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A facile Brönsted acidic-mediated cyclisation of 2-allyl-1-arylaminocyclohexanes to octahydroacridine derivatives

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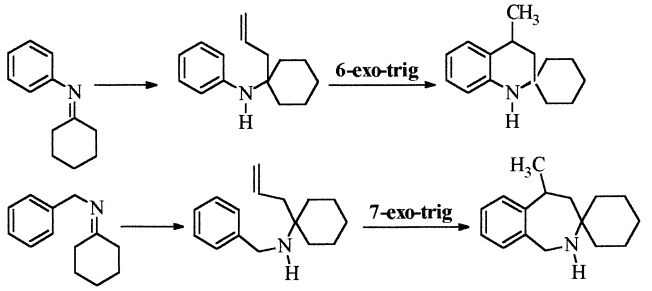
Abstract

The classical acidic cyclisation has been used for the preparation of new substituted octahydroacridines starting from readily available 2-allyl-1-*N*-arylaminocyclohexanes. © 2000 Published by Elsevier Science Ltd.

Intramolecular cyclisation reactions are among the most valuable synthetic methods for the preparation of carbo- and heterocycles. An internal Friedel–Crafts cyclisation with alkene moiety constitutes the basis of many natural product syntheses.[1,2] Recently, we described a new, simple and efficient synthesis of 3,4-dihydrospiro[1*H*-quinoline-2,1′-cyclohexanes][3] and 1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1′-cyclohexanes],[4] which are interesting biological targets. This method consists of a cationic cyclisation of *gem*-allyl-*N*-arylaminocyclohexanes and can be considered as a 6-*exo*-trig or a 7-*exo*-trig process where an allyl moiety acts as an internal electrophilic C_3 synthon (Eq. (1)).



(1)

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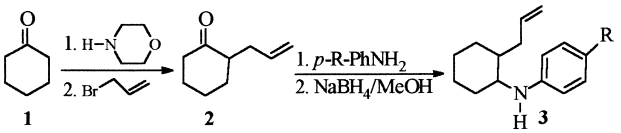
In the course of our research programme aimed at the preparation of bioactive nitrogen-containing heterocycles,[5] we addressed the chemistry of 2-allyl-1-*N*-arylaminocyclohexanes under acidic conditions. Acridines and their reduced forms are an important feature of many natural products and medicinally important agents.[6] The synthesis of the octahydroacridine skeleton are well-documented.[7] However, to our knowledge, the synthetic potential of aminocyclohexanes to construct an acridine ring, has not been explored. In this paper, we describe the synthesis of octahydroacridines via an acidic-mediated cyclisation reaction of 2-allyl-1-*N*-arylaminocyclohexanes obtained from 2-allylcyclohexanone.

The starting compound 2-allylcyclohexanone **2**, was prepared from ketone **1** via enamine derivative using Stork's method.[8] Treatment of **2** with aniline or different *p*-substituted anilines and catalytic amounts of acetic acid in refluxing benzene afforded the corresponding ketimines, which were immediately subjected to a reduction with $NaBH_4$ methanolic solution, furnishing 2-allyl-1-*N*-arylaminocyclohexanes **3** in 71–98% overall yields (Eq. (2)). Yield from the crude amines refers to material isolated by alumina chromatography, using heptane as eluent.



Amine	3a	3b	3c	3d	3e	3f
R	H	Me	Cl	F	Br	OMe
Cis/Trans	3.9	3.7	4.8	4.6	4.1	4.7
Yield, %	75	98	90	95	88	71

(2)

As noted, amines **3** are a mixture of two diastereoisomers with respect to the position of allyl and arylamino fragments on the cyclohexane ring. In order to determine the spatial structure of these amines, one of them (amine **3f**) was methylated with CH_3I in the presence of acetone and potassium bicarbonate. Based on ^1H, ^{13}C NMR (BB), DEPT-135, HMQC, HMBC and HMQC-TOCSY techniques applied to amine **3g** it was possible to assign all protons and carbons of aminocyclohexanes **3a–f** (Fig. 1). The '*cis*' and '*trans*' designations are referred to the spatial relationship between the protons at C-1 and C-2 of cyclohexane ring.

