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Microwave-assisted one-pot synthesis of substituted tetrahydrocarbazole and 8,9,10,11-tetrahydro-7*H*-pyrido[*a*]carbazoles

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Abstract—One-pot synthesis of one-substituted tetrahydrocarbazole and 4-substituted 8,9,10,11-tetrahydro-7*H*-pyrido[*a*]carbazoles from substituted quinolinylhydrazines and cyclohexanone in acetic acid was performed by microwave irradiation in a controlled temperature with simultaneous cooling system in closed vessel. The optimization procedures of process variables, power, temperature, and irradiation time are reported in detail, and the results from microwave processes are compared with conventional ones.

Microwave-assisted organic synthesis (MAOS) in controlled conditions is an invaluable technique for medicinal chemistry and drug discovery applications. Indeed, in recent developments, the use of microwave irradiation to simplify and improve classic organic reactions has become a very popular method, because it often leads to higher yields, cleaner reactions, and shorter reaction times.[1]

In connection with the multi-step synthesis of some anticancer compounds of our interest, we adopted Fischer indole synthesis[2] as the most suitable for obtaining key carbazole intermediate **11** for novel planned substituted pyridocarbazoles (work in progress). Carbazole and pyridocarbazole are well-known pharmacophores present in many biological active compounds, especially antiproliferative ones and various methods have been used to synthesize them.[3] Of these, Fischer indole synthesis remains one of the most exploited methods.[4] Apart from that, it is also one of the most important processes in heterocycle chemistry, leading to a large variety of hetero-polycycle biological active compounds containing the indole nucleus and in some cases is the only method reaching target structures. Simply, starting from an arylhydrazine, a cyclohexanone hydrazone compound can provide indole derivatives by a thermal cyclization reaction carried out in several different but mostly strong acidic conditions. Successful results often depend on these specific conditions which, in turn, depend on the presence of certain groups on the starting hydrazine.[5]

In recent years, microwave indole synthesis has been useful in achieving rate acceleration and high yields in thermal cyclization with various ketones.[6a–c] More recently, one pot approaches to carbazoles or indoles under controlled microwave irradiation were reported in which efficient procedures for performing difficult Fischer syntheses in the presence of catalysts or NCW (near-critical region of water) have been established.[6d–f]

We therefore performed an indole-modified Fischer synthesis to obtain the intermediate 6,7,8,9-tetrahydro-1-methoxy-3-nitro-5*H*-carbazole (**11**) from 2-methoxy-4-nitro-hydrazine (**1**) by two procedures: one consisting of the two-step conventional method, and the other of a microwave-assisted one-pot synthesis, in order to shorten the synthetic pathway to our final compounds (Scheme 1A and B). The above two procedures leading to carbazole derivative **11** are described here. Moreover, in order to evaluate the feasibility of the microwave irradiation method in yielding tetrahydropyridocarbazoles starting from various quinoline hydrazine derivatives, the conventional and microwave-catalyzed syntheses of

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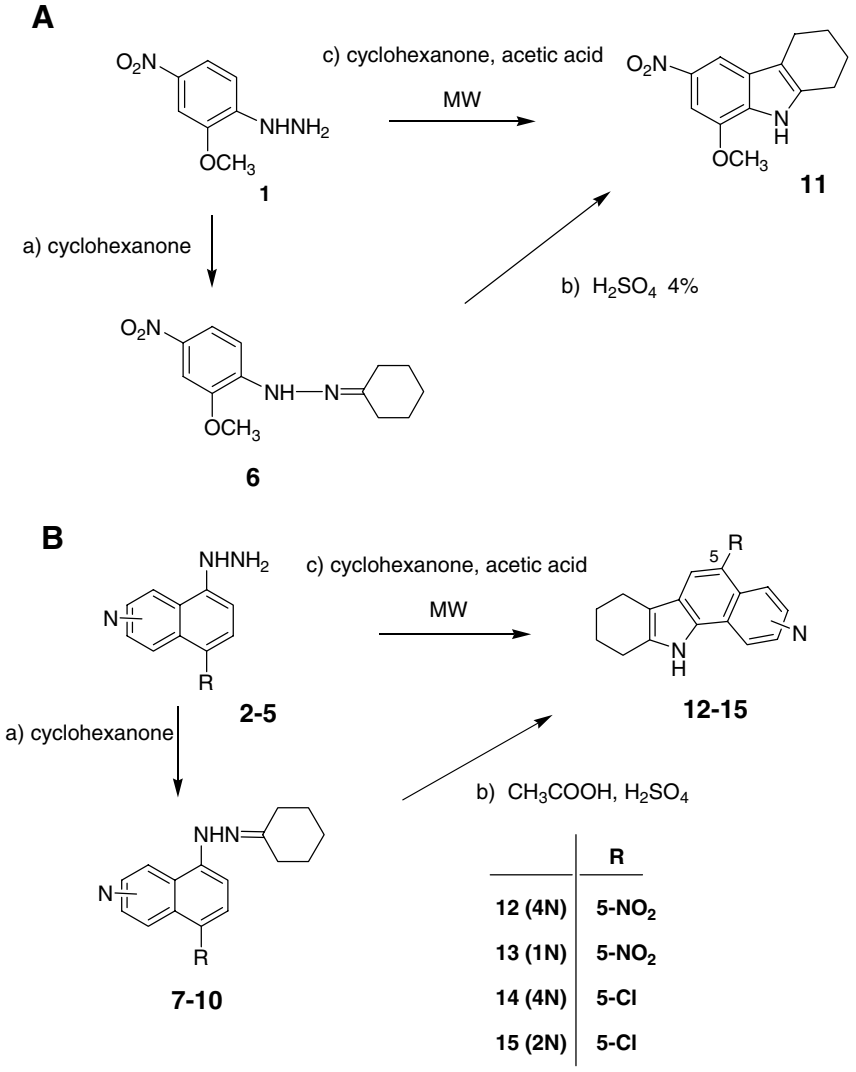

