Functionalization of Aromatic Molecules Using HOF·CH_3CN and CH_3OF

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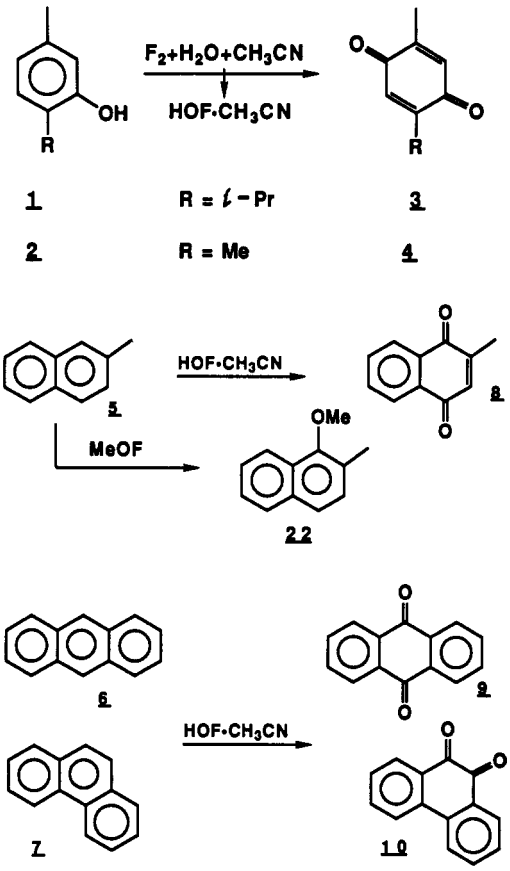
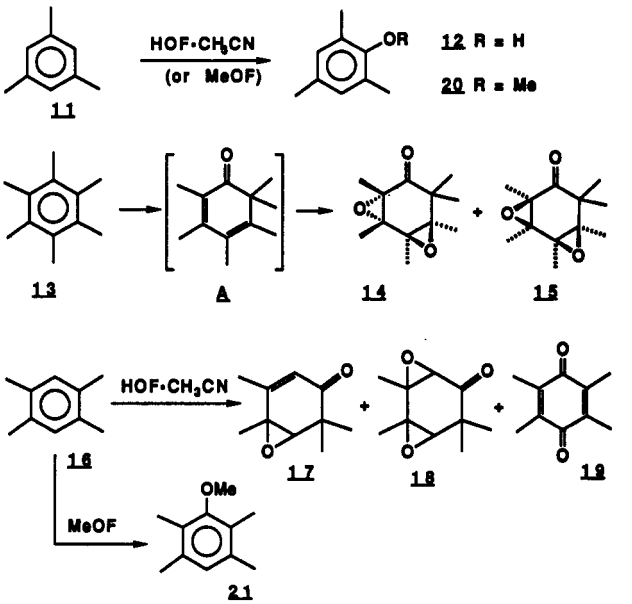
Elemental fluorine has convincingly gained its place in organic chemistry as a fluorinating agent with great potential.[1] Recently, we have shown that the element can be used for making HOF·CH_3CN, which is a powerful oxygen-transfer agent capable of transforming olefins to epoxides,[2] activating tertiary C–H bonds,[3] and oxidizing aromatic amines.[4] Earlier, fluorine also helped us to make the elusive methyl hypofluorite,[5] the smallest organic molecule not previously prepared. MeOF acts as a source for the unprecedented electrophilic methoxylium species[6] and as a such has a potential to perform unique reactions.

Many oxygenated aromatic derivatives have interesting biological properties including antifungal, antibiotic, and anticarcinogenic agents.[7] In the rare cases where these were made directly, radical oxidants, strong peracids, or ozone were employed.[8] We report here on the oxidation of several types of aromatic molecules using as oxidants the HOF·CH_3CN complex[9] and the novel MeOF.

