I. The Reaction of Carboxylic/Thiocarboxylic Acids with Isonitriles

II. Ruthenium Hydride Ring Opening of an Azetidinium Cation

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ABSTRACT

I. The Reaction of Carboxylic/Thiocarboxylic Acids with Isonitriles

II. Ruthenium Hydride Ring Opening of an Azetidinium Cation

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The mechanism of the reaction of benzoic acid with cyclohexyl isonitrile leading to *N*-cyclohexyl-*N*-formylbenzamide has been studied quantitatively. The reaction is first order in each reagent and has the activation parameters $\Delta H^{\ddagger}$ = 16.9(5) kcal mol^{-1} and $\Delta S^{\ddagger}$ = −26(1) cal mol^{-1}K^{-1} in toluene. There is a dramatic solvent effect: hydrogen bond accepting solvents retard the rate of the reaction by deactivation of the carboxylic acid. A plot of log(rate constant) vs β (hydrogen bond acceptor basicity of the solvent) is a straight line with a substantial negative slope, implying that the reaction is retarded by hydrogen bonding to the solvent but not affected significantly by other solvent properties. It is speculated that the related Passerini reaction is affected in a similar matter, although quantitative data for this reaction are sparse in the literature.

Variation of concentrations allows control over the product distribution in the reaction of carboxylic acids and isonitriles. With low concentrations of the acid, the *N*-formylamide is obtained in good yield because low concentrations suppress the nucleophilic interception of the intermediate formimidate carboxylate mixed anhydrides (FCMAs), which leads to the undesired anhydride and formamide.

With arylacetic acids, *N*-formylamides (the products of a unimolecular process) are obtained with low concentrations of the reactants and high reaction temperatures. At

low temperatures and high concentrations, captodative alkenes (the products of a bimolecular process) are obtained instead.

In contrast to the high temperatures needed for RNC + RCO_2H → *N*-formylamide, thioacids react at ambient temperature with isonitriles to give *N*-thioformylamides. Transient intermediates can be observed during the reaction. Two thio-analogues of the FCMA are suggested by NMR spectral evidence. However, the structure of a third intermediate (which forms more slowly than the other two) remains unknown. Several mechanisms for this reaction are kinetically indistinguishable because the three intermediates interchange more rapidly than the product-forming step (which is irreversible). The solvent effect observed with carboxylic acids is not observed with thioacids, presumably because of the weaker hydrogen bond donating strength of the S−H in the thioacid.

The mechanism and temperature dependence of the hydride ring opening of a phenyl azetidinium cation has been studied. The reaction with CpRu(dppm)H (dppm = bis(diphenylphosphino)methane) is first order in both the hydride and the azetidinium. Extrapolation of the rate constant to −64 °C (the temperature at which an analogous aziridinium ring opening was previously examined) shows that aziridiniums undergo hydride ring opening $10^6 - 10^7$ times faster. This result implies that aziridiniums are much more electrophilic than azetidiniums, although these two rings have a strain energy difference of only 2.1 kcal mol^{-1}.

Nucleophilic attack on azetidiniums generally occurs at the less substituted position in accords with an S_N2 mechanism. However, with a phenyl substituent, hydride transfer by half-sandwich ruthenium complexes occurs preferentially at the more

substituted position (*ca.* 5:1) giving the straight-chain amine. More reactive hydrides (borohydrides, $LiAlH_4$) erode this preference.

As is the case with electrophilicity, there is a significant difference in the reduction potential between a phenyl aziridinium (E_{pc} = −0.93 V vs FcH^+/FcH) and a phenyl azetidinium (E_{pc} = −1.43 V). While the phenyl aziridinium has been previously shown to undergo single electron reduction by Cp*Ru(dppf)H ($E_{1/2}$ = −0.63 V, dppf = 1,1'-bis(diphenylphosphino)ferrocene), the phenyl azetidinium failed to react with the same reagent. The azetidinium did react with decamethylcobaltocene ($E_{1/2}$ = −1.94 V) giving the expected straight-chain ring-opened amine among a mixture of products; none of the branched amine was detected.

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Chapter 5: Ruthenium Hydride Ring Opening of an Azetidinium Cation

LIST OF ABBREVIATIONS

Bn	benzyl
n-Bu	normal butyl
CCl_4	carbon tetrachloride
$CDCl_3$	deuterated chloroform
CD_2Cl_2	deuterated dichloromethane
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
CI^+	chemical ionization
ClO_4^-	perchlorate
COSY	correlation spectroscopy
Cp	η^5-cyclopentadienyl
Cp*	η^5-pentamethylcyclopentadienyl
CV	cyclic voltammetry
Cy	cyclohexyl
d	day
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DIPA	diisopropylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-d_6	deuterated dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppm	1,1-bis(diphenylphosphino)methane
dppf	1,1'-bis(diphenylphosphino)ferrocene
E	electron withdrawing group
EDG	electron donating group
EWG	electron withdrawing group
EPR	electron paramagnetic resonance
equiv	equivalent
ESR	electron spin resonance
Et	ethyl
Et_3N	triethylamine
EtOH	ethanol
FAB	fast atom bombardment
FcH	ferrocene
FcH^+	ferrocenium
FcH^+/FcH	ferrocenium/ferrocene redox couple
FCMA	formimidate carboxylate mixed anhydride

