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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.

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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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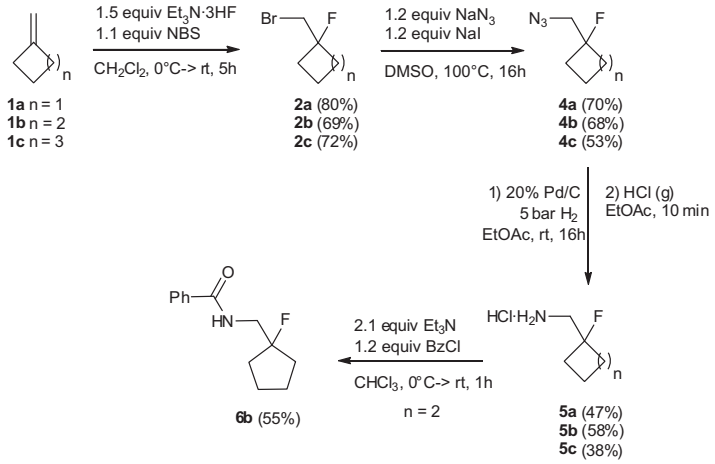
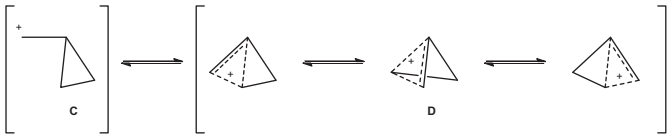


Scheme 1. Synthesis of 1-aminomethyl-1-fluorocycloakanes **5a–c**.

(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]

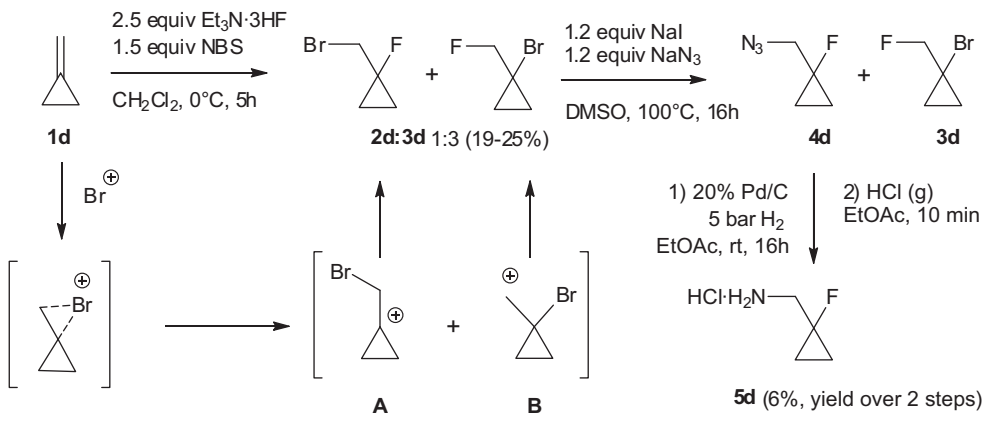
Most of the computational studies report a close proximity in energy of the cyclopropylcarbinyl cation **C** and these bicyclobutonium structures **D**, which results in an equilibrium between these two types of cations.[13,16] This explains the stability of the 1-bromocyclopropylmethylcarbenium ion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

was that, after the workup, the solvent was distilled off at atmospheric pressure to prevent loss of the very volatile azide **4d**. Without further purification, the mixture of 1-azidomethyl-1-fluorocyclopropane **4d** and 1-fluoromethyl-1-bromocyclopropane **3d** was reduced under H_2-pressure (5 bar) in ethyl acetate.

The pure 1-bromomethyl-1-fluorocycloalkanes **2a–c**, obtained after a vacuum distillation, were treated with 1.2 equiv of NaN_3 and 1.2 equiv of NaI in DMSO at 100 °C to give bromide by azide displacement, yielding the fluorinated (azidomethyl)cycloalkanes **4a–c**.[19] The reduction of these fluorinated azido compounds **4a–c** was achieved applying H_2-pressure (5 bar) in the presence of Pd/C (20 wt%) in ethyl acetate. Finally, 1-aminomethyl-1-fluorocycloalkanes **5a–d** were precipitated as hydrochloric acid salts by bubbling dry HCl gas through the crude mixture, delivering the salts **5a–c** in acceptable yields (38–58%) (Scheme 1) and the hydrochloric salt **5d** in 6% yield over two steps (Scheme 2).[20] 1-Aminomethyl-1-fluorocyclopentane **5b** was treated with triethylamine in chloroform (to liberate the free amine) and immediately reacted with benzoyl chloride, yielding *N*-[(1-fluorocyclopentyl)methyl]benzamide (55%) **6b**.[21] Structural analyses of the fragmentation patterns (MS, EI) of the fluorinated bromomethyl- **2a–c** and (azidomethyl)cycloalkanes **4a–c** further established their structures (Supporting information).

In conclusion, a convenient synthetic pathway towards new fluorinated building blocks was developed via an easy three-step procedure, starting from methylenecycloalkanes. The introduction of fluorine was achieved by regioselective bromofluorination of these olefins, except for methylenecyclopropane, which gave rise to a mixture of regioisomers. Substitution of bromide by azide led to the corresponding fluorinated (azidomethyl)cycloalkanes in good yields. Subsequent hydrogenation of the latter azides furnished 1-aminomethyl-1-fluorocycloalkanes, which were isolated as their stable hydrochloride salts. The latter fluorinated (aminomethyl)cycloalkanes can be considered as new building blocks in synthetic medicinal chemistry.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.127.

