copper-mediated C(aryl)–O, C(aryl)–N, C(aryl)–S bond formations have been published.[1,4,5]

The reaction of 2-halogen benzoic acids with phenols and aromatic amines using copper salts or metal as catalyst is known as the Ullmann condensation (Scheme 1).[6] Several alcohols have been satisfactorily used as solvents in this reaction of which the most commonly used is isoamyl alcohol. Other alcohols of higher boiling points are usually employed when high temperatures are required.



X = Cl, Br, I
Y = O, NH

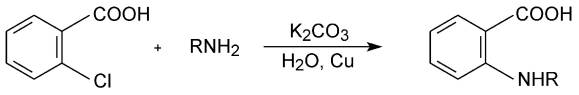
Scheme 1

Excess amine has been also used as the solvent in the condensation, but the yields are not usually as good as when amyl alcohol is employed.[7] The dry method, developed by Ullmann[8] is commonly used when the solvents do not bring about good results.

Different theories have appeared in the scientific literature about the role of water in this reaction.[9–11] It has been reported that sometimes it is advantageous to remove most of the water formed during the neutralization by distilling off part of the solvent before or during the reaction. However, the use of water at temperatures up to 130 °C has given good results in certain cases.[7]

We found when the reaction between 2-chlorobenzoic acid and aniline was carried out in water, with one equivalent of potassium carbonate, the reaction took place satisfactorily, and *N*-phenylanthranilic acid was obtained in good yield and high purity.[12a] In these conditions, the reaction is conducted essentially between the potassium 2-chlorobenzoate and the amine, with a pH of seven maintained during the course of the reaction.

As a continuation of our previous studies on the Ullmann condensation,[12] in this paper we describe the synthesis of 2-(alkylamino)benzoic acids using water as a solvent with or without the presence of ultrasound irradiation (Scheme 2). This is the first example of Ullmann condensation conditions using aliphatic amines instead of aromatic amines in the presence of water as solvent.



Scheme 2

It is well known that 2-(alkylamino)benzoic acids are interesting compounds because of their hypolipidemic properties useful in counteracting the consequences of hyperlipidemia.[13] A condition involving elevated cholesterol, phospholipid and/or triglyceride levels in the blood, and of hyperlipoproteinemia, involving an imbalance of the lipoproteins. The most serious condition associated with hyperlipidemia and hyperlipoproteinemia is atherosclerosis, the most common cause of coronary artery disease.

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We analyzed the influence of some parameters on the condensation of 2-chlorobenzoic acid and substituted primary alkylamines to obtain the corresponding 2-(alkylamino)benzoic acids. Thus, we studied the reaction time and the quantities of potassium carbonate, taking as a model the condensation of 2-chlorobenzoic acid and propylamine in water as solvent.

It was observed, as in the synthesis of N-phenylanthranilic acids,[12a] that when we used 3% (by weight) of copper and two equivalents of alkylamine per mole of 2-chlorobenzoic acid with one equivalent of potassium carbonate, the reaction took place satisfactorily within 7.5 hours and the 2-(propylamino)benzoic acid was obtained in 56% yield. The use of smaller or larger quantities of potassium carbonate (0.5 or 2 equiv) led to decreased yields (18% or 23%, respectively).

To establish the minimum time necessary for the reaction, some experiments were performed. Experimental results demonstrated that the best yield was obtained with a reaction time of five hours. When the reaction was left more than five hours the yield remained constant. Using this method (K_2CO_3, 1 equiv; Cu, 3%; alkylamine, 2 equiv; 5 h) several 2-(alkylamino)benzoic acid derivatives were synthesized; Table 1 shows the yields obtained in each case. Yields were superior to those reported in the literature using other procedures.[13,18–20]

When we used secondary amines the reaction did not take place satisfactorily, but with cyclic amines we obtained salicylic acid.

It is well known that the substitution of chlorine atom onto a benzene ring does not take place easily, but 2-halogencarboxylic acids in the presence of copper permit the formation of an intermediary copper chelate, which facilitates nucleophilic substitution.[14] This copper chelate is destroyed in a basic media and then it is not possible to obtain salicylic acid, but we demonstrated that if pyridine is present, there is competition between the nucleophilic agent and the hydroxide group. We studied the effect of pyridine on the Ullmann Condensation and demonstrated that pyridine acts as a co-catalyst and results in reduced reaction times.[12b–d] These results suggest that pyridine stabilizes the intermediate copper complex;[12c] perhaps the cyclic amines have the same effect as pyridine.

