

The effect of the reaction conditions on the course of the reactions of hindered phenols with N-F reagents

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Dedicated to Prof. Miha Tišler on the occasion of his 75th birthday

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Abstract

2,4,6-Trialkyl substituted phenols were selectively transformed in high yield to *para*-quinols or *para*-quinol ethers by reaction with the N-fluoro-1,4-diazoniabicyclo[2.2.2]octane salt analogues SelectfluorTM F-TEDA-BF₄ or AccufluorTM NFTh in acetonitrile in the presence of water or alcohols. At low temperature 2,4,6-tri-*tert*-butylphenol in pure acetonitrile gave 2-fluoro and 4-fluoro substituted cyclohexadienone products with both reagents, while at elevated temperature 2-fluoro-4,6-di-*tert*-butylphenol was quantitatively formed. The mechanism postulated the SET process, thus forming cation-radical intermediates, as the key step of the reaction was proposed.

Keywords: Phenols, oxidation, *p*-quinol derivatives, alkoxylation, N-fluoro diazonia compounds

Introduction

The extensive application of various types of organofluorine compounds¹ has resulted in a continuous general interest in their related chemistry.² The introduction of organic molecules incorporating a reactive N-F bond as versatile mild fluorinating reagents³ in the last decade has had a revolutionary influence on research in the field of the chemistry of organofluorine molecules. Derivatives of the N-fluoro-1,4-diazoniabicyclo[2.2.2] octane salts promoted by Banks⁴ possess optimal stability/reactivity characteristics and as easy handling, cost effective, commercially available reagents are convenient for routine laboratory work as well as for large scale applications.⁵ The oxidative power of Banks' reagents is lower in comparison with other

types of »electrophilic« mild fluorinating reagents (fluoroxy derivatives or xenon fluorides), but is among the highest in the series of N-F reagents.⁶ Therefore we can expect a certain decrease in the selectivity of their reactions due to competition between fluorofunctionalisation and oxidation, particularly when oxidisable functional groups or heteroatoms are present in the target molecule. Benzylic and phenolic hydroxy groups which carry a great deal of this oxidation/fluorofunctionalisation competitive dualism can represent a considerable selectivity diminishing factor, but are also useful precursors for selective transformation of organic molecules with electrophilic fluorinating reagents.^{2d, 7}

