Microwave-enhanced solid phase synthesis of 1,4,8-triazaspiro[4.5]decan-2-ones

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Dedicated to Professor Joan Bosch on the occasion of his 60th birthday

Abstract
An enhanced synthesis of 1,4,8-triazaspiro[4.5]decan-2-one derivatives on SynPhase lanterns using microwave irradiation is reported. In comparison to the conventional heating procedure, microwave irradiation considerably accelerated the formation of the spiroimidazolidinone system.

Keywords: Spiroimidazolidinone, 1,4,8-triazaspiro[4.5]decan-2-one, SynPhase™ lanterns, microwave synthesis, solid-phase synthesis

Introduction

Exploration of G-protein-coupled receptor (GPCR) ligands in drug discovery is an outstanding subject in constant progress in today's pharmaceutical research.[1] Several motives have been identified in the structure of GPCR ligands. These moieties are referred to "privileged structures" and have successfully been utilized for the design of novel ligands.[1a-b,2] Within the known "privileged structures", spiropiperidines have provided potent agonists and antagonists for different biological GPCR targets.[3] Spiro-piperidine-imidazolidinones constitute a versatile example of such templates.[4] Recently, we reported a methodology for the solid phase synthesis of 1,4,8-triazaspiro[4.5]decan-2-one derivatives using SynPhase™ lanterns as solid support (Figure 1). This methodology allowed the preparation of 8-benzyl-4-(*p*-substituted-benzyl)-1,4,8-triazaspiro[4.5]decan-2-ones **1** and 2-(8-benzyl-2-oxo-1,4,8-triazaspiro[4.5]dec-1-yl)acetamides **2** from Rink amide lanterns (Scheme 1).[5] The key step of the synthesis was the

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formation of the spiroimidazolidinone system which was performed by condensation of *N*-benzyl-4-piperidone onto amino acid amides **3** and dipeptides **4** linked to the solid support, respectively. This step was accomplished after a reaction time of 10 days for the preparation of compounds **1**,[5a,b] whereas it was completed after 24 h for the synthesis of compounds **2**.[5c] Although in both strategies, the HPLC purities and yields of the spiroimidazolidinones were satisfactory, the long reaction time was the limiting factor of the process.

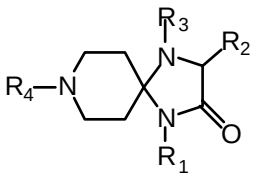
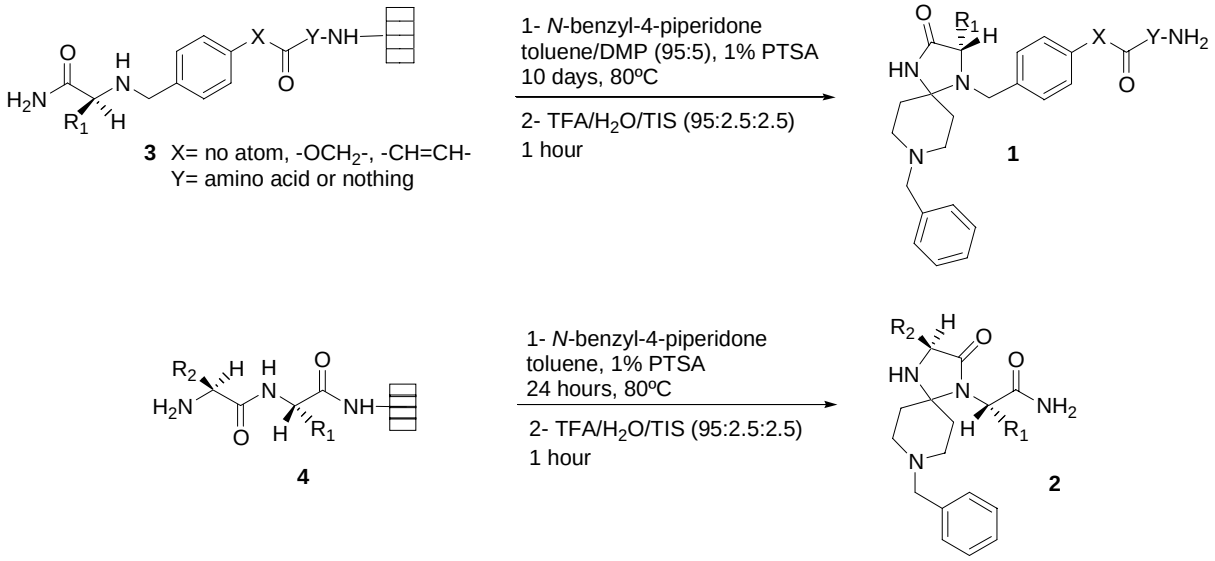


Figure 1. Structure of 1,4,8-triazaspiro[4.5]decan-2-one system.



