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Biogenetically Inspired Synthesis of Marine C_6N_4 2-Aminoimidazole Alkaloids: Ab Initio Calculations, Tautomerism, and Reactivity

Robert Abou-Jneid, Said Ghoulami, Marie-Thérèse Martin, Elise Tran Huu Dau, Nathalie Travert, and Ali Al-Mourabit*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France

ali.almourabit@icsn.cnrs-gif.fr

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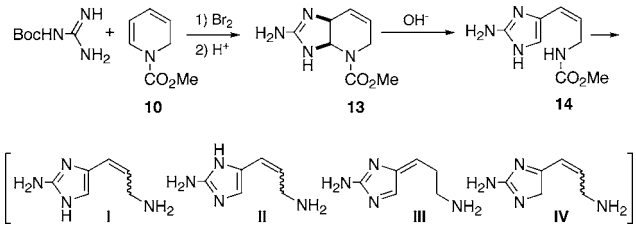
ABSTRACT



A simple synthesis of the fused tetrahydro-imidazopyridine 13 was accomplished via selective addition of protected guanidine to *N*-carbomethoxy-1,2-dihydropyridine in the presence of bromine. Base-mediated semicleavage of the aminal gave 4-substituted 2-aminoimidazole 14. With this new method, natural marine metabolite 3-amino-1-(2-aminoimidazol-4-yl)-prop-1-ene (1) and derivatives may now be prepared from pyridine. Ab initio calculations of the energies of tautomers I–IV and deuteration experiments have provided insight into their reactivity.

Marine metabolite 3-amino-1-(2-aminoimidazol-4-yl)-prop-1-ene **1** (Figure 1) was isolated from the Axinellidae sponges *Teichaxinella morchella* and *Ptilocaulis walpersi* collected in the Caribbean and southern Atlantic.[1] Compound **1** is a member of the common biogenetically related class of compounds defined by the presence in their structures of bromopyrrole carboxamide and 2-aminoimidazole units. The isolation and synthesis of pyrrole 2-aminoimidazole natural compounds have been documented in a series of reports.[2] The structural complexity and diversity of these alkaloids continue to challenge synthetic organic chemists two decades after the first synthesis of dibromophakelline reported by Büchi and co-worker.[3]

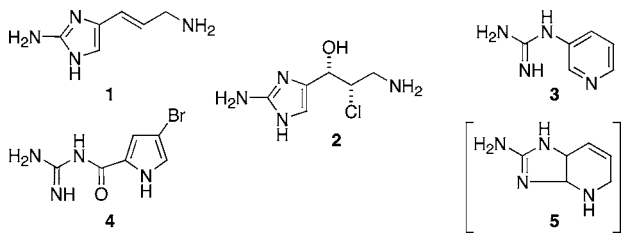


Figure 1. Structures of the marine metabolites containing 2-aminoimidazole, pyrrole, and pyridine moieties.

To date, syntheses of the substituted 2-aminoimidazole key structural motif **1** are limited.[4] Webber reported the single example of the addition of acetylated guanidine to α-bromo-

(1) Wright, A. E.; Chiles, S. A.; Cross, S. S. *J. Nat. Prod.* **1991**, *54*, 1684−1686.

(2) (a) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Princep, P. R. *Nat. Prod. Rep.* **2003**, *20*, 1−48 and references therein (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1−48 and references therein. (c) Berlink, R. G. S. *Nat. Prod. Rep*. **2002**, *19*, 617−649. (d) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753−1783.

(3) Foley, L. H.; Büchi, G. *J. Am. Chem. Soc*. **1982**, *104*, 1776−1777. Using the method of: Lancini, G. C.; Lazzari, E.; Arioli, V.; Bellani, P. *J. Med Chem*. **1969**, *12*, 775−780. For recent syntheses, see: Wiese, K. J.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett*. **2002**, *43*, 5135−5136 and references therein.

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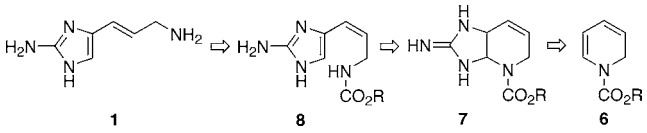
ketone.[5] However, due to the reactivity of **1** and the presence of the unsaturated side-chain at position 4, effort is required to secure an alternative and more direct strategy for its synthesis.

As a part of our program to develop new syntheses and to understand the biomimetic reactivity of 2-aminoimidazole marine metabolites, for which compound **1**, as a central precursor, is of great interest for biogenetic considerations,[6] we describe here a new biogenetically inspired synthesis of **1** and the study of its tautomeric behavior.

