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Palladium-Catalyzed Cyanomethylation of Aryl Halides through Domino Suzuki Coupling−Isoxazole Fragmentation

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Supporting Information

ABSTRACT: A one-pot protocol for the cyanomethylation of aryl halides through a palladium-catalyzed reaction with isoxazole-4-boronic acid pinacol ester was developed. Mechanistically, the reaction proceeds through (1) Suzuki coupling, (2) base-induced fragmentation, and (3) deformylation as shown by characterization of all postulated intermediates. Under optimized conditions ($PdCl_2$dppf, KF, DMSO/H_2O, 130 °C) a broad spectrum of aryl bromides could be converted into arylacetonitriles with up to 88% yield.

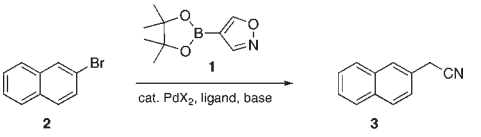
The arylacetonitrile unit is found as a structural motif in several important drugs, including the calcium channel blocker *verapamil*, the antitussive drug *isoaminile*, the aromatase inhibitor *anastrozole*, or the phosphodiesterase-4 inhibitor *cilomilast*.[1] Due to the versatile reactivity of both the cyano and the adjacent α-methylene group, arylacetonitriles also represent valuable intermediates for the synthesis of other relevant molecules such as monoamine neurotransmitters,[2] arylpropionic acids[3] (or amides), or various heterocycles.[4]

Arylacetonitriles are commonly prepared from side-chain-substituted arenes by functional group interconversion.[5] Other methods require drastic or rather specialized conditions.[6] In principle, the transition-metal-catalyzed coupling of an aryl halide with an acetonitrile anion equivalent represents a particularly appealing approach to arylacetonitriles.[7] In 1984, Migita reported the Pd-catalyzed coupling of bromoarenes with α-tributylstannylacetonitrile.[7a] Later, Frejd described the Ni-catalyzed coupling of aryl-zinc reagents with bromoacetonitrile.[7b] More recently, Hartwig reported a (Zn-mediated) Pd-catalyzed method for the coupling of aryl bromides with TMS-acetonitrile,[7c,d] which rapidly found application in drug research.[7e−g]

In the course of our medicinal chemistry program we recently attempted to attach a 4-isoxazolyl substituent to different arenes by means of Pd-catalyzed Suzuki coupling[8] starting from aryl bromides and isoxazole-4-boronic acid pinacol ester (**1**). However, in all cases rather complex mixtures were obtained which contained the corresponding arylacetonitriles as the main products in 16 to 28% isolated yield (for a typical example see Scheme 1).

This surprising finding prompted us to investigate the reaction in more detail in order to understand the mechanism and to possibly improve the yield of the valuable arylacetonitrile products. Here, we disclose the results of this study, which has indeed led to the development of an efficient and general new protocol for the cyanomethylation of bromoarenes and related substrates.

Scheme 1. Cyanomethylation of 2-Naphthyl Bromide (2) by Pd-Catalyzed Reaction with the 4-Isoxazolyl Boronate 1



As a standard system for the initial optimization of reaction parameters we selected the reaction of 2-naphthyl bromide (**2**) with boronate **1** to (2-naphthyl)acetonitrile (**3**) (Scheme 1 and Table 1).[9] Under typical Suzuki conditions (using *n*-propanol or DMF as a solvent, $PdCl_2(PPh_3)_2$ as a catalyst, and aqueous Na_2CO_3 as a base) a complex mixture was obtained from which **3** could be isolated in an about 40% yield, under both microwave-assisted (130 °C, 30 min) or simple thermal conditions (90 °C, 16 h) (Table 1, entries 1 and 2). Using $PdCl_2$dppf as a catalyst, DMF was identified as a suitable solvent, which in combination with potassium fluoride (as one of several bases tested) afforded the cyanomethylated product **3** in a respectable isolated yield of 86% (Table 1, entry 11).

While a rather clean and high-yielding transformation was also observed with Cs_2CO_3 or CsOH as a base, the use of NaOH led to the increased formation of two more polar side products, which were identified as the amide and the carboxylic acid corresponding to **3** (formed by nitrile hydrolysis). Obviously, KF is an ideal (mild) base, which efficiently mediates the desired transformation without inducing the hydrolysis of the product **3**. This base (KF) also proved to be superior to other fluorides such as LiF, CsF, or TBAF (Table 1, entries 11 to 14).

