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# A convenient approach towards the 1-aminomethyl-1-fluorocycloalkane scaffold

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ABSTRACT

A three-step synthesis towards 1-aminomethyl-1-fluorocycloalkanes was developed starting from methylenecycloalkanes. Methylenecyclobutane, methylenecyclopentane and methylenecyclohexane were first bromofluorinated to provide the corresponding Markovnikov products, 1-bromomethyl-1-fluorocycloalkanes, which were then converted towards the title compound via azide substitution and hydrogenation. The bromofluorination of methylenecyclopropane, however, led to both the Markovnikov and the anti-Markovnikov product.



The introduction of fluorine into organic compounds has already proven its relevance with regard to the modulation of the biological properties (lipophilicity, acidity, basicity, ...) of these compounds.[1] Furthermore, the constant need for innovation in the pharmaceutical and the agrochemical sector stimulates the search for new and active fluorinated building blocks.[2] Such a building block should be easily accessible, stable and potentially multifunctional to use in several syntheses. Over the years a broad diversity of methods has been developed to prepare fluorine-containing compounds. In particular, the introduction of fluorine and the simultaneous creation of a reactive electrophilic centre in the β-position with respect to fluorine is of high interest. This can be achieved by a non-symmetrical bromofluorination addition reaction across a wide range of olefinic moieties, including terminal, endocyclic, electron-deficient and electron-rich alkenes.[3] The high functional group tolerance and regioselectivity of the bromofluorination reaction applied to olefins make this approach a very useful, efficient and versatile method to synthesize monofluorinated building blocks starting from diverse alkenes.[4]

The goal of this research is to develop a synthetic pathway towards novel 1-aminomethyl-1-fluorocycloalkanes starting from the corresponding methylenecycloalkanes, as the synthesis of these fluorinated (aminomethyl)cycloalkane building blocks has not been discussed in the literature so far. Furthermore, it is believed that these fluorinated compounds are suitable for use in the construction of libraries in medicinal chemistry research. Fluorinated cycloalkanes in general are widely encountered in active substances for the treatment of asthma, diabetes, multiple sclerosis, psychiatric diseases and cancer,[5] as well as in insecticides[6] and herbicides.[7]

The synthesis of 1-aminomethyl-1-fluorocycloalkanes was initiated from commercially available methylenecycloalkanes **1a–c**. Only methylenecyclopropane **1d** had to be synthesized starting from 3-chloro-2-methylpropene and potassium bis(trimethylsilyl)amide (KHMDS) under vigorous reflux in toluene, according to a literature method.[8]

Fluorine was introduced in the first step of the synthesis of 1-aminomethyl-1-fluorocycloalkanes by a bromofluorination addition across the exocyclic double bond of methylenecycloalkanes by triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) and *N*-bromosuccinimide (NBS) in dichloromethane. The bromofluorination reaction is generally recognized as a very mild and useful method to introduce fluorine.[4]

The regioselectivity of this addition is influenced by the nature of the alkene, although usually the addition of fluoride takes places at the most substituted carbon atom, leading to a Markovnikov addition product.[3,4,9,10] For the four- to six-membered methylenecycloalkanes **1a–c**, the bromofluorination with 1.5 equiv of triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) and 1.1 equiv of *N*-bromosuccinimide (NBS) in dichloromethane led exclusively to 1-bromomethyl-1-fluorocycloalkane Markovnikov adducts **2a–c** in good yields (69–80%) after 5 h (Scheme 1).[12] For methylenecyclopropane **1d**, however, the regioselectivity was found to be different. After bromofluorination, both regioisomers **2d** and **3d** were isolated from a complex mixture in a 1:3 ratio, in a much lower yield

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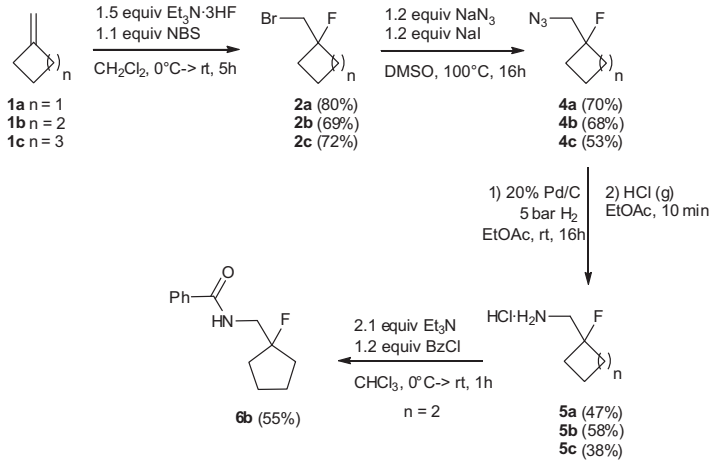
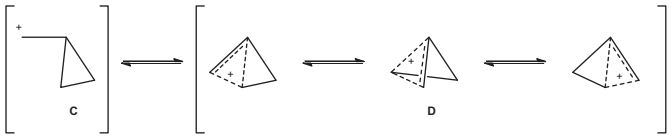



