Ritter-type fluorofunctionalisation as a new, effective method for conversion of alkenes to vicinal fluoroamides

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A range of alkenes are converted to vicinal fluoroacetamides in high yield by reaction with 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Accufluor™ NFTh) in acetonitrile solution.

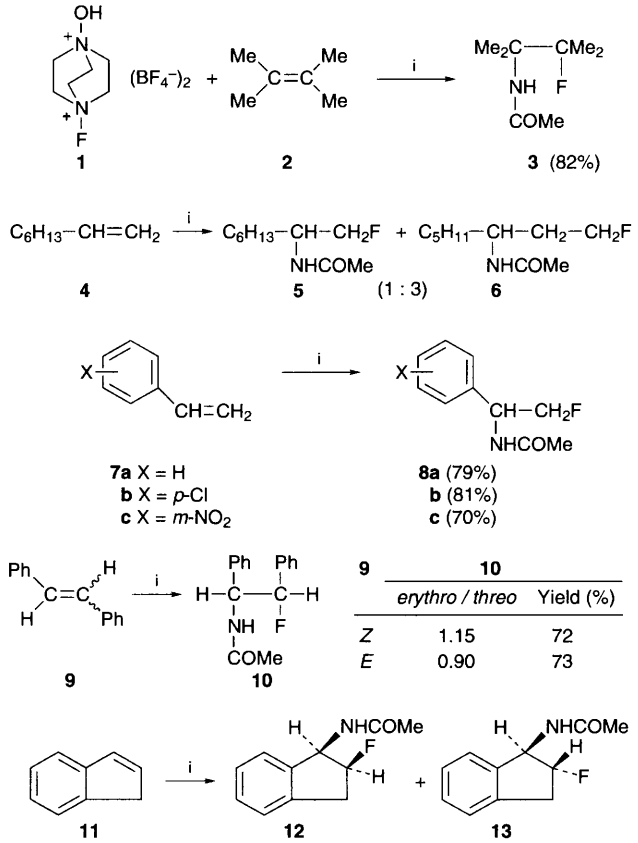
The recent introduction of various organic compounds incorporating a reactive N–F bond as reagents for selective fluorination of organic molecules under mild reaction conditions[1] represents a significant result of very intensive research in this field of organic chemistry,[2] which has been of increasing importance in recent decades mainly due to the biomedicinal and other applications of organofluorine compounds.[3] This family of N–F reagents was enlarged recently by the promotion and application of 1-fluoro-4-alkyl- and 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane salts[4–6] as site-selective, easily handled and cost-effective fluorinating reagents.

The reactions of 'electrophilic' fluorination reagents with alkenes have been intensively studied.[1,2] These reactions are in general addition or addition–elimination processes involving β-fluoro carbocations as the key intermediates. The presence of an external nucleophile is not necessary for selective addition to carbon–carbon double bonds when elemental fluorine, XeF_2 or some fluoroxy compounds are used as fluorinating reagents. In these cases the fluoro carbocationic intermediate could be trapped by the nucleophilic part of the reagent, resulting in the formation of a Markovnikov-type adduct. On the other hand, when alkenes were fluorinated with various N–F reagents, the presence of a good external nucleophile, such as water or methanol, was considered to be essential in order to avoid the formation of complicated product mixtures. Only in some cases, when highly stabilised fluoro carbocations were involved, could reasonable yields of addition–elimination products be isolated.[1,5,6b] We now report that by using 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Accufluor™ NFTh, **1**)† the selective fluorination of a comprehensive range of alkenes can also be achieved with the solvent acetonitrile as nucleophile.

In a typical experiment, to a solution of tetramethylethene **2** (2 mmol) in distilled MeCN (30 ml) was added NFTh **1** (710 mg, 2.2 mmol) and the reaction mixture stirred at 70 °C. After 30 min the reagent was consumed and after the usual work-up the formation of 2-fluoro-3-acetamido-2,3-dimethylbutane **3** in 93% yield was established.‡ The vicinal fluoroamide **3** was also formed almost quantitatively when the reaction was carried out in the presence of up to a hundred-fold molar excess of water, indicating that it did not compete with the solvent. Oct-1-ene **4** was also readily converted with NFTh to a mixture of two fluorinated products in 74% overall yield, determined after separation by GLC as 1-fluoro-2-acetamidooctane **5** and 1-fluoro-3-acetamidooctane **6** in 1:3 relative ratio. For the regioselective formation of vicinal fluoroacetamides from styrene derivatives **7**, the use of anhydrous MeCN (less than 0.02% water content) was necessary. Styrene **7a** gave 1-fluoro-2-acetamido-2-phenylethane **8a** in high yield, and its *p*-chloro (**7b**) or *m*-nitro (**7c**) derivatives were transformed into corresponding fluoroamides **8b** and **c** as well. The reaction of *p*-methoxystyrene resulted in a complex reaction mixture, thus indicating that strong stabilisation of a carbocation intermediate diminished the selectivity of the rection.

