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Microwave-mediated solventless synthesis of new derivatives of marine alkaloid Leucettamine B

Jean-René Chérouvrier, François Carreaux and Jean Pierre Bazureau*

Université Rennes 1, Institut de Chimie, Synthèse & Electrosynthèse Organiques 3, UMR 6510, Bât. 10A, Campus de Beaulieu, Avenue du Général Leclerc, CS 74205, 35042 Rennes Cedex, France

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Abstract—New access to *N*-alkyl derivatives of the marine alkaloid Leucettamine B are described using two three-step convergent routes. For the formation of the 2-amino imidazolone ring, the key steps involve solvent-free condensations under microwaves and guanylation reactions with non-sterically hindered primary amines.

The 2-amino imidazolone core, a derivative of cyclic guanidine, represent an interesting pharmacophore that displays a wide range of pharmacological activities (for example, they present hypoglycemic[1] and hypotensive[2] activities and they have been used also as inhibitors of NF-κB activation[3] and protein kinase C[4]). Over the past decade, an increasingly important number of 2-amino imidazolone derivatives have been isolated from marine natural products,[5] in particular those derived from sponges. Among these are (Fig. 1) the Dispacamide,[6] isolated from *Carriban Agelas* sponges, among which some members show a potent antihistamine activity, or Leucettamine B from the sponge *Leucetta microraphis* Haeckel (alcarea class) of the Argulpelu Reef in Palau,[7] which has been shown to possess a role as mediator of inflammation.[8] For these alkaloids, their total synthesis[9,10] has been also reported.

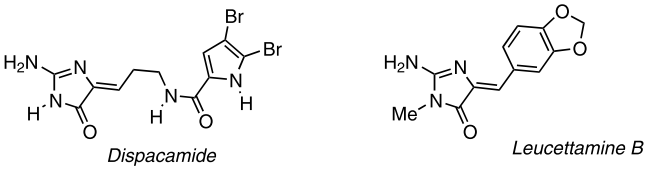

Figure 1.

During the course of our ongoing studies dealing with the development of eco-friendly methodologies (solvent-less reaction conditions[11] with/or without room temperature ionic liquid[12]) that could readily be adapted for combinatorial and/or parallel synthesis under microwave[13] irradiations (μω), of relevant core structures with potential therapeutic interest,[14] we focused our attention on the 2-amino imidazolone nucleus of Leucettamine B. For the synthesis of 5-ylidene-3,5-dihydroimidazol-4-ones there are several known methods[15] which have one or more limitations and their 2-alkylamino derivatives are not easily accessible by general routes. Thus, we decided to develop an economical and high yielding method suitable for producing a wide variety of 2-amino imidazolone derivatives. Here we wish to disclose two efficient and convergent approaches to a stereocontrolled synthesis of 2-alkylamino derivatives of Leucettamine B (Scheme 1).

The starting 3-substituted-2-thioxo-imidazolin-4-ones[16] **3a–c** were easily prepared in large scale (up to 20 g) with good yields (~96%) by addition of commercial isothiocyanates **2a–c** (R^1 = Me, Bu, Ph) to methyl glycinate hydrochloride in basic medium (Table 1). With the 2-thiohydantoines **3** in hand, we have investigated two convergent approaches for the synthesis of precursors of Leucettamine B. In the first route (from **3** to **7a–c** via **5**), regioselective *S*-alkylation (with methyliodide **4a**) gave the 2-methylsulfanyl-3,5-dihydro-imidazol-4-ones **5a–c** in the first step (Table 1). Then, condensation of *N*-3,4-(methylenedioxy)benzylidenepropylamine **6** with the 2-methylsulfanyl-3,5-dihydroimidazol-4-ones **5** conveniently provided stereochemically the (5*Z*) 5-benzo-

Keywords: 2-amino imidazolone; Leucettamine B derivatives; solvent-free; condensation; microwaves; guanylation.

