Efficient Synthesis of 4-Fluorocyclohexa-2,5-dienone Derivatives Using N-Fluoro-1,4-diazoniabicyclo[2.2.2]octane Salt Analogues

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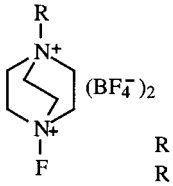
Abstract: 4-Fluorocyclohexa-2,5-dienone derivatives were obtained in high yield by reaction of *para* substituted phenols with 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoro-borate) (**1a**, Selectfluor™ F-TEDA-BF_4) or its 4-hydroxy analogue (**1b**, Accufluor™ NFTh) in acetonitrile. Estrogen steroids were readily converted to 10β-fluoro-1,4-estradiene-3-one derivatives in high yields.

Key words: fluorinated ketones, halogenation, phenols, steroids

Continuous and intensive interest in the synthesis of fluorinated organic molecules is based on extensive applications of various type of organofluorine compounds.[1] The long known fact that a fluorine atom has a profound effect on an organic molecule biological activity[2] has raised the intensity of research dealing with new reagents and methods for site-selective fluorofunctionalisation of organic molecules.[3] These efforts have been significantly rewarded in the last decade by introduction of various organic molecules incorporating a reactive N-F bond as versatile mild fluorinating reagents.[4] Derivatives of N-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts promoted by Banks,[5] represent an important group of »electrophilic« fluorinating reagents from the N-F class which, due to their optimal stability/reactivity characteristics and lower toxicity, in addition to unpretentious handling demands, are convenient not only for routine laboratory work, but also for large scale application.[6] Electrophilic fluorinating reagents are also strong oxidants[7] which, due to possible competition between fluorofunctionalisation and oxidation, can decrease the selectivity of their reactions, when oxidisable functional groups or heteroatoms are included in the target molecule. On the other hand, some heteroatom containing functional groups have also been found to be useful precursors for the selective fluorination of organic molecules.[6b, 8] The phenolic functional block carries a great deal of this oxidation/fluorofunctionalisation competitive dualism and, due to its frequent presence as a structural part of bioactive molecules, investigations of the reactions of phenols with fluorinating reagents are of considerable interest for the organic chemists.[1-3]

In our continuing interest in the reactions of N-F reagents with phenols[9] we now report an effective method for the preparation of 4-fluorocyclohexa-2,5-dienone derivatives starting from a comprehensive range of phenol structural block containing organic molecules by reaction with 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (**1a**, Selectfluor™ F-TEDA-BF_4)[10] or its 4-hydroxy analogue (**1b**, Accufluor™ NFTh).[11]



R = CH_2Cl: **F-TEDA BF_4**
R = OH : **NFTh**

Figure

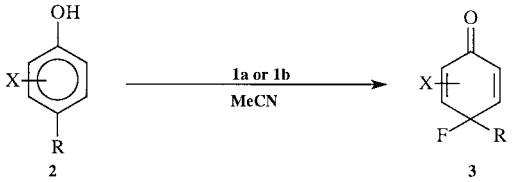
In a typical experiment[12] we treated 3,4-dimethylphenol (**2c**) with an equimolar amount of F-TEDA-BF_4 in acetonitrile for 4.5 hours at room temperature, and after a work-up procedure, we isolated 4-fluoro-3,4-dimethylcyclohexa-2,5-dienone[13] (**3c)** in 84% yield (entry 3, Table). Since in our previous report we used a series of hydroxy substituted aromatic molecules as precursors for α,α-difluoro cyclohexadienone derivatives,[9a] we decided to study how the variation of the structure of the phenolic substrate and the reaction conditions affect the course of the reaction preferentially towards the formation of 4-fluorocyclohexadienone-like products.