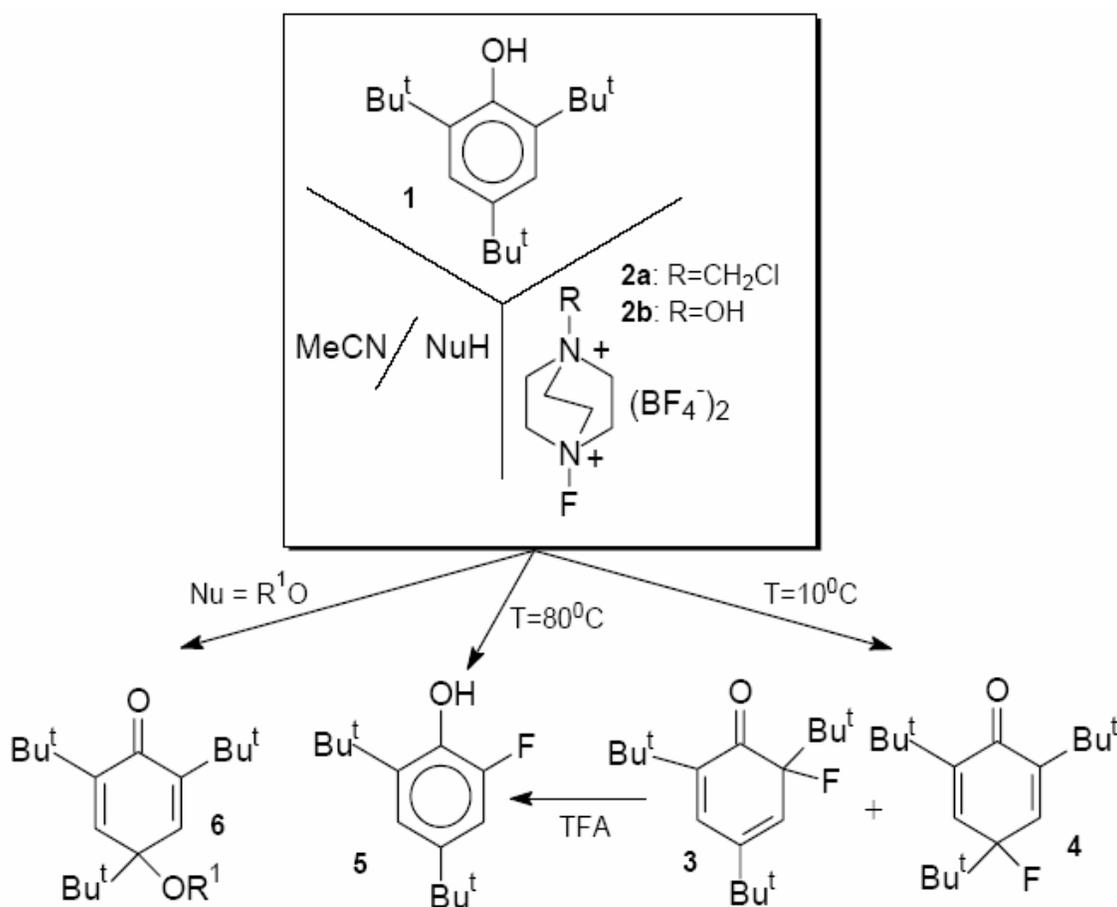
In our continuing interest in the reactions of N-F reagents with phenols^{7d-f} we now report the transformations of sterically hindered phenols with 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2] octane bis(tetrafluoroborate) (**2a**, SelectfluorTM F-TEDA-BF₄) and its 4-hydroxy analogue (**2b**, AccufluorTM NFTh).

Results and Discussion

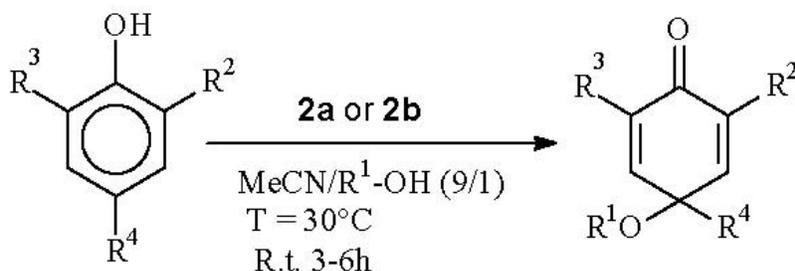
In a typical experiment we treated 2,4,6-tri-tert-butylphenol (**1**, **Scheme 1**) with a 10% molar excess of F-TEDA-BF₄ (**2a**) in acetonitrile at 10°C, and after a work-up procedure we isolated a mixture of 2-fluoro-2,4,6-tri-tert-butyl-cyclohexa-3,5-dienone (**3**) and 4-fluoro-2,4,6-tri-tert-butyl-cyclohexa-2,5-dienone (**4**) in 4:1 relative ratio and 85% cumulative yield. At room temperature the course of the reaction became more complex and besides products **3** and **4**, 2-fluoro-4,6-di-tert-butylphenol (**5**) was also detected in the crude reaction mixture, while at 80°C an almost quantitative amount of fluoro-dealkylated product **5** was obtained after a few minutes reaction. Almost the same results were obtained when NFTh was used as the reagent. It is evident that in these cases the formation of 2-fluoro and 4-fluoro substituted cyclohexadienone type of products (**3** and **4**), also observed in our previous report^{7f}, is a kinetically controlled process, while fluoro-dealkylation gave a thermodynamically more stable product. 2-Fluoro-4,6-di-tert-butylphenol (**5**) could also be obtained after treatment of product **3** with trifluoroacetic acid.

