

Facile Synthesis of Cyanoarenes from Quinones by Reductive Aromatization of Cyanohydrin Intermediates

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Abstract: A novel synthesis of cyanoarenes from quinones by using PCl_3 as the reagent for reductive aromatization of cyanohydrin intermediates is reported. *In-situ* IR spectroscopic measurements were conducted to monitor the reactions and to develop a convenient one-pot protocol. 1,4-Dicyanobenzene **2** and 9,10-dicyanoanthracene **3** were prepared by the new procedure.

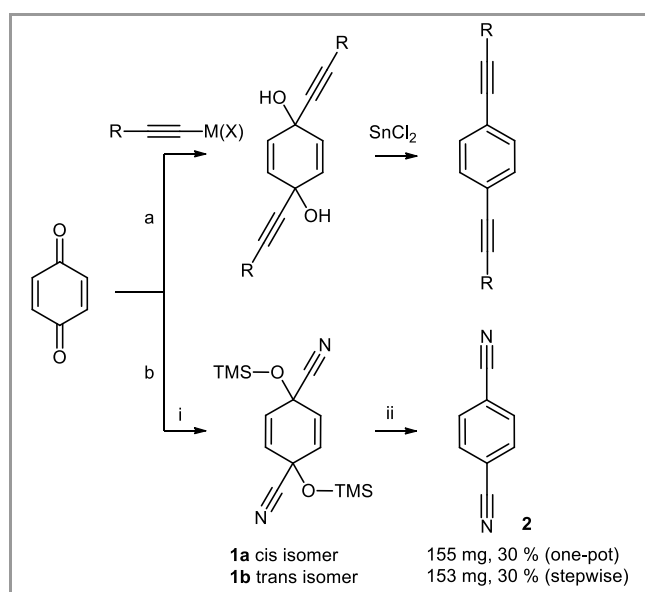
Key words: arenes, cyanohydrins, nitriles, quinones, reduction

Quinones, and in particular 1,4-benzoquinones, are frequently used building blocks in organic synthesis due to their widespread availability and their modifiability by numerous reactions.¹ In recent years, modification by nucleophilic attack of acetylides at the carbonyl functionalities of quinones and subsequent reductive aromatization (mostly) using SnCl_2 (Scheme 1, a) has gained significant attention in organic synthesis, particularly in the field of organic functional materials.² TIPS-pentacene—to name just one of the most prominent compounds synthesized by this approach—is a frequently used and well-investigated material for organic field-effect transistors.³

The corresponding introduction of cyanides instead of acetylides has not been described in the literature, although theoretical calculations suggest that cyano substituents increase the electron affinity, reduce the internal reorganization energy and promote the π -stacking of molecules.⁴ These properties render cyanoarenes particularly promising for (n-type) organic semiconductors. The development of a facile and cheap synthesis of these compounds from quinones therefore represents a major benefit to a broad field of organic chemistry. Using quinones as reactants enables the preparation of many compounds from available substrates; on the other hand, it allows for substitution patterns that are difficult to realize using alternative methods.⁵

Unlike lithium acetylides, cyanides favor 1,4-addition to benzoquinones over 1,2-addition. This problem can be overcome by the application of trimethylsilyl cyanide (TMS-CN) for the synthesis of stable (silylated) cyanohydrins. Following a protocol for the mild and efficient preparation of cyanohydrins in acetonitrile⁶ using CsF as catalyst, but carrying out the reaction at lower temperatures of 0°C, resulted in a 1:1 cis:trans isomeric mixture of **1a-b** (Scheme 1, b). The isomer ratio was determined by ^1H NMR

spectroscopy after evaporation of the solvent. The ^1H NMR signals of the trans isomer **1b** were published recently in a crystallographic report,⁷ which allowed assignment of the signals to the respective isomers.



Scheme 1 (a) Well-established synthesis of ethynyl substituted aromatic compounds. (b) Novel synthesis of cyanated aromatic compounds: nucleophilic attack (i): TMS-CN, CsF, acetonitrile, 0°C, 10 min; reductive aromatization (ii): PCl_3 , DMF, acetonitrile, 0°C-rt, 1.5 h.

