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Microwave-assisted synthesis of 5-carboxymethoxy-*N*-acetyltryptamine derivatives

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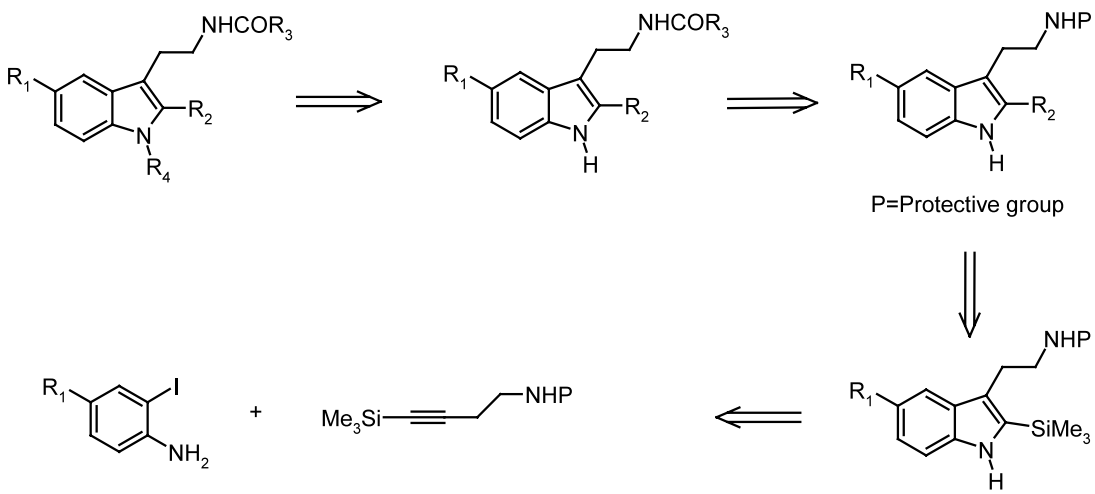
Abstract—The synthesis of the indole core structure was investigated using microwave irradiation. The experimental microwave conditions described allow significant rate enhancements and good yields compared to conventional reaction conditions.

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) is the main hormone secreted by the vertebrate pineal gland during darkness.[1] It is by now well known that it is involved in the regulation of the circadian rhythm and can be used to control associated diseases.[2] Melatonin is implicated in a number of physiological and pathological states in humans, among others in sleep processes,[3] seasonal and winter depression.[4] It has antioxidant properties,[5] alleviates jet-lag and has been claimed to be effective in treating disorders such as cancers[6] or psychiatric disorder.[7,8] The potential therapeutic implications of melatonin justify the considerable interest in the search of new structures able to be agonists or antagonists of this hormone.[9,10]



Scheme 1.

Keywords: melatoninergic analogs; microwave irradiation; palladium coupling.

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In a search for new melatoninergic analogs and with the aim to speed up the drug discovery process, we planned to realise the synthesis of the indole skeleton using solid phase methodology in association with microwave irradiation. This last method is known to allow a striking reduction in reaction times, good yields and cleaner reactions than the purely thermal procedures.[11]

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.[12] Although in most of the few published examples significant rate enhancements were observed, the benefits associated with this new methodology have not been rigorously established and the reasons for the observed rate enhancements remain unclear.[12b–d]

In the present paper, we report the synthesis, in homogeneous phase, of the indole core structure under microwave irradiation, in order to establish its feasibility and to identify standard experimental conditions, which could be transposed to solid support synthesis.

The retrosynthetic pathway (Scheme 1) suggests that generation of various indole derivatives may start with a palladium-mediated reaction between 2-iodoaniline derivatives and functionalised acetylenes. The expected strategy may allow us to obtain pharmacomodulations in positions 1, 2 and 5 of the indole moiety, but also to vary the *N*-acyl groups on the side chain. These four positions have been reported as very important in structure–affinity relationships.[13]

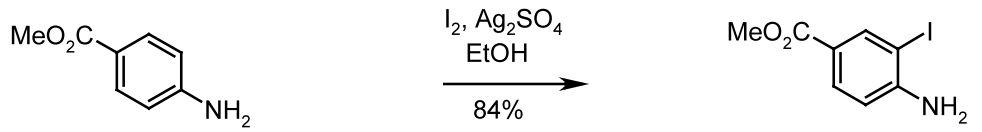
The basic structure **2** chosen to undergo the palladium-mediated coupling reaction was synthesised in one step from commercially available methyl 4-aminobenzoate **1** by treatment of methyl *p*-aminobenzoate with iodine in the presence of silver sulfate (Scheme 2).[14]

The other partner, *N*-[4-(1,1,1-trimethylsilyl)-3-butyn-1-yl]acetamide **8**, was obtained, in six steps, from but-3-ynol **3** (Scheme 3). After protection of **3** by a tosyl group, the protected compound **4** undergoes an anionic reaction followed by reaction with trimethylsilyl chloride to lead to the desired product **5** in a good yield. The azido derivative **6** was synthesised by reaction of **5** with sodium azide and treated by lithium aluminium hydride to generate amine **7**, which was immediately acetylated into the expected acetylene **8** (yield: 70% for the last two steps).