We further investigated the effect of solvent polarity and the presence of an external nucleophile on the course of the reaction of hindered phenol **1** with F-TEDA-BF₄ or NFTh, and found that during reaction of the tested phenol in methanol at room temperature the reagent was not consumed even after a 72 hour reaction time, while at elevated temperatures the reactions resulted in a complex reaction mixture. On the other hand, in a MeCN/MeOH 9:1 solvent mixture 2,4,6-tri-tert-butylphenol (**1**) transformed at 30°C selectively to 4-methoxy-2,4,6-tri-tert-butyl-cyclohexa-2,5-dienone (**6b**, Table) in high yield. The selective formation of *para* quinol

ether derivative **6b** was achieved when at least a five fold molar excess of methanol was present in the reacting mixture, while by lowering its concentration, the relative amount of fluorinated products **3**, **4**, and **5** increased. Under optimised reaction conditions **1** was readily transformed to the corresponding *para* quinol ethers also when ethanol (entry 3, **Table**), propanol (entry 4) or 1,2-ethanediol (entry 5) were present in the reaction mixture, while in the presence of water the selectivity of the reaction was found to be poor and only a moderate yield of the *para* quinol derivative was detected among other, mainly fluorinated reaction products **3**, **4**, and **5**. On using NFTh as the reagent the reactions also lead to products **6** in high yields. 2,6-Di-tert-butyl-4-methylphenol (**7**) reacted to the corresponding *para* quinol **8a** or *para* quinol ethers (**8b-e**) too, and under the mentioned reaction conditions almost quantitative transformation could be achieved with F-TEDA-BF₄ as well as with NFTh. We also established the same results when 2,4,6-trimethylphenol (**9**) was treated with **2a** or **2b**. *Para* quinol **10a** or *para* quinol ethers **10b-f** were also formed in excellent yield, except in the case of 2,2,2-trifluoethanol (entry 14) where we succeeded in isolating product **10d** only in moderate yield.



Scheme 1

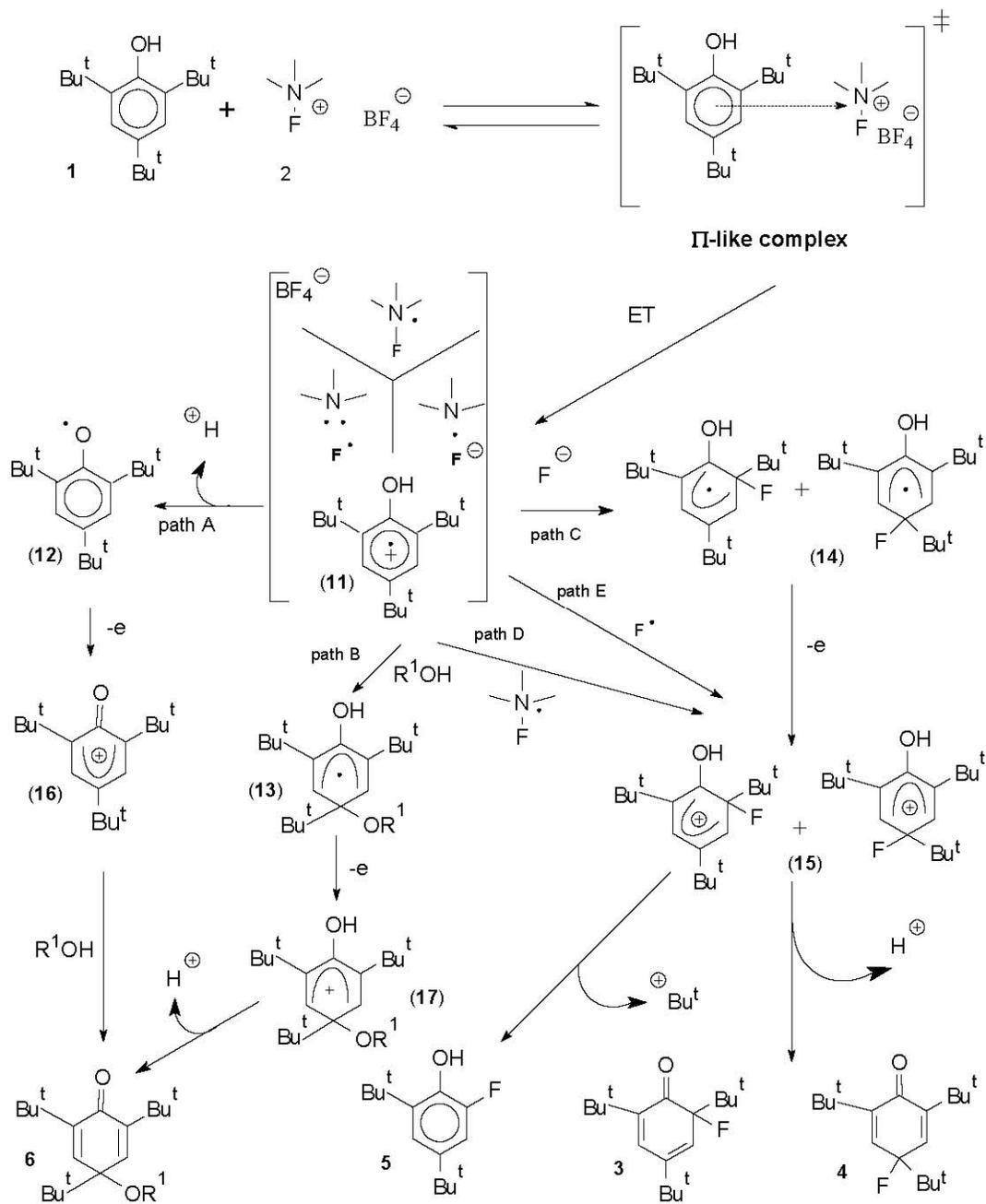
Table 1. Mild, selective oxidation of alkyl substituted phenols using Selectfluor™ F-TEDA (**2a**) or Accufluor™ NFlTh (**2b**)

