Isocyanides known since 1850s. Their exact structure was solved later with modern abinitio calculations. Characteristic hideous smell or pungent stench. Term "isonitrile" not accepted by IUPAC.

Physical data:
- IR: 2150-2110 cm⁻¹ weak-medium intensity
- 13C-NMR: 156-170 ppm
- Their carbon atom is formally divalent.

-> Very unusual electronic structure:
- Reacts as carbene,
- with nucleophiles,
- with electrophiles,
- in radical reactions
- and is isoelectronic with CO therefore a broad organometallic chemistry.

Furthermore and not covered here:

\[
\begin{align*}
R^1_N & \equiv \equiv N \\
R^2 & \equiv \equiv N \\
R^1_N & \equiv \equiv O \\
X & \equiv \equiv N
\end{align*}
\]

X = F, Cl, Br, I

Literature Reviews

α-anion chemistry of isocyanides

Hoppe, D. ACIE, 1974, 789

Multicomponent reactions


Organometallic chemistry of isocyanides

Aumann, R.; ACIE, 1988, 1456-1467.

Radical reactions of isocyanides


TosMic reagent


Natural products

Edenborough, M. S.; Herbert, R. B. Naturally occurring isocyanides, NPR, 1988,229-245.
Isocyanide containing natural products

- Xanthocillin first reported NP 1956 Hagedorn and Toenjes.
- From a biogenetical point of view isothiocyanates, formamides, isocyanates, and thiocyanates belong there too.
- Historical: First found in marine sources then terrestrial.
- Xanthocillin and cyclopentyl type.
- To day isolated from: bacteria, fungi, cyanobacteria, marine sponges and their predators.
- Isolation of isocyanide containing NPs difficult due to reactivity (trace acid, nucleophiles etc.)

Cyclopentyl isocyanides
Dermadin
Trichoviridin

Xanthocillines
Dermadin and trichoviridin soil sample (fungus) active against staphylococcus aureus
xanthocillines soil sample (fungus) antiviral antibiotics

Sesquiterpenes
Axanes
Aromadendranone
Eudesmane
Spirooxane

Skeletal types that contain isocyanides
(Eudesmanes, Axanes, Aromadendranone, Epimaaliane, Cadinane, Spirooxane, Bisabolane, Pupukeanane, Gualane.)
Only contain one NC-functionality in contrast to diterpenes.
Isolation: marine organisms (mollusks, sponges)

Indolalkaloids
Hapalindole A
Ambiguine E
Welwitindolinones
Fischer indole

Isolated by cyanobacteria fischeraella species prenylated indolalkaloids

Diterpenes
Kalihinol E
Amphilectanes

Diterpenes with trans or cis deca lin core
Devided in Tetrahydrofuran and -pyran types
Isolation: marine sponge active against Bacillus subtilis, Staphylococcus aureus, and Candida albicans.


Syntheses of Isocyanides

1. Reaction of alkyl iodides with silver salts

\[
\text{R}^1\text{I} + \text{AgCN} \rightarrow \text{[R}^1\text{NC-Agl]} \xrightarrow{\text{KCN}} \text{R}^1\text{NC}
\]

\[
\text{R}^1 = \text{primary alkyl}
\]

\[
\text{R}^1 + \text{E}^+ [\text{Ag(CN)}_2^-] \xrightarrow{\text{MeCN}} \text{R}^1\text{NC}
\]

\[
\text{R}^1 = \text{Me, CH}_2\text{CH}_2\text{I}; \text{E} = \text{Me}_3\text{Si, Ph}_3\text{PMe, Ph}_2\text{As}
\]


2. From epoxides and oxetanes

\[
\text{R}^2\text{R}'\text{R}''\text{SO} + \text{R}^3\text{R}'\text{R}''\text{SON} \xrightarrow{\text{KCN}, \text{15 hours, } \text{N}_2} \text{R}^2\text{R}'\text{R}''\text{NC}
\]

\[
\text{Zr} = \text{Zr}
\]

NOTE: Ti(OiPr)_4AlCl_3, Et_3AlCl lead to CYANIDES
ZnCl_2, ZnCl_2 lead to ISOCYANIDES


3. Reaction of tertiary alcohols with TMS-cyanide

\[
\text{R}^1\text{OH} \xrightarrow{1 \text{TMSCN}, \text{ZnCl}_2, \text{MeCN}, \text{rt}} \text{R}^1\text{NC}
\]

\[
\text{R}^1 = \text{Me, Et, (CH}_2\text{CH}_2\text{H}_2; \text{Me}_2\text{Si, Ph}_3\text{PMe, Ph}_2\text{As}
\]