2. Synthesis of the indole core 9

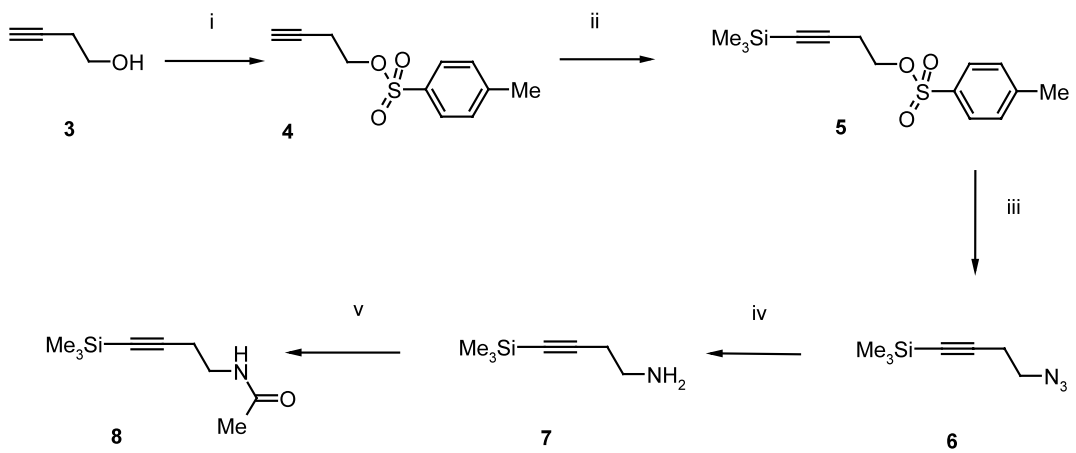
2.1. Classical thermal heating

The palladium-catalysed coupling reaction of **2** and **8** (ratio: 1/3) was realised with $Pd(OAc)_2$, NaOAc and Ph_3P in the presence of LiCl, which is known[15] to provide an excellent regioselectivity. The expected indole derivative **9** was obtained in a good yield (70%) (the ratio between the quantity of **2** and **8** is very important; if it is too low a lower yield was obtained) (Table 1). The high regioselectivity observed in this reaction suggested insertion of the intermediate arylpal-



1 **2**

Scheme 2.



3 **4** **5** **6** **7** **8**

Scheme 3. *Reagents and conditions*: (i) Et_3N (2 equiv.), TsCl (1 equiv.), CH_2Cl_2, 0°C→rt, 7 h, 82%; (ii) BuLi (1.05 equiv.), THF, 1 h, −78°C then Me_3SiCl (1.5 equiv.), −78°C→rt, 1 h, 89%; (iii) NaN_3 (3 equiv.), DMA, 60°C, 2 h 30 min, 84%; (iv) $LiAlH_4$ (0.6 equiv.), Et_2O, rt, 4 h; (v) Ac_2O (1.2 equiv.), pyridine (2.5 equiv.), CH_2Cl_2, rt, 24 h, 70% on the two last steps.

Table 1. Preparation of indole **9** from compounds **2** and **8**

Classical thermal heating (oil bath)				
Ratio **2**/**8** (equiv.)	Solvent	Reaction time (h)	Temperature (°C)	Yield of **9** (%)
1/1	DMA[a]	4	100	42
1/3	DMA[a]	4	100	70

[a] DMA: *N*,*N*-dimethylacetamide.

