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Selective and Effective Fluorination of Organic Compounds in Water Using Selectfluor F-TEDA-BF_4

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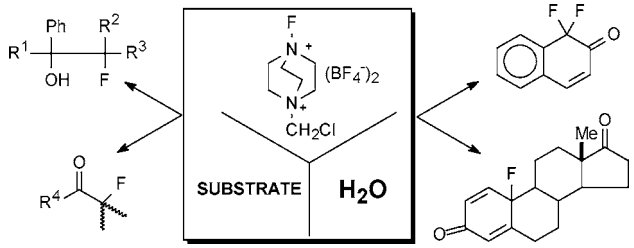
ABSTRACT



Selective and effective fluorination of various types of organic compounds performed in water as the reaction medium using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor F-TEDA-BF_4) is reported. 2-Naphthole and 2-methoxynaphthalene were thus transformed to 1,1-difluoro-2(1H)naphthalenone, estrone to 10β-fluoro-1,4-estradien-3,17-dione, phenyl-substituted alkenes to vicinal fluorohydrins, and various ketones, 1,3-diketones, or β-ketoesters to corresponding α-fluoro or α,α-difluoro ketones.

The use of water as the medium for organic reactions was rediscovered in the early 1980s,[1] triggering a more widespread interest in the field, which considering many scientific, economic, and ecological challenges resulted in very intense basic and applied research in the last two decades.[2,3] As water is the most benign and cheapest liquid in the world, in addition to its essential role in life processes, the use of water should be one of the priority issues in modern organic chemistry and a basic challenge in view of the "green" approach[4] to organic compound transformations.

The versatile application of organofluorine compounds in several branches of industry and medicine[5] is generating a permanent impetus to research their related chemistry.[6] Developing new reagents and methods for site-selective introduction of a fluorine atom into organic molecules under mild reaction conditions has for a long time been one of the main themes of these efforts. A very important breakthrough was accomplished by the introduction and broad synthetic

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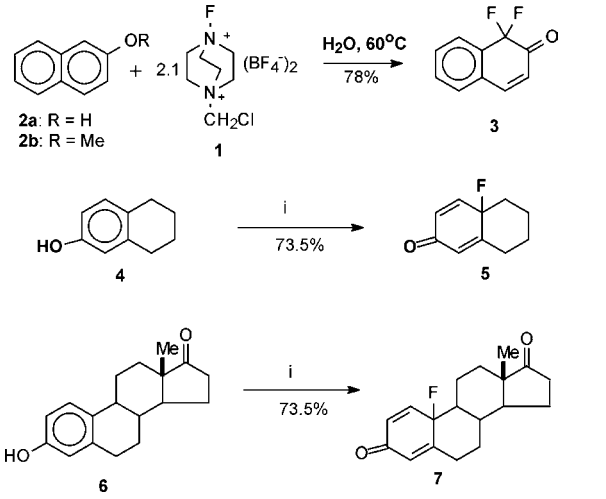
application of organic derivatives incorporating a reactive N−F bond as mild fluorinating reagents.[7] 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **1**, scientifically introduced in the 1990s[8] and soon after commercialized as Selectfluor F-TEDA-BF_4, became one of the most important reagents for "electrophilic" fluorofunctionalization of organic compounds,[9] which in addition to being today an ordinary benchtop material in research laboratories is also multiton per year produced chemical for several industrial applications.[10]

Fluorination of organic compounds in pure water obviously has not been an issue of much scientific interest so far.[11] F-TEDA-BF_4 should be a convenient reagent for water-mediated transformations of organic compounds since it is easily soluble (0.16 g/mL) and relatively stable in water,[12] but only a few attempts to obtain potential advantage from this fact have been reported so far.[13] To try to remedy this deficiency we now report a preliminary screening of fluorination of a wide range of organic compounds with F-TEDA-BF_4 in water.

The prejudices that ruled out the use of water as the medium for organic reactions originated in several reasons, where insolubility of the reactants and the incompatibility of the intermediates with water were the main ones. To avoid this disadvantage we started our screening with phenols, which are at least slightly soluble in water. In a typical experiment, we suspended 1 mmol of 2-naphthole (**2a**, Scheme 1) in 5 mL of water, and after 5 min of vigorous stirring at 60 °C, F-TEDA-BF_4 was added. After a few minutes, homogenization of reaction mixture took place followed by continuing precipitation of yellow crystals recognized as 1,1-difluoro-2(1*H*)-naphthalenone **3**. Stirring for 30 min at 60 °C and addition of 2.1 mmol of F-TEDA-BF_4 were sufficient for water-mediated transformation of **2a** to **3** isolated after purification by flash chromatography in 78% yield. The ether analogue of **2a**, 2-methoxynaphthalene (**2b**), was also transformed under the same reaction conditions after 2 h into **3**. Encouraged by this result, which from the point of view of selectivity as well as of efficiency is comparable with those obtained in analogous reactions of **2a** in MeCN,[14] we proceeded in our screening with the alkyl-substituted phenol type of compounds known as precursors

