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Synthesis of 2-Phenoxyquinoline-3-carboxylic acids by Microwave Assisted Ullmann Condensation

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Ullmann condensation of 2-chloroquinoline-3-carboxylic acids with substituted phenols yielded substituted 2-phenoxyquinoline-3-carboxylic acids in high yield under microwave conditions. The structures were confirmed by spectral and analytical data. The compounds were screened for their antimicrobial potency.

Key Words: Microwave irradiation, Ullmann condensation, Aryl ethers, Heterocyclic compounds.

INTRODUCTION

Ullmann and Wagner described the reactivity of the halogen in 2-chlorobenzoic acids towards anilines and phenols in presence of potassium carbonate and a copper catalyst leading to the synthesis of aryl amines and aryl ethers[1]. The diverse nature of chemical reactions involves different chemical strategies directed towards environmentally sound and eco-friendly methods and envisages minimum hazards while designing the new process.

To achieve this goal, an alternative reaction condition to accomplish desired chemical transformation with elimination of the hazardous conventional solvents, microwave irradiation (MWI) has gained popularity as a powerful non-conventional tool for rapid, efficient and eco-friendly synthesis of a variety of compounds because of the selective absorption of microwave energy by polar molecules[2].

The application of microwave irradiation to provide enhanced reaction rate, high yield and cleaner products[3-7] leading to the formation of carbon-hetero atom bonds under solvent free conditions has had a considerable growth in the last decade.

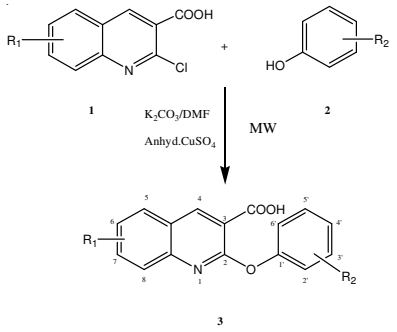
Since 2-chloro-3-formylquinolines are potential precursors for many heterocyclic compounds, we report here an elegant and simple microwave assisted synthesis of the aryl ethers *viz.*, 2-phenoxyquinoline-3-carboxylic acids (3a -3h). Our attempt to synthesize the same products in conventional method went in vain with an inappreciable yield.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on Bruker AVIII 500 MHz NMR spectrophotometer. TMS was used as an internal standard and the solvent was either $CDCl_3$ or DMSO-d_6 according to the solubility of the product. Mass spectra were recorded on Shimadzu QP2010 Plus GC-MS system. The reactions were carried out in an LG domestic microwave oven which provides a maximum of 800 w power.

General procedure for the synthesis of 2-phenoxyquinoline-3-carboxylic acids (3a-h): The starting compounds 2-chloroquinoline-3-carboxylic acids (**1**) were prepared by oxidation of the respective 2-chloro-3-formylquinolines using alkaline $KMnO_4$.

A mixture of 2-chloroquinoline-3-carboxylic acid derivative (10 mmol), phenol derivative (25 mmol), anhydrous potassium carbonate (15 mmol), anhydrous copper sulphate (8 mmol) and 5 drops of DMF, was completely triturated, taken into a Pyrex-glass Erlenmeyer flask and irradiated in a domestic microwave oven for 4-8 min with 30 s intervals at 480 w. After the completion of the reaction as inferred by TLC, the mixture was cooled to 10 ºC and purified by dissolving in aqueous sodium hydroxide solution (10 %) and then regenerating by adding AcOH : H_2O (1:3) (**Scheme-I**).



	R_1	R_2
3a	H	H
b	H	2'-CH_3
c	H	4'-CH_3
d	6-CH_3	H
e	6-CH_3	2'-CH_3
f	6-CH_3	4'-CH_3
g	8-CH_3	4'-CH_3
h	8-CH_3	2'-Cl

Scheme-I

RESULTS AND DISCUSSION

It was observed that above 480 w, the reaction mixture was decomposed. The compounds were characterized by IR, ^{1}H NMR and mass spectral studies and the analytical data were found to be in agreement with theoretically calculated values (Tables 1 and 2).

Conclusion

We have tried a simple and convenient onestep process to synthesize heterocyclic aromatic phenoxyethers. All the synthesized compounds were screened for their invitro antibacterial activity against the Gram +ve bacterium, *Staphylococcus aureus* and the Gram-ve bacterium *Salmonella typhi* by disc

TABLE-1
CHARACTERIZATION DATA OF 3

Compound*	m.p. (°C)	Yield (%)	Time (min)	m.f. (m.w.)	Elemental analysis (%): Found (calcd.)		
					C	H	N
3a	228-30	78	4	$C_{16}H_{11}NO_3$ [265]	72.51 (72.45)	4.22 (4.18)	5.21 (5.28)
3b	218-20	72	8	$C_{17}H_{13}NO_3$ [279]	73.23 (73.11)	4.73 (4.69)	5.11 (5.02)
3c	>300	70	6	$C_{17}H_{13}NO_3$ [279]	73.19 (73.11)	4.76 (4.69)	5.06 (5.02)
3d	164-66	79	8	$C_{17}H_{13}NO_3$ [279]	73.32 (73.11)	4.63 (4.69)	5.13 (5.02)
3e	>300	68	8	$C_{18}H_{15}NO_3$ [293]	73.83 (73.71)	5.13 (5.15)	4.71 (4.78)
3f	198-200	63	6	$C_{18}H_{15}NO_3$ [293]	73.92 (73.71)	5.19 (5.15)	4.75 (4.78)
3g	174-76	70	8	$C_{18}H_{15}NO_3$ [293]	73.85 (73.71)	5.23 (5.15)	4.71 (4.78)
3h	178-80	56	8	$C_{17}H_{12}NO_3Cl$ [313]	64.89 (65.08)	3.72 (3.86)	4.37 (4.46)

