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First synthesis of parazoanthine-A and its *O*-Me derivative

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ABSTRACT

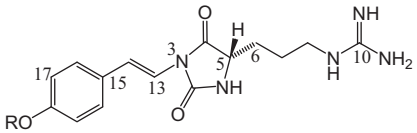
Parazoanthine A (7.0% overall yield) and its *O*-methyl derivative (6.2% overall yield) were prepared by a concise biomimetic synthesis based on the coupling reaction of L-arginine methyl ester dihydrochloride with isocyanate derivatives of *p*-coumaric acid and 4-methoxy-cinnamic acid, respectively. The synthetic approach is designed to obtain a wider class of parazoanthine analogs.

Parazoanthines are a group of unique naturally-occurring marine alkaloids reported to date only from the Mediterranean sea anemone *Parazoanthus axinellae*.[1] These molecules exhibit the chemical framework characterized by the presence of a 3,5-alkyl disubstituted hydantoin core bearing a terminal guanidine and an aromatic ring. Even though hydantoins and derivatives have been widely used in biological screenings in numerous pharmaceutical applications including convulsants[2] and antimuscarinics,[3] antiulcers and antiarrythmics,[4] antivirals, antidiabetics,[5] serotonin and fibrinogen receptor antagonists,[6] inhibitors of the glycine binding site of the NMDA receptor,[7] and antagonists of leukocyte cell adhesion,[8] no relevant biological activity has been evidenced for parazoanthines.[1] With the aim of getting natural parazoanthines along with the new derivatives to be used in biological screening programs, we started with the chemical synthesis of the first member of the group, parazoanthine A (**1**) and a concurrent investigation of a sample of *P. axinellae*.[9]

Here we report a simple biomimetic strategy for the synthesis of parazoanthine A (**1**). The corresponding *O*-Me derivative (**2**), not previously reported, but detected as the minor component of parazoanthine mixture,[9] was also prepared (Fig. 1).

The key-step of the strategy was the coupling reaction (Fig. 2) between the commercially available L-arginine methyl ester dihydrochloride and the opportunely prepared isocyanates **3** and **3a**, by using *N*-ethylmorpholine in *N*,*N*-dimethylformamide according to Stilz et al.[10]

The preparation of compounds **3** and **3a** is illustrated in Figure 3. Commercially available *p*-coumaric acid (**4**) and 4-methoxy-cinnamic acid (**4a**) were treated with sodium azide,



1, R=H
2, R=Me

Figure 1. Parazoanthine A (**1**) and its *O*-Me derivative (**2**).

triphenylphosphine, and trichloroacetonitrile in acetonitrile[11] to give the corresponding intermediate azide derivatives **5** and **5a**. The subsequent Curtius rearrangement of **5** and **5a** in toluene at 68 °C overnight[12] led to the isocyanates **3** and **3a**, respectively, which were freshly used due to their instability.

In Stilz et al. procedure[10] the use of *N*-ethylmorpholine in DMF led to the formation of an urea derivative which was cyclized to give the hydantoin framework only by the subsequent treatment with 6 N HCl under reflux. We observed that in our case the formation of the hydantoin moiety just occurred after the treatment with *N*-ethylmorpholine in DMF (Fig. 2) whereas the following use of 6 N HCl revealed to be disadvantageous because of the formation of a complex mixture of products. Thus, this step was not considered in our synthetic scheme.

In the coupling reaction (Fig. 2) the obtained yields were quite low if compared to those reported by Stilz et al. (Ref. 10). This was probably due to the less nucleophilic reactivity of the isocyanate nitrogen atom being this functional conjugated to the double bond. However, with the aim at improving the yields, different experimental conditions in the coupling step were used. In particular, the temperature was varied in the range of 20–60 °C, distinct solvents including DMF, DMSO, and THF were used, and *N*-ethylmorpholine was added in the range of 1–3 equiv.

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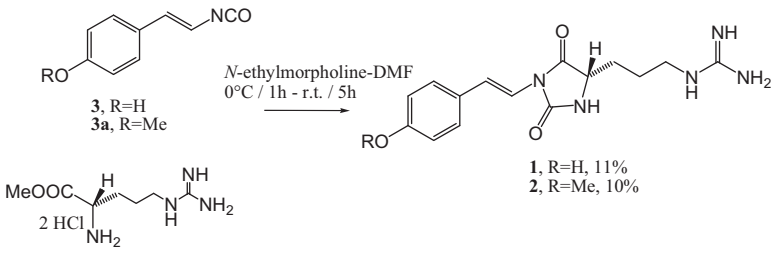

Figure 2. Coupling reaction to get parazoanthine A (**1**) and the *O*-Me analog (**2**).

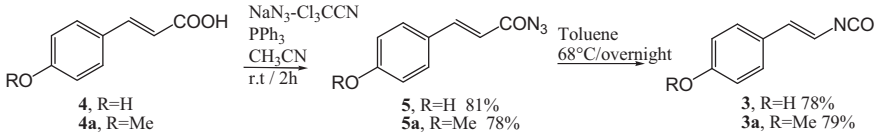

Figure 3. Preparation of synthetic isocyanate precursors of parazoanthine A and its *O*-Me-analog.

Compounds **1** and **2** were obtained in the best yield of 11% and 10%, respectively, by carrying out the reaction at rt, in DMF, and with 1.2 equiv of *N*-ethylmorpholine. The C-5 chirality was preserved by the coupling reaction.

The spectral data of synthetic parazoanthine A (**1**) were identical to those of natural compound.[1] *O*-Me parazoanthine A (**2**) showed ^{1}H and ^{13}C NMR spectroscopic data similar to parazoanthine A differing only in the presence of the methoxy group on the aromatic ring instead of the hydroxyl function (see Supplementary Supporting Information).

This is the first synthetic strategy of a member of parazoanthine class that could open the way for the preparation of other natural and not natural analogs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.066.

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