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Synthesis of dialkyl cyanoboronates and their application in palladium-catalyzed cyanation of aryl halides

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Abstract—A new type of cyanoboronate **4** was prepared and used as a new cyano group source in palladium-catalyzed cyanations of aryl and heteroaryl halides to afford the corresponding aryl and heteroaryl nitriles. © 2001 Elsevier Science Ltd. All rights reserved.

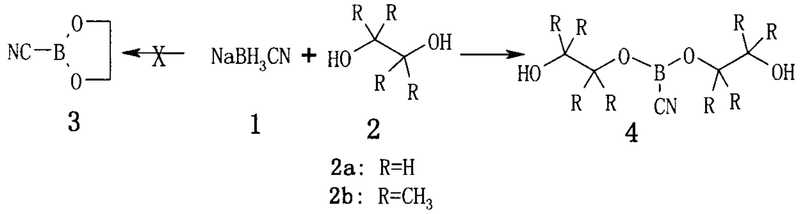
1. Introduction

Aryl nitriles are very important materials because of their wide applications in laboratory and industry studies. Various methods have been reported for their synthesis.[1] The most convenient one is the stoichiometric reaction of aryl halides with copper(I) cyanide at high temperature, but the product isolation is very troublesome due to the formation of the copper complex in the course of reaction.[2] The Reissert–Henze cyanation of π-deficient heteroarene N-oxides,[3] and the electrophilic cyanation of π-excessive heteroaromatics[4] are also known as efficient methods for preparation of aryl and heteroaryl cyanides. But these methods have proven to be of limited use for some specific substrates.

Palladium-catalyzed displacement of aryl halides and triflates with cyanide ion to afford the corresponding aryl nitrile has been reported as a more favorable alternative.[5,6] Although many modifications[5c–d,7–9] have been developed about the ligand sets, the use of covalent or the cyano group sources, these procedures have only been useful for the preparation of benzonitrile derivatives.[6] A general procedure of palladium-catalyzed cyanation, applicable to the preparation of aryl and heteroaromatic nitriles, has not been well developed. Furthermore, there is no report about the application of dialkyl cyanoboronate as the cyanide source in the palladiun-mediated cyanation, although potassium, sodium, trimethylsilyl and zinc cyanides have been used widely. In this paper we introduce the synthesis of dialkyl cyanoboronates and their application as a new cyanide source in palladium-catalyzed cyanation.

2. Results and discussions

Cyanoboronate derivatives are new types of organoboron compounds, the preparation and properties of which have been not reported up to now in any literatures.[10–14] In our initial studies, we wanted to synthesize cyclic dialkyl cyanoboronate **3** (Scheme 1), by treatment of 1,2-dihydroxy compound **2** with one equivalent of sodium cyanoborohydride $NaBH_3CN$ **1**. But as a result, we found acyclic compound **4** was produced and no cyclic compound **3** was observed. More interestingly, dialkyl cyanoboronate **4** was obtained as the single product whether one or two equivalents of 1,2-dihydroxy compound **2a** or **2b** was used in the



Scheme 1.

Keywords: dialkyl cyanoboronate; palladium; cyanation; aryl halide.

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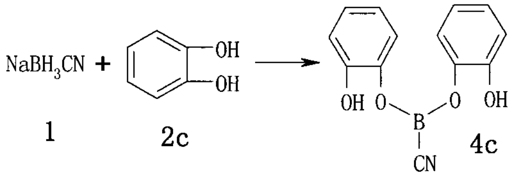


Scheme 2.

reaction. Under the same conditions, treating **2c** with compound **1** afforded compound **4c** (Scheme 2).

Although the mechanism of production of compound **4** in our reaction was unclear, it was necessary to employ *vicinal*-dihydroxy compound **2**. Employing simple alcohols such as methanol, ethanol and *tert*-butanol in place of 1,2-dihydroxy compounds **2** gave trialkylborates and no dialkyl cyanoboronate **4** was observed.

In order to explore the properties of dialkyl cyanoboronate **4**, we carried out the cyanation reaction of compound **4** with aryl or heterocyclic aryl halides catalyzed by palladium. First we studied the effects of different bases, palladium catalysts, temperature and solvents using the model reaction of 4-bromo-1-nitro benzene with dialkyl cyanboronate **4b**. The results are summarized in Table 1.

As shown above, the best result was obtained by using Pd $(PPh_3)_4$ as the catalyst (entry 4), the yields dropped significantly when $PdCl_2(Ph_3P)_4$ was used. Potassium phosphate was the best choice of base over other organic and inorganic bases. THF was a better solvent than toluene in this reaction.

