Synthetic Utility and Mechanistic Implications of the Fries Rearrangement of Hydroquinone Diesters in Boron Trifluoride Complexes

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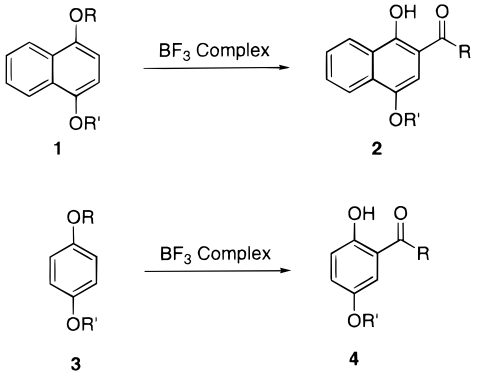
Reactions of boron trifluoride methyl and ethyl etherate complexes with hydroquinone diesters yield monomethyl and monoethyl derivatives of acetylhydroquinones. The use of sterically hindered boron trifluoride etherate complexes results in acetylhydroquinone derivatives. This procedure represents a one-step synthesis of acetylhydroquinone derivatives, important building blocks for a variety of synthetic applications.

Constant interest in the synthesis of quinone-related compounds stems from their diverse biological activity, including antimicrobial and cytotoxic properties.[1] Acetyl quinone derivatives are of particular interest due to the proximity of the carbonyl to the quinone ring.[2] Several acetyl quinones are natural products[3] whereas others have served as versatile synthetic intermediates[4] and biosynthetic precursors.[3] In our continued investigations into quinone alkylations,[5−8] we required a convenient, versatile preparation of acetylquinone derivatives. Previous work has demonstrated that acetylquinones can be prepared from the oxidation of corresponding hydroquinones, the latter obtained from the Fries rearrangement of aromatic esters followed by hydrolysis.[9] While useful, these reactions are of limited synthetic scope and mechanistically lacking in detail. Herein, we report here the synthetic utility and mechanistic details of our findings.

Results and Discussion

Earlier studies have shown that the Fries rearrangements of 1,4-diacetoxynaphthalene **1a** in BF_3−acetic acid complex results in 4-acetoxy-2-acetyl-1-naphthol **2a** in good yield.[2] These results were born out in our laboratory as well as the analogous reaction of 1,4-diacetoxybenzene **3a** which resulted in 5-acetoxy-2-hydroxyacetophenone **4a** in 94% yield as shown in Scheme 1. In each instance, no evidence of a second Fries rearrangement was observed. This observation is consistent with previous reports stating that Fries reactivity is reduced by the presence of electron-withdrawing groups, in this case the acyl group at carbon 2 resulting from the initial Fries rearrangement.[10] To assess the scope and limitations of this reaction, the dipropionate ester of hydroquinone **3b** was subjected to identical reaction conditions to that of **3a** which resulted in a mixture of **4a** (82%) and 5-acetoxy-2-hydroxypropiophenone **4b** (9%) as determined by GCMS and NMR. On the basis of these results, we can conclude that the BF_3−acetic acid complex acts as a acyl donor for both the carbon acylation and subsequent oxygen acylation at position 5.

Scheme 1



Substrate	BF_3 Complex	Product
1a R=R'=Ac	BF_3-OAc	**2a** R=Me R'=Ac (89%)
3a R=R'=Ac	BF_3-OAc	**4a** R=Me R'=Ac (94%)
3b R=R'=C(O)Et	BF_3-OAc	**4a** R=Me R'=Ac (82%)
		4b R=Et R'=Ac (9%)
1a R=R'=Ac	BF_3-OMe_2	**2b** R=Me R'=Me (89%)
3a R=R'=Ac	BF_3-OMe_2	**4c** R=Me R'=Me (90%)
1a R=R'=Ac	BF_3-OEt_2	**2c** R=Me R'=Et (92%)
3a R=R'=Ac	BF_3-OEt_2	**4d** R=Me R'=Et (90%)
3a R=R'=Ac	BF_3-OPr_2	**4e** R=Me R'=H (89%)
		4f R=Me R'=Pr (9%)
3a R=R'=Ac	BF_3-OBu_2	**4e** R=Me R'=H (62%)
3b R=R'=C(O)Et	BF_3-OBu_2	**4g** R=Et R'=H (42%)
1a R=R'=Ac	BF_3-OBu_2	**2d** R=Me R'=H (83%)