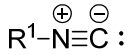
h	hour
HCl	hydrochloric acid
HMBC	heteronuclear multiple bond correlation
HMCTS	hexamethylcyclotrisiloxane
HOBt	hydroxybenzotriazole
HSQC	heteronuclear single quantum coherence
IR	infrared
J	coupling constant
K	equilibrium constant
k	rate constant
LAH	lithium aluminum hydride
$LiAlH_4$	lithium aluminum hydride
LDA	lithium diisopropylamide
LRMS	low resolution mass spectroscopy
M	molarity (molar)
*m*CPBA	meta-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
$Me\text{-}NO_2$	nitromethane
MeOH	methanol
metallo-FCMA	metallo-analogue of FCMA
min	minute
mV	millivolt
$NaBH_4$	sodium borohydride
NaCl	sodium chloride
NaOH	sodium hydroxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
OMe	methoxy
OTf	trifluoromethanesulfonate
Ph	phenyl
$POCl_3$	phosphorus oxychloride
PPh_3	triphenylphosphine
P−P	a chelating bisphosphine ligand

RCN	nitrile
RCO_2H	carboxylic acid
RNC	isonitrile
RNHCHO	formamide
s	second
T_1	spin-lattice relaxation time
t-Bu	tertiary butyl
TCE	1,1,2,2-tetrachloroethane
TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
thio-FCMA	thio-analogue of FCMA
TLC	thin layered chromatography
TMS	tetramethylsilane
tol-d_8	deuterated toluene
V	volt

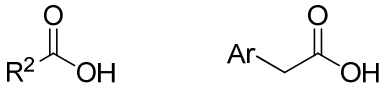
LIST OF COMPOUND NUMBERS AND NUMBERING SCHEME

Part I The Reaction of Carboxylic/Thiocarboxylic Acids with Isonitriles

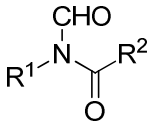
1 isonitrile



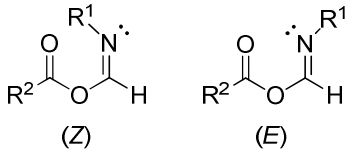
2 carboxylic acid



3 *N*-formylamide

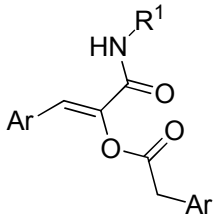


4 formimidate carboxylate mixed anhydride (FCMA, an isoimide)

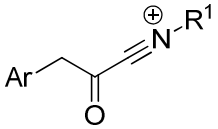


(*Z*) (*E*)

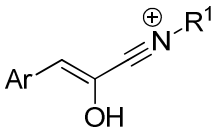
5 (*Z*)-captodative alkene



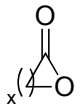
6 intermediate shown below



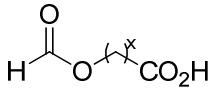
7 intermediate shown below



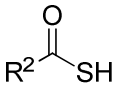
8 lactone



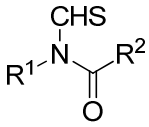
9 formate ester/acid



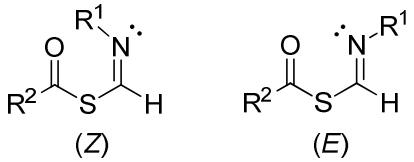
10 thioacid



11 *N*-thioformylamide

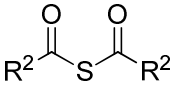


12 thio-analogue of FCMA (thio-FCMA)

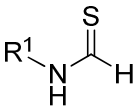


(*Z*) (*E*)

13 thioanhydride = anhydrosulfide



14 thioformamide



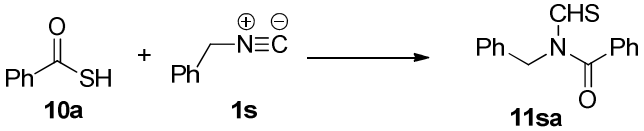
15 unidentified intermediate 3 in the reaction of **1** + **10**

Compounds **3**, **4**, **5**, **11**, **12**, **13**, **14**, and **15** are numbered as:

$\#_{xy}$

x = isonitrile substituent
y = acid substituent

Ex:

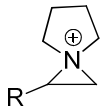


10a **1s** **11sa**

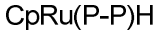
Part II

Chapter 5: Ruthenium Hydride Ring Opening of an Azetidinium Cation

1 aziridinium cation



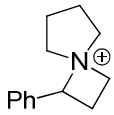
2 half-sandwich ruthenium hydride complex



