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Custom Development & Manufacturing Organization (CDMO)

# Rapid Access to Cyano Aromatics via Friedel-Crafts Reaction with Cyanogen Chloride and Dicyanogen

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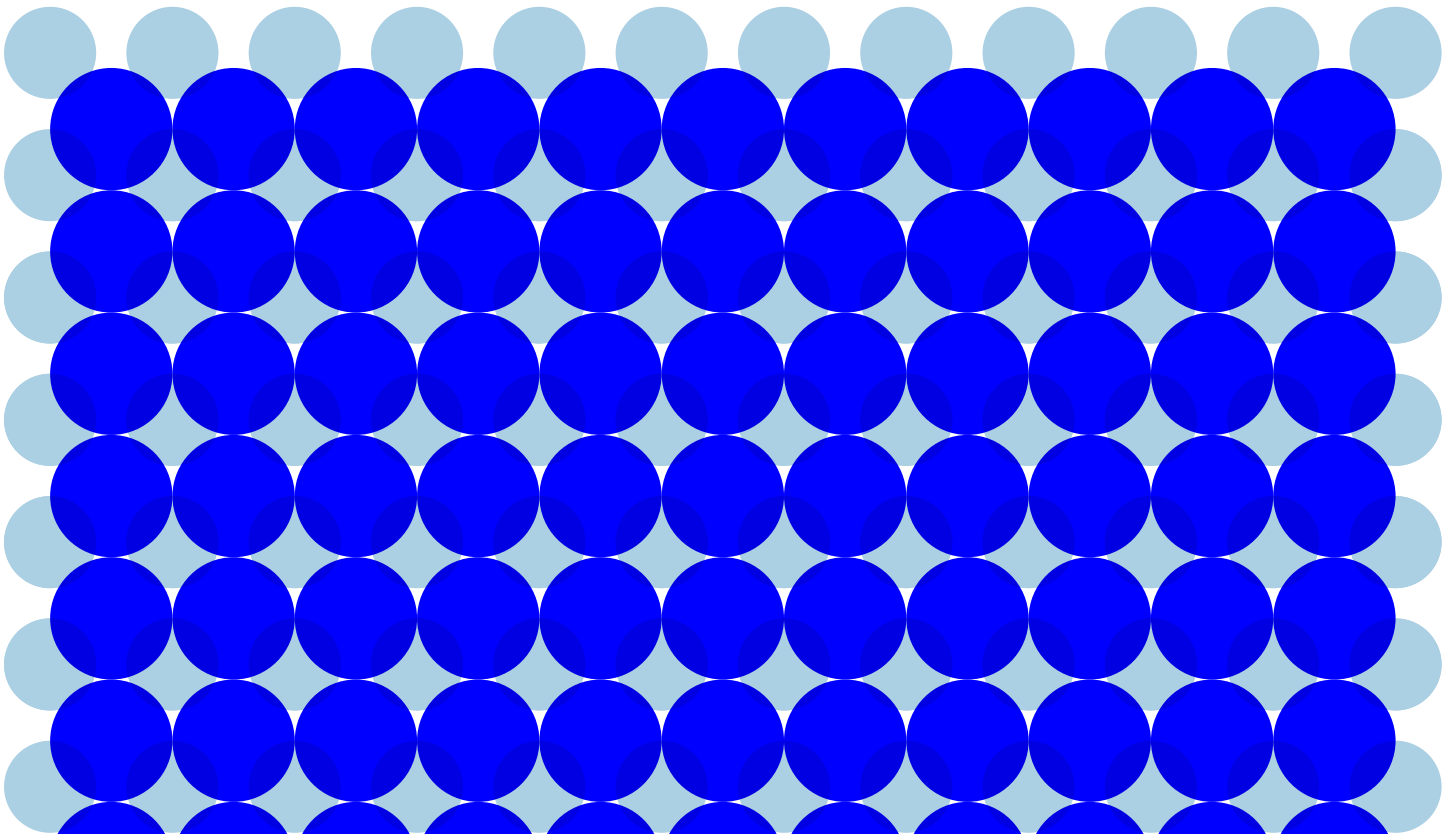
Aromatic nitriles are of high interest and numerous methodologies to access them were developed over time. Unfortunately, those often rely on multiple steps or complex transformations. On the other hand, direct cyanogenation by Friedel-Crafts reaction presents an efficient tool to access those derivatives in a one-step synthesis, maximizing the atom economy, with a relatively simple procedure. Based on the uses of dicyanogen and cyanogen chloride, this powerful technology requires collaboration with a backward integrated CDMO.