Thymol (1) and 2,5-dimethylphenol (2), phenols unsubstituted at the para position, reacted with HOF·CH_3CN to form immediately thymoquinone (3) and 2,5-dimethyl-1,4-benzoquinone[10] (4) both in about 30% yield. Although the hydroxy group in the starting material directs the oxidation to the para position, apparently via the corresponding hydroquinone, its presence is not a prerequisite for the oxidation to take place. Thus, polyaromatics such as 2-methylnaphthalene (5), anthracene (6), and phenanthrene (7) reacted with HOF·CH_3CN in less than 1 min to produce the corresponding *p*-quinones 8, 9, and 10 in 45%, 30%, and 90% yield, respectively. Since we have already shown that HOF·CH_3CN is a source of the powerful electrophilic hydroxylium species,[3] it would be reasonable to assume that the first step in these oxidations would be formation of the corresponding phenols which are then further oxidized to the *p*-quinones. This assumption can be proved using an electron-rich



aromatic molecule without pairs of hydrogens at the ortho or para position to each other such as mesitylene (11). This was oxidized only to monohydroxy 2,4,6-trimethylphenol (12) in 45% yield, although a full conversion should be avoided to minimize tar formations.



Lacking aromatic hydrogens, hexamethylbenzene (13) reacts with HOF·CH_3CN to form a 1:1 diastereomeric mixture of the ketodiepoxides 14[11] and 15 in 50% yield. It is reasonable to assume that both derivatives originate

(1) Rozen, S. *Acc. Chem. Res.* **1988**, *21*, 307. Boguslavskaya, L. S.; Kartashov, A. V.; Chuvatkin, N. N. *Russ. Chem. Rev. (Engl. Trans.)* **1990**, *59*, 501. Rozen, S. *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991; pp 56–67.

(2) (a) Rozen, S.; Kol, M. *J. Org. Chem.* **1990**, *55*, 5155. (b) Hung, M. H.; Smart, B. E.; Feiring, A. E.; Rozen, S. *J. Org. Chem.* **1991**, *56*, 3187.

(3) Rozen, S.; Brand, M.; Kol, M. *J. Am. Chem. Soc.* **1989**, *111*, 8325.

(4) Kol, M.; Rozen, S. *J. Chem. Soc., Chem. Commun.* **1991**, 567.

(5) Rozen, S.; Hebel, D.; Kol, M. 199th ACS National Meeting; Boston, MA, 1990; FLUO-17. See also: *Chem. Eng. News*, **1990** May 7, p 62. Kol, M.; Rozen, S.; Appelman, E. H. *J. Am. Chem. Soc.* **1991**, *113*, 2648.

(6) Rozen, S.; Mishani, E.; Kol, M. *J. Am. Chem. Soc.* **1992**, *114*, 7643.

(7) (a) Gaudians, G.; Koch, T. H. *J. Am. Chem. Soc.* **1990**, *112*, 9423. (b) Demuth, M. R.; Garett, P. E.; White, G. D. *J. Am. Chem. Soc.* **1976**, *98*, 634. (c) Asakawa, Y.; Matsuda, R.; Tori, M.; Sono, M. *J. Org. Chem.* **1988**, *53*, 5453. (d) Olah, G. A.; Ernst, T. D. *J. Org. Chem.* **1989**, *54*, 1204.

(8) See refs 7c,d and 11.

(9) Pure HOF was prepared by Appelman about 20 years ago: Appelman, E. H. *Acc. Chem. Res.* **1973**, *6*, 113. However, it is not a practical synthetic reagent since it is extremely difficult to make and its explosive instability limits its production to minute amounts.

(10) Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627.

(11) Zadok, E.; Rubinraut, S.; Frolow, F.; Mazur, Y. *J. Am. Chem. Soc.* **1985**, *107*, 2489.

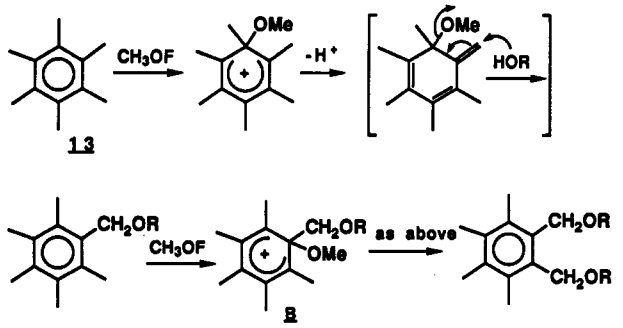
0022-3263/93/1958-1593$04.00/0

from the same rearranged α,α-dimethyl ketone intermediate **A** which then is further oxidized. Durene (**16**) showed a combination of both reaction courses producing the unsaturated keto epoxide **17**[12] (25% yield) which may be further oxidized to **18** in analogy to the oxidation of hexamethylbenzene. However, about 10% of duroquinone (**19**), which stemmed from oxidation of the aromatic hydrogens, was also isolated.

