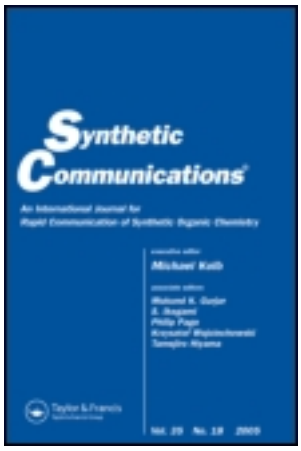


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of N-Phenylanthranilic Acid Derivatives Using Water as Solvent in the Presence of Ultrasound Irradiation

Maite L. Docampo Palacios [a] & Rolando F. Pellón Comdom [a]

[a] Centro de Química Farmacéutica, La Habana, Cuba

Version of record first published: 17 Aug 2006.

To cite this article: Maite L. Docampo Palacios & Rolando F. Pellón Comdom (2003): Synthesis of N-Phenylanthranilic Acid Derivatives Using Water as Solvent in the Presence of Ultrasound Irradiation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:10, 1771-1775

To link to this article: http://dx.doi.org/10.1081/SCC-120018938

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 10, pp. 1771–1775, 2003

Synthesis of *N*-Phenylanthranilic Acid Derivatives Using Water as Solvent in the Presence of Ultrasound Irradiation

Maite L. Docampo Palacios and Rolando F. Pellón Comdom*

Centro de Química Farmacéutica, La Habana, Cuba

ABSTRACT

An improved synthesis of *N*-phenylanthranilic acid using water as solvent can be achieved by ultrasound irradiation. A number of *N*-phenylanthranilic acids were prepared in good yields in a very short reaction time.

The synthesis of *N*-phenylanthranilic acid has been reported using DMF[1] and MEK[2] under sonication. Sonochemistry is an important method for increasing reaction rates of chemical reactions, thus allowing in many cases, for milder reaction conditions. In homogeneous systems, bond-breaking often initiates the sonochemical reaction. In heterogeneous

*Correspondence: Rolando F. Pellón Comdom, Centro de Química Farmacéutica, Apartado 16042, La Habana, Cuba; Fax: (537) 336471; E-mail: pellonrf@cqf.co.cu.

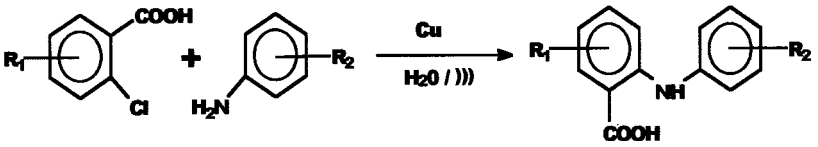
DOI: 10.1081/SCC-120018938 0039-7911 (Print); 1532-2432 (Online)

systems there is the additional benefit that ultrasound is a very efficient tool for increasing mass transport.[3–5]

A study of some parameters which influence the Ullmann-Goldberg reaction of *o*-chlorobenzoic acid and substituted anilines for the synthesis of *N*-phenylanthranilic acids was done, showing that these acids can be obtained efficiently using water as solvent, in presence of copper as catalyst and potassium carbonate as acid acceptor.[6]

The use of pyridine as cocatalyst has been reported by us to obtain *N*-phenylanthranilic acid in water or amyl alcohol as solvent in order to reduce the reaction times.[7]

In the present work we decided to examine the effect of ultrasound on the Ullmann-Goldberg reaction in the synthesis of *N*-phenylanthranilic acids from *o*-chlorobenzoic acid and substituted anilines using water as solvent.



RESULTS AND DISCUSSION

In a previous communication we reported the synthesis of *N*-phenylanthranilic acid by the Ullmann-Goldberg reaction using 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 *o*-chlorobenzoic acid in 5 h reaction time.[6]

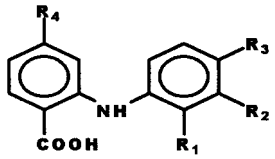
When we used these conditions for the reaction of *o*-chlorobenzoic acid with aniline under ultrasonic irradiation the *N*-phenylanthranilic acid was obtained in 81% yield after only 20 min.

It is noteworthy that with longer ultrasonic irradiation times the yield of the acid remains constant. With less than 20 min irradiation the reaction yield is reduced, e.g., 15 min gives a yield of only 58%.

Table 1 shows the *N*-phenylanthranilic acid derivatives synthesized using water as solvent with and without ultrasonic irradiation and its corresponding melting points.

All experiments performed in this work were repeated five times. The yields reported represent an average of the values obtained for each reaction with an standard deviation of 1.5 in all cases.

Table 1. Results of the syntheses of *N*-phenylanthranilic acid derivatives.