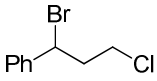
3 metal hydride radical cation complex

4 metal dihydride cation complex

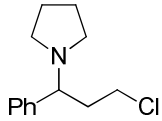
5a azetidinium cation



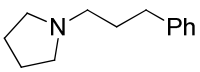
6a synthetic intermediate shown below



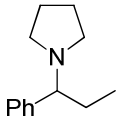
7a synthetic intermediate shown below



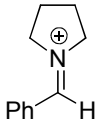
8a straight chain product amine



9a branched product amine



10a imminium cation



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Part I

The Reaction of Carboxylic/Thiocarboxylic Acids with Isonitriles

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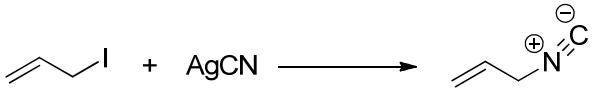
Chapter 1

Properties, Synthesis and Reactivity of Isonitriles

A brief overview of isonitrile chemistry will be provided followed by a description of the synthesis of the isonitriles used in later chapters.

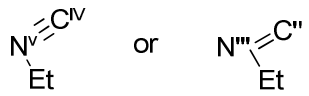
1.1 Discovery and Structure of Isonitriles

Isonitriles[1] were first synthesized by Meyer (1856) and Lieke (1859), although they did not recognize them as such, believing they had produced the isomeric nitriles in the reaction of silver cyanide with halides such as allyl iodide (eq 1).[2] They did note an overwhelming pungent odor which forced Lieke to work outdoors. The characteristic foul odor would be a discussion point for many early encounters with isonitriles.[2-3]

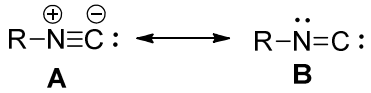


(1)

Gautier was the first to deduce the actual isomeric relationship between isonitriles and nitriles,[4] proposing the two structures in eq 2 which are similar to the modern day resonance structure representations of isonitriles (eq 3).



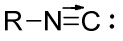
(2)



(3)

Resonance structure **A** was originally proposed[5] by Lindemann and Wiegrebe, shortly after Langmuir suggested that each atom in carbon monoxide obeys the octet

rule.[6] The NC stretching frequencies of isonitriles are closer to that of nitriles than those of imines[7] (see Section 1.5), suggesting a greater contribution from structure **A**. Furthermore, the intensity of the IR band is greater in isonitriles than those of the corresponding nitriles, suggesting a large polarization of the NC bond.[8] Dipole moment measurements demonstrate negative polarization toward the isocyano carbon, as expected from **A** but not from **B**.[9] Electron diffraction, electron spin resonance and microwave studies have unambiguously found that the C-N-C linkage in isonitriles is linear and that the C-N bond length in isonitriles is less than 0.02 Å longer than that in the corresponding nitriles.[9f, 10] Hydrogen bonding studies have demonstrated interaction with the isocyano carbon only and not with the nitrogen, further supporting a greater contribution from **A**.[11] However, recent modern Valence Bond calculations[12] have found **B**, the structure favored by Nef due to reactivity,[13] to be the major contributor.[14] These authors reconcile their calculations and the previous experimental data by suggesting the representation in eq 4, which was originally used by Ugi,[15] as the best description of an isonitrile. Double bond character has been inferred from bending frequencies,[16] while the force constant of isonitriles has been measured to be somewhat smaller than that in the corresponding nitriles.[17]



(4)

Old literature suggests that isonitriles have surprisingly low toxicity in mammals ("oral and subcutaneous doses of 500-5000 mg/kg can be tolerated by mice").[18]

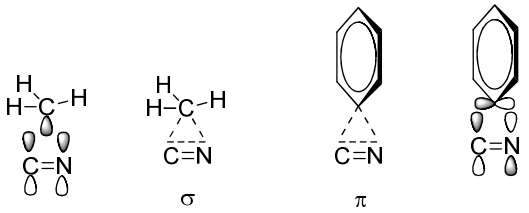
1.2 Stability of Isonitriles

Isonitriles irreversibly isomerize to the more stable nitriles above 180 °C, as shown in eq 5.[19]

$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{C} \xrightarrow{\Delta} R-C\equiv N \qquad (5)$$

The mechanism of the rearrangement is thought to be internal substituent migration to the isocyano carbon, similar to the migrations in the Beckmann[20] and in the Wolff[21] rearrangements. The transition states shown in Figure 1.1 have been suggested by experiments[22] and calculations[23] for aliphatic and aromatic isonitriles, respectively. The rearrangement of *p*-tolylisonitrile to only *p*-tolunitrile, without the formation of any ortho- or meta- isomers, supports the intramolecular mechanism.[24] Furthermore, optically active isonitriles have been shown to rearrange with retention of configuration; secondary alkyls, such as that in cyclobutylisonitrile, do not undergo Wagner-Meerwin type rearrangements[25] during isomerization. Both results imply synchronous bond-breaking and bond-forming in the transition state.[22a, 22e, 22h-j] The isomerization has also been induced by radical initiators and UV radiation.[26]

Figure 1.1 The transition state of isonitrile isomerization.



