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Superelectrophilic chemistry of amino-nitriles and related substrates

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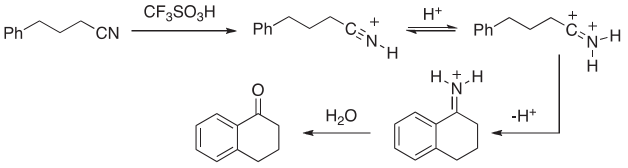
ABSTRACT

The superacid-promoted Houben/Hoesch reactions of amino-nitriles and related compounds have been studied. The nitriles form dicationic electrophiles and react with benzene in fair to good yields (12–95%). The intermediate iminium ions may also be reduced to the benzylic amines by $NaBH_4$ or H_2.

1. Introduction

The Houben/Hoesch reaction is an acid-catalyzed reaction of nitriles with aromatic compounds leading to aryl ketones.[1] It has been known for many years that the conversion works best with activated arenes (i.e., good nucleophiles) and a mechanism is proposed, which involves protonation at the nitrile nitrogen to form the nitrilium ion. Typically, nitrilium ions are only moderately electrophilic, as they are incapable of reacting with benzene or deactivated arenes (i.e., weak nucleophiles). However, Shudo and Ohwada found evidence for diprotonated, superelectrophilic species in the reactions of nitriles in Brønsted superacids (Eq. 1). Superacidic media was shown to enhance the reactivities of the nitriles toward weak nucleophiles, such as benzene. Upon hydrolysis of the iminium ion intermediates, the aryl ketones were obtained. In work with superelectrophiles, it has been shown that electrophiles may exhibit greatly enhanced reactivities when adjacent to a stable cationic center (i.e., an ammonium or pyridinium group).[3] In the following manuscript, we describe our studies of Houben/Hoesch-type reactions involving ammonium/nitrilium dications and other related superelectrophiles. We also describe our efforts to reduce the iminium ion intermediates as a direct route to benzylic amines.



(1)

2. Results and discussions

Our initial experiments examined the reactions of amino-nitriles and related substrates. For example, 3-aminopropionyl nitriles were reacted in superacidic CF_3SO_3H with benzene (Table 1, entries 1 and 2). These reactions provided the expected aryl ketones in excellent yields, following aqueous hydrolysis. This represents a new route to the Mannich base **10**, a useful intermediate in the synthesis of biologically active compounds and an analogue of kynuramine.[4,5] In the case of the secondary amine, product isolation was facilitated by conversion to its amide (**11**). The 2-aminoethanoyl nitriles also gave the desired products, however the yields were somewhat lower (entries 3–5). When product **14** was isolated, a minor biproduct was also obtained. Benzil was formed in 10% yield along with product **14**. With cyanamide (**5**), benzamide (**13**) is formed as a product, although it is isolated in just 12% yield (entry 6). Aryl nitriles were also found to give the expected diaryl ketones (entries 8–9).

When H_2SO_4 or CF_3CO_2H were used as acid catalysts, little or no product **10** was formed in the reaction of compound **1** with benzene. The stronger acid system CF_3SO_3H–SbF_5 was also used in a reaction (**1** with benzene). Although product **10** was formed, it was contaminated with significant amounts of antimony(III)triphenyl.

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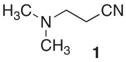
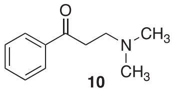
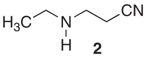
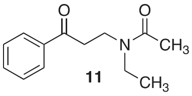
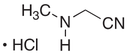
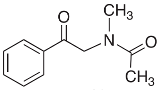
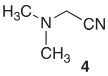
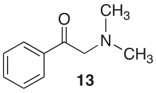
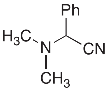
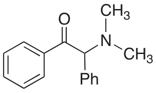
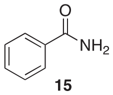
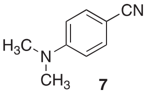
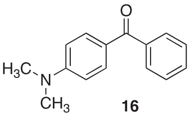
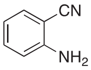
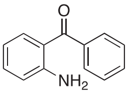
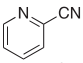
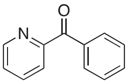
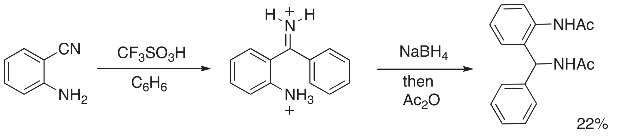
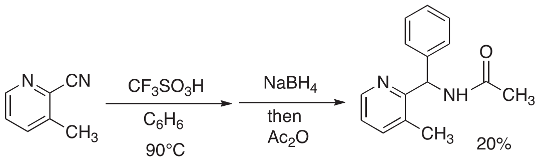
Table 1
Products and isolated yields for the reaction of compounds **1**–**9** with CF_3SO_3H and C_6H_6