	R				% Yield (using water as solvent)		M.p. (°C) uncorrected	
No.	R_1	R_2	R_3	R_4	5 h Reflux	20 min Ultras.	Lit.	Obt.
1	H	H	H	H	86	88	183–84[8]	184
2	H	H	COOH	H	63	65	290[9]	289–90
3	COOH	H	H	H	79	81	294[10]	293–94
4	H	H	NO_2	Cl	58	61	235[11]	234–35
5	NO_2	H	H	H	78	79	219[9]	218–219
6	H	OCH_3	H	H	80	82	132[12]	131–32
7	H	H	OCH_3	H	86	90	181[13]	181–82

Calculated and experimental microanalysis

		Calculated (%)		Experimental (%)	
No.	Formula	C	H	C	H
1	$C_{13}H_{11}NO_2$	73.24	5.16	73.38	5.28
2	$C_{14}H_{11}NO_4$	65.37	4.28	65.49	4.19
3	$C_{14}H_{11}NO_4$	65.37	4.28	65.21	4.34
4	$C_{13}H_9ClN_2O_4$	53.33	3.08	53.19	3.18
5	$C_{13}H_{10}N_2O_4$	60.46	3.88	60.26	4.01
6	$C_{14}H_{13}NO_3$	69.14	5.35	69.26	5.41
7	$C_{14}H_{13}NO_3$	69.14	5.35	68.91	5.23

With pyridine as cocatalyst the reaction between *o*-chlorobenzoic acid and aniline in water to give *N*-phenylanthranilic acid is accelerated and complete after 2 h.[7]

Using the conditions mentioned in this article i.e., 1 eq. K_2CO_3/mole *o*-chlorobenzoic acid, 2 moles of aniline, Cu powder (3% w/w referred to *o*-chlorobenzoic acid) but adding pyridine as cocatalyst (15% w/w referred to *o*-chlorobenzoic) in presence of ultrasonic irradiation (20 kHz) the reaction was complete after 15 min.

As was previously mentioned using 15 min without pyridine only 58% yield was obtained. So this fact demonstrated that in presence of ultrasonic irradiation pyridine catalyzed the reaction.

These conditions were employed for each derivative obtained in Table 1 using 15 min reaction time. In all cases, the yield obtained was similar to those obtained after 20 min, when no pyridine was present.

EXPERIMENTAL PART

Standard Procedure

A mixture of *o*-chlorobenzoic acid (6.26 g; 0.04 mol), aniline (7.45 g; 0.08 mol), anhydrous potassium carbonate (2.76 g; 0.02 mol), copper powder (0.2 g), pyridine (1.58 g; 0.02 mol) and water 25 mL was treated for 20 min with ultrasonic irradiation using a sonic horn at 20 kHz. The reaction mixture was cooled to 10°C and acidified with diluted HCl (1:1). The solid was filtered and washed with water, and extracted with boiling water. The *N*-phenylanthranilic acid obtained can be recrystallized of $EtOH/H_2O$ (1:1).

CONCLUSIONS

The use of ultrasound irradiation accelerated the synthesis of *N*-phenylanthranilic acid using water as solvent. A number of *N*-phenylanthranilic acid derivatives were prepared in good yield in a very short reaction time.

REFERENCES

1. Carrasco, R.; Pellón, R.F.; Elguero, J.; Goya, P.; Páez, J.A. The use of ultrasound in the synthesis of *N*-arylanthranilic acids by the Ullmann-Goldberg reaction. Synth. Commun. **1989**, *19* (11&12), 2077–2080.
2. Hanoun, J.P.; Tensglia, A. A convenient synthesis of *N*-arylanthranilic acid using ultrasound in the Ullmann-Goldberg condensation. Synth. Commun. **1995**, *25* (16), 2443–2448.
3. Abdulla, R.F. Ultrasound in organic synthesis. Aldrichimica Acta **1988**, *21*, 31–42.

4. Pestman, M.J.; Engberts, J.B.; Jong, F. Sonochemistry: theory and applications. Recueil des Travaux Chimiques des Pays-Bas. **1994**, *113*, 533–542.
5. Goldberg, Y. Sturkovich, R.; Lukevics, E. Heterocyclic sonochemistry. Heterocycle **1989**, *29* (3), 597–627.
6. Pellón, R.F.; Carrasco, R.; Rodés, L. Synthesis of *N*-phenylantranilic acids using water as solvent. Synth. Commun. **1993**, *23* (10), 1447–1453.
7. Pellón, R.F.; Mamposo, T.; Carrasco, R.; Rodés, L. Use of pyridine as cocatalyst in the synthesis of *N*-phenylanthranilic acid. Synth. Commun. **1996**, *26* (20), 3877–3883.
8. Allen, C.F.H.; McKee, G.H.W. Acridone. Org. Synth. **1939**, *19*, 6–9.
9. Ullmann, F. On arylanthranilic acid. Ann. **1907**, *355*, 312–358.
10. Drozdov, N.S.; Bekhli, A.F. ms-Derivs of acridine(XI) prepn. of acridone and 9-chloroacridone and their derivs. J. Gen. Chem. (USSR) **1938**, *8*, 1505–1511.
11. Aggarwal, M.L.; Sen-Gupta, I.; Ahmad, B. Acridine derivs. (I). J. Indian Chem. Soc. **1945**, *22*, 41–43.
12. Lehmstedt, K.; Schrader, K. Acridine(XVI) preparation of 1- and 3-substituted acridones from 3′ substituted diphenylamine-2-carboxylic acids. Chem. Ber. **1937**, *70 B*, 838–849.
13. Bauer, K. Reactions of acridine. Chem. Ber. **1950**, *83*, 10–14.

Received in the USA August 16, 2002

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016