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Fluoro-substituted ketones from nitriles using acidic and basic reaction conditions

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ABSTRACT

Fluoro-substituted aliphatic nitriles are shown to undergo the Houben–Hoesch reactions with arenes in CF_3SO_3H to give fluoro-substituted ketones in good yields. The fluorine substituents appear to enhance the reactivities of the nitriles (and the nitrilium ion intermediates) compared to similar aliphatic nitriles. Fluoro-substituted ketones are also shown to be accessible through the reactions of organometallic reagents and fluoro-substituted nitriles.

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Introduction

The Houben–Hoesch reaction is an acid-catalyzed reaction of nitriles with aromatic compounds leading to aryl ketones.[1] It has previously been shown that nitriles having electron withdrawing groups can form fairly reactive electrophiles in the Houben–Hoesch reaction. This has been the basis for synthetic methodologies leading to halogen-substituted ketones,[2] aminoketones,[3] *N*-heterocyclic ketones,[3] and other products.[4] Likewise, Shudo and Ohwada have described a superacid-promoted Houben–Hoesch reaction in which dicationic species are formed and these superelectrophilic conversions are shown to give good yields of aryl ketones.[5]

Although chlorinated alkylnitriles have been shown to provide good yields of the corresponding chlorinated alkyl aryl ketones,[6] similar conversions with fluorinated alkylnitriles have not been extensively studied, the only example being the reaction of activated arenes with trifluoroacetonitrile (catalyzed by $ZnCl_2$/HCl).[7] However, α-fluorinated ketones are useful synthetic intermediates[8] and a direct route to these compounds would have significant value. Fluorine-substituted ketones are often prepared via electrophilic fluorinations and by other routes.[9,10] In the following Letter, we describe a direct route to fluorinated ketones using the Houben–Hoesch reaction and fluorinated nitriles. The superacid-promoted chemistry is also shown to compliment synthetic reactions of organometallic reagents and fluorinated nitriles.

Results and discussion

A variety of fluoro-substituted aliphatic nitriles are commercially available and convenient synthetic methods can provide ready access to these substrates.[11] For example, fluoroacetonitrile and difluoroacetonitrile were reacted with *p*-chloroanisole in the presence of CF_3SO_3H and the respective ketones (**1** and **2**) were formed in good yields (Fig. 1). A series of arenes were reacted with mono-, di-, and trifluoroacetonitrile (Table 1). With fluoroacetonitrile and benzene, α-fluorinated acetophenone (**3**) is prepared in 89% isolated yield. This result indicates that the electrophilic intermediate is fairly reactive, because a similar reaction with acetonitrile produces only a moderate amount of acetophenone. Electrophilic activation by fluorine is well known, as carbonyl

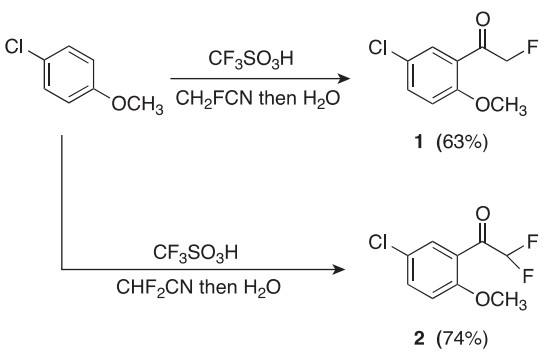

Figure 1. Superacid-promoted reactions of fluoro-substituted acetonitriles.

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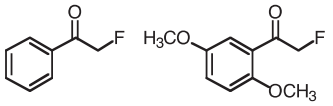
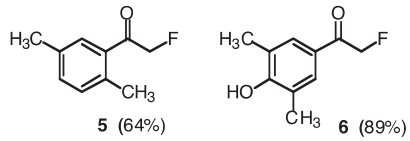
Table 1
Products and yields from the reactions of fluoro-substituted acetonitriles

Products from CH_2FCN, CF_3SO_3H, arene:

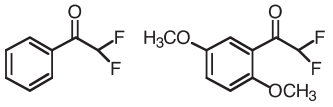


3 (89%) **4** (66%)