Silyl isonitriles exist at room temperature in an equilibrium with their nitrile isomer (eq 6). The nitrile isomer is still thermodynamically favored.[27]

$$R_3Si-\overset{\oplus}{N}\equiv\overset{\ominus}{C} \rightleftharpoons R_3Si-C\equiv N \qquad (6)$$

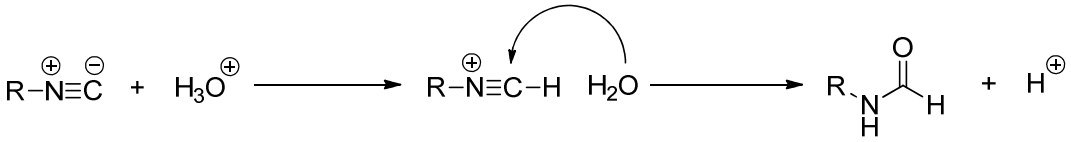
Isonitriles oligomerize even near room temperature, an observation made in the early days of their investigation.[13a, 19a, 28] Oligomerizations can be induced by Lewis acids,[29] and several controlled polymerization methods have been disclosed.[30] The

present author has found that filtration of isonitriles as a toluene or dichloromethane solution through a plug of oven-dried silica gel (about 0.5 inches in a 5 inch glass pipette) effectively removes the resins that form during storage.

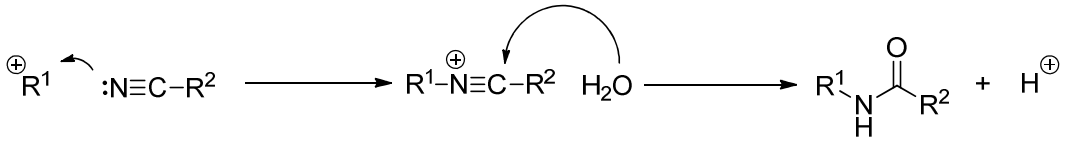
1.3 Acid-Base Chemistry of Isonitriles

The only quantitative data regarding the basicity of the isocyano carbon is from Sung and Chen, who measured the pK_a of cyclohexylnitrilium ion (0.86, water, 26 °C).[31] It is not surprising that isonitriles react with strong acids, forming formamides in accord with the mechanism in Scheme 1.1,[31-32] analogous to the Ritter reaction, Scheme 1.2.[33] Formamides were first obtained by Lieke when he attempted to hydrolyze what he believed were nitriles.[2a]

Scheme 1.1 The mechanism of acid catalyzed hydrolysis of isonitriles.

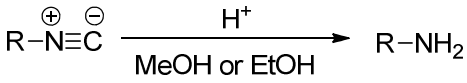


Scheme 1.2 The mechanism of the Ritter reaction.



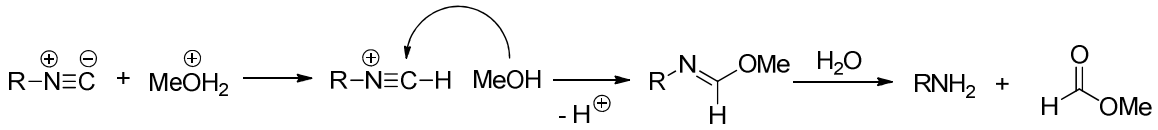
There is a mechanistically uncertain but well precedented transformation of isonitriles to amines in acidic alcohol solutions (eq 7).[28a, 34] The present author proposes the mechanism in Scheme 1.3, where protonation of the isonitrile is followed by nucleophilic attack by the alcohol. The resulting formimidate should be susceptible to hydrolysis by adventitious water. Although there have been no reports of the required formate byproduct, the latter may have been lost during workup or an evaporation step.

This reaction has recently been applied to the development of a polymer-supported *p*-toluenesulfonic acid as an isonitrile scavenger.[35]

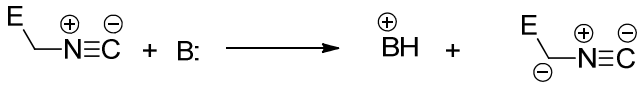


(7)

Scheme 1.3 Proposed mechanism for acid alcoholysis of isonitriles.



