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Synthetic approaches towards an indole alkaloid isolated from the marine sponge *Halichondria melanodocia*

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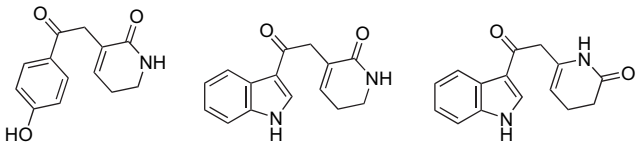
Abstract—The exocyclic analogue of the indole alkaloid isolated from the marine sponge *Halichondria melanodocia* has been prepared via olefination of a phosphonoester derived from 3-(2-bromoacyl)indole. The formation of an unexpected indolylazepine is also discussed.

1. Introduction

Marine organisms, such as sponges and tunicates, constitute a unique and vast resource for the discovery of bioactive molecules with novel structures. Many marine alkaloids have generated interest not only due to their various and often striking pharmacological activities but also as challenging problems for structure elucidation and synthesis.[1]

As far back as in 1979 two lactams were isolated from the isopropanol extracts of an algae-infested Caribbean sponge, *Halichondria melanodocia*.[2] The structures of the lactams were assigned as the related phenol and indole derivatives **1** and **2**, respectively (Fig. 1). Although structure **3** was discussed as an alternative for **2**, it was disregarded since it was incompatible with the chemical shift data.

To the best of our knowledge, the biological activity of the lactams isolated from *H. melanodocia* has not yet been evaluated, neither have their structures been confirmed via synthesis. It also seems to be uncertain whether the alkaloids are produced by the sponge itself or by the associated algae and bacteria.



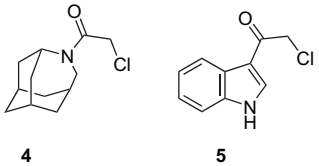
1 2 3

Figure 1.

2. Results and discussion

Our continuous interest in marine indole alkaloids[3] attracted our attention towards compound **2**. Since chloroacetylazahomoadamantane (**4**) (Fig. 2) has been reported to react with triethyl phosphonoacetate at the α-position,[4] we believed that 2-chloro-1-(1*H*-indol-3-yl)-ethanone (**5**)[5] could similarly afford the appropriate building block in our attempts to synthesise **2**. It was conceived that such a phosphonoester building block should provide a possibility to introduce the double bond in the correct position of the lactam.

Hence, triethyl phosphonoacetate was treated with a base (NaH) followed by the Boc-protected chloroacyl indole **6a**. The yields of **7a** were quite modest, under the conditions initially evaluated (NaH, THF), seldom over 30%, largely depending on the co-formation of product **8**[4] together with unreacted starting material (Scheme 1). Other bases were



4 5

Figure 2.

Keywords: *Halichondria melanodocia*; Indole alkaloids; Exocyclic; Lactams.
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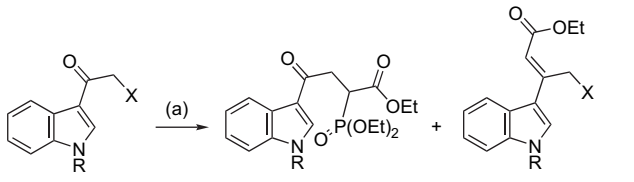
tried as well (BuLi, *t*-BuOK, LDA, DBU) with the result of either inferior yields or more by-product formation. Solvent and temperature changes did not improve the yield but, since we noticed that in the presence of a catalyst (NaI or Bu_4NI) the yields improved (less than 10% product without catalyst), we suspected that other 3-(2-haloacyl)indoles could give superior results. As expected, changing the chlorine atom to bromine or iodine (compounds **6b–d**) improved the yields significantly. As a consequence, the formation of **8** was minimised. Changing to a polar aprotic solvent improved the yields even further.



6a X = Cl, R = Boc
6b X = Br, R = Boc
6c X = I, R = Boc
6d X = Br, R = SO_2Ph

7a R = Boc
7b R = SO_2Ph

8 X = Cl, R = Boc

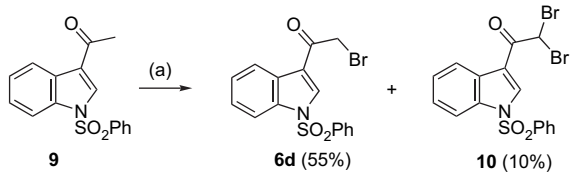
Scheme 1. (a) NaH; other reagents and conditions see Table 1.