In order to reduce the reaction time and improve the yields we examined the effect of ultrasound irradiation on the synthesis of 2-(propylamino)benzoic acid, using the conditions previously mentioned.

In previous work, conditions were optimized for the use of the Ullmann condensation on the synthesis of 2-fenoxibenzoic acids,[15a] N-phenylanthranilic acids,[15b] and salicylic acid[15c] in the presence of water as solvent using ultrasound irradiation.

The beneficial effects (i.e., shorter reaction times at lower temperatures, higher yields, and narrower product distribution) of ultrasonic waves on a broad spectrum of chemical reactions have been reported by several research groups.[16] Prominent among these successes are those reactions involving metals. Presumably, the mechanism is simple: the cavity produced by the passage of ultrasonic waves through the solvent gives rise to sufficiently high temperatures and pressures to clean the surface of the metal of hindering impurities formed before and during the reaction.[6,17]

In homogeneous systems, bond-breaking often initiates the sonochemical reaction. In heterogeneous systems there is the additional benefit that ultrasound is a very efficient tool for increasing mass transport.[18]

To establish the minimum time necessary for the reaction, we scanned various reaction times (10 to 30 min). 2-(Propylamino)benzoic acid was obtained in 76% yield after only 20 minutes. It is noteworthy that with longer ultrasonic irradiation times the yield of the acid remains constant. With an irradiation time of less than 20 minutes the reaction yield is reduced, and with a reaction time of 15 minutes a yield of only 55% results.

Once the time required for the reaction was established, a series of 2-(alkylamino)benzoic acids were synthesized employing the above conditions (Table 1; K_2CO_3, 1 equiv; Cu, 3%; amine, 2 equiv; ultrasonic irradiation; 20 min).

In conclusion, we have demonstrated the advantage of using ultrasound and water as solvent in the synthesis of 2-(alkylamino)benzoic acids, resulting in an environmentally friendly alternative to the classical procedures.

Table 1 Results of the Synthesis of Substituted 2-Carboxyalkylamines[a]

No	R	Yield (%)	
		Classical heating[b]	Ultrasonic irradiation[c]
1	Methyl[19]	52	78
2	Ethyl[19]	54	74
3	Propyl[19]	56	76
4	Butyl[19]	59	81
5	Isobutyl[13]	57	80
6	Pentyl[20]	58	78
7	Octyl[13]	71	88
8	Dodecyl[13]	74	89
9	Glycyl[21]	82	87

[a] All the products were characterized by analytical and spectroscopic data.
[b] Yield of isolated and recrystallized products after 5 h reflux.
[c] Yield of isolated and recrystallized products 20 min of ultrasonic irradiation.

2-(Propylamino)benzoic Acid; Typical Procedure (Water as Solvent)

A mixture of 2-chlorobenzoic acid (0.04 mol, 6.26 g), *i*-$PrNH_2$ (0.08 mol, 5.6 mL), anhyd K_2CO_3 (0.02 mol, 2.8 g), and Cu powder (0.003 mol, 0.2 g) was refluxed in H_2O (25 mL) for 5 h. The reaction mixture was cooled and acidified with dilute HCl (1:1). The solid was filtered off, washed with H_2O and dissolved in aq NaOH solution (10%). The basic solution was acidified with AcOH–H_2O (1:3) to pH 5. The 2-(propylamino)benzoic acid crystallized and was filtered off, then washed with H_2O and recrystallized from EtOH–H_2O (1:1).

2-(Propylamino)benzoic Acid; Typical Procedure (Ultrasonic Irradiation)

A mixture of 2-chlorobenzoic acid (0.04 mol, 6.26 g), *i*-$PrNH_2$ (0.08 mol, 5.6 mL), anhyd K_2CO_3 (0.02 mol, 2.8 g), Cu powder, (0.003 mol, 0.2 g), and H_2O (25 mL) was irradiated for 20 min with a sonic horn at 20 kHz. The reaction mixture was acidified with dilute HCl (1:1). The solid was filtered off, washed with H_2O, and dissolved in aq NaOH solution (10%). The basic solution was acidified with AcOH–H_2O (1:3) to pH 5. The 2-(propylamino)benzoic acid crystallized and was filtered off, then washed with H_2O and recrystallized from EtOH–H_2O (1:1).

All experiments performed in this work were repeated five times. The yield reported represents an average of the values obtained for each reaction. The identity of the products was checked by elemental analyses, ^{1}H NMR spectra, mass spectra, and by comparison of TLC[15] with authentic samples. Melting points were compared with those reported in the literature

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