Scheme 1

Microwave irradiation has become a powerful and easily controllable heating source for organic synthesis.[6] It has been shown to offer considerable advantages over conventional heating, improving several organic reactions. Among other applications, microwaves are used to shorten reaction times, enabling rapid optimization of procedures and accelerating the synthesis of organic compounds.

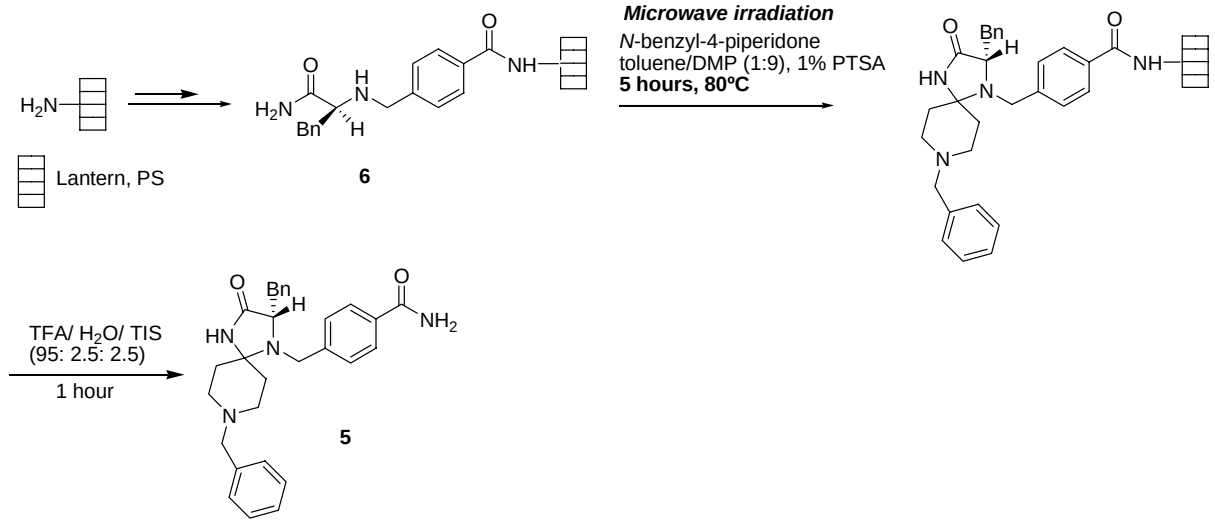
Microwave-assisted solid phase synthesis of 1,4,8-triazaspiro[4.5]decan-2-ones has never been reported. In this work, microwave heating was used to improve our previous methodology for the synthesis of this type of spirocyclic compounds on SynPhase lanterns. In particular, it was our aim to shorten the reaction time of the spiroimidazolidinone formation step. We report here our study concerning the comparison of reaction conditions, HPLC purity and yield of 1,4,8-

triazaspiro[4.5]decan-2-one synthesis by microwave irradiation and conventional heating techniques.

Results and Discussion

Our initial investigations involved evaluation of the stability of SynPhase lanterns under microwaves. Three parameters were examined: the solvent, the microwave exposure time and the temperature. These parameters were selected on the basis of our previously reported optimum conditions for the formation of the spiroimidazolidinone system by the conventional heating procedure. Thus, commercially available L-sized polystyrene Rink amide lanterns[7] with a loading of 15 μmol were subjected to microwave irradiation for 10, 20, or 60 min at 60 or 80ºC in toluene, 2,2-dimethoxypropane (DMP), or various mixtures of toluene/DMP. After the irradiation period, no alteration of the lanterns was observed except for those immersed in DMP at 80ºC.

