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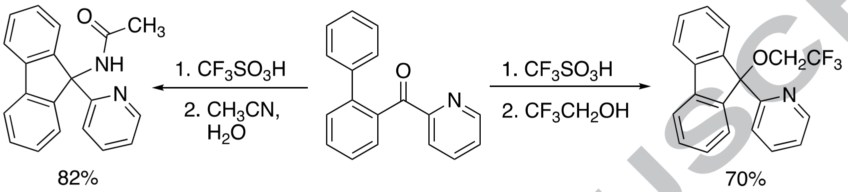

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Functionalized fluorenes *via* dicationic electrophiles

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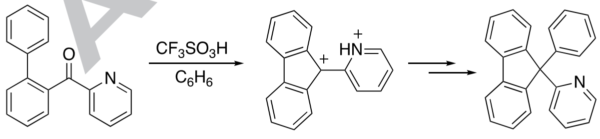
ABSTRACT

Dicationic fluorenyl cations are shown to react with nitriles to provide amide-functionalized fluorenes. A similar reaction with alcohols gives ether derivatives. The chemistry is initiated by the reactions of *N*-heterocyclic ketones in a superacidic solution. This leads to cyclizations involving 2-biphenyl groups and formation of the reactive fluorenyl cations.

Introduction

The fluorene ring system is a useful scaffold for many applications. It is a common ring system in natural products and its derivatives are frequent synthetic targets.[1,2] Its photo-physical properties make it highly useful in dyes/pigments,[3] light harvesting arrays,[4] and solar cell applications.[5] It has also been used as a building block for polymers, electronics, and material science applications.[6] Due to the broad utility of the fluorene ring system, there has been considerable interest in the development of synthetic methods leading to these compounds.[7] Recently, we described a superacid-promoted route to diarylfluorenes from aromatic ketones (Fig. 1).[8] For example, the reaction of 2-pyridyl ketone (**1**) with benzene in triflic acid (CF_3SO_3H) provides diarylfluorene (**3**) in high yield (91%). The chemistry involves formation of the superelectrophilic fluorenyl cation **2** from condensation of the 2-pyridyl ketone in the superacid. Using stable ion conditions and low temperature ^{13}C NMR, the dicationic species (**2**) was directly observed.[9] We demonstrated that the dication **2** was a useful electrophile for reactions with carbon nucleophiles such as benzene. Based on the electrophilic reactivities of **2** and related fluorenyl dications, we sought to determine if synthetic methodologies could be developed with other nucleophilic reagents. The results of these studies are presented in this letter.



1 **2** **3** 91%

Figure 1. The preparation of diarylfluorene **3**.

Results and Discussion

Our previous study showed that dicationic fluorenyl cations could be generated conveniently through the condensation of diaryl ketones in superacid.[8,9] The required ketones (**4**) have been prepared *via* two routes (Fig. 2). In one synthetic method, 2-phenylbenzonitrile is reacted with an organolithium reagent, and after hydrolytic workup, the desired ketone **4** is produced. The other approach involves generating 2-lithiobiphenyl from 2-bromobiphenyl and utilizing aldehydes to build the structure. The intermediate product alcohol is then oxidized to the ketone **4**.

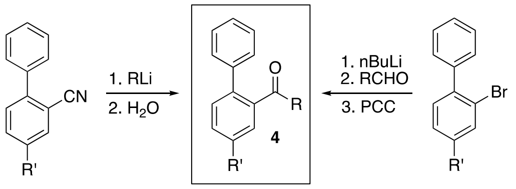


Figure 2. The synthesis of biaryl ketone substrates.

Our initial experiments sought to generate the reactive fluorenyl cations and produce amide products *via* nucleophilic reactions involving nitriles (Ritter reaction, Table 1). Using ketone **1** and acetonitrile, the expected amide-functionalized fluorene **5** was isolated in 82% yield. Optimization experiments revealed that the best conditions for generating the fluorenyl cations were in excess CF_3SO_3H (35 equiv.) at -35 °C. If more weakly acidic media is used, the diaryl ketone (**1**) is recovered unreacted in the product mixtures. These included sulfuric acid, methanesulfonic acid, trifluoroacetic acid (TFA), or mixtures of TFA and triflic acid. Thus, the heterocyclic ketone is

Table 1. Products and yields for the reactions of diaryl ketones in the Ritter reaction.

