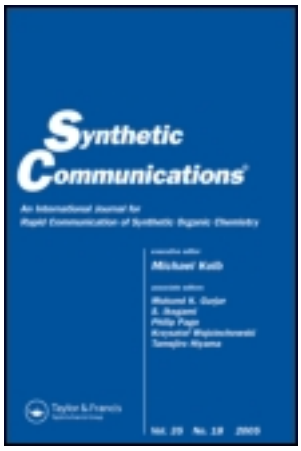

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Synthesis of 11*H*-Pyrido[2,1-b]quinazolin-11-one and Derivatives Using Ultrasound Irradiation

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ABSTRACT

An improved synthesis of 11*H*-pyrido[2,1-b]quinazolin-11-one and derivatives, by the condensation of 2-chlorobenzoic acid and 2-aminopyridine derivatives in *N*,*N*-dimethylformamide (DMF) is reported using ultrasound irradiation. The derivatives were prepared in good yield and in a short reaction time.

In a previous communication[1] we reported the use of *N*,*N*-dimethylformamide as solvent in the Ullmam-Goldberg condensation of 2-chlorobenzoic acid (I) with 2-aminopyridine (II) for the synthesis of 11*H*-pyrido[2,1-b]quinazolin-11-one (IV). This reaction proceeds through

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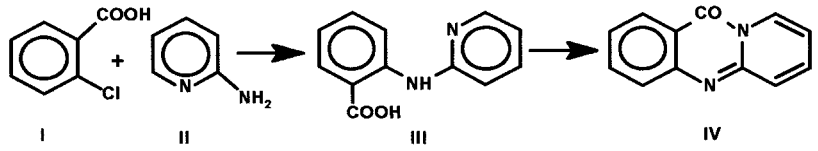
the corresponding 2-(2-pyridilamine) benzoic (III) acid which cyclizes in the reaction medium.

The conditions studied for the condensation used one equivalent of potassium carbonate, 2 equivalents of amine, 3% Cu (in weight) per mol of 2-chlorobenzoic acid and dimethylformamide as solvent.



Recently, an interesting series of substituted 11*H*-pyrido[2,1-b]quinazolin-11-ones has been studied as antiallergic,[2] cell protectants[3] and hypolipemic agents.[4]

In the present communication, we describe the use of ultrasound irradiation in the synthesis of 11*H*-pyrido[2,1-b]quinazohn-11-one derivatives, in order to shorten reaction times.

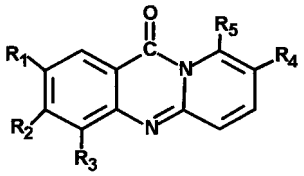
RESULTS AND DISCUSSION

First, we studied the effect of ultrasonic irradiation on the reaction rate for the synthesis of 11-pyrido[2,1-b]quinazolin-11-one, obtained by condensation of 2-chlorobenzoic acid with 2-aminopyridine in DMF (Table 1). The best yield was obtained at 20 min reaction time, when we used more than 20 min the yield remained constant, which was confirmed by standard deviation values. All experiments were repeated five times. The yields reported represent an average of the obtained values for each reaction.

Table 1. Ultrasonic irradiation in synthesis of 11*H*-pyrido[2,1-b]quinazolin-11-one: yield dependance on time.

Ultrasonic irradiation time (min)	Yield of 11H-pyrido[2,1-b]-quinazolin-11-one (%)	Standard deviation (S)
30	72	1.5
25	71	1.0
20	71	1.5
15	56	1.5

Table 2. Results using ultrasound irradiation (20 min) vs. reflux (6 h) in DMF as solvent.



