Microwave-assisted synthesis of *N*-phenylanthranilic acids in water

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N-Phenylanthranilic acid derivatives were synthesised using the Ullmann condensation of 2-chlorobenzoic acid with aniline derivatives under microwave irradiation in aqueous media. The method offers better yields in shorter reaction times compared to classical heating approaches using water as solvent.

Keywords: Ullmann condensation, microwave irradiation, *N*-phenylanthranilic acids, copper sulfate, catalysis

The application of microwave irradiation has some significant advantages compared to classical heating techniques. Microwaves (MW) generate rapid intense heating of polar substances with consequent significant reduction in reaction times, cleaner reactions that are easier to work up and, in many cases, higher yields.[1,2] The procedure is environmentaly friendly.[3]

N-phenylanthranilic acid and its derivatives have been studied as anti-inflammatory agents and as precursors of acridones and acridines which present bioactive properties such as anti HIV, antibacterial and antifungal activities.[4]

The Ullmann condensation was first described more than a century ago. This reaction typically involves the coupling of aromatic halides with anilines and phenols for the synthesis of aryl amines and aryl ethers.[5] However, the harsh reaction conditions such as high temperatures, strong bases, stoichiometric amounts of copper or copper salts, and long reaction times, led to severe limitations in the general use of this reaction, especially on a large scale. The recent developments in the copper-mediated (both stoichiometric and catalytic) reactions of aryl boronic acids,[6,7] iodonium salts,[8] siloxanes,[9] stannanes,[10] plumbanes,[11] bismuthates,[12,13] and trifluoroborate salts[14] as aryl donors permit the use of this reaction in more suitable conditions using in almost all cases dichloromethane as solvent, but still involving large reaction times (6–48 h). Some advances in the use of ultrasound,[15] and microwaves[16] in enhancing reaction rates have been reported. However, these have not resulted in widespread popularity or use. The reaction of 2-halogeno benzoic acids with phenols and aromatic amines using copper salts or metal as catalyst is a particular case of the Ullmann condensation. Several alcohols[17] 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. The dry method, developed by Ullmann,[18] is commonly used when the solvents do not give good results. Different criteria have appeared in the scientific literature about the role of water in this reaction.

In previous work,[19] we described for the first time the Ullmann condensation of 2-chlorobenzoic acid with aniline for the synthesis of *N*-phenylanthranilic acid which was carried out using water as solvent. A study of several parameters which influence the Ullmann condensation of 2-chlorobenzoic acid and substituted anilines was carried out, demonstrating that the *N*-phenylanthranilic acids could be obtained efficiently using water as solvent, in presence of copper as catalyst and potassium carbonate as acid acceptor. Under these conditions a typical yield was 76% after a reaction time of 5 hours. This reaction was also performed under ultrasonic irradiation using water as solvent; a typical yield of 88% was obtained after 20 min.[15]

There are few references related to the use of microwave-assisted reaction in aqueous media.[20,21] In the present work, we examined the effect of microwave irradiation on the Ullmann condensation in aqueous media for the synthesis of *N*-phenylanthranilic acid using the reaction of 2-chlorobenzoic acid with aniline in presence of anhydrous copper sulfate catalyst as a model, employing the condition previously optimised.[7]

Using 1 equivalent of potassium carbonate, 3% (by weight) of copper and 2 equivalents of amine per mole of 2-chlorobenzoic acid we scanned powers from 200–800 W. The best yield (98± 3%) was obtained in 5 minutes and a power of 500 W for the synthesis of *N*-phenylanthranilic acid. We observed that powers superior to 500 W increase the decomposition of the reaction products.

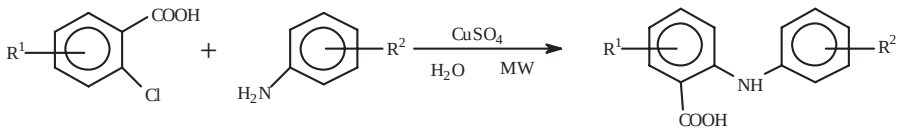
Table 1 shows several *N*-phenylanthranilic acid derivatives synthesised under microwave irradiation at 500 W in aqueous media. The time required to obtain the major yield was determined in each case. Table 2 reports microanalysis data and the molecular ions in the mass spectra obtained.