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12. *The general procedure is exemplified for the synthesis of 1-bromomethyl-1-fluorocyclopentane **2b***. An ice cooled solution of methylenecyclopentane (2.0 g, 24.2 mmol) and triethylamine trihydrofluoride (6 mL, 36.4 mmol) in dry dichloromethane (50 mL) was treated with *N*-bromosuccinimide (4.8 g, 26.6 mmol). After the removal of the ice bath the reaction was continued for 5 h at room temperature. The reaction mixture was poured into ice water (50 mL), made slightly basic with aqueous 28% ammonia and extracted with dichloromethane (3 × 30 mL). The combined extracts were washed with 0.1 M hydrochloric acid (3 × 20 mL) and saturated sodium bicarbonate solution (3 × 20 mL). After drying over magnesium sulfate and evaporation of the solvent, the crude mixture was purified by distillation under reduced pressure, yielding 1-bromomethyl-1-fluorocyclopentane **2b** (3.0 g, 69%) as pure compound. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63–2.14 (8H, m), 3.59 (2H, d, J = 18.7 Hz). ^{13}C NMR (J = 75 MHz, $CDCl_3$): δ 24.5, 37.0 (d, J = 24.2 Hz), 37.7 (d, J = 28.8 Hz), 104.2 (d, J = 180.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$):δ −142.1 to −141.6 (1F, m). IR ν_{max} 2964, 1433, 1340, 1256, 1213, 985, 839, 656. GC–MS (EI) m/z (%): 180/182 (M^+, 0.02), 101 (M^+-Br, 15), 87 (100), 81 (43), 67 (56), 59 (10), 41 (19).
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19. *The general procedure is exemplified for the synthesis of 1-azidomethyl-1-fluorocyclopentane **4b***. Sodium azide (0.43 g, 6.6 mmol) was added to a stirred solution of 1-bromomethyl-1-fluorocycloalkane (1.0 g, 5.5 mmol) and sodium iodide (0.99 g, 6.6 mmol) in anhydrous DMSO (10 mL). The mixture was allowed to react for 16 h at 100 °C. After cooling down, H_2O (15 mL) was added and the mixture was extracted with pentane (3 × 10 mL). The combined organic phases were washed with H_2O (3 × 10 mL) and brine (2 × 10 mL). Drying over magnesium sulfate and evaporation under reduced pressure yielded 1-azidomethyl-1-fluorocyclopentane **4b** (0.54 g, 68). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60–2.07 (8H, m), 3.42 (2H, d, J = 20.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 35.9 (d, J = 24.2 Hz), 57.1 (d, J = 25.4 Hz), 106.1 (d, 177.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −145.7 to −145.1 (1F, m). IR (ATR, cm^{-1}): ν_{N3} 2095; ν_{max} 1340, 1279, 1034, 923, 891. GC–MS (EI) m/z (%): 143 (M^+, 0.9), 87 (58), 67 (100), 59 (24), 41 (43).
20. *The general procedure is exemplified for the synthesis of 1-aminomethyl-1-fluorcyclopentane hydrochloride **5b***. A solution of 1-azidomethyl-1-fluorocyclopentane (130 mg, 0.91 mmol) in EtOAc (3 mL), and 20 wt% of Pd/C was stirred under H_2 pressure (5 bar) for 16 h at room temperature. The mixture was then filtered over Celite® and the solids were washed with ethyl acetate (10 mL). After introduction of dry HCl (g) the obtained crystals were filtered and washed with diethyl ether to obtain the pure compound **5b** (82 mg, 58%). White crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61–2.18 (8H, m), 3.29 (1H, d, J = 19.3 Hz), 8.65 (3H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 36.2 (d, J = 23.1 Hz), 46.0 (d, J = 24.2 Hz), 103.5 (d, J = 176.5 Hz).^{19}F NMR (282 MHz,

$CDCl_3$): δ −148.2 to −147.6 (1F, m). IR (ATR, cm^{-1}): ν_{NH} 2959; ν_{max} 2871, 1598, 1512, 1456, 1351, 1101, 978, 849.

21. *Synthesis of N-[(1-fluorocyclopentyl)methyl]benzamide* ***6b***. To a stirred solution of 1-aminomethyl-1-fluorcyclopentane hydrochloride (82 mg, 0.53 mmol) in dry chloroform (2 mL) was added triethylamine (112 mg, 1.13 mmol). After 10 min the mixture was cooled to 0 °C and benzoyl chloride (82 mg, 0.58 mmol) was added. The reaction was stopped after 1 h by adding H_2O (1 mL). The aqueous phase was extracted with chloroform (3 × 1 mL) and the combined organic phases were washed with 0.1 M HCl (2 × 1 mL) and saturated $NaHCO_3$ (2 × 1 mL). After drying over magnesium sulfate and evaporation of the solvent, the crude mixture was purified via column chromatography on silicagel (petroleum ether/EtOAc 7:1), yielding *N*-[(1-fluorocyclopentyl)methyl]benzamide **6b** (65 mg, 55%) as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60–2.06 (8H, m), 3.76 (2H, dd, J = 22.6, 5.5 Hz), 6.64 (1H, br s), 7.38–7.54 (3H, m), 7.79 (2H, d, J = 7.7 Hz) . ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1 , 35.9 (d, J = 23.1 Hz), 46.3 (d, J = 23.1 Hz), 107.0 (d, J = 174.2 Hz), 127.1, 128.7, 131.7, 134.5, 167.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ −146.4 to −145.9 (1F, m). IR (ATR, cm^{-1}): ν_{NH} 3296; $\nu_{C=O}$ 1638; ν_{max} 2963, 2935, 1548, 1317, 1159, 1002, 803, 696, 664. HRMS (ES) calcd for $C_{13}H_{16}FNO$: 222.1289 $[M+H]^+$; Found: 222.1287.