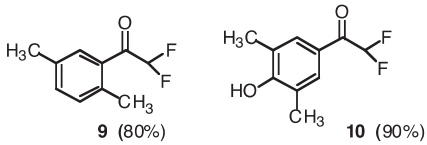


5 (64%) **6** (89%)

Products from CHF_2CN, CF_3SO_3H, arene:

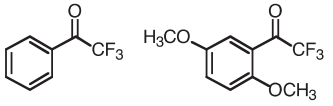


7 (91%) **8** (85%)

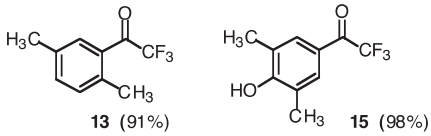


9 (80%) **10** (90%)

Products from CF_3CN, CF_3SO_3H, arene:



11 (88%) **12** (0%)

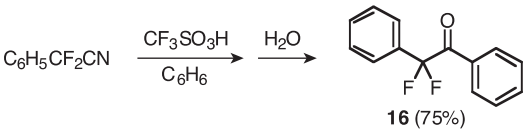


13 (91%) **15** (98%)

groups and carboxonium ions show greater electrophilic reactivities when substituted by fluorine atom(s).[12] Reactions with aryl ethers, a dialkyl-substituted benzene, and a phenol also provide the products (**4–6**) from the Houben–Hoesch reaction. Unexpectedly, the yields for these conversions are lower than that with benzene, despite the use of activated arenes (i.e., stronger nucleophiles). This may be the result of partial protonation of the activated arenes, as phenols and aryl ethers are known to be protonated in superacid.[13]

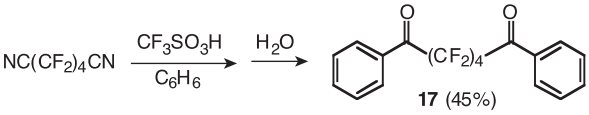
Similar reactions utilizing difluoroacetonitrile also provide the Houben–Hoesch products (**7–10**) in good yields. In general, the product yields were higher than those obtained with fluoroacetonitrile. This is likely due to enhanced electrophilic activation from the second fluorine substituent. We also examined the reactions of trifluoroacetonitrile. At room temperature, this substance is a gas so it was condensed at −78 °C and dissolved in CH_2Cl_2. The resulting solution was reacted with arenes (dissolved in CH_2Cl_2) and CF_3SO_3H at 0 °C and allowed to warm to room temperature. The conversions using trifluoroacetonitrile were generally good, producing the trifluoromethyl ketones in high yields. Although 1,4-dimethoxybenzene does provide the expected ketone product (observed in solution by GC–MS), isolation of the product leads to massive decomposition or polymerization. With the good conversion to α,α,α-trifluoroacetophenone (**11**), it is again clear that trifluoroacetonitrile forms a highly electrophilic intermediate with CF_3SO_3H. Interestingly, acetonitriles are known for their tendencies to form triazines in strong acid, but no triazines are formed with the fluoro-substituted acetonitriles.

Besides fluoro-substituted acetonitriles, several other types of nitriles gave ketone products in fair to good yields. The fluoro-substituted benzyl cyanide leads to ketone **16** (Eq 1). Although benzylic fluoro-substituents are known to form carbocations in superacid,[3a] there is no evidence for such chemistry in this system. The dinitrile (**17**) provides the 1,6-diketone from reaction with benzene in superacid (Eq 2). Houben–Hoesch



(1)

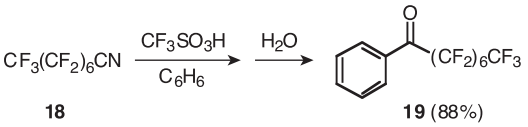
16 (75%)



(2)

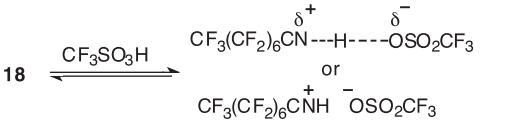
17 (45%)

reactions of aliphatic dinitriles (without fluoro-subsitituents) have been studied previously and reaction at both nitrile groups has been somewhat rare.[14] Likewise, a perfluorinated ketone (**19**) is formed from the perfluorooctanenitrile (Eq 3). This conversion is considered representative for these Houben–Hoesch reactions. Since superacid is necessary for these reactions with arenes, it suggests either partial or complete protonation of the nitrile group (Eq 4). There is evidence for diprotonated, superelectrophilic nitriles being involved in some Houben–Hoesch reactions,[5] however, such intermediates are unlikely in the present case. It is expected that the fluoro-substituents reduce that basicity of the nitrile, so diprotonation would be extremely difficult.