The results are very satisfactory giving short reaction times and good yields.

In conclusion, the use of microwave irradiation enhances the Ullmann condensation in aqueous media for the synthesis of *N*-phenylanthranilic. Several *N*-phenylanthranilic acid derivatives were prepared in good yield in a very short reaction time.

Experimental

General: Starting materials came from commercial sources. Melting points were measured using a GALLENKANMP hot apparatus and are uncorrected. The reactions were carried out in a Gold Star domestic microwave oven modified and equipped with an upright reflux condenser and mechanical stirrer, which allows the selection of output power up to 1000 Watts and 2.45 G Hz. TLC analyses were run on 60 F254 silica gel chromatoplates from Merck using a mixture of *n*-buthanol:acetic acid:water 6:1:1 as an eluent and visualisation with a 254 nm UV lamp. ^{1}H NMR spectra were recorded on a Bruker AC 250 Z spectrometer at 300 K. Chemical shifts are expressed in ppm relative to TMS as internal standard and in DMSO-*d6* as a solvent. Coupling constants are expressed in Hz. Mass spectra were recorded with a spectrometer TRIO 1000 FISIONS Instruments by electronic impact (EI). Microanalyses were performed by the Microanalyses service ¨Instituto de Biorgánica¨ University of La Laguna, Tenerife, Spain.



Scheme 1

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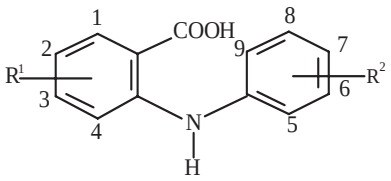
Table 1 Results of the synthesis of substituted *N*-phenylanthranilic acid under microwave irradiation



