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The fragmentation of polyfluorinated benzylic alcohols: the first observation of pentafluorophenyl anion as a good leaving group

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Abstract—Treatment of a series of pentafluorobenzylic alcohols with sodium methoxide in DMSO results in a rapid carbon–carbon cleavage reaction, yielding a ketone or aldehyde as well as pentafluorobenzene, which undergoes subsequent nucleophilic aromatic substitution (NAS). In methanol solvent, the fragmentation is very slow, and NAS without fragmentation occurs almost exclusively. In methanol/DMSO mixtures, both processes are observed simultaneously. This appears to be the first report of the fragmentation of pentafluorobenzylic alcohols.

Reactions that result in the cleavage of carbon–carbon bonds are relatively rare. Most of these reactions involve alkoxides fragmenting to give ketones and generally require stabilized carbanion leaving groups.[1] Some common examples include the haloform reaction and the retro-aldol reaction. However, examples involving less-stabilized[2] or even non-stabilized[3] carbanions are known, though extreme steric crowding[3b] or high temperatures[3c] are often required.

Several *trans*-1-aryl-4-*tert*-butylcyclohexanols are effective gelling agents for nonpolar organic solvents.[4] In an attempt to prepare derivatives of *trans*-1-pentafluorophenyl-4-*tert*-butylcyclohexanol (**1**) by nucleophilic aromatic substitution (NAS), we found that the reaction with sodium methoxide in DMSO resulted in the formation of 4-*tert*-butylcyclohexanone and 2,3,5,6-tetrafluoroanisole (Scheme 1). Neither the fragmentation nor the substitution of pentafluorobenzylic alcohols appears to have been previously reported,[5] with the only reference to a substitution reaction having first required protection of the hydroxy group.[6] We initiated a study of this reaction using the more-available (and non-gelling) cis isomer **2**. Although GC–MS was initially used (and verified the formation of ketone), the best technique for studying these reactions proved to be ^{19}F NMR. The identities of all species were established by NMR and GC–MS, generally with comparison to authentic materials.

The reaction of **2** (~0.1 M) with 2 equiv of sodium methoxide (25 wt% solution in methanol) in polar aprotic solvents was very fast (Scheme 2). In DMSO and DMF, the reaction was complete in <4 min. Acetonitrile gave a somewhat slower reaction (complete in 5–10 min), THF slower yet (~65% complete in 60 min), and *tert*-butanol, dichloromethane and benzene were all much less reactive (~10% complete at 60 min), though some insolubility of the methoxide was evident in the case of benzene.

We found that the very rapid cleavage reaction observed in DMSO slows considerably with the addition of increasing amounts of methanol, and NAS without cleavage becomes the dominant reaction. The reaction of *trans* isomer **1** was slow enough in 35:65 (v/v) DMSO-d_6:CH_3OH at room temperature (~50% complete in 1.5 h) that it could be conveniently monitored by ^{19}F NMR. Under these conditions (~0.1 M in **1**, 2 equiv NaOMe), we could observe both the NAS product before cleavage (**3**) and pentafluorobenzene, indicating that the reaction was clearly proceeding by two pathways. The ^{19}F spectra revealed that the initial step of path A (Scheme 3) was 5–10 times faster than the initial step of path B. Pentafluorobenzene serves as a reactive intermediate, present only at low levels (⩽20% of all fluorinated species) with its initial rate of formation being only somewhat faster than its conversion to

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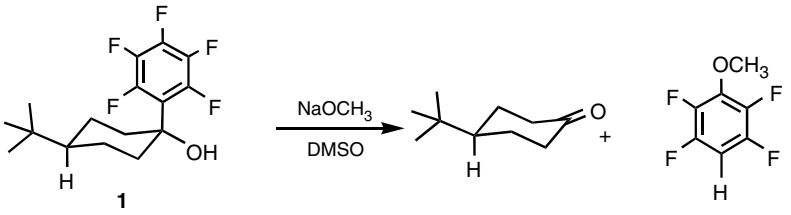
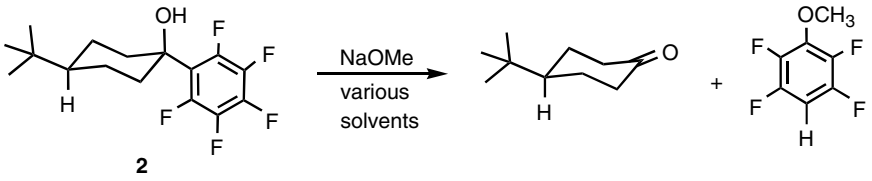
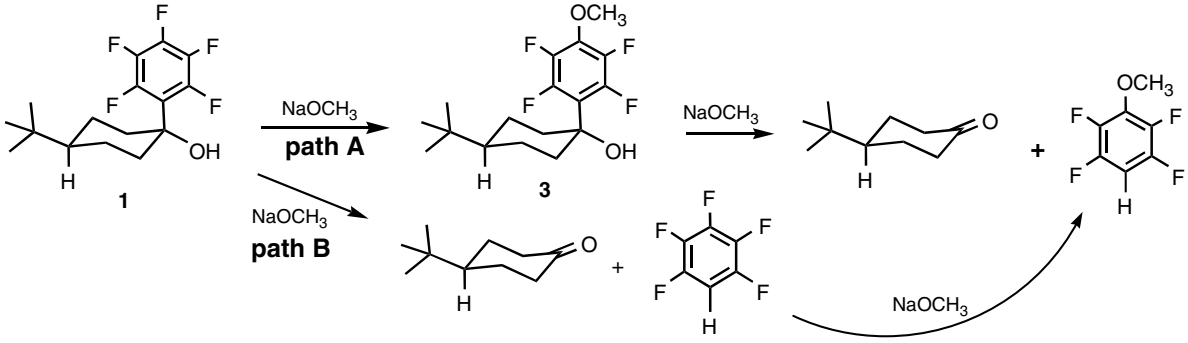


Scheme 1.



