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Microwave-induced by-products in the synthesis of 2-(4-methyl-2-phenylpiperazinyl)pyridine-3-carbonitrile

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ABSTRACT

The Letter describes the investigation of an industrial reaction of *N*-methylphenylpiperazine and chloro nicotinonitrile, under microwave heating. Besides the formation of the expected 2-(4-methyl-2-phe nylpiperazinyl)pyridine-3-carbonitrile (**4**), extension of the scale leads to unexpected by-products. A specific pathway due to the formation of a reactive 'ionic alkylating intermediate' formed in situ under microwave conditions is proposed to explain the results observed.

1. Introduction

The use of adapted reactants and techniques offering operational, economic, and environmental benefits over conventional methods, is becoming crucial in the preparation and development of biologically active molecules. Microwave irradiation has gained popularity throughout both industry and academia since it was found to be an effective heating source applicable to a wide range of reactions.[1,2] The main benefits of microwaves are significant rate enhancements, higher product yields, and easier handling of reaction mixtures. The release of dedicated instruments for organic synthesis in the market has allowed a rapid development of microwave-assisted organic synthesis. Experiments can be carried out in monomode or multimode devices using different techniques such as open or sealed conditions, solvent-less procedures or solvent conditions.[3]

Our research project consisted of developing an easy access to piperazinoazepines with pharmaceutical interest[4] and we were particularly interested in finding a rapid preparation method of 2-(4-methyl-2-phenylpiperazinyl)pyridine-3-carbonitrile **4**. Traditional synthetic methods allowing access to this scaffold involve a preliminary N-alkylation of the piperazine scaffold and a subsequent cyclization into the corresponding pyrido-azepine. This specific alkylation is a key step in the preparation of the antidepressant mirtazapine.[5] This reaction is generally performed with bases, transition metal-catalyzed processes, phase transfer catalysts or solid phase synthesis.[6] Long reaction times and high temperatures are often required. In the current industrial context, we need to manage well-established procedures and methodologies, with environmental and safe benefits over conventional methods. Improving chemistry in a 'green approach' suggests exploring microwave heating. The aim of our work was to reinvestigate under microwaves an industrial reaction in order to identify what the advantages of these novel conditions are over classical conditions, with expectation for further developments. This down-scaling approach is not common and the main work published in the literature consists in transferring traditional lab-scale reactions into microwave reactors or domestic ovens. This Letter describes our work and the surprising results obtained.

2. Results

The reaction investigated was the synthesis of 2-(4-methyl-2-phenylpiperazinyl)pyridine-3-carbonitrile **4** via condensation of chloronicotinonitrile **1** and 1-methyl-3-phenylpiperazine **3** in dimethylformamide (DMF) in the presence of potassium fluoride. This reaction has been previously optimized and is performed on industrial scale.[5] Using traditional heating, the reaction is completed after 5 h in refluxing DMF in an isolated yield of 73%. It proceeds via an intermediate 2-fluoronicotinonitrile **2** (Scheme 1).[7,8] During the process, reaction of water with compound **1** (the presence of water being brought by moist KF) and further condensation

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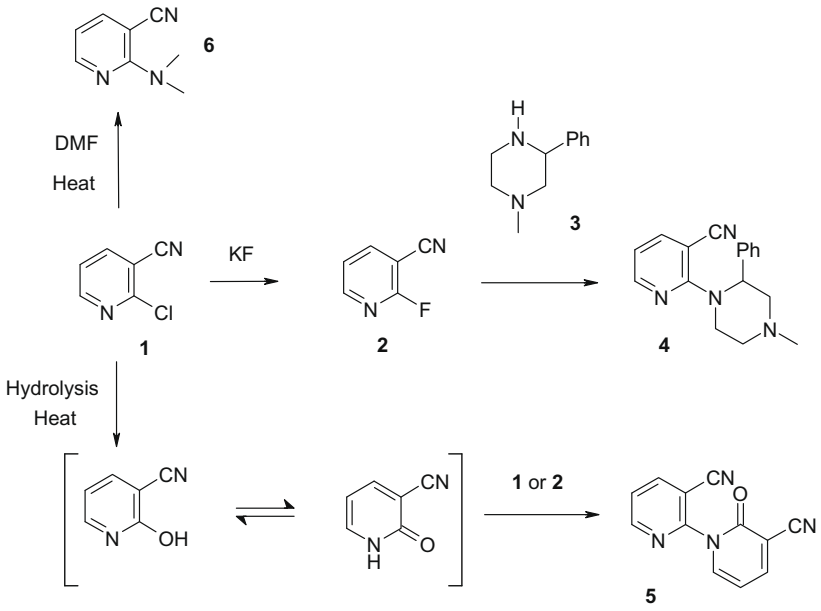