R\text{\textsuperscript{1}}\text{CN}


4. From deoxygenation of isocyanates

\[
\text{R'\text{CO}} \xrightarrow{\text{P(CiMe}_3)_3, 160^\circ\text{C}} \text{R'\text{NC}}
\]

\[
\text{R'} = \text{Me, Et, (CH}_2\text{CH}_2\text{H}_2; \text{Me}_2\text{Si, Ph}_3\text{PMe, Ph}_2\text{As}
\]

\[
\text{R'} = \text{Me, Et, (CH}_2\text{CH}_2\text{H}_2; \text{Me}_2\text{Si, Ph}_3\text{PMe, Ph}_2\text{As}
\]

\[
\text{R'} = \text{Me, Et, (CH}_2\text{CH}_2\text{H}_2; \text{Me}_2\text{Si, Ph}_3\text{PMe, Ph}_2\text{As}
\]

\[
\text{R'} = \text{Me, Et, (CH}_2\text{CH}_2\text{H}_2; \text{Me}_2\text{Si, Ph}_3\text{PMe, Ph}_2\text{As}
\]

NOTE: Comparison of several phosphites revealed that triethyl- and tributyl phosphites are effective, but trimethyl and triphenyl are not. Conventional phosphites DON'T work with aromatic isocyanates therefore

5. From desulfuration of isocyanates

\[
\text{R'}\text{SNC} \xrightarrow{\text{Ba(SH)}_2(1 \text{equiv.)}, \text{Et}_2\text{O, rt}} \text{R'}\text{NC}
\]

\[
\text{R'} = \text{Me, Et, (CH}_2\text{CH}_2\text{H}_2; \text{Me}_2\text{Si, Ph}_3\text{PMe, Ph}_2\text{As}
\]

Alternative conditions: P(OEt)_3 rt

same principle different name - which?

6. From Carbamates by deoxygenation with trichloro silane/triethylamine

\[
\text{R'NHCO}_{\text{Me}} \xrightarrow{\text{Cl}_{3}\text{SiH, R}_{3}\text{NH}} \text{CHCl}_{3}, 20^\circ \text{C} \quad \text{R'NC}
\]


7. By dehalogenation of isocyanide dihalides

\[
\text{R'N} \xrightarrow{\text{A: R}_{2}\text{P}} \text{X} \\
\text{B: Cl} \\
\text{C: Mg} \\
\text{D: CHCl}_{3}, 75-85^\circ \text{C} \quad \text{R'NC}
\]

Hollschmidt, H. Angew. Chem. (1957) 74, 994

8. By dehydration of Formamides

\[
\text{R'NHCHO} \xrightarrow{\text{acylating reagent, base}} \text{R'NC}
\]

acylating reagent = DCCI, DCCl, COCl, POCl, SOCl, DMF, AlCl
base = R'NH, R'OHN, py, quinoline, NaNOH


8a. By dehydration with phosgene or diphosgene

<table>
<thead>
<tr>
<th>(\text{R}^1)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>90</td>
</tr>
<tr>
<td>t-Bu</td>
<td>82</td>
</tr>
<tr>
<td>Cl</td>
<td>90</td>
</tr>
<tr>
<td>Br</td>
<td>90</td>
</tr>
<tr>
<td>I</td>
<td>82</td>
</tr>
</tbody>
</table>


8b. By dehydration with triphosgene

\[
\text{R'NHCHO} \xrightarrow{(\text{ClCO})_{2}\text{CO, Et}_{3}\text{N}} \text{R'NC}
\]

\[
\text{R'NHCHO} \xrightarrow{\text{ICl}_{2}\text{CO}, \text{Et}_{3}\text{N}, \text{Ph}_{3}\text{P}} \text{R'NC}
\]

Ref: Roume, H., Horwell, D. C., Petch, M. C. Tetrahedron (1964) 47, 4763
8c. By dehydration with vilsmeier reagent or thionyl chloride

8d. By dehydration with vilsmeier reagent or phosphoryl chloride

8e. With other reagents

Mechanism?
Reactions of Isonitriles

α-alkali-metalated isonitriles:

react with electrophiles to give, olefines, vinylisocyanides, ketones, 1-amino-alcohols, 3-amino-alcohols, straight chain and branched and β-functional α-amino acids.

Further a variety of 5, 6, and 7-membered heterocycles (aza, diaza, oxva-aza, thia-aza).

