NMR integration). The oil was flash chromatographed using silica gel and 64:35:1 hexane/CH_2Cl_2/ethanol. A small sample was purified by HPLC (85:14:1 hexane/CH_2Cl_2/ethanol). **6a**: ^1H NMR ($CDCl_3$) δ 1.2–1.8 (m, 14 H), 1.94 (t, 1 H, J = 2.6 Hz) 2.0–2.1 (m, 2 H) 2.2 (t of d, 2 H, J = 2.6, 7.0 Hz) 2.2–2.4 (m, 1 H) 2.6 (m, 1 H) 2.7 (m, 1 H) 4.48 (m, 1 H, J = 5.5, 7.47 Hz) 5.1–5.2 (m, 2 H) 5.7 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.0, 25.9, 29.3, 29.6, 29.89, 29.96, 33.3, 35.5, 36.4, 39.7, 68.8, 79.55, 85.4, 118.5, 135.2, 179.5; IR (NaCl disks) 3200 (s), 2100 (m), 1770 (s), 1180 (s) cm^{-1}. The cis isomer **6b** was also present with key multiplets centered at δ 4.35 and 2.4. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.68; H, 10.09.

2-(2′,3′-Dihydroxypropyl)-4-(dec-9″-ynyl)-γ-butyrolactone (1). A mixture of 33 mg (0.28 mmol) of 4-methylmorpholine *N*-oxide monohydrate, 120 mg H_2O, and 90 μL of acetone and 18.5 mg of a 1% OsO_4 solution in *tert*-butyl alcohol, was prepared. To this, with ice-bath cooling, was slowly added 60 mg (0.23 mmol) of the **6a + 6b** mixture.[4a] After the solution was stirred 4.5 h at 0 °C, 2.3 mg of $NaHSO_3$, 28 mg of Florosil, and 0.2 mL of H_2O were added to the mixture. After filtration, the pH was adjusted to 7 with 0.5 M H_2SO_4 and the acetone was removed by rotary evaporation. The pH was then adjusted to 3 and the mixture was saturated with NaCl, extracted twice with ethyl acetate, and dried ($MgSO_4$). NMR of the product (43 mg (63%)) suggested the product was almost exclusively the desired diols 1. One of the trans isomers (relative stereochemistry 2′*S*,4*S*,2*S*), was isolated by recrystallization from CH_2Cl_2/CCl_4, mp 74–76 °C: ^1H NMR ($CDCl_3$) δ (see Table I) ^{13}C NMR ($CDCl_3$) δ 18.4, 25.3, 28.4, 28.6, 28.9, 29.2, 29.3, 33.9, 34.3, 35.3, 37.1, 66.7, 68.1, 70.6, 79.5, 84.7, 180.7; IR (NaCl disks) 3587–3337 (br m), 3300 (m), 2114 (w), 1754 (s), 1179 (m) cm^{-1}; MS (direct probe) m/e (relative intensity) 265 (17), 159 (100, M-$(CH_2)_8C{\equiv}CH$), 116 (56), 95 (61), 81 (78), 67 (94), 55 (72), 41 (89); exact mass (chemical ionization, M + 1) m/e calcd for $C_{17}H_{29}O_4$ 297.2066, found 297.2056. This MS was similar to that of rubrynolide except for the strong peak at 159 amu. The remaining isomers were characterized after acetylation and semi-preparative HPLC (see below).

2-(2′,3′-Diacetoxypropyl)-4-(dec-9″-ynyl)-γ-butyrolactone (9–12). A 15-mg sample of the synthesized isomers of 1 (the filtrate from the above crystallization) and a few crystals of DMAP were added to a dry reaction vial. Then 0.5 mL of dry CH_2Cl_2, 100 μL of Et_3N, and 70 μL of acetic anhydride were added, and the solution was stirred 2 h at room temperature. The solution was concentrated and run through a 4 × 0.3 cm plug of silica gel (30:70 ethyl acetate/hexane). The concentrated fraction containing diacetates was separated by HPLC (60:38.75:1.25 hexane/ether/ethanol).