Under these optimum conditions, we expanded the cyanation reaction to other aryl and heterocyclic aryl halides. The results are described in Table 2.

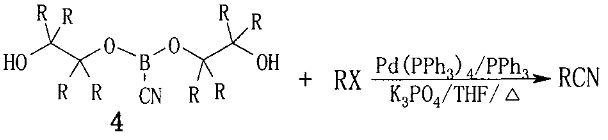
As shown in Table 2, most of aryl halides react with dialkyl cyanoboronate **4** to afford the corresponding nitrile products (entries 1–10), but the cyanation reaction proceeded slowly and the yields changed widely according to different substituents in the aryl halide substrates. It was reported[15] the treatment of 1-chloro-3-iodobenzene with KCN in HMPA in the presence of palladium acetate afforded a mixture of 3-chlorobenzonitrile and 1,3-benzenedicarbonitrile (77:23), while in our system 4-chloro-1-iodobenzene and 1,4-diiodobenzene gave 4-chloro-benzonitrile and 4-iodobenzonitrile as the single product, respectively. No dicyanation products were detected (entries 3–4), but the yields were unsatisfactory. At the same time, heteroaryl halides, such as 2-iodo-thiophene (entry 12) and *N*-methylsulfonyl-3-iodoindole (entry 11), can also react with dialkyl cyanoboronate **4** to give heteroaryl nitriles. The mechanism of the

Table 1. Effects of reaction conditions on Pd-catalyzed cynation of 4-nitro-bromobenzene with compound **4b**

Entry	Base	M-complex	T (°C)	Time, days	%,Conversion[a]
1	K_3PO_4	$Pd(PPh_3)_4$–PPh_3	25[b]	6	76
2	K_3PO_4	$PdCl_2(PPh_3)_2$–PPh_3	50[b]	6	12
3	Et_3N	$Pd(PPh_3)_4$–PPh_3	50[b]	10	15
4	K_3PO_4	$Pd(PPh_3)_4$–PPh_3	50[b]	6	97
5	$AgNO_3$	$Pd(PPh_3)_4$–PPh_3	50[b]	6	2
6	K_3PO_4	$Pd(PPh_3)_4$–PPh_3	100[c]	6	80

[a] Conversion determined by GC–MS.
[b] Reaction in THF.
[c] Reaction in toluene.

Table 2. Pd-catalyzed cyantion of aryl and heterocydic aryl halides with compound **4**



Entry[a]	Substrate	Time	%, Conv[b]	Product
1	Iodobenzene	24 h	80 (78)	Benzonitrile
2	4-Trifuloromethyl-2-nitro-1-chlorobenzene	24 h	40 (19)	4-Trifuloromethyl-2-nitrobenzonitrile
3	4-Chloro-1-iodobenzene	17 h	67 (37)	4-Chloro-benzonitrile
4	1,4-Diiodobenzene	42 h	13 (10)	4-Iodobenzonitrile
5	4-Nitro-1-bromobenzene	6 d	97 (89)	4-Nitrobenzonitrile
6	4-Nitro-1-iodobenzene	48 h	58 (50)	4-Nitrobenzonitrile
7	2,4-Dinitro-1-chlorobenzene	12 h	33 (32)	2,4-Dinitro-benzonitrile
8	2,4-Dinitro-1-bromobenzene	10 h	64 (60)	2,4-Dinitro-benzonitrile
9	1-Bromo-naphthalene	24 h	87 (72)	1-Cyano-naphthalene
10	1-Iodo-naphthalene	10 h	72 (69)	1-Cyano-naphthalene
11	*N*-Methylsulfonyl-3-iodoindole	24 h	49 (39)	*N*-Methylsulfonyl-3-cyano-indole
12	2-Iodo-thiophene	24 h	83 (75)	2-Cyano-thiophene

[a] Compound **4a** was used in entry 1and compound **4b** was used in entries 2–12.
[b] Conversion was determined by GC–MS and the parenthesis is the isolated yield based on starting halide.

palladium-catalyzed cyanation of dialkyl cyanoboronate **4** with aryl halides, would be similar to that of cross-coupling reaction,[6] including oxidative addition of aryl halides to catalyst, ligand exchange of cyano anion with halogen anion and reductive elimination.

