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Stereoselective reduction of *N*-(3-arylcyclobutylidene)amines

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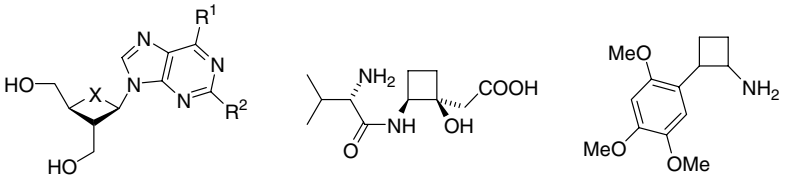
Abstract—*N*-Alkylimines derived from cyclobutanones have not been evaluated in depth as building blocks for organic synthesis, although these compounds are, among others, good precursors for interesting 3-arylcyclobutylamines. The reduction of various *N*-alkyl-*N*-(3-arylcyclobutylidene)amines with $LiAlH_4$ yielded cis-substituted cyclobutylamines as the only stereoisomers. When borane was used as a reducing agent, an intermediate imine–borane complex could be isolated as a stable compound.

Although cyclobutanones represent an important class of compounds, which are widely used as building blocks for the synthesis of a variety of natural products or (heterocyclic) bioactive compounds, the corresponding imines have not been studied in depth. It is surprising that, until recently, no *N*-(3-arylcyclobutylidene)amines had been described, despite the potential of such compounds in organic synthesis.[1] Imines derived from 3-arylcyclobutanones could lead directly to interesting cyclobutylamines, which are compounds of considerable physiological importance. In that respect, cyclobut-A (**1b**) and -G (**1c**) can be mentioned, which are carbocyclic analogues of the natural oxetanocin (**1a**), and are potent antiviral agents exhibiting broadspectrum activity against herpes viruses and HIV (see Fig. 1).[2]

N-Acylcyclobutylamine **2**, isolated from *Streptomyces rochei* strains, displays antimicrobial activity against both G^+- and G^--bacteria and also has herbicidal properties.[3,4] From a medicinal point of view, 2-arylcyclobutylamines **3** were evaluated as conformationally constrained analogues of dopamine to gain insight in the conformational requirements of phenethylamines to their respective receptors. Among others, this research showed that in contrast to the *trans*-isomer **3b**, no hallucinogenic effects were associated with the *cis*-derivative **3a**.[5]

N-Alkyl-3,3-diphenylcyclobutylamines **4** and **5** are antidepressants and inhibit urinary bladder contractions, respectively (see Fig. 2).[6] Derivatives **6** are lipoxygenase



1a X = O, $R^1 = NH_2$, R^2 = H (Oxetanocin)
1b X = CH_2, $R^1 = NH_2$, R^2 = H (Cyclobut-A)
1c X = CH_2, R^1 = OH, $R^2 = NH_2$ (Cyclobut-G)

2

3a *cis*
3b *trans*

Figure 1.

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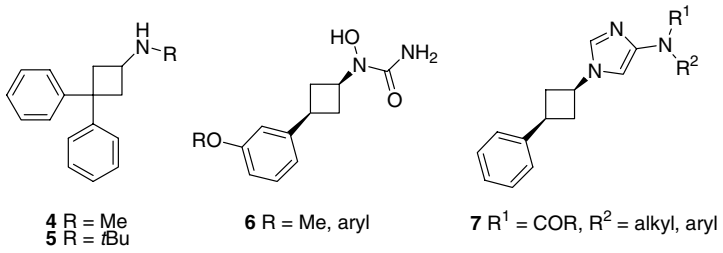
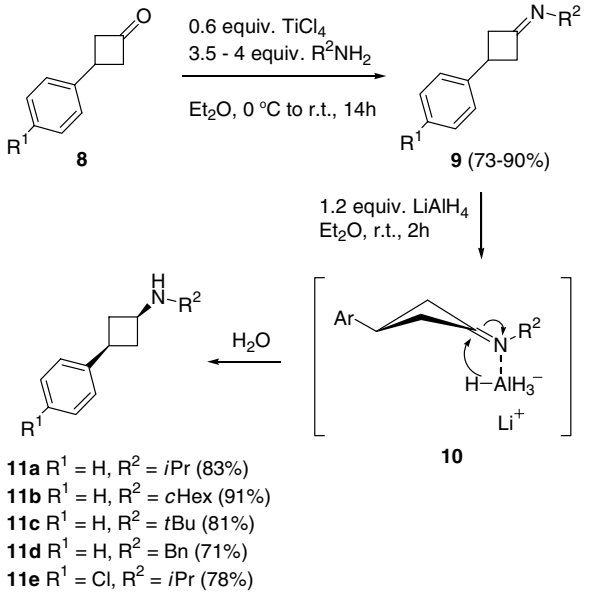


Figure 2.

inhibitors and thus inhibit the biosynthesis of leukotrienes (anti-inflammatory),[7] while aminoimidazolyl substituted cyclobutanes **7** are glycogen synthase kinase (GSK-3) inhibitors.[8]

The major synthetic pathways described in the literature leading to cyclobutylamines make use of Curtius rearrangements of cyclobutanecarboxylic acids,[9] substitution reactions on *O*-mesylated cyclobutanols, for example, by NaN_3,[2d,10] [2+2]-cycloaddition reactions using enamines[11] or via reductions of cyclobutanone oximes,[10a,12] each method has its benefits and drawbacks when specifically substituted cyclobutylamines are envisaged. Although iminium salts of 3-arylcyclobutanones already yielded 3-arylcyclobutylamines after reduction, this reaction resulted in mixtures of *cis*- and *trans*-isomers (ratio cis:trans 3:2 to 13:1).[13] The present letter describes a stereoselective reduction of *N*-(cyclobutylidene)amines towards *cis*-3-arylcyclobutylamines without the formation of the *trans*-isomers.