The four acetylation products 9–12 gave two pairs of overlapping peaks at 33.6-, 34.8-, 42.4-, and 45.2-mL retention volumes, respectively, in a 2:3:4:1 ratio.[21] Heart cuts of each compound were collected and analyzed. The first and last compounds were cis lactones and the second and third were trans lactones as shown by NMR in Table III. A 50:50 mixture of rubrenolide and rubrynolide was acetylated similarly. Acetylated rubrynolide eluted at a 33.6-mL retention volume. In addition to identical HPLC retention times, acetylated rubrynolide and the first-eluting synthetic derivative gave superimposable mass, IR, ^1H and ^{13}C NMR spectra, and capillary GC column retention times (some decomposition occurred on the column). The synthetic and the natural compounds were mixed in a 3:2 ratio, and this mixture gave no new NMR peaks relative to the two separate products: ^1H NMR ($CDCl_3$) see Table III; ^{13}C NMR ($CDCl_3$) δ (lactone carbonyl too weak to observe) 19.0, 21.3, 21.5, 25.8, 25.9, 29.0, 29.3, 29.5, 29.9, 30.3, 32.7, 36.1, 36.3, 38.4, 65.7, 68.7, 69.9, 79.7, 171.16, 171.22; IR (NaCl disks) 3291 (m), 2117 (w), 1770 (s), 1743 (s), 1462 (m), 1372 (m), 1223 (s), 1043 cm^{-1}; MS m/e (relative intensity) 307 (9, M–CH_3), 201 (18), 67 (16), 55 (21), 42 (100).[1b]

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Supplementary Material Available: Details of the synthesis of 3 and 7 as well as a ^{13}C NMR spectrum of synthetic 1a (3 pages). Ordering information is given on any current masthead page.

(21) This ratio is somewhat biased since, prior to acetylation, the diol mixture was depleted of the isomer that would acetylate to give 10.

Anhydrous Hydrogen Fluoride Catalyzed Friedel–Crafts Reactions of Thioaromatic Compounds

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Sulfur-containing aromatic ketones, e.g., 4-mercaptoacetophenone[2] (1), 4-(methylthio)acetophenone[3] (**2a**), and 4′-(methylthio)-2-methylpropiophenone (**2b**), are potential intermediates for the synthesis of industrially useful compounds. 4-Mercaptoacetophenone has been used as an intermediate for the synthesis of 4-mercaptostyrene acetate[4] (4) and its polymers.[5] On the other hand, **2b** is an intermediate for the synthesis of a new UV cure photoinitiator.[6] Furthermore, 6,2-substituted naphthalenes, especially with a carbonyl substituent at the 2-position, have been found to be extremely useful in the pharmaceutical,[7] polymer,[7] and dye[8] industry.

4-Mercaptoacetophenone has been prepared from 4-hydroxyacetophenone involving Newman–Kwart rearrangement.[2] An alternate synthesis of 1 from 4-aminoacetophenone is also reported.[5] Commercially, **2b** is produced via $AlCl_3$-catalyzed Friedel–Crafts reaction of thioanisole with isobutyryl chloride.[6] Friedel–Crafts acylations for the synthesis of aromatic ketones are most commonly achieved by the use of $AlCl_3$ as a catalyst.[9] These acylations sometimes require 2 equiv of $AlCl_3$ to generate 1 mol of product. Aluminum chloride is not a

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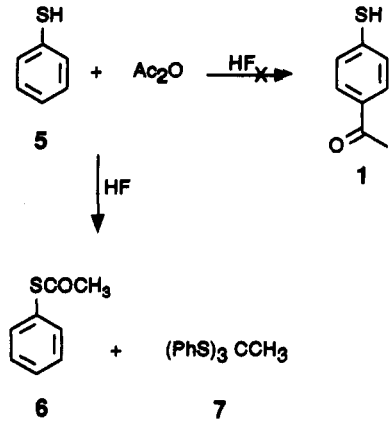
Scheme I

