

Synthesis of Phthalonitriles Using a Palladium Catalyst

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Abstract: An easy synthetic method to obtain phthalonitriles from *o*-dibromobenzenes under mild conditions in high yields using Zn(CN)₂ and a catalytic amount of tris(dibenzylideneacetone)dipalladium and 1,1'-bis(diphenylphosphino)ferrocene is described.

Key words: cyanation, *o*-dibromobenzenes, palladium, phthalonitriles

Phthalonitriles are the most important starting materials for preparation of metal-free and metal phthalocyanines.¹ A common pathway for the preparation of phthalonitriles proceeds by the cyano-dehalogenation process known as Rosenmund–von Braun reaction.² Starting from 1,2-dibromobenzenes and reacting them with cuprous cyanide, in refluxing DMF, this reaction often proceeds unsatisfactorily concerning the yields. The harsh reaction conditions and subsequent oxidation of nitrile–cuprous halide, for example, with NH₄OH/air or O₂, FeCl₃ and HCl, prohibit the presence of many functional groups.^{2,3} The use of cuprous cyanide also generally leads to the formation of the corresponding copper phthalocyanine as a byproduct.

In our earlier work⁴ we proposed an easier method to prepare substituted phthalonitriles from substituted catechols via their corresponding aryl bistriflates. The displacement of the triflate groups in catechol triflates by cyanide ions proceeded in high yields using zinc cyanide and tris(dibenzylideneacetone)dipalladium [Pd₂(dba)₃] and 1,1'-bis(diphenylphosphino)ferrocene (DPPF) as catalyst. The mild conditions tolerate numerous functional groups and represent an improvement to the Rosenmund–von Braun reaction for the synthesis of phthalonitriles.

Transition-metal-catalyzed cyanation of halobenzenes is an alternate to Rosenmund–von Braun reaction for the preparation of substituted benzonitriles. Most common catalysts for exchange of halobenzenes or triflates with cyanide are transition-metal complexes of the platinum group, especially palladium or nickel complexes.⁵ In general the cyanation of bromo- and iodobenzenes has been performed in the presence of an excess of cyanide sources like sodium, potassium, or zinc cyanide and potassium hexacyanoferrate(II) in dipolar aprotic solvents like DMF, DMAC, or NMP at 100–160 °C. Various sources for pal-

ladium such as PdCl₂, Pd/C, Pd(OAc)₂ and Pd₂(dba)₃ have been employed successfully to convert the halobenzenes into the corresponding benzonitriles.⁶

As an other alternative to Rosenmund–von Braun reaction and our earlier triflate method for the preparation of substituted phthalonitriles we now introduce palladium-catalyzed cyanation of mono- and disubstituted *o*-dibromobenzenes with Pd₂(dba)₃ and DPPF as the catalyst system in dimethylacetamide (DMAC) as solvent with Zn(CN)₂ as cyanating agent at a temperature of 100–120 °C (Table 1).⁷ The reaction can be performed without an inert atmosphere, which is otherwise a necessary condition for other palladium-catalyzed reactions. The use of inert gas was avoided by using a small amount of polymethylhydrosiloxane (PMHS).⁸ Moreover, we did not find any traces of corresponding phthalocyanine byproduct. The reaction also is easier to perform as our earlier described route via catecholtriflates.⁴ Tris(dibenzylideneacetone)dipalladium, DPPF, and Zn(CN)₂ was used earlier with some iodo- and bromobenzenes as well as aryltriflates which react with formation of the corresponding benzonitriles.⁹ To the best of our knowledge, however, this catalyst system has not been applied for the synthesis of phthalonitriles starting with *o*-dibromobenzenes.