The C_6N_4 derivatives of **1** such as girolline (**2**),[7] pyraxinine (**3**),[8] and **4**[9] were isolated from the *Axinellidae* and *Agelasidae* families of sponges. Although pyraxinine is a pyridine derivative, it may be biogenetically considered as being derived from the same intermediate **1** as girolline (Figure 1). Thus, cyclization of **1**, cleavage of the resulting aminal **5**, and aromatization to pyridine could occur to afford pyraxinine (**3**). This is presumed to be a minor process, since girolline is accompanied by only small amounts of pyraxinine. However, the significance of the chemical connection between **1** and **3** oriented us to use pyridine for the synthesis of the natural compound **1**.

We reasoned that if **1** and **3** were connected to the intermediate relay **5**, then the synthesis of **1** should be accessible from pyridine through a bicyclic compound of type **5**. Our approach would involve a preparation of **7** from guanidine derivatives and the known *N*-alkylcarbamoyl 1,2 dihydropyridine (**6**) (Scheme 1) followed by the unprecedented ring

Scheme 1. Targeted 2-Aminoimidazole Derivatives from 1,2-Dihydropyridine



cleavage reaction of **7** into **8**, affording the appropriately substituted (*Z*)-isomer of the 2-aminoimidazole precursor of **1**. We assumed that both of the two new reaction steps (**6** → **7** and **7**→ **8**) would require special focus. The electron-withdrawing alkyl or aryl-carbamoyl group should assist the regioselective aminal cleavage and afford the aromatic 2-aminoimidazole derivative **8**.

A literature survey revealed that dihydropyridine **6** is accessible from pyridinium salts by careful reduction with borohydride reagents.[10] Despite the instability of dihydropyridines, Fowler reported that an *N*-carboalkyloxy substituent stabilizes the dihydropyridine and permits its use for preparative chemistry. We studied the reaction of various free and protected guanidines with the carbomethoxydihydropyridine (**10**) in the presence of bromine or NBS. The expected bicyclic product **13** was obtained when 3−4 equiv of Boc-guanidine[11] were added to the dihydropyridine **10** in a mixture of DMF/MeCN in the presence of bromine. Removal of the Boc protecting group by direct treatment of nonseparated regioisomers **11** and **12** with 2 M HCl afforded compound **13** in 71% yield. Compounds **11** and **12** could be isolated by flash chromatography on silica gel. Cis-fused bicyclic **13** was fully characterized by NMR spectroscopy.[12] Interestingly, when the reaction was carried out using 1 or 2 equiv of Boc-guanidine, only moderate yields of **13** were obtained. The regioselective cleavage of the aminal bond N_1-C_2 of **13** into **14** was achieved in 85% yield by boiling for 5 min in aqueous 1 M NaOH. However, the yield of the reaction was dramatically time and temperature dependent. The yield of reaction decreased when scaled up to multigram quantities. The instability of the allylic amine **14** under basic conditions thus limits its preparation in large quantities.[13] Assuming the manifold pH-dependent reactivity of 2-aminoimidazoles substituted by an allylamine at position 4, we have investigated the chemical behavior of **14** under acidic and basic conditions.

If we consider the natural product **1**, there are four tautomeric forms that implicate the protons H_1, H_3, H_5, and H_7 (Figure 2). The low relative energy differences between

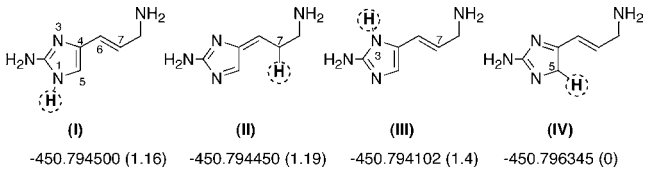


Figure 2. Ab initio calculations of the four tautomers of **1**: total energies (a.u.) at the 6-316* level with relative energies in parentheses (kcal/mol).

the four tautomers (<1.40 Kcal/mol) obtained by ab initio calculations[14] at the 6-316* level suggest the possible coexistence of the tautomers under the same conditions. In our previous paper, we outlined that the reactivity of the tautomers is probably at the origin of the molecular diversity

(4) (a) Daninos, S.; Al-Mourabit, A.; Ahond, A.; Zurita, M. B.; Poupat, C.; Potier, P. *Bull. Soc. Chim. Fr.* **1994**, *131*, 590−599. (b) Olofson, A.; Yakushjin, K.; Horne. D. A. *J. Org. Chem.* **1997**, *62*, 7918−7919. (c) Berrée, F.; Bleis, P. G.-L.; Carboni, B. *Tetrahedron Lett.* **2002**, *43*, 4935−5138.

(5) Little, T. L.; Webber, S. E.; *J. Org. Chem.* **1994**, *59*, 7299−7305.

(6) Al-Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237−243 and references therein.