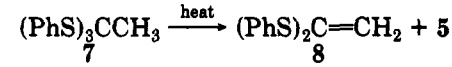


recyclable catalyst and poses enormous disposal and environmental problems in an industrial process. Anhydrous hydrogen fluoride (HF) has been shown to be a recyclable catalyst for Friedel–Crafts and Fries rearrangement. Industrial processes have been developed where anhydrous HF is used as a recyclable catalyst for the commercial production of 4-hydroxyacetophenone, an intermediate for *N*-acetyl-4-aminophenol (acetaminophen) from phenol.[10a,b] A commercial process for the production 4′-isobutylacetophenone, an intermediate in ibuprofen production, has been developed via the acylation of isobutylbenzene using anhydrous HF-catalyzed acylation technology.[10c] Unlike $AlCl_3$, anhydrous HF or BF_3 has been shown to be very effective in the regioselective acylation of 2-substituted naphthalenes to the corresponding 6,2-acylation products.[11]

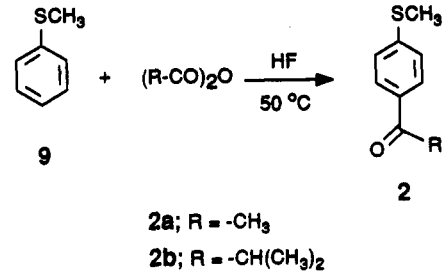
We have been seeking to extend the scope of this useful technology for the production of other commercially useful aromatic ketones. In this paper, we would like to communicate the details of our investigation for the acylation of aromatic thiols and sulfides using anhydrous HF.

Anhydrous HF-catalyzed acylation of phenol for the production of 4-hydroxyacetophenone is normally achieved at 40–80 °C in liquid HF in a Hastelloy-C autoclave.[10] Under similar conditions, phenyl acetate undergoes Fries rearrangement to afford 4-hydroxyacetophenone in high yield. HF-catalyzed acylation of thiophenol (**5**) with acetic anhydride for the synthesis of **1** was attempted at 50 and 80 °C. Under these conditions, we did not observe acylation of the aromatic ring. There were two major products formed in this reaction. The minor product (10–15%) was characterized as the phenyl thioacetate (**6**) based on GC retention times and mass spectral fragmentation pattern as compared to an authentic sample of **6**. On the basis of the NMR analysis and the melting point, the major product of this reaction (~74%) was characterized as 1,1,1-tris(phenylthio)ethane (**7**). We believe **7** is formed via HF-catalyzed condensation of **5** with **6** (Scheme I). In a separate experiment, HF-catalyzed Fries rearrangement of thiophenyl acetate was also unsuccessful; the major product of this reaction was also characterized as **7**. We postulate, under the reaction conditions, **6** reacts with anhydrous HF to afford **5** and acetyl fluoride (most probably a reversible reaction). Reaction of **5** with unreacted **6** affords **7** as shown in Scheme I. Boron trifluoride catalyzed condensation of **5** with **6** for the synthesis of **7** has been reported in the literature.[12] During the GC analysis of the reaction mixture, we also observed the presence of 1,1-bis(phenylthio)ethylene (**8**) (~50%) and thiophenol (22–23%). Some of the thiophenol may have been unconverted thiophenol; most of the thiophenol is probably formed via the pyrolysis of **7** in the GC's injection port. Pyrolysis of the orthothioesters, e.g., **7** to ketene thioacetal, e.g., **8** and **5**, is known[13] (Scheme II). Analysis of the product via HPLC revealed the presence of traces of thiophenol (<1%).