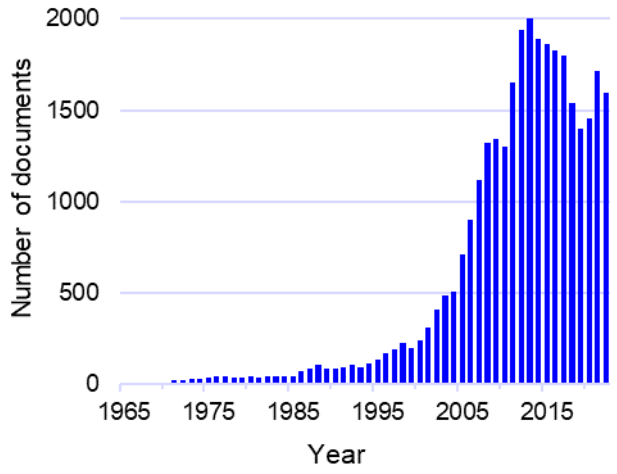
# Rapid Access to Cyano Aromatics via Friedel-Crafts Reaction with Cyanogen Chloride and Dicyanogen

**In order to unlock access to aromatic nitriles, a straightforward transformation is highly sought-after. The Friedel-Crafts direct cyanogenation offers an elegant solution that is based on the production and handling of reagents with somehow challenging profiles (safety and toxicity). Arxada is proud to offer this technology to its partners, thanks to its backward integration and a deep expertise in handling and reacting these special reagents.**

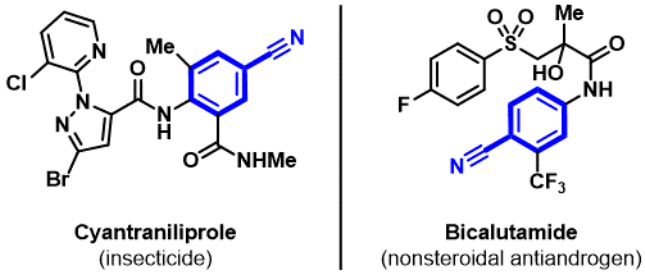
Aromatic nitriles gained a strong interest over the last few decades, as can be seen by the increasing number of patents on the topic discussing their incorporation in active ingredients, emphasized by examples of substances already on the market (Figure 1).

*Figure 1. Aromatic nitriles-containing derivatives: a popular motif with raising interest.*

*1.a. Patents filled with active ingredients bearing aromatic nitriles for therapeutics or agricultural uses.*




*1.b. Example of two marketed active ingredients bearing an aromatic nitrile.*




The popularity of such moieties (ie the aromatic nitriles) can be rationalized in the literature thanks to the significant importance of nitriles as physicochemical modulators for small molecule active ingredients, as well as their impact on pharmacokinetics, including drug kinetic, and bioavailability.[2]

A comprehensive literature search reveals that a variety of methods are available to prepare these aromatic nitriles, including, amongst others, the Sandmeyer reaction, the Rosenmund–von Braun reaction, or some metal-catalyzed cyanation reactions.[3] In most cases, those transformations rely on already decorated aromatics (ie with a diazonium or a halogen group for example), that require synthesis of the said decorated aromatic in the first place. In addition to these multi-step syntheses, some patents / publications are discussing the use of a Friedel-Crafts reaction to access aromatic nitriles. This latest transformation is advantageous since the reaction does start with a non-decorated aromatic (Figure 2).

*Figure 2. Examples of the synthetic methods for aromatic nitriles.*


[1] Search performed with SciFinder, in June 2023, restricted to benzonitrile as a building block in the agrochemical and pharmaceutical industries.

