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Superelectrophilic chemistry of amino-nitriles and related substrates

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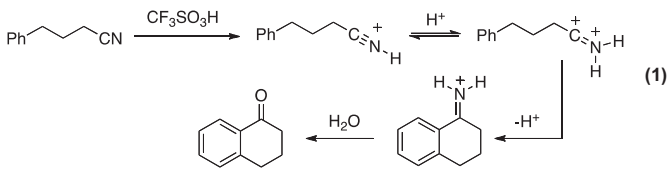
ABSTRACT

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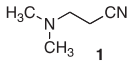
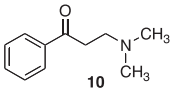
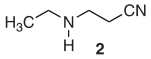
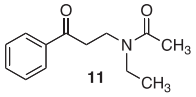
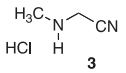
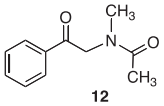
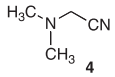
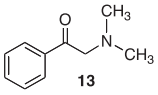
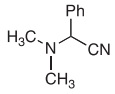
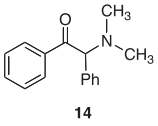
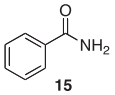
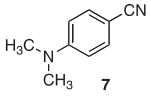
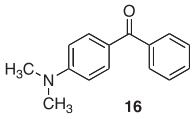
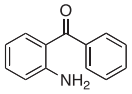
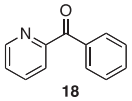
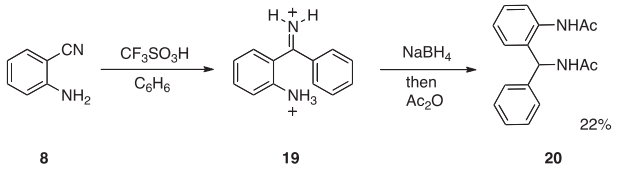
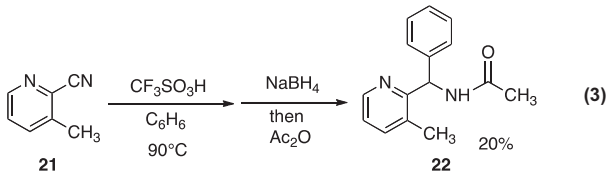
Table 1
Products and isolated yields for the reaction of compounds **1**–**9** with CF_3SO_3H and C_6H_6

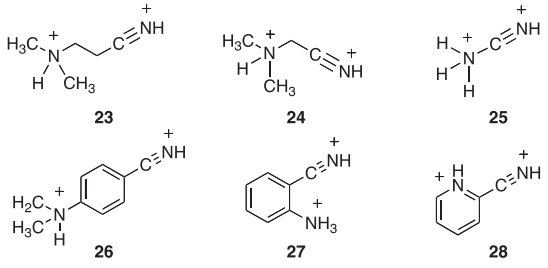
Entry	Nitrile	Product	Yield %
1	 **1**	 **10**	95
2	 **2**	 **11**	98
3	 **3**	 **12**	59
4	 **4**	 **13**	44
5	 **5**	 **14**	64
6	NH_2-CN **6**	 **15**	12
7	 **7**	 **16**	70
8	 **8**	 **17**	88
9	 **9**	 **18**	25

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.





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**).