Scheme II



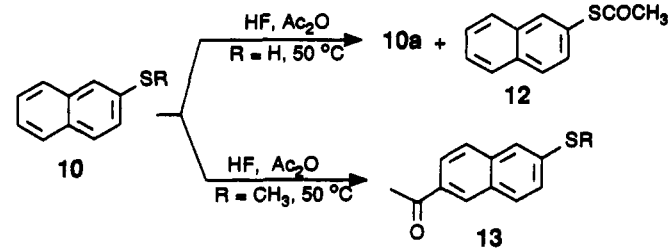
Scheme III



2a; R = -CH_3

2b; R = -$CH(CH_3)_2$

Scheme IV



10a; R = H

10b; R = CH_3

Anhydrous HF-catalyzed Friedel–Crafts reactions of thioanisole (**9**) with acetic and isobutyric anhydride were also evaluated. Reaction of thioanisole with acetic anhydride afforded **2a** in >90% yield. Anhydrous HF catalyzed acylation of thioanisole with isobutyric anhydride afforded 4′-(methylthio)-2-methylpropiophenone (**2b**) in ~68% yield. These reactions proceed with high regioselectivity to the 1,4-isomers (Scheme III).

The reaction of 2-thionaphthol (**10a**) with acetic anhydride in anhydrous HF at 50 and 80 °C for the synthesis of 6-acetyl-2-mercaptonaphthalene (**11**) was unsuccessful. GC analysis of the crude reaction product suggested the presence of unreacted **10a** (43–49%) and 2-thionaphthyl acetate **12**; (28–43%) (Scheme IV). The GC retention time and mass spectral fragmentation pattern of **12** was different from an authentic sample of **11**, prepared via the hydrolysis of 6′-aceto-2′-naphthyl-*N*,*N*-dimethylthiocarbamate.[14] The presence of the ketene thioacetal as

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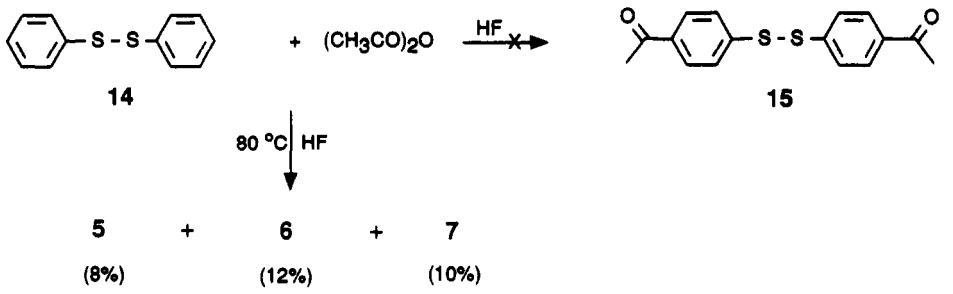
Scheme V



observed in the thiophenol experiment was not detected.

Anhydrous HF-catalyzed condensation of 2-(methylthio)naphthalene (**10b**) with acetic anhydride at 50 or 80 °C proceeded in >95% conversion and 6-acetyl-2-(methylthio)naphthalene (**13**) was isolated in high yield. This reaction proceeded with high regioselectivity. The presence of 1-acetyl-2-(methylthio)naphthalene was not detected. Highly regioselective acylation of 2-methoxynaphthalene to 6-methoxy-2-acetylnaphthalene has been observed to take place in anhydrous HF.[11a]

We have also made some unsuccessful attempts for the acylation of phenyl disulfide (**14**) to afford 4,4'-bis(acylphenyl) disulfide (**15**). HF-catalyzed acylation of **14** with acetic anhydride at 50 °C for 3 h afforded essentially no reaction products, only starting material was recovered. At 80 °C, however, we observed ~35% conversion of **14** to unwanted products, namely **6** (12%), **7** (10%), and **5** (8%) (Scheme V). Thiophenyl acetate (**6**) has been reported as the major product during the $AlBr_3$-catalyzed Friedel–Crafts acylation of **14** with acetyl chloride.[15]

In summary, anhydrous HF has been found to be an effective Friedel–Crafts catalyst for the acylation of (alkylthio)aromatics to the corresponding acylation products. Unlike acylation of phenol to 4-hydroxyacetophenone,[10a,b] acylation of thiophenol did not afford 4-mercaptoacetophenone but another product characterized as 1,1,1-tris(thiophenyl)ethane. Attempted acylation of phenyl disulfide in anhydrous HF led to the cleavage of the disulfide linkage.