In contrast, isonitriles are generally stable to base and are often synthesized under basic conditions. Notable exceptions are isonitriles containing α-protons flanked with electron-withdrawing substituents, such as a sulfonyl, amido or carboxy functionality (eq 8), which increase stabilization of the anionic charge. Bases as weak as diisopropylamine induce racemization of these isonitriles.[36]



(8)

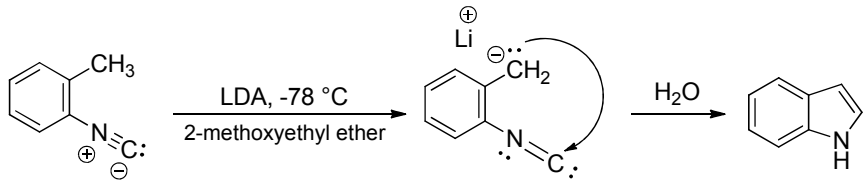
1.4 Reactivity of Isonitriles in Organic Chemistry

In their first 100 years of existence, there was little exploration of the chemistry of isonitriles due to their repulsive odors and the lack of a reliable synthesis. With the advent of modern ventilation and robust synthetic routes (see Section 1.6), interest in isonitriles synthetically has been engendered by the diverse reactivity of the formally divalent carbon; the isocyano carbon can react as either an electrophile or a nucleophile, depending on the reaction conditions.

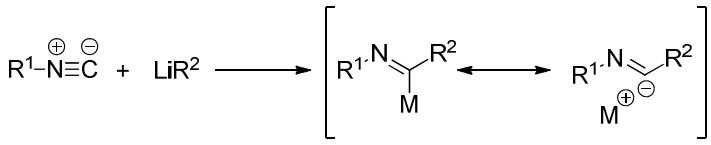
Isonitriles can react as electrophiles in the presence of powerful nucleophiles.[37] For example, Saegusa and co-workers developed an efficient synthesis of indoles using

nucleophilic attack onto the isocyano carbon by ortho-alkyl lithiated phenyl isonitriles (Scheme 1.4).[38]

Scheme 1.4 Saegusa's indole synthesis via nucleophilic attack on the carbon of an isonitrile.



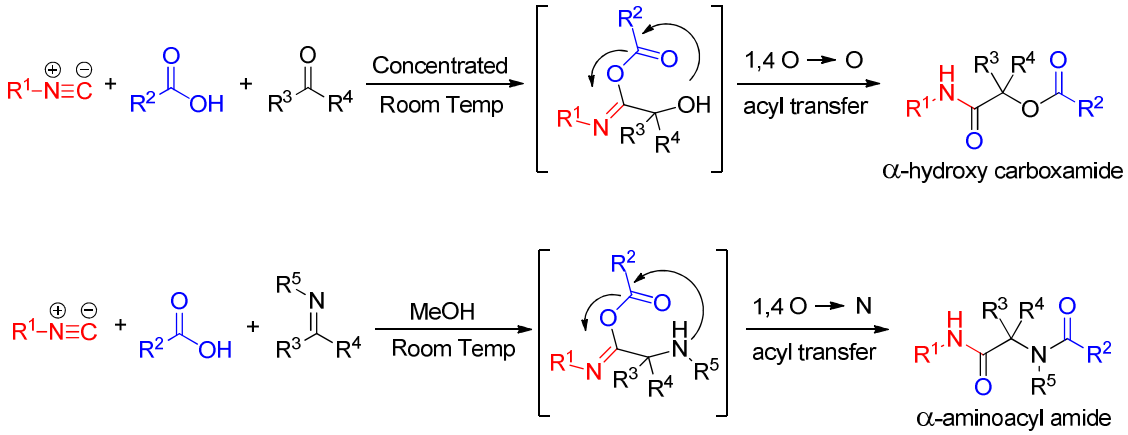
Isonitriles can be metalated by silylstannanes[39], Grignard reagents[40] and organolithiums[41] (eq 9), yielding acyl anion equivalents.[42] Some isonitriles, such as methyl, allyl, benzyl or others containing acidic α-hydrogens, are metalated on the alkyl group instead.[43]



(9)

The Passerini and Ugi multicomponent reactions, Scheme 1.5, offer classic examples of isonitriles reacting as nucleophiles.[44]

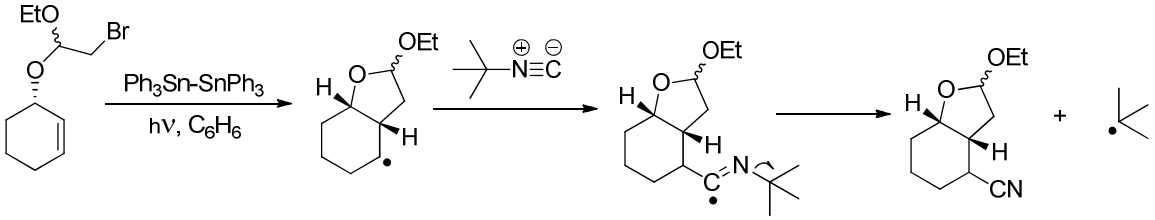
Scheme 1.5 The Passerini (top) and Ugi (bottom) multicomponent reactions.