[2] F.F. Fleming, L. Yao, P.C. Ravikumar, L. Funk, B. C. Shook, J. Med. Chem. 2010, 53(22), 7902–7917.

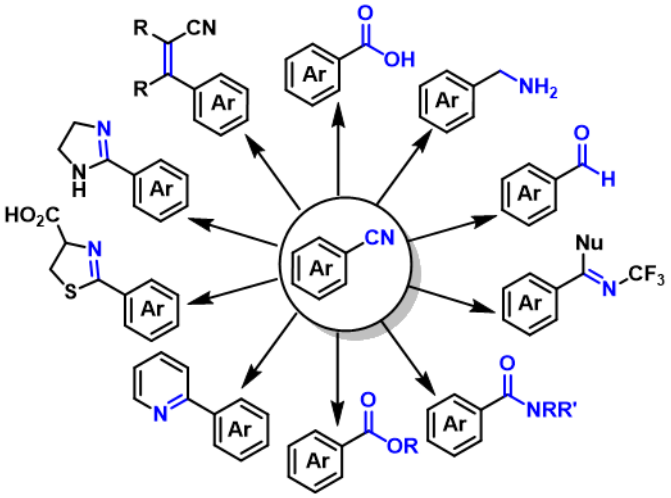
[3] G. Yan, Y. Zhang and J. Wang, Adv. Synth. Catal. 2017, 359, 4068–4105.

The first mention of C. Friedel and J.M. Crafts synthetic methods is from 1877.[4] The Friedel-Crafts direct cyanogenation with a variety of Lewis acids, but with a preference towards $AlCl_3$, was then described, relying mainly on the use of cyanogen bromide (Br-CN) and cyanogen iodide (I-CN) as reagents.[5] However, those bromo and iodo reagents often lead to the corresponding undesired aromatic halogen as a side product. This direct cyanogenation was also described using cyanogen chloride (Cl-CN) in the presence of $AlCl_3$,[6] preventing the formation of the corresponding chloro-aromatic side products.

To summarize, the Friedel-Crafts direct cyanogenation of aromatic systems with cyanogen chloride allows the formation of aromatic nitriles in one chemical step, using a relatively simple procedure. The main cyano sources required are cyanogen ((CN)2) and/or cyanogen chloride (Cl-CN), which, due to their toxic profiles, cannot be transported. As a result, in a situation where performing a Friedel-Crafts cyanogenation is relevant, a producer with backward integration for these cyano reagents with the abilities and expertise to handle them, is necessary.

Last but not least, if cyano-containing active ingredients are popular, the cyano group is also of high interest for the organic chemists thanks to its great versatility, offering numerous opportunities for further derivatization (Figure 3).

*Figure 3. Selected examples of aromatic nitrile derivatizations.*




**The Arxada Visp site presents itself as an ideal partner to perform Friedel-Crafts cyanogenation, having the necessary (CN)2 and Cl-CN backward integrated networks, and the relevant multipurpose assets to perform the actual Friedel-Crafts reaction. The related chemistries can be performed at various scales with high yields and purities. In addition, of course, the company which is specialized in the production and handling of these usually highly reactive and toxic cyano reagents, is performing under high environmental, health, and safety standards.**

## Acknowledgments

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## Our offer


- **One-step synthesis of aromatic nitriles from kg to mt**
- **Cyano reagents' backward integration**
- **Safe production and handling of cyano derivatives**
- **Ability to derivatize on-demand**
- ***Focus on what matters to you***

For further information and/or if you would like Arxada to support your project(s), get in touch with:
**myproject@arxada.com**

[4] C. Friedel, J.M. Crafts, Compt. Rend. 1877, 84, 1392 & 1450.

[5] S. Kobayashi, T. Busujima, S. Nagayama, Chem.Eur.J. 2000, 6(19), 3491-3494; H.O.House, Modern Synthetic Reactions, Benjamin Inc., Menlo Park, 1972.

[6] J. Bartek, P. Willa, Lonza AG, 2002, Method for the production of biphenyl-4-carbonitrile, US7002034; F.S. Fawcett, R.D. Lipscomb, J. Am. Chem. Soc. 1960, 82(6), 1509–1510.

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