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New approaches to the synthesis of canthin-4-one alkaloids and synthetic analogues

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Dedicated to Professor Rolf Huisgen on the occasion of his 95th birthday

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ABSTRACT

Two novel approaches to the canthin-4-one ring system have been worked out. Claisen-type condensation of 1-acetyl-β-carboline with *N*-acyl benzotriazoles gives, via intermediate 1,3-diketones, 6-alkylcanthin-4-ones in one single operation, but this protocol is restricted to small alkyl substituents. An alternative approach, via 1-ethynyl-β-carboline and 1-isoxazolyl-β-carbolines, followed by reductive isoxazole cleavage and cyclization, is more versatile. 5,6-disubstituted canthin-4-ones are accessible via iodination at C-5 and subsequent Pd-catalyzed cross-coupling.

1. Introduction

The canthin-4-one alkaloids represent a very small chemotype of natural products.[1] Until now only three representatives, tuboflavine (5-ethylcanthin-4-one), norisotuboflavine (**1a**, R=methyl), and isotuboflavine (**1b**, R=ethyl) have been found in nature.[2,3] Another one was claimed, but its structure was revised later to be a canthin-6-one.[4] Significant antimicrobial activities have been shown for the parent canthin-4-one and some of its derivatives.[5] Synthetic canthin-4-ones exhibit phosphodiesterase-inhibitory activity.[6] Further, canthin-4-ones were used as intermediates for the synthesis of antimicrobial polycyclic compounds.[5,7] Ring transformation reactions of canthin-4-ones with guanidinium salts give 1-(2-aminopyrimidin-4-yl)-β-carbolines, e.g. the anxiolytic alkaloid annomontine,[8,9] and its antimalarial analogue C-117.[10]

Multistep total syntheses with very poor overall yields have been worked out decades ago for confirmation of the structures of the three alkaloids.[11–13] Another multistep approach to the canthin-4-one backbone was published in a patent.[6] Later, our group developed a versatile approach to the canthin-4-one ring system (**1**) via a condensation of 1-acyl-β-carbolines (**A**) with amide acetals or Bredereck's reagent (*tert*-butoxy-bis(dimethylamino)methane) to give enaminoketones (**B**), which undergo cyclization under the reaction conditions[4,8] (Fig. 1).

The interesting biological activities of the canthin-4-ones prompted us to explore alternative approaches to this tetracyclic ring system, with the prospect of being able to perform diverse functionalizations on the ring system.

In a first approach we aimed at a modification of our reported protocol by substitution of the orthocarboxylic acid derivatives (amide acetals and others) for easier accessible activated carboxylic acid derivatives. With these building blocks we intended to prepare 1,3-diketones (**C**) from 1-acyl-β-carbolines in a Claisen-type condensation. Cyclization of the diketones was expected to give the canthin-4-one scaffold (**1**). In a second approach we intended to find alternatives to the 1-acyl-β-carboline intermediates, since these are accessible only by using laborious methods (radical reactions,[8,14,15] organometallic chemistry[16]) or expensive organostannane building blocks.[17] 1-Isoxazolyl-β-carbolines (**D**) were considered as versatile intermediates, which should give primary enaminoketones (**E**) upon reductive ring cleavage,[18] and the latter were expected to cyclize to the canthin-4-one ring system in a similar manner as known for tertiary enaminoketone intermediates (**B**) (Fig. 1).

