

Karolinska Institutet
Institutionen för Biovetenskaper
Enheten för Organisk Kemi

Synthetic studies towards 7- and 8-membered *N*-heterocycles, particularly 1,4-Pyrrolobenzodiazepines

Total synthesis of Fuligocandin A and B

AKADEMISK AVHANDLING

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ABSTRACT

This dissertation is concerned with the synthesis of 7- and 8-membered *N*-heterocycles, particularly 1,4-pyrrolobenzodiazepines. A non-chromatographic method for conversion of carbonyl-functionalities to the corresponding thiocarbonyls is described.

A formal total synthesis of the pyrrolobenzodiazepine natural product DC-81 was developed starting from vanillin. The tricyclic core structure was successfully obtained in 6 steps and several approaches for transformation of this key diamide to obtain the target molecule DC-81 was investigated.

A convergent and concise synthesis of the pyrrolobenzodiazepine natural products fuligocandin A and B was developed employing Eschenmoser sulfide contraction as a key step. Fuligocandin B could be obtained in optically active form and the method was applied to obtain a number of vinyllogous amides.

The thionating power of a reagent obtained from P₄S₁₀ and pyridine was investigated and the actual structure of the crystalline reagent could for the first time be conclusively determined and confirmed by X-ray crystallography. A range of carbonyl compounds have been converted to the corresponding thiocarbonyl derivatives without the need for chromatographic purification.

The final part of this thesis features synthetic studies towards 7- and 8-membered heterocycles starting from anthranilnitrile. Accordingly, addition of Grignard reagents to *N*-acylderivatives of anthranilnitrile resulted in the formation of 1,4-benzodiazepin-3-ones and the method was also applied to obtain the higher homologue 1,5-benzodiazocin-4-one. Furthermore, the imino-intermediates initially formed by reaction of anthranilnitrile and Grignard reagents could be transformed to dibenzo-1,5-diazocines. Thus, an unusual bridged *N*-heterocycle was isolated and its structure was confirmed by X-ray crystallography.

Keywords: 1,4-Pyrrolobenzodiazepines, DC-81, 1,4-benzodiazepin-3-one, 1,5-benzodiazepin-4-one, dibenzo[b,f][1,5]-diazocine, fuligocandin, Eschenmoser sulfide contraction, alkaloid, total synthesis, vinyllogous amides, TRAIL, thionation reagent, Lawesson's reagent, thioamide.

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