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# Solvent directing immediate fluorination of aromatic ketones using 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)†

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**Reactions of aryl alkyl ketones with 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Accufluor™ NFTh) in methanol result in selective and almost quantitative formation of the corresponding α-fluoroketones, while in acetonitrile exclusive fluorofunctionalisation of the activated aromatic ring take place.**

The strategic introduction of a fluorine atom into organic molecules has attracted considerable current interest in related fields of chemistry[1] since this element often induces beneficial changes in the physicochemical and biological properties[2] of organic compounds. The ever increasing application of these fluorofunctionalised compounds has given a strong impetus to the academic as well as the industrial evaluation of new reagents and methods for selective fluorination under mild reaction conditions. In the last decade the introduction of numerous organic molecules incorporating a reactive N–F bond as versatile, mild, electrophilic fluorinating reagents[3] has created new challenges and revolutionarily influenced achievements in this field of organic chemistry.

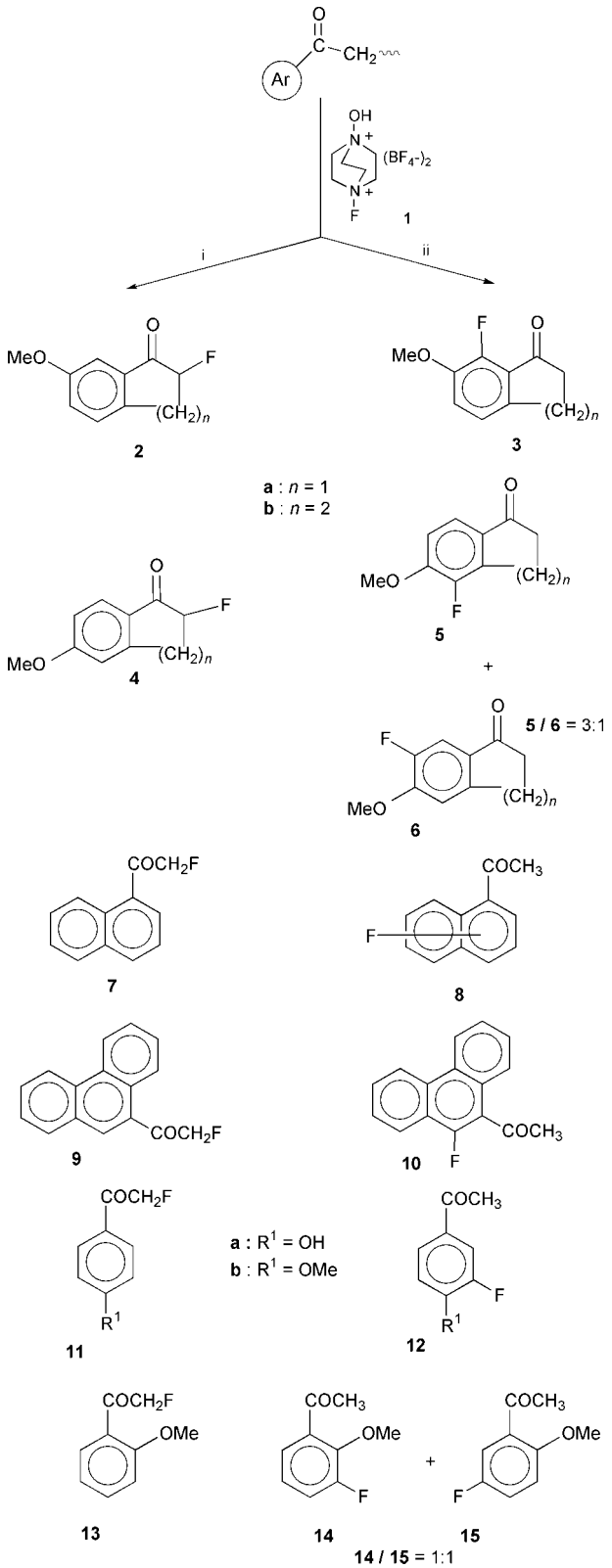
Fluorofunctionalisation of organic compounds bearing a carbonyl functional group has been of special interest,[1] since this reactive moiety is often present in bioactive molecules or in potentially valuable building blocks for the synthesis of more sophisticated organofluorine derivatives. The position α to the carbonyl seems to be the most strategic one for the introduction of fluorine,[4] but when using electrophilic fluorinating reagents prior activation through enolate anions or enol ethers is necessary, except for sufficiently activated 1,3-dicarbonyl substrates. The presence of other active sites, such as an activated aromatic ring, in a target molecule often provokes lower regioselectivity of fluorofunctionalisation, thus making the task considerably more difficult. We now report the reactions of 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Accufluor™ NFTh[5]) with alkyl aryl ketones bearing a strongly activated aromatic ring.