While some of the above transformations have been performed with other oxygen-transfer agents in similar or lower yields, electrophilic aromatic methoxylations are unknown in organic synthesis. Methyl hypofluorite offers a unique opportunity for accomplishing such a goal.

MeOF prepared at −45 °C reacted with aromatic molecules only on warming the reaction mixture to room temperature. Thus, mesitylene (**11**) and durene (**16**) were converted to 2,4,6-trimethyl-[13] and 2,3,5,6-tetramethylanisole[14] (**20** and **21**) in 50% and 90% yield respectively. The electrophilic nature of the reagent could be demonstrated in the regioselective methoxylation of 2-methylnaphthalene (**5**) to 1-methoxy-2-methylnaphthalene (**22**)[15] in 30% yield.

Hexamethylbenzene (**13**) reacted with MeOF to give the mono- and dibenzylic methoxylation products (**23** and **24**)[16] in 40% and 25% yield, respectively. The proposed mechanism outlined below accommodates all the experimental findings.



The tendency for an ortho substitution is explained by the formation of **B** which should be the most stable arenium ion. Consistent with this mechanism is the finding that the source of the benzylic methoxy group was methanol rather than the methyl hypofluorite, since in the presence of ethanol the ethoxylation product **25**[17] was also formed and isolated in 50% yield.

In conclusion, fluorine and reagents derived from it demonstrate a unique ability to serve not only as fluorinating agents but also as attractive candidates for various aromatic oxidations. The unparalleled speed of the reaction gives hope that in the future other isotopes, such as ^{18}O and the important short-living ^{11}C, can be introduced by this method into many biologically important molecules.[18]

Experimental Section

^1H NMR spectra (δ) were recorded at 360 or 200 MHz with $CDCl_3$ as solvent and Me_4Si as an internal standard. The proton broad band decoupled ^{13}C NMR spectra were recorded at 50.30 MHz, and $CDCl_3$ served as solvent and TMS as internal standard. IR spectra were recorded as neat films, in $CHCl_3$ solution or in KBr pellets.

General Procedure for Working with Fluorine. Fluorine is a strong oxidizer and a very corrosive material. An appropriate vacuum line made from copper or monel in a well-ventilated area should be constructed for working with this element. A description of the setup and the procedure for working with elemental fluorine has been given previously.[19] For the occasional user, however, various premixed mixtures of F_2 in inert gases are commercially available. The reactions themselves can be carried out in glass vessels. If elementary precautions are taken, work with fluorine is relatively simple and we have had no bad experience working with this element.

General Procedure for Producing Hypofluorous Acid in Acetonitrile. Mixtures of ca. 15% F_2 with nitrogen were used in this work. The gas mixture was prepared in a secondary container before the reaction was started. This mixture was then passed at a rate of about 400 mL per min through a cold (−15 °C) and vigorously stirred mixture of 70 mL of CH_3CN and 3.5 mL of H_2O. The formation of the oxidizer was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. We have thus achieved concentrations of more than a 0.5 mol/L of the oxidizing reagent.

General Procedure for Oxidation of Aromatics with HOF·CH_3CN. An appropriate amount of aromatic compound, usually 30–40 mmol (0.33–1 equiv relative to the HOF) was dissolved in about 10 mL of $CHCl_3$ cooled to 0 °C and added in one portion to the reaction vessel in which the oxidizing agent had been prepared. The reaction was stopped after 1 min by neutralization with saturated sodium bicarbonate solution. The mixture was then poured into 500 mL of water, extracted with $CHCl_3$, and washed with $NaHCO_3$ and water until neutral. The organic layer was dried over $MgSO_4$ and the solvent evaporated, preferably at room temperature. The crude product was usually purified by vacuum flash chromatography using silica gel 60-H (Merck) and if needed also by HPLC (Waters) on Merck's LiChrosorb Si-100. Yields are of isolated compounds unless otherwise indicated, and the purity was usually confirmed by GC using 5% SE-30 or 10% OV-17 columns. The spectral and physical properties of the known products thus obtained were compared either with those of authentic samples (when commercially available) or with the properties reported in the literature. In every case excellent agreement was obtained. Unless otherwise indicated new compounds were properly identified by ^1H NMR, ^{13}C NMR, IR, MS, and microanalysis.

