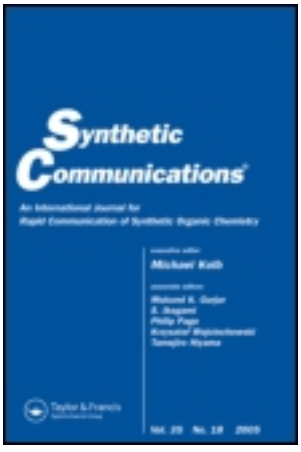

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Fast Synthesis of Substituted N-Phenylanthranilic Acids Using Ullmann Condensation Under Microwave Irradiation in Dry Media

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Fast Synthesis of Substituted N-Phenylanthranilic Acids Using Ullmann Condensation Under Microwave Irradiation in Dry Media

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Abstract: Substituted N-phenylanthranilic acids using the Ullmann condensation under microwave irradiation in dry media were obtained in good yield and short reaction times.

Keywords: Microwave irradiation, N-phenylanthranilic acid, Ullmann condensation

N-Phenylanthranilic acid and its derivatives have been studied as anti-inflammatory agents and as precursors of acridones and acridines that present bioactive properties such as anti-HIV, antibacterial, and antifungal activities.[1]

In previous work, the Ullmann condensation of 2-chlorobenzoic acid with aniline for the synthesis of N-phenylanthranilic acid was carried out using water as solvent.

Under these conditions, the yield obtained was 76% after a reaction time of 5 hours.[2]

This reaction was also performed under ultrasonic irradiation and a yield of 81% was obtained after 20 min.[3]

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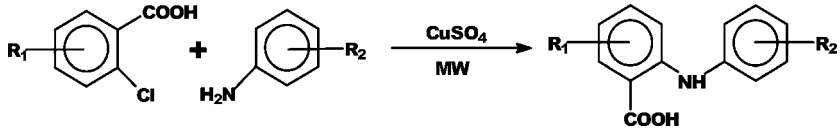
In the past decade, the use of microwave heating in organic synthesis, mainly in dry media, has seen exponential growth. At present, it is possible to carry out chemical reactions rapidly under mild conditions in a domestic, commercially available microwave oven. The risk of explosions was eliminated, the purity and the yield of the product increased, and the reaction times shortened by 10- to 500-fold; as such, these reaction are friendly to the environment.[4,5]

In the present work, we examined the effect of microwave irradiation on the Ullman condensation in dry media for the synthesis of N-phenylanthranilic acid derivatives.

RESULTS AND DISCUSSION

In previous work, Ullmann condensation conditions were optimized for the synthesis of N-phenylanthranilic acid in the presence of water as solvent. The best yield was obtained with 1 equivalent of potassium carbonate, 3% (by weight) of copper, and 2 equivalents of amine per mole of 2-chlorobenzoic acid, and a reaction time of 5 h.[2]



To short the reaction time and improve the yield we examined the effect of microwave irradiation on the Ullmann condensation in dry media using the reaction of 2-chlorobenzoic acid with aniline in the presence of anhydrous copper sulfate catalyst as a model to optimize the reaction conditions.

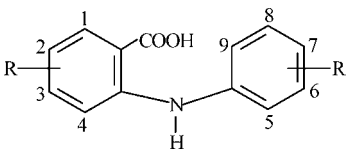
To establish the power necessary for the reaction, we scanned various levels from 240–800 W. In all cases we could observe that when exceeding 240 W, decomposition of the reaction products increased after 3 min. The best yield of N-phenylanthranilic acid (98%) was obtained at 90 s and 240 W.

To study the effect of the inorganic support in the synthesis of N-phenylanthranilic acid, bentonite was chosen. In a previous article this support was used successfully in the synthesis of diphenylamine under microwave irradiation.[6] In our case, however, no increase in yield was observed, and neither did the reaction time decrease.

Table 1 shows several N-phenylanthranilic acids synthesized under microwave irradiation at 240 W. The ^{1}H NMR data and melting points (uncorrected) reported are compared with those obtained using traditional conditions reported in literature. Table 2 reports microanalysis data and molecular ion in mass spectra that was obtained.

To check the possibility of intervention of specific (not purely thermal) microwave effects, the synthesis of these compounds was performed, changing

Table 1. Results of the synthesis of substituted N-phenylanthranilic acid under microwave irradiation at 240 W (physical and ^{1}HNMR data)



Substituents		Conditions		Yield (%)	Mp (°C), uncorrected		
No.	R	T (°C)[a]	t (min)	M.W.	Obt.	Lit.[7]	^{1}H NMR (DMSO-d_6/TMS_{int}), δ (ppm)
1	H	150	1.50	98	184	183–4	6.18 (dd H_4); 6.45 (t H_2); 7.05 (t H_7); 7.25 (d,d H_5, H_9); 7.50 (t H_3); 7.60 (t H_6,H_8); 7.78 (d,d H_1)
2	5-OCH_3	135	2.50	90	175–6	176	6.28 (dd H_4); 6.45 (t H_2); 6.52 (dd H_9); 6.70 (t H_8); 6.85 (t H_7); 7.52 (dd H_6); 7.63 (t H_3); 7.86 (dd H_1); 3.60 (s OCH_3)
3	6,7-CH_3	140	2.25	92	187–8	188–9	6.33 (dd H_4); 6.65 (t H_2); 7.11 (dd H_9); 7.25 (s H_5); 7.53 (dd H_8); 7.58 (t H_3); 7.95 (dd H_1); 1.8 (s CH_3-7); 2.3 (s CH_3-6)
4	3-NO_2; 7-CH_3	150	1.33	86	220–1	221	6.95 (dd H_5,H_9); 7.40 (dd H_6,H_8); 7.67 (d H_2); 7.91 (d H_1); 8.12 (s H_4); 2.35 (s CH_3)
5	3-NO_2	160	2	95	232–3	232–4	6.90 (t H_7); 7.35 (dd H_5,H_9); 7.55 (dd H_6,H_8); 7.63 (d H_2); 7.89 (d H_1); 8.15 (s H_4)
6	3-Cl	160	5	87	203–4	204	6.88 (t H_7); 6.97 (d H_2); 7.31 (dd H_5,H_9); 7.56 (dd H_6,H_8); 7.85(s H_4); 8.22(d H_1)