Scheme 1 [a]



[a] Reaction conditions: (i) 1 mmol of substrate, 1.05 mmol of F-TEDA-BF_4 (**1**), 5 mL of H_2O, 60 °C, 2−6 h.

for synthesis of 4-fluorocyclohexa-2,5-dienone derivatives.[15] 5,6,7,8-Tetrahydro-2-naphthole **4** was thus readily transformed by F-TEDA-BF_4 in aqueous medium to 4α-fluoro-5,6,7,8-tetrahydro-(4α*H*)-naphthalen-2-one **5** and estrone **6** to 10*β*fluoro-1,4-estradien-3,17-dione (**7**, Scheme 1).

Phenyl-substituted alkenes have often been used as tools for testing new reagents or methodologies for transformation of alkenes under electrophilic reaction conditions. This was also the case when fluorofunctionalizations of alkenes using "electrophilic" fluorinating reagents was the object of research.[5−9] Alkenes are usually immiscible with water, so that we were not really surprised when treatment of selected alkenes **8** with F-TEDA-BF_4 under the reaction conditions used in the above-mentioned case of phenols did not give such good results. More intense stirring of the reaction mixture to disperse the drops of alkene in water as much as possible helped in increasing the conversion of starting material to products, but a considerable and satisfactory improvement in the efficiency of the reaction was finally achieved by using a surfactant compound that presumably acted as an emulsifier of the alkene in water and promoted its transformation with water-soluble F-TEDA-BF_4 within a reasonable reaction time. We used one of the most common anionic types of surfactant, i.e., sodium lauryl ether sulfate, commercially declared as $C_{12}-C_{14}O(C_2H_4O)_2SO_3Na$ under the trade name Genapol LRO, and found that a 0.05% water solution of this material is optimal for regioselective and almost quantitative transformation of phenyl-substituted alkenes **8** to vicinal fluorohydrins **9** (Scheme 2) by F-TEDA-BF_4. Water is in this case the source of the external nucleophile and the reaction medium, while the regiochemistry as well as efficiency of the addition process is the same as that observed when acetonitrile was used as the solvent and water or alcohols were added as nucleophiles.[16]

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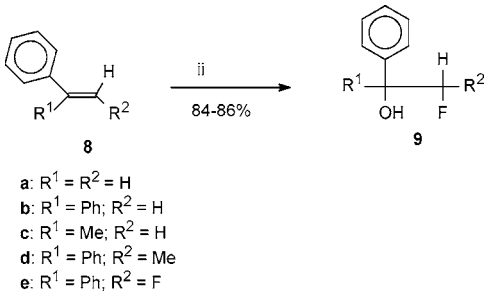
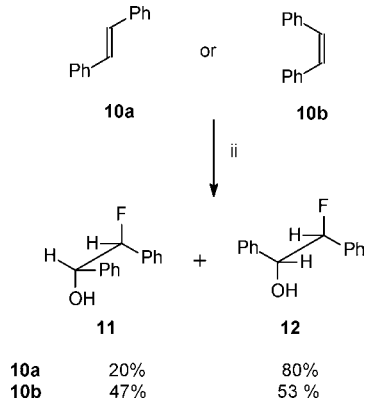
Scheme 2 [a]



[a] Reaction conditions: (ii) 1 mmol of **8**, 1.1 mmol of F-TEDA-BF_4, 5 mL of 0.05% water solution of surfactant sodium lauryl ether sulfate (Genapol LRO), 60 °C, 6−24 h.

We further preliminarily checked the stereochemistry of this fluorohydroxylation addition reaction and took (*E*)- and (*Z*)-1,2-diphenylethene (**10a** and **10b**, Scheme 3) as the tools

Scheme 3 [a]



[a] Reaction conditions: (ii) 1 mmol of **10**, 1.1 mmol of F-TEDA-BF_4, 5 mL of 0.05% water solution of surfactant sodium lauryl ether sulfate (Genapol LRO), 60 °C, 24 h.

often used for stereochemical evaluation of addition reactions in the case of other fluorinating reagents.[5−9] Both alkenes were transformed with F-TEDA-BF_4 in water to a mixture of the diastereoisomers D,L-*threo*- (**11**) and D,L-*erythro*-1-fluoro-2-hydroxy-1,2-diphenylethane (**12**). In the case of the (*E*)-isomer **10a** the formation of the *erythro* stereoisomer **12** was found to be predominant, while complete lack of stereoselectivity of the addition process was observed when the (*Z*)-isomer **10b** was treated with F-TEDA-BF_4 in water solution of Genapol LRO (Scheme 3). These results are similar to those observed when the same substrates were treated in a MeCN solution of F-TEDA in the presence of MeOH,[17] indicating that the reaction mechanism is probably alike.