No.	Substituent	% Yield using ultrasound (20 min)	% Yield in 6 h at refluxing in DMF as solvent	*m/e*
1	R_1=R_2=R_3=R_4=R_5=H	75	64	196
2	R_4=CH_3	82	77	210
3	R_5=CH_3	69	48	210
4	R_1=OCH_3	79	72	226
5	R_2=Cl	65	49	330
6	R_3=NO_2	67	52	241
7	R_1=NO_2	78	72	241
8	R_1=R_3=NO_2	89	84	286
9	R_2=NO_2	63	25	241

In Table 2 we compare the results using ultrasound irradiation (20 min) vs. reflux (6 h). In all cases the yield obtained using ultrasound is superior. It is interesting to mention that in the case of Entry 3, the 2-[(6-methyl-3-pyridinyl)amino]benzoic acid was obtained with reflux. This acid was cycled using sulfuric acid at 100°C to the corresponding 9-methyl-11H-pyrido[2,1-b]quinazolin-11-one. Employing ultrasound irradiation only 9-methyl-pyrido quinazolone derivative was obtained.

EXPERIMENTAL PART

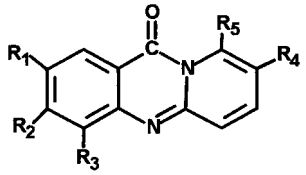
General Procedure

Synthesis of 11*H*-pyrido[2,1-b]quinazolin-11-one derivatives using DMF as solvent.

A mixture of 2-chlorobenzoic acid derivative (6.26 g; 0.04 mol), anhydrous potassium carbonate (2.76 g; 0.02 mol), 2-aminopyridine derivative (7.52 g; 0.08 mol), copper powder (0.2 g) in DMF (25 mL) was irradiated for 20 min with a sonic horn at 20 kHz. The reaction mixture was slowly

added to water (100 mL), then left to stand overnight. The precipitate 11*H*-pyrido[2,1-b]quinazolin-11-one was purified by dissolving in the corresponding solvent (see Table 3) and charcoal treatment. The R_f values were obtained using a mixture of toluene:acetic acid (2:1).

Table 3. 11H-Pyrido[2,1-b]quinazolin-11-one derivatives synthesized and analytical results.



No.	Substituent	Yield (%)	M.p. (°C) (uncorrected)	M.p. (°C) Reported	R_f
1	R_1=R_2=R_3=R_4=R_5=H	75	211–212[a]	210[5,6]	0.60
2	R_4=CH_3	82	151–152[b]	152–153[5,7]	0.63
3	R_5=CH_3	69	90–92[a]	92–93[5]	0.61
4	R_1=OCH_3	79	158–160[b]	157[5,6]	0.71
5	R_2=Cl	65	190–191[b]	190–192[5,6]	0.67
6	R_3=NO_2	67	199[c]	198[5]	0.69
7	R_1=NO_2	78	257–258[c]	258[5]	0.70
8	R_1=R_3=NO_2	89	287–289[c]	288–289[5]	0.73
9	R_2=NO_2	63	207–209[b]	208[5]	0.72

Calculated and experimental microanalysis

		Calculated (%)		Experimental (%)	
No.	Formula	C	H	C	H
1	$C_{12}H_8N_2O$	73.47	4.08	73.40	4.23
2	$C_{13}H_{10}N_2O$	74.28	4.76	74.53	5.11
3	$C_{13}H_{10}N_2O$	74.28	4.76	74.36	4.88
4	$C_{13}H_{10}N_2O_2$	69.03	4.42	68.90	4.25
5	$C_{12}H_7ClN_2O$	62.47	3.04	62.61	3.19
6	$C_{12}H_7N_3O_3$	59.75	2.90	59.55	2.84
7	$C_{12}H_7N_3O_3$	59.75	2.90	59.88	2.67
8	$C_{12}H_6N_4O_5$	50.35	2.10	50.49	1.91
9	$C_{12}H_7N_3O_3$	59.75	2.90	59.63	2.63

[a]Crystallized from ethanol/water; [b]crystallized from ethanol; [c]crystallized from dioxanel/water.

The yield, R_f value, melting point (uncorrected) and the elemental analysis for each 11*H*-pyrido[2,1-b]quinazohn-11-one derivatives obtained are reported in Table 3.

CONCLUSIONS

The use of ultrasound irradiation improved the synthesis of 11*H*-pyrido[2,1b]quinazolin-11-one derivatives using DMF as solvent. A number of pyridoquinazolone derivatives were prepared in good yield in a very short reaction time.

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