Scheme 1. Synthesis of **4**, **5,** and **6** from **1** (or **2**).

of the hydrolyzed intermediate on nicotinonitrile derivative **1** lead to low quantities of a by-product characterized as 1-(2-cyanophenyl)-2-oxohydropyridine-3-carbonitrile (**5** in Scheme 1).[9,10]

In the case studied, apart from some general microwave-assisted N-alkylations,[11] only one method of preparation of mono-N-substituted piperazines combining solid phases synthesis and microwave heating has been reported.[12] The preparation of *N*-arylpiperazinones has also been described via microwave-enhanced Goldberg reactions.[13]

Initial microwave experiments were performed at 150 °C in DMF on 1 mmol scale on a monomode system and a control of temperature by infrared pyrometer. After optimization, the reaction reached completion after 1 h of irradiation and the desired product **4** was isolated in 78% yield. As expected, an enhancement in the reaction rate and a shorter reaction time were observed. Experiments carried out in the presence of DMF at higher temperatures (>150 °C) were not successful. Another by-product was detected and identified as the 2-(*N*,*N*-dimethylamine)-3-pyridinecarbonitrile **6**.[9] Formation of this product probably results from reaction of **1** (or **2**) with dimethylamine generated by microwave-accelerated thermal degradation of DMF into the mixture (Scheme 1). This phenomenon was recently reported for reactants like DMSO,[14] formamide,[15] and DMF which has been yet utilized as a liquid source of carbon monoxide and dimethylamine in microwave-accelerated aminocarbonylations of aryl halides.[16]

Table 1
Investigation of microwave-assisted synthesis of **4** from chloronicotinonitrile **1**[9,18]

S.M.[a]	Microwave reaction conditions[b]	Product **4**[c] (%)
1+**3**	NMP,150 °C, 30 min	73
1+**3**	NMP, 180 °C, 30 min	88
1+**3**	NMP, 200 °C, 15 min	99

[a] S.M.: starting material.
[b] Performed on 1 mmol scale on monomode system (300 W), under sealed vials.
[c] Product conversion (%) based on the GC and GC/MS analysis after work-up.

N-Methylpyrrolidone (NMP), another polar aprotic solvent, is now a common replacement for DMF in pharmaceutical industry. It allows working at 200 °C and is known for its efficiency to transform electromagnetic energy into thermal energy.[17] Investigating various parameters (time, temperature, and power input) we observed that the reaction time decreased by increasing the temperature (200 °C). Under these conditions, completion of the reaction was possible within 15 min, as indicated in Table 1.

Large-scale experiments (15 mmol scale) were carried out in sealed vials in a multimode microwave device.[18] Various temperatures (180, 190, and 200 °C) were attempted and the results compared with data obtained in the previous monomode trials. Besides formation of the expected compound **4**, and the usual carbonitrile **5**, four novel by-products **8**–**11**[9] were detected in all cases (Table 2 and Fig. 1).

Table 2
Extension of the scale of microwave experiments[18] starting from **1** and 1-methyl-3-phenylpiperazine **3** or salt derivative **12**[a]

S.M.	Reactor	Temperature and time	Product **3**[b] (%)	Product **4**[b] (%)	Side-products: **8**,**10**,**11**[b] (%)	Side-products: **5**/**9**[b] (%)
1+**3**	Sealed	200 °C, 15 min	2	37	5, 10, 16	8
1+**3**	Sealed	190 °C, 15 min	4	51	3, 4, 6	8
1+**3**	Sealed	180 °C, 15 min	3	50	2, 3, 4	7
1+**3**	Open	190 °C, 15 min	<1	84	/	2 (**5** only)
1+**3**	Sealed[c]	180 °C, 120 min	4	85	/	2 (**5** only)
1+**12**	Open	190 °C, 15 min	<1	64	1, <1, 3	4
1+**12**	Sealed	200 °C, 15 min	<1	58	1, 3, 6	7

[a] Performed on 15 mmol scale from **1**+**3** or **1**+**12** on multimode system.
[b] % Based on the GC/MS analysis after work-up, residual of **1** and **2** not included, retention times of **5** and **9** were identical in GC analysis.
[c] Autoclave, use of traditional heating.