Applying the best conditions found so far (KF, DMF, 90 °C) we next tested a set of different Pd-catalysts, most of which were generated *in situ* from a Pd-source and a promising ligand such as 2-(di-*tert*-butylphosphino)-biphenyl (**4**),[10] DavePhos (**5**),[10] the Beller ligand (**6**),[11] or X-Phos (**7**)[12] (Figure 1). However, as the results given in Table 1 (entries 15−22) demonstrate, none of these catalysts surpassed $PdCl_2$dppf. While $Pd(t\text{-}BuP_3)_2$[13] and the combinations of **4**-$PdCl_2$, **5**-$Pd(OAc)_2$, and **6**-$Pd(OAc)_2$ proved to be quite active (to give **3** in 68 to 76% yield) significantly lower yields (conversions) were observed for

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Table 1. Variation of Reaction Conditions in the Cyanomethylation of (2-Naphthyl)bromide (2) According to Scheme *1*'[a]

Entry	Pd	Base	Solvent	*T* (°C)	Yield[b] (%)
1	$PdCl_2(PPh_3)_2$	Na_2CO_3	*n*-propanol	130[c]	42
2	$PdCl_2(PPh_3)_2$	Na_2CO_3	*n*-propanol	90	38
3	$PdCl_2(PPh_3)_2$	Na_2CO_3	DMF	90	39
4	$PdCl_2$dppf	Na_2CO_3	*n*-propanol	90	<5[d]
5	$PdCl_2$dppf	Na_2CO_3	DMF	90	42
6	$PdCl_2$dppf	Na_2CO_3	THF	90	29
7	$PdCl_2$dppf	Cs_2CO_3	DMF	90	71
8	$PdCl_2$dppf	CsOH	DMF	90	68
9	$PdCl_2$dppf	NaOH	DMF	90	50
10	$PdCl_2$dppf	K_3PO_4	DMF	90	35
11	**$PdCl_2$dppf**	**KF**	**DMF**	**90**	**86**
12	$PdCl_2$dppf	LiF	DMF	90	<5[d,e]
13	$PdCl_2$dppf	CsF	DMF	90	35[e]
14	$PdCl_2$dppf	TBAF	DMF	90	53
15	$Pd(tBu_3P)_2$	KF	DMF	90	69
16	$Pd(OAc)_2$, **4**	KF	DMF	90	59
17	$Pd(OAc)_2$, **5**	KF	DMF	90	69
18	$Pd(OAc)_2$, **6**	KF	DMF	90	76
19	$PdCl_2$, **4**	KF	DMF	90	68
20	$PdCl_2$, **6**	KF	DMF	90	15[d]
21	$Pd(dba)_2$, **6**	KF	DMF	90	42[d]
22	$Pd(dba)_2$, **7**	KF	DMF	90	29[d,e]
23	$PdCl_2$dppf	KF	DMF	130	70
24	$PdCl_2$dppf	KF	DMSO	90	56
25	**$PdCl_2$dppf**	**KF**	**DMSO**	**130**	**88**
26	$PdCl_2$dppf	KF	DMSO	130[c]	77
27	$PdCl_2$dppf	KF	DMSO	130	79[f]

[a] Conditions: **1** (1.2 equiv), **2** (1.0 equiv), base (3 equiv, 1 M in water), Pd-cat./L (10 mol %), 0.1 M solution in solvent, 16 h. [b] Isolated yield. [c] Reaction was irradiated in a microwave reactor for 30 min. [d] Yield of **3** determined by UPLC. [e] In this case, unreacted **2** was detected by UPLC: 48% (entry 12), 9% (entry 13), 2% (entry 22). [f] Isoxazole-4-boronic acid (1.2 equiv) was used instead of **1**. The structures of ligands **4** to **7** are shown in Figure 1.

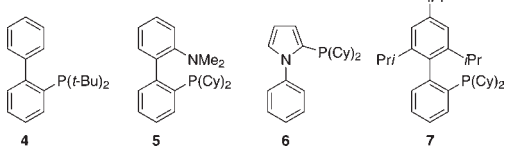
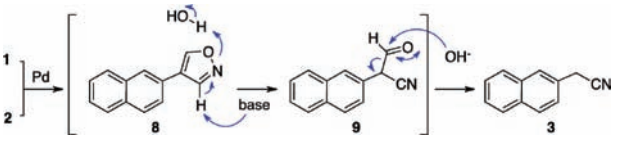


Figure 1. Some of the ligands tested (see Table 1).