Table 1

Indole derivative	Solvent	Other conditions	Yield **7a/7b** (%)	Yield **8** (%)
6a X=Cl, R=Boc	THF	Bu_4NI, rt, 18 h	27	14
6a X=Cl, R=Boc	THF	Bu_4NI, reflux, 4 h	42	n.i
6a X=Cl, R=Boc	THF	Bu_4NI, 0 °C to rt, 18 h	24	n.i
6a X=Cl, R=Boc	Toluene	Bu_4NI, reflux, 3 h	22	n.i
6a X=Cl, R=Boc	DMF	NaI, 60 °C, 36 h	—	—
6a X=Cl, R=Boc	THF	NaI, rt, 18 h	26	26
6d X=Br, R=SO_2Ph	THF	NaI, rt, 1.5 h	72	—
6a X=Cl, R=Boc	THF	rt, 18 h	8	n.i
6c X=I, R=Boc	THF	rt, 18 h	56	n.i
6b X=Br, R=Boc	THF	rt, 18 h	49	n.i
6c X=I, R=Boc	DMF	rt, 18 h	70	—
6d X=Br, R=SO_2Ph	DMF	NaI, rt, 18 h	56	—
6b X=Br, R=Boc	DMF	rt, 18 h	71	—
6d X=Br, R=SO_2Ph	DMF	rt, 18 h	64	—

rt=Room temperature, n.i.=not isolated.

Compound **6d**[6] was synthesised via bromination of 3-(1-benzenesulfonyl-1*H*-indolyl)-ethanone (**9**)[7] using pyridinium hydrobromide perbromide.[8] The minor co-product, the dibromo derivative **10**, could easily be separated from the main product by column chromatography (Scheme 2).



9 **6d** (55%) **10** (10%)

Scheme 2. (a) Py·HBr_3, $CHCl_3$, reflux 30 min.

The Horner–Wadsworth–Emmons olefination of **7a** and **7b** with *N*-Boc-3-aminopropionaldehyde[9] did however only proceed in a very modest yield. Using BuLi as the base afforded compound **11a** and **11b** in low yields, around 20%. Other bases tried (DBU, LDA, *t*-BuOK, $[(CH3)_3Si]_2NK$, NaH) failed to give the desired product (Scheme 3).

The plan was to remove the Boc-protecting groups and cyclise the amine to the desired lactam. However, treatment of **11a** with 20 equiv TFA and subsequent treatment with $NaHCO_3$ gave the seven-membered heterocycle **12** instead of the expected free amine or the six-membered heterocycle **2**. Also, quite surprisingly, the indole nitrogen remained Boc-protected despite the acid treatment. Due to the rather unstable enamine character of compound **12**, optimal conditions for preparation and isolation are still an issue, as is the deprotection of this compound.

It seems likely that the azepine formation could be induced by the electron withdrawing Boc-protecting group on the indole nitrogen, which would render the carbonyl at the 3-position of the indole more susceptible for attack than the ester functionality. Consequently, removal of the benzenesulfonyl group of **11b** under standard conditions afforded **13**, which was further reacted with *N*-hydroxysuccinimide (HOSu). Surprisingly, during hydrolysis of the ester of **11a** the acidic workup also removed the indole Boc-protecting group, affording compound **13**. This situation is in contrast with the treatment of **11a** with trifluoroacetic acid or formic acid where the amine group is more easily deprotected.

Attempts to accomplish the cyclisation to the lactam under basic conditions, prior to removal of the amine-protecting group were unsuccessful and did not afford the six-membered ring. Instead, treatment of **14** with DBU at −78 °C actually demonstrated the nucleophilic behaviour of DBU, resulting in an *N*-ε-caprolactam derivative.[10]

The *N*-succinimide ester **14** was treated with TFA, and thereafter with a biphasic mixture of aqueous $NaHCO_3$ solution and CH_2Cl_2. A six-membered lactam could thereafter be isolated from the mixture (Scheme 4). However, when comparing the data for this particular lactam with the data reported for the natural compound, it was realised that the exocyclic compound **15** was the product, rather than the endocyclic natural alkaloid. In the ^1H NMR spectrum of compound **15**, it was quite evident that the double bond had migrated, since all three methylenic groups are coupled and one proton *singlet* appears at δ 6.40. For the natural product, a one proton *triplet* appears at δ 6.64, which is coupled with one methylene group, also the methylene bridge appears as a broad singlet. Whether the exocyclic lactam **15** is the kinetic product in this reaction is uncertain, but there are indications from similar examples in the literature.[11]

The exocyclic analogue of the indole alkaloid isolated from the marine sponge *H. melanodocia* has thus been prepared in our laboratory. All attempts to produce the endocyclic lactam and thus to be able to confirm the structure assigned for the natural product to date have been unsuccessful.