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Regioselective homolytic substitution of benzo[*c*][2,7]naphthyridines

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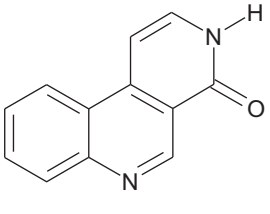
ABSTRACT

Benzo[*c*][2,7]naphthyridines bearing electron-withdrawing substituents (bromo, acetyl) at C-4 undergo regioselective homolytic substitutions at C-5 with nucleophilic 1,3,5-trioxanyl and ethoxycarbonyl radicals under Minisci conditions. Surprisingly, mainly 5,6-dihydro derivatives are formed in these reactions. Rearomatization with manganese dioxide leads to 4,5-disubstituted benzo[*c*][2,7]naphthyridines, which should be attractive building blocks for the synthesis of pyridoacridine alkaloids. Homolytic methylation at C-5 takes place with methyl radicals generated from acetic acid and acetaldehyde, respectively.

1. Introduction

Among the vast number of alkaloids isolated from living organisms until now, only two tricyclic benzo[*c*][2,7]naphthyridines have been described, namely perlolidine (**1**) from the perennial ryegrass (*Lolium perenne*)[1] and the 4-pyridylbenzo[*c*][2,7]naphthyridine subarine (**2**) from a Singaporean ascidian[2] (Fig. 1). Recently, substituted benzo[*c*][2,7]naphthyridines have been described to exhibit antiinflammatory,[3] antimalarial[4] and kinase-inhibitory activities.[5]



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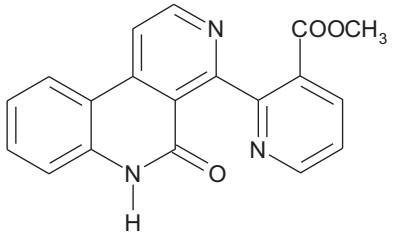

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Fig. 1. Benzo[*c*][2,7]naphthyridine alkaloids perlolidine (**1**) and subarine (**2**).

But of particular significance is the occurrence of this tricyclic ring system as a common partial structure in numerous marine alkaloids commonly named 'pyridoacridine alkaloids'.[6] These aromatic alkaloids from sponges, tunicates, corals and other marine invertebrates, consist of four up to seven annulated (hetero)aromatic rings and show manifold biological activities.[7] Of high significance are the antitumour activities based on topoisomerase inhibition[8] and reductive DNA cleavage mediated by reactive oxygen species,[9] as well as the antiparasitic activities.[10]

The pentacyclic alkaloids represent the most important subclass of the pyridoacridine alkaloids, and can be divided into the amphimedine-type alkaloids (e.g., amphimedine (**3**) and meridine (**4**)) and the ascididemin-type alkaloids (e.g., ascididemin (**5**) and kuanoniamine A (**6**)) on the basis of the different arrangements of the five rings (Fig. 2).

Numerous essentially different strategies have been worked out for the construction of the amphimedine-type ring system,[6,9] whereas most of the approaches to ascididemim-type pyridoacridines use the one-pot pyridine annelation protocol that had

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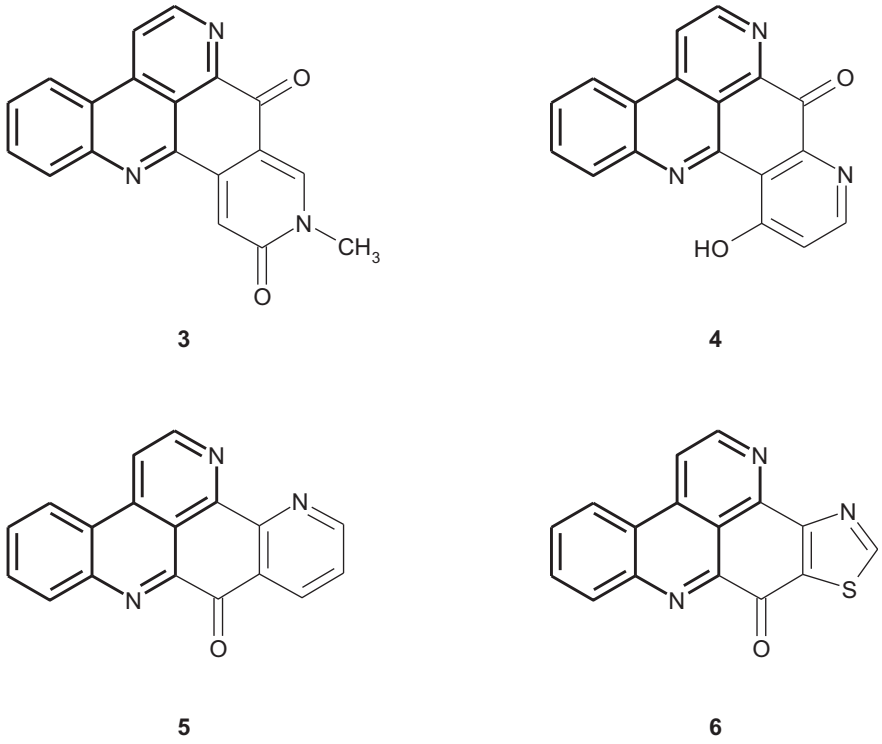