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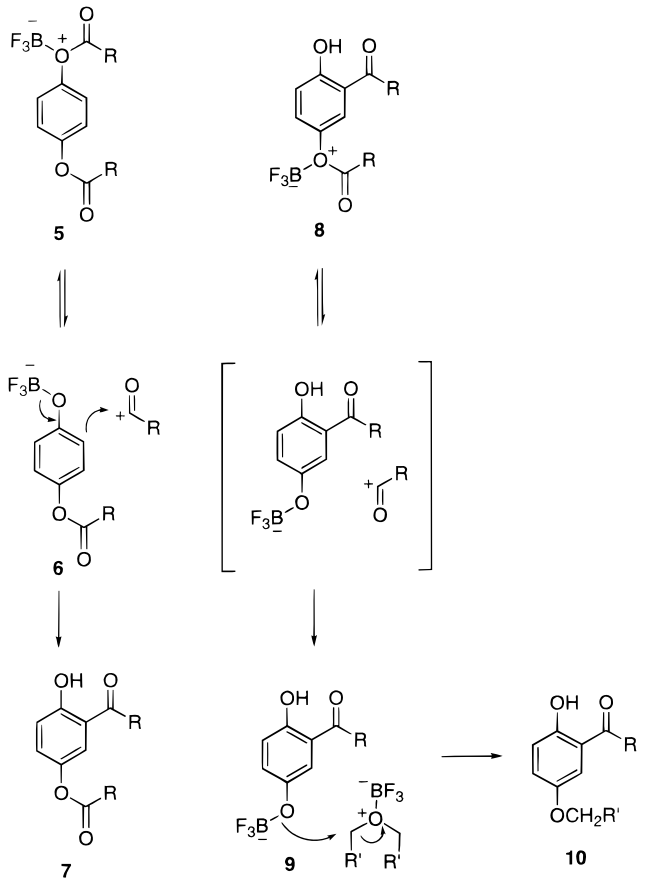
In an effort to eliminate the participation of the BF_3 complex as an acyl donor, we investigated the use of BF_3−etherate complexes. Reaction of **1a** with BF_3−dimethyl etherate resulted in formation of 2-acetyl-4-methoxy-1-naphthol **2b** (89%) as the only observed product. Similar results were observed for the reaction of **3a** resulting in 2-hydroxy-5-methoxyacetophenone **4c** in 90% yield. The use of BF_3−diethyl etherate complex with **1a** and **3a** gave similar results giving 2-acetyl-4-ethoxy-1-naphthol **2c** and 4-ethoxy-2-hydroxyacetophenone **4d**, respectively. These results indicate that the acyl groups of compounds **2b**,**c** and **4c**,**d** are derived from the corresponding diacetoxyaromatic and that the BF_3−etherate complexes act as an alkylating agent toward the oxygen meta to the acyl group. To our knowledge, this is the first reported case of boron trifluoride−etherate complexes acting as an alkylating agent.

Previous reports have indicated that the transfer of the acyl group may involve intermolecular and/or intramolecular transfer of the acyl group depending on the substrate.[11,12] To determine the nature of acyl transfer for the aforementioned systems, a crossover experiment was performed employing **1a** and **3b.** Reaction of equimolar concentrations of **1a** and **3b** in BF_3−diethyl etherate complex resulted in a mixture of products. Compounds derived from **3b** were identified as 4-ethoxy-2-hydroxyacetophenone **4d** (43%) and 4-ethoxy-2-hydroxypropiophenone (52%). Also present in the reaction mixture were products derived from **1a**, which were identified as 2-acetyl-4-ethoxy-1-naphthol **2c** (59%) and 4-ethoxy-2-propionyl-1-naphthol (40%) as determined by GCMS. On the basis of the presence of 4-ethoxy-2-hydroxyacetophenone and 4-ethoxy-2-propionyl-1-naphthol in the reaction mixture, one can conclude that a significant portion of the observed products result from intermolecular acyl transfer, presumably through an acylium ion intermediate.[11,13]

The use of alkoxy-substituted acetophenone and propiophenone derivatives has been reported in the syntheses of chalcone derivatives, which are inhibitors of cyclooxygenase and 5-lipoxygenase.[14] In an attempt to expand the synthetic utility of these compounds, we investigated the use of other BF_3−etherate complexes, attempting to synthesize ether analogues of **2** and **4**. Reaction of **3a** with BF_3−dipropyl etherate resulted in formation of a mixture of 2,5-dihydroxyacetophenone **4e** (89%) and 2-hydroxy-5-propoxyacetophenone **4f** (9%). Identification of **4f** was based on GCMS and NMR data of the crude reaction mixture as compared to an authentic sample synthesized by a previously reported method.[15] Reaction of **3a** with BF_3−dibutyl etherate resulted in formation of **4e** as the only observed product**.** Likewise, the reaction of **3b** with BF_3−dibutyl etherate resulted in 2,5-dihydroxypropiophenone **4g** in 42% yield. No oxygen alkylation was observed. Similar results were observed for the reaction of **1a** resulting in 2-acetyl-1,4-dihydroxynaphthalene **2d** in 83% yield. The use of BF_3−THF complex with **1a** and **3a** also resulted in formation of **2d** and **4e**, respectively, in similar yield. Once again, oxygen alkylation was not observed. While unexpected, the aforementioned boron trifluoride complexes can be used to carry out a one-pot synthesis of acetyl hydroquinone derivatives. Subsequent oxidation of these hydroquinone derivatives using resin-bound periodate can convert the hydroquinones to acetylquinones in near quantative yields.[16]