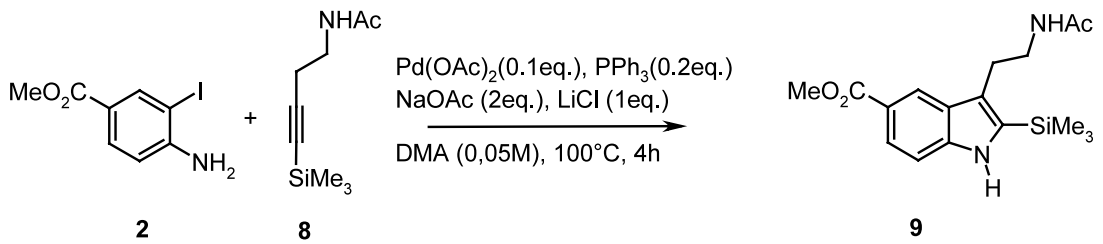
ladium species into the alkyne from the less hindered side. In order to confirm this hypothesis, desilylation of compound **9** was performed in a trifluoroacetic acid/DCM mixture (1/4:v/v), leading to the expected 2-unsubstituted indole; the specific ^{1}H NMR chemical shift of proton H-2 is consistent with the position of the side chain at 3 (Scheme 4).

2.2. Microwave experiments[16]

Generation of the indole **9** under microwave irradiation was studied with a microwave oven especially designed for organic synthesis. Preliminary experiments performed at constant temperature were not satisfactory and the best conditions were obtained by a strict power control of the focused microwave irradiation.[16] For a later application on solid support the temperature must be lower than 140°C (thermal stability of polystyrene). In power controlled experiments, the previous solvent (DMA) was changed by a mixture (DMF/ACN) which allowed us to not exceed this temperature under a strict power control of microwave irradiation; no change at constant temperature was observed by this modification. As described in Table 1, the ratio between the quantity of compounds **2** and **8** is very important (Table 2).

Treatment of **9** with 1.5 equivalents of NIS (*N*-iodosuccinimide) in DCM at reflux during 24 h afforded the iodo derivative **10**, which could be later involved in various palladium-mediated reactions, allowing access to various 2-substituted indoles (Scheme 5).

The reaction conditions for the preparation of **10** were transposed to our open microwave oven, allowing a substantial increase in the yield (58→88%) and a striking reduction in the reaction time (24 h→11 min) (Table 3).



2 **8** **9**

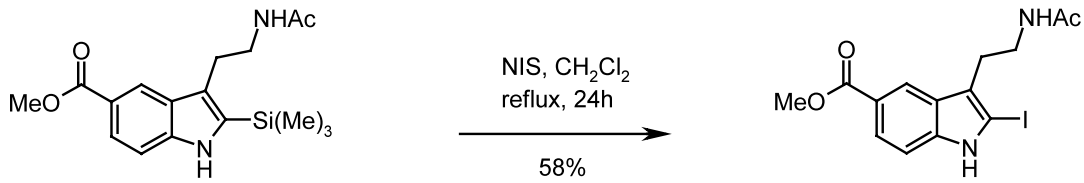
Scheme 4.

Table 2. Preparation of indole **9** from compounds **2** and **8**

Microwave irradiation: constant temperature; solvent: DMA; ratio **2/8**: 1/1		
Reaction time (min)	Temperature (°C)	Yield of **9** (%)
30	100	34
60	100	37
120	100	50
120	120	63

Microwave irradiation: strict power control				
Ratio **2**/**8** (equiv.)	Solvent (V:V)	Reaction time (min)	Irradiation power (W)	Yield of **9** (%)
1/1	DMF/toluene (2:1)	17	45	72
1/1	DMF/ACN[a] (2:1)	17	45	74
1/1	DMF/ACN[a] (2:1)	8	60	78
1/1	DMF/ACN[a] (2:1)	17	60	78
1/3	DMF/ACN[a] (2:1)	10	60	84

[a] DMF/ACN: *N*,*N*-dimethylformamide/acetonitrile.



9 **10**

Scheme 5.

Table 3. Microwave synthesis of **10**

Ratio **9**/NIS (equiv.)	Solvent	Reaction time (min)	Irradiation power (W)	Yield of **9** (%)
1/1	Dichloromethane	14	60	88
1/1.5	Dichloromethane	11	60	94

In conclusion, we performed an access to the indole core of melatonin analogs via palladium-mediated heteroannulation of internal alkyne **8** with *o*-iodoaniline derivative **2**. This synthesis is a further example of the utility of microwaves in organic chemistry, confirming that conventional thermal procedures can be substituted by microwave irradiation. The experimental microwave conditions described in this paper are now well established and our goal is to combine solid phase synthesis with microwave heating in order to speed up drug discovery process and also to demonstrate the real interest of a such association.

Acknowledgements

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16. Focused microwave irradiations were carried out at atmospheric pressure with a Synthewave S402 Prolabo microwave reactor (300 W, monomode system) with quartz reactors, visual control, irradiation monitored by PC computer, infrared measurement and continuous feedback temperature control.