Entry	Phenol	R ¹	Product	Yield (%) ^{a)}	
				2a	2b
1		a: H		29 [19]	32 [21]
2		b: Me		86 [79]	90 [82]
3		c: Et		84 [75]	83 [72]
4		d: Pr		86 [77]	89 [79]
5		e: HOCH ₂ CH ₂		87 [79]	91 [83]
6		a: H		88 [78]	86 [75]
7		b: Me		91 [82]	94 [87]
8		c: Et		85 [75]	93 [81]
9		d: HOCH ₂ CH ₂		92 [81]	88 [78]
10		e: CH ₃ OCH ₂ CH ₂		88 [78]	91 [82]
11		a: H		84 [76]	88 [78]
12		b: Me		93 [85]	95 [86]
13		c: Et		92 [82]	93 [81]
14		d: CF ₃ CH ₂		47 [38]	44 [32]
15		e: HOCH ₂ CH ₂		83 [76]	91 [81]
16		f: CH ₃ OCH ₂ CH ₂		87 [79]	86 [77]

^a Determined from ¹H NMR spectra of crude reaction mixture using benzyl alcohol as internal standard; values in square brackets refer to the isolated pure products.

Considering the results obtained we can conclude that reactions of hindered phenols with N-fluoro-1,4-diazonia bicyclo[2.2.2]octane salt analogues require undemanding, but well defined reaction conditions in order to assure the selectivity of the course of reaction. Competition between fluorination and oxidation of target molecules could be completely avoided and by

choosing appropriate reaction conditions we can effectively and selectively favour one or other process. This fact gives a considerable advantage to the present method over known more or less efficient syntheses of *para*-quinol derivatives using hypervalent iodine compounds,^{8,9,10} thallium (III) salts,¹¹ dimethyldioxirane,¹² hexacyanoferrate(III) analogues,¹³ manganese dioxide,¹⁴ oxygenation in the presence of Cu(II)¹⁵ or Fe(II)¹⁶ catalysts, or electrochemical procedures.¹⁷