In a typical experiment we treated 6-methoxy-1-indanone with NFTh in acetonitrile solution under reflux and in the crude reaction mixture established a high yield (68%) of 7-fluoro-6-methoxyindan-1-one (**3a**, Scheme 1). The observed regioselectivity of the reaction was quite different from that in the case of the same reaction of unsubstituted indan-1-one where regiospecific fluorination of the α-carbonyl position was observed.[6] Although the result of this reaction was expected since the aromatic part of the substrate is strongly activated and suitable for fluorofunctionalisation,[3] we checked the effect of the solvent on the course of the reaction and found that by using methanol as the reaction medium, the regiochemistry of the fluorination process changed dramatically, leading the reaction towards quantitative formation of 2-fluoro-6-methoxyindan-1-one (**2a**, Scheme 1). Encouraged by the possibility that the regioselectivity of fluorination of these types of ketones could be regulated only by the solvent used, we further investigated the reactions of NFTh with a series of methoxy substituted benzocycloalkan-1-one derivatives‡ and found that in methanol 7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one was transformed to 2-fluoro-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**2b**) in over 90% yield, while in acetonitrile the fluorofunctionalisation of the aromatic ring took place regioselectively at position 8, thus forming 8-fluoro-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**3b**). Solvent directed regioselective fluorination was also observed in the case of 5-methoxyindan-1-one or 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one: 2-fluoro derivatives **4** were exclusively formed in methanol, while in acetonitrile fluorination of the aromatic ring was again found to be favoured but not regiospecific and two isomers **5** and **6** in a relative ratio of 3:1 were isolated from the crude reaction mixture.

Direct fluorination of methyl aryl ketones in the α-carbonyl position was found to be considerably less effective than the corresponding functionalisation of dialkyl or alkyl aryl ketones,[6] but by using methanol as reaction medium the NFTh mediated transformation of acetophenone to fluoromethyl phenyl ketone was readily accomplished in over 80% yield. This fact encouraged us to also use the protocol described for the fluorofunctionalisation of methyl aryl ketones bearing an activated aryl part of the molecule. 1-Acetylnaphthalene was, following reaction with NFTh in methanol, thus effectively and regioselectively transformed to fluoromethyl 1-naphthyl ketone **7**, while the reaction in acetonitrile was in this case found to be unselective and up to six mono and difluoro isomers of the substrates were detected in the crude reaction mixture. On the other hand, the analoguous reaction of 9-acetylphenanthrene resulted in the formation of high yield fluoromethyl 9-phenanthryl ketone **9** if methanol was used as the solvent, while exclusive formation of 9-acetyl-10-fluorophenanthrene **10** was established when the reaction was performed in acetonitrile. We further found that strong electron donating substituents on the *para* position of acetophenone did not interfere with the effectiveness of the reactions. Fluorination of 4-hydroxy- or 4-methoxyacetophenone resulted in the high yield formation of the corresponding fluoromethylacetophenones **11** and 3-fluoro substituted derivatives **12**, respectively, depending on the solvent used. Similar results were also obtained with *ortho* substituted acetophenones: fluoromethyl-2-methoxyacetophenone **13** was formed in methanol and a 1:1 mixture of 3-fluoro- (**14**) and 5-fluoro-2-methoxyacetophenone (**15**) in acetonitrile mediated reactions. Unfortunately, derivatisation of acetophenone with an electron donating substituent at the *meta* position caused complete loss of the selectivity of the reaction, and in both solvents only a complex mixture of fluorinated products was observed.

