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An Iminophosphorane-Mediated Efficient Synthesis of the Alkaloid Leucettamine B of Marine Origin.

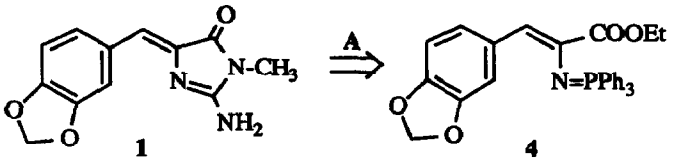
Pedro Molina*, Pedro Almendros, Pilar M. Fresneda

Departamento de Química Orgánica, Facultad de Química,
Universidad de Murcia, Campus de Espinardo, E-30071, Murcia, Spain.

Abstract. *The first synthesis of the alkaloid Leucettamine B, by a four-step sequence in a overall yield of 50%, is discribed. The key step, formation of the 2-aminoimidazole ring, involves a tandem aza-Wittig/carbodiimide-mediated annulation process.*

Certain secondary metabolites of marine origin are no-traditional, guanidine-based alkaloids that possess a broad spectrum of powerful biological activities.[1] The guanidine moiety is must frequently found in the guise of a 2-aminoimidazole that is generally substituted with alkyl groups on carbon or nitrogen. Recently leucettamine B **1** has been isolated from the sponge *Leucetta microraphis* Haeckel (Calcarea class) of the Argulpelu Reef in Palau.[2]

In the course of our studies directed towards the synthesis of nitrogen-containing heterocycles based on the heterocyclization reaction of C=C-conjugated heterocumulenes, we have developed the tandem aza-Wittig/ heterocumulene-mediated annulation.[3] Although a few examples of its application in the imidazole field exist,[4] this methodology has proved to be highly suitable for the preparation of the leucettamine B **1**. Herein we wish to report the successful realization of the step A in one flask process permitting a quick access to compound **1**.



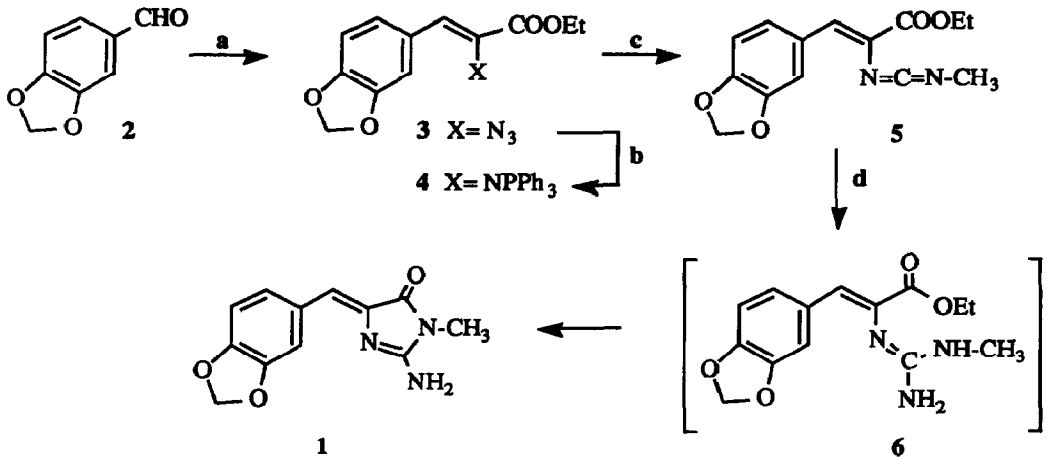
1 **4**

Conversion of aldehyde **2** into azide **3** was performed in 75% yield by reaction with ethyl azidoacetate under standard conditions.[5] Staudinger reaction of azide **3** with triphenylphosphine provided the iminophosphorane **4** in excellent yield (92%). Aza-Wittig type reaction of iminophosphorane **4** with methyl isocyanate at room temperature furnishes the carbodiimide **5** in almost quantitative yield, which was used without further purification for the next step. When a toluene solution of carbodiimide **5** was treated with ammonia at 45°C the leucettamine B **1** was obtained in 80% yield[6] through a guanidine-substituted intermediated **6**, which undergoes regioselective imidazole ring-formation across the ester and methylamino functionality.

The E/Z configuration of the exocyclic double bond for related compounds[7] has been assigned on the basis of a larger H-C (7), C (5) $^{1}H-^{13}C$ heteronuclear coupling constant in the E form (J=9.8-11.0 Hz) than in the Z form (J= 4.2-5.2 Hz). Configuration Z for compound **1** prepared in this work is assigned on the basis of the value of coupling constant (J= 5.4 Hz) observed, and is the same that the natural leucettamine B.

In conclusion, we have developed an efficient four-step synthesis of the alkaloid leucettamine B from readily

available starting materials in an overall yield of 50%. This synthesis, which involves as key step an aza Wittig/ carbodiimide-mediated annulation to build up the 2-aminoimidazole ring, allows the preparation of leucettamine B in multigran-scale.



Reagents and conditions: a) N_3CH_2COOEt, NaEtO, -15°C (75%); b) Ph_3P, CH_2Cl_2, r.t. (92%); c) CH_3-N=C=O, toluene, r.t. (90%); d) NH_3, sealed tube, 45°C (80%).

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6. *Typical Procedure*: To a solution of iminophosphorane **4** (1.2g, 2.4 mmol) in dry toluene (40 ml), was added dropwise a solution of methylisocyanate (0.14g, 2.4 mmol) in the same solvent (10 ml). The solution was stirred at room temperature under nitrogen for 32 h. A mixture of the toluene solution of carbodiimide **5** and an excess of liquid ammonia (5 ml) was heated in a sealed tube at 45°C for 10 h. The precipitated solid was collected by filtration and recrystallized from toluene to give **1** (0.47g, 80%), m.p. 253-255°C, as yellow prisms. Satisfactory elemental analysis was obtained, the IR spectrum, EI-mass spectrum and the whole pattern of ^1H and ^{13}C-NMR signals were identical to the natural leucettamine B.[2]
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