Experimental Section

Melting points were determined on a Mel-Temp melting point apparatus. ^1H and ^{13}C NMR spectra were recorded on an IBM AF-200 spectrometer. The chemical shifts are reported in parts per million (δ) from internal tetramethylsilane, and the coupling constant (J) are given in Hz. IR spectra were recorded on a Nicolet 20SXB FT-IR Spectrometer. GC analyses were carried out with the use of a Hewlett-Packard 5890 gas chromatograph using a 30-m DB-1, 1.0-μm column with 0.32 i.d. GC/MS spectra were obtained on a Hewlett-Packard bench-top instrument equipped with a 5970 mass selective detector. Anhydrous HF was purchased from Matheson Gas Products Co. 2-Thionaphthol, thiophenol, and phenyl disulfide were purchased from Aldrich Chemical Co. 2-(Methylthio)naphthalene was prepared via methylation of 2-thionaphthol with dimethyl sulfate. Anhydrous HF is an extremely toxic substance; both acute and/or chronic toxicity can occur. Anhydrous HF is a highly corrosive acid that can severely burn skin and eyes. Before using anhydrous HF, it is important to first learn all the safety procedures involved in handling anhydrous HF.[16] All reactions should be carried out in efficient hoods equipped with HF monitors. Personal protective equipment must be worn when handling anhydrous HF.

General Procedure for Anhydrous HF-Catalyzed Acylations of Thioaromatics. A 300 cm^3 Hastelloy-C reactor equipped with a stirrer, HF cylinder, and a KOH scrubber was charged with 0.1 mol of the thioaromatic compound and 0.15 mol of acetic anhydride or isobutyric anhydride. The reactor was chilled to −40 °C and evacuated with a water aspirator, and anhydrous HF (4.0 mol) was transferred to the reactor. The reactor was gradually warmed to room temperature and heated to the desired reaction temperature for the desired reaction time. After the heating period was over, the reactor was cooled to room temperature and the HF was vented to a KOH scrubber. The reactor was purged with nitrogen for an additional 0.5 h and chilled in ice. The contents of the reactor were diluted with ethyl acetate (500 mL) and transferred to a flask containing ice–water (500 mL). The reaction mixture was neutralized to pH 6.0 with 45% aqueous KOH. The ethyl acetate layer was separated, washed with water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator. The following experiments were conducted following this general procedure.

Thiophenol with Acetic Anhydride: 1,1,1-Tris(phenylthio)ethane (7). The reaction of thiophenol and acetic anhydride at 50 and 80 °C afforded oily solids, 8.5 g and 9.8 g, respectively. HPLC analysis of the solid revealed the presence of **7** (74%) and **6** (11%); <1% thiophenol was also present in the product mixture. Recrystallization of a 2.0-g sample from the 80 °C run (hexane:$CHCl_3$ = 9:1) afforded **7** as a white crystalline solid (1.2 g): mp 145–46 °C (lit.[12] mp for **7** 145–46 °C); ^1H NMR ($CDCl_3$) δ 7.71–7.27 (m, 15 H), 1.43 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.79, 132.48, 129.36, 128.51, 70.67 and 29.36.

4-(Methylthio)acetophenone (2a). The reaction of thioanisole (**9**) with acetic anhydride at 50 and 80 °C for 3 h and workup afforded **2a** in 95 and 93% yield, respectively. GC and NMR analysis of the crude product confirmed the presence of only **2a** and no other isomer or impurity: mp (unrecrystallized sample from 80 °C run) 80–82 °C (lit.[17] mp 80 °C); ^1H NMR δ ($CDCl_3$) 7.86–7.21 (AA'BB' quartet, 4 H), 2.54 (s, 3 H), 2.49 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.88, 145.75, 133.48, 128.59, 124.93, 26.22 and 14.67; IR (KBr) 1661 (vs), 1590 (s), 1260 (s) cm^{-1}.

