# Electrophilic Cyanation and Industrial Application

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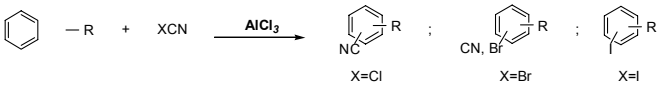
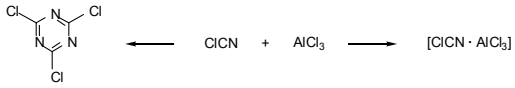
The unique supply chain on the Valais site of Lonza AG, Switzerland provides good access to a multitude of basic chemicals - among these is the highly reactive cyanogen chloride, available in ton quantities.
Research on advanced applications of our basic chemicals prompted us to investigate the direct electrophilic cyanation of aromatic systems using cyanogen chloride using Lewis-acids (the so called Friedel-Crafts-Karrer synthesis).




First mentioned in literature 1884 by C. Friedel and J.M. Crafts
Works best if R = -alkyl or –Oalkyl.
Selectivity follows regular substitution rules for aromatic systems.

[1] P. Karrer , E. Rebmann, E. Zeller, *Helv.Chim.Acta*, **1920**, 3, 227-261
[2] V.P. Wystrach, **1952**, US-P 2584409
[3] G.W. Gray, B. Jones, *J.Chem.Soc.*, **1954**, 679
[4] P.H. Gore, F.S. Kamounah, A.Y. Miri, *Tetrahedron*, **1979**, 35, 2927-2929
[5] L. Eberson, F. Radner, *Acta Chem.Scand.*, **1992**, 46, 312-314

## $AlCl_3$ and ClCN – how do they come together ?



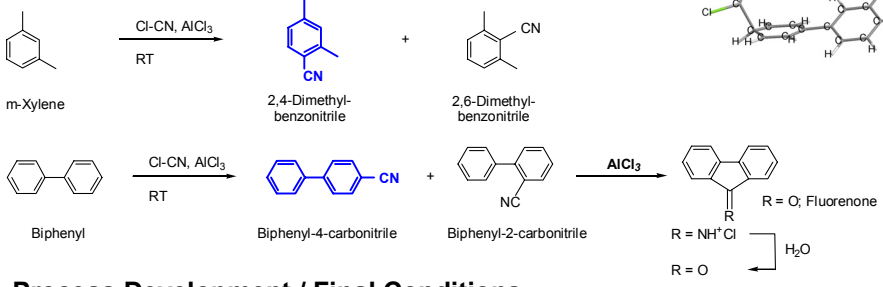

## Questions for Process Development

**What is the best solvent for this reaction type?**

| | |
|---|---|
| **$CS_2$, most common in literature** | × |
| **Reaction in substance** | • **for liquid acceptors** |
| **Chloro-alkanes and –aryls** | • **for solid acceptors** |

**What is the mechanism of this reaction and how is ClCN activated?**
**Is the [$AlCl_3$·ClCN] complex stable at higher temperatures?**
**According to literature, biphenyl does NOT react!**
**Is selectivity a problem and can isomers be separated easily?**
**What is the best work-up procedure and are produced nitriles stable?**
**Are there process conditions where accumulation can be avoided?**

## Investigated Systems




## Process Development / Final Conditions

| Process | Starting Material | Solvent | $AlCl_3$ /ClCN 1/1 | Process temperature | Process | Work up | Yield raw (nitrile) | Purity (GC) | Purificatio method | Yield | Purity (GC) | Amount produced |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | [mol equiv.] | | | | | [area%] | | | [area%] | [kg] |
| 2,4-Dimethyl-benzonitrile | m-Xylene | m-Xylene | Solvent in excess | 20°C | 1 | a | 96% rel. to ClCN | 72.0 | c | 80% | 99.0 | 5.5 |
| Biphenyl4-carbonitrile | Biphenyl | Chloro - benzene | 1.2 | 80°-110°C | 2 | b | quant. | 75.4 | d | 60% | 98.5 | 4.3 |

**Process**
1 $AlCl_3$ and m-Xylene were pre-mixed. Gaseous ClCN was injected. The reaction took place instantaneously.
2 $AlCl_3$ was suspended in chloro-benzene and gaseous ClCN was injected. The suspension was heated to 80°C and a solution of biphenyl in chlorobenzene was added. After heating to 110°C, the reaction was held for ca. 4 hours.
The process was patented in WO 03037848.