Almost complete lack of diastereoselectivity was observed, similar to fluorination reactions where β-fluoro carbocations were postulated as reaction intermediates.[1,2,5] *Z*- and *E*-stilbenes **9** were readily transformed with NFTh in anhydrous MeCN into an almost equimolar mixture of the *erythro* and *threo* diastereoisomeric pair of vicinal fluoroacetamides **10**, while indene **11** under the same reaction conditions gave a 1:1 mixture of *cis*- (**12**) and *trans*-2-fluoro-1-acetamidoindane (**13**).

We studied the kinetics of the reaction of styrene **7a** with NFTh in anhydrous MeCN and found that the consumption of NFTh followed first order reaction kinetics with a rate constant of 1.3×10^{-4} s^{-1}. The reaction course leading to vicinal fluoroamides can be rationalised assuming the formation of β-fluoro carbocationic intermediates which are attacked by the nucleophilic nitrogen of the acetonitrile molecule following the Ritter-type reaction,[7] resulting in vicinal fluoroacetamides. We believe that the stability of the β-fluoro carbocation is a key feature regulating the course of the reactions of NFTh with alkenes. The substrates from which a strongly stabilised



Scheme 1 *Reagents and conditions*: i, alkene (2 mmol), **1** (2.2 mmol), MeCN (30 ml), 70 °C, 1–24 h

β-fluoro carbocation can be formed (*i.e.* α,α-diphenyl alkenes) preferred to be attacked by a good external nucleophile, otherwise the addition–elimination process was found to be predominant.[6b] The substrates forming unstable carbocations, or those with poor stabilisation (*i.e.* alkyl-substituted alkenes) were involved in Ritter-type reactions with the nitrile solvent, resulting in the formation of vicinal fluoroamides. Styrene and its derivatives were found to be the most sensitive substrates. Styrene **7a** underwent fluoroamidation in the absence of a sufficient concentration of an external nucleophile,¶ while in the case of α-methylstyrene even trace amounts of a good external nucleophile were enough for its predominant collapse with a cation intermediate.‖

The present report opens new possibilities for the direct and effective preparation of vicinal fluoroamides with some advantages over some other routes for construction of this functional block,[8] which carried potential bioactivity.[3] In order to expand the scope of the method, examination of the reaction of NFTh with some cyclic and bicyclic alkenes in the various types of nitriles is in progress.

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Footnotes

† Accufluor™ NFTh is produced and commercialised by Allied- Signal, Buffalo, USA. A MSDS (Material Safety Data Sheet) is available from Dr George Shia, AlliedSignal Inc., Buffalo Research Laboratories, 20 Peabody Street, Buffalo, New York 14210, USA.

‡ The yields were determined from ^{19}F NMR spectra of crude reaction mixtures using octafluoronaphthalene as internal standard and calculated to starting material. The yields in Scheme 1 refer to isolated pure compounds. The spectroscopic data for all isolated compounds are in agreement with assigned structures.

§ A solution (55 ml) of styrene (114.4 mg, 1.1 mmol) and NFTh (194.7 g, 0.605 mmol) in anhydrous MeCN was thermostatted at 60 °C and stirred. At five intervals of 10 min, 10 ml aliquots of the reaction mixture were taken out and mixed with 20 ml of a 0.02 M aqueous solution of KI, and the liberated iodine titrated with 0.05 M $Na_2S_2O_3$. The logarithms of the values of NFTh concentration so obtained were correlated with reaction time, resulting in a linear relationship with a very high value for the correlation constant (r = 0.998).

¶ For exclusive formation of vicinal fluorohydrine not less than a fifty-fold molar excess of water had to be present in the reaction mixture, otherwise both products were formed in a ratio that depended on the concentration of water.

‖ Three fluorinated products were formed even in anhydrous MeCN: the vicinal fluoroacetamide 1-fluoro-2-acetamido-2-phenylpropane (15%), the addition–elimination product α-fluoromethyl styrene (15%) and the vicinal fluorohydrine 1-fluoro-2-hydroxy-2-phenylpropane (70%).

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