The rapid reaction using 3 eq of TMS-CN and 20 mol% CsF was monitored by *in-situ* IR spectroscopic measurements (Figure 1, top left). To follow the conversion of the starting material, the carbonyl vibrational bands were integrated in a range of 1730 to 1628 cm^{-1} . Cyanohydrin formation was monitored by plotting the area of a newly appearing peak at 1138 to 1100 cm^{-1} (intermediate peak).

Direct reductive aromatization of **1a-b** toward target compound **2** (Scheme 1, b) using SnCl_2 (or Zn) proved to be impossible. This reaction yields 4-cyanophenol, as was previously described when applying SmI_2 as reducing agent in a similar reaction.⁸ Deprotection of **1a-b** and following reductive aromatization may appear to be a suitable solution to this problem, but results in the back-formation of 1,4-benzoquinone.

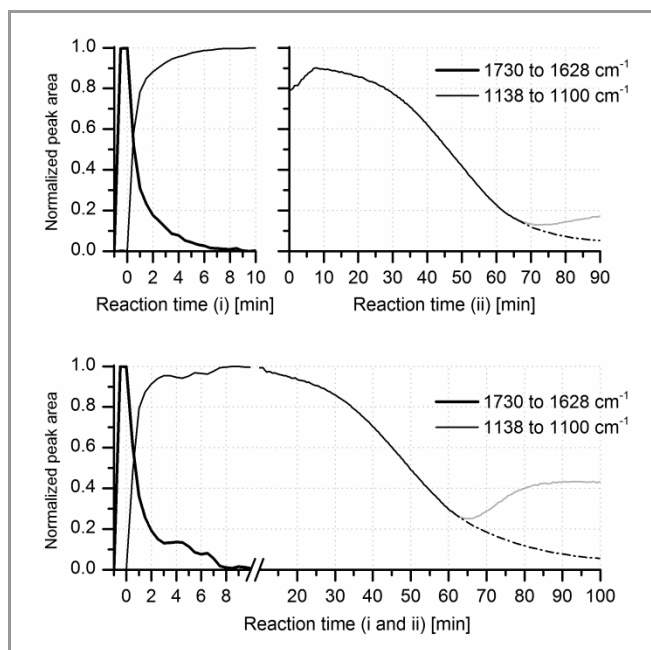


Figure 1 *In-situ* IR spectroscopic measurements of the reactions toward **1a-b** (i) and **2** (ii): stepwise (top) and one-pot reaction (bottom); peaks integrated from 1730 to 1628 cm^{-1} (carbonyl vibrational bands), 1138 to 1100 cm^{-1} (intermediate peak); solid lines: measured values, dotted lines: expected values (deviation attributed to precipitation at the IR probe).

Inspired by the work of Yamaguchi et al.,⁹ we applied POCl_3 in dry pyridine for aromatization toward **2**, and product formation was indeed observed. However, we obtained a significant amount of aromatic byproduct that we were not able to efficiently separate from **2** using column chromatography. This byproduct was attributed to chlorinated dicyanobenzene based on GC-MS measurements. We assume chlorination (substitution of an O-TMS group) followed by a similar elimination-rearrangement step as described for the reaction of 3,6-dimethoxy-3,6-dimethyl-1,4-cyclohexa-diene to methoxyxylenes¹⁰ to be responsible for the formation of this byproduct.

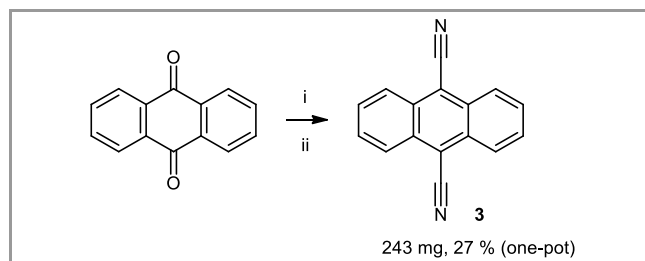
Based on these results and due to the reducing properties of PCl_3 ,¹¹ we tested it as reagent for reductive aromatization. Indeed, addition of PCl_3 to a solution of crude **1a-b** in acetonitrile afforded **2** if two small drops of DMF were added (153 mg, 30 % yield). Only a very small amount of the aforementioned byproduct was observed (larger amounts of DMF resulted in increased byproduct formation). Conversion was again monitored by *in-situ* IR spectroscopic measurements (Figure 1, top right). The lower peak area at the starting point of the reaction is explained by precipitation of the intermediate product when the reaction was cooled to 0°C for addition of DMF and PCl_3 . The reaction was then allowed to warm to room temperature, resulting in increased solubility and, thus, in an increased intermediate product peak area in the early stage of the aromatization reaction.

