MICROWAVE ACTION ON 2-(ARYLAMINO)-NICOTINIC ACID DERIVATIVES

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ABSTRACT : Microwave action on adsorbed 2-(arylamino)-nicotinic acid derivatives allows to obtain, depending on the pH of the substrate, the corresponding N-amino substituted pyridines by decarboxylation or the naphthyridone derivatives by cyclization reaction.

INTRODUCTION

Benzo[b]-1,8-naphthyridine-5-ones have been synthesized with a view to obtain new anticancer agents. These compounds can be prepared by cyclization of the corresponding 2-(arylamino)-nicotinic acid derivatives (1). Due to the fact that reaction conditions are generally tedious, e.g. the reaction takes place in the presence of polyphosphoric acid or phosphorus oxychloride, and yields are not very high, we tried to improve the cyclization reaction using dry medium procedure under microwave activation.

Bentonite clay was previously used for performing acid-catalysed cyclodehydration of benzoylbenzoic acids (2) and that of 2-carboxylic acid-diphenylamines (3). Results obtained in doing so, led us to extend this procedure to the cyclization reaction of 2-(arylamino)-nicotinic acid derivatives. Substrates were absorbed on bentonite with various pH values or on p-toluenesulfonic acid, taking advantage of the well known dehydration catalytic activities of this compound, before to be subjected to the action of microwaves.

EXPERIMENTAL

Our treatment precincts an original one and consists of a parallepipedic microwave-cavity H 101 resonance mode. The condition for a maximum field distribution on the material was fulfilled by using at the end of the cavity a mobile short circuit.

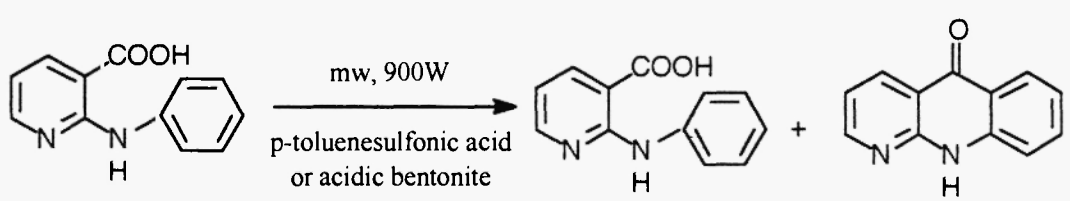
The reaction were performed in a quartz open vessel. Reactions were monitored by TLC on silicagel 60 F 254 (MERCK), with benzene-ethanol mixture (8:2, V/V) as eluent. Spots were visualised at 254 nm wavelength. Bentonite is from Gurasada (Romania). Composition is as follows : SiO_2(73.4%), Al_2O_3(14.35%), Fe_2O_3(1.72%), CaO(0.52%), MgO(2.32%), K_2O(0.44%), Na_2O(0.29%), TiO_2(0.24%). In order to obtain acidic bentonite, the latter was treated with concentrated boiling hydrochloric acid. The resulting pH of the solid material was around 3-4.

General procedure : The 2-(arylamino)-nicotinic acid derivative is dissolved into a minimum volume of ether and Gurasada acidic bentonite (or p-toluenesulfonic acid) is added to the solution. The solvent is then evaporated and the dry mixture is irradiated with microwaves. Finally, crude is extracted with boiling ethanol. Resultsof microanalyses are within ± 0.4% of the theoretical values. M.p. are given uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Varian GEMINI-300 MHz spectrometer using TMS as internal standard.

RESULTS AND DISCUSSION

Action of microwave on 2-(N-phenylamino)-nicotinic acid **1**, allows to obtain either 2-(N-phenylamino)-pyridine **2** or benzo b-[1,8] naphthyridine-5-one **3** depending on the nature and the pH value of the solid support used.

Reaction scheme is given in figure 1.