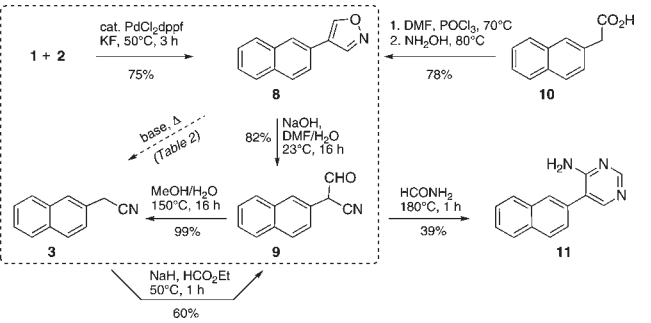
4-$Pd(OAc)_2$-, **6**-$PdCl_2$-, and the $Pd(dba)_2$-derived complexes of **6** and **7**.

Finally, we probed whether the cyanomethylation reaction could be performed (under the optimized conditions) at even higher temperatures. However, running the reaction at 130 °C in DMF afforded the nitrile **3** in only 70% yield (compare entries 11 and 23 in Table 1), possibly due to DMF activation at this temperature resulting in dehalogenation.[14] We were then pleased to identify DMSO as a particularly suitable solvent. At 130 °C a remarkably clean transformation was observed yielding the product in 88% isolated yield (Table 1, entry 25). Lower yields

Scheme 2. Proposed Mechanism for the Formation of 3



Scheme 3. Synthesis and Interconversion of Proposed Reaction Intermediates and Products of the Cyanomethylation Process



of **3** were obtained under microwave irradiation or when isoxazole-4-boronic acid was used instead of the pinacol ester **1** (Table 1, entries 26 and 27).

As a mechanistic rationale for the observed formation of **3** we assumed a base-induced fragmentation of the primary cross coupling product, i.e. the isoxazole **8**, to give the α-formyl-nitrile **9**, which in turn is converted to **3** by a retro-Claisen-type process (Scheme 2).

To shed light on the proposed reaction mechanism (and to investigate the influence of the reaction parameters on the individual steps of the sequence) we synthesized and characterized all the proposed intermediates (Scheme 3).

A pure reference sample of **8**, prepared in two steps from (2-naphthyl)acetic acid (**10**),[15] allowed us to identify this compound as an intermediate always appearing in small quantities during the cyanomethylation process (UPLC analysis). When the Suzuki coupling was performed under milder conditions (cat. $PdCl_2$dppf, KF, DMF/H_2O, 50 °C, 1 h) it was possible to suppress the fragmentation and to isolate **8** in 75% yield. On heating to 90 °C in the presence of an aqueous base, **8** effectively underwent fragmentation to afford **3**.[16] By variation of conditions (Table 2) we could show that heat, base, and water are required for this process. CsF or NaOH were less effective (some nitrile hydrolysis was observed with NaOH). In the presence of KF the fragmentation proceeded also smoothly in methanol as a solvent.

An authentic sample of the aldehyde **9** as a proposed intermediate of the fragmentation process (generated through deprotonation at the 3-position of the isoxazole **8**)[17] was prepared by Claisen condensation[4d] of **3** with ethyl formate (Scheme 3). This compound proved to be identical with an intermediate regularly appearing in the UPLC chromatograms of the cyanomethylation reaction mixtures (as a characteristic double peak, probably resulting from tautomerization). **9** could also be obtained from **8** in 82% yield by treatment with aqueous NaOH at room temperature. As the NMR spectra of **9** are quite complex (tautomeric mixture of *E*- and *Z*-enol forms) its identity was

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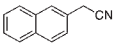
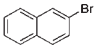
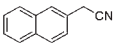
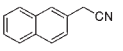
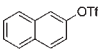
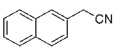
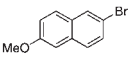
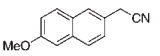
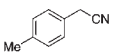
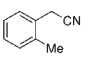
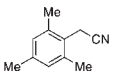
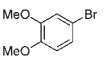
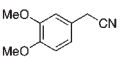
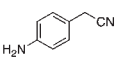
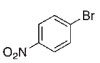
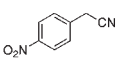
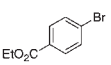
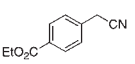
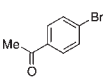
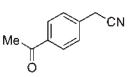
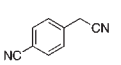
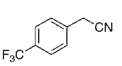
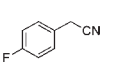
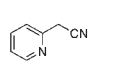
Table 2. Fragmentation of 4-(2-Naphthyl)-isoxazole 8 to Nitrile 3[a]