As the reaction progressed, precipitation at the IR probe was observed, which led to a deviation of the measured values (Figure 1, grey lines) from the expected results (Figure 1, dotted lines). However, an estimation of the reaction time as 90 min turned out to be consistent with GC-MS measurements.

Furthermore, we were able to synthesize **2** in a convenient one-pot reaction without isolating the intermediate compounds **1a-b**. TMS-CN was added just until the carbonyl vibrational bands disappeared completely, thus 1.0 eq TMS-CN was added, followed by another two additions of 0.1 eq each (Figure 1, bottom). After stirring for 10 min, two drops of DMF and 1.0 eq of PCl_3 were added and the reaction was allowed to warm to room temperature. After 1.5 h, the reaction was diluted with dichloromethane and filtered directly through a pad of silica using dichloromethane as eluent. Evaporation of the solvent afforded 155 mg white 1,4-dicyanobenzene **2** with a yield of 30 %.¹²

A greater excess of TMS-CN turned out to inhibit aromatization in one-pot reactions. However, if the solvent and excessive TMS-CN are evaporated in vacuo, the reaction not only proceeds in acetonitrile, but also in dichloromethane and in THF. Application of other reducing agents such as phosphorous acid, diethyl phosphite, trimethyl phosphite, sodium phosphite and sodium sulfite instead of PCl_3 did not result in any product formation.

To investigate the applicability of the reaction conditions to larger and less soluble substrates, we synthesized 9,10-dicyanoanthracene **3** from 9,10-anthraquinone (Scheme 2). *In-situ* IR spectroscopic measurements were not suitable for monitoring the reaction progress due to the above mentioned low solubility. However, according to GC-MS measurements, cyanohydrin formation was complete after 5 h and aromatization was complete overnight. Yields of 27 % (243 mg) were achieved after work-up. Larger amounts of DMF (0.5 eq) were added to allow for a one-pot synthesis despite a larger excess of TMS-CN (1.0 eq excess). This is possible in the synthesis of **3**, since a byproduct formation by rearrangement as for **2** is not feasible.



Scheme 2 One-pot synthesis of 9,10-dicyanoanthracene **3** from 9,10-anthraquinone: nucleophilic attack (i): TMS-CN, CsF, acetonitrile, 0°C, 5 h; reductive aromatization (ii): PCl_3 , DMF, acetonitrile, 0°C-rt, overnight.

In conclusion, the developed protocol is notable due to its convenience and straightforwardness. For the first time, reductive aromatization of cyanohydrins to dicyanoarenes was demonstrated. One-pot conversion to the respective arenes was demonstrated for both

1,4-benzoquinone, which is prone to 1,4-addition and rearrangements, and of 9,10-anthraquinone, which is characterized by low solubility in acetonitrile.

Supporting Information including complete experimental and instrumental details for the synthesis and characterization is available online at <http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083>.

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- (12) General procedure (one-pot): 1,4-Benzoquinone (1.0 eq) was dissolved in acetonitrile (1 M) and added to a suspension of CsF (0.2 eq) in acetonitrile (0.2 M) at 0°C. The reaction was carefully purged with argon and TMS-CN (2.0 eq) was added dropwise, followed by another two additions after 4 min (0.1 eq) and 6 min (0.1 eq). After 10 min total stirring time, DMF (2 small drops) and PCl₃ (1.0 eq) were added. The reaction was allowed to warm to room temperature and stirred for 90 min. The resulting suspension was diluted with dichloromethane and flashed directly over a pad of silica using dichloromethane as the eluent. Evaporation of the solvent afforded 1,4-dicyanobenzene **2** as a white solid (30 % yield).

Short title: Synthesis of Cyanoarenes from Quinones**Graphical Abstract:**