Microwave-assisted synthesis of 2-phenoxybenzoic acids

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Substituted 2-phenoxybenzoic acid derivatives were synthesised in high yield and in short reaction times using the Ullmann condensation of 2-chlorobenzoic acid with phenol derivatives under microwave irradiation in dry media.

Keywords: ullmann condensation, microwave irradiation, 2-phenoxybenzoic acids, copper sulfate, catalysis

There is high demand for new methods for the synthesis of substituted 2-phenoxybenzoic acids owing to their importance as bactericides.[1] Furthermore, they are important intermediates in the synthesis of bioactive xanthones.[2] The diaryl ether motif is abundant in a number of natural products, including important medicinal compounds such as vancomycin[3] and chloropeptins.[4]

Ullmann and Wagner described more than a century ago the reactivity of the halogen in 2-chlorobenzoic acids towards anilines and phenols, in the presence of potassium carbonate and a copper catalyst leading to the synthesis of aryl amines and aryl ethers.[5]

The classical arylation of phenols with aryl halides under Ullmann conditions using copper powder or copper salts requires harsh reaction conditions as a result of the poor nucleophilicity of phenoxide and the low reactivity of the aryl halide involved. The reactions have to be carried out in a temperature range of 120–250°C by using a high boiling solvent or neat reagents over an extended period of time.[6] The reaction of 2-halogenobenzoic acids with phenols using copper salts or metal as catalyst is a particular case of the Ullmann condensation. Several alcohols[7] have been satisfactorily used as solvents in this reaction. The usual procedure for the synthesis of 2-phenoxybenzoic acid using the Ullmann condensation is to reflux a mixture of the 2-halogenobenzoic acid with a phenol in a solvent, often amyl alcohol, in the presence of copper as catalyst and a base such as potassium carbonate to remove the hydrogen halide liberated in the reaction.[8] The dry method, developed by Ullmann,[9] is commonly used when the solvents do not bring good results.

In a previous paper,[10] phenols were shown to react in three hours with 2-chlorobenzoic acid in the presence of copper and pyridine as catalysts to from substituted 2-phenoxybenzoic acids by Ullmann condensation using water as the solvent. When the condensation was accomplished with water as solvent but without pyridine the corresponding 2-phenoxybenzoic acid was not obtained. The optimum conditions were: 2-chlorobenzoic acid: phenol: potassium carbonate: pyridine, as 1: 2.5: 1.5: 0.75 in the presence of Cu 3% (by weight) related to 2-chlorobenzoic acid in 2.4 h reaction time. Several other 2-phenoxybenzoic acid derivatives were prepared using these conditions.

The application of microwave heating in organic chemistry has had a considerable growth in the last decade.[11] Microwave reactions under solvent-free conditions are attractive in offering reduced pollution and also offer low cost together with simplicity in processing and handling.[12,13]

In order to decrease the reaction times and improve the yields, we examined the effect of microwave irradiation on the Ullmann condensation in dry media taking as a model the reaction of 2-chlorobenzoic acid with phenol and anhydrous copper sulfate as a catalyst using the optimum concentration conditions above mentioned. In this work, the effect of microwave irradiation in the Ullmann condensation under solvent-free conditions was examined for the synthesis of 2-phenoxybenzoic acids and their derivatives.

To establish the power necessary for the reaction, we scanned various levels from 240 to 800 W. In all cases we observed that when exceeding 560 W decomposition of the reaction products increased after 2 minutes. The best yield of 2-phenoxybenzoic acid (83%) was obtained at 3 minutes and 560 W. It is interesting to note that in this case it was not necessary to use pyridine as co-catalyst.

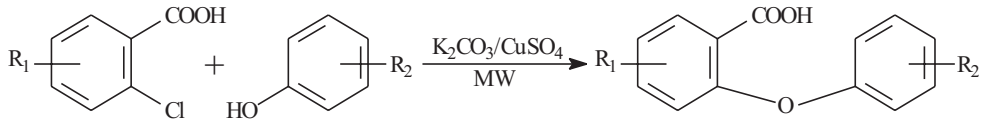
Table 1 shows several 2-phenoxybenzoic acids synthesised under microwave irradiation at 560 W. The reported ^{1}H NMR data and melting points (uncorrected) are compared with those obtained using traditional conditions reported in the literature. Table 2 reports microanalysis data and molecular ion data obtained from mass spectra.