* Corresponding author. Fax: + (33) 02 23 23 63 74; e-mail: jean-pierre.bazureau@univ-rennes1.fr

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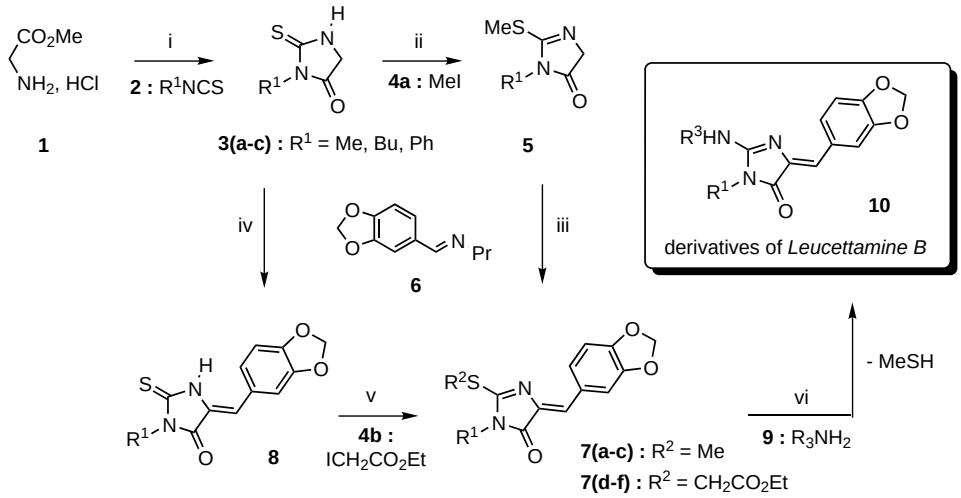

Scheme 1. *Reagents and reaction conditions*: (i) Et_3N 1 equiv., R^1NCS 1 equiv., Et_2O or AcOEt, reflux, 15 h. (ii) K_2CO_3 0.5 equiv., **4a** 1.5 equiv., MeCN, 40°C, 14 h. (iii) **6** 1 equiv., μω (in the Synthewave® 402 reactor), 70°C, 1 h. (iv) **6** 1 equiv., μω, 80°C, 1 h. (v) K_2CO_3 0.5 equiv., **4b** 1 equiv., MeCN, 80°C, 14 h. (vi) **9** 7–10 equiv., 50°C, 2–7 days.

Table 1. Results of the preparation of 2-thiohydantoines **3**, **8** and imidazolones **5**

R^1	Compound **3**	Yield of **3** (%)[a]	Compound **5**	Yield of **5** (%)[a]	Compound **8**	Yield of **8** (%)[a]
Me	**3a**	95	**5a**	95	**8a**	77
Bu	**3b**	96	**5b**	96	**8b**	75
Ph	**3c**	97	**5c**	90	**8c**	87

[a] Yield obtained after purification by recrystallization.

[1,3]-dioxo-5-ylmethylene-2-methylsulfanyl-3,5-dihydro-imidazol-4-ones **7a–c** in yields ranging from 71 to 89% (Table 2) with good purity by simple exposure of neat reactants for 1 h to focused microwaves[17] (in the Synthewave® 402 reactor). The adequate reaction conditions were found after several experiments (at various powers, temperatures and irradiation times). It should be noted that the ^1H, ^{13}C NMR data of **7a**[18] (R^1, $R^2=Me$) were identical with those previously reported.[10a,11a] Imine[19] **6** was quickly synthesized in large scale from 2 equiv. of (volatile) propylamine and 1 equiv. of piperonal using solvent-free conditions under focused microwave irradiations.

In the second route (from **3** to **7d–f** via **8**), the preparation of 2-thioxo-imidazolidin-4-ones **8a–c** was easily achieved under microwaves without solvent at 80°C during 1 h from an equimolar mixture of 2-thiohydantoin **3** and imine **6**. The desired 2-thioxo-imidazolidin-4-ones **8a–c** were obtained in good yields (Table 1) and in all cases, the condensation reactions were stereospecific. The (5*Z*)-stereochemistry of **8a–c** was based on the shielding effect of the carbonyl group on the olefinic proton H-5 (**8a–c**: $\delta_{H\text{-}5}=6.51$–6.65 ppm). In the second step, addition of ethyl iodoacetate **4b** to **8** gave regioselective *S*-alkylation with retention of the (5*Z*)-stereochemistry and produced in good yields the 5-benzo-