No	R^1, R^2	t/min[a]	Yield.[b] ± SD/%	M.p.[c]/°C[22]	H^1 NMR δ, ppm, *J*, Hz[d]
1	R^1=R^2=H	5	98±3	184	6.18(dd, $J_{4,3}$=7.9, $J_{4,2}$=1.15, H_4); 6.45(t, $J_{2,1}$=7.6, $J_{2,3}$= 7.4, $J_{2,4}$=1.15, H_2); 7.05(dd, $J_{7,8}$=$J_{7,6}$=7.5, $J_{7,9}$=$J_{7,5}$=1.1, H_7); 7.25(dd, $J_{5,6}$=$J_{9,8}$=8.0, $J_{5,7}$=$J_{9,7}$=1.1, H_5,H_9); 7.50(t, $J_{3,2}$=7.4, $J_{3,4}$=7.9, $J_{3,1}$=1.7, H_3); 7.60(dd, $J_{6,7}$=$J_{8,7}$=7.5, $J_{6,5}$=$J_{8,9}$=8.0, H_6,H_8); 7.78(dd, $J_{1,2}$=7.6, $J_{1,3}$=1.7, H_1); 8.90 (s, OH,NH)
2	R^1=H R^2=5-OCH_3	7	90±3	175-6	6.28(dd, $J_{4,3}$=7.8, $J_{4,2}$=1.2, H_4); 6.45(t, $J_{2,1}$=7.6, $J_{2,3}$= 7.4, $J_{2,4}$=1.2, H_2); 6.52(dd, $J_{9,8}$=7.9, $J_{9,7}$=1.5, H_9); 6.70 (t, $J_{8,9}$=7.9, $J_{8,7}$=7.6, $J_{8,6}$=1.3, H_8); 6.85(t, $J_{7,6}$=7.9, $J_{7,8}$=7.6, $J_{7,9}$=15, H_7); 7.52(dd, $J_{6,7}$=7.9, $J_{6,8}$=1.3, H_6); 7.63(t, $J_{3,2}$=7.4, $J_{3,4}$=7.8, $J_{3,1}$=1.6, H_3); 7.86(dd, $J_{1,2}$= 7.6, $J_{1,3}$=1.6, H_1); 3.60(s OCH_3); 6.70 (s, OH,NH)
3	R^1=H R^2=6,7-$(CH_3)_2$	7	92±4	187-8	6.33(dd, $J_{4,3}$=7.8, $J_{4,2}$=1.1, H_4); 6.65(t, $J_{2,1}$=7.7, $J_{2,3}$= 7.6, $J_{2,4}$=1.1, H_2); 7.11(dd, $J_{9,8}$=8.2, $J_{9,5}$=1.8, H_9); 7.25 (d, $J_{5,9}$=1.8, H_5); 7.53(d, $J_{8,9}$=8.2, H_8); 7.58(t, $J_{3,4}$=7.8, $J_{3,2}$=7.6, $J_{3,1}$=1.75, H_3); 7.95(dd, $J_{1,2}$=7.7, $J_{1,3}$=1.75, H_1); 1.8 (s CH_3-7); 2.3 (s CH_3-6); 8.90 (s, OH,NH)
4	R^1=3-NO_2 R^2=H	5	95±3	232-3	6.90(t $J_{7,8}$=$J_{7,6}$=7.5, $J_{7,9}$=$J_{7,5}$=1.2, H_7); 7.35(dd, $J_{9,8}$=$J_{5,6}$= 8.1, $J_{9,7}$=$J_{5,7}$=1.2, H_5,H_9); 7.55(dd, $J_{8,7}$=$J_{6,7}$=7.5, $J_{6,5}$= $J_{8,9}$=8.1, H_6,H_8); 7.63 (dd, $J_{2,1}$=8.4, $J_{2,4}$=2.1, H_2); 7.89 (d, $J_{1,2}$= 8.4, H_1); 8.15(d, $J_{4,2}$=2.1, H_4); 8.50 (s, OH,NH)
5	R^1=Cl R^2=H	10	87±4	203-4	6.88(dd $J_{7,6}$= $J_{7,8}$=7.5, $J_{7,5}$=$J_{7,9}$=1.2, H_7); 6.97(dd, $J_{2,1}$= 8.65, $J_{2,4}$=1.95, H_2); 7.31(dd, $J_{5,6}$=$J_{9,8}$=7.8, $J_{5,7}$=$J_{9,7}$=1.2, H_5, H_9); 7.56(dd, $J_{6,7}$=$J_{8,7}$=7.5, $J_{6,5}$=$J_{8,9}$=7.8, H_6,H_8); 7.85 (d, $J_{4,2}$= 1.95, H_4); 8.22(d, $J_{1,2}$= 8.65, H_1); 9.00 (s, OH,NH)
6	R^1=3-Cl R^2=5-OCH_3	8	94±4	201-2	6.49(dd, $J_{9,8}$=7.9, $J_{9,7}$=1.4, H_9); 6.75(t, $J_{8,9}$=7.9, $J_{8,7}$= 7.4, $J_{8,6}$=1.3, H_8); 7.04(t, $J_{7,8}$=7.4, $J_{7,6}$=8.1, $J_{7,9}$=1.4, H_7); 7.15(dd, $J_{2,1}$=8.6, $J_{2,4}$=2.0, H_2); 7.50(dd, $J_{6,7}$=8.1, $J_{6,8}$=1.3, H_6); 7.86(d, $J_{4,2}$=2.0, H_4); 8.13(d, $J_{1,2}$=8.6, H_1); 3.81(s OCH_3); 7.00 (s, OH,NH)
7	R^1=3-NO_2 R^2=7-OCH_3	7	93±3	233-5	7.05(m, J^*=8.8, H_5,H_9); 7.23(m, J^*=8.8, H_6, H_8); 7.68(dd, $J_{2,1}$=8.2, $J_{2,4}$=2.25,H_2); 7.81 (d $J_{1,2}$=8.2, H_1); 8.17(d $J_{4,2}$=2.25, H_4); 3.71(s OCH_3); 8.50 (s, OH,NH)
8	R^1=3-NO_2 R^2=5-COOH	8	85±3	323-5	6.35(dd, $J_{9,8}$=7.9, $J_{9,7}$=1.1, H_9); 6.51(t, $J_{7,6}$=7.65, $J_{7,8}$= 7.45, $J_{7,9}$=1.1,H_7); 7.78(dd, $J_{2,1}$=8.4, $J_{2,4}$=2.2, H_2); 8.08 (t, $J_{8,7}$=7.45, $J_{8,9}$=7.9, $J_{8,6}$=1.5, H_8); 8.19(d, $J_{1,2}$= 8.4, H_1); 8.27(dd, $J_{6,7}$=7.65, $J_{6,8}$=1.5, H_6); 8.32(d, $J_{4,2}$= 2.2, H_4); 7.01 (s, 2 OH,NH)
9	R^1=H R^2=5-COOH	9	82±3 (desc)	294	6.55(dd, $J_{4,3}$=$J_{9,8}$=7.8, $J_{4,2}$=$J_{9,7}$=1.15, H_4,H_9); 6.69(t, $J_{2,3}$= $J_{7,8}$=7.35, $J_{2,1}$=$J_{7,6}$=7.6, $J_{2,4}$=$J_{7,9}$=1.15, H_2,H_7); 8.01(t, $J_{3,2}$= $J_{8,7}$=7.35, $J_{3,4}$=$J_{8,9}$=7.8, $J_{3,1}$=$J_{8,6}$=1.6, H_3,H_8); 8.35(dd, $J_{1,2}$=$J_{6,7}$=7.6, $J_{1,3}$=$J_{6,8}$=1.6, H_1,H_6); 6.90(s, 2 OH,NH)
10	R^1=3-Cl R^2=7-CH_3	7	95±4	227-30	6.95(m, J^*=8.4, H_5,H_9); 7.08(dd, $J_{2,1}$=8.7, $J_{2,4}$=2.1, H_2); 7.34(m, J^*=8.4 H_6,H_8); 7.85(d, $J_{4,2}$=2.1, H_4); 8.23(d, $J_{1,2}$=8.7, H_1); 2.53(s, CH_3); 9.10(s, OH,NH)