In order to check the possibility of intervention of specific (non-purely thermal) microwave effects, the synthesis of these compounds was performed, changing only the heating mode, using a thermo-regulated oil bath for the same reaction times and temperatures as involved in the microwave experiments. In all cases no reaction was detected by TLC. The effect of microwaves could be due to an increase in material-wave interactions during the course of the reaction.[14-16] This is because the polarity of the system is enhanced from the ground state to the transition state and so microwave irradiation diminishes the activation energy, accelerating the reaction.[17]

Experimental

General

Starting materials came from commercial sources. Melting points were measured using a Gallenkamp melting point 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 Watts. TLC analyses were run on 60 F254 silica gel chromatoplates from Merck using a mixture of ethyl acetate: chloroform: acetic acid (8: 6: 1) as an eluent and visualisation by 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 DMSO-*d6* as a solvent. Mass spectra were recorded with a TRIO 1000 FISIONS Instruments spectrometer by electron impact (EI). Microanalyses were performed



Scheme

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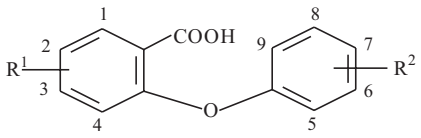
Table 1 Results of the synthesis of substituted 2-fenoxibenzoic acid under microwave irradiation



