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SYNTHESIS OF 11H-PYRIDO[2,1-b]QUINAZOLIN-11-ONE AND DERIVATIVES

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Abstract: The synthesis of 11H-pyrido[2,1-b]quinazolin-11-one (IV) and derivatives, by the condensation of o-chlorobenzoic acid and 2-aminopyridine in DMF is reported.

11H-Pyrido[2,1-b]quinazolin-11-one (IV) was synthetized by Zeide in 1924 [1] by the dry method reported by Ullmann for the condensation between o-chlorobenzoic acid and 2-aminopyridine (II) with copper powder as catalyst. Also obtained was 2-(2-pyridilamine) benzoic acid which cyclized in the reaction medium.

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

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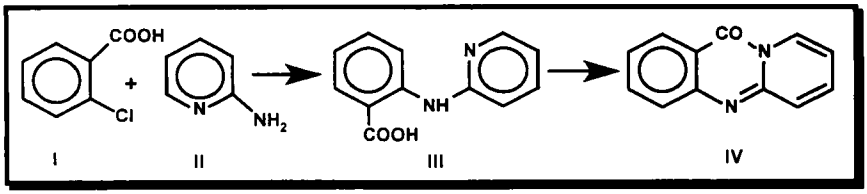


Figure 1

The aim of this report is to present a simple procedure for the synthesis of 11H-pyrido[2,1-b]quinazolin-11-one (IV) and derivatives using N,N-dimethylformamide (DMF) as solvent. This is a continuation of our studies on the Ullmann-Goldberg condensation [5-7]

RESULTS AND DISCUSSION

In a previous communication [5] we reported the synthesis of N-phenylanthranilic acids by the Ullmann-Goldberg condensation using water as solvent. The best yield was obtained with one equivalent of potassium carbonate, 3% (by weight) of copper and 2-equivalents of amine per mole of o-chlorobenzoic acid.

When we used these conditions for the condensation of (I) with (II), the 11H-pyrido[2,1-b]quinazolin-11-one (IV) was obtained in only 13% yield. Salicylic acid was obtained as a by product which was isolated together with unreacted o-chlorobenzoic acid.

In table 1 are shown the results of different experiences of the condensation between (I) and (II) using water as solvent, and copper powder as catalyst (3 % in weight

Table 1. Effect of potassium carbonate on the reaction yield using water as solvent.

Equiv of K_2CO_3	0	1	2	2.5
Yield of 11H-pyrido [2,1-b]quinazolin-11-one (%)	13	13	13	13
Yield of salicylic acid (%)	0	38	60	64

relative to I) employing different quantities of K_2CO_3. The reaction time in all cases was 6 hours.

In order to improve the synthetic procedure for 11H-pyrido[2,1-b]quinazolin-11-one (IV) we used DMF as solvent, changing the K_2CO_3 equivalents number. These results are shown in table 2. In all cases we used 2 moles of 2-aminopyridine with copper powder as the catalyst (3 % in weight relative to I). The reaction time, in all cases was 6 hours.

The use of DMF reduce the posibility of o-chlorobenzoic acid hydrolysis (salicylic acid formation). In this reaction, the 2-aminopyridine can act as a cocatalyst in the copper catalyzed chlorine substitution [6].

When the reaction between (I) and (II) was carried out in DMF with one equivalent of K_2CO_3, the reaction proceeded with 66% yield. These conditions were used for the synthesis of several 11H-pyrido[2,1-b]quinazolin-11-one derivatives.

Table 2. Effect of K_2CO_3 on the reaction yield using DMF as solvent.

Equivalents of K_2CO_3	0	1	2.5	3	4
Yield (%)	10	66	26	27	29

In table 3 are shown the 11H-pyrido[2,1-b]quinazolin-11-one derivatives synthetized, the molecular weights determined by mass spectrometry, the corresponding melting points (uncorrected) and the recristallization solvents. In table 4 are reported the calculated and experimental microanalysis results.