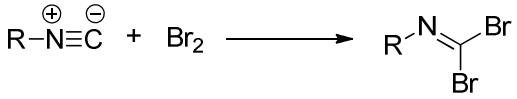
Mayr and co-workers have quantified the nucleophilicity of isonitriles.[45] They demonstrated that the range of isonitrile nucleophilicity spans just two orders of magnitude, with the most nucleophilic isonitriles (*t*-Bu, Bn, xylyl) being comparable to pyrroles, allylsilanes and silyl enol ethers, while the least nucleophilic isonitriles (4-cyanophenyl and tosylmethyl) are comparable to furans. Free cyanide ion is 10−13 logarithmic units more nucleophilic than isonitriles.[46]

The isocyano carbon is also susceptible to radical addition.[26c, 47] For example, Stork has trapped bromo-acetal radical cyclization adducts with *t*-butyl isonitrile to form target cyclic nitriles (Scheme 1.6).[48]

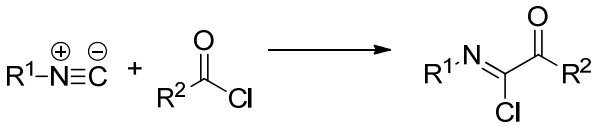
Scheme 1.6 Stork's radical trapping by *t*-butyl isonitrile.



Other important α-additions include the addition of bromine/chlorine forming isonitrile dihalides[13b, 49] (eq 10) and the addition of acid chlorides forming α-keto imidoyl chlorides (eq 11).[13, 15, 50] Both adducts can undergo secondary transformations.



(10)



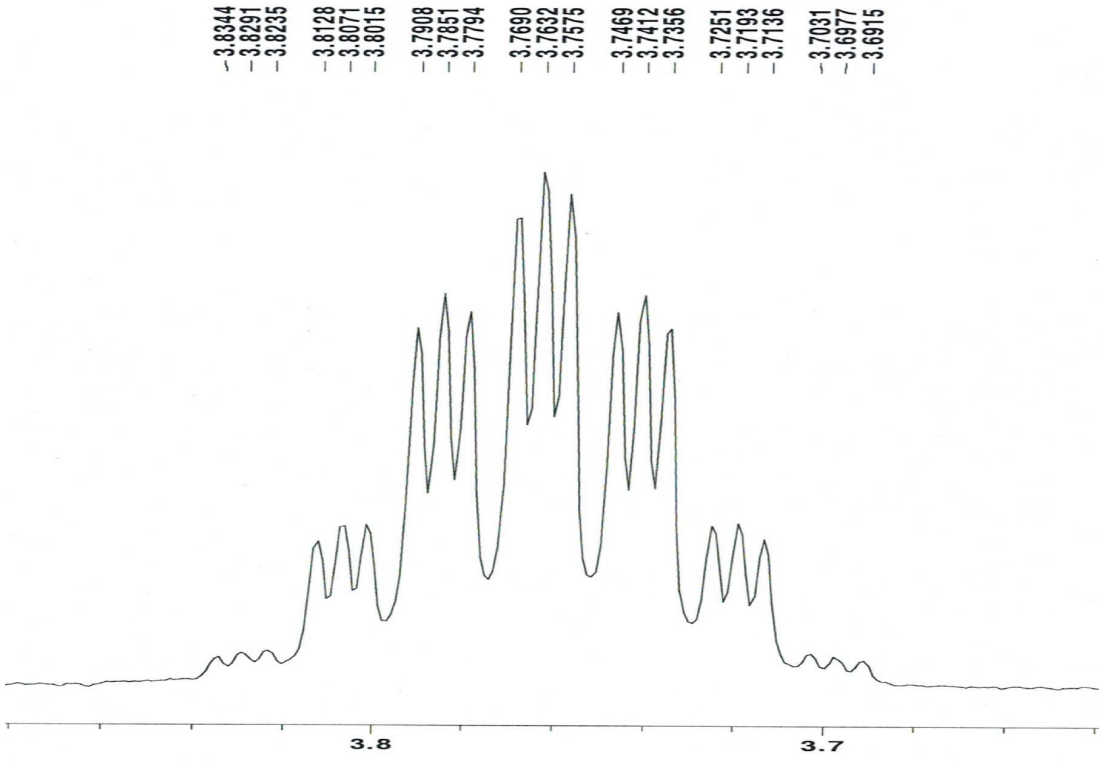
(11)

1.5 Spectroscopic Characteristics of Isonitriles

The most diagnostic spectroscopic feature of isonitriles is their IR absorbance around 2130 cm^{-1}, with aliphatic isonitriles generally absorbing at higher wavenumbers

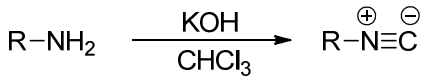
than aromatic isonitriles. No other organic functional group absorbs in this region (nitriles absorb about 100 cm^{-1} higher).[7, 11d, 11f, 51] Loss of CN is common in the electron impact mass spectroscopy of isonitriles.[52] In the ^{13}C NMR, the isocyano carbon signal is typically 150 - 170 ppm.[53] The ^{1}H NMR chemical shifts of protons adjacent to the isocyano nitrogen are similar to the corresponding protons of the parent amines and formamides. However, the α and β hydrogens of isonitriles sometimes show splitting from ^{14}N, due to slow quadrupolar relaxation in the highly symmetric electronic environment as the result of a very small field gradient at nitrogen.[22a, 54] For example the methyl protons of *t*-butyl isonitrile give rise to a triplet at 1.45 ppm (J_{NH} = 2 Hz). Similarly, Figure 1.2 shows the methine proton of isopropyl isonitrile observed as a septet (split by the six methyl ^{1}H, J_{HH} = 6.6 Hz) of triplets (split by the ^{14}N, J_{NH} = 1.7 Hz).