4-Methyl- (**2a**) or 4-*iso*-propylphenol (**2b**) were found to be more advantageous substrates for the preparation of 4-fluorocyclohexa-2,5-dienone derivatives than 4-*tert*-butylphenol, where the *ortho/para* regioselectivity of fluorofunctionalisation favoured the formation of the 2-fluoro substituted product with NFTh in MeCN, and especially in MeOH.[9a] A methyl as well as an *iso*-propyl substituent at position 4 of the phenol moderately favoured *ipso* attack of the fluorine moiety, so that in both cases 4-fluorocyclohexa-2,5-dienone derivatives (**3a**, **3b**[14]) could be isolated as the main reaction product, although in moderate yield (entries 1and 2, Table). By replacing the alkyl substituent with any other substituent (Ph, NO_2, F, OMe), the reaction with both reagents became complex and only traces of 4-fluorocyclohexadienone derivatives were observed in the crude reaction mixtures. We further checked the selectivity of the reaction in a series of *meta, para*-disubstituted phenol derivatives and found that 3-methyl-4-*iso*-propylphenol (**2d**) was readily transformed into 4-fluoro-4-*iso*-propyl-3-methylcyclohexa-2,5-dienone[15] (**3d**) and 3,4,5-trimethylphenol (**2i**) to 4-fluoro-3,4,5-trimethylcyclohexa-2,5-dienone[16] (**3i**), as well as their cyclic an-

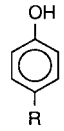
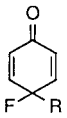
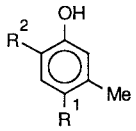
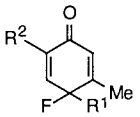
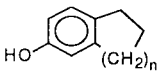
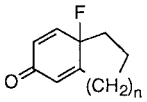
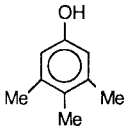
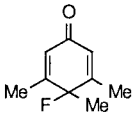
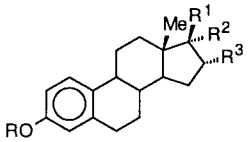
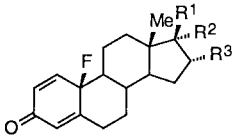
alogues 5-indanol (**2g**) and 5,6,7,8-tetrahydro-2-naphthol (**2h**) to the corresponding 4-fluorocyclohexa-2,5-dienone derivatives **3g** and **3h** in 80-94 % yield (Table, entries 4-9). The formation of 2-chloro-4-fluoro-4,5-dimethylcyclohexa-2,5-dienone[17] (**3e**) in high yield was also observed when 2-chloro-4,5-dimethylphenol (**2e**) was treated with F-TEDA BF_4 or NFTh, while only a moderate amount of the desired product could be obtained if 3-methyl-4-fluorophenol (**2f**) was taken as the substrate.

Considering the results obtained, some general conclusions regarding the reactions of *para*-substituted phenols with F-TEDA BF_4 or NFTh can be pointed out. A methyl, or at least an *n*- or *iso*-alkyl substituent *para* to the hydroxy group seems to be the crucial term directing the reaction towards *ipso* attack of the fluorine moiety, resulting in the addition-elimination process, thus forming 4-fluorocyclohexa-2,5-dienone analogues. An additional methyl group at *meta* position of the phenol substantially improved the regioselectivity of the reaction, directing the fluorinating reagent attack preferentially to position 4 of the substrate (entry 3-9).

Table Fluorination of 4-substituted Phenols using 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]-octane-bis(tetrafluoroborate) (1a, Selectfluor ™ F-TEDA BF_4) and 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]-octane]-bis(tetrafluoroborate) (1b, Accufluor ™ NFTh)



2 3

Entry	Phenol (2)		Reaction cond. time (h)	T(°C)	Product (3)	Yield[a] (%) 1a	1b	Lit. yield (%)
1		**a**: R=Me	20	22		60 [52]	55 [45]	68 [26]
2		**b**: R=iPr	24	22		55 [44][b]	53 [44]	
3		**c**: R^1=Me, R^2=H	4.5	22		84 [76][b]	83 [74]	
4		**d**: R^1=iPr, R^2=H	7	22		80 [71][b]	78 [69]	
5		**e**: R^1=Me, R^2=Cl	5	70		76 [68]	73 [66]	
6		**f**: R^1=F, R^2=H	18	70		49 [38]	47 [35]	17 [25]
7		**g**: n=1	4.5	22		85 [77]	83 [74]	42 [26]
8		**h**: n=2	4.5	22		86 [77]	85 [75]	66 [26]
9		**i**	4.5	22		93 [82][b]	90 [84]	
								
10	j: R=H, R^1+R^2=O, R^3=H		3.5	45		90 [79]	83 [73]	66[22], 77[26], 81[23]
11	k: R=H, R^1=OH, R^2=R^3=H		4	45		88 [81]	82 [76]	63 [22]
12	l: R=R^3=H, R^1=OH, R^2=C_2H		4	45		86 [78]	83 [75]	55 [22]
13	m: R=Me, R^1+R^2=O, R^3=H		4	45		93 [84]	90 [81]	
14	n:R=Me,R^1=OH, R^2=C_2H, R^3=H		4.5	45		84 [75]	81 [72]	
15	o: R=R^2=H, R^1=R^3=OH		5	45		85 [73]	81 [70]	

[a] Determined from ^{19}F NMR spectra of crude reaction mixture using octafluoronaphthalene as internal standard; values in square brackets refer to the isolated pure products, [b] highly higroscopic liquid compounds.