The exchange of the bromo atoms in *o*-dibromobenzenes against CN groups depends upon the substituents in the *para* position of the bromo atoms in the benzene ring: *o*-dibromobenzene (**1a**) itself and the dibromobenzenes **2a–6a**¹⁰ with electron-donating substituents in these positions in comparatively short reaction times are converted into the corresponding phthalonitriles **1b–6b** in yields between 80 and 96% (Table 1). This is also true for 3,4-dibromoaniline (**7a**) and 3,4-dibromoacetanilide (**8a**).¹¹ As expected, 3,4-dibromophenol (**10a**)^{12a} is also easily converted into the corresponding phthalonitrile **9b**; the same applies to the protected *tert*-butyl(3,4-dibromophenoxy)dimethylsilane (**9a**)^{12a} leading to 4-hydroxyphthalonitrile (**9b**). The latter is probably formed after an initial deprotection of **9a** to form **10a**, which is subsequently converted into 4-hydroxyphthalonitrile (**9b**).

Also bromine and fluorine in *para* position to the reacting bromide as in 1,2,4,5-tetrabromobenzene (**11a**), 1,2-dibromo-4-fluorobenzene (**12a**), and 1,2-dibromo-4,5-difluorobenzene (**13a**) allow an easy exchange of the bromine atoms against CN groups. Fluoro atoms are stable against an exchange reaction with the catalyst system.

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Table 1 Palladium-Catalyzed Cyanation of Various *o*-Dibromobenzenes

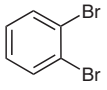
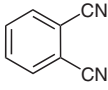
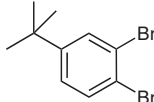
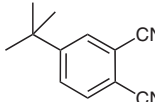
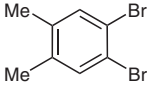
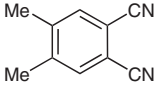
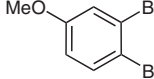
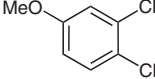
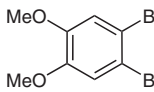
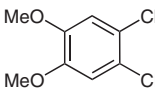
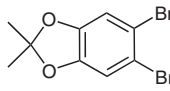
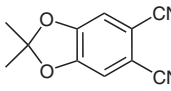
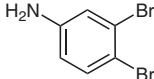
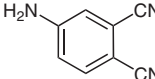
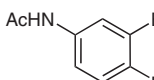
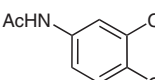
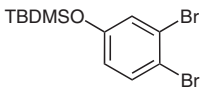
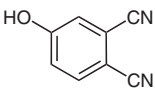
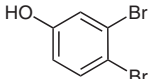
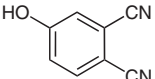
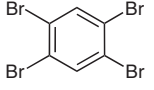
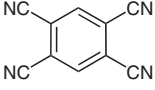
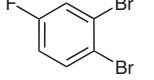
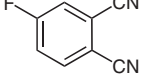
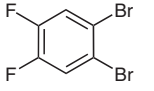
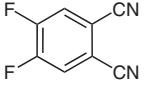
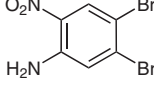
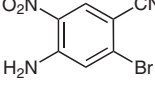
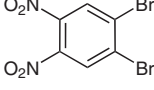
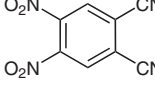
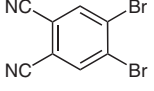
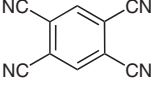
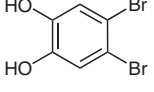
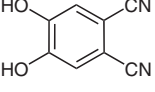
Substrate	Product ^a	Temp (°C)	Time (h)	Yield (%)
1a 	1b 	100	3	86
2a 	2b 	120	2	80
3a 	3b 	110	2	96
4a 	4b 	110	1.5	95
5a 	5b 	120	2.5	90
6a 	6b 	120	2	80
7a 	7b 	110	2	91
8a 	8b 	100	1.5	97
9a 	9b 	100	2	90
10a 	9b 	110	1.5	89
11a 	11b 	100	8	72
12a 	12b 	100	2	87
13a 	13b 	100	3	92
14a 	14b 	120	6	62
15a 	15b 	100–120	3–5	–
16a 	11b 	100	4	73
17a 	17b 	100–120	3–5	–

Table 1 Palladium-Catalyzed Cyanation of Various *o*-Dibromobenzenes (continued)

Substrate	Product ^a	Temp (°C)	Time (h)	Yield (%)
18a 	18b 	100	4	78
19a 	19b 	110	1	93

^a Physical data of all synthesized phthalonitriles were in agreement with the data reported in the literature.