(*continued*)

Table 1. Continued

Substituents		Conditions		Yield (%) M.W.	Mp (°C), uncorrected		^{1}H NMR (DMSO-d_6/TMS_{int}), δ (ppm)
No.	R	T (°C)[a]	t (min)		Obt.	Lit.[7]	
7	3-Cl; 5-OCH_3	165	4	94	201–2	201	6.49 (dd H_9); 6.75 (t H_8); 7.04 (dd H_7); 7.15 (d H_2); 7.50 (dd H_6); 7.86 (s H_4); 8.13 (d H_1); (s OCH_3)
8	3-NO2; 7-OCH_3	155	2	93	233–5	235	7.05 (dd H_5,H_9); 7.23 (dd H_6,H_8); 7.68 (d H_2); 7.81 (d H_1); 8.17 (s H_4); 3.71 (s OCH_3)
9	3-NO2; 5-COOH	100	5	85	323–5	324–5	6.35 (dd H_9); 6.51 (t H_7); 7.78 (d H_2); 8.08 (t H_8); 8.19 (d H_1); 8.27 (dd H_6); 8.32 (s H_4)
10	5-COOH	115	3	82	294 (desc)	295 (desc)	6.55 (dd H_4,H_9); 6.69 (dd H_2,H_7); 8.01 (dd H_3,H_8); 8.35 (dd H_1,H_6)
11	3-Cl; 7-CH_3	125	2	95	227–30	226–31	6.95 (d H_5,H_9); 7.08 (d H_2); 7.34 (d H_6,H_8); 7.85 (s H_4); 8.23 (d H_1)

[a]Temperature at the end of the reaction.

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

No.	Formula	Experimental (%)			Calculated (%)			Molecular ion m/z
		C	H	N	C	H	N	
1	$C_{13}H_{11}NO_2$	73.22	5.20	6.57	73.28	4.95	6.63	213
2	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	68.92	5.44	5.50	243
3	$C_{15}H_{15}NO_2$	74.67	6.27	5.81	74.85	6.15	5.90	241
4	$C_{14}H_{12}N_2O_4$	61.76	4.44	9.72	61.80	4.42	9.70	272
5	$C_{13}H_{10}N_2O_4$	60.47	3.90	10.85	60.39	4.08	10.93	258
6	$C_{13}H_{10}ClNO_2$	63.04	4.07	5.66	62.97	4.22	5.83	247/249
7	$C_{14}H_{12}ClNO_3$	60.55	4.36	5.04	61.00	4.48	4.94	277/279
8	$C_{14}H_{12}N_2O_5$	58.33	4.20	9.72	58.10	4.18	9.96	288
9	$C_{14}H_{10}N_2O_6$	55.63	3.33	9.27	55.60	3.44	8.97	302
10	$C_{14}H_{11}NO_4$	65.37	4.31	5.44	65.46	4.27	5.30	257
11	$C_{14}H_{12}ClNO_2$	64.25	4.62	5.35	65.33	4.65	5.79	261/263

only the heating mode and using a thermoregulated oil bath for the same reaction times and temperatures. In all cases no reaction was detected (TLC).

EXPERIMENTAL

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 Panasonic domestic microwave oven, which allows the selection of output power up to 800 W. 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 a visualisation at 254-nm with a 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 DMSO-*d6* as a solvent. Mass spectra were recorded with a spectrometer TRIO 1000 Fisions Instruments by electronic impact (EI). Microanalyses were performed by the Servicio de Microanálisis del Instituto de Biorgánica de la Universidad de La Laguna, Tenerife, España.

Standard Procedure

Synthesis of N-phenylanthranilic Acid under Microwave Irradiation in Dry Media

A mixture of 2-chlorobenzoic acid (1.56 g, 0.01 mol), aniline (1.86 g, 0.02 mol), anhydrous potassium carbonate (0.69 g, 0.005 mol), and anhydrous

copper sulfate (0.25 g, 0.0016 mol) was completely triturated, placed into a Pyrex® open Erlenmeyer flask, and irradiated in a domestic microwave oven for 1–5 min. When the irradiation was stopped, the final temperature was measured with a $\pm 0.5\,^{\circ}C$ error by introducing a glass thermometer into the reaction mixture. The mixture was allowed to cool to $10\,^{\circ}C$ and acidified with diluted HCl (1 : 1). The solid was filtered off, washed with water, and extracted with boiling water. N-Phenylanthranilic acid was 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, ^1H NMR spectra, mass spectra, and by comparison of TLC with authentic samples.

Synthesis of N-Phenylanthranilic Acid under Microwave Irradiation in Dry Media with Bentonite as Support

Natural bentonite (Smectita) (4 g) was added to thus reaction mixture of as support. The bentonite is original from Cuba and has the following composition: SiO_2 (50.3%), Al_2O_3 (19.3%), CaO (11.4%), Fe_2O_3 (9.9%), MgO (3.0%), Na_2O (2.8%), K_2O (5%), MnO (0.4%).

CONCLUSIONS

The use of microwave irradiation enhanced the Ullmann condensation in dry media for the synthesis of N-phenylanthranilic. A number of N-phenylanthranilic acid derivatives was prepared in good yield in a very short reaction time.

ACKNOWLEDGMENT

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