Fig. 2. Pyridoacridine alkaloids of the amphimedine-type (**3** and **4**) and of the ascididemin-type (**5** and **6**). The benzo[*c*][2,7]naphthyridine partial structures are highlighted.

been developed by our group in the course of the syntheses of the alkaloids sampangine[11] and ascididemin (**5**)[12] for the construction of ring E as the final step.

In continuation of our research on pyridoacridine alkaloids[12,13] we intended to develop a versatile approach to structurally diverse alkaloids and analogues thereof by starting from appropriate 4,5-disubstituted benzo[*c*][2,7]naphthyridines. This approach was previously realized in total syntheses of amphimedine (**3**),[13c,14] but in both the amphimedine and ascididemin series a number of failures[14a,15] have been published, and several groups announced work on such cyclisations, but never provided the results.[1d,16]

For our purpose the new building blocks should bear substituents at both C-4 and C-5 of the tricyclic ring system, and at least one of them was to be a carbonyl or carboxyl function as precursor of the keto groups of the target alkaloids (Fig. 2). As the simultaneous introduction of both substituents in the course of the construction of the tricyclic ring system did not appear practicable, we decided to work out a methodology for subsequent introduction of appropriate substituents at C-5 into 4-monosubstituted benzo[*c*]-[2,7]naphthyridines. Related work was performed by Quéguiner's group,[17] who converted 4-substituted benzo[*c*][2,7]naphthyridines to 4,5-disubstituted derivatives by nucleophilic addition of organometallic compounds (alkyl, aryl, vinyl) to the imino group in ring B, followed by rearomatization with mild oxidizing agents. This approach is, however, not suitable for the introduction of ester and related functionalities. Hence we decided to explore homolytic substitutions of 4-substituted benzo[*c*][2,7]naphthyridines. This methodology, known as the Minisci reaction,[18] allows for the direct homolytic substitution of protonated azaarenes with nucleophilic radicals at the *ortho* and/or *para*-position of the protonated ring nitrogen. Starting from appropriate precursors and using radical generation conditions, functional groups like alkyl, acyl, hydroxymethyl, trioxanyl, alkoxycarbonyl and aminocarbonyl can be introduced with no need to have a typical leaving group at the pertinent ring position. Starting from 4-substituted benzo[*c*][2,7]-naphthyridines the major challenge was to manage the substitution to occur regioselectively at C-5 (in ring B), and not at C-2 (in ring C). Only few, mostly serendipitous regioselective Minisci reactions have been described previously for bi- and tricyclic hetarenes containing two or more ring positions that should be susceptible to homolytic substitution.[19] Since N-protonation of the heterocyclic ring is a prerequisite for Minisci-type homolytic substitution,[20] we intended to gain regioselectivity by reducing the basicity of ring C by introducing electron-withdrawing substituents at C-4. This should lead to preferred protonation of N^6 in ring B, and consecutively to regioselective functionalization at C-5. In previous work we found that acetyl and bromo substituents next to the ring nitrogen decrease reactivity of pyridine rings towards nucleophilic radicals,[19a,b] consequently 4-bromobenzo[*c*][2,7]naphthyridine (**7**) and 4-acetylbenzo[*c*][2,7]naphthyridine (**8**) were selected as starting materials for our investigations (Fig. 3). Particularly, the bromo substituent in **7** appeared to be highly useful, since it should enable us to introduce variable substituents at this position later on by transition metal-catalyzed cross coupling reactions.

2. Results and discussion

4-Bromobenzo[*c*][2,7]naphthyridine (**7**) had been prepared previously by reaction of the alkaloid perlolidine (**1**) with $POBr_3$.[21] Since **1** is problematic due to its extremely poor solubility in any solvent, we worked out a new and even shorter approach to **7** that avoids the use of **1**. In the style of our total synthesis of perlolidine (**1**),[1e] easily available 3-cyano-4-methylquinoline (**9**) was converted to the enamine **10** using Bredereck's reagent (*tert*-butoxy-bis(dimethylamino)methane). Treating this crude intermediate with HBr in glacial acetic acid[22] gave the building block **7** in excellent yield. The acetyl derivative **8** was obtained from **7** in 95% yield by Stille coupling with (1-ethoxyvinyl)tributylstannane and subsequent hydrolysis of the crude enol ether **11** with hydrochloric acid (Scheme 1).

For the introduction of an aldehyde equivalent at C-5 we intended to utilize a protocol developed by the Minisci group comprising