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Microwave-Assisted Solid-Phase Synthesis of 5-Carboxamido-*N*-acetyltryptamine Derivatives

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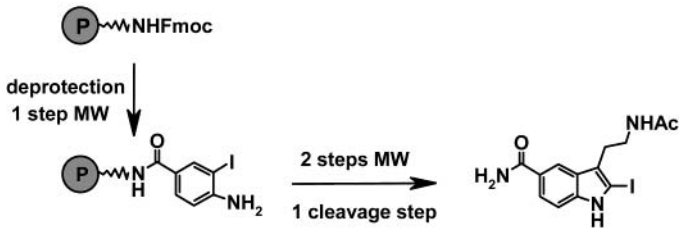
ABSTRACT



The synthesis of the indole skeleton of new melatoninergic analogues was realized using solid-phase methodology in association with microwave irradiation. This combination speeds up the solid-phase drug discovery process in rigorously established conditions.

Solid-phase organic synthesis provides a powerful means for the preparation of compound libraries and has been successfully used for the construction of both oligomeric compounds and small molecules.[2] However, solid-phase synthesis still exhibits several shortcomings owing to the nature of the heterogeneous reaction conditions.

Nonlinear kinetic behavior, slow reactions, solvation problems, and degradation of the polymer support resulting from long reaction times are some of the problems experienced in solid-phase organic synthesis.[3] Microwave irradiation is known to allow striking reduction in reactions times, good yields, and cleaner reactions over conventional thermal procedures.[4] In very recent years, the concept of speeding up resin-bound chemistry by microwave activation has created a lot of interest, both from the academic and industrial communities.[5]

We recently published an original investigation of the synthesis, in a homogeneous phase, of the indole core of melatonin analogues.[6] This synthesis confirmed that conventional thermal procedures can be substituted by micro-

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wave irradiation. The experimental microwave conditions described in this previous paper are well-established, and our goal is now to combine solid-phase synthesis with microwave heating in order to speed up drug discovery processes and also to demonstrate the real interest of a such association.

In this paper we report the transposition of the solid-support synthesis of the indole core of melatonin analogues under microwave irradiation. Comparison with classical thermal methods was also studied and will be discussed.

The acid-labile *Rink*[7] linker was chosen for connection of aromatic iodide to polystyrene.[8] Generation of the indole skeleton under microwave irradiation was studied with a microwave oven especially designed for organic synthesis.[9] Preliminary solid-phase experiments were performed at constant temperature. Confirming the results recently obtained in homogeneous phase, these conditions were not satisfactory, and we observed that the best results were obtained by a strict power control of the focused microwave irradiation. For our application on solid support, the temperature must be lower than 140 °C (thermal stability of polystyrene). In this case dichloromethane (DCM) or a mixture of *N*,*N*-dimethylformamide (DMF)/acetonitrile (ACN) as solvent allows us to not exceed this temperature under a strict power control of the microwaves.

Generation of various indole derivatives was performed in five steps via a palladium-mediated reaction between 2-iodoaniline derivatives and functionalized acetylenes.

The peptidic coupling of 4-amino-3-iodobenzoic acid **1** on *Rink* amide resin was performed, in 48 h, in dioxane. Following the pathway previously published,[7] the palladium-catalyzed coupling reaction of **2** and **3**[10] (ratio, 1/5) was realized with $Pd(OAc)_2$, NaOAc, and Ph_3P in the presence of LiCl, which is known to provide excellent regioselectivity[11] (Scheme 1).