Schoellkopf and Gerhart in 1968 found out that isonitriles are α-acidic. Deprotonation is carried out at -70 °C with nBuLi in THF or NaH, NaOEt, KOtBu or DBU depending on the substituents next to the isocyanide functionality.

Schoellkopf, U; Gerhart, F. ACIE,7, 1968 805

1. Chainextension of amines

Here isocyanides are masked α-amino carbamions

\[
\text{N} \quad \text{NC} \quad \text{nBuLi} \quad \text{THF} \quad -70^\circ C \quad \text{Mel} \quad \text{acid-hydrolysis} \quad \text{NH}_2
\]

Schoellkopf, U; Gerhart, F. ACIE,7, 1968 805

8f. By the Carbylamine reaction

\[
\text{R}^1\text{NH}_2 \quad \xrightarrow{\text{CHCl}_3, \text{base}} \quad \text{H}^1\text{N}_2\text{Cl} \quad \xrightarrow{\text{ZnCl}_2} \quad \text{R}^1\text{NC}
\]

80

NOTE: Especially useful for aromatic isocyanides


Which other reactions contain α-eliminations??

2. γ- and ε-amino alcohols

General:
γ-amino alcohols from carbonyl addition
ε-amino alcohols from epoxide opening

\[ \text{MeO} \quad \text{NC} \quad \overset{\text{nBuLi, THF, -70°C}}{\longrightarrow} \quad \text{OH} \quad \text{NC} \quad \text{OMe} \]

Problem is stereoselectivity


3. Olefination, generation of vinyl-formamides

\[ \overset{\text{LiOCN}}{\Delta} \rightarrow \quad \text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{E} \rightarrow \text{from trans} \quad \text{Z} \rightarrow \text{from cis} \]

Can be written as [3+2] cycloaddition

Woodward, R. B.; Hofmann R ACIE, 1969, 8, 781
**Nucleophilic α-attack on isocyanides - generation of imidoyllithiums:**

**Requirement: No α-protons**

- $\text{R}^1\text{Li} + \text{R}^2\text{NC}$
  - $\text{H}_2\text{O}$, then $\text{K}^+$,
    - 50-95%
  - $\text{EtOH}$ or pentane
  - $\text{PhCHO}$, then $\text{H}^+$
  - $\text{R}^1 = \text{Et}$, 91%

- $\text{CO}_2$, then $\text{K}^+$,
  - 52-80%

- $\text{N}^+\text{Bu}^-$
  - $\text{COCl}_2$, then $\text{H}^+$
  - $\text{R}^1 = \text{Bu}$, 90%

- $\text{Bu}^-$
  - $\text{CO}_2\text{Et}$, then $\text{Et}$
  - 64%

**Cyanation of organolithiums (with TrNC as reagent):**

- $\text{Ph}^-\text{NC}$ + $\text{R}^-\text{Li}$ in THF, -78°C
- $\text{R}^-\text{CN}$

---

**Oxidative α-addition to isocyanides**

Isocyanides react violently with halogens!!!

- $\text{PhNC} + \text{I}_2$, $\text{Cl}_2$, $\text{Br}_2$, $\text{F}_2$
  - $\text{PhNBr}$, 69%

- $\text{PhNC} + \text{tBuOCl}$
  - $\text{PhN(OtBu)}$, 75%

- $\text{NO}_2\text{S}^-\text{Cl}$ + $\text{PhNC}$
  - $\text{PhN(NO}_2\text{S})\text{Cl}$, 38%

---

**Addition of acylchlorides**

- $\text{PhNC} + \text{ClCOCl}$
  - $\text{MeOC}^-\text{Cl}$
  - $\text{H}_2\text{O}$
  - $\text{NHPh}$

---

The TosMic-reagent (construction of heterocycles)

1. Preparation of TosMic

\[
\text{POCl}_3 + \text{CH}_2\text{O} + \text{H}_2\text{NCHO} \xrightarrow{\text{H}_2\text{O}, \text{AcOH}, 90^\circ\text{C}} \text{p-Tol-SO}_2\text{-CHNHCHO}
\]

TosMic = colorless crystals

Originally prepared by irradiation of pTsCH₂N₂ in HCN


Synthesis of TosMic-derivatives

<table>
<thead>
<tr>
<th>Step</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TosMic</td>
</tr>
<tr>
<td>2</td>
<td>TosMic</td>
</tr>
<tr>
<td>3</td>
<td>TosMic</td>
</tr>
</tbody>
</table>

2. Synthesis of oxazoles and pyrroles and imidazoles

Yields depend on aldehyde but typically >50%


Mechanism?

