

One-pot Graebe-Ullmann Synthesis of γ -Carbolines under Microwave Irradiation

Andrés Molina, Juan J. Vaquero, José L. García-Navio and Julio Alvarez-Builla*

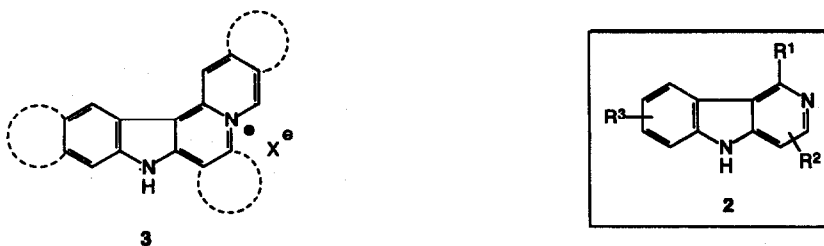
Departamento de Química Orgánica. Universidad de Alcalá. 28871 Alcalá de Henares. Madrid. Spain.

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Abstract: One-pot efficient and simple synthesis of γ -carboline derivatives by the Graebe-Ullmann method was conducted in a commercial microwave oven in a few minutes at a low energy level and using erlenmeyer flasks as adequate reaction vessels. Yields are similar to those obtained by conventional heating.

Some very recent examples of the applications of microwave energy in organic synthesis include Fischer cyclizations,¹ preparation of enantiopure α -hydroxy- β -lactams,² ortho ester Claisen rearrangement³ and our reported Hantzsch 1,4-dihydropyridine synthesis.⁴

In the course of a project directed towards the development of new antitumor compounds, the γ -carboline system **2** was selected as precursor of indolo[3,2-a]quinolizinium derivatives **3** capable of behaving as DNA intercalators⁵ and bis-intercalators⁶ when linked by an appropriate chain.



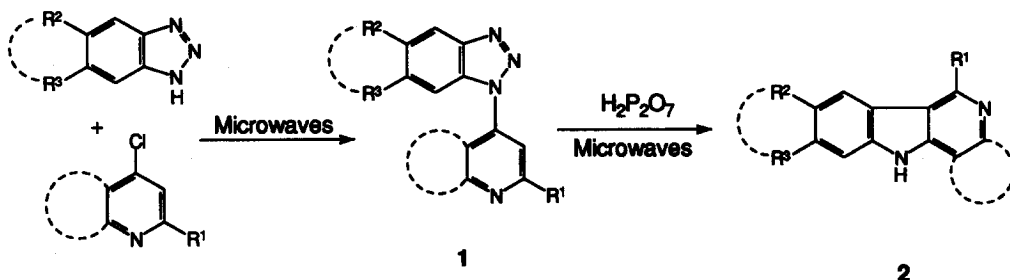
Scheme 1

One of the most widely used methods of γ -carboline synthesis,⁷ the Fischer reaction,⁸ involving electrophilic attack on a pyridine system and ring closure, often fails completely or proceeds in low yield unless forcing thermal conditions^{9,10} or activating of the pyridine ring.¹¹ Furthermore, oxidation of the resulting tetrahydro derivative may also be difficult.¹² An alternative approach is to use the Graebe-Ullmann

reaction that involves the preparation of a 4-pyridylbenzotriazole¹³ or 1-phenylpyrido[3,4-d]triazole derivative¹⁴ which on treatment with polyphosphoric acid gives the fully aromatic γ -carboline directly.

However, in this simple approach the preparation of the benzotriazole derivative requires high temperatures and even higher are needed in the subsequent thermolysis, being the yields highly dependent of the control of temperature, specially in the formation of γ -carboline system.