In conclusion, a new type of cyanoboronate **4** was prepared. As a new cyano group source, they can be used in palladium-catalyzed cyanation of aryl and heteroaryl halides to afford the corresponding aryl and heteroaryl nitriles, but the yields were unsatisfactory.

3. Experimental

NMR spectra were recorded as $CDCl_3$ solutions on a VXL-300 instrument. The ^1H NMR (300 MHz) chemical shifts are reported as δ values in ppm relative to tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin–Elmer 983 FT–IR spectrometer. Mass spectral measurements were performed on a Fining 4021 or Fining MAT 8403 gas chromatography/mass spectrometer at 70 eV. All solvents were purified and dried by standard techniques before use. $NaBH_3CN$ was purchased from Aldrich. Pd $(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ were prepared according to literature procedures.[5a,16] All reactions were monitored by thin layer chromatography (TLC) using silica gel GF254. Products were purified by chromatography on silica gel manufactured in Qingdao Marine Chemical Factory, eluting with the solvent mixture of petroleum ether (bp 60–90°C) and ethyl acetate.

3.1. General procedure for the preparation of dialkyl cyanoboronates 4

To a 0°C cooled solution of sodium cyanoborohydride **1** (630 mg, 0.01 mol) and vicinal dihydroxy compound **2** (0.02 mol) in THF (4 mL), under argon was dropped a solution of dry hydrogenchloride-diethyl ether (1N, 10 mL). After completion, the resultant mixture was stirred for another 1 h at 0°C. The precipitate was filtered and the filtrate was evaporated. The residue was subjected to bulb-to-bulb distillation. The dialkyl cyanoboronate **4** was obtained as a viscous liquid. This material was very air and water-sensitive, it must be stored in low temperature under inert atmosphere.

3.1.1. Di(2-hydroxyethyl) cyanoboronate 4a. (1.22 g, 77%); bp 80–85°C/0.1 mmHg; ν_{max}(neat) 3401, 2265, 1399, 1349,1106, 1083 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.03–4.05 (4H, m), 4.21 (4H, t); *m/z* (EI) 159 (M^+, 24), 157 (M^+-2,100), 133 (M^+-CN, 6), 128 (M^+-CH_2OH, 41%); HRMS (EI): M^+, found: 159.0700. $C_5H_{10}NO_4B$ requires 159.0703. M^+-2, found 157.0512. $C_5H_8NO_4B$ requires 157.0546.

3.1.2. Di(1,1,2,2-tetramethyl-2-hydroxyethyl) cyanoboronate 4b. (1.97 g, 73%); bp 118–120°C/0.1 mmHg; ν_{max}-(neat) 3430, 2254, 1450, 1375, 1147, 1098 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.63 (broad s, 2H), 1.20 (s, 24H); *m/z* (EI) 271 (M^+, 5), 270 (100), 255 (54), 133 (4%); HRMS (EI): M^+, found 271.1953. $C_{13}H_{26}NO_4B$ requires 271.1955. M^+-1, found: 270.1874. $C_{13}H_{25}NO_4B$ requires 270.1877.

3.1.3. Di(2-hydroxyphenyl) cyanoboronate 4c. (2.08 g, 82%); bp 173–175°C/0.1 mmHg; ν_{max}(neat) 3451, 2299, 1364, 1192, 1095 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ_H 6.65–6.98 (m, Ar–H); *m/z* (EI) 255 (M^+, 1), 254 (100), 228 (2), 109 (64%); HRMS (EI): M^+, found 255.0705. $C_{13}H_{10}NO_4B$ requires 255.0703. M^+-1, found 254.0588. $C_{13}H_9NO_4B$ requires 254.0624.

3.2. General procedure for palladium-catalyzed cyanation using dialkyl cyanoboronate 4a or 4b as the cyano group source

The substrate (0.5 mmol), dialkyl cyanoboronate **4a** or **4b** (0.6 mmol), $Pd(PPh_3)_4$ (28 mg, 0.025 mmol), PPh_3 (12 mg, 0.05 mmol), and anhydrous potassium phosphate (80 mg, 0. 75 mmol) were placed in a flask which was flushed with Argon. Freshly redistilled THF (5 mL) was added via syringe. The resulting mixture was heated to 50°C under argon with vigorous agitation. Then the mixture was cooled to room temperature, diluted with diethyl ether (20 mL), and filtered through a pad of celite. The filtrate was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated by rotary evaporation. This residue was subjected to GC–MS for determination of the conversion, the isolated yields were obtained after further purification of the residue by silica gel chromatography (ethyl acetate/petroleum).

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