*3a, e, h are soluble in $CDCl_3$ and others are in DMSO

TABLE-2
SPECTRAL DATA OF THE SYNTHESIZED 2-PHENOXYQUINOLINE-3-CARBOXYLIC ACIDS (**3a-h**)

S. No.	Compound	IR (KBr, cm^{-1})	^{1}H NMR (δ/ppm)	Mass
1	3a	1262 (C-O str), 2822-3357 (broad, carboxylic -OH), 3080 (aromatic C-H str)	9.13 (s, 1H, C_4-H), 7.95 (d, 1H, C_8-H), 7.76 (d, 2H, C_2'and C_6'-H), 7.54-7.51 (m, 3H, C_5, C_6 and C_7-H), 7.39-7.32 (m, 3H, C_3', C_4', C_5'-H)	265 (M^+), 221(M-44), 128 (M-137)
2	3b	1253 (C-Ostr), 2751-3385 (broad, carboxylic -OH), 3065 (arom C-H str)	8.84 (s, 1H, C_4-H), 8.07 (d, 1H, C_8-H), 7.72 (d, 1H, C_5-H), 7.60-7.50 (m, 2H, C_6 and C_7-H), 7.25-7.09 (m, 4H, C_3', C_4', C_5' and C_6'-H), 2.35 (s, 3H, C_2'-CH_3)	
3	3c		8.92 (s, 1H, C_4-H), 8.16 (d, 1H, C_8-H), 7.62 (d, 1H, C_5-H), 7.61-7.52 (m, 2H, C_6 and C_7-H) 7.56-6.63 (m, 4H, C_2', C_3', C_5' and C_6'-H), 2.34 (s, 3H, C_4'-CH_3)	
4	3d	2811-3390 (broad, carboxylic -OH), 3078 (arom CH str), 1258 (C-O str)	8.14 (s, 1H, C_4-H), 7.41 (1H, d, C_8-H), 7.35 (d, 1H, C_7-H), 7.39 (s, 1H, C_5-H), 7.19-6.75 (m, 5H, Ar-H), 2.40 (s, 3H, C_6-CH_3)	
5	3e		8.97 (s, 1H, C_4-H), 8.04 (d, 1H, C_8-H), 7.73 (d, 1H, C_7-H), 7.62 (s, 1H, C_5-H), 7.47-7.07 (m, 4H, C_3', C_4', C_5' and C_6'-H), 2.51 (s, 3H, C_6-CH_3), 2.40 (s, 3H, C_2'-CH_3)	
6	3f		8.89 (s, 1H, C_4-H), 8.71 (d, 1H, C_8-H), 8.62 (d, 1H, C_7-H), 7.79 (s, 1H, C_5-H), 7.55-6.9 (m, 4H, C_2', C_3', C_5', C_6'-H), 2.46 (s, 3H, C_6-CH_3), 2.40 (s, 3H, C_4'-CH_3)	
7	3g		8.49 (s, 1H, C_4-H), 7.72-7.47 (m, 3H, C_5, C_6 and C_7-H), 7.23-7.06 (m, 4H, C_2', C_3', C_5'and C_6'-H), 2.43 (s, 3H, C_8-CH_3), 2.34 (s, 3H, C_4'-CH_3)	
8	3h		9.09 (s, 1H, C_4-H), 7.79-7.55 (m, 3H, C_5, C_6, C_7-H), 7.49-7.30 (m, 4H, C_3', C_4', C_5' and C_6'-H), 2.35 (s, 3H, C_8-CH_3)	313(M^+), 315(M+2). 269(M-44)

TABLE-3
ANTIBACTERIAL DATA-ZONES OF INHIBITION (mm)

Compound	*Staphylococcus aureus* (mm)				*Salmonella typhi* (mm)			
	50 (μg/mL)	100 (μg/mL)	150 (μg/mL)	200 (μg/mL)	50 (μg/mL)	100 (μg/mL)	150 (μg/mL)	200 (μg/mL)
3a	4	5	8	8	0	0	0	0
3b	5	6	6	8	2	2	3	4
3c	3	3	4	4	3	5	5	6
3d	6	6	7	8	2	4	4	6
3e	2	4	5	4	16	16	18	19
3f	0	2	2	2	13	14	17	20
3g	10	14	16	17	8	9	10	10
3h	0	0	0	0	2	4	4	5
Streptomycin	20	28	-	-	22	30	-	-
Gentamycin	22	29	-	-	24	32	-	-

diffusion method and compared with the standards streptomycin and gentamycin (Table-3). All the tested compounds were evaluated at 50-200 µg/mL concentrations. The culture media used was Muller Hinton agar. The zone of inhibition was measured in mm after 24 h of incubation at 37 ºC.

An examination of data revealed that **3g** has shown better activity against *Staphylococcus aureus* (10-17 mm). Compound **3e** (16-19 mm) and **3f** were found to be more potent against *Salmonella typhi* with respect to streptomycin (13-20 mm).

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