(7) Ahond, A.; Bedoya-Zurita, M.; Colin, M.; Fizames, C.; Laboute, P.; Lavelle, F.; Laurent, D.; Poupat, C.; Pusset, M.; Pusset, J.; Thoison, O.; Potier, P. C. R. *Acad. Sci. Paris, Série II* **1981**, *307*, 145−148.

(8) Al-Mourabit, A.; Pusset, M.; Chtourou, M.; Gaigne, C. Ahond, A. Poupat, C.; Potier, P. *J. Nat Prod.* **1997**, *60*, 290−291.

(9) Scheuer, P. J. *Marine Natural Products*; Academic Press: London New York, 1981; Vol. IV, pp 70−73.

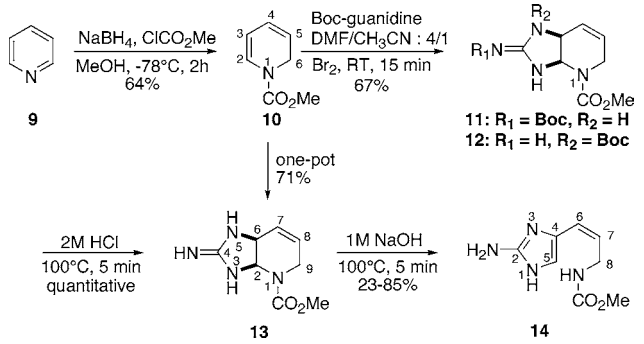
(10) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321−1323.

(11) Boc-guanidine was prepared by the adaptation of the method reported by Goodman: Zapf, C. W.; Creighton, C. J.; Tomioka, M.; Goodman, M. *Org. Lett.* **2001**, *3*, 1133−1136.

(12) Compound **7** gave satisfactory one- and two-dimensional NMR spectra. The stereochemistry of the cis-fused structure was elucidated by two-dimensional NOESY experiments.

(13) Efforts to optimize this step have demonstrated that different N-substitutions on the guanidine and dihydropyridine groups are important. To evaluate the scope of the method, a general study of the reaction including urea derivatives and *N*-acyldihydropyridines will be reported elsewhere.

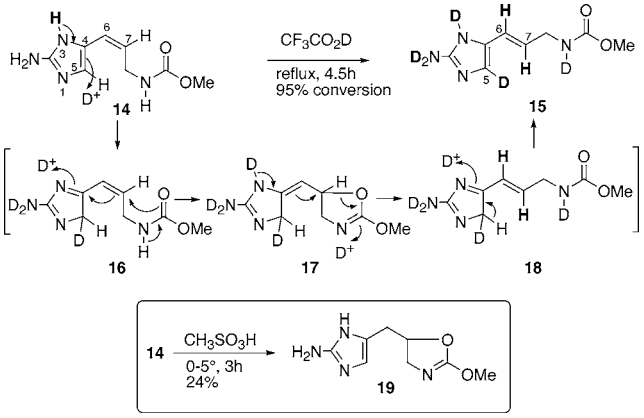
Scheme 2. Preparation of 2-Aminoimidazole from Pyridine



observed in this family of metabolites.[6,15] We therefore decided to deuterate positions 5 and 7 of **14** to allow comprehensive investigation of the influence of the tautomerism on the reactivity. Hydrogen−deuterium exchange was followed by NMR.

Compound **14** was treated with acids under various conditions with a view to promote both isomerization and deuteration steps. Refluxing compound **14** in CF_3CO_2D for 8 min resulted in simultaneous acid-catalyzed *Z*/*E* isomerization and 40% H−D exchange of H_5 uniquely (Scheme 3). 95% H_5−D exchange was observed after 4 h 30 min of

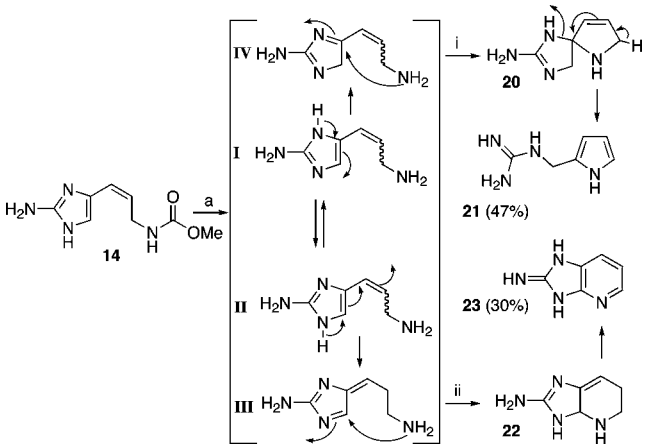
Scheme 3. Deuteration Experiments and Reactivity of the Tautomers