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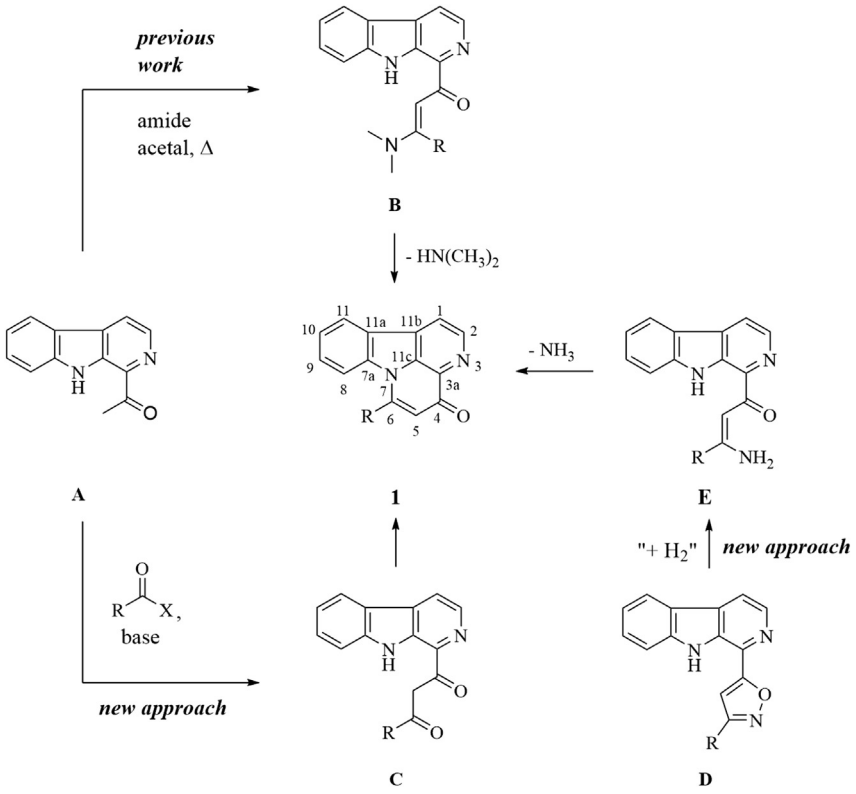
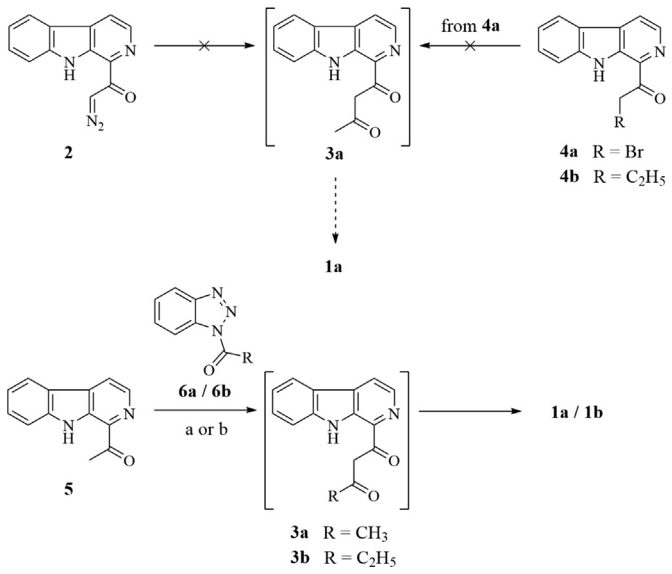


Fig. 1. Previous approach to canthin-4-ones (**A**→**B**→**1**), and two new approaches (**A**→**C**→**1**, **D**→**E**→**1**).

2. Results

2.1. 1,3-Diketone route

From previous investigations we had various 1-substituted β-carbolines in hand, which were considered as precursors for the desired 1,3-diketones. Due to anticipated troubles caused by the NH-acidic proton of the pyrrole partial structure of β-carboline precursors, we first investigated 1,3-diketone syntheses, which do not require the use of strong bases. Known diazoketone **2**[15] was reacted with acetaldehyde and $SnCl_2$ following a procedure of Padwa,[19] but complete decomposition was observed. Next, a 1,3-diketone synthesis starting from known α-bromoketone **4a**[15] and acetyl chloride, catalyzed by GaI_3[20] was explored. Under mild conditions no conversion was seen, upon heating the bromoketone decomposed, without giving any identifiable product (Scheme 1). Finally, we succeeded in preparation of norisotuboflavine (**1a**) in 34% yield by reacting 1-acetyl-β-carboline (**5**)[14,17] with *N*-acetylbenzotriazole (**6a**)[21,22] and 2 equiv of LDA in THF at 0–20 °C, obviously via the 1,3-diketone **3a**. In the same manner, alkaloid isotuboflavine (**1b**) was obtained from methyl ketone **5** and *N*-propanoylbenzotriazole (**6b**)[21] in 16% yield (Scheme 1). Significantly lower yields were obtained with the base *tert*-butyllithium. As an alternative we explored the 'soft enolization' protocol of Lim et al.[23] Thus, 1-acetyl-β-carboline (**5**) was reacted with the *N*-acylbenzotriazoles **6a**/**6b**, $MgBr_2 \cdot OEt_2$, and *i*-Pr_2NEt in CH_2Cl_2. No conversion was obtained under standard reflux conditions. However, a significant conversion was achieved under microwave irradiation at 70 °C, giving the alkaloids **1a** and **1b** in 34 and 16% yields. At higher temperatures and in other solvents (1,4-dioxane, diglyme) significant decomposition was observed. Unfortunately, this reaction was very sensitive to steric hindrance, and could not be extended to the synthesis of the corresponding 6-phenyl and 6-cyclopropyl analogues of the alkaloids.



Scheme 1. Approaches to 1,3-diketone intermediates and synthesis of alkaloids **1a**/**1b**. a) $MgBr_2 \cdot OEt_2$, *i*-Pr_2NEt, methylene chloride, microwave 100 W, 70 °C, 34%/16%; b) LDA, THF, 0 °C—rt, 34%/16%.

We also investigated, whether 5,6-disubstituted canthin-4-ones are accessible with this protocol. For this purpose condensation of 1-butanoyl-β-carboline (**4b**)[7] with *N*-acetylbenzotriazole (**6a**) was attempted. This experiment was unsuccessful, demonstrating another limitation of the 1,3-diketone route.

So the 1,3-diketone route provided a novel access to the alkaloids norisotuboflavine (**1a**) and isotuboflavine (**1b**), but was not generally applicable to the synthesis of variably substituted canthin-4-ones. Thus, we worked out an alternative approach to the desired scaffold.