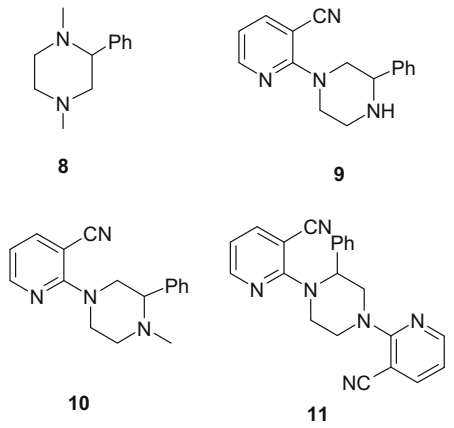


Figure 1. Four main by-products.

The reaction (same concentration and scale of starting material) conducted in an open vessel under microwave irradiation at 190 °C or in an autoclave using traditional heating at 180 °C, was complete and cleaner since only compound **5** (2%) was observed as a by-product besides formation of the substituted pyridine **4** (Table 2).

3. Discussion

In a large number of the microwave-assisted reactions investigated here, the yields for the expected product **4** were similar to the yields described for the industrial-scale reaction, but time was considerably reduced (from 5 h to 15 min).

The formation of by-products **8-11** could be explained via an intermediate **7** itself resulting from a non selective attack of 1-methyl-3-phenylpiperazine **3** on chloronicotinonitrile **1**. A possible pathway is described in Scheme 2: formation of methylated compound **8** and demethylated product **9** could be directly initiated from intermediate **7**. Further alkylation of compound **9** could lead to compound **10** (regio-isomer of **4**) and a second reaction of chloronicotinonitrile **1** with compound **9** could lead to the tricyclic product **11**.

Formation of the methylating reagent **7** and its by-products **8**–**11** can be explained via an ionic monohydrochloride salt (**12**) formed in situ from the reaction of free HCl (liberated during the course of the reaction and trapped into the closed vessel). The ionic character of this salt seems to induce its high capacity to transform electromagnetic energy into thermal energy at the temperature and frequency used in this study (Scheme 2).

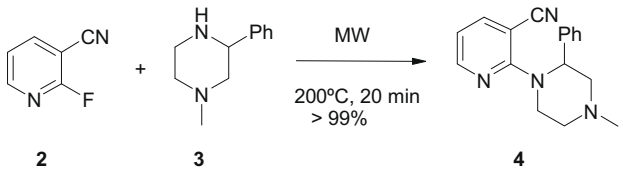
The monohydrochloride salt **12** was prepared from commercial *N*-methylphenylpiperazine and experiments were performed under microwaves, in open and closed vessels. Formation of the previous impurities **8**–**11** was observed in both cases (Table 2); it confirms the importance of a synergic effect of microwaves and pressure into the appearance of salt **12**, methylating agent **7,** and consequently of by-products **8**–**11**.

To complete our study, chloronicotinonitrile was replaced by fluoronicotinonitrile as the starting compound. The reaction was complete and clean and whatever the conditions used, none of the by-products (**5**, **8**–**11**) were detected (Scheme 3, Table 3).