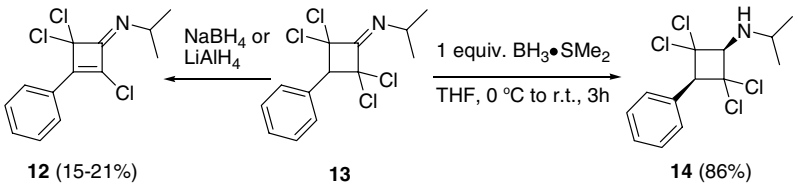
To establish a straightforward route towards 3-arylcyclobutylamines, *N*-(cyclobutylidene)amines **9** were prepared from readily available 3-arylcyclobutanones using titanium(IV) chloride as an activating and dehydrating agent.[1] The obtained imines **9** were reduced with $LiAlH_4$ in diethyl ether at room temperature giving rise to the corresponding amines as single stereoisomers (checked by GC-analysis). DIFNOE-experiments revealed the *cis*-configuration for the substituents. This result is most probably due to the combination of both electronic and steric effects, where the preference of the attack of the hydride to the imine happens to be pseudo-axial for stereoelectronic reasons (cf. analogous results described in the literature concerning the reduction of 4-substituted cyclohexanones).[13] In addition, the steric hindrance of the aryl moiety also directs most probably the hydride attack to the imine in a pseudo-axial manner, which is in accordance to the results obtained when 3-substituted cyclobutanones are reduced.[14] It should be mentioned that analogous reductions of iminium salts of cyclobutanones, as described in the literature, resulted in mixtures of stereoisomers, most probably because of the increased reactivity of the iminium bond towards reduction.[15] Using the synthetic procedure as depicted in Scheme 1, *cis*-*N*-alkyl-3-arylcyclobutylamines **11a**–**e** were synthesized in good yields.



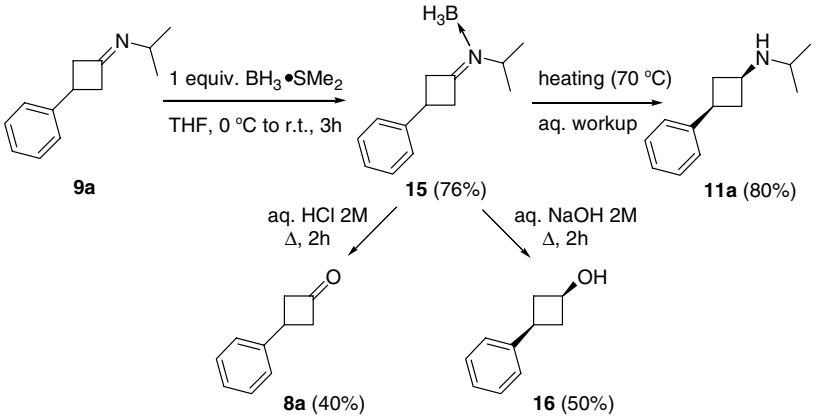
Scheme 1.

During the course of a reactivity study of halogenated *N*-(cyclobutylidene)amines, attempts were made to reduce imine **13**[1] to obtain the corresponding cyclobutylamine (Scheme 2). However, when standard reduction procedures were performed using $NaBH_4$ or $LiAlH_4$ no reduction occurred, but reaction mixtures were obtained containing the dehydrochlorinated *N*-(cyclobutenylidene)amine **12**.

On the other hand, when borane was used as a reducing agent, a clean reduction took place towards the tetra-



Scheme 2.



Scheme 3.

chlorinated cyclobutylamine **14**, probably because of the less alkaline properties of borane as compared to ionic reducing agents, such as $LiAlH_4$ or $NaBH_4$ and thus promoting a reduction over a dehydrochlorination reaction. Also in this case only the *cis*-substituted cyclobutylamine **14** was obtained, which was confirmed by DIFNOE analysis. To verify whether the use of borane could further increase the yield of the reduction of 2,2,4,4-unsubstituted *N*-(cyclobutylidene)amines **9**, imine **9a** ($R^1 = H$, $R^2 = i$-Pr) was treated with borane-dimethylsulfide in THF analogous to the reduction of imine **13**. However, in this case no reduction product was formed, but a stable complex between the imine **9a** ($R^1 = H$, $R^2 = i$-Pr) and borane was formed as evidenced by IR- and NMR-spectroscopy (including ^{11}B NMR) and by the fact that the heating (melting, mp = 68 °C) of the obtained crystals indeed resulted in cyclobutylamine **11a** (Scheme 3). The complex **15** was stable at room temperature and could even be purified by flash chromatography on silica gel. Treatment of the complex **15** with aqueous HCl or aqueous NaOH yielded 3-phenylcyclobutanone **8a** and *cis*-3-phenylcyclobutanol **16**, respectively. The latter cyclobutanol **16** could arise from the reduction of the formed cyclobutanone (due to hydrolysis of the activated imine bond of complex **15**) by a borane isopropylamine complex, which is also formed during hydrolysis. Although the reduction of imine **9a** using borane also results in cyclobutylamine **11a**, no increase in yield could be established as compared to the reduction with $LiAlH_4$.

In conclusion it can be stated that a stereoselective reduction was accomplished by reaction of *N*-(cyclobutylidene)amines with $LiAlH_4$ leading to *cis*-3-arylcyclobutylamines, which are of interest in pharmaceutical and medicinal chemistry. The use of borane as reducing agent gave rise to a stable imine–borane complex, which yielded the corresponding cyclobutylamine when heated.

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Supplementary data

Supplementary data (experimental procedures and full characterization data for new compounds **9d**, **11a–e**, **14** and **15**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.023.

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