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An unusual boron tribromide-mediated, one-pot bromination/cyclization reaction. Application to the synthesis of a highly strained cyclopenta[1,3]cyclopropa[1,2-*b*]pyrrolizin-8-one

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ABSTRACT

Performing Jefford's cyclization of ethyl 2-pyrrol-1-ylcyclohex-2-ene-1-carboxylate (**5**) using boron tribromide in refluxing dichloromethane led to a *trans–cis* bromopyrrolohydrindolone **7** whose debromination in alkaline medium afforded a highly strained cyclopenta[1,3]cyclopropa[1,2-*b*]pyrrolizin-8-one **6**. Compound **7** and two of its diastereoisomers were synthesized in order to better understand this unusual reaction and more generally the reactivity of these systems.

Tripentones constitute a heterocyclic family bearing some very interesting biological properties widely studied by several teams around the world.[1–8] Among these activities, antineoplastic properties are particularly displayed by some tripentones such as compound MR22388 which appears as a very potent cytotoxic derivative[9] with specific FLT3-ITD kinase inhibitor activities and a great potential interest in the treatment of acute myeloid leukemia. During the course of our work aiming at developing some novel tripentones, we wished to synthesize the hitherto unknown tetrahydropyrroloindolone **1** (Fig. 1).

To achieve this goal we started from ethyl 2-oxocyclohexanecarboxylate (**2**) which was submitted to ammonium carbamate in refluxing methanol.[10] The reaction led quantitatively to ethyl 2-aminocyclohexenecarboxylate (**3**) which was involved in a pyrrolation reaction under Clauson-Kaas conditions.[11] The reaction afforded in 50% yield a mixture of pyrrole derivatives **4** and **5** in 2:1 proportions respectively, whereas the starting material **2**, issued from the hydrolysis of **3**, was mainly recovered (Scheme 1).

Compounds **4** and **5**, which were not separable, were both engaged in a cyclization reaction using boron tribromide according to Jefford's method.[12] Beside ketone **2** and the desired tetrahydropyrroloindolone **1**, this reaction afforded, after an alkaline treatment, an unexpected tetracyclic compound. The latter was identified using ^{2}D NMR experiments as 1,2,3,3a-tetrahydrocyclopenta[1,3]cyclopropa[1,2-*b*]pyrrolizin-8(3b*H*)-one (**6**) (Scheme 2). The structure of the latter was confirmed by X-ray diffractometry (Fig. 2).

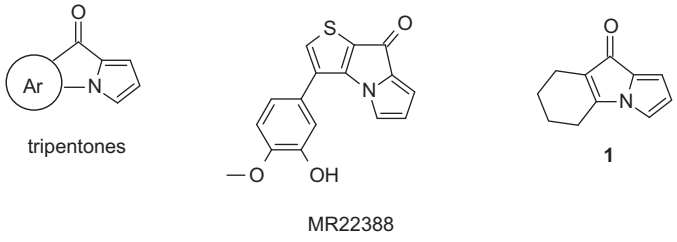

Figure 1. Structure of tripentones, MR22388, and compound **1**.

In order to understand this surprising synthesis, we investigated the reaction carried out under conditions deprived from the alkaline treatment. In this case, formation of *trans–cis* bromopyrrolohydrindolone **7** was observed, which was isolated in 30% yield and its relative configuration was unambiguously confirmed by NOE experiments (Scheme 3). The following plausible mechanistic rationale addressing the formation of the observed products could be proposed. We believe that the aromaticity of the pyrrole ring in **8** is not restored as usual through the elimination of BBr_3 and EtOH but through the formation of another intermediate **9** bearing a cationic carbon. The latter could be diastereoselectively brominated by the $OBBr_3$ group[13] leading to

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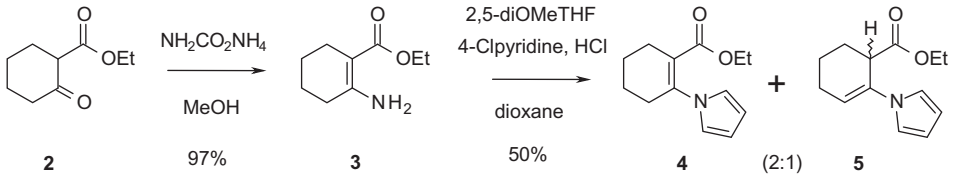
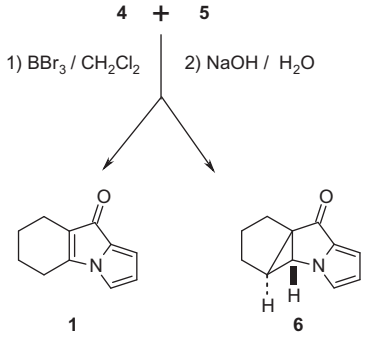


Scheme 1. Synthesis of compounds **3**–**5**.



