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INTRAMOLECULAR ARYNE CYCLOADDITION APPROACH TO ARISTOLACTAMS.

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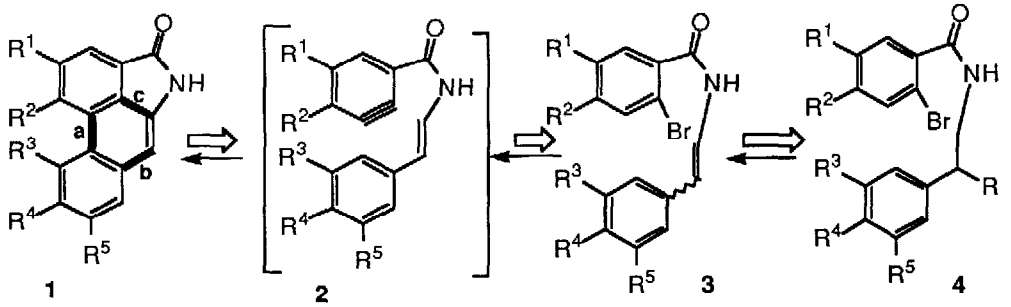
Summary. A new procedure for the total synthesis of aristolactams, based on the intramolecular Diels-Alder reaction between styrene and aryne, is described.

Aristolactams are a group of alkaloids[1-3] structurally and probably biogenetically related to aporphines[1,2] and aristolochic acids[1-3]. Although the chemistry and pharmacology of these parent compounds has been intensively studied[2], those of aristolactams has been poorly investigated and only a few reports of their partial synthesis appear in the literature[3].

Some years ago we undertook a systematic study of the total synthesis of aristolactams, which led us to develop three alternative routes for the generation of the phenanthrene ring system present in this class of compounds. The first one had as a key step the formation of de-aryl-aryl carbon bond **a**, by means of a photocyclization[4]. The second and more recent alternative was based on the simultaneous formation of bonds **a** and **b**, through an Intermolecular Benzyne Cycloaddition[5].

We report now the preliminary results of the third strategy, characterized by a key step including the simultaneous formation of bonds **a** and **c** via an Intramolecular Benzyne Cycloaddition between an styrenic diene and an arynic dienophile.



a $R^1=R^2=R^4=OMe$, $R^3=R^5=H$
b $R^1=R^2=R^4=R^5=OMe$, $R^3=H$
c $R^1=R^2=R^3=R^4=OMe$, $R^5=H$

The crucial point in this synthetic strategy was the choice of a suitable method for the generation of the aryne, considering the following two factors: the availability of precursors with different substitution pattern and the stability of the substrates under the reaction conditions. The method of choice in our case was the dehydrohalogenation of aryl halides with LDA[6]. Accordingly, we planned our synthesis using type **3** styrylamides as key intermediate compounds.

Styrylamide **3a** was obtained using a new procedure of synthesis recently developed by us for the preparation of some natural occurring styrylbenzamides and related compounds[7]. Thus, amide **4a** (R=H) was obtained in good yield by condensation of *o*-bromoveratric acid and *p*-methoxyphenylethylamine. Subsequent oxidation of this amide with DDQ in acetic acid yielded quantitatively the corresponding O-acetyl derivative **4a** (R=OAc). Pyrolitic elimination at 250ºC afforded the desired styrylamide **3a,** in 75 % yield, as a mixture of E and Z isomers (3:1).

The key cycloaddition step was carried out by adding the E isomer of styrylamide **3a** to a cooled (0ºC) solution of LDA in THF, prepared *in situ* from n-BuLi and diisopropylamine. Work-up of the reaction mixture allowed aristolactam **1a** to be isolated in 35% yield. Its spectroscopic data agree with those reported for the natural compound[8].

Further confirmation of the usefulness of this synthetic strategie was obtained by the analogous transformation of styrylbenzamide **3b**, which was prepared in 72% yield in a similar way as **3a** from *o*-bromoveratric acid and homoveratrylamine. Treatment of the E isomer of **3b** with LDA (THF, 0ºC) led to the expected aristolactams **1b** and **1c**, both isolated from the reaction mixture in approximately 15% yield each. N-methyl derivative of compound **1b**, prepared by treatment with sodium hydride and methyl iodide, was identical to an autentical sample previously obtained by us from the decarbonylation of 4,5-dioxoaporphine alkaloid pontevedrine[9]. On the other hand, aristolactam **1c** represents the first example of a 1,2,10,11-tetrasubstituted aristolactam[1-3].

In our opinion this unoptimized procedure possesses great synthetic potential. Further work it is in progress in order to improve the yield in aristolactams and to apply this strategy to the synthesis of other alkaloids.

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