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A practical synthesis of highly functionalized aryl nitriles through cyanation of aryl bromides employing heterogeneous Pd/C: in quest of an industrially viable process

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Abstract—Preparation of aryl nitrile **2a** through classical Rosenmund-von Braun reaction of aryl bromide **1a** resulted in a poor yield (61%) due to a high reaction temperature (165 °C) and a lack of efficient procedure for separating **2a** from a large quantity of heavy metal waste (Cu salts). To address these issues, a practical synthesis of multifunctional aryl nitriles through cyanation of aryl bromides has been developed with heterogeneous Pd/C used as the catalyst. Treatment of aryl bromides **1** with $Zn(CN)_2$ in the presence of Pd/C, Zn, $ZnBr_2$ and PPh_3 in DMA provided aryl nitriles **2** involving those carrying sterically demanding electron-rich substituent in good yields and in highly reproducible manner. The activity of Pd/C is highly dependent on the properties of the Pd/C. Oxidic thickshell type catalyst Pd/C D5 was found to furnish the highest rate acceleration and yield. The use of heterogeneous Pd/C might anchor and disperse Pd over the solid support of the catalyst, at least in the initial stage of the reaction, to assure the formation of monomeric Pd complex without precipitating to inactive Pd black. The use of a slightly excess of $Zn(CN)_2$ (0.6 equiv) and air oxidation of phosphine ligand, after end of the reaction, converted Pd species to insoluble phosphine-free Pd cyanides, from which Pd was recovered in high yield through simple filtration followed by usual recovery process involving combustion.

1. Introduction

Development of an industrially viable process for drug synthesis forces one to consider a number of factors to affect feasibility of the reaction as well as economy of the overall sequence. For protection of the ecology, the reaction with lower environmental impact is required as well. Meanwhile, Pd-catalyzed cross coupling reaction has recently been underscored as a synthetic methodology and its application to large-scale production of chemicals carrying various functional groups has been extensively investigated with some measure of success.[1] As significance of aryl nitriles in the drug synthesis[2] increases, so does the demand for the truly efficient synthetic method. Synthesis of aryl nitriles through Pd-catalyzed cyanation of aryl halides[3] represents one of the most direct approaches to this important class of compounds. In contrast to remarkable leading-edge technologies, accomplished on the Pd-catalyzed C–C and C–X (X=N, O and S) bond forming reaction such as Suzuki–Miyaura coupling, Heck reaction, amination and amidation in the past decade,[1c] Pd-catalyzed cyanation is far from perfect and still needs further investigation for subjecting to scalable and cost-effective preparations. Intensive efforts to improve the reaction have currently been undertaken not only in academia but also in pharmaceutical industries. However, they still pose many challenges, when aimed at applying for commercial-scale production. They need inherently very expensive and/or toxic phosphine ligand or additive. Cyanation of aryl halides carrying sterically demanding electron-rich substituent, such as amino and hydroxyl group, has hardly been accomplished, still posing a big challenge for the practical use. Reported herein is a course of our investigations to develop a more versatile and industrially viable process for the cyanation of aryl bromides.[4]

2. Results and discussion

2.1. Synthesis of aryl nitrile 2a through Rosenmund-von Braum reaction of aryl bromide 1a

Cyanation of aryl bromide was first investigated applying classical Rosenmund-von Braun reaction[5] with 3-bromo-4-hydroxymorpholinobenzamide (**1a**) used as the typical