Table 2. Results of the preparation of 2-alkylsulfanyl-3,5-dihydro-imidazol-4-ones **7(a-f)** and 2-alkylamino-3,5-dihydro-imidazol-4-ones **10a–f**

Compound **7**	R^1	R^2	Yield of **7** (%)[a]	Compound **10**	R^1	R^3	Reaction time (days)[b]	Yield of **10** (%)[c]
7a	Me	Me	89	**10a**	Me	Pr	7	48
7b	Bu	Me	71	**10b**	Me	Bu	4	47
7c	Ph	Me	85	**10c**	Bu	Pr	5	84
7d	Me	CH_2CO_2Et	92	**10d**	Bu	Bu	4	76
7e	Bu	CH_2CO_2Et	78	**10e**	Ph	Pr	4	46
7f	Ph	CH_2CO_2Et	89	**10f**	Ph	Bu	2	50

[a] Isolated yields.
[b] Reaction time in days.
[c] Yield obtained after crystallization in ether.

[1,3]-dioxo-5-ylmethylene-2-ethyloxycarbonylmethylsulfanyl-3,5-dihydro-imidazol-4-ones **7d–f**) (Table 2).

During the study, we found that the guanylation (**7→10** with **9**) is the central step in the 2-amino imidazolone synthesis for new derivatives of Leucettamine B (Scheme 1). There have been many reports[20] around guanylation conditions, reagents[21] and precursors[22] for guanylation. Starting with **7a** (R^1, R^2=Me) and isopropylamine in large excess (~5–7 equiv.) using solventless reaction conditions, we obtained after 7 days at room temperature the 2-isopropylamino imidazolone **10** in poor yield (12%) together with by-products. It could not be isolated by flash chromatography due to partial decomposition by ring opening of the 2-isopropylamino imidazolone **10**. Similarly, when *t*-butylamine was employed, no reaction occurred at 35°C and only the formation of decomposition of products was observed when the reaction conditions were forced (reflux, 7 days). These results indicate that this guanylation reaction seems to be influenced by the steric effect of the primary amines.[23] Accordingly, when non-sterically hindered primary amines **9** (**9a**: propylamine, **9b**: *n*-butylamine, **9**: 7–10 equiv.) were allowed to react with the 2-methylsulfanyl-3,4-dihydro-imidazol-4-ones **7a–c** at 50°C without solvent for a period of 2–7 days (reaction progress was conveniently monitored by ^{1}H NMR spectroscopy), the guanylation reaction took place and the desired 2-alkylamino imidazolinones **10** as new derivatives of Leucettamine B were isolated (after elimination of excess of volatile amine **9** in vacuo) by crystallization and repeated washing with ether in yields ranging from 46 to 84% (Table 2). The structure of the new 2-amino imidazolinones **10** were substantiated by the ^{1}H, ^{13}C NMR and HRMS analysis.[24]

In summary, we report versatile and efficient routes to new derivatives of the marine alkaloid Leucettamine B. The precursors were synthesized by condensation reactions of *N*-3,4-(methylenedioxy)benzylidenepropylamine **6**, respectively, with 2-thioxo-imidazolin-4-ones **3** and 2-methylsulfanyl-3,4-dihydro-imidazol-4-ones **5** using solvent-free reaction conditions assisted by focused microwave technology. The final guanylation step gave good results only with non-sterically hindered primary amines **9**. Work is now in progress to study the protein kinase C inhibition activities[25] of these new 2-alkylamino imidazolones[26] **10**. The results of these pharmacological activities will be reported in due course.