Effect of microwaves on the condensation of *N*-benzyl-4-piperidone onto an amino acid amide linked to a SynPhase lantern was then investigated. For this purpose, compound **5** was chosen as model and the optimum conditions for the spiroimidazolidinone system formation under conventional heating procedure were taken as starting point (Scheme 2). In a first optimization study the following solvents were analyzed: toluene, DMP, toluene/DMP (9:1), and toluene/DMP (5:5) (Table 1). For each experiment, one lantern **6** was immersed in a suspension of 1M *N*-benzyl-4-piperidone and 1% *p*-toluenesulfonic acid (PTSA) in the corresponding solvent, and subjected to microwave irradiation at 60 or 80ºC for 10 or 20 min. After washing the lanterns and trifluoroacetic acid (TFA) cleavage, high-performance liquid chromatography (HPLC) and electrospray ionization-mass spectrometry (ESI-MS) analysis revealed that only the initial amide released from the acidolysis of **6** was obtained. We then decided to increase the DMP content in the reaction mixture as well as the reaction time and temperature. Thus, the reaction was carried out in toluene/DMP (1:9) in the presence of 1% PTSA at 80ºC for 1, 3, 5 or 7 hours, and at 90ºC for 1 hour (Table 1). TFA cleavages were performed and relative conversion[8] to the spiroimidazolidinone **5** was calculated. The best result was obtained by exposure of **6** to microwaves for 5 hours at 80ºC, leading to a 81% conversion to the desired spirocyclic compound **5**. Longer reaction times (7 hours) did not increase the conversion rate (82%), whereas higher temperature (90ºC) promoted the formation of the 2-imidazolidinone **7** (13%) (Figure 2). This secondary product, formed by condensation of DMP onto the amide **6**, was also obtained when the conventional heating procedure was followed.[5a]



Scheme 2

Table 1. Experimental conditions for the condensation of *N*-benzyl-4-piperidone onto lanterns **6** under microwave irradiation

Solvent	Temperature (ºC)	Reaction time	Amide,[a] Purity (%)[b]	**5**, Purity (%)[b]	**7**, Purity (%)[b]
Toluene	60 or 80	10 or 20min	100	-	-
Toluene/DMP (9:1)	60 or 80	10 or 20min	100	-	-
Toluene/DMP (5:5)	60 or 80	10 or 20min	100	-	-
DMP	60	10 or 20min	100	-	-
Toluene/DMP (1:9)	80	1 hour	94	6	-
		3 hours	80	20	-
		5 hours	16	81	3
		7 hours	14	82	4
	90	1 hour	12	75	13

[a]Amide obtained after TFA cleavage of **6.**
[b]HPLC purities are given as area %.

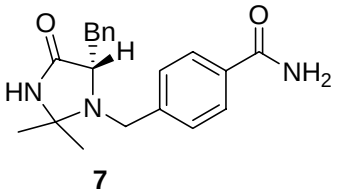
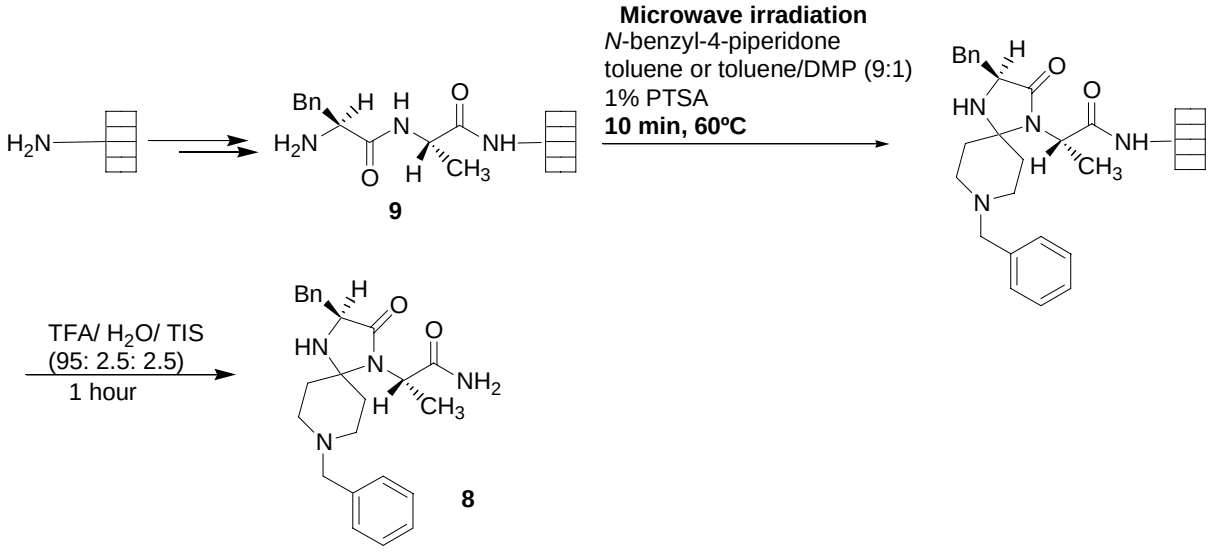