(3)

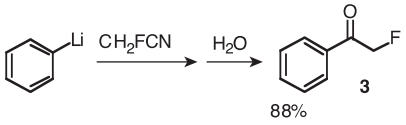
18 **19** (88%)



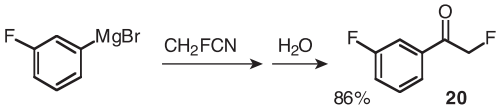
(4)

Although these Houben–Hoesch reactions have not been optimized, good yields have been obtained of the fluorine-substituted ketones. In a typical procedure, the nitrile (1 mmol) is dissolved in 1 mL of the arene nucleophile to which is added 0.5 mL of triflic acid (5.6 mmol). For solid arenes, $CHCl_3$ may be used as a co-solvent. The solution is stirred at 50 °C overnight and it is then poured over ice. The products are extracted into chloroform and isolated using standard methods. Other acids systems (H_2SO_4, CF_3CO_2H, and sulfated zirconia) were also examined in the reaction of fluoroacetonitrile with benzene, but only superacidic CF_3SO_3H provided a useful yield of the α-fluoroacetophenone. In Whalley's report of the Houben–Hoesch reaction with trifluoroacetonitrile, highly activated arenes (resorcinol and alkylated derivatives) gave the corresponding ketones from reactions with $ZnCl_2$ and HCl.[7] This suggests that weaker acids systems can effectively promote the Houben–Hoesch reaction with fluoro-substituted nitriles, but it is only effective with activated aromatic compounds. Also noteworthy, several previous studies have utilized CF_3SO_3H as an acid catalyst to give Houben–Hoesch products from activated arenes and nonfluorinated aliphatic nitriles.[15]

The superacid-promoted Houben–Hoesch reactions provide a complimentary set of products to those from organometallic reactions. For example, phenyllithium and 3-fluorophenyl-magnesium bromide provide the α-fluoroacetophenones (**3** and **20**). Product **20** is notable because it possesses *meta*-oriented

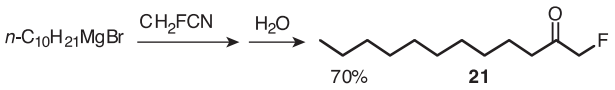


(5)

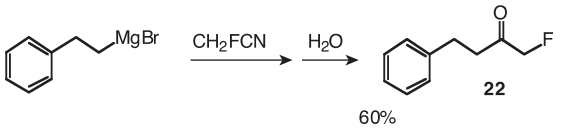


(6)

substituents, a pattern not normally accessible by electrophilic aromatic substitution. We have also found aliphatic Grignard reagents provide the fluoro-substituted ketone (**21** and **22**) in reasonable yields (Eqs. 7 and 8). Organometallic reactions with nitriles are well-known as a route to ketones of varied structures.[16] Previous studies have shown that aliphatic nitriles often require forcing conditions or hydrocarbon solvents to favor organometallic addition.[16a] However, the fluoro-substituted nitriles provide the expected ketone products without the need of unusual solvent combinations or other reagents.



(7)



(8)

Conclusion

Fluoro-substituted aliphatic nitriles have been shown to react with arenes in superacid-promoted Houben–Hoesch reactions. The reaction provides a convenient route to mono-, di-, and trifluoromethyl ketones. Two important factors appear to be involved: the superacidic CF_3SO_3H more readily forms the required nitrilium ions and the fluoro-substituents enhance the electrophilic reactivities of the nitrilium ions. The fluoro-substituted aliphatic nitriles also react efficiently with organometallic reagents to afford the fluoro-substituted ketones.[17]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.125.

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17. Some fluorinated compounds are known to be highly toxic, so work with these compounds should only be done by properly trained personnel.