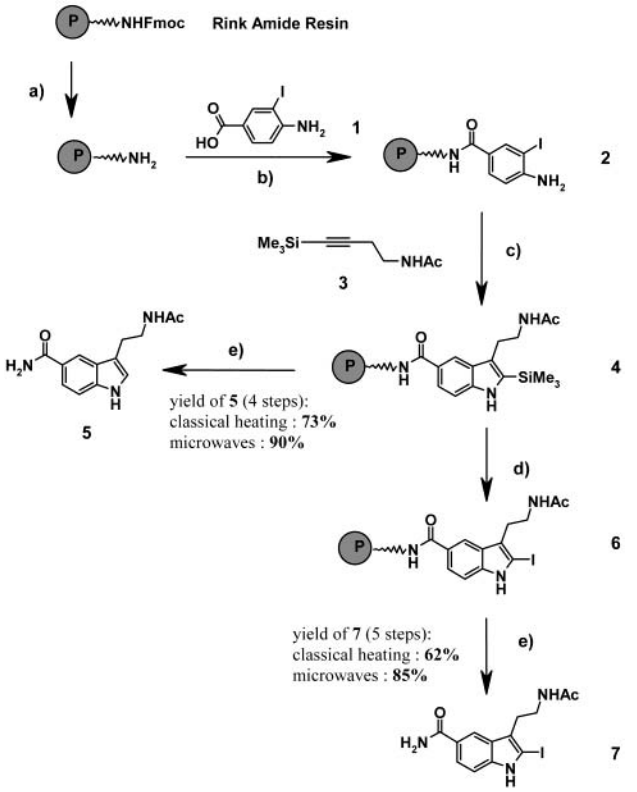
The attempted indole derivative **4** was cleaved to obtain the expected compound **5** in a good yield (74%) (the ratio between the quantity of **2** and **3** is very important; if it is too small, lowest yields were observed) (Table 1).

The high regioselectivity observed in this reaction suggested insertion of the intermediate arylpalladium species into the alkyne from the less hindered side.

Treatment of **4** with 3 equiv of NIS (*N*-iodosuccinimide) in DCM at reflux during 24 h afforded the iodo derivative **6**, which could be later involved in various palladium-mediated reactions, allowing access to various 2-substituted indoles (Scheme 1).

To evaluate the stability of the resin under microwaves, the *Rink* amide polystyrene was placed under microwave

Scheme 1. Solid-Phase Synthesis of 5-Carboxamido-*N*-acetyltryptamine[a]



[a] Reagents and conditions (for time and yield see Table 1): (a) piperidine 20%, DMA, rt, 60 min; (b) **1** (4.4 equiv), TBTU (4.4 equiv), HOBT (2 equiv), NEt_3 (14.4 equiv), DMAP (1 equiv), dioxane; (c) **3** (5 or 3 equiv, see table), $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), LiCl (2 equiv), NaOAc (4 equiv), DMA; (d) NIS (3 or 1.5 equiv, see table), CH_2Cl_2; (e) cleavage, TFA, 20%, CH_2Cl_2, rt.

Table 1. Classical Heating and Microwave Solid-Support Experiments;[12] Ratio **2**/**3** = 1/5 and **3**/NIS = 1/3

	conventional thermal heating[a]			microwave irradiation; strict power control[b]		
step	reaction time	temp (°C)	yield (%)	reaction time	power (W)	yield (%) after step **e**
b	48 h	rt	100[c]	3 min	45	100[c]
c	24 h	100	100[c]	13 min	60	80[c]
c	24 h	100	100[c]	2 × 13 min	60	100[c]
d	24 h	40	62[d] (5 steps)	14 min	60	100[c]; 85[d] (5 steps)

[a] Oil bath. [b] In these experiments the temperature did not reach the critical value of 140 °C (thermal stability of polystyrene) [c] Conversion rate was determinated by ^1H NMR after cleavage with TFA−CH_2Cl_2 (1/4 v/v). [d] Yield after purification by flash chromatography.

(7) Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787−3790.

(8) The Rink resin had previously been used in microwave-assisted solid-phase chemistry; see ref 5f.

