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Total syntheses of isonaamine C and isonaamidine E

Heather M. Lima, Beatriz J. Garcia-Barboza[†], Nicole N. Khatibi[†], and Carl J. Lovely^{*}

Department of Chemistry & Biochemistry, University of Texas at Arlington, Arlington, TX 76019

Abstract

The total syntheses of two alkaloids isolated from a marine sponge of the *Leucetta* sp. have been accomplished in 6 and 7 steps starting from a 4,5-diiodoimidazole derivative. Grignard mediated halogen-metal exchange was used to install the benzyl side chain. C2 substitution was accomplished via lithiation followed by quenching with trisyl azide which provided isonaamine C after hydrogenation. Isonaamidine E was then prepared from isonaamine C via introduction of the hydantoin ring by reaction with an activated parabanic acid.

Keywords

Leucetta; 2-aminoimidazole; 4,5-diiodoimidazole; azidation; methylparabanic acid

Marine sponges of the *Leucetta* and *Clathrina* genera produce a number of imidazole-containing alkaloids that are characterized by a 2-amino or *N*-imidazolidinedionyl group at C2, and varying benzyl substitution at C4 and C5 on the imidazole.^{1,2} Isonaamine C (**1**)³ and isonaamidine E (**2**) isolated by Wright in 2002,⁴ among others, are representative examples of this class of natural products (Figure 1).⁵ Calcaridine A (**5**)^{6,7} is an example of the more highly oxidized members of this family. Many of these alkaloids have been reported to exhibit varying biological activity including those of interest in this manuscript. Both isonaamine C (**1**) and isonaamidine E (**2**) were found to be cytotoxic against stomach (HM02) and liver (HepG2 and Huh7) cancer cell lines with GI₅₀ values in the range of 1.3 to 7.0 µg/mL.⁴

A robust, efficient, and adaptable synthetic strategy developed by our lab to access this family of natural products centers around the functionalization of 4,5-diiodoimidazoles via halogen-metal exchange of Grignard reagents to prepare the benzyl substituted framework.² C2 substitution using *n*-BuLi and TsN₃ or TrisN₃ to ultimately lead to the 2-amino substituted target following reduction has been a very effective method as evidenced by the successes in our own lab^{7–9} and in numerous other examples. This manuscript will detail the application of this approach in the total syntheses of isonaamine C (**1**) and isonaamidine E (**2**).

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^{*}Corresponding author. Tel.: +1-817-272-5446; fax: +1-817-272-3808; lovely@uta.edu.

[†]Undergraduate coworkers

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Supplementary Material

Experimental procedures and copies of ¹H and ¹³C NMR data for all new compounds are available.

The sequential functionalization of 4,5-dihaloimidazoles with Grignard reagents has been well documented, and follows the order of C5, then C4.^{10–12} However, C4 functionalization of *N*-benzyl substituted derivatives leading to C4 benzyl substitution has not been demonstrated before, and the occurrence of competitive lateral metalation of the *N*-benzyl side chain is a possible complication.^{13; 14} Therefore, the application of this synthetic strategy to isonaamine C provides the first example of selective C4 metalation in the presence of an *N*-benzyl substituent. Going forward, 4,5-diiodoimidazole (**6**) was treated with NaH, then 4-methoxybenzyl chloride to give the PMB-protected imidazole **7**. Treatment of **7** with EtMgBr induced a halogen-metal exchange at C5 selectively which when quenched with water resulted in an overall reduction leading to the 4-iodoimidazole intermediate **8** (Scheme 1).

Treatment of **8** with another round of EtMgBr followed by 3,4-dimethoxybenzaldehyde (**9**) led to a mixture of alcohol **10** and the corresponding ketone **12**, which is thought to form via an Oppenauer-type oxidation as a result of coordination through the magnesium alkoxide salt and the benzaldehyde **9** (Scheme 2).^{15–17} However, it was found that the formation of the ketone by-product could be minimized by the addition of the prepared Grignard reagent to a dilute solution of the aldehyde at room temperature. In addition, the crude mixture of products isolated from the Grignard reaction could be treated with NaBH₄ in MeOH to provide **10** in 73% yield over the two steps.

Reduction of **10** with Et₃SiH and TFA^{7–9} led to **11** allowing access to the necessary bis-benzyl substituted framework of isonaamine C and isonaamidine E. The 2-amino substituent was introduced by treatment of **11** with *n*-BuLi and quenched with TrisN₃ to give **13** which was reduced via hydrogenation on Pd/C resulting in isonaamine C (**1**) in 86% yield. The hydantoin ring of isonaamidine E was introduced following the literature procedure involving reaction of 1-methylparabanic acid and BSA leading to the activated acid **14**.^{8; 9; 18; 19} Upon treatment of **1** with **14**, isonaamidine E (**2**) was isolated in 51% yield from **1** (Scheme 3). In both cases, the spectroscopic data for compounds **1** and **2** agree with reported values.⁴

In conclusion, isonaamine C (27% overall) and isonaamidine E (14% overall) have been synthesized in 6 and 7 steps respectively from **7** following a general synthetic route developed by us to access this family of natural products. Central to this approach is the application of the chemoselective reactivity of 4,5-dihaloimidazole substitution that has allowed for the controlled elaboration of imidazoles, including those having *N*-benzyl substituents, leading to the desired benzyl substituted core of the target alkaloids. To date a number of *Leucetta* and *Clathrina* alkaloids have been synthesized following this strategy attesting not only to its versatile and efficient nature, but also its potential applicability in medicinal chemistry projects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Examples of *Leucetta* alkaloids

Scheme 1.
Substitution of 4,5-diiodoimidazole

Ar = 3,4-dimethoxyphenyl

Oppenauer-like transition state
leading to ketone **12**

Scheme 2.
Grignard reaction leading to **10** and **12**

Scheme 3.
Total synthesis of isonaamine C and isonaamidine E