We report here a practical and simple one-pot Graebe-Ullmann γ -carboline synthesis in an open vessel using a domestic microwave oven. Our initial intention was to carry out the process in dry media using silica gel or montmorillonite as solid supports.¹⁵ Various attempts of irradiation of equimolecular mixtures of 4-chloropyridine and benzotriazole on these acid supports were all unsuccessful, only giving the corresponding pyridylbenzotriazole in moderate yield (less than 50%), and no traces of the γ -carboline **2a** were detected. However, when a non supported mixture was irradiated in the absence of solvent the condensation product **1a** was obtained in fairly good yield (90%). Subsequent microwave irradiation of the isolated pyridylbenzotriazole in the presence of pyrophosphoric acid gave, with evolution of nitrogen, the desired γ -carboline. Interestingly, when the crude reaction mixture, containing the pyridylbenzotriazole, was irradiated in the presence of the acid, the expected **2a** was isolated with no significant diminution of yield. This result was convenient since it eliminated the need to isolate the pyridylbenzotriazole derivatives **1**. Using these conditions the γ -carboline derivatives **2a-i** were prepared with the yields shown in the Table.

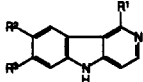
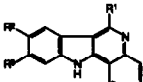
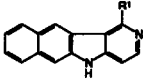
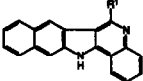


Scheme 2

In a typical experiment the benzotriazole derivative (2 mmol) and the corresponding 4-chloroazine (2 mmol) contained in an erlenmeyer (10 ml capacity) were placed in the microwave oven¹⁶ and irradiated at 160 watts¹⁷ for the time listed in the Table. The reaction mixture was allowed to reach room temperature and then the pyrophosphoric acid (16 mmol) was added. Keeping on the power at 160 watts, the mixture was irradiated until the evolution of nitrogen ceased (4-6 min). The reaction mixture was then triturated with water (5 ml) and basified with aqueous solution of sodium hydroxide (15%). The precipitate was filtered and purified by recrystallization or column chromatography (silica gel 200-400 mesh, Merck, ethyl acetate as eluent) to yield pure γ -carbolines **2a-i**.

In summary, using this simple and easily reproducible procedure the γ -carboline system is available in just one-pot in similar or higher yields than by the classical method, and in all cases with reduction of the reaction time.

Table. γ -Carboline derivatives 2 prepared under microwave irradiation

Compound No.	R ¹	R ²	R ³	MICROWAVE		CONTROL ^b		Mp (°C) ^{c,d}
				Time ^a (min)	Yield (%)	Yield (%)		
 2a	H	H	H	7	6	60	62[38] ^e	230-231 (H ₂ O-MeOH)
2b	H	Me	Me	10	4	71	67[19] ^e	251-252 (CH ₃ CN)
 2c	H	H	H	7	7	76	80[77] ^f	336-337 (CH ₃ CN)
2d	H	Me	Me	10	4	81	78	360 (EtOH)
2e	Me	H	H	7	6	32	35	295-296 (CH ₃ CN)
2f	Me	Me	Me	10	5	48	48	330-331 (EtOH)
 2g	H	-	-	10	6	30	28	281-282 (MeOH-H ₂ O)
 2h	H	-	-	10	5	45	50	342 (MeOH-H ₂ O)
2i	Me	-	-	10	5	35	32	330-331 (CH ₃ CN)

^aFirst value refers to formation of condensation compounds 1 and second to γ -carbolines 2.^bControls were run heating between 150-210 °C equimolecular amounts (2 mmol) of the reactants for 15-30 min. Thermolysis of 1 was carried out at 150 °C for 1.5-2 hours.^cSatisfactory spectroscopic and analytical data ($\pm$ 0.4% for C, H, N) were obtained for all new compounds.^dCompounds 2e-i were isolated by column chromatography. ^eYields in brackets are those reported in the literature in ref 13c (preparation of 1a-b) and 13d (thermolysis of 1a-b to give 2a-b) and 13f (2c).^fYield in brackets is reported in the literature in ref 13f and is referred to the thermolysis of the corresponding triazole 1c which is obtained in a 53% yield by a two steps procedure.

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16. The domestic microwave oven -Balay model BA HN991 AA703- was purchased in a local store. The oven has a variable timing cycle from 5 s to 45 min and a continuous variable heating cycle from 90 through 500 W of power output. The microwave frequency is 24.5 MHz and the oven's capacity is 18 l. Power generated by the oven was measured before every experiment by the method described by Watkins, K. W. *J. Chem. Ed.* **1983**, 60, 1043.
17. The reaction was tested in the range 150-400 watts and it was found that power plays an important role in the process with significant reduction in yield when higher levels were used.

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