Scheme 2. Synthesis of compounds **1** and **6**.

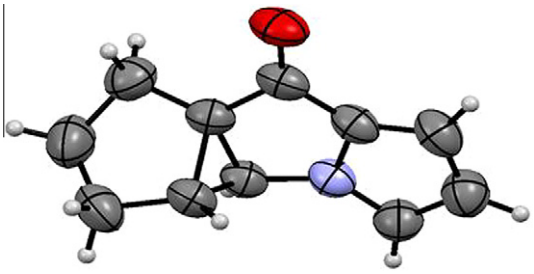
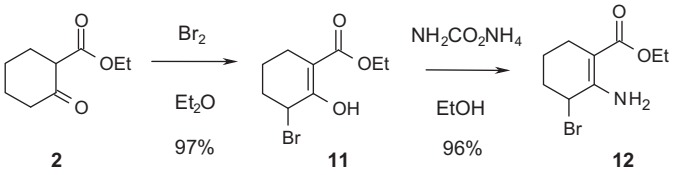


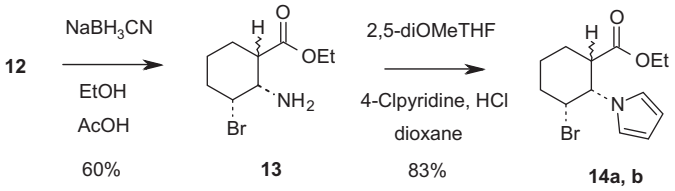
Figure 2. Crystal structure of compound **6**.

the more stable bromo derivative **10**. The latter would be finally hydrolyzed into **7** whose deprotonation in alkaline medium in the alpha position of its carbonyl group, would lead to a cyclization into **6** after HBr elimination. More classically, isomer **4** would afford at the same time the cyclization into **1**.

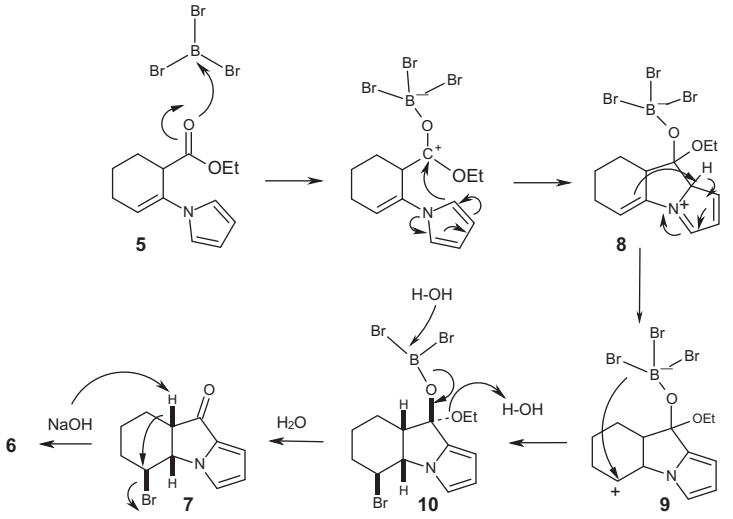
To the best of our knowledge, the use of boron tribromide had never led to such a one-pot bromination/cyclization reaction. In order to confirm this surprising reaction and the structure of its products, we undertook the unequivocal synthesis of compounds **6** and **7**. We started with the bromination of **2** using bromine in Et_2O which led selectively to the monobromo derivative **11** (Scheme 4).[14] Under treatment with ammonium carbamate in EtOH, the latter gave then quantitatively enamine **12**.



Scheme 4. Synthesis of compounds **11** and **12**.



Scheme 5. Synthesis of compounds **13** and **14a**,**b**.



Scheme 3. Hypothetical mechanism proposed for the synthesis of compounds **1** and **7**.