General Procedure for Producing Methyl Hypofluorite. Mixtures of ca. 20% F_2 in N_2 were passed at a rate of about 400 mL per min through a cold (−45 °C) mixture of 60 mL of CH_3CN and 3.0 mL of CH_3OH in a thin-walled PTFE reactor. The formation of the oxidizer was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. A total of 10–20 mmol of methyl hypofluorite (0.15–0.30 M) was thus formed.

General Procedures for Oxidation of Aromatics with Methyl Hypofluorite. An appropriate amount of aromatic substrate (2.5–5 mmol, ca. 0.25 equiv relative to MeOF) was dissolved in about 5 mL of CH_2Cl_2, cooled, and added in one

(12) While a description of a product having spectroscopic data identical to **17** has appeared in the literature, the authors propose a somewhat different structure for that material [compound **7** in ref 7c]. The structure we propose is, however, more consistent with the ^{13}C NMR data, as well as with the proposed mechanism (see Experimental Section).

(13) Miller, B. *J. Org. Chem.* **1977**, *42*, 1404.

(14) Conforth, J.; Sierakowski, A. F.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2299.

(15) Burdon, M. G.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 5855.

(16) Wasserman, H. H.; Mariano, P. S.; Keehn, P. N. *J. Org. Chem.* **1971**, *36*, 1765. While formation of other isomers of **24** or anisol derivatives could not be excluded, we have not detected them, and their yields, if formed, are lower than 5% each.

(17) Maini, S.; Mandolini, L. *J. Org. Chem.* **1978**, *43*, 3236. To prove that the above ethoxylation is not a consequence of "ethyl hypofluorite", 1,1-diphenylethylene was dissolved in chloroform/ethanol and added to MeOF solution. Only the MeO, F adduct: 1,1-diphenyl-1-fluoro-2-methoxyethane (ref 5) was formed.

(18) The ^{11}C isotope is very important in positron emitting transaxial tomography (PET). Attempts to perform such reactions are underway.

(19) See, for example: Rozen, S.; Zamir, D. *J. Org. Chem.* **1990**, *55*, 3552.

portion to the reaction vessel in which the oxidizing agent had been prepared at −45 °C. The reaction vessel was then allowed to warm to room temperature until no oxidizer was left. The workup was the same as described for the reactions with $HOF{\cdot}CH_3CN$. An alternative procedure was also used with comparable results: a stream of nitrogen was passed through the original reactor used for producing the MeOF while a gradual rise to room temperature was allowed. This carried the MeOF into a reaction vessel containing an appropriate amount of the aromatic substrate (ca. 0.10 equiv) dissolved in about 5 mL of CH_3CN. The reaction was stopped when no oxidizing material was left and then worked up as above. It should be noted that with this procedure a full conversion was usually not achieved partly because of the volatility of the reagent as well as because of its relative instability as the temperature is increased.

The identity of the products **3**, **8**, **9**, **10**, **12**, and **19** was established by direct comparison with commercial samples. Compounds **4**, **14**, **17**, and **20–25** are known in the literature and referenced throughout the paper. We felt, however, that for some derivatives we should present a somewhat more extensive spectral information which is given below. The physical and spectral features for new compounds are also given. Yields and reaction conditions are mentioned in the Discussion.