Figure 2. Structure of the by-product **7.**

A similar optimization study was performed to establish the best conditions for the preparation under microwave irradiation of spiroimidazolidinone derivatives from dipeptidyl-lanterns. In this case, compound **8** was selected as model system (Scheme 3). Condensation of *N*-benzyl-4-piperidone onto dipeptide **9** was also carried out in the presence of 1% PTSA by varying the solvent (toluene, DMP or mixtures toluene/DMP), the reaction temperature (60 or 80°C) and time (10 or 20 min) (Table 2). In this study, an increase of the microwave exposure time (from 10 to 20 min) or the temperature (from 60 to 80ºC) was not correlated with an increase of the conversion rate. For each solvent, these reaction conditions provided the same result. On the other hand, large amounts of DMP in the reaction mixture led to the formation of a by-product that could not be identified. The highest conversion percentage to the final product **8** (87%) was obtained when the reaction was performed in toluene or toluene/DMP (9:1) for 10 or 20 min at 60 or 80ºC.



Scheme 3

Table 2. Experimental conditions for the condensation of *N*-benzyl-4-piperidone onto lanterns **9** under microwave irradiation

Solvent	Temperature (ºC)	Reaction time (min)	**8**, Purity (%)[a]
Toluene	60 or 80	10 or 20	87
Toluene/DMP (9:1)	60 or 80	10 or 20	87
Toluene/DMP (5:5)	60 or 80	10 or 20	76
DMP	60	10 or 20	66

[a]HPLC purities are given as area %.

To demonstrate the advantage of performing spiroimidazolidinone synthesis under microwave irradiation, we compared the obtained optimal conditions to those described in our previous synthesis which was performed by conventional heating (Table 3).[5] Exposition of the reaction mixtures to microwaves allowed an important reduction in the reaction time for the preparation of both compounds **5** and **8**. In the case of **5**, this shorter reaction time required a larger amount of DMP compared to the conventional heating procedure. Although these conditions led to a slight decrease in the conversion to **5**, formation of the spiroimidazolidinone system was reached within 5 hours instead of 10 days by conventional heating. The reaction time for the preparation of spiroimidazolidinone **8** was reduced from 24 hours to 10 min. In this case, no modification in the conversion percentage to **8** was detected and the yield calculated from the initial lantern loading was comparable to that obtained by conventional heating.

Table 3. Comparison of reactions performed under conventional heating with those performed under microwave conditions

Compd	Heating method	Solvent	Temperature (ºC)	Reaction time	Purity (%)[a]	Yield (%)
5	Conventional	Toluene/DMP (95:5)	80	10 days	95	90
	Microwave	Toluene/DMP (1:9)	80	5 hours	81	76
8	Conventional	Toluene	80	24 hours	87	88
	Microwave	Toluene	60	10 min	87	86

[a]HPLC purities are given as area %.

Conclusions

In summary, synthesis of 1,4,8-triazaspiro[4.5]decan-2-one derivatives was significantly improved using microwave reaction conditions. In particular, the reaction time for the spirocycle formation was greatly reduced and then provide us an attractive methodology for the preparation of 1,4,8-triazaspiro[4.5]decan-2-ones. Extension of this methodology to include more elaborate substrates is currently going on in our laboratory.

Experimental Section

General Procedures. All microwave experiments were performed using the microwave Ethos SEL labstation from Milestone equipped with a dual magnetron system (1600W). The experiment time, temperature and power were controlled with the EasyControl software package.