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**

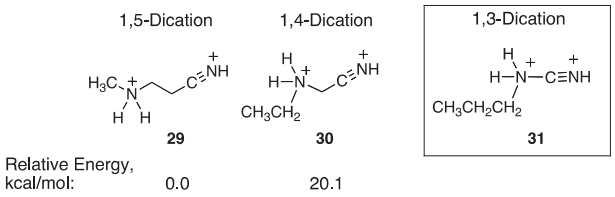
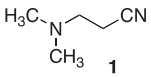
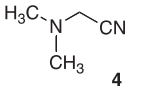
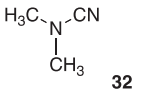
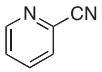
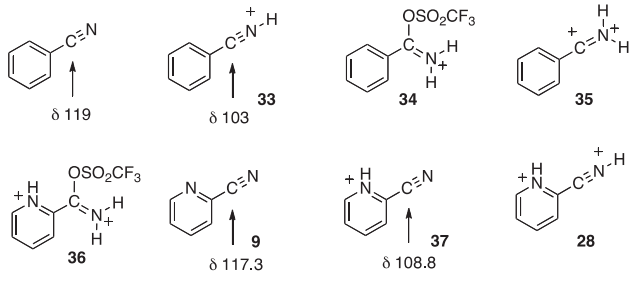


Fig. 1. Calculated relative energies for superelectrophiles **29** and **30**.

Table 2
^{13}C NMR data for compounds **1**, **4**, **30**, and **9** in solutions of varying acidity (analyses done at 25 °C, except CF_3SO_3H samples, which were done at −30 °C)

Substrate	Solvent	^{13}C NMR signals
 **1**	$CDCl_3$	16.2, 45.0, 54.5, 118.7
	CF_3CO_2H	12.5, 42.8, 52.4, 113.8
	CF_3SO_3H	12.6, 43.0, 51.4, 110.8
 **4**	$CDCl_3$	44.0, 47.3, 114.5
	CF_3CO_2H	43.1, 44.3, 108.4
	CF_3SO_3H	43.7, 44.5, 107.2
 **32**	$CDCl_3$	40.3, 119.2
	CF_3CO_2H	35.1, 158.5
	CF_3SO_3H	a. 39.3, 133.1
		b. 41.2, 144.0
 **9**	$CDCl_3$	117.3, 127.2, 128.6, 133.9, 137.3, 151.2
	CF_3CO_2H	108.8, 123.2, 130.3, 131.7, 144.3, 147.3
	CF_3SO_3H	109.2, 122.3, 130.8, 132.3, 144.2, 148.3

show similar trends in the ^{13}C NMR spectra. In CF_3CO_2H solution (H_o −2.7), compounds **1** and **4** exhibit significant shifts for the methyl groups and the nitrile carbons. This is a consequence of the amine group being protonated by the CF_3CO_2H. When the compounds are dissolved in superacidic CF_3SO_3H (H_o −14.1), the nitrile carbons are shifted further upfield. This shift of the ^{13}C resonances is likely due to protonation of the nitrile and formation of the nitrilium ion. Interestingly, compound **1** shows a change of chemical shift for the nitrile carbon of 3.0 ppm in CF_3SO_3H versus CF_3CO_2H, while compound **4** shows a change of just 1.2 ppm for the nitrile carbon. This may suggest a greater degree of protonation for compound **1** in the superacid compared to compound **4**. Dimethylcyanamide (**32**) was also studied in these acidic solutions, however the data suggests rapid conversion to the triazine. When compound **32** is dissolved in CF_3SO_3H, two sets of peaks are observed. Although the peaks cannot be definitively assigned, it is likely that they are from protonated triazine species. Compound **9** exhibits a fairly significant shift of the nitrile ^{13}C resonance in CF_3CO_2H solution (δ 108.8) compared to $CDCl_3$ solution (δ 117.3).



When compound **9** was dissolved in CF_3SO_3H, the ^{13}C spectrum suggested an equilibrium between two major components (see Supplementary data). With the complexity of this spectrum, it was difficult to make peak assignments. Another sample was prepared with FSO_3H, a slightly stronger superacid (H_o −15.1).[9] The resulting ^{13}C spectrum had six major resonances (Table 2). Five small peaks (from a minor component of the equilibrium) were also visible in the spectrum: δ, 127.7, 132.7, 134.0, 144.2, 148.8, and 163.7.