Scheme 2

Discussion of the possible mechanisms of reactions of “electrophilic” fluorinating reagents with organic compounds is still far from closed. The main subject of dispute is whether the reactions proceed through direct fluorine transfer, or through two-step electron transfer (ET). Fluorine transfer is postulated as a classical S_N2 process where nucleophilic attack of an electron-rich reaction centre on fluorine results in displacement of the ligand part of the reagent, which must necessarily be a better leaving group than fluoride. The electron transfer mechanism, on the other hand, anticipates the initial formation of a charge-transfer complex between an electron-rich organic molecule and the electron-deficient fluorinating reagent, which after one-electron transfer transforms to organic molecule cation radical active intermediate as the precursor of fluorinated or non-fluorinated products.³ The formation of cation radicals has also been confirmed by ESR and UV spectroscopy in the case of halogenations of activated aromatics with N-halogen reagents (NBS, NCS),¹⁸ and since N-F reagents are even stronger oxidants, the ET reaction pathway of their reaction with organic molecules is very believable. Nevertheless, it was generally accepted that the course of these reactions is strongly sensitive to the structure of the N-F reagent, the organic molecule and the reaction conditions, and that it is very difficult to define unequivocally the reaction channel through which the products are formed.³

On the basis of the data gathered and reported in this paper, we believe that the ET process is the main and most probable reaction pathway in the reactions of F-TEDA-BF₄ or NFTh at least with the phenols selected for the present study, and that the formation of the cation-radical (**11**) is the key step of these reactions (**Scheme 2**). After electron transfer from the electron-rich phenol **1** to the electron-demanding reaction centre of reagent **2**, besides the formation of the cation-radical **11**, very reactive fluorine carrying species like F[•], F⁻ and N-F could be formed and regulate the course of the reaction. The transformation of cation-radical **11** to the products observed can proceed through at least five main channels depending on reaction conditions.

As **11** is very acidic, proton loss (path A) thus forming radical intermediate (**12**), followed by immediate another electron transfer thus forming the cyclohexadienone cation (**16**) which readily collapses with an external source of nucleophiles to the final product **6**, represents the first reaction channel. The second channel also leads to the same product where primary attack of an external nucleophile on cation-radical **11** (path B), followed by electron transfer from radical (**13**) thus forming cationic intermediate (**17**), which stabilises by proton loss to the product **6** is anticipated as the possible reaction pathway.

In the formation of the observed fluorinated products all three already mentioned active species carrying a fluorine atom could be involved. In the first case the fluoride anion attacks the cation-radical **11** (path C) at the *ortho* and *para* position, thus forming fluoro-substituted radical intermediate (**14**) which, after second electron transfer, transforms to the corresponding fluoro carbocationic species (**15**). At this point the reaction could split in two ways depending on the

reaction temperature. At lower temperatures (**15**) stabilises through proton loss to 2- or 4-fluoro-substituted cyclohexadienone final products **3** and **4**, while at higher temperatures regioselective *ortho* attack and stabilisation through tert-butyl cation loss to the thermodynamically more stable 2-fluoro-substituted phenol **5** takes place. Direct formation of fluoro-substituted carbocation intermediate (**15**) could be reached also after N⁺-F (path D) or F⁺ (path E) attack on the cation-radical (**11**). In neat acetonitrile the channels C, D and E were found to be the main reaction processes, while in the presence of water or alcohols as the source of the external nucleophile, channels A and B were mainly used for product formation.

Experimental Section

General Procedures. Materials 1-Fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2] octane bis(tetrafluoroborate) (**2a**, SelectfluorTM F-TEDA-BF₄) from Apollo and 1-fluoro-4-hydroxy-1,4-diazoniabicyclo [2.2.2] octane bis(tetrafluoroborate) (**2b**, AccufluorTM NFTh as 50% mixture with Al₂O₃) from AlliedSignal, 2,4,6-tri-tert-butylphenol (**1**), 2,6-di-tert-butyl-4-methylphenol (**7**), and 2,4,6-trimethylphenol (**9**) from Aldrich were used. Combustion elemental analysis of new compounds was performed at Microanalytisches Labor Pascher. ¹H and ¹⁹F nmr spectra were performed on a Varian EM 360L instrument at 60 MHz for proton and at 56.4 MHz for fluorine resonance. CDCl₃ was used as solvent and TMS or CFC₃ as internal standard.