Figure 1.2 The ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of $(H_3C)_2C\mathbf{H}$-NC.

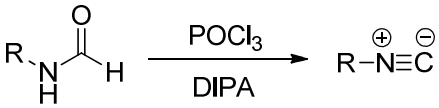


1.6 Synthesis of Isonitriles

Although it was first reported by Lieke and Meyer,[2] Gautier is often given credit for the silver cyanide method (eq 1, section 1.1) because of his early contributions to isonitrile chemistry.[3a, 4, 19a, 55] Gautier's attempts to dehydrate *N*-monosubstituted formamides to isonitriles failed because he did not add base to quench the strong acid which was also liberated.[19a] Hofmann, another early investigator of isonitriles, first reported the transformation of amines into isonitriles by potassium hydroxide and chloroform ("the carbylamine method," eq 12) in 1867.[3b, 56] The next major advance in isonitrile synthesis occurred 90 years later: Ugi and co-workers successfully dehydrated *N*-monosubstituted formamides with oxalyl chloride or phosphorous oxychloride in the presence of excess base.[57] Shortly thereafter they reported that dehydration was best achieved by phosphorous oxychloride with 2.7 equiv of diisopropylamine (DIPA, eq 13).[58] Other dehydrating conditions have been reported.[59]

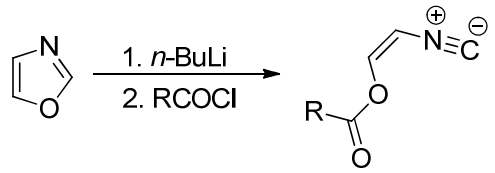


(12)



(13)

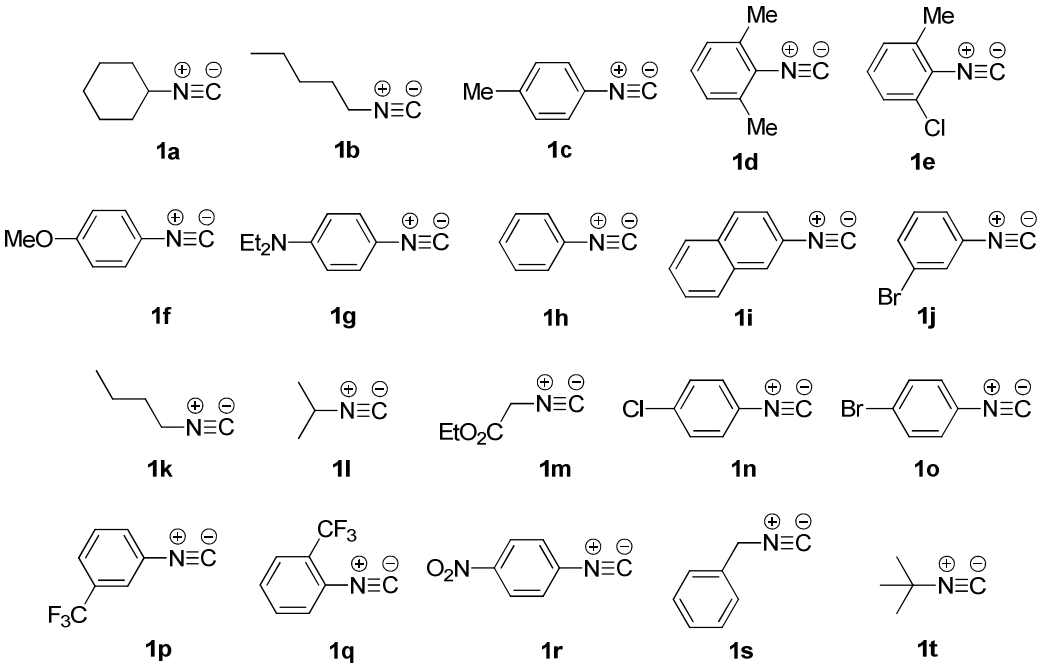
The desulfurization of an isothiocyanate to an isonitrile has been accomplished[60] in a complex molecule; the method also deoxygenates isocyanates.[61] The conversion of amines into isonitriles by the dichlorocarbene generating thermal decomposition of trichloroacetate gives disappointing yields (eq 12 with this reagent).[62] Alcohols can be converted into isonitriles with TMSCN and an activator.[63] Deprotonation of oxazoles results in an equilibrium between the anion and a ring-opened α–isocyano enolate.[64] The latter can be acylated to give purportedly fragrant, unsaturated isonitrile esters (eq 14).[65]



(14)

The isonitriles (**1**) used in the present work are shown in Figure 1.3. They were either commercially available (**1a-1b**, **1d-1e**, **1i**, **1k-1m**, **1t**) or synthesized (**1c**, **1f-1h**, **1j**, **1n-1s**) by a modified version of Ugi's $POCl_3$/DIPA method.[58] Notably, the reaction was found to be complete within 10 minutes rather than 1-8 h, and the slow bicarbonate quench, during which some isonitrile decomposition occurs, was found to be unnecessary.