There is very little published ^{13}C NMR data for nitrilium ions.[10] Shudo and Ohwada have reported that *N*-protonated benzonitrile (**33**) exhibits a ^{13}C NMR resonance at 103 ppm for the nitrilium carbon, shifted upfield from benzonitrile itself (119 ppm).[2] This is consistent with the results from compounds **1** and **4**, where increasing levels of acidity shift the nitrile resonance upfield. This again suggests formation of the superelectrophilic, dicationic species **23** and **24** in CF_3SO_3H. Interestingly, the earlier studies also found evidence for the formation of a triflate adduct (**34**) from benzonitrile.[2b] In our study of compound **9**, we observed a complex ^{13}C spectrum from CF_3SO_3H, including two triflate quartets. These observations are consistent with the formation of the triflate adduct **36**. In FSO_3H solution, compound **9** appears to form mainly the monocationic species **37**. There is very little change in the ^{13}C spectra from CF_3CO_2H and FSO_3H solutions, suggesting that the superelectrophile **28** is formed in low concentration in superacid. The minor component of the equilibrium is assumed to a fluorosulfonate adduct. With the CF_3SO_3H solutions of compounds **1**, **4**, and **32**, the ^{13}C spectra showed no evidence for the triflate adducts.

As described in the Shudo and Ohwada's study, there is evidence for the involvement of diprotonated, superelectrophilic species (i.e., **35**) in the superacid-promoted Houben/Hoesch reaction.[2] Superelectrophile **35** is formed by double protonation at the nitrile group of benzonitrile and it is capable of reacting with the weak nucleophile benzene. In our results, the dicationic electrophiles are generated by protonation at a strong base site followed by protonation at the nitrile group. These superelectrophiles exhibit similar, or in some cases enhanced, reactivities compared to dications, such as **35**. For example, it was reported that benzonitrile reacts with benzene in CF_3SO_3H to give benzophenone in 14% yield.[2b] Similar conversions involving superelectrophiles **26**–**28** give diaryl ketones in yields ranging from 25 to 70% (Table 1).

3. Conclusion

In summary, we have found that amino-nitriles and related substrates may be effective reagents in the superacid-promoted Houben/Hoesch reaction. With 3-aminopropionyl nitriles, this represents a new method for preparing Mannich base-type products. Reactivity trends and NMR data indicate that dicationic superelectrophiles are involved in these transformations. Moreover, we have found that the iminium ion intermediates may be directly reduced to amine-type products in a one-pot conversion.

4. Experimental section

4.1. General methods

Trifluoromethanesulfonic acid was freshly distilled prior to use. Reagents and solvents were obtained from commercial suppliers and used as received. Reactions were performed using oven-dried glassware with an argon atmosphere. Low resolution mass spectra were obtained from a commercial GC equipped with a mass selective detector. High resolution mass spectra were obtained from an external analytical services lab. All products were characterized by ^1H and ^{13}C NMR and mass spectroscopic methods. Known compounds exhibited spectral data consistent with those reported in the literature.

4.2. General preparation of the ketones

The amino-nitrile (1 mmol) is dissolved in dry CH_2Cl_2 (5 mL) to which is added benzene (2 mL). With stirring, triflic acid (2 mL) is then slowly added and the reaction mixture is stirred overnight at 60–80 °C. The mixture is then quenched by pouring the solution over ice/water. The aqueous solution is then made basic by slow addition of 10 M NaOH and the solution is extracted twice with chloroform. The organic layer is washed with water, brine (2×20 mL) and dried over anhydrous sodium sulfate. In the event that imine/ketone mixtures are obtained, it may be necessary to stir the triflic acid/ice/water mixture for few hours in order to ensure complete hydrolysis. The products are purified via column chromatography (silica gel; hexanes/ether).