The specific influence of the *para* substituents on the reactivity of the bromo atoms can be seen especially clearly with 4,5-dibromo-2-nitroaniline (**14a**):¹³ only the bromo atom in the *para* position to the electron-donating NH₂ group is exchanged against the CN group, the strong electron-attracting NO₂ group ($\sigma_{p\text{-NO}_2} = 0.778$) in *para* position to the second bromo atom prevents its exchange. This is supported by the results with 1,2-dibromo-4,5-dinitrobenzene (**15a**)¹⁴ which does not react with formation of the corresponding dinitroththalonitrile **15b**.

Contrary to 1,2-dibromo-4,5-dinitrobenzene (**15a**), 4,5-dibromophthalonitrile (**16a**)¹⁵ also with two but lesser electron-attracting CN groups ($\sigma_{p\text{-CN}} = 0.628$) in *para* position to the bromine atoms reacts with formation of 1,2,4,5-tetracyanobenzene (**11b**) although in somewhat lower yields.

In spite of the fact that 3,4-dibromophenol (**10a**) was converted in high yields into the 4-hydroxyphthalonitrile (**9b**), 4,5-dibromocatechol (**17a**) even after a longer reaction time could not be reacted to form 4,5-dihydroxyphthalonitrile (**17b**). This is probably due to a partial decomposition of the catalyst because of its reaction with catechol **17a**. 2,3-Dibromopyridine (**18a**) also reacts under the applied conditions with formation of 2,3-dicyanopyridine (**18b**) in good yield. Only one dibromonaphthalene was investigated: 6,7-dibromo-2,2-dimethylnaphtho[2,3-*d*][1,3]dioxole (**19a**)¹⁶ was converted in a yield of 93% into the corresponding naphthalonitrile **19b**¹⁷ within one hour at 110 °C.

In conclusion we have described another easier alternative to Rosenmund–von Braun reaction, which can be easily used to synthesize mono- and disubstituted phthalonitriles containing various functional groups.

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- (7) **Synthesis of Substituted Phthalonitriles – General Procedure**
A 25 mL two-neck round-bottom flask was charged with 1 mmol of *o*-dibromobenzene in DMAC (2 mL) and PMHS (20 mg) was added at r.t. The reaction mixture was heated to the required temperature (Table 1) and Pd₂(dba)₃ (20 mg, 2 mol%) and DPPF (15 mg, 2.7 mol%) were added. Afterwards, Zn(CN)₂ (117 mg, 1 mmol) was added in 4–5 portions during the time mentioned in Table 1 till TLC indicated completion of the reaction. The reaction mixture was cooled, diluted with EtOAc and filtered. Filtrate was washed with H₂O, dried with MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography using CH₂Cl₂ as eluent.
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- (10) (a) **Synthesis of 1,2-Dibromo-4-*tert*-butylbenzene (2a)**
To a solution of 1-bromo-4-*tert*-butylbenzene (8 g, 0.04 mol) in CCl₄ (5 mL) in the presence of a small amount of iron powder was added a solution of bromine (9.5 g, 0.12 mol) in CCl₄ (4 mL) at 5 °C over 10 min. The mixture was stirred at 15 °C for 2 h. Solvent was evaporated and product was purified by column chromatography using CH₂Cl₂–hexane (1:1) as eluent; yield 11 g (92%). ¹H NMR (400