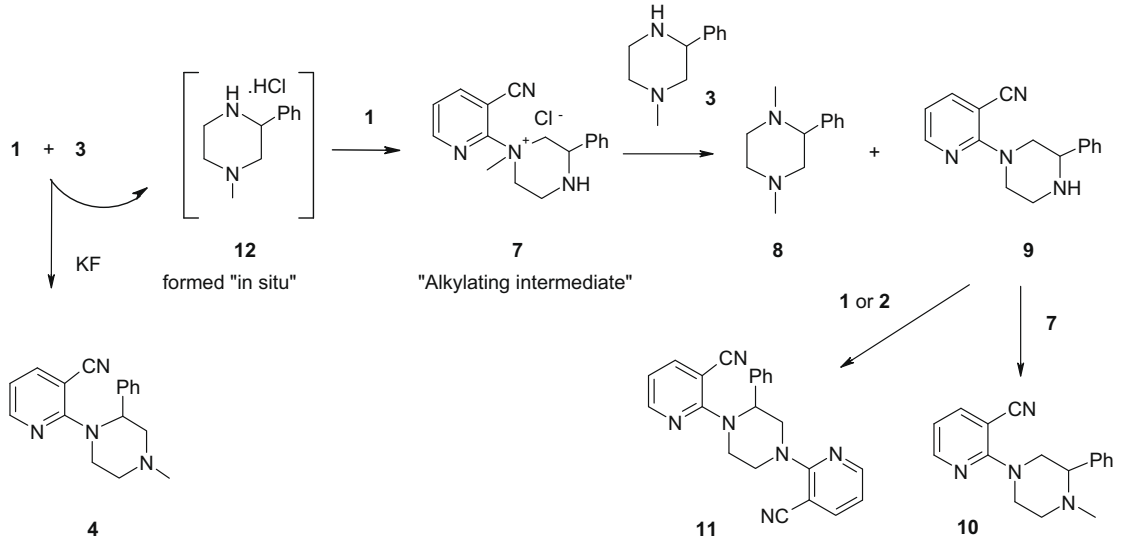
In the aforementioned case, we rationalize that HF must be less absorbent to microwave irradiation than HCl and thus none of the by-products are formed indicating that ionic interactions between the starting materials and the selected reagents can indeed influence product distribution. It is noteworthy that product **5** is not observed under these conditions, this result confirms the hypothesis of its formation from **1** (see Scheme 1).[9]

4. Conclusion

We studied the reaction of *N*-methylphenylpiperazine and chloronicotinonitrile under a microwave field with various conditions of pressure, times, and temperatures. Compared to a traditional heating mode, microwaves allowed reduction in reaction time and preserved good yields. Our work also demonstrated the difficulty to transpose a large-scale reaction performed at atmospheric pressure to a lab-scale microwave-assisted process carried out in a



Scheme 3. Synthesis of **4** from **2**.



Scheme 2. Suggested mechanism for the formation of **8**–**11**.

Table 3
Microwave experiments starting from 2-fluoro-3-pyridinecarbonitrile **2** and 1-methyl-3-phenylpiperazine **3**[18]

S.M.	Reactor	Reaction conditions[a]	**4**[b] (%)
2+3	Sealed[c]	200 °C (MW), 20 min	>99
2+3	Sealed[d]	200 °C (MW), 20 min	>99
2+3	Sealed[e]	190 °C, 20 min	>99

[a] Performed on 6 mmol scale.
[b] Product conversion (%) and selectivity based on the GC and GC/MS analysis after work-up.
[c] Performed on monomode system.
[d] Performed on multimode system.
[e] Preheated oil bath, preheating time not included: 30 min.

sealed vessel. The presence of unexpected by-products was specifically observed under these microwave conditions and not in usual thermal processes. In contrast, working under microwaves at atmospheric pressure gave very satisfactory results and data collected in this study show the real interest to use microwave for enhancing processes. In our case, the use of microwaves suggests the existence of 'ionic alkylating intermediates' which have an important role in the mechanism of the reaction and therefore, into formation of by-products.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.068.

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18. *Microwave experiments*: Reactions in sealed vessels were conducted in two commercial microwave systems: One single mode (Initiator EXP 60 from Biotage) with a power output ranging from 0 to 300W and one multimode cavity (Ethos MicroSynth from Milestone) with a microwave power delivery system ranging from 0 to 1000 W. Experiments in the single mode were performed in 2–5 mL glass vials. The temperature was monitored via an IR sensor located on the side of the vessel. The vessel contents were stirred by means of a rotating magnetic plate located below the microwave cavities and Teflon-coated magnetic stir bars inside the vessel. Experiments in multimode systems were carried out in closed 10 or 25 mL reactors made of quartz or glass. Open vessel experiment was carried out in a 250 mL round bottomed flask fitted with a reflux condenser. The temperature was monitored via a fiber-optic contact thermometer protected in a Teflon-coated ceramic gain inserted directly into the reaction mixture. The vessel contents were stirred by means of an adjustable rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar inside the vessel. Temperature, pressure, and power profiles were monitored using commercially available softwares provided by the manufacturers.