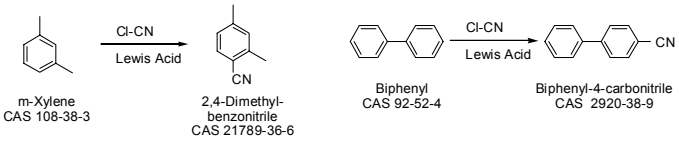
**Work-up**
a Reaction mixture was poured on HCl conc. Phases separated and organic phase evaporated (wiped film).
b Reaction mixture was poured on cold water. Precipitated imminium-chloride removed by filtration. Phases subsequently separated and and organic phase evaporated (wiped film).

**Purification**
c High-vacuum distillation over a high performance column.
d Crystallisation.

## Reaction Mechanism – single or double $AlCl_3$ activated ?

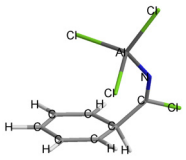
| Starting Material | Reagent | Solvent | Time, Temperature | Products | Yield (Nitril) |
|---|---|---|---|---|---|
| | 1eq. $AlCl_3$ 1eq. ClCN | Excess Starting Material | 8h, 60 - 80°C (Bc) | | < 1% GC |
| | 2eq. $AlCl_3$ 1eq. ClCN | Excess Starting Material | 1,5h, 75 - 80°C (Cb) | | 70,7% isolated |

The applicability of this type of reaction for industrial production of aromatic nitriles is demonstrated in this presentation. An overview of the investigated systems as well as some related literature will be given. The reaction was analysed by molecular modelling methods and a potential mechanism is proposed. Finally, the industrial application is illustrated on the two examples 2,4-dimethylbenzonitrile and biphenyl-4-carbonitrile.

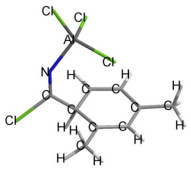



## Structure Comparison of σ-complexes:

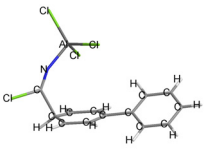
**Benzene:**
+ 26.7 kcal/mol



**m-Xylene:**
+ 16.9 kcal/mol

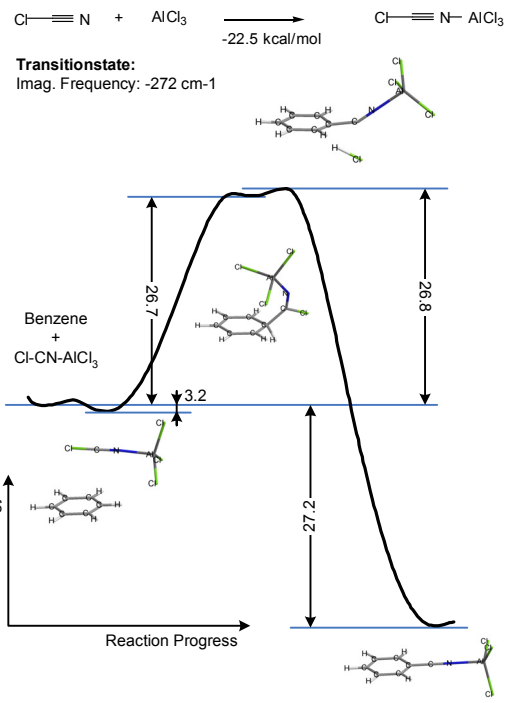


**Biphenyl**
+ 15.3 kcal/mol

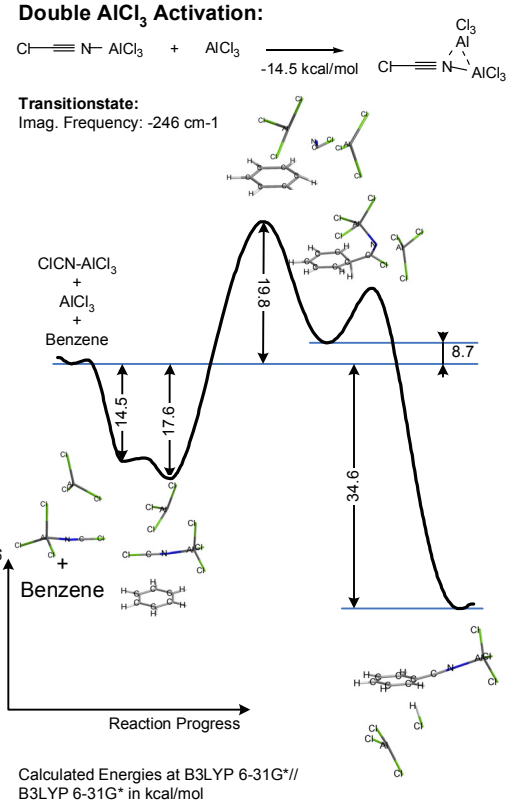


## Proposed Reaction Mechanisms

### Single $AlCl_3$ Activation:




### Double $AlCl_3$ Activation:




Calculated Energies at B3LYP 6-31G*// B3LYP 6-31G* in kcal/mol