Entry	Base	Solvent	T (°C)	Yield[b] (%)
1	–	DMF	90	0
2	KF	DMF	23	3
3	KF	DMF	90	96 (95)[c]
4	KF	DMF	90	<5[d]
5	CsF	DMF	90	53
6	NaOH	DMF	90	69
7	KF	MeOH	90	97

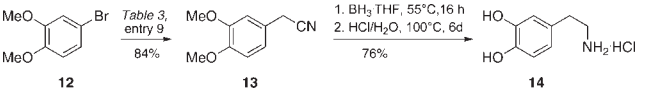
[a] Conditions: **8**, base (3 equiv, 1 M in water), 1 h. [b] Yield of **3** determined by UPLC. [c] Isolated yield. [d] Nonaqueous conditions.

Table 3. Cyanomethylation of Various Substrates[a]

Entry	Ar-X	Ar-CH_2-CN	Yield[b] (%)
1			3[c]
2			88
3			90
4			66
5			74
6			82
7			69
8			64
9			84
10			74
11			49
12			71
13			86
14			72
15			68
16			81
17			65

[a] Conditions: Ar–X (1 equiv), **2** (1.2 equiv), KF (3 equiv, 1 M in water), $PdCl_2$dppf (10 mol %), DMSO (0.1 M sol.), 130 °C, 16 h. [b] Isolated yield. [c] Conversion determined by UPLC.

Scheme 4. A Short Synthesis of Dopamine (14)



12 13 14

additionally corroborated by conversion into the 4-aminopyrimidine derivative **11**[4a] (Scheme 3). The transformation of **8** to **9** at room temperature demonstrates the crucial role of heat for the second step (**9** to **3**) of the one-pot fragmentation of **8** to **3**, and the results summarized in Table 2 also confirm the particular role of potassium fluoride for the optimized cyanomethylation protocol. This base is strong enough to promote the Suzuki coupling and to induce the fragmentation of **8** to **3** at elevated temperatures while it does not catalyze the formation of byproducts resulting from nitrile hydrolysis.

Applying the optimized conditions, we then demonstrated the scope of the cyanomethylation protocol employing a broad range of substrates (Table 3). Not unexpectedly, the yields obtained with different 2-naphthyl halides and the triflate reflect the rate order for the initial oxidative addition step (I ≈ Br > OTf ≫ Cl).[8] Interestingly, no significant differences were observed in the reactivity of various aryl bromides carrying either electron-withdrawing or -donating substituents. In all cases investigated, the product was obtained in good yield (64–86%), the only exception being 4-nitrophenyl-acetonitrile (49%).

To demonstrate the usefulness of the cyanomethylation protocol developed, we finally applied the methodology in a short synthesis of the naturally occurring neurotransmitter dopamine (**14**) (Scheme 4). Starting from 3,4-dimethoxy-bromobenzene (**12**) the cyanomethylated product **13** was obtained in 84% yield (Table 3, entry 9). Conversion of the nitrile function to the corresponding amine[18] using borane as a reducing agent and subsequent cleavage of the methylethers by prolonged heating with aqueous hydrochloric acid[19] then afforded dopamine-hydrochloride (**14**) in 64% overall yield from **12** (Scheme 4).

In conclusion, we have discovered, optimized, and applied a novel methodology for the cyanomethylation of aryl halides. Using commercially available isoxazole-4-boronic acid pinacol ester as a reagent (acetonitrile anion equivalent) the process exploits a Suzuki cross-coupling with subsequent base-induced isoxazole fragmentation and opens an efficient access to a broad spectrum of arylacetonitriles in an operationally simple and reliable fashion.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902. (b) *The Merck Index*, 13th ed.; O'Neil, M. J., Ed.; Merck & Co.: Rahway, NJ, 2001.

(2) (a) Norregaard, L.; Gether, U. *Curr. Opin. Drug Discover Dev.* **2001**, *4*, 591. (b) *Comprehensive Medicinal Chemistry*; Pergamon Press: 1990; Vol. 3, Chapter 12.

(3) Higgs, G. A.; Higgs, E. A.; Moncada, S. *Comprehensive Medicinal Chemistry*; Pergamon Press: 1990; Vol. 2, p 147.