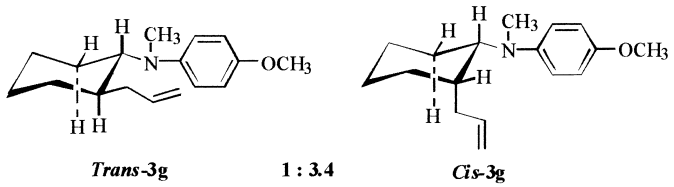
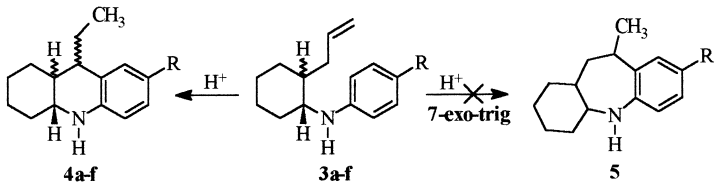


Figure 1.

Thus, under the reaction conditions used, the reduction of the imine C=N bond leads to the exclusively equatorial amines **3a–f**.

Finally, these amines were subjected to acidic-catalysed cyclisation (H_2SO_4, 80–100°C). Based on our previous experiments,[3,4] we expected the preferential formation of heterocycle **5**, via a 7-*exo*-trig cyclisation (Eq. (3)). However, under the conditions chosen the major products were octahydroacridines **4a**–**f**, which could have been cyclised via a 6-*exo*-trig process as an electrophilic Friedel–Crafts intramolecular alkylation, or by a [$4\pi^+$+2π] process as a cationic aza-Diels–Alder intramolecular addition.[7d] Compounds **4a**–**f** were obtained as maroon viscous oils with 69–83% yields.



(3)

We surmise that under those acidic conditions the octahydroacridine ring formation could occur through a rearrangement of a secondary carbocation generated from the allyl fragment to another secondary carbocation linked to a cyclic carbon. An alternative, but less probable reaction mechanism could consist in an intramolecular cycloaddition of cationic 2-azabutadiene preformed from a secondary carbocation via a fission of C1–C2 bond.

Isolated octahydroacridines, having three stereogenic centres, also represent a mixture of four diastereoisomers in a 3:3:1:1 ratio, which differs with respect to the arrangement of the ethyl group at C-9 and of proton at C-4a. We assume that the major isomers could be formed from the *cis* form of amines **3a**–**f**, and consequently possess the structure of *cis*-annulated octahydroacridines with ethyl group at C-9 in equatorial and/or axial orientation, respectively (Fig. 2).

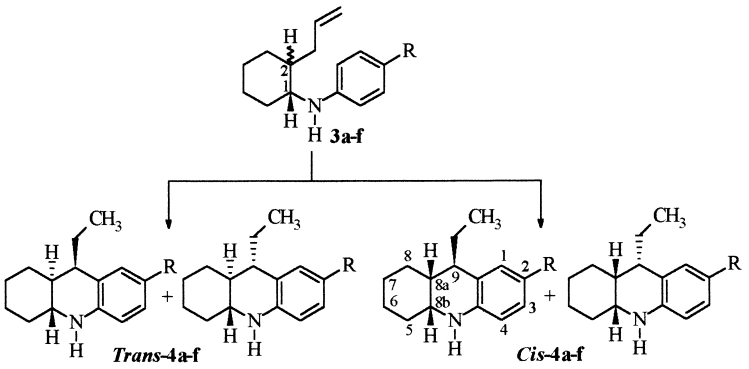


Figure 2.

The structural elucidation of **3a**–**g** and **4a**–**f** was mainly based on NMR studies. The ^1H and ^{13}C NMR data and 2D experiments allowed an unambiguous statement of the formation of the acridine ring.[9]

In summary, we have demonstrated the formation of the acridine ring from 2-allyl-1-*N*-arylaminocyclohexanes **3**. Although this synthesis lacks stereochemical control of the ring fusion, this

simple method allows to build substituted octahydroacridines **4** from the commercially available materials. The study on mechanism of their formation as well as on separation of individual amines **3** and on octahydroacridine diastereoselective synthesis is in progress in our laboratory.

Acknowledgements

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9. The ratios of isomers were determined by ^{13}C NMR measurement. All the products gave satisfactory elemental analyses and spectral data (IR, MS, and NMR) consistent with their structures.