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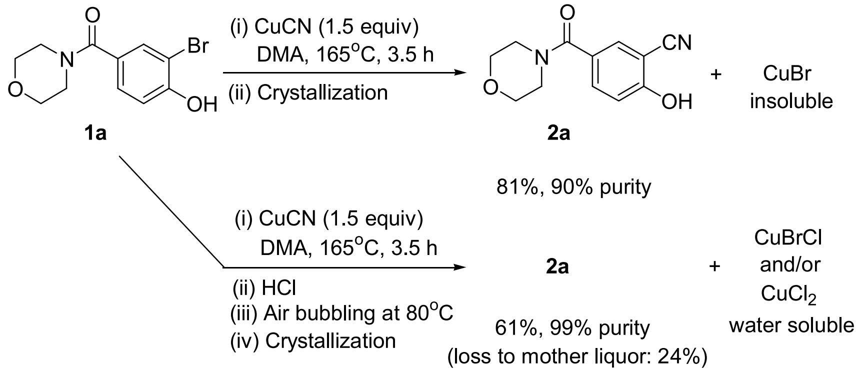


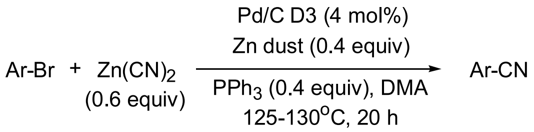
Scheme 1. The Rosenmund-von Braun reaction of **1a** to **2a** and isolation of the product **2a**.

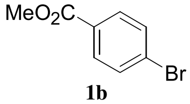
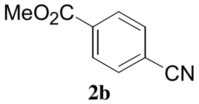
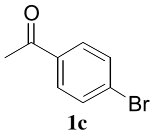
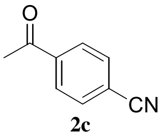
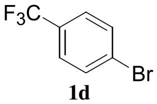
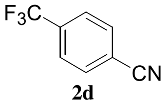
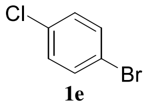
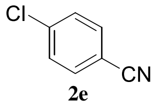
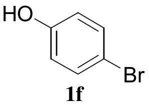
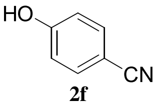
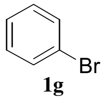
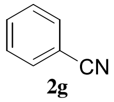
substrate (Scheme 1). Treatment of **1a** with CuCN (1.5 equiv) in DMA at 165 °C for 3.5 h gave desired aryl nitrile **2a** in 93% yield (98% conversion), accompanied by a small amount of hydration byproduct, 3-carbamoyl-4-hydroxymorpholinobenzamide (**3**) (**2a**/**3**=95:5). Isolation of the product **2a** was initially conducted by direct crystallization of the residue that was obtained by evaporation of DMA. Purity of the resulting **2a** was, however, at most 90%, as it was contaminated with a large amount of insoluble Cu^{I} salts. The use of an alternative workup, involving oxidation of the insoluble Cu^{I} salts to soluble and easy-removable Cu^{II} analogues (CuClBr and/or CuCl$_2$)[6] and subsequent crystallization, provided much purified **2a** (purity: 99%). However, the yield was moderate (61%), because of considerable loss of **2a** to the mother liquor.

2.2. Synthesis of aryl nitrile 2a through cyanation of aryl bromide 1a with Zn(CN)$_2$ employing Pd/C, Zn and PPh$_3$

To lower the reaction temperature and to eliminate the formation of a large amount of hazardous Cu salts, we investigated Pd-catalyzed cyanation of aryl bromides as an alternative method. In a series of our synthetic studies of

Table 1. Cyanation of various aryl bromides **1b–g** to aryl nitriles **2b–g** with Zn(CN)$_2$ in the presence of Pd/C D5, Zn and PPh$_3$



Entry	Substrate **1b–g**	Substrate **2b–g**	Conv. (%)[a]	Assay yield (%)[a]
1[b]	 **1b**	 **2b**	29–100	31–72
2	 **1c**	 **2c**	99	93
3	 **1d**	 **2d**	100	91
4	 **1e**	 **2e**	100	58
5	 **1f**	 **2f**	6	—[c]
6	 **1g**	 **2g**	0	—[c]

[a] Determined by HPLC.

[b] The reaction was conducted at 130–150 °C for 20–24 h.

[c] Not determined.