Encouraged by the above mentioned results, we applied the reaction to a series of estrogen steroids (**2j-o**) and found that estrone (**2j**) as well as its methyl ether derivative could be almost quantitatively converted to 10β-fluoro-1,4-estradiene-3,17-dione (**3j**). 17α-Ethynylestradiol (**2l**) and its methyl ether analogue were also converted to 10β-fluoro-3-oxo-1,4-estradien-17α-ethynyl-17β-ol (**3l**) in very high yield, as well as β-estradiol (**2k**) to 10β-fluoro-3-oxo-1,4-estradien-17β-ol (**3k**) and estriol (**2o**) to 10β-fluoro-3-oxo-1,4-estradien-16α,17β-diol[18] (**3o**). In all cases only trace amounts of aromatic ring fluorinated products were detected in the crude reaction mixtures. The opposite regioselectivity of fluorofunctionalisation of estrogen steroids on the other hand was observed when N-fluoro pyridinium salts were used as the fluorinating reagent, and only 2-fluoro- and 4-fluoro estrogen derivatives were formed.[19, 20]

The more or less efficient synthesis of 4-fluorocylohexa-2,5-dienones was previously reported to have been carried out using electrophilic fluorinating reagents (trifluoromethylhypofluorite CF_3OF,[21] perchloryl fluoride ClO_3F,[22] N-fluoroperfluoroalkylsulfonylimides,[23] fluorine[24]) or HF in combination with oxidants[25, 26] as the source of fluorine atom. The use of these very reactive and toxic reagents requires special laboratory equipment and stringent safety precautions. The simple experimental protocol also acceptable to non-specialised organic laboratories, in addition to a high level of regioselectivity and efficiency of the fluorination of a comprehensive range of phenols with F-TEDA BF_4 or NFTh as reagents are the advantages that make the synthetic method presented a very convenient procedure for the preparation of 4-fluorocyclohexa-2,5-dienones. Mechanistic elucidation of these reactions in order to formulate some general conclusions concerning the reactions of N-fluoro reagents with phenols are in progress, and will be the subject of a future publication.

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(10) Selectfluor™ F-TEDA-BF_4 is produced and commercialised by Air Products and Chemicals, Inc.

(11) Accufluor™ NFTh is produced and commercialised by AlliedSignals, Inc. We are indebted to Dr. George Shia for providing us with free samples of the reagent.

(12) The following reaction procedure is typical. To a solution of 5 mmol of substrate (entry 1-15 , Table) in MeCN (50 ml) 1.77 g (5 mmol) F-TEDA BF_4 or 1.6 g (5 mmol) NFTh was added and the reaction mixture stirred at room or elevated temperature (Table) 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, insoluble material filtered off and the solution, except in the case of steroids (entry 10-15), washed with 10% aqueous KOH (50 ml) in order to remove traces of starting material or unwanted *ortho* fluorinated phenols. The organic layer was then washed with water, dried over Na_2SO_4 and the solvent evaporated. The isolated crude reaction mixtures were analysed by ^1H (at 60 MHz, TMS as standard) and ^{19}F nmr (at 56.4 MHz, CCl_3F as standard) and TLC, and pure products were obtained after flash chromatography over SiO_2. The spectroscopic data for the known compounds **3a**,[24] **3f**,[25] **3g**,[26] **3h**[26] and **3j-n**[22] were in agreement with the literature, while unknown products were fully characterised as listed below.

(13) (±)**3,4-Dimethyl-4-fluorocyclohexa-2,5-dienone (3c)**: hygroscopic liquid compound; ^1H NMR: δ =1.60(d,J=21.6Hz, 3H), 2.1(s, 3H), 6.0(s, 1H), 6.1(d, J=10 Hz, 1H), 6.9(dd, J=10 Hz, J=7.5 Hz); ^{19}F NMR: δ = -153.8(dq, J=21.6 Hz, J=7.5 Hz); IR(neat): ν_{CO} = 1670 cm^{-1}; MS: *m/z*: 140 (M^+, 48%), 125(23), 112(48), 97(100), 91(25), 77(25); HRMS: calcd for C_8H_9FO: 140.0637, found: 140.0633. anal.calcd for $C_8H_9FO \cdot 1/4H_2O$: C 66.42, H 6.62; found: C 66.42, H 6.47.

