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UNUSUAL REACTIVITY OF PENTAFLUOROBENZYL AROMATIC ETHERS UNDER FRIEDEL-CRAFTS REACTION CONDITIONS

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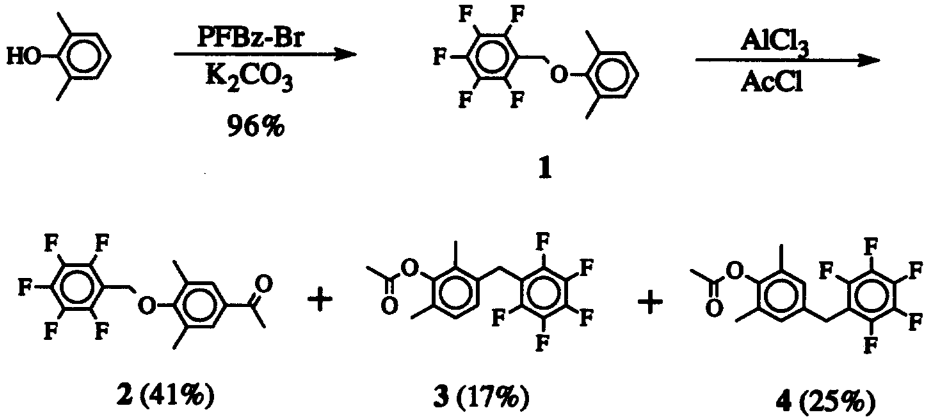
ABSTRACT: A pentafluorobenzyl (PFBz) ether of 2,6-dimethylphenol undergoes a PFBz rearrangement, which appears to be intermolecular, yielding a 2:3 ratio of *meta* to *para* migration. Only ether bond cleavage takes place in a corresponding PFBz ether of 2,6-difluorophenol. Both sets of products are unusual, and it is suggested that they are both due to high reactivity of the PFBz-oxy moiety with the $AlCl_3$ catalyst.

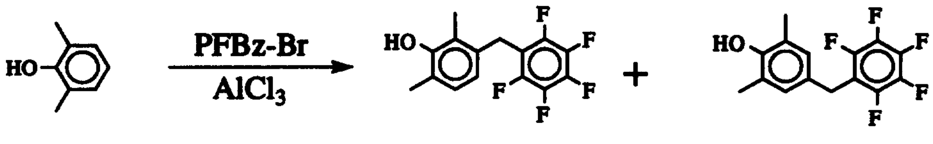
Although the rearrangement of benzyl aromatic ethers in the presence of Lewis acids has been known for many years,[1-3] such rearrangements have not been reported for pentafluorobenzyl (PFBz) aromatic ethers. While attempting to synthesize pentafluorobenzyloxy substituted aromatic ketones from corresponding aromatic ethers by a Friedel-Crafts acetylation in the presence of aluminum chloride, we have found the PFBz to rearrange. This work is part of our effort to develop PFBz aromatic ethers as molecular labels.[4]

When a mixture of pentafluorobenzyl 2,6-dimethylphenyl ether (**1**, 4.43 mmol), acetyl chloride (5.1 mmol), and aluminum chloride (5.2 mmol) is stirred in methylene chloride overnight at room temperature, besides the expected acetylated product **2**, two aromatic acetates, **3** and **4**, are also obtained in a ratio of 2:3.[5] The total yield of these three products is 83%. Apparently **3** and **4** are the products of a PFBz rearrangement followed by an acetylation of the resulting phenol intermediates by the excess of acetyl chloride. No 2',4'-dimethyl-3'-pentafluorobenzyloxyacetophenone, the possible *meta* acetylated product, is found.



For the rearrangement of benzyl phenyl ether, an *intra*molecular reaction mechanism has been suggested based on the fact that the only rearrangement product is *o*-benzylphenol.[2] Additional evidence for an intramolecular mechanism is the rearrangement of some optically active aryl α-phenylethyl ethers with retention of configuration.[3] However, we observe *meta* and *para* migration of the PFBz moiety, at least when *ortho* migration is blocked. Further, when we monitored the above reaction of **1** by gas chromatography, small amounts of pentafluorobenzyl chloride (**5**) and 2,6-dimethylphenyl acetate (**6**) were found, revealing at least some dissociation of the PFBz moiety from **1**.

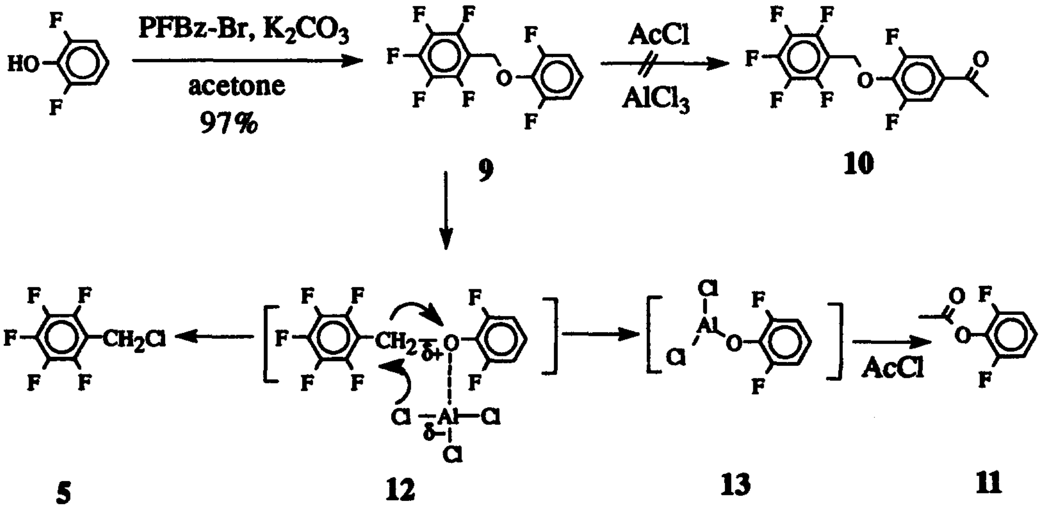
This opens up the possibility that **2** and **3** arise from an *inter*molecular migration of the PFBz moiety, possibly *via* the intermediate formation of PFBzCl. If this is true, then one would anticipate that the Friedel-Crafts reaction of 2,6-dimethylphenol with PFBzBr would yield a similar ratio of *meta* to *para* pentafluorobenzylated products. Indeed, this reaction, shown here, forms **7** and **8** in a ratio of 2:3.5.