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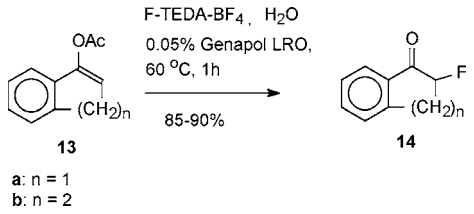
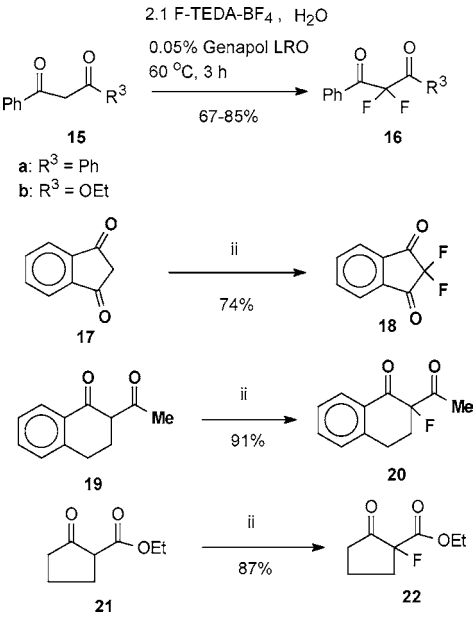
Fluorofunctionalization of organic compounds bearing a carbonyl group has been for a long time of special interest,[5,6] since this reactive functional site is often present in bioactive molecules or in potential building blocks for their synthesis, while the carbon atom α to the carbonyl group seems to be the most strategic one for fluorination.[18] Direct α-fluorination of ketones with F-TEDA-BF_4 in water was found not to be so efficient as in the case when MeCN or MeOH was used as solvent,[19] but by activation of the target molecule by enolization to enolacetates almost quantitative formation of the corresponding α-fluoro ketone could be achieved. Enolacetates of 1-indanone (**13a**, Scheme 4) or 1-tetralone **13b** were thus readily transformed to 2-fluoro-1-indanone **14a** or 2-fluoro-3,4-dihydronaphthalen-1(2*H*)-one **14b**, respectively.

Scheme 4



We further examined 1,3-diketones and *β*-ketoesters as tools for water-mediated fluorofunctionalization with F-TEDA-BF_4 and established that both types of compounds could also in this way be readily converted to α-fluoro derivatives (Scheme 5). In the series of 1,3-diketones 1,3-

Scheme 5 [a]



[a] Reaction conditions: (ii) 1 mmol of **17**, **19**, or **21**, 1.1 mmol of F-TEDA-BF_4, 5 mL of 0.05% water solution of surfactant sodium lauryl ether sulfate (Genapol LRO), 60 °C, 2−4 h.

diphenyl-1,3-propandione **15a** and 1,3-indandione **17** were thus converted to α,α-difluoro derivatives **16a** and **18** in high yield with 2 equiv of F-TEDA-BF_4 and 2-acetyl-1-tetralone **19** quantitatively to 2-acetyl-2-fluoro-3,4-dihydronaphthalene-1(2*H*)-one **20** with 1 equiv of **1**, while ethyl 3-oxo-3-phenylpropanoate **15b** was transformed to the 2,2-difluoro-substituted product **16b** with 2 mmols of F-TEDA-BF_4 and ethyl 2-oxocyclopentanecarboxylate **21** to its α-fluoro derivative **22** with 1 equiv of the reagent. Unfortunately, in the case of targets **15** and **17** the corresponding monofluoro-substituted products could not be selectively obtained as reported when MeCN was used as the reaction medium.[20]

On the basis of the above-mentioned results, we can in conclusion claim that water could and should be used as a reaction medium for fluorination of organic molecules with Selectfluor F-TEDA-BF_4. The selectivity and efficiency of the reactions performed in water[21] were found to be, at least in the series of studied organic compounds and some rare previous reports,[13] comparable with those where other organic solvents, mainly MeCN and MeOH, have been used. The cost economy and environmental benefits so achieved represent an important contribution to the green chemistry approach to this field of organic chemistry.

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Supporting Information Available: Yields and spectral data of all product isolated. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Demineralized water solution of the surfactant Genapol LRO (5 mL, 0.05%) was poured over 1 mmol of target organic compound and the suspension mixture magnetically stirred in a glass vessel for 10 minutes at 60 °C. Selectfluor F-TEDA-BF_4 (1.05 or 2.1 mmol) was then added and the reaction mixture stirred at 60 °C until the consumption of the reagent was established by KI starch paper indication. Water (10 mL) was added to the mixture, which after cooling to room temperature was extracted by *tert*-butylmethyl ether (20 mL). The organic layer was washed with water (20 mL) and dried (Na_2SO_4), and the solvent was evaporated. The crude products were analyzed by ^{19}F and ^1H NMR, and pure material was obtained by flash chromatography (SiO_2) or TLC (SiO_2) purification.