Reaction protocol

To a solution of 5 mmol of substrate (**1**, **7**, or **9**, Table) in MeCN or MeCN/ROH 9:1 mixture (50 ml) 1.95 g (5.5 mmol) F-TEDA BF₄ or 1.76 g (5.5 mmol) NFTh was added and the reaction mixture stirred at 30°C until KI starch paper showed the consumption of the reagent (3-6 hours). The solvent was removed under reduced pressure and the crude reaction mixture dissolved in CH₂Cl₂, insoluble material filtered off, the solution washed with water, dried over Na₂SO₄, and the solvent evaporated. The isolated crude reaction mixtures were analysed by ¹H and ¹⁹F nmr and TLC, and pure products were obtained after flash chromatography over SiO₂. The spectroscopic data for the known compounds **5**¹³, **3** and **4**¹⁹, **6a**, **6b**, **8b** and **10b**¹¹, **6e**²⁰ **6c** and **6d**²¹, **10a** and **10c**⁸, **10d**²², **8a**⁹, and **8c**¹⁴ were in agreement with the literature, while unknown products were fully characterised as listed below.

2,6-Bis(1,1-dimethylethyl)-4-(2-hydroxyethoxy)-4-methylcyclohexa-2,5-dienone (8d). Oily; ¹H NMR: δ 1.27-1.40(br s, 21H); δ 3.37(t, 2H, J=5Hz); δ 3.70(t, 2H, J=5Hz); δ 6.50(s, 2H). IR (neat): 1664, 1642 cm⁻¹. MS: m/z 280(10); 265(76); 224(100); 219(30); 209(98); 205(47); 163(43); 149(26); 91(21); 77(13); 57(97); anal. calcd. for C₁₇H₂₈O₃: C 72.82, H 10.06; found: C

72.72, H 10.19.

2,6-Bis(1,1-dimethylethyl)-4-(2-methoxyethoxy)-4-methylcyclohexa-2,5-dienone (8e).

Hygroscopic liquid compound; $^1\text{H NMR}$: δ 1.23-1.37(br s, 21H); δ 3.40(br s, 7H); 6.50(s, 2H). IR (neat): 1663; 1641 cm^{-1} . MS: m/z 294(3); 279(18); 238(39); 223(20); 219(13); 205(34); 189(12); 177(11); 161(26); 91(18); 77(16); 59(100); anal. calcd. for $\text{C}_{18}\text{H}_{30}\text{O}_3$: C 73.43, H 10.27; found: C 73.59, H 10.39.

4-(2-Hydroxyethoxy)-2,4,6-trimethylcyclohexa-2,5-dienone (10e).

Hygroscopic liquid compound; $^1\text{H NMR}$: δ 1.38(s, 3H); δ 1.88(s, 6H); 2.90(br s, 1H); 3.23-3.73(m, 4H); 6.55(s, 2H). IR (neat): 1672; 1635 cm^{-1} . MS: m/z 196(12); 181(7); 168(1); 152(48); 135(100); 124(14); 109(20); 91(46); 79(18); HRMS calcd for $\text{C}_{11}\text{H}_{16}\text{O}_3$ 196.1099, found 196.1104; anal. calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_3$: C 67.32, H 8.22; found: C 66.59, H 8.26.

4-(2-Methoxyethoxy)-2,4,6-trimethylcyclohexa-2,5-dienone (10f).

Hygroscopic liquid compound; $^1\text{H NMR}$: δ 1.33(s, 3H); δ 1.87(s, 6H); 3.33(br s, 7H); 6.50(s, 2H). IR (neat): 1671; 1640 cm^{-1} . MS: m/z 210(4); 195(8); 182(1); 178(1); 152(44); 135(100); 121(4); 107(13); 91(47); 79(19); 59(84); anal. calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_3$: C 68.54, H 8.63; found: C 68.45, H 8.78.

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