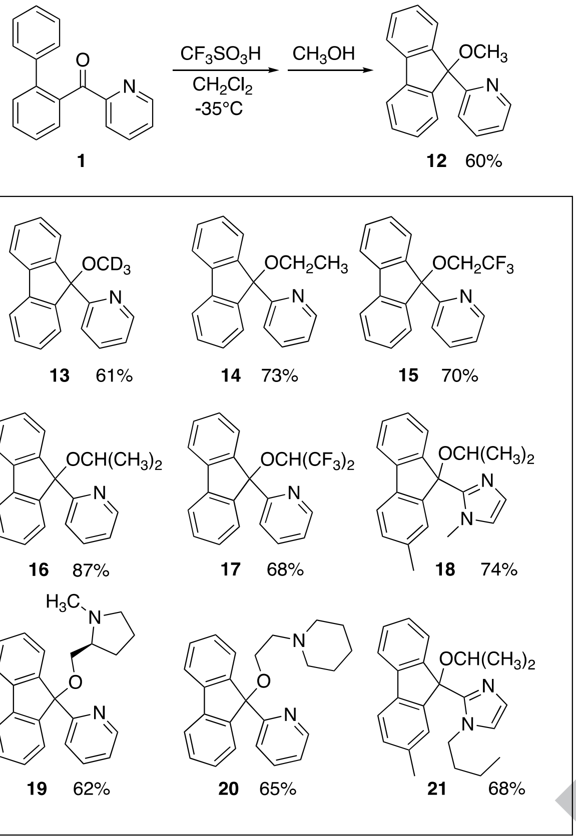
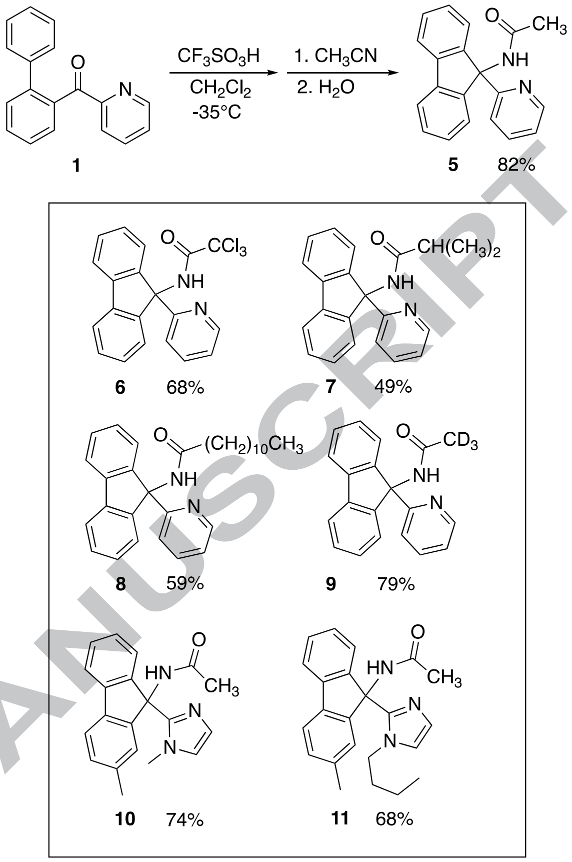


Table 2. Products and yields for the reactions of diaryl ketones with alcohols.



reacted with superacid at -35 °C followed by the addition of excess acetonitrile. Using the optimized procedure, other nitriles, such as trichloroacetonitrile, isopropylnitrile, and decylnitrile, provided the respective fluorenyl amides (**6-8**). Using deuterated acetonitrile, the corresponding amide (**9**) is isolated in good yield. With an imidazole-based ketone, the fluorenyl amides **10** and **11** are prepared. Although several efforts were made to extend the chemistry with aromatic nitrile, such as benzonitrile, the superacidic media gave large amounts of the trimeric products (i.e.- 1,3,5-triphenyltriazine).[10]