No	R^1,R^2	T[a]/°C	t[b]/min	Yield/%[c]	M.p. [d]/m.p. (lit)/°C	H^1 NMR δd (ppm), J/Hz[e]
1	$R^1 = R^2 = H$	120	3	83	110-12/113 [18]	7.85(dd, $J_{1,2}$ = 8.0, $J_{1,3}$ = 1.8, H_1); 7.51(dt, $J_{3,2}$ = 8.1, $J_{3,4}$ = 8.3, $J_{3,1}$ = 1.8, H_3); 7.42(dd, $J_{6,5} = J_{8,9}$ = 8.4, $J_{6,7} = J_{8,7}$ = 7.7, H_6, H_8); 7.36(dt, $J_{2,1}$ = 8.0, $J_{2,3}$ = 8.2, $J_{2,4}$ = 1.1, H_2); 7.25(dd, $J_{7,6} = J_{7,8}$ = 7.7, $J_{7,5} = J_{7,9}$ = 1.5, H_7); 7.15 ($J_{4,3}$ = 8.3, $J_{4,2}$ = 1., H_4); 6.90 (dd, $J_{5,6} = J_{9,8}$ = 8.4, $J_{5,7} = J_{9,7}$ = 1.5, H_5, H_9)
2	R^1 = 3-Cl R^2 = H	150	3	82	114-16/115[18]	7.86(d, $J_{1,2}$ = 8.2, H_1); 7.60(dd, $J_{6,5} = J_{8,9}$ = 8.5, $J_{6,7} = J_{8,7}$ = 7.6, H_6, H_8); 7.49(dd, $J_{2,1}$ = 8.2 $J_{2,4}$ = 2.0 H_2); 7.18(dd, $J_{7,6} = J_{7,8}$ = 7.6, $J_{7,5} = J_{7,9}$ 1.2, H_7); 7.01(d, $J_{4,2}$ = 2.0, H_4); 6.88(m, $J_{5,6} = J_{9,8}$ = 8.5, $J_{5,7} = J_{9,7}$ = 1.2, H_5, H_9)
3	R^1 = H R^2 = 5-Cl	130	3	77	114-15/114[18]	7.82(dd, $J_{1,2}$ = 7.9, $J_{1,3}$ = 1.9,H_1); 7.63(dt, $J_{3,4}$ = 8.1, $J_{3,2}$ = 7.7, $J_{3,1}$ = 1.9, H_3); 7.50(dd, $J_{6,7}$ = 8.2 $J_{6,8}$ = 1.5 H_6); 7.38(dt, $J_{8,7}$ = 8.3, $J_{8,9}$ = 8.4, $J_{8,6}$ = 1.5 H_8); 7.33(dt, $J_{2,1}$ = 7.9, $J_{2,3}$ = 7.7, $J_{2,4}$ = 1.2, H_2); 7.25(dt, $J_{7,6}$ = 8.2, $J_{7,8}$ = 8.3, $J_{7,9}$ = 1.4, H_7); 7.11(dd, $J_{4,3}$ = 8.1, $J_{4,2}$ = 1.2, H_4); 6,97 (dd, $J_{9,8}$ = 8.4, $J_{9,7}$ = 1.4, H_9)
4	R^1 = 3-Cl R^2 = 5-Cl	140	4	78	164-65/163[18]	7.88(dd, $J_{1,2}$ = 8.3, H_1); 7.58 (dd, $J_{6,7}$ = 8.1, $J_{6,8}$ = 1.7 H_6); 7.34(m, $J_{8,7}$ = 8.0, $J_{8,9}$ = 7.8, $J_{8,6}$ = 1.6, $J_{2,1}$ = 8.3, $J_{2,4}$ = 2.0, H_8, H_2); 7.23(dt, $J_{7,6}$ = 8.1, $J_{7,8}$ = 8.0, $J_{7,9}$ = 1.4, H_7); 6,99 (dd, $J_{9,8}$ = 8.1, $J_{9,7}$ = 1.4, H_9); 6.91(d, $J_{4,2}$ = 2.0, H_4)
5	R^1 = H R^2 = 5,7-Cl	125	7	75	166-67/166[18]	7.81(dd, $J_{1,2}$ = 8.15, $J_{1,3}$ = 1.8,H_1); 7.75(d, $J_{6,8}$ = 2.6, H_6); 7.58(dt, $J_{3,2}$ = 7.9, $J_{3,4}$ = 7.7, $J_{3,1}$ = 1.8, H_3); 7.45(dd, $J_{8,9}$ = 8.5, $J_{8,6}$ = 2.6, H_8); 7.41(dt, $J_{2,1}$ = 8.15, $J_{2,3}$ = 7.9, $J_{2,4}$ = 1.3, H_2); 7.12(dd, $J_{4,3}$ = 7.7, $J_{4,2}$ = 1.3, H_4); 6,90(d, $J_{9,8}$ = 8.5, H_9)
6	R^1 = 3-Cl R^2 = 5,7-Cl	150	10	75	169-70/169[18]	7.90(d, $J_{1,2}$ = 8.3, H_1); 7.71(d, $J_{6,8}$ = 2.4, H_6); 7.39(dd, $J_{8,9}$ = 8.7, $J_{8,6}$ = 2.4, H_8); 7.36(dd, $J_{2,1}$ = 8.3, $J_{2,4}$ = 1.9, H_2); 7.07(d, $J_{4,2}$ = 1.9, H_4); 6,96 (d, $J_{9,8}$ = 8.7, H_9)
7	R^1 = H R^2 = 5-CH_3	135	3	79	133-34/133[18]	7.83(dd, $J_{1,2}$ = 8.1, $J_{1,3}$ = 1.7,H_1); 7.62(dt, $J_{3,2}$ = 8.3, $J_{3,4}$ = 8.0, $J_{3,1}$ = 1.7, H_3); 7.39(dt, $J_{2,1}$ = 8.1, $J_{2,3}$ = 8.3, $J_{2,4}$ = 2.6, H_2); 7.30(m, $J_{6,7}$ = 7.3, $J_{6,8}$ = 1.2, $J_{8,7}$ = 7.7, $J_{8,9}$ = 7.8, H_6,H_8); 7.17(dd, $J_{4,3}$ = 8.0, $J_{4,2}$ = 2.6, H_4); 7.02(dt, $J_{7,6}$ = 7.3, $J_{7,8}$ = 7.7, $J_{7,9}$ = 1.2, H_7); 6.88 (dd, $J_{9,8}$ = 7.8, $J_{9,7}$ = 1.2, H_9); 2.23(s, CH_3)
8	R^1 = H R^2 = 6-CH_3	130	3	80	94-96/95[18]	7.81(dd, $J_{1,2}$ = 8.2, $J_{1,3}$ = 1.5,H_1); 7.67(dt, $J_{3,2}$ = 7.9, $J_{3,4}$ = 7.8, $J_{3,1}$ = 1.5, H_3); 7.42(dt, $J_{2,1}$ = 8.2, $J_{2,3}$ = 7.9, $J_{2,4}$ = 2.7, H_2); 7.32(t, $J_{8,7}$ = 8.4, $J_{8,9}$ = 8.6, H_8); 7.21 (dd, $J_{4,3}$ = 7.8, $J_{4,2}$ = 2.7, H_4); 6.90 (dt, $J_{7,8}$ = 8.4, $J_{7,5} = J_{7,9}$ = 1.1, H_7); 6.85 (m, $J_{9,8}$ = 8.6, $J_{5,7} = J_{9,7}$ = 1.1, $J_{5,9}$ = 2.1, H_5,H_9); 2.32(s, CH_3)
9	R^1 = H R^2 = 7-CH_3	120	3	81	117-19/118[18]	7.84(dd, $J_{1,2}$ = 7.7, $J_{1,3}$ = 1.3,H_1); 7.61(dt, $J_{3,2}$ = 8.1, $J_{3,4}$ = 7.9, $J_{3,1}$ = 1.3, H_3); 7.37(dt, $J_{2,1}$ = 7.7, $J_{2,3}$ = 8.1, $J_{2,4}$ = 2.3, H_2); 7.28(m, J^* = 8.7, H_6,H_8); 7.19 (dd, $J_{4,3}$ = 7.9, $J_{4,2}$ = 2.3, H_4); 6.89(m, J^* = 8.7, H_5,H_9); 2.27(s, CH_3)

