Pergamon

Tetrahedron Letters, Vol. 37, No. 20, pp. 3591-3594, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00630-2

High Yield Direct Fluorofunctionalisation of Ketones Using Accufluor™ - NFTh Fluorinating Reagent#

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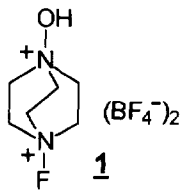
Abstract *Direct regioselective conversion of a variety of cyclic and acyclic ketones to α-fluoroketones was achieved in high to excellent yield using 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate) [Accufluor™ - NFTh] in acetonitrile solution.*

Site selective fluorination of organic compounds continues to be a research area of increasing importance[1] due to biomedical, agricultural and other applications of organofluorine compounds. [2] Efforts to develop mild and selective fluorinating reagents have been significantly rewarded by introduction and commercialisation of various organic molecules incorporating a reactive N-F bond.[3] This family of compounds, which appears to be one of the most attractive group of reagents for fluorination, was enriched considerably by the promotion of 1-fluoro-4-alkyl-1,4-diazoniabicyclo[2.2.2]octane salts,[4] very soon confirmed as versatile fluorinating reagents with F-TEDA-BF_4 as the most representative and widely used one.



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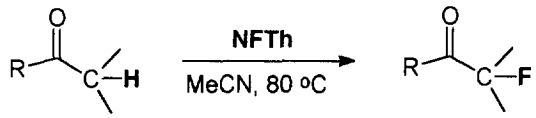
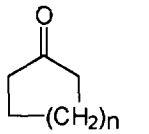
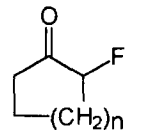
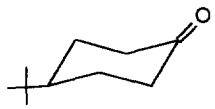
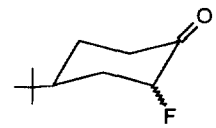
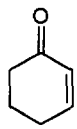
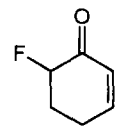
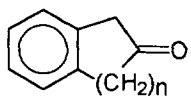
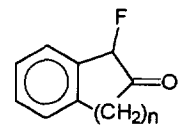
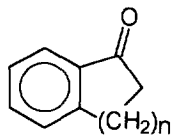
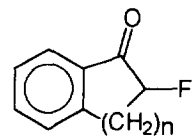
Organic compounds possessing an α-fluorocarbonyl moiety are considered to be of potential biological interest.[2] Research dealing with the synthesis and chemistry of this functional block has been a shared and important interest of organic chemists[1, 6] but so far, no synthetically useful direct α-fluorofunctionalisation of monocarbonyl compounds by any electrophilic reagent has been reported. Derivatisation of monocarbonyl compounds to metal enolates, enol acetates, trimethylsilyl enol ethers or enamines, as the first step preceding fluorination, is often necessary. We now report direct α-fluorination of ketones using 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)[7] (**1**, *Accufluor™ NFTh*), very recently promoted as a new fluorinating reagent,[5b,8] which is also already commercially available.[9]

Dedicated to Prof. Miha Tišler on the occasion of his 70th birthday

Table 1 *Direct α-Fluorination of Ketones using 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2] octane bis(tetrafluoroborate) (**1**, Accufluor™ NFTh)* [a].



Entry	**Ketone**	*Reaction time (h)*	**α-Fluoro ketone**	*Yield* [b] *(%)*
1	$(C_4H_9)_2CO$	12	$C_4H_9COCHFC_3H_7$	91 [81]
2	$C_6H_{13}COCH_3$	10	$C_5H_{11}CHFCOCH_3$	86 [78]
3	 n=1	8		80 [70]
4	n=2	8		92 [84]
5	n=3	8		85 [78]
6	n=4	8		85 [78]
7		2		85 [c]
8		8		82 [72]
9	 n=1	1		88 [80]
10	n=2	0.5		81 [75]
11	 n=1	8		95 [88]
12	n=2	8		95 [88]
13	n=3	8		90 [82]
14	$PhCOCH_3$	48	$PhCOCH_2F$	33 [23]
15	$PhCOCH_2CH_3$	30	$PhCOCHFCH_3$	88 [80]
16	$PhCOCH(CH_3)_2$ [d]	12	$PhCOCF(CH_3)_2$	83 [74]

a) Reaction conditions: 2 mmols of ketone, 2.2 mmols of NFTh, 30 ml of MeCN, 80°C; b) Determined from ^{19}F nmr spectra of crude reaction mixture; the values in square brackets refer to the isolated pure products; c) 1 : 1.2 ratio of *cis* and *trans* product; d) 3 ml of 15% aqueous HF was added to the reaction mixture at the beginning of the reaction.