Scheme 1.

some substituted tetrahydropyridocarbazoles are also reported. Conventional and microwave syntheses are compared and discussed.

As regards the conventional method (Scheme 1A), by taking advantage of our past experience on strategies for the synthesis of tetrahydropyridocarbazoles,[7] 2-methoxy-4-nitro-phenylhydrazine chloride **1** was condensed with cyclohexanone and this was submitted to acid cyclization to carbazole **11** by Amberlist®. By the same pathway, quinoline and isoquinoline hydrazines **2**–**5** furnished first condensed products **7**–**10** and then cyclized products **12**–**15**, by a refluxing mixture of CH_3COOH and H_2SO_4, in good yields (Scheme 1B) (Supplementary data). In the meantime, we applied microwave one-pot synthesis, as previously described by Sidar (hydrazine derivative and cyclohexanone in acetic acid) for unsubstituted tetrahydrocarbazole.[5]

To the best of our knowledge, this is the first time that microwave-catalyzed Fischer indole synthesis has been achieved with substituted phenyl– and quinoline–hydrazine derivatives and that reaction conditions have been systematically optimized by means of a single-mode microwave reactor with focused waves (Discover, CEM). The latter allows the accurate control of power and temperature (by infrared detection) during the course of the reaction, and the regulation of microwave power is automatic and dependent on planned temperature.[8]

The conditions (temperature, microwave power, time) for synthesis of the carbazole compounds **11**–**15** are reported in detail below.[9]

For compound **11**, we developed optimization of the method (Table 1) with the aim of increasing the yield: first, the power set point was 100 W and the temperature reached was 100 °C. The conditions were then maintained constant by a cooling system for 6 min yielding 67% (experiment 1). In subsequent experiments, the temperature was increased and the time reduced with increasing yields (until 80%, experiment 3). We found that, for a shorter period of time at 140 °C, transformation of the substrate was not complete, whereas for longer periods the yield of product **11** decreased, probably due to the degradation processes.

Table 1. Microwave-assisted reactions of arylhydrazines **1**–**5** and cyclohexanone to tetrahydrocarbazole **11**, 5-nitro-tetrahydropyridocarbazoles **12** and **13**, and 5-chloro-tetrahydropyridocarbazoles **14** and **15**

Product	Experiment	MW[a] (W)	Temperature (°C)	Time (min)	Yield (%)
11	**1**	100	100	6	67
	2	100	115	4	73
	3	100	140	3	80
12	**1**	100	100–130	3–10	—
	2	100	140	3	78
	3	100	150	6	58
	4	100	150	1–30	51
13	**1**	100	150	6	60
	2	100	150	3	80
14	**1**	100	150	3	95
15	**1**	100	150	3	95

[a] Maximal power set to reach the temperature. During the reaction time, microwave power was reduced to maintain temperature constant.

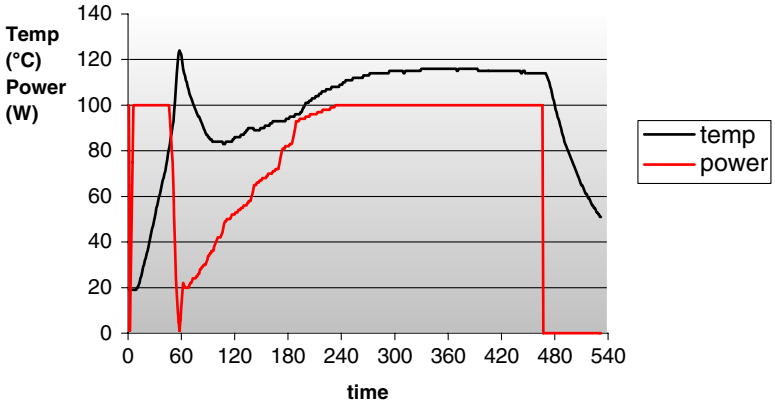

Figure 1. Temperature and microwave power profiles of reaction to **11** (experiment 2).