**Scheme 1.** Synthesis of 1-aminomethyl-1-fluorocycloakanes **5a–c**.

(19–25%) as compared to the other cycloalkanes (Scheme 2). In the literature, the bromofluorination of isobutene has been shown to lead exclusively towards the Markovnikov product, that is 1-bromo-2-fluoro-2-methylpropane,[9] which excludes sterical hindrance as a determining factor for the regioselectivity in the bromofluorination of methylenecyclopropane.[11] As the bromofluorination is generally considered to follow an ionic mechanism,[10b] the stability of the cyclopropyl carbenium ions, that is 1-(bromomethyl)cyclopropyl cation **A** and 1-bromocycloprop-1-ylmethylcarbenium ion **B**, will probably play a crucial role in the regioselectivity of this reaction (Scheme 2).

Numerous experimental and computational studies have been reported on the structure and energetics of the cyclopropylcarbinyl cation,[13] however its structure has not yet been fully established.[13,14] Despite the fact that the cyclopropylcarbinyl carbenium ion is a primary cation, it is assumed that this ion is a quiet stable ion, in which the three-membered ring stabilizes the positively charged centre.[15] This stability can probably be explained by an equilibrium which involves a set of σ-delocalized bicyclobutonium structures. (Scheme 3).[13–16]

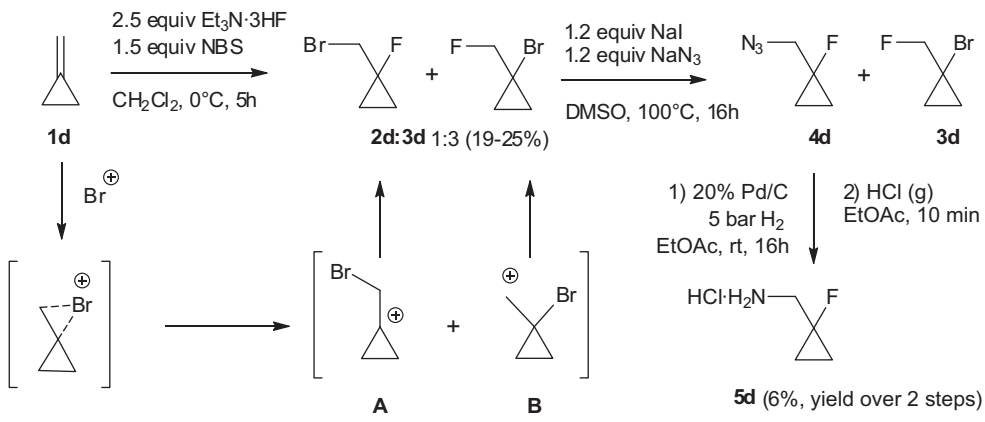
Most of the computational studies report a close proximity in energy of the cyclopropylcarbinyl cation **C** and these bicyclobutonium structures **D**, which results in an equilibrium between these two types of cations.[13,16] This explains the stability of the 1-bromocyclopropylmethylcarbenium ion and, as a consequence, the formation of the anti-Markovnikov product, 1-bromo-1-fluoromethylcyclopropane **3d**.




**Scheme 3.** σ-Delocalized bicylobutonium structures.

In addition, 1-substituted cyclopropyl cations are only considered to be stabilized when the substituent is a strong π-donor (i.e., $NR_2$, OR). For other substituents the barrier to ring opening is so small that it is unlikely that these cations will exist.[17] The formation of this cation **A**, which is attacked by a nucleophilic fluorine atom yielding the Markovnikov product, is reported here, but the low yield and the low regioselectivity point out the unstability of this cation. In the literature, only a few non-symmetrical addition reactions have been performed on methylenecyclopropane **1d**. For example, the reaction of methylenecyclopropane **1d** with HOBr[18c] (NBS in $H_2O$) or PhSeBr[18e] yielded, in agreement with our results, (mainly) the anti-Markovnikov products.[18]

The crude mixture of cyclopropanes **2d** and **3d** was first filtered over a silica plug and eluted with pentane. After evaporation of the solvent the mixture was distilled at atmospheric pressure, yielding several fractions with different regioisomeric ratios (**2d**:**3d**), ranging from 1:6 to 2:1. Subsequently a mixture of these bromofluorinated cyclopropanes **2d**:**3d** (1:3) was treated with $NaN_3$ and NaI analogously to the other cycloalkanes **2a–c**. The only difference




**Scheme 2.** Bromofluorination of methylenecyclopropane **1d**.