1 **2** **3**

Fig. 1

The decarboxylation reaction is the major reaction when p-toluenesulfonic acid is used as support. In these conditions the 2-(N-phenylamino) pyridine **2** can be easily prepared while the cyclization reaction prevails when bentonite at pH about 6 is used. In contrast both reaction products **2** and **3**, are obtained by working on bentonite at pH=2-3. Results are summarized in Table 1.

Table 1. Compounds obtained from 2-(N-phenylamino)nicotinic acid **1** under microwave activation conditions*.

Solid support	Compound	Yield (%)	m.p. (lit m.p.) °C
p-Toluenesulfonic acid	**2**	70	152-154[149-154(4)]
Bentonite at pH=3-4	**2** + **3**	40 + 20	-
Bentonite at pH=6-6.5	**3**	60	278-279[278-279(4)]

*200 mg of **1** absorbed on 400 mg solid support was used , irradation time was 1 min (4x15 seconds). Products were purified by column chromatography on silicagel using the a benzene-ethanol mixture descrided above.

With respect to these results, the action of microwaves on different 2(N-arylamino)-nicotinic acids adsorbed on bentonite at pH=6-6.5 was investigated with a view to prepare various benzo-b[1,8]-naphthyridine-5-ones (Fig. 2).

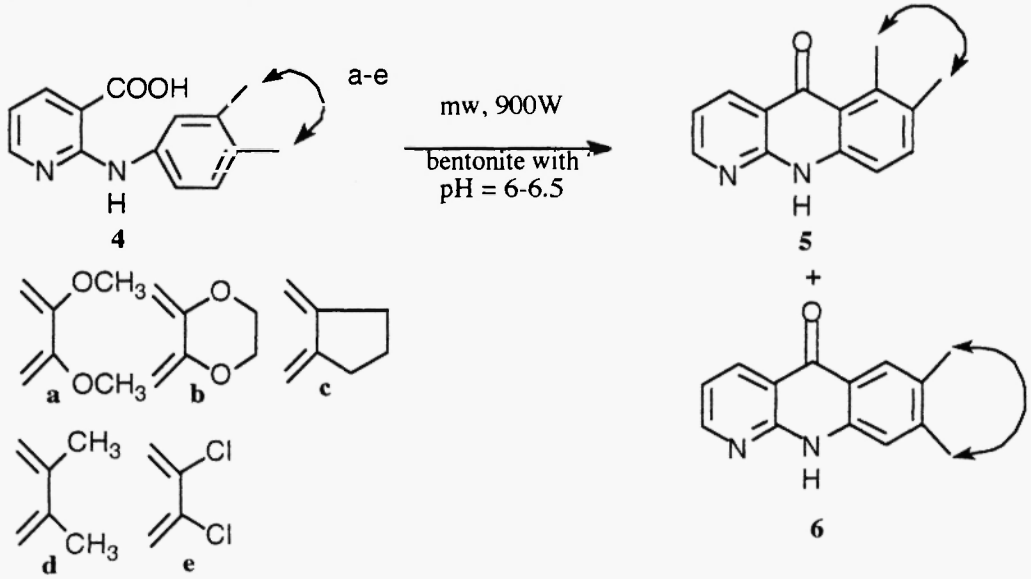


Fig. 2

The starting 2-(N-phenylamino)-nicotinic acids were prepared according to the methods previously reported (5). Isomers were separated by column chromatography on silicagel, using anhydrous ether as eluent.

Compounds obtained are gathered in Table 2. Each compounds were characterized by ^{1}H and ^{13}C NMR spectroscopies. Data which are in full agreement with those previously published (1), are not reported.

Table 2. Compounds obtained from various 2-(N-aminophenyl)-nicotinic acids absorbed on pH = 6-6.5 bentonite under microwave activation conditions*

Compound	Yield %	m.p.
5a	85	342
5b	80	340
5c + **6c**	30 + 35	360
5d + **6d**	40 + 30	330
5e + **6e**	20 + 35	> 400 + 323

* Reaction conditions are those detailed in Table 1 (foot-note)

Thus, it can be concluded that benzo[1,8-d]naphthyridone derivatives cane be obtained in short time with good yields under microwave activation conditions.

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