Figure 1 shows the graph of the MW reaction to **11**. In ramptime (time to reach necessary conditions) power was maximal to reach chosen temperature. Power and temperature were then adjusted to achieve constant conditions.

We then carried out MW reactions with various polycycle hydrazine derivatives and optimized reaction variables each time. For compound **12**, we found that, starting at constant power of 100 W with temperatures ranging from 100 to 130 °C, the reaction did not proceed, the same prolonging reaction times. At 140 °C, for 3 min the yield was 78%. Reaction times longer or shorter than 3 min decreased yields (1–30 min) (Table 1).

The same results were obtained with the reaction giving compound **13**: 3 min at 150 °C with a set point of 100 W increased the yield to 80% (Table 1, experiment 2).

The last two reactions concern chloro-tetrahydropyridocarbazoles derivatives **14** and **15**, for which the best conditions found with previous reactions were applied. The excellent results are shown in Table 1 (experiment 1).

In summary, we optimized the variables (power, temperature, time) of some microwave irradiation reactions in order to obtain substituted carbazole and pyridocarbazole derivatives by one-pot MW Fischer indole synthesis. Higher product yields, cleaner reaction products, and

Table 2. Comparison between microwave-assisted synthesis and conventional method to obtain tetrahydrocarbazoles and tetrahydropyridocarbazoles by Fischer indole synthesis

Entry	Compound	Time MW[a] (min)	Yield MW[b] (%)	Time conv.[c] (h)	Yield conv.[d] (%)
1	**11**	3	80	8–10	36
2	**12**	3	78	4–5	53
3	**13**	3	80	4–5	62
4	**14**	3	95	4–5	53
5	**15**	3	95	4–5	48

[a] Time of reactions under microwave irradiation giving best results.
[b] Yield of reactions under microwave irradiation giving best results.
[c] Time of two-step conventional synthesis.
[d] Final yield of two-step conventional synthesis.

shorter reaction times (hours to minutes) make the above methods advantageous in comparison with the traditional two-step heating method (Table 2). We also stress the fact that optimization of method variables (entries 1–3) reveals the best reaction conditions, which can also be immediately applied to other substituted hydrazino-quinolines (entries 4 and 5), thus confirming the generality and usefulness of the method. The new tetrahydrocarbazole and tetrahydropyridocarbazoles described here are very important precursors of final mono- and bi-functionalized 7*H*- and 11*H*-pyridocarbazoles, to be biologically assayed as anticancer agents. Therefore, microwave-catalyzed Fischer indole synthesis, in shorter times and with higher yields provided a series of new small molecules, which have turned out to be very active in preliminary assays of antiproliferative activity (work in progress).

Supplementary data

Traditional two-step procedures to compounds **6**–**10** and **11**–**15** are described. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.099.

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8. This single-mode system includes a cooling feature, which allows for fast reaction quenching by compressed gas forced into the reaction cavity. The system can also activate the cooling feature during reactions, to control a bulk temperature rise. If compressed air is introduced into the cavity while microwave irradiation is simultaneously applied, thermal heat does not accumulate in the reaction mixture. Large amounts of energy can still be applied while the bulk temperature remains low, resulting in higher product yields and cleaner chemistries.
9. General MW procedures are represented below. All MW reactions were performed in a Discover® monomode reactor (IR detector for temperature) from CEM corporation.
   Procedure for carbazole synthesis (**11**). The mixture of cyclohexanone (0.1 ml) and 2-methoxy-4-nitro-phenylhydrazine (equimolar ratio) in acetic acid (9 ml) was placed in a 10 ml vial closed with a silicon septum and containing a magnetic stirring bar. The tube was placed in the microwave cavity (Discover, CEM) and subjected to MW irradiation. The MW power set point was programmed at 100 W and the temperature set point at 100, 115, and 140 °C for the three experiments. Irradiation was stopped after 6, 4, and 3 min, respectively, from the moment at which the temperature remained constant (cooling while heating system). After cooling to room temperature, the reaction mixture was poured into cold water, neutralized with $NaHCO_3$ and extracted with ethyl acetate (40 ml × 3 times). Organic layers were dried and evaporated, and the product was practically pure, with 67%, 73% and 80% yields, respectively.
   Procedure for synthesis of tetrahydropyridocarbazoles (**12**–**15**). The mixture of cyclohexanone (0.1 ml) and compounds **2**–**5** in equimolar ratios, in acetic acid (9 ml) and two to three drops of concentrated H_2SO_4, was placed in a 10 ml vial closed with a silicon septum and containing a magnetic stirring bar. The tube was placed in the microwave cavity (Discover, CEM) and subjected to MW irradiation. The set conditions are reported in the text (Table 1). After cooling to room temperature, the reaction mixtures were poured into cold water, neutralized with $NaHCO_3$, and extracted with ethyl acetate. Organic layers were dried and evaporated, and the products were practically pure. Yields are reported in the text (Table 1).