(14) **4-Fluoro-4-isopropylcyclohexa-2,5-dienone (3b)**: hygroscopic liquid compound; ^1H NMR : δ = 1.05(d, J=9 Hz, 6H), 2.10(m, 1H), 6.20(d, J=12 Hz, 2H), 6.95(dd, J=12 Hz, J=6 Hz, 2H); ^{19}F NMR : δ = -153.3(m); IR(neat): ν_{CO} = 1670 cm^{-1}; MS: *m/z*: 154 (M^+, 6%), 139(20), 112(100); HRMS: calcd for $C_9H_{11}FO$ 154.0794, found 154.0800; anal.calcd for $C_9H_{11}FO \cdot 1/3H_2O$: C 67.48, H 7.34; found: C 67.56, H 7.15.

(15) (±)**4-Fluoro-4-isopropyl-3-methylcyclohexa-2,5-dienone (3d):** hygroscopic liquid compound; ^1H NMR: δ = 0.7(d, J=10 Hz, 3H), 1.17(d, J=10 Hz, 3H), 2.0(s, 3H), 2.3(m, 1H), 6.13(s, 1H), 6.3(d, J=10 Hz, 1H), 6.93(dd, J=10 Hz, J=10Hz); ^{19}F NMR: δ = -160.0 (dd, J=10 Hz, J=10 Hz). IR(neat): ν_{CO} = 1680 cm^{-1}. MS *m/z*: 168 (M^+ , 2%), 153(1), 126 (100), 125(25), 97(10); HRMS: calcd for $C_{10}H_{13}FO$: 168.0950; found: 168.0953; anal. calcd. for $C_{10}H_{13}FO \cdot 1/2H_2O$: C 67.78, H 7.96; found: C 68.02, H 7.28.

(16) **4-fluoro-3,4,5-trimethylcyclohexa-2,5-dienone (3i)**: hygroscopic liquid compound; ^1H NMR: δ = 1.44(d, J=21 Hz, 3H), 2.1(s, 6H), 5.97(s, 2H); ^{19}F NMR: δ = -160.5 (q, J=21 Hz); IR: ν_{CO} = 1678 cm^{-1}; MS m/z: 154 (M^+, 42%), 139(25),

126(55), 111(100), 109(40), 91(27);HRMS: calcd for $C_9H_{11}FO$ 154.0794, found 154.0801; anal. calcd for $C_9H_{11}FO \cdot 1/5H_2O$: C 68.51, H 7.28; found: C 68.83, H 7.10.

(17) mp73.0-74.0°C; ^{1}H NMR: δ = 1.73(d, J=21 Hz, 3H), 2.2(br.s 3H), 6.2(br.s 1H), 7.15(d, J=7 Hz); ^{19}F NMR: δ = -152.3(dq, J=21 Hz, J=7 Hz); IR: ν_{CO} = 1679 cm^{-1}; MS *m/z*: 176 (M^++2, 7%), 174(M^+, 21), 159(20), 148(25) 146(75), 133(15), 131(45), 111(100), 109(51),95(90), 91(65); anal. calcd. for C_8H_8ClFO: C 55.03, H 4,62; found: C 55.33, H 4.60.

(18) **10β-fluoro-3-oxo-1,4-estradien-16α,17β-diol (3o)**: mp 189.2-190.1°C (decomp); ^{1}H NMR: δ = 0.7-2.8(m, 16H), 3.3-4.4(m, 4H), 6.1(s, 1H), 6.26(d, J=10 Hz), 7.17(dd, J=7.5 Hz, J=10 Hz); ^{19}F NMR: δ = -168.5(dd, J=7.5 Hz, J=29 Hz); R: ν_{CO} = 1672 cm^{-1}; MS *m/z*: 306 (M^+, 15%), 288(25), 247(55), 163(43), 138(55), 126 (100), 125(78) 109(72), 95(56); anal. calcd for $C_{18}H_{23}FO_3$: C 70.57, H 7.57; found: C 70.47, H 7.80.

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