We found that after refluxing a mixture of 5-nonanone and NFTh dissolved in acetonitrile[10] an excellent yield of 4-fluoro-5-nonanone could be obtained. Half a days reaction with a 10% excess of the reagent **1**[11] was found to be sufficient for conversion of the ketone to its α-fluoro derivative. In **Table 1** the collected results of this highly effective direct transformation show that quite comprehensive types of ketones could be fluorinated α to the carbonyl group, without prior activation. 2-Octanone (*entry* 2) was converted exclusively to 3-fluoro-2-octanone, indicating regiospecificity of the reaction, and high to excellent yield formation of the corresponding α-fluoro ketone was also achieved in the cycloalkanone (*entries* 3-6), and 2- and 1-benzocycloalkanone series (*entries* 9-13). 4-tert-Butylcyclohexanone (*entry* 7) was converted to a 1 : 1.2 mixture of cis and trans 2-fluoro-4-tert-butylcyclohexanone. In the case of 2-cyclohexen-1-one (*entry* 8), the α-methylene carbon, and not the C-C double bond was found to be the reactive centre for the fluorofunctionalisation with NFTh under the mentioned reaction conditions, and the 6-fluoro derivative was isolated in high yield as the sole product. On the other hand, only one third of acetophenone (*entry* 14) could be converted to fluoromethylphenyl ketone, even after 2 days of refluxing in the presence of as much as a two fold of excess of **1**. Derivatisation of the benzene ring with a p-methoxy group resulted in exclusive flurofunctionalisation of the ring and 3-fluoro-4-methoxy-acetophenone in 48% yield was isolated, while a m-trifluoromethyl group reduced the reactivity of the substrate even more and only starting material accompanied by a low yield (10%) of α-fluoro ketone was detected in the crude reaction mixture after 2 days reaction. The α-methylene carbon atom in the case of propiophenone (*entry* 15) molecule, on the other hand, was readily fluorofunctionalised resulting in the formation of 2-fluoropropiophenone after 30 h reaction with **1**. 2-Methyl-1-phenyl-1-propanon (*entry* 16) was again found to be almost unreactive under the general reaction conditions, but by adding 3 ml of 15% aqueous HF to the reaction mixture, transformation of the starting material to 2-fluoro-2-methyl-1-phenyl-1-propanon was achieved in high yield. In all cases presented in **Table 1**, none, or only a trace amount, of α,α-difluoro ketone products were detected in the crude reaction mixture.

We further made preliminary checks on the effect of the presence of nitrobenzene as a radical inhibitor, and of solvent polarity on the efficiency of the fluorination, and found that in the case of 2-tetralone, as the most reactive of the studied ketones, a radical inhibitor has no

Table 2 *The Effect of Radical Inhibitor and the Solvent Polarity on the Transformation of 2-Tetralone to 1-Fluoro-2-tetralone* [a)]

Solvent	Yield of Fluorination (%)
MeCN + 1 mmol $PhNO_2$	81
MeCN : CH_2Cl_2 = 9 : 1	78
MeCN : CH_2Cl_2 = 4 : 1	55
MeCN : CH_2Cl_2 = 2 : 1	22

a) Standard reaction conditions: 1 mmol of 2-tetralone, 1.1 mmol of NFTh, 15 ml MeCN, T=80°C, react. t. 0.5 h

effect on the course of reaction (**Table 2**). On keeping other reaction parameters constant and lowering only the solvent polarity, a considerably lowered transformation of starting material into fluorinated product was observed. We also reacted 2-tetralone with F-TEDA-BF_4 under the standard reaction conditions and found that in this case a high yield (83%) of 1-fluoro-2-tetralone could also be isolated.

On the basis of the results presented it can be concluded that 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) is a convenient and highly effective reagent for direct fluorofunctionalisation of ketones regioselectively to the α-carbonyl carbon atom. Application of this reaction to direct fluorination of more sophisticated ketones and an investigation of its mechanism, as well as comparative studies with other N-F reagents are in progress, and will be be the subject of a future publication.

Acknowledgement The financial support of the Ministry of Science and Technology of the Republic of Slovenia is acknowledged.

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7. Poss, A.J.; Shia, G.A. *US Patent No. 5,459,267;* **1995**.
8. Poss, A.J.; Shia, G.A. *210th ACS National Meeting,* Chicago **1995**, Book of Abs., ORGN 052.
9. Accufluor™ NFTh is produced and commercialised by *AlliedSignal*, 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. We are also indebted to Dr. George A. Shia (AlliedSignals Inc.) for motivating us to use the new *Accufluor™ NFTh* reagent in our research and providing us with free samples of the material.
10. *General reaction procedure* : To a solution of a ketone (2 mmols) in 30 ml of acetonitrile, 490 mg (2.2 mmols) of NFTh was added and the reaction mixture stirred at 80°C until all the reagent was dissolved and then heated under reflux until KI starch paper showed consumption of the fluorinating reagent. The reaction was stopped and the solvent removed under reduced pressure. A crude reaction mixture was dissolved in CH_2Cl_2 (50 ml), insoluble material filtered off and the solution washed with saturated aqueous $NaHCO_3$ and water, dried over Na_2SO_4 and the solvent evaporated. Isolated crude reaction mixture was analysed by ^1H and ^{19}F nmr and GLC and the amount of fluorinated products determined from ^{19}F nmr spectra using octafluoronaphthalene as internal standard. Pure products were obtained after flash chromatography over SiO_2 .
11. The activity of **1** was determined by iodometric titration which revealed that 1 g of **1** (3.11 mmol; dried for 3 h at 25 °C under reduced pressure) liberated 3.08 ± 0.02 mmol of iodine.

(*Received in UK* 6 *March* 1996; *revised* 2 *April* 1996; *accepted* 3 *April* 1996)