3. Imidazoles from sym-triazines

3. Synthesis of thiazoles and 1,2,4-triazoles


How come there are two products??


4. TosMic as an umpolung reagent for formaldehyde


5. Synthesis of alkanes


6. The use of chiral TosMics


Silver catalysis:
allphatic and aromatic aldehydes are converted to aminoalcohols.
Synthesis of $\alpha$-hydroxy aldehydes

$\text{R}^{'\text{SO}_2} \text{NC} \rightarrow \text{Ph} \rightarrow \text{R}^{'\text{SO}_2} \text{NHCHO}$

ee 16%

Isocyanides in multicomponent reactions

Definition: A multicomponent reaction (MCR) is a reaction where more than two starting materials are INITIALLY reacted together to form one product, and essentially all the atoms are incorporated into the product. If not put together in the beginning then it's "just" a one pot reaction.

1. The Passerini and Ugi reaction

Mechanism?

Passerini (3 components)

$\text{R}^1 \text{OH} + \text{CN}^+ \rightarrow \text{R}^2 \rightarrow \text{R}^3 \rightarrow \text{NH}$

Ugi (4 components)

$\text{R}^1 \text{OH} + \text{CN}^+ \rightarrow \text{R}^2 \rightarrow \text{R}^3 \rightarrow \text{NH}_2 \rightarrow \text{R}^4 \rightarrow \text{NH}$

*only 1 new stereocenter formed!!*

Stereochemical control gained through the amine or isonitrile component. The Oxo-component has hardly any influence. Reactions are typically carried out in alcoholic solutions at rt. or in toluene/benzene at reflux. Sometimes lewis or broensted acids are added in catalytic amounts to facilitate the reaction.

chiral amines suitable for stereinduction in U-MCR and P-MCR
the chiral auxiliary part can be cleaved off after the reaction

Typical reaction:

$\text{NH}$

$\text{MeOH, 53%}$

$\text{COOMe}$
**Applications of MCRs in Drug Discovery**

A vast number of different structures rapidly accessible => VERY useful in drug discovery

Abbott scientists:
Tubulin inhibitors same mode of action as Colchicine

**Isocyanide Chemistry**

MCRs in combination with other reactions

GlaxoSmithKline (GSK):
p38 kinase inhibitor against rheumatoid arthritis
Isonitrile produced on a 500kg scale !!!

Applications of MCRs in Natural product synthesis

Which bonds are made and where are the components

Ecteinascidin builds up 60% of the skeleton of Ecteinascidin 743

Organometallic chemistry of isocyanide

As isocyanides are isoelectronic to carbon monoxide, they have a similar behaviour towards transition metals.

1. Aza-Pauson-Khand reaction

$$\text{R}_1^+ + R_2^\text{N} = R_1^+ + R_2^\text{N} \rightarrow \text{R}_1^+ \text{N} = R_2$$

2. Reaction of isocyanides with Carbene complexes

$$X = \text{O-alkyl}, \text{S-alkyl}, \text{NR}_2, \text{PR}_3$$

$$\text{R}_1^+ = \text{alkyl, aryl, alkenyl, alkyne}$$

$$M = \text{Cr, Mo, W, Mn, Fe, Os, Th, U}$$

$$L_n = \text{CO, PR}_3, \text{I}^5\text{C}_3\text{H}_5$$

Keteneiminium complexes are formed. Complexation depends on the type of metal. For the reactivity: Umpolung of the keteniminium reactivity

Other possibilities of coordination:

Favoured when M = electron donating

References:


Keteneimines are they chiral?

In contrast to metal free keteneimines, metal complexed ones react like 1,3 dipoles. The metal undergoes a shift to the central atom! Protic nucleophiles can attack to give aminocarbe complexes.

\[
L_nM = \begin{cases} 
\text{NHR}^1 & \text{R} \text{MeOH} \\
\text{CN-R}^1 & \text{EtO}_2 \\
\end{cases}
\]

\[
\begin{align*}
L_nM &+ CN-R^1 \rightarrow L_nM \text{N-R}^1 \\
\end{align*}
\]

\[X= \text{O-alkyl, S-alkyl, NR}_2, \text{PR}_3]

\[R,R^1= \text{alkyl, aryl, alkenyl, alkynyl}\]

nucleophiles: alcohols, thiols, amines, H_2O

\[L_nM= [\text{Cr(CO)}_3], [\text{Mo(CO)}_3], [\text{W(CO)}_3], [\text{Mn(CO)}_2\text{Cp}], [\text{Fe(CO)}_4]\]