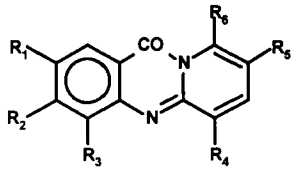
In the case of compounds 3, 10 and 11, the acids (III) were obtained. They were cyclized with sulfuric acid (80%) at 100 °C to the corresponding 11H-pyrido-[2,1-b]quinazolin-11-ones.

EXPERIMENTAL PART

Synthesis of 11H-pyrido[2,1-b]quinazolin-11-one (IV). A mixture of o-chlorobenzoic acid (6.26 g; 0.04 mol), 2-aminopyridine (7.52 g; 0.08 mol) anhydrous potassium carbonate (2.76 g; 0.02 mol), copper powder (0.2 g) and N,N-dimethylformamide (25 mL), was kept at reflux for six hours.

The mixture is slowly added with shaking to water (100 mL), then left to stand overnight. The precipited 11H-pyrido[2,1-b]quinazolin-11-one (5.02 g; 64% yield)

Table 3. 11H-pyrido[2,1-b]quinazolin-11-one derivatives obtained, and its melting points and molecular weights determined by mass spectrometry.



Nº	R_1	R_2	R_3	R_4	R_5	R_6	Yield %	m.p.ºC uncorr.	m/e	Ref
1	H	H	H	H	H	H	64	211-2[1]	196	8-9
2	H	H	H	H	CH_3	H	77	151-2[2]	210	8-10
3	H	H	H	H	H	CH_3	48	90-5[1]	210	8
4	MeO	H	H	H	H	H	72	158-60[2]	226	8-9
5	H	Cl	H	H	H	H	49	190-1[2]	230-2	8-9
6	H	H	NO_2	H	H	H	52	199-202[3]	241	8
7	NO_2	H	H	H	H	H	72	257-8[3]	241	8
8	NO_2	H	NO_2	H	H	H	84	287-9[3]	286	8
9	H	NO_2	H	H	H	H	25	207-9[2]	241	8
10	NO_2	H	H	H	NO_2	H	77	276-8[3]	286	8
11	NO_2	H	H	NO_2	H	H	45	287-9[3]	286	8

[1]Recrystallized from ethanol/water; [2]Recrystallized from ethanol; [3]Recrystallized from dioxane/water.

Table 4. Calculated and experimental microanalysis

Nº	Formula	% Calculated			% Experimental		
		C	H	N	C	H	N
1	$C_{12}H_8N_2O$	73.46	4.11	14.28	73.48	4.25	14.24
2	$C_{13}H_{10}N_2O$	74.27	4.79	13.32	74.10	5.16	13.01
3	$C_{13}H_{10}N_2O$	74.27	4.79	13.32	74.00	5.08	13.96
4	$C_{13}H_{10}N_2O_2$	69.02	4.46	12.38	68.65	4.23	12.03
5	$C_{12}H_7Cl\ N_2O$	62.49	3.06	12.15	62.67	3.22	12.27
6	$C_{12}H_7N_3O_3$	59.75	2.93	17.42	59.85	2.86	17.56
7	$C_{12}H_7N_3O_3$	59.75	2.93	17.42	59.58	2.63	17.74
8	$C_{12}H_6N_4O_5$	50.36	2.11	19.58	50.64	1.64	19.70
9	$C_{12}H_7N_3O_3$	59.75	2.93	17.42	59.68	3.32	17.45
10	$C_{12}H_6N_4O_5$	50.36	2.11	19.58	50.89	1.75	19.40
11	$C_{12}H_6N_4O_5$	50.36	2.11	19.58	50.59	2.65	19.45

is purified by dissolving in ethanol and boiling with charcoal. It separates in yellow crystals, m.p. 211-12(lit. 211 °C) [1].

The others derivatives were synthetized by the same procedure. The corresponding melting points, recrystallization solvents and m/e values are shown in table 3.

CONCLUSION

N,N-dimethylformamide can be used as solvent in the Ullmann- Goldberg condensation for the synthesis of 11H-pyrido[2,1-b]quinazolin-11-one derivatives using one equivalent of potassium carbonate, 2 moles of 2-aminopyridine per mol of o-chlorobenzoic acid and 3% Cu.

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