[a]Time at which maximum yield was obtained. [b]Yield of isolated products by microwave irradiation ± standard deviation. [c]Melting point uncorrected. [d]J^*=$J_{5,6}$ + $J_{5,8}$ for AA 'xx' systems.

Table 2 Microanalysis data and molecular ion in mass spectra of substituted *N*-phenylanthranilic

		Calculated and experimental microanalyses						Mass spectra
		Experimental (%)			Calculated (%)			Molecular ion
Nº	Formula	C	H	N	C	H	N	*m/z*
1	$C_{13}H_{11}NO_2$	73.2	5.2	6.6	73.3	4.95	6.6	213
2	$C_{14}H_{13}NO_3$	69.1	5.4	5.8	68.9	5.4	5.5	243
3	$C_{15}H_{15}NO_2$	74.7	6.3	5.8	74.85	6.15	5.9	241
4	$C_{13}H_{10}N_2O_4$	60.5	3.9	10.85	60.4	4.1	10.9	258
5	$C_{13}H_{10}ClNO_2$	63.0	4.1	5.7	63.0	4.2	5.8	247/249
6	$C_{14}H_{12}ClNO_3$	60.55	4.4	5.0	61.0	4.5	4.9	277/279
7	$C_{14}H_{12}N_2O_5$	58.3	4.2	9.7	58.1	4.2	10.0	288
8	$C_{14}H_{10}N_2O_6$	55.6	3.3	9.3	55.6	3.4	9.0	302
9	$C_{14}H_{11}NO_4$	65.4	4.3	5.4	65.5	4.3	5.3	257
10	$C_{14}H_{12}ClNO_2$	64.25	4.6	5.35	65.3	4.65	5.8	261/263

General procedure: A mixture of 2-chlorobenzoic acid (0.01 mol), aniline derivative (0.02 mol), anhydrous potassium carbonate (0.005 mol), anhydrous copper sulfate (0.016 mol) and water 15 ml was placed into a 50 ml glass round bottom Pyrex flask and irradiated in a household microwave oven modified and equipped with an upright reflux condenser and mechanical stirrer for the time indicated in Table 1. At the end of the exposure to microwaves, the mixture was cooled to 10 °C and acidified with diluted HCl (1:1). The solid was filtered off, washed with water and extracted with boiling water. *N*-phenylanthranilic acid was recrystallised from EtOH/H_2O (1:1).

Yield 2.02 g (98±3 %). All experiments performed in this work were repeated five times. The yield reported represents an average of the obtained values for each reaction. The identity of the products was checked by elemental analyses, ^{1}H NMR spectra, mass spectra and by TLC using a mixture of *n*-butanol:acetic acid:water 6:1:1 as an eluent and compared with authentic samples. Melting points were compared with those reported in the literature.[22]

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