7 **8**

Thus, we suggest that the rearrangement of the PFBz group in the Friedel-Crafts reaction of **1** is intermolecular. While PFBzCl may be an intermediate, it is also known that ethers can function as alkylating agents in Friedel-Crafts reactions.[6] The two *ortho* methyl groups in **1** may promote the intermolecular *vs* intramolecular migration of PFBz, but the inherent reactivity properties of the pentafluorobenzyl moiety in **1** may be critical (*e.g.* pentafluorophenyl is somewhat more inductively electron-withdrawing than phenyl[7]), as supported by additional observations cited below.

Another unexpected result also provided some support for the proposed intermolecular rearrangement of **1**. When we tried to convert **9** to **10** by a Friedel-Crafts reaction with acetyl chloride, only **5** and **11** were formed in a ratio of 1:1 and a yield of 90%.[8] But Friedel-Crafts acetylations of polyfluorinated aromatic compounds are known,[9] and Kelly acetylated 2,3-difluorophenyl dodecyl ether in this way (48% yield).[10] We suggest that intermediate **12** readily forms and decomposes as shown to form **5** and intermediate **13**, with subsequent acetylation of the latter to yield **11**.



Thus, high reactivity of the pentafluorobenzyloxy moiety in the aromatic ethers **1** and **9** with aluminum chloride appears to be behind the unusual reactions that we report here.

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5. Compound **2**: ^{1}H NMR(CDCl$_3$), δ: 2.36(s, 6H, CH$_3$Ar), 2.57(s, 3H, CH$_3$CO), 4.92(s, 2H, CH$_2$O), 7.67(s, 2H, H-C2' & H-C6') ppm; ^{13}C NMR(CDCl$_3$), δ: 16.1(CH$_3$Ar), 26.5(CH$_3$CO), 60.1(CH$_2$O), 110.2(C1", $^2J_{C\text{-}F}$ =18Hz), 129.5(C2' & C6'), 131.4(C3' & C5'), 133.6(C1'), 137.5(C2" & C6", $J_{C\text{-}F}$ =258Hz), 141.8(C4", $J_{C\text{-}F}$ =256Hz), 145.9(C3" & C5", $J_{C\text{-}F}$ =250Hz), 158.7(C4'), 197.5(C=O) ppm. **3:** ^{1}H NMR(CDCl$_3$), δ: 2.12(s, 3H, CH$_3$ on C2'), 2.17(s, 3H, CH$_3$ on C6'), 2.36(s, 3H, CH$_3$CO), 3.99(s, 2H, CH$_2$), 6.77(d, 1H, J =7.8Hz, H-C4'), 6.98(d, 1H, J=7.8Hz, H-C5') ppm; ^{13}C NMR(CDCl$_3$), δ: 12.3(CH$_3$ on C2'), 16.3(CH$_3$ on C6'), 20.5(CH$_3$CO), 25.5(CH$_2$), 113.4(C1", $^2J_{C\text{-}F}$ =18Hz), 125.8(C4' or C5'), 128.1(C5' or C4'), 128.4(C2' or C6'), 128.9(C6' or C2'), 134.3(C3'), 137.5(C2" & C6", $J_{C\text{-}F}$ =253Hz), 140.0(C4", $J_{C\text{-}F}$ = 253Hz), 145.2(C3" & C5", $J_{C\text{-}F}$ =249Hz), 148.3(C1'), 168.8(C=O) ppm. **4:** ^{1}H NMR(CDCl$_3$), δ: 2.11(s, 6H, CH$_3$Ar), 2.32(s, 3H, CH$_3$CO), 3.92(s, 2H, CH$_2$), 6.92(s, 2H, H-Ar)ppm; ^{13}C NMR(CDCl$_3$), δ: 16.3(CH$_3$Ar), 20.4(CH$_3$CO), 27.5(CH$_2$), 114.3(C1", $^2J_{C\text{-}F}$ = 19Hz), 128.5(C3' & C5'), 130.5(C2' & C6'), 134.8(C4'), 137.5(C2" & C6", $J_{C\text{-}F}$ =252Hz), 139.9(C4", $J_{C\text{-}F}$ = 252Hz), 144.9(C3" & C5", $J_{C\text{-}F}$ =249Hz), 147.1(C1'), 168.9(C=O) ppm.
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8. Even after 24 hours of reaction at room temperature, no **10** formed. We obtained anauthentic sample of **10** by pentafluorobenzylating 3',5'-difluoro-4'-hydroxyacetophenone; Xu, L. and Giese, R. W.; *unpublished results.*
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