Lithium-Halogen Exchange Reactions of 3,3-Dichloro-2-azetidinones

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Previously, the synthesis of 2-aryl-3,3-dichloroazetidines and their ring transformation towards functionalized aziridines via intermediate 2-azetines has been described. The scope of their reactivity was further investigated and it was found that reaction of 2-aryl-3,3-dichloroazetidines with lithium aluminum hydride in diethyl ether led to a mixture of trans-2-aryl-3-chloroazetidines and cis-2-aryl-3-chloroazetidines. In order to characterize unequivocally the new compounds, their synthesis was performed independently. While this was straightforward for the trans derivatives, the synthesis of cis-2-aryl-3-chloroazetidines proved to be more difficult. The straightforward synthesis of 4-aryl-3-chloro-2-azetidinones by [2+2]-cycloaddition between chloroketene and the appropriate imine is known to give exclusively trans-stereoselectivity, or mainly trans-stereoselectivity when different substituents are present on the aromatic group. Although some methods are known that give mainly cis-stereoselectivity by in situ generation of the ketene from the corresponding acid and an activating compound, these methods were not elaborated towards application to α-halogenated acids. Therefore, the use of metal-halogen exchange reactions on 3,3-dichloroazetidin-2-ones 1 to accomplish the aforementioned goal was investigated.

4-Aryl-3,3-dichloroazetidinones 1 were easily obtained by [2+2]-cycloaddition between dichloroketene and the appropriate imine. The compounds were used as substrates in the subsequent lithium-halogen exchange strategy. The use of proton sources allowed to synthesize 4-aryl-3-chloro-2-azetidinones, although the stereochemical outcome of each reaction was somewhat different. To avoid steric interactions, the incoming electrophile preferentially approaches the intermediate 3 from the opposite face of the space in which the aryl-substituent resides. This reasoning satisfactorily explains the formation of cis-4-aryl-3-chloro-2-azetidinones. This stereochemistry was also observed when alkyl halides were used as electrophiles. In these cases, only the formation of the cis-3-alkyl-3-chloro-4-phenylazetidin-2-ones 4 was detected.