Scheme 2



On the basis of these observations, a plausible mechanism is shown in Scheme 2. Reaction of hydroquinone diesters with boron trifluoride gives the Lewis adduct **5**. Dissociation of **5** results in formation of an acylium ion−aromatic anion pair. The acylium ion can diffuse from the solvent cage, accounting for the intermolecular nature of the reaction as observed in the cross-over experiment. Electrophilic aromatic substitution of the acylium ion with **6** results in **7**. Reaction of **7** with boron trifluoride gives the second Lewis adduct **8** which also dissociates to an ion pair. The electron-withdrawing effects of the acetyl group on **9** deactivates the ring, disfavoring acyl alkylation. Oxygen alkylation of **9**, resulting from nucleophilic addition to the boron trifluoride etherate complex, results in formation of **10**. Increasing the steric effects of the ether complexes disfavors alkylation allowing for formation of acetylhydroquinone via protonation.

In conclusion, the use of boron trifluoride etherate complexes represents a convenient one-step synthesis of acetylhydroquinones, acetylnaphthohydroquinones, and their respective monomethyl and monoethyl ethers, all of which can serve as important building blocks for a variety of synthetic applications. Currently we are in-

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vestigating the scope of this reaction in regard to other nonquinoid substrates.

Experimental Section

General Methods. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were determined in $CDCl_3$ unless otherwise specified. Chemical shifts are reported in ppm downfield from internal TMS (δ). Melting points were obtained with open capillary tubes and are uncorrected. Compounds **1a**, **3a**, and **3b** were prepared using previously reported procedures.[17,18] All other materials were obtained from commercial suppliers.

General Procedure for Fries Rearrangement. In a 10-mL round-bottom flask equipped with a condenser and a stir bar were placed 4.0 mL of boron trifluoride complex and 1.0 g of the aromatic diester. Heat was then applied, and the mixture was refluxed for 1 h. The resulting solution was allowed to cool to room temperature and then poured into water and extracted with dichloromethane. The organic phase was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The crude products were purified by flash chromatography (silica gel, 30% acetone/hexane) or recrystallization. All reported compounds are known except for those listed below.[19−25]

2-Acetyl-4-methoxy-1-naphthol (2b). Following the general procedure, a solution of 1,4-diacetoxynaphthalene (1.0 g) in boron trifluoride dimethyl ether complex (4.0 mL) afforded **2b** (788 mg, 89%). Recrystallization from ethanol afforded a yellow solid; mp 161−164 °C. ^{1}H NMR ($CDCl_3$) δ 13.75 (s, 1H), 8.55 (dd, J = 8.5, 2.0 Hz, 1H), 8.17 (dd, J = 8.5, 2.0 Hz, 1H), 7.82 (dt, J = 8.5, 2.0 Hz, 1H), 7.65 (dt, J = 8.5, 2.0 Hz, 1H), 6.56 (s, 1H), 3.98 (s, 3H), 2.83 (s, 3H); ^{13}C NMR δ 203.68, 157.35, 147.32, 129.69, 126.59, 125.89, 124.32, 121.85, 111.93, 106.59, 100.64, 55.62, 26.99. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.19; H, 5.54.

2-Acetyl-4-ethoxy-1-naphthol (2c). Following the general procedure, a solution of 1,4-diacetoxynaphthalene (1.0 g) in boron trifluoride diethyl ether complex (4.0 mL) afforded **2c** (867 mg, 92%). Recrystallization from ethanol afforded a yellow solid; mp 113−115°. ^{1}H NMR ($CDCl_3$) δ 13.74 (s, 1H), 8.60 (dd, J = 8.3, 1.4 Hz, 1H), 8.23 (dd, J = 8.3, 1.4 Hz, 1H), 7.83 (dt, J = 8.3, 1.4 Hz, 1H), 7.66 (dt, J = 8.3, 1.4 Hz, 1H), 6.51 (s, 1H), 4.16 (q, J = 6.9 Hz, 2H), 2.80 (s, 3H), 1.57 (t, J = 6.9 Hz. 1H); ^{13}C NMR δ 196.52,163.42, 148.20, 134.48, 133.79, 127.95, 126.61, 125.72, 122.75, 110.79, 96.86, 64.05, 23.26, 14.59. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.89; H, 6.08.

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Supporting Information Available: Detailed experimental procedures and compilation of NMR data for all compounds and MS spectra of new compounds **2b** and **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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