(9) Focused microwave irradiations were carried out at atmospheric pressure with a Synthewave S402 Prolabo microwave reactor (300 W, monomode system), which has quartz reactors, visual control, irradiation monitored by PC computer, infrared measurement, and continuous feedback temperature control (Commarmot, R.; Didenot, R.; Gardais, J. F. French Patent 84/03496, 1986; *Chem. Abst.* **1986**, *105*, 17442.)

(10) *N*-[4-(1,1,1-Trimethylsilyl)-3-butyn-1-yl]acetamide **3** was obtained, in six steps, from commercially available but-3-ynol (see ref 7).

(11) (a) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355−5358. (b) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689−6690.

(12) All reactions reported here were performed on a scale of 150−200 mg of beads (0.7 mmol/g) allowing the isolation of at least 20 mg of crude product. Yields, therefore, refer to the weight of product purified by flash chromatography. Analysis of products was performed by ^1H NMR (250 MHz) and mass spectroscopy.

irradiation for 5, 15, or 20 min, with strict power control (30, 60, or 75 W), in the presence of various solvents (dichloromethane, dimethylacetamide, or a mixture DMF/ACN, 2/1 v/v). After washing and drying of the solid support, the aromatic iodide moiety **1** was coupled using the standard peptidic conditions described above. After cleavage (TFA/CH_2Cl_2, 1/4 v/v) calculation of the quantity of the resulting amide allowed determination of the stability of the support. In the conditions described in this paper no alteration of the polymer was detected. The solid-phase reaction conditions for the preparation of **2**, **4**, and **6**, were transposed to our open microwave oven. Successful results are summarized in Table 1.

For each procedure studied, exposition of the reaction mixtures to microwaves allowed a substantial increase in the yields and a striking reduction in the reaction times (e.g., coupling of **1** to the resin was reached in only 3 min, instead of 48 h at room temperature or 12 h at 50 °C by conventional heating). Curiously, an incomplete conversion into **4** was observed (80%).

No modification was detected by increasing the amount of compound **3**, changing the irradiation power, or varying reaction times. The desired 5-carboxamide-*N*-acetyltryptamine derivative **4** was obtained with complete conversion after a double coupling (Table 1). This procedure implied a complete removal of all reagents and byproducts by washing off the resin before submitting it to identical coupling conditions for a second time.

A very spectacular decrease in the reaction time of step **d** (conversion of the trimethylsilyl into an iodo group) was also detected (24 h → 14 min, Table 1).

To demonstrate the real advantage of associating microwaves and solid-phase synthesis, we compared the results obtained in the present study with the data described in our previous work with a methyl ester (Table 2). It is important to observe that the considerable enhancement (short times and very good yields) of this multistep procedure results from the microwave irradiation of the reaction mixtures and was not affected by the transposition of the process to solid-support conditions.

Table 2. Classical Heating and Microwave Homogeneous-Phase Experiments; Ratio **2**/**3** = 1/3 and **3**/NIS = 1/1.5

	conventional thermal heating			microwave irradiation; strict power control		
step	reaction time	temp (°C)	yield[a] (%)	reaction time	power (W)	yield[a] (%) after step **e**
c	4 h	100	70	10 min	60	84
d	24 h	40	58	11 min	60	94

[a] Yield after purification by flash chromatography.

In conclusion, studying an easy and original access to the indole core of melatonin analogues via palladium-mediated heteroannulation of internal alkyne **3** with *o*-iodoaniline derivative **2**, we confirm that conventional thermal procedures can be substituted by microwave irradiation.

The 2-iodo derivative obtained could be used to obtain further modifications in this position via Suzuki, Stille, Heck, or Sonogashira palladium-mediated coupling reaction. With well-established experimental conditions, it is now possible to combine solid-phase synthesis with microwave heating in order to speed up the drug discovery process. In connection with recent published results,[5] this work demonstrates the real advantage of such an association for a rapid access to novel molecules with potential pharmacological value and opens the door to wider application of microwaves in solid-phase organic synthesis.

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