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18. (a) Typical procedure for the preparation of *(5Z) 5-benzo[1,3]dioxol-5-ylmethylene-3-methyl-2-methylsulfanyl-3,5-dihydro-imidazol-4-one* (**7a**): In a cylindrical quartz tube (∅ = 1.5 cm) were placed successively the 3-methyl-2-methylsulfanyl-3,5-dihydro imidazol-4-one **5a** (1.44 g., 10 mmol) and the *N*-3,4-(methylenedioxy)-benzylidenepropylamine **6**[19] (1.91 g, 10 mmol). Then, the tube was introduced into a Synthewave® 402 Prolabo microwave reactor [2.45 GHz, adjusted power within the range 0–300 W and a wave guide (single mode T_{01}) fitted with a stirring device and an IR detector of temperature]. Microwave irradiation was carried out at 70°C during 60 min (the microwave oven is monitored by a computer which allows the temperature of the reaction mixture to be adjusted). The mixture was allowed to cool down. After addition of 20 ml of a mixture of solvent (CH_2Cl_2/hexane/Et_2O: 1/1/1) in the reactor, the precipitate was filtered off, washed twice with the same solvent (10 ml) and dried in a dessicator over $CaCl_2$. Recrystallization from pentane gave pure compound **7a** in 89% yield as yellowish needles (mp = 195–197°C). HRMS, *m/z*: 276.0576 (calcd for $C_{13}H_{12}N_2O_3S$: 276.0569). ^1H NMR (300 MHz, $CDCl_3$, TMS as internal ref.) δ 2.71 (s, 3H), 3.14 (s, 3H), 6.00 (s, 2H), 6.82 (d, 1H, J = 8.1 Hz), 6.86 (s, 1H, =CH), 7.37 (dd, 1H, J = 8.1, 1.5 Hz), 8.04 (d, 1H, J = 1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, TMS as internal ref.) δ 12.92 (q, J = 144 Hz), 26.48 (q, J = 141 Hz), 101.41 (t, J = 174 Hz), 108.44 (d, J = 165 Hz, C-2′), 110.87 (dt, J = 167, 7.2 Hz, C-6′), 123.83 (ddd, J = 156, 5.5, 4.3 Hz, =CH), 128.05 (dt, J = 162, 6.2 Hz, C-5′), 129.07 (sm, C-3′), 137.05 (s, C-5), 147.95 (sm, C-1′), 149.09 (sm, C-4′), 164.17 (sm, C-4), 169.95 (sm, C-2); (b) Part of this work was presented at the '*The First International Rhodia Conference: Organic Chemistry, Novel methods for the future*', Ecole Normale Supérieure de Lyon, 2–5 July 2001, Lyon, France. Poster Abstracts: A-5, p 29.

19. Solventless preparation of *N*-3,4-(methylenedioxy)-benzylidenepropylamine **6** using focused microwave technology (Synthewave® 402 reactor, Prolabo[17]): After irradiation of the mixture at 60°C for 30 min and elimination of excess of propylamine in vacuo, compound **6** was used without further purification.

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24. Selected spectral data of *(5Z) 5-benzo[1,3]dioxol-5-yl-methylene-3-methyl-2-propylamino-3,5-dihydro-imidazol-4-one* (**10a**) HRMS, *m/z*: 287.1279 (calcd for $C_{15}H_{17}N_3O_3$: 287.0932). Mp = 191–192°C from ether. ^1H NMR (300 MHz, $CDCl_3$, TMS as internal ref.) δ 1.02 (t, 3H, J = 7.4 Hz); 1.74 (s, 2H, J = 7.3 Hz); 3.11 (s, 3H); 3.54 (q, 2H, J = 6.2 Hz); 4.95 (br s, 1H, NH); 5.98 (s, 2H); 6.62 (s, 1H); 6.81 (d, 1H, J = 8.1 Hz); 7.34 (dd, 1H, J = 8.1, 1.4 Hz); 7.99 (d, 1H, J = 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, TMS as internal ref.) δ 11.5 (qt, J = 126, 4.0 Hz); 22.8 (tq, J = 135, 3.7 Hz); 25.2 (q, J = 140 Hz); 43.7 (tq, J = 142, 7 Hz); 101.10 (t, J = 173 Hz); 108.40 (d, J = 164 Hz, C-2′); 110.30 (dt, J = 164, 7.1 Hz, C-6′); 116.80 (dt, J = 157, 3.5 Hz, =CH); 126.10 (dt, J = 162, 6.2 Hz, C-5′); 130.20 (d, J = 7.8 Hz, C-3′); 138.10 (s, C-5); 146.60 (s, C-1′); 147.70 (sm, C-4′); 157.20 (sm, C-4); 170.40 (sm, C-2).

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26. The new 2-alkylamino imidazolone derivatives of Leucettamine B **10** will be evaluated in a drug discovery program (protein kinase C inhibition activities) at the 'Station Biologique de Roscoff, BP 74, 29682-Roscoff Cedex, France'.