Reaction between $HOF{\cdot}CH_3CN$ and hexamethylbenzene (13) produces two keto diepoxides, the first of which was identified as 3β,4β:5α,6α-diepoxy-2,2,3α,4α,5β,6β-hexamethylcyclohexanone (**14**)[11], an oil: IR 1710 cm^{-1}; ^1H NMR 1.56 (6 H, s), 1.43 (3 H, s), 1.35 (3 H, s), 1.26 (6 H, s); ^{13}C $NMR_{(Hdecoupled)}$ 207.5 (*C*O), 70.7, 67.7, 65.8, 65.6 (epoxides' carbons), 47.2 (*C*Me_2) 23.2, 20.8, 16.2, 15.5, 15.0, 14.0 (6 Me); MS (*m/z*) 167 [$(M - Ac)^+$], 139 [$(M - Ac - CO)^+$], 125. The second ketodiepoxide, 3β,4β:5β,6β-diepoxy-2,2,3α,4α,5α,6α-hexamethylcyclohexanone (**15**), is a new compound: mp 115 °C (pentane/ether); IR 1725 cm^{-1}; ^1H NMR 1.56 (3 H, s), 1.53 (3 H, s), 1.40 (3 H, s), 1.32 (3 H, s), 1.21 (3 H, s), 1.16 (3 H, s); ^{13}C $NMR_{(Hdecoupled)}$ 207.1, 70.0, 61.7, 60.6, 56.6, 49.9, 21.3, 17.8, 16.7, 15.3, 14.8, 12.3; MS (m/z): 167 [$(M - Ac)^+$], 139 [$(M - Ac - CO)^+$], 125. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.39; H, 8.57.

Reaction between $HOF{\cdot}CH_3CN$ and durene (16) produces along with duroquinone (**19**), the keto epoxide **17**: IR 1715 cm^{-1}; ^1H NMR 3.16 (1 H, s), 2.82 (1 H, s), 1.57 (3 H, s), 1.56 (3 H, s), 1.28 (3 H, s), 1.22 (3 H, s); ^{13}C NMR 67.12, 60.81 (epoxide's *C*), 68.20, 62.96 (epoxide's *C*H), 22.72, 22.18, 18.39, 18.28 (4 Me). The keto diepoxide **18**, which was also formed, was isolated in purity of higher than 90% (GC analysis), and its spectral properties are in full agreement with the proposed structure: IR 1670 cm^{-1}; ^1H NMR 5.81 (1 H, d, J = 1.3 Hz), 3.18 (1 H, s), 2.13 (3 H, d, J = 1.25 Hz), 1.55 (3 H, s), 1.32 (3 H, s), 1.16 (3 H, s); ^{13}C NMR 200.5, 157.7, 126.0, 68.8, 43.0, 24.5, 21.0, 21.0, 18.8; MS (*m/z*) 166 (M^+), 151 [$(M - CH_3)^+$], 123 [$(M - Ac)^+$].

Reaction between MeOF and Hexamethylbenzene (16). With MeOH as a solvent pentamethylbenzylmethyl ether (**23**)[16] is produced: ^1H NMR 4.49 (2 H, s), 3.41 (3 H, s), 2.30 (6 H, s), 2.20 (9 H, s); ^{13}C NMR 134.8, 133.3, 132.4, 131.4 (C_{ar}), 69.6 (CH_2O), 58.0 (OCH_3), 16.8, 16.5, 16.1 (5 Me); MS (*m/z*) 192 (M^+), 160 [$(M - CH_3OH)^+$]. The bis(methyl ether) **24**[16] is also formed: mp (MeOH) 72 °C; ^1H NMR 4.51 (4 H, s), 3.43 (6 H, s), 2.30 (6 H, s), 2.21 (6 H, s); ^{13}C NMR 135.5, 133.8, 132.6 (C_{ar}), 69.1 (CH_2O), 58.2 (OCH_3), 16.7, 16.0 (4 Me); MS (*m/z*) 222 (M^+), 190 [$(M - CH_3OH)^+$]. In EtOH as a solvent the corresponding ethyl ether **25**,[17] mp 28 °C, was isolated and identified: ^1H NMR 4.53 (2 H, s), 3.57 (2 H, q, J = 7 Hz), 2.30 (6 H, s), 2.20 (9 H, s), 1.23 (3 H, t, J = 7 Hz); MS (*m/z*) 206 [M^+], 160 [$(M - CH_3CH_2OH)^+$].

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