Comparison hydrolysis of keteneimine

\[
R^1\text{N=O} \underset{H_2O}{\overset{\text{R}^1\text{H}}{\rightleftharpoons}} \text{R}^1\text{NHCO} \]

[3+2]-Cycloadditions

\[L_nM + CN-R^1 \rightarrow \text{EtO}_2 \\
a=b \rightarrow L_nM \text{N-R}^1 \rightarrow \text{EtO}_2 \]

\[a=b: \text{O=CHR, RN=CO}, \text{RN=CNHR}, \text{L}_nM= [\text{W(CO)}_3], [\text{Mn(CO)}_2\text{Cp}], \text{Reaction at room temperature}\]

Rearrangements of metal-keteneimines

1. Keteneimine aminocarbe rearrangement
   rearrangement takes place readily, triggered by oxygen/peroxides

\[
\begin{align*}
\text{R}^1\text{N=O} & \rightarrow \text{R}^1\text{N=O} \\
\end{align*}
\]

\[L_nM= [\text{Cr(CO)}_3], [\text{Mo(CO)}_3], [\text{W(CO)}_3]\]
**Dimerization of Keteneimine ligands**

\[
\begin{align*}
L_nM &= [\text{Cr(CO)}_5], [\text{Mo(CO)}_5], [\text{W(CO)}_5] \\
X &= \text{OME} \\
L_nM &= [\text{Cr(CO)}_5], [\text{Mo(CO)}_5], [\text{W(CO)}_5]
\end{align*}
\]

Reaction at room temperature

**Isocyanides in Radical chemistry**

Isocyanides participate in radical additions like CO... (isoelectronic!!)

Difference to CO radical addition:
They don't undergo \(\alpha\)-fragmentation but \(\beta\)-fragmentation instead to give nitriles. Therefore isocyanides without good \(\beta\)-leaving groups are preferred substrates.

In the process of radical addition the so called imidoyl radical is formed which then undergoes further reactions.

**Addition of isocyanides to keteneimine complexes:**

1. Addition of isocyanide to metal with displacement of keteneimine

\[
\begin{align*}
L_nM &= [\text{Cr(CO)}_5], [\text{Mo(CO)}_5], [\text{W(CO)}_5] \\
X &= \text{OME} \\
L_nM &= [\text{Cr(CO)}_5], [\text{Mo(CO)}_5], [\text{W(CO)}_5]
\end{align*}
\]

2. \([3+1]\) or \([2+2]\) CA of isocyanides to keteneimine complex

\[
\begin{align*}
L_nM &= [\text{Cr(CO)}_5], [\text{Mo(CO)}_5], [\text{W(CO)}_5] \\
X &= \text{OME} \\
L_nM &= [\text{Cr(CO)}_5], [\text{Mo(CO)}_5], [\text{W(CO)}_5]
\end{align*}
\]

3. \([2+1+1]\) CA of 2 isocyanides to N-C-bond of keteneimine

The total synthesis of Camptothecin

Danishesky tetracycle

2 steps

The chemistry is very convergent and therefore gives easy access to analogs.

Fukuyama Indole Synthesis:

\[ R = \text{should be electron withdrawing if} \ R = \text{alkyl then by-product B formed} \]

Yields >70%

R=H, or I

Mechanism of rxn? Why is by-product formed?

Further elaboration to yield 2,3 disubstituted indoles


Isocyanide Chemistry

Conclusions:

For the making of isocyanides:
There is a variety of different reagents available which show different reactivities check carefully which one suits your substrate!!

For α-anion chemistry of isocyanides:
Alkylation takes place stepwise (no problem of double alkylation)
It represents the umpolung of a carbonyl functionality
A variety of different functionalities are accessible.

For α-addition chemistry of isocyanides:
Two ways: 1. generation of imidoyllithium and addition of electrophile
2. Oxidative
TosMic-reagent for construction of all kinds of heterocycles!!

MCRs:
Wide applications in drug-design couple with other reactions and you get a
dramatic increase in molecular complexity

Organometallic chemistry:
No broad application so far, huge variety of different structures

Radical chemistry:
Problem of β-elimination!!
selene or stannylidamides as analog starting units

Needs for Development:

General problem of reactions where isocyanides participate is the
stereoselectivity. There are some specific solutions but nothing general like
the Evans auxiliary
MCRs, chiral TosMic give ee’s to some extent but a large range of
improvement exists.
Organometallic chemistry there is no chiral transition metal complex in
application
In Organometallic chemistry of isocyanides there is probably the most chance
to discover something new.