reflux in CF_3CO_2D. Unexpectedly, no detectable H_7−D exchange was observed.[16] The isomerization of (*Z*)-isomer **14** into the (*E*)-isomer **15** without deuteration of position 7 was explained by the assistance of the carbonyl group and the formation of the detected oxazoline **19** (Scheme 3). The rate of intramolecular cyclization of the most stable tautomer species **16** to the oxazoline **17** is probably too rapid to allow any deuteration by further proton exchanges. The intermediate **17** protects proton H_7. The proposed mechanism is in agreement with previous ab initio studies giving the lowest energy level for the tautomer **IV** (Figure 2). Nevertheless, the drastic acidic conditions required for the *Z*/*E* isomerization/deuteration of **14** is intriguing. The presence of **19** was also observed by NMR when **14** was refluxed with aqueous 6 M HCl. Importantly, we were able to purify **19** in 24% yield after treatment of **14** with methanesulfonic acid at 0−5 °C (Scheme 3). A similar result involving an imidazolone derivative was reported by Horne and co-workers.[17]

To prevent the carbonyl assistance, hydrolysis of the methylcarbamoyl group was attempted under various conditions. When aqueous 1 M NaOH was boiled for 20−25 min, **14** yielded pyrrole derivative **21** in yields varying from 20 to 47% (Scheme 4). Compound **21** was obtained in 47% yield

Scheme 4. Tautomerism and Reactivity of 3-Amino-1-(2-aminoimidazolyl)-prop-1-ene **1**[a]



[a] Reaction conditions: (a) 1 M NaOH, (i) 25 min reflux, **21** (47%), (ii) 48 h rt, **23** (30%).

by heating the mixture **11** + **12** for 25 min in 1 M NaOH. Total deprotection and cyclization occur rapidly. When **14** was stirred in 1 M NaOH at room temperature for 48 h, formation of **23**, isolated in 30% yield, became predominant. Horne and co-workers noticed the formation of an oxidized intermediate relating **22** to **23**, but no characterization of this

(14) Total energies of the four tautomers **I**−**IV** of **1** were performed with ab initio calculations using the Gaussian 98 program (see ref 14a). All the structures were optimized with gradient techniques using the 6-316* basis set, which includes one orbital polarization function on C and N (see ref 14b): (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998. (b) Hariaran, P. C.; Pople, J. A. *Theor. Chim. Acta*. **1973**, *28*, 213−222.

(15) Endo, T.; Tsuda, M.; Okada, T.; Mitsuhashi, S.; Hima, H.; Kikuchi, K.; Mikami, Y.; Fromont, J.; Kobayashi, J. *J. Nat. Prod*. **2004**, *67*, 1262−1267.

(16) For isomerization−deuteration, see also: (a) Lindel, T.; Hochgürtel, M. *J. Org. Chem.* **2000**, *65*, 2806−2809. (b) Daninos-Zeghal, S.; Al-Mourabit, A.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1997**, *53*, 7605−7614.

(17) Barrios Sosa, A. C.; Yakushijin, K.; Horne, D. A. *Org. Lett*. **2000**, *2*, 3443−3444.

intermediate was given.[4b] These results provide further strong evidence that tautomers **I**−**IV** are formed in the reaction mixture. The outcome of the reaction can be understood in terms of thermodynamic and kinetic influences. It is clear that the regioselectivity of the cyclization reflects the presence of the electrophilic tautomers **I** and **IV** (Scheme 4), which are derived from the nucleophilic species **II** and **III**, respectively. The temperature probably does not influence the orientation of the cyclizations of the species **III** into **22** or **IV** into **20** but permits the rearrangement of the intermediate **20** into **21**. Longer reaction times at room temperature favor the oxidative aromatization of **22** into **23**.

Comparison of the natural compounds **3** with **23** and **4** with **21** indicates the possible common origin of **1**, **3**, and **4**. The understanding of the chemical reactivity of **1** under controlled conditions is undoubtedly one of the most direct ways to achieve the synthesis of complex polycyclic pyrrole-2-aminoimidazole alkaloids.[6] However, more studies will be needed before targeting selective biomimetic polycyclic monomers and dimers.

In conclusion, an efficient biogenetically inspired method for the synthesis of marine 2-aminoimidazole derivatives has been developed. The flexibility of the described reaction sequence can be applied to the synthesis of a large number of heterocyclic natural and unnatural derivatives. Further work directed toward the synthesis of oroidin and polycyclic marine pyrrole 2-aminoimidazoles using the above studies is currently underway and will be reported soon.

Acknowledgment. We gratefully acknowledge Dr. Robert Dodd for the improvements to this manuscript and Dr. Anne Zaparucha for fruitful discussions.

Supporting Information Available: Experimental details, spectral data, and ^{1}H and ^{13}C spectra for **11**−**15**, **19**, **21**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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