Figure 1.3 Isonitriles used in this work.



1.7 Experimental Section

Dichloromethane (DCM) was purified by a Grubbs system.[66] Diisopropylamine (DIPA) was distilled from calcium hydride. 2-Chloro-6-methylphenyl isonitrile was dried *in vacuo*. Aromatic isonitriles were stored at −15 °C and aliphatic isonitriles were

stored at −5 °C. *N*-Substituted formamides were prepared by standard methods[67] or were commercially available.

NMR spectra were recorded with a 300 MHz Bruker spectrometer in $CDCl_3$ and are referenced to TMS or $CHCl_3$ (^1H δ7.26). IR spectra were obtained neat as a thin film on a NaCl salt plate.

Isonitriles were prepared by a modified version of the procedure reported by Ugi.[58]

2-Trifluoromethylphenyl isonitrile (1q).

To a stirring 0 °C mixture of DIPA (2.7 equiv, 4.3 mL) and *N*-(2-trifluoromethylphenyl)formamide[68] (2.12 g) in DCM (0.9 M, 12.44 mL) was added $POCl_3$ (1.1 equiv, 1.15 mL) dropwise under argon. After 5 min at 0 °C and 15 min at room temperature, 3 mL water was added and mixed vigorously until the organic layer became clear. The organic layer was separated, loaded onto a short silica gel flash column, and eluted with DCM to give 1.7 g (89%) of a foul smelling off white solid. **1q** melts near room temperature to a blue liquid, which resolidifies to an off-white solid on cooling. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.53-7.62 (m, 3H, Ar), 7.72-7.74 (m, 1H, Ar). IR (cm^{-1}): 2126.

4-Methylphenyl isonitrile (1c).

2.184 g of the corresponding formamide yielded 1.8 g (95%) as a foul-smelling yellow liquid after drying *in vacuo* 20 min. **1c** darkened during storage. ^1H NMR (300 MHz, $CDCL_3$, δ): 2.84 (s, 3H, CH_3), 7.18-7.29 (m, 4H, Ar). IR (cm^{-1}): 2125.

4-Diethylaminophenyl isonitrile (1g).

1.43 g of the corresponding formamide yielded 1.165 g (90%) as an orange solid.

^{1}H NMR (300 MHz, $CDCL_3$, δ): 1.16 (t, 6H, *J*=7 Hz, $N(CH_2C\mathbf{H}_3)_2$), (q, 4H, *J*=7 Hz, $N(C\mathbf{H}_2CH_3)_2$), 6.53-6.56 (m, 2H, Ar), 7.17-7.20 (m, 2H, Ar). IR (cm^{-1}): 2116.

3-Trifluoromethyphenyl isonitrile (1p).

2.78 g of the corresponding formamide[69] yielded 2.0 g (80%) as a foul-smelling yellow liquid which became dark green after drying *in vacuo* 10 min. **1p** is somewhat volatile.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.56-7.58 (m, 2H, Ar), 7.65-7.70 (m, 2H, Ar).

IR (cm^{-1}): 2129.

Phenyl isonitrile (1h).

2.35 g of the corresponding formamide yielded 790 mg (40%) of the foul-smelling liquid[70] after drying *in vacuo* briefly. The liquid **1h** darkens on storage and is volatile.

3-Bromophenylisonitrile (1j).

2.06 g of the corresponding formamide yielded 1.53 g (81%) of a foul-smelling yellow liquid which became dark green after drying *in vacuo* 10 min. The liquid **1j** is somewhat volatile. ^{1}H NMR (300 MHz, $CDCL_3$, δ): 7.28-7.37 (m, 2H, Ar), 7.55-7.59 (m, 2H, Ar).

IR (cm^{-1}): 2126.

4-Bromophenyl isonitrile (1o).

2.549 g of the corresponding formamide yielded 2.2 g (95%) as a foul-smelling white solid.[70] IR (cm^{-1}): 2126.

4-Chlorophenyl isonitrile (1n).

2.715 g of the corresponding formamide yielded 2.1 g (88%) as a foul-smelling pale yellow solid.[70] IR (cm^{-1}): 2126.

4-Nitrophenyl isonitrile (1r).

2.69 g of the corresponding formamide yielded 2.35 g (98%) as a yellow solid[58] with a mild odor.

1.8 References

1. The term 'isonitrile' is used throughout this work. They are also known as 'isocyanides' and, in the older literature (including in many of the citations that follow), as 'carbylamines'.

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