Entry	Nitrile	Product	Yield %
1	 **1**	 **10**	95
2	 **2**	 **11**	98
3	 **3**	 **12**	59
4	 **4**	 **13**	44
5	 **5**	 **14**	64
6	NH_2-CN **6**	 **15**	12
7	 **7**	 **16**	70
8	 **8**	 **17**	88
9	 **9**	 **18**	25

The final step of the Houben/Hoesch reactions involves hydrolysis of the iminium ion intermediate to form the aryl ketone (Eq. 1). It is known that imines and iminium ions can be reduced to give amine-type products. For example, amines have been prepared from the nitriles and Grignard reagents via imine reduction.[6] There are no similar reports however of the reduction the Houben/Hoesch intermediates, and so we examined this as a possible route to benzylic amines. In this regard, 2-aminobenzonitrile (**8**) reacts with benzene in CF_3SO_3H to produce the iminium dication (**19**, Eq. 2). When this intermediate product is reacted with $NaBH_4$ in methanol followed by acetic anhydride, the amide product (**20**) is isolated. The same reaction sequence provides the pyridine derivative **22** in 20% yield. We have also found that the iminium ion may be reduced to the amine-type products using H_2 with Pd/C. A common impurity in these reactions is the diaryl ketone, suggesting that the dicationic iminium ions (i.e., **19**) may not be stable. Formation of the respective aryl ketones probably limits the yields for these conversions, nevertheless this Houben/Hoesch chemistry represents a direct route to the benzylic amines.

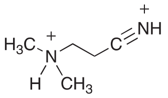


8 **19** **20** (2)



21 **22** (3)

In considering the mechanisms for these conversions, it is proposed that diprotonated superelectrophilic species are involved in the conversions. Initial protonation is expected to occur at the strong base site (amine or pyridine nitrogen). A Freidel/Crafts-type reaction with benzene requires further protonation at the nitrile group. This suggests superelectrophilic intermediates **23**–**28**. Although a second protonation at the nitrile group is conceivable, especially in light of Shudo and Ohwada's previous work (vide supra),[2] this seems unlikely due to the very high charge density on these ions (**23**–**28**). There does appear to be a correlation between reaction yields and the relative distance between charge centers. As the charge centers are in closer proximity on the diprotonated superelectrophile, the reaction yields drop off. For example, superelectrophile **23** is a 1,5-dication and it gives product **10** in 95% yield, superelectrophile **24** is a 1,4-dication and it gives product **13** in 44% yield, while superelectrophile **25** is a 1,3-dication and it gives benzamide (**15**) in just 12% yield. This trend probably reflects the relative ease by which the corresponding dications are formed in the superacid, since it is expected that the 1,4-dication would be a more powerful electrophile than the 1,5-dication. Electron-deficient nitriles are well known for their tendencies to form the triazine ring system[7] and this may also be a competing side reaction. If this is the case for cyanamide, the competing trimerization to melamine limits the yield of benzamide (**15**).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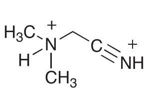
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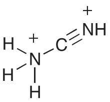
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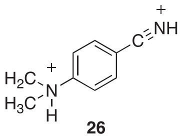
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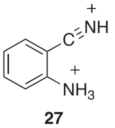
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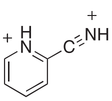
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Isomeric dications **29**–**31** were also studied by DFT calculations at the B3LYP 6-311G (d,p) level of theory and charge proximity dramatically influenced the relative stability of the ions (Fig. 1).[8] As such, the 1,5-dication (**29**) is found be 20 kcal/mol more stable than the 1,4-dication (**30**). Attempts to locate a stable minimum for dication **31** were not successful.

NMR experiments were also done to characterize the intermediates formed from the amino-nitriles in acidic media. Compounds **1**, **4**, **9**, and dimethylcyanamide (**32**) were studied in solutions of increasing acidity (Table 2). Both compounds **1** and **4**