4'-(Methylthio)-2-methylpropiophenone (2b). The reaction of **9** (24.8 g, 0.2 mol) with isobutyric anhydride (34.8 g, 0.22 mol) in HF (120 g, 6.0 mol) at 60 °C for 3 h and workup afforded the crude product as a dark brown liquid (37.7 g). GC analysis of the crude product revealed the presence of **2b** (87% pure). Distillation of the crude product under reduced pressure afforded **2b** as a colorless liquid (solidified upon cooling) 29.2 g (91% pure by GC), bp 102–104 °C (0.5 mmHg), mp 38–40 °C. Recrystallization of the distilled product (20.0 g) with 50 mL ethanol/water (8:2) afforded white crystals (15.4 g): mp 44–45 °C (lit.[18] mp 40–41 °C); ^1H NMR ($CDCl_3$) δ 7.87–7.19 (AA'BB' quartet J = 10.9, 4 H), 3.47 (m, 1 H), 2.46 (s, 3, H), 1.17 (d, J = 6.8, 6 H); ^{13}C NMR ($CDCl_3$) δ 203.15, 145.27, 132.25, 128.53, 124.91, 34.90, 19.01, 14.55; IR (KBr) 1665 (vs), 1580 (vs), 1095 (s) cm^{-1}.

6-Acetyl-2-(methylthio)naphthalene (13). The reaction of 2-(methylthio)naphthalene with acetic anhydride at 50 °C for 3 h and workup afforded a brown solid (19.7 g). The reaction at 80 °C afforded a gray solid (18.0 g). GC analysis of both the crude products indicated the presence of mainly one isomer. The crude product from the 50 °C run (7.0 g) was distilled on a Kugelrohr

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apparatus to afford a yellow solid (4.1 g). GC analysis of the distilled product showed only one isomer. The crude product from the 80 °C run (5.0 g) was distilled to afford a yellow solid (2.75 g). Recrystallization of the solid from absolute alcohol afforded a white crystalline solid, mp 120–121 °C (lit.[19] mp 120 °C for 6-acetyl-2-(methylthio)naphthalene: ^{1}H NMR ($CDCl_3$) δ 8.37–7.37 (m, 6 H), 2.70 (s, 3 H) and 2.59 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 197.71, 140.1, 135.93, 133.61, 129.93, 129.49, 127.02, 125.93, 124.72, 121.86, 26.53 and 15.08; IR (KBR) 1668 (vs), 1612 (s), 1280 (s), 1270 (s), 865 cm^{-1}.

Phenyl Disulfide with Acetic Anhydride. The reaction of phenyl disulfide at 80 °C for 3 h and workup afforded an oil (22.9 g). CG analysis of the product indicated the presence of **5** (8%), **6** (12%), **7** (10%), and **14** (65%).

Acknowledgment. We thank G. L. Sosa for technical assistance and Dr. B. Segmuller for valuable help with the NMR analyses.

Registry No. 2a, 1778-09-2; **2b**, 53207-58-2; **5**, 108-98-5; **6**, 934-87-2; **7**, 14859-20-2; **8**, 18889-01-5; **9**, 100-68-5; **10a**, 91-60-1; **11**, 135455-69-5; **12**, 831-23-2; **13**, 62759-49-3; **14**, 882-33-7; acetic anhydride, 108-24-7; isobutyryl chloride, 79-30-1.

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Micellar Catalysis of Organic Reactions. 32. S_NAr Reactions of 1,5-Difluoro-2,4-dinitrobenzene and Related Compounds in the Presence of Cationic Micelles

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Introduction

The effects of cationic micelles on the S_NAr reactions of hydroxide ions with DNFB, one of the classic substrates for this type of reaction, have been widely studied. For example, micelles of CTAB significantly catalyze the hydroxydefluorination of this substrate[1] and a 60-fold optimum catalysis was observed at 20 mM CTAB.