[a]Temperature at the end of the reaction. [b]Time at which maximum yield was obtained.
[c]All experiments performed in this work were repeated five times. The yield reported represents an average of the values for each reaction [d]Melting point uncorrected. [e]$J^* = J_{5,6} + J_{5,8}$ for the AA'XX' system.

Table 2 Microanalyses data and molecular ion data in the mass spectra of substituted 2-penoxybenzoic acid

		Calculated and experimental microanalyses				Mass spectra[18]
		Experimental (%)		Calculated (%)		Molecular ion
No	Formula	C	H	C	H	*m/z*
1	$C_{13}H_{10}O_3$	72.8	4.8	72.9	4.7	214
2	$C_{13}H_9ClO_3$	62.9	3.85	62.8	3.65	248/250
3	$C_{13}H_9ClO_3$	62.9	3.8	62.8	3.65	248/250
4	$C_{13}H_8Cl_2O_3$	54.7	2.9	55.15	2.85	282/284/286
5	$C_{13}H_8Cl_2O_3$	55.4	3.2	55.15	2.85	282/284/286
6	$C_{13}H_7Cl_3O_3$	48.6	2.3	49.2	2.2	316/318/320/322
7	$C_{14}H_{12}O_3$	73.5	5.4	73.7	5.3	228
8	$C_{14}H_{12}O_3$	73.85	5.0	73.7	5.3	228
9	$C_{14}H_{12}O_3$	73.5	5.45	73.7	5.3	228

by the Microanalyses service "Instituto de Biorgánica" University of La Laguna, Tenerife, Spain.

A mixture of the 2-chlorobenzoic acid derivative (10 mmoles), phenol derivative (25 mmoles), anhydrous potassium carbonate (15 mmoles), anhydrous copper sulfate (8 mmoles), and 3 drops of DMF, was completely triturated, placed into a Pyrex-glass open Erlenmeyer flask and irradiated in a domestic microwave oven for 3-10 minutes using intervals of 30 s at 560 W (Table 1). When the irradiation was stopped, the final temperature was measured by introducing a glass thermometer with a ±0.5°C error into the reaction mixture. The mixture was allowed to cool to 10°C and was acidified with diluted HCl (1: 1). The solid was filtered off, washed with water and dissolved in aqueous sodium hydroxide solution (10%). The solution was acidified with AcOH: H_2O (1: 3) crystallising the corresponding 2-phenoxybenzoic acid which was recrystallised 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 for each reaction. The identity of the products was checked by elemental analyses, ^{1}H NMR spectra, mass spectra and by comparison with authentic samples on TLC.

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