(4) (a) Davies, H. W.; Piggott, H. A. *J. Chem. Soc.* **1945**, 347. (b) Guzman-Perez, A.; Maldonado, L. A. *Synth. Commun.* **1991**, *21*, 1667. (c) Khlifi, A.; El Efrit, M. L.; Zantour, H. *J. Soc. Chim. Tunisie* **2006**, *8*, 1. (d) Lisowski, V.; Nghia Vu, D.; Feng, X.; Rault, S. *Synthesis* **2002**, 753.

(5) Selected references: (a) Gomberg, M; Buchler, C. C. *J. Am. Chem. Soc.* **1920**, *42*, 2067. (b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. *Org. Lett.* **2000**, *2*, 1737. (c) Telvekar, V. N.; Rane, R. A. *Tetrahedron Lett.* **2007**, *48*, 6051. (d) Kangani, C. O.; Day, B. W.; Kelley, D. E. *Tetrahedron Lett.* **2008**, *49*, 914. (e) Chen, G.; Wang, Z.; Wu, J.; Ding, K. *Org. Lett.* **2008**, *10*, 4573.

(6) See, for instance: (a) Makosza, M.; Winiarski, J. *J. Org. Chem.* **1980**, *45*, 1534. (b) Kurz, M. E.; Lapin, S. C.; Mariam, A.; Hagen, T. J.; Qian, X. Q. *J. Org. Chem.* **1984**, *49*, 2728. (c) Khanapure, S. P.; Biehl, E. R. *J. Org. Chem.* **1990**, *55*, 1471. (d) Stazi, F.; Maton, W.; Castoldi, D.; Westerduin, P.; Curcuruto, O.; Bacchi, S. *Synthesis* **2010**, 3332.

(7) (a) Kosugi, M.; Ishiguro, M.; Negishi, Y.; Sano, H.; Migita, T. *Chem. Lett.* **1984**, 1511. (b) Frejd, T.; Klingstedt, T. *Synthesis* **1987**, 40. (c) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330. (d) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824. (e) Baldwin, J. J. (Vitae Pharmaceuticals, Inc.) U.S. Patent WO 2008/124575, 2008; *Chem. Abstr.* 149:471340. (f) Zhuo, J.; Xu, M.; He, C.; Zhang, C.; Qian, D.; Burns, D. M.; Li, Y.; Metcalf, B.; Yao, W. (Incyte Corporation) U.S. Patent WO 2008/064157, 2008; *Chem. Abstr.* 149:10050. (g) Besidski, Y.; Claesson, A.; Csjernyik, G.; Gravenfors, Y.; Kers, I.; Skogholm, K.; Sohn, D. (AstraZeneca AB) U.S. Patent WO 2008/130319, 2008; *Chem. Abstr.*149:534057.

(8) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Miyaura, N.; de Meijere, A.; Diederich, F. *Metal Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH; Weinheim, 2004.

(9) The reactions were monitored and the crude reaction products analyzed by means of UPLC (see Supporting Information).

(10) (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (b) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

(11) Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38.

(12) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

(13) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (d) Kudo, N; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282. (e) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555.

(14) (a) See ref 8b, p 80. (b) Ghosez, I.; Franc, C.; Denonne, F.; Cuisiner, C.; Touillaux, R. *Can. J. Chem.* **2001**, *79*, 1827.

(15) (a) Church, R.; Trust, R.; Albright, J. D.; Powell, D. *J. Org. Chem.* **1995**, *60*, 3750. (b) Zlotin, S. G.; Kislitsin, P. G.; Samet, A. V.; Serebryakov, E. A.; Konyushkin, L. D.; Semenov, V. V.; Buchanan, A. C., III; Gakh, A. A. *J. Org. Chem.* **2000**, *65*, 8430.

(16) Takagi, S.; Yasuda, H. *Yakugaku Zasshi* **1959**, *79*, 467.

(17) (a) Johnson, W. S.; Petersen, J. W.; Gutsche, C. D. *J. Am. Chem. Soc.* **1947**, *69*, 2942. (b) Jain, S. M.; Pawar, R. A. *Indian J. Chem.* **1975**, *13*, 304.

(18) Theodore, L. J.; Nelson, W. L. *J. Labelled Compd. Radiopharm.* **1989**, *27*, 491.

(19) Budnik, J. CZ Patent CS 227998 B1 19840514, 1984; *Chem. Abstr.* 106:18256.