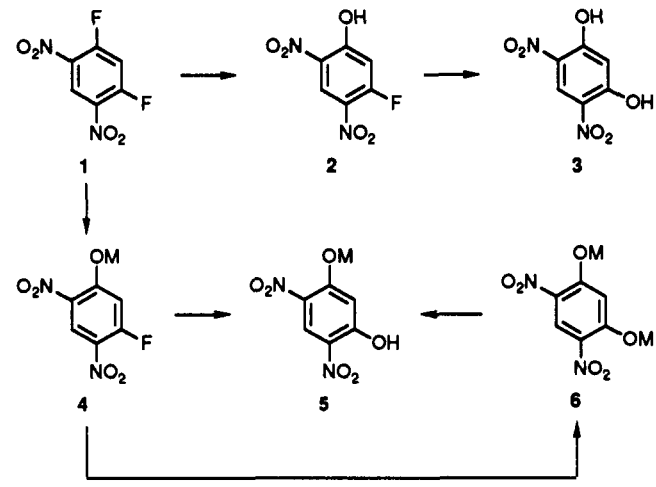
Monohydroxy-functionalized micelles, e.g., CHEDAB and 2-OH-CTAB also catalyze the reaction, in this case by a nucleophilic mechanism in which an aryl micellar ether is formed during the reaction. This aryl micellar ether is subsequently converted, by a second S_NAr reaction, into 2,4-dinitrophenol, the normal product of the hydroxydefluorination reaction.[2]

β-Cyclodextrin also catalyzes the reaction by a similar mechanism,[2] although in this case an arylcyclodextryl ether is formed and subsequently decomposed during the reaction.

Reaction in the presence of dihydroxy micelles of CDHPDAB resulted in the transient formation of a micellar-bound spiro-Meisenheimer complex from the intermediate aryl micellar ether.[3]

We now report the results of a study of the reaction of DFDNB and related compounds, with hydroxide ions, in the presence of the above micelles. This substrate is of interest because it contains two potential nucleofuges (fluoride), both of which are activated by nitro groups at ortho and para positions.

Scheme I[a]



[a] M = micelle.

Results and Discussion

(a) Reactions with Hydroxide Ions in CTAB. The reaction of DFDNB with hydroxide ions, in the presence of micelles of CTAB, occurs in two distinct phases. At 30 °C, in the presence of 0.01 M NaOH, an instantaneous reaction leads to the production of 5-fluoro-2,4-dinitrophenol (**2**), λ_{max} 345 (A = 0.8) and 395 nm (A = 0.95). The UV–vis spectrum of this product was identical with that of an authentic sample prepared in water. This product was stable at 30 °C, but on heating the reaction mixture to 66 °C a slow reaction leading to 4,6-dinitroresorcinol (**3**), λ_{max} 335 (A = 1.3) and 424 nm (A = 0.97), was observed.

4,6-Dinitroresorcinol had previously been reported[4] as the product of a slow reaction of 1,5-diiodo-2,4-dinitrobenzene with a boiling aqueous solution of dilute hydroxide ions, although there was no report of an intermediate product in that case.

The difference in the rates of these two stages of reaction can be rationalized after a consideration of the substituent effects operational on each reaction. The first stage of reaction is rapid because of the presence of a good nucleofuge (fluoride) and nitro groups at the ortho and para positions relative to the nucleofuge. The corresponding reaction of 2,4-dinitrofluorobenzene, with hydroxide ions in CTAB, is also rapid[1] for the same reasons, with a first-order rate constant, $k_1 = 7.2 \times 10^{-2}$ s^{-1}, and a half-life of 10 s. In the second stage of reaction a good nucleofuge (fluoride) is still present, but the accelerating effect of the two nitro groups is now opposed by the strong electron-releasing effect of the ionized phenolic hydroxyl group at the meta position ($\sigma_{m\text{-}O^-} = -0.71$).[5] On the other hand, the extra fluorine present in DFDNB has only a small electronic effect on the reaction center ($\sigma_{m\text{-}F} = 0.06$) during the first stage of reaction.[5]

The corresponding reaction of (BrDNFB) also occurred in two distinct phases, a very fast reaction at 30 °C in which the fluoride was displaced and a very slow reaction at 66 °C in which the bromide was displaced. The difference in rates of the slow reactions of these two substrates at 66 °C is typical of the large F/Br rate ratios

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