JOC*Note*

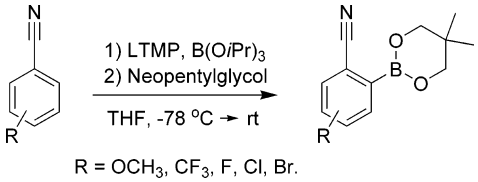
Synthesis of Substituted 2-Cyanoarylboronic Esters

Morten Lysén, Henriette M. Hansen, Mikael Begtrup, and Jesper L. Kristensen*

Department of Medicinal Chemistry, The Danish University of Pharmaceutical Sciences, Universitetsparken 2, DK-2100 Copenhagen, Denmark

jekr@dfuni.dk

Received November 21, 2005



The synthesis of substituted 2-cyanoarylboronic esters is described via lithiation/in situ trapping of the corresponding methoxy-, trifluoromethyl-, fluoro-, chloro-, and bromobenzonitriles. The crude arylboronic esters were obtained in high yields and purities and with good regioselectivities.

Arylboronic acid derivatives have become very valuable tools in organic synthesis. They have gained immense popularity in the synthesis of biaryls via cross-coupling reactions, and much effort is still devoted to the development of these reactions with respect to catalyst design, coupling partners, and application of different arylboronic derivatives.[1] The popularity of arylboronic acid derivatives can be attributed to them being nontoxic, "shelf-stable carbanions". This has spawned the development of many new applications for these derivatives, and the list of applications continues to grow: synthesis of arylglycines,[2] asymmetric Rh-catalyzed 1,4-additiones to conjugated systems,[3] coupling with amines, alcohols, and thiols,[4] synthesis of arylhalides.[5] With this increasing use of arylboronic acid derivatives, the demand for efficient protocols for the preparation of diversely substituted arylboronic acid derivatives is an ever more pressing issue. Traditionally, arylboronic acid derivatives have been prepared by reacting an aryllithium intermediate, generated by deprotonation or halogen/metal exchange, with a trialkylborate.[6] Alternatively, arylboronic acid derivatives can be synthesized from aryl halides via Pd(0)-catalyzed coupling with tetraalkoxydiboron or dialkoxyborane.[7] Recently, the borylation of aromatic and heteroaromatic systems via Ir-catalyzed C−H activation has also been developed.[8]

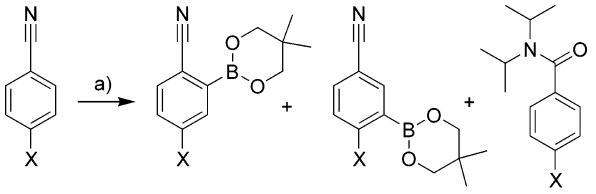
When synthesizing ortho-substituted arylboronic derivatives, the directed ortho metalation (DOM) is an obvious choice for generating the required organometallic intermediate, since it has become one of the most reliable reactions available to the synthetic chemist for the preparation of 1,2-disubstituted aromatic systems.[9] Innumerable examples of its use in synthesis have appeared since its discovery in the 1930s by Wittig and Gilman.[10] The ability of different substituents to direct metalation has been studied extensively, and a hierarchy between different directed metalation groups (DMGs) has been established experimentally.[9b] The DOM, and other metalation reactions, are usually viewed as stepwise processes. Step one is the generation of a metalated species via the action of a suitable base. Step two is the reaction of that intermediate with the chosen electrophile. This is also reflected in the way it is done experimentally: First, the base is added to a solution containing the substrate, and then, after a specified period of time has passed, the electrophile is added. Alternatively, the substrate is added to a solution containing the base so-called "inverse addition." Intuitively, certain requirements must be fulfilled for this approach to be successful: (1) Metalation must prevail over nucleophilic attack of the base on the DMG or other functionalities in the substrate. (2) The stabillity of the metalated species is important. Even if the metalation step is fast, some decomposition, rearrangement, or self-condensation, etc., might be faster. Thus, the metalated species will be consumed before the electrophile is introduced. (3) If the metalation is reversible, the base must be sufficiently strong to fully deprotonate the substrate, i.e., there should be a difference of at least 4 pK_a units between the base and the substrate. Otherwise, one would expect that the reaction would give a mixture of unchanged substrate, desired product, and possibly the product arising from the reaction between the base and the electrophile.

In 1983, Krizan and Martin introduced the concept of in situ trapping, i.e., using a sterically hindered base to generate an unstable lithio intermediate in the presence of an electrophile.[11] It is based on the following principle: Although the base may not be strong enough to fully deprotonate the substrate, and the lithiated species is unstable, *the introduction of an electrophile that is compatible with the base, but reacts with the lithiated species*, will push the reaction to completion, via an in situ trapping of the lithiated species. In 1998, Caron and Hawkins reported a variant of this reaction, using LDA/B(O-*i*-Pr)$_3$ to synthesize ortho-substituted arylboronic acids.[12] Later, we broadened the scope of this approach using LTMP/B(O-*i*-Pr)$_3$ for the synthesis of ortho-substituted aryl- and heteroarylboronic

(1) For an extensive list of references, see: Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201.
(2) Petasis, N. A.; Goodman, A.; Zavualov, I. A. *Tetrahedron* **1997**, *53*, 16463.
(3) Hayashi, T. *Pure Appl. Chem.* **2004**, *76*, 465.
(4) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.
(5) (a) Thompson, A. L. S.; Kabalka, G. W.; Akula, M. R.; Huffman, J. W. *Synthesis* **2004**, *4*, 547. (b) Szumigala, R. H.; Devine, P. N.; Gauthier, D. R.; Volante, R. P. *J. Org. Chem.* **2004**, *69*, 566.
(6) König, W.; Scharrnbeck, W. *J. Prakt. Chem.* **1930**, *128*, 153.
(7) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458.
(8) (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 391. (c) Ishiyama, T.; Takagi, J.; Nobuta, Y.; Miyaura, N. *Org. Synth.* **2005**, *82*, 126.
(9) (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(10) (a) Wittig