Considering the results obtained, we can point out some important facts which in general facilitate the task of fluorofunctionalisation of ketones considerably. Using Accufluor™

† The results of characterisation of **2a**, **2b**, **3a**, **3b**, **4a**, **4b**, **5a**, **6a** and **9** are available as electronic supplementary information (ESI). See http://www.rsc.org/suppdata/cc/b0/b003488f/




**Scheme 1** *Reaction conditions*: i, MeOH, reflux for 0.5–4 h, if necessary hydrolysis with 10% HCl in MeCN; ii, MeCN, reflux for 0.5–4 h.

NFTh direct and selective fluorination can be effectively achieved even of those ketones bearing an activated aromatic part of the molecule, while alkyl aryl regioselectivity of fluorofuctionalisation could be regulated by the solvent. When methanol is used as solvent the substrate is regioselectively fluorinated at the α-carbonyl position, while in acetonitrile medium the same molecule reacts as an activated aromatic substrate and fluorination of the aryl ring is favoured. In addition, reaction is also effective with methyl aryl ketones, which makes the method convenient for direct α-carbonyl fluorination of a comprehensive range of ketones. Mechanistic elucidation of these reactions is in progress and on the basis of preliminary results we can assume that a subtle interplay of keto–enol tautomerism of the studied ketones plays a crucial role on the course of these reactions. In methanol, the keto–enol equilibrium lies sufficiently on the side of an enol form and a substrate reacts with NFTh as an alkene, following the reaction pathway similar to our recent observations,[7] resulting in α-fluoroketones. This assumption is reasonable since we already established that in the case of fluorination with N–F reagents activated alkenes[7] are for several decades more reactive than activated aromatics.[8] In acetonitrile keto–enol equilibrium is less favourable and the activated aromatic ring became the most reactive part of the substrate.

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## Notes and references

‡ To a solution of 2 mmol of ketone in 20 mL of methanol or acetonitrile 1.35 g of Accufluor™ NFTh (2.1 mmol of active compound) was added and the suspension heated under reflux for 0.5 to 4 h until KI starch paper showed the consumption of the fluorinating reagent. The reaction solvent was removed under reduced pressure and the crude reaction mixture dissolved in $CH_2Cl_2$ (50 mL), insoluble material filtered off, the solution washed with water (50 mL), dried over $Na_2SO_4$ and the solvent evaporated. The isolated crude reaction mixtures were analysed by $^1$H and $^{19}$F NMR. The amounts of fluorinated products were determined from the $^{19}$F NMR spectra of crude reaction mixtures using octafluoronaphthalene as an additional standard and yields between 90–95% for α-fluoro carbonyl products or 70–75% of fluoro aromatics (**3**, **5** + **6**, **10**, **12** and **14** + **15**) were obtained. Since crude α-fluoro carbonyl derivatives were often formed mainly in dimethylketal form, hydrolysis with 10% HCl solution in MeCN, followed by crystallisation of α-fluoro ketone was necessary in order to obtain pure products (75–85% yield) **2**, **4**, **7**, **9**, **11**, and **13**, while fluoro aromatic derivatives were purified by preparative TLC ($SiO_2$, $CH_2Cl_2$) and 55–65% yield of satisfactory pure products obtained. New compounds were fully characterised by NMR, MS, and IR spectroscopy and their purity verified by combustion analysis.†

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5 Accufluor™ NFTh is commercially available as 50% w/w on alumina. We are indebted to Dr George Shia from AlliedSignals, Inc. for providing us with free samples of the reagent.
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