With the use of alcohols, the superelectrophilic fluorenyl dications gives ether products (Table 2). Thus, ketone **1** undergoes conversion to the fluorenyl cation (**2**) which can be trapped with methanol to provide the fluorenyl ether **12**. Similarly, the deuterated ether (**13**) is prepared from D$_4$-methanol. This procedure involves reacting the heterocyclic ketone with superacid at -35 °C followed by the addition of excess methanol to the mixture. Products **12** or **13** are then isolated by column chromatography. With the addition of ethanol or trifluoroethanol, products **14** and **15** are isolated in good yields. Isopropanol and its fluorinated derivative also provide the expected ethers (**16** and **17**) in good yields from ketone **1**. Amino alcohols are effective nucleophiles for this coupling reaction, as the amine group is readily solvated/protonated in the acid phase. Thus, the prolinol derivative provides **19** in fair yield and the piperidine derivative gives alcohol **20**. As with the Ritter reaction, the imidazole-based ketones provide ether products (**18** and **21**) in good yield from the reaction with isopropanol.

The conversions described above involve a series of dicationic intermediates (Fig. 3). In the reactions of ketone **1**, two equivalents of superacid lead to formation of the dicationic carboxonium ion **22**. The high electrophilic reactivity of the carboxonium group leads to rapid ring closure *via* an intramolecular Friedel-Crafts reaction. Proton transfer steps then provide the dicationic oxonium ion **23**. In our previous NMR studies of this system, neither dication **22** or **23** were visible by low temperature NMR in FSO$_3$H-SbF$_5$ solution – indicating that both were extremely short-lived intermediates.[9] Loss of water from **23** provides the reactive fluorenyl dication (**2**) - a cleanly formed ion, observable by NMR studies.[9] Quenching the solution with methanol leads to another oxonium dication

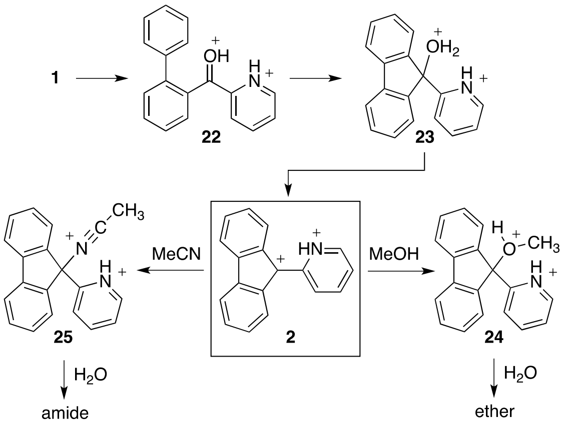


Figure 3. Proposed mechanism for the formation of amide and ether products.

(**24**). While it is conceivable that an equilibrium exists between ions **2** and **24**, this type of equilibrium likely favors the oxonium dication (**24**). Computational studies indicated that dication **2** possesses some anti-aromatic character due to electrostatic effects on the fluorenyl cation π-system.[9] This type of electronic destabilization should tend to enhance the reactivity of the fluorenyl cation towards nucleophilic attack – forcing the equilibrium toward oxonium ion **24**. In the Ritter reaction, acetonitrile reacts to form the dicationic nitrilium ion **25**. There have been reports to suggest dicationic nitrilium ions, such as **25**, may form adducts with the triflate ion.[11] Nevertheless, ion **25** or the corresponding triflate adduct provides the amide product from aqueous workup. The proposed mechanism may explain why excess superacid is needed to carry out the transformations. The high acidity is necessary to generate an appreciable concentration of the initial dicationic carboxonium ion (**22**). Moreover, the superacidity is associated with conditions of extremely low nucleophilicity.[12] This allows the fluorenyl dication (**2**) to form in high concentrations, enabling good conversions with the nitrile and alcohol nucleophiles.

Conclusion

In summary, we have found that functionalized fluorenes may be prepared by the reactions of superelectrophilic fluorenyl cations with nitrogen (nitriles) and oxygen (alcohols) nucleophiles. This work compliments our earlier study involving the S_EAr reactions of superelectrophilic fluorenyl cations and their reactions with carbon nucleophiles (arenes). The chemistry is only promoted by the use of excess triflic acid, which is necessary to generate the dicationic intermediates in this chemistry. Previously, the quantitative recycling of triflic acid has been described.[13]

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Supplementary Material

Experimental procedures, analytical data, and NMR spectra of new compounds.

Highlights:

*Functionalized fluorenes are prepared in a superacid-promoted reaction.

*Cyclization of biaryl ketones leads to reactive 9-fluorenyl carbocations.

*The 9-fluorenyl carbocations react with alcohols to give ethers and nitriles to give amides.