- MHz, CDCl₃): δ = 7.59 (d, ⁴J = 2.3 Hz, 1 H), 7.50 (d, ³J = 8.4 Hz, 1 H), 7.16 (dd, ³J = 8.4 Hz, ⁴J = 2.3 Hz, 1 H), 1.27 (s, 9 H) ppm. MS (EI): *m/z* (%) = 291.8 (45) [M]⁺, 276.8 (100). (b) Ashton, P.; Girreser, U.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Raymo, F. M.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 5422. (c) Andersh, B.; Murphy, D. L.; Olson, R. J. *Synth. Commun.* **2000**, *30*, 2091. (d) Wenderski, T.; Light, K. M.; Ogrin, D.; Bott, S. G.; Harlan, C. J. *Tetrahedron Lett.* **2004**, *45*, 6851. (e) Ivanov, A. V.; Svinareva, P. A.; Tomilova, L. G.; Zefirov, N. S. *Russ. Chem. Bull. Int. Ed.* **2001**, *50*, 919.
- (11) **Synthesis of 1,2-Dibromo-4-acetanilide (8a)**
3-Bromoacetanilide was brominated with NBS in acetone with catalytic amounts of HCl^{10c} to give after purification by column chromatography 1,2-dibromo-4-acetanilide (**8a**) in 90% yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.84 (s, 1 H), 7.50 (d, ³J = 8.8 Hz, 1 H), 7.38 (br s, 1 H), 7.30 (d, ³J = 8.8 Hz, 1 H), 2.15 (s, 3 H) ppm. MS (EI): *m/z* (%) = 293.0 (100) [M]⁺.
- (12) (a) **Synthesis of tert-Butyl-(3,4-dibromophenoxy)dimethylsilane (9a) and 3,4-Dibromophenol (10a)**
The hydroxy group in 3-bromophenol was protected with *tert*-butyldimethylsilyl chloride in the presence of imidazole to give *tert*-butyl(3-bromophenoxy)dimethylsilane quantitatively.^{12b} ¹H NMR (400 MHz, CDCl₃): δ = 7.09–7.04 (m, 2 H), 7.01–6.96 (m, 1 H), 6.79–6.70 (m, 1 H), 0.96 (s, 9 H), 0.18 (s, 6 H) ppm. MS (EI): *m/z* (%) = 286.0 (20) [M]⁺, 231.0 (100), which was brominated with NBS.^{10c} After purification by column chromatography *tert*-butyl(3,4-dibromophenoxy)dimethylsilane (**9a**) was obtained in 78% yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.41 (d, ³J = 7.5 Hz, 1 H), 7.10 (d, ⁴J = 2.5 Hz, 1 H), 6.64 (dd, ³J = 7.5 Hz, ⁴J = 2.5 Hz, 1 H), 0.95 (s, 9 H), 0.18 (s, 6 H) ppm. MS (EI): *m/z* (%) = 365.9 (40) [M]⁺, 308.9 (100). *tert*-Butyldimethylsilyl group in **9a** was deprotected with tetrabutylammonium fluoride^{12b} to give 3,4-dibromophenol (**10a**) in 92% yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.28 (d, ³J = 8.6 Hz, 1 H), 7.02 (s, 1 H), 6.55 (d, ³J = 8.6 Hz, 1 H) ppm. MS (EI): *m/z* (%) = 252.0 (100) [M]⁺. (b) Tew, G. N.; Pralle, M. U.; Stupp, S. I. *J. Am. Chem. Soc.* **1999**, *121*, 9852.
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- (16) (a) **Synthesis of 6,7-Dibromo-2,2-dimethylnaphtho[2,3-d][1,3]dioxole (19a)**
To 5.6 g (17.6 mmol) of 2,3-dibromo-6,7-dihydroxynaphthalene^{16b} dissolved in toluene (40 mL) toluene and anhydrous acetone (5 mL) was added P₂O₅ in three portions during 48 h while the reaction mixture was heated at 50 °C. The solution was diluted with toluene (50 mL), washed with H₂O, 10% NaOH soln, H₂O and brine. Combined organic phase was concentrated with a rotary evaporator. Purification of the crude product was carried out by column chromatography using dichloromethane as eluent; yield 3.42 g (57%). ¹H NMR (400 MHz, CDCl₃): δ = 7.88 (s, 2 H), 6.87 (s, 2 H), 1.71 (s, 6 H) ppm. MS (EI): *m/z* (%) = 357.9 (60) [M]⁺, 342.8 (100). (b) Youssev, T. E.; Hanack, M. J. *Porphyryns Phthalocyanines* **2002**, *6*, 571.
- (17) Compound **19b**: ¹H NMR (400 MHz, CDCl₃): δ = 8.05 (s, 2 H), 7.10 (s, 2 H), 1.77 (s, 6 H) ppm. MS (EI): *m/z* (%) = 250.0 (40) [M]⁺, 235.0 (100), 210.0 (50).