The temperature was monitored through the ATC-400FO Automatic Fiber Optic Temperature Control System immersed into a standard Milestone reference vessel. This equipment regulates the power to achieve and maintain the selected temperature. HPLC analyses were run on a ThermoQuest instrument using an analytical C_{18} Kromasil column (4.6 × 40 mm; 3.5 μm particle size). A linear gradient of (0−100%) B at flow rate of 1.0 mL/min over 7 min was used; eluent A: H_2O/0.1% TFA, eluent B: acetonitrile/0.1% TFA. Purity estimates are based upon area percent of the peaks detected at 220 nm. Mass spectra were recorded on a Navigator quadrupole mass spectrometer (Finnigan AQA ThermoQuest) equipped with an electrospray ion source. The instrument was operated in the positive ESI(+) ion mode at a probe tip voltage of 3 kV.

General procedure for the microwave-assisted synthesis of 4-(2,8-dibenzyl-3-oxo-1,4,8-triazaspiro[4.5]dec-1-ylmethyl)benzamide (5) and 2-(3,8-dibenzyl-2-oxo-1,4,8-triazaspiro [4.5]dec-1-yl)propionamide (8)

For each experiment, a glass vial was charged with a suspension of 1M *N*-benzyl-4-piperidone (927 μL) and 1% PTSA (50 mg) in 5 mL of solvent and then the corresponding starting material linked to a L-sized polystyrene Rink amide lantern[7] (15 μmol) was immersed into it. The open vial was placed into a microwave process vessel and subjected to microwave irradiation. Firstly, a microwave ramp (700W maximum) was applied for 5 min to reach the selected temperature and then microwave irradiation was continued maintaining this temperature for the corresponding irradiation time. After microwave exposure, upon cooling, the solvent was removed and the lantern was washed in DMF (3 × 5 min) and CH_2Cl_2 (2 × 5 min). The spiroimidazolidinone was cleaved from the lantern by treatment with TFA/H_2O/triisopropylsilane (TIS) (95:2.5:2.5). After 1 hour at room temperature, the lantern was removed, the solution was concentrated under a stream of N_2 and the compound was precipitated with dry Et_2O, centrifuged and decanted. Precipitation, centrifugation and decantation operations were repeated twice. The resulting residue was dissolved in acetonitrile/H_2O (50:50, v/v) containing 0.1% TFA, frozen at -80ºC, lyophilized, analyzed for purity on HPLC, and characterized by ESI-MS.

4-(2,8-Dibenzyl-3-oxo-1,4,8-triazaspiro[4.5]dec-1-ylmethyl)benzamide (5). The starting amino acid amide **6** linked to the Synphase lantern was prepared as previously reported.[5b] According to the general microwave procedure, the lantern was exposed to microwave irradiation at 80ºC for 5 hours in toluene/DMP (1:9). HPLC analysis revealed that the spiroimidazolidinone **5** was obtained (t_R = 4.4 min, 81% purity) together with 4-(5-benzyl-2,2-dimethyl-4-oxoimidazolidin-1-ylmethyl)benzamide (**7**) (t_R = 4.5 min, 3% purity) and initial amide released from TFA cleavage of **6** (t_R = 3.3 min, 16% purity). The final product **5** (76% yield) was characterized by ESI-MS (*m/z* calcd. for $C_{29}H_{32}N_4O_2$ 468,25; found 469.0 $[M+H]^+$).

2-(3,8-Dibenzyl-2-oxo-1,4,8-triazaspiro[4.5]dec-1-yl)propionamide (8). The starting dipeptide **9** linked to the Synphase lantern was prepared as previously reported.[5c] According to the general microwave procedure, the lantern was exposed to microwave irradiation at 60ºC for 10 min in toluene. The obtained spiroimidazolidinone **8** (86% yield) was analyzed by HPLC (t_R = 4.4 min,

87% purity) and the structure was confirmed by ESI-MS (*m/z* calcd. for $C_{24}H_{30}N_4O_2$ 406,24; found 406.9 $[M+H]^+$).

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7. SynPhase™ lanterns were purchased from Mimotopes, Pty Ltd, Clayton, Australia.
8. Based on HPLC peak areas at 214 and 254 nm of compound **5** and compound obtained after TFA cleavage of **6**.