4.3. General preparation of the amides

Using the same procedure, the triflic acid-promoted reaction is conducted and then the mixture is cooled in an ice bath and a methanolic solution (10 mL) of $NaBH_4$ (5 mmol) is added (argon atmosphere). The solution is left to stir overnight at room temperature. The mixture is then poured over ice/water and made basic by slow addition of 10 M NaOH. The solution is extracted twice with chloroform. The organic layer is washed with water, brine (2×20 mL) and dried over anhydrous sodium sulfate. The amine is further acylated by direct addition of acetic anhydride (1 mmol). The products are purified via column chromatography (silica gel; hexanes/ether).

4.3.1. N-Ethyl-N-(3-oxo-3-phenylpropyl)acetamide ***11***. Yield 98% as a viscous, yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz; mixture of cis/trans isomers) minor component: δ 1.12 (t, 3H, J=4.2 Hz), 2.12 (s, 3H), 3.25 (t, 3H, J=4.2 Hz), 3.40 (q, 2H, J=4.2 Hz), 3.73 (t, 3H, J=4.2 Hz), 7.45–7.49 (m, 2H), 7.56–7.60 (m, 1H), 7.92–7.94 (m, 2H); major component: δ 1.18 (t, 3H, J=4.2 Hz), 2.07 (s, 3H), 3.30 (t, 3H, J=4.2 Hz), 3.37 (q, 2H, J=4.2 Hz), 3.68 (t, 3H, J=4.2 Hz), 7.42–7.45 (m, 2H), 7.53–7.56 (m, 1H), 7.95–7.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz; mixture of cis/trans isomers) minor component: δ 12.9, 21.5, 37.4, 40.4, 43.3, 127.9, 128.8, 133.4, 136.5, 170.4, 197.8; major component: δ 14.1, 21.4, 37.3, 42.0, 44.5, 128.1, 128.6, 133.3, 136.7, 170.6, 199.2. Low resolution mass spectrum (EI) m/z: 219 (M^+), 176, 105, 77, 58. High resolution mass spectrum, calcd for $C_{13}H_{17}O_2N$, 219.12593, found 219.12710.

4.3.2. N-(2-(Acetamido(phenyl)methyl)phenyl)acetamide ***20***. Yield 22% as a light yellow solid, mp: 178–180 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.16 (s, 3H), 2.24 (s, 3H), 2.54 (s, 1H), 6.61 (d, 1H, J=9.5 Hz), 6.98–7.00 (m, 2H), 7.08 (t, 1H, J=7.5 Hz), 7.30–7.45 (m, 4H), 7.95 (d, 1H, J=8 Hz), 9.16 (s, 1H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 23.2, 24.2, 51.5, 124.9, 125.2, 126.3, 126.9, 127.6, 128.5, 128.7, 128.8, 133.8, 134.8, 136.3, 139.4, 169.7, 170.9. Low resolution mass spectrum (EI) m/z: 283 (M^+), 264, 239, 222, 197, 180, 164, 145, 119, 104, 77, 62, 43. High resolution mass spectrum, calcd for $C_{17}H_{18}O_2N_2$, 282.13683, found 282.13759.

4.3.3. N-((3-Methylpyridin-2-yl)(phenyl)methyl)acetamide ***22***. Yield 20% as a viscous, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.07 (s, 3H), 2.26 (s, 3H), 6.34 (d, 1H, J=8 Hz), 7.19–7.26 (m, 2H), 7.29–7.34 (m, 2H), 7.48 (dd, 1H, J=0.5, 7.5 Hz), 7.91 (d, 1H, J=7 Hz), 8.48 (dd, 1H, J=1.0, 5.0 Hz). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 18.2, 23.5, 53.8, 122.7, 127.5, 128.2, 128.5, 131.3, 138.9, 140.6, 145.7, 156.6, 169.1. Low resolution mass spectrum (EI): m/z: 240 (M^+), 197, 181, 147, 106, 43. Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 72.72; H, 6.82; N, 10.79.

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Supplementary data

Computational methods and results, characterization data, and spectra of compounds are associated with this article as supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.04.038.

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