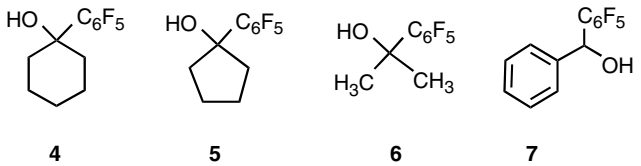
Scheme 2.



Scheme 3.

tetrafluoroanisole. Under these conditions, synthetically useful amounts (~60–70%) of substitution product **3** accumulated; methoxy substitution clearly inhibits subsequent cleavage. However, slow cleavage of compound **3** was also evident, confirmed by submitting isolated samples to the same reaction conditions.

A variety of pentafluorobenzylic alcohols (**4**–**7**, Scheme 4) were prepared to evaluate the generality of the reaction, that is, to determine whether ring size, acyclic nature, and aldehyde versus ketone products had a significant effect. These were made by the addition of pentafluorophenylmagnesium bromide[7] to the corresponding ketone or aldehyde, and all have been reported previously[8] except **5**.[9] Upon exposure to sodium methoxide in DMSO-d_6, all of these underwent rapid cleavage (100% complete in <4 min) to tetrafluoroanisole.



Scheme 4.

However, in DMSO-d_6/methanol mixtures, differences in the reactivity of the various alcohols became apparent. Conveniently slow reaction rates were obtained in 45:55 (v/v)% DMSO-d_6:CH_3OH using 0.1 M substrate and 5 equiv of sodium methoxide at 25 °C. The reactions were monitored by ^{19}F NMR to >90% disappearance of starting alcohol in all cases. The pseudo first-order plots exhibited good linearity ($r^2 \geqslant 0.98$) and an almost 10-fold difference in reactivities (Table 1). In particular, the axial aryl group in **1** makes that substrate easily the most reactive due to relief of strain resulting from the fragmentation reaction.

Table 1. Pseudo first-order kinetics for the disappearance of pentafluorobenzylic alcohols after treatment with 5 equiv of NaOMe in 45:55 (v/v)% DMSO-d_6:CH_3OH

Compound	Rate constant (min^{-1})	Linearity (r^2)	Half-life (min)
1	4.7×10^{-2}	0.978	15
2	5.1×10^{-3}	0.996	132
4	9.4×10^{-3}	0.997	74
5	7.4×10^{-3}	0.998	94
6	1.4×10^{-2}	0.989	51
7	9.4×10^{-3}	0.991	74

The mechanism of the first step in pathway B is clearly formation of the alkoxide followed by cleavage to the ketone and the pentafluorophenyl anion, the latter protonating to form the observed C_6F_5H. In theory, the pentafluorophenyl anion could re-add to the carbonyl group, and an experiment designed to test this was done. The *trans* alcohol **1** in THF was treated with butyllithium, and besides cleavage products, small amounts of the *cis* isomer **2** were observable by GC–MS. Thus, the pentafluorophenyl anion appears to be an intermediate in the cleavage.

Given the propensity for pentafluorobenzylic alkoxides to undergo cleavage, it is interesting to consider how Grignard reactions, which initially produce alkoxides, are able to produce the corresponding alcohols with any efficiency. The answer appears to involve the degree of negative charge on the alkoxide oxygen, and depends on the nature of the solvent and of the metal. As observed in our initial solvent studies, alkoxides are much more prone to cleavage in the more highly ionizing dipolar aprotic solvents rather than in the ether solvents used for Grignard reactions. Previous studies[3a] on the cleavage of alkoxides by loss of unstabilized carbanions found that DMSO promoted the reactions, and HMPT greatly so. In addition, the more covalent magnesium alkoxides are less prone to cleavage than are the more ionic sodium salts. The latter point was established by treating alcohol **2** with magnesium methoxide in DMSO; only partial cleavage (~50%) occurred in 15 min, as opposed to complete cleavage occurring almost immediately using sodium methoxide.

We have established the ease and generality of cleavage of polyfluorobenzylic alcohols, as well as conditions under which substitution without cleavage can be accomplished. Those wishing to accomplish synthetic manipulations of these types of compounds should be aware of the pertinent considerations.

Acknowledgments

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References and notes

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9. NMR ($CDCl_3$) data for compound **5**: ^1H: 1.80 (m, 2H), 1.93 (m, 2H), 2.09 (m, 3H, incl. OH), 2.36 (m, 2H). ^{13}C: 22.4, 40.4 (t, $J = 4.5$), 81.2, 119.2 (tm, $J = 63$), 137.7 (dm, $J = 238$), 138.9 (dm, $J = 240$), 145.3 (dm, $J = 242$). ^{19}F (relative to C_6H_5F at −113.26): −138.1 (approx. dd, $J = 23$, 6, 2F), −157.8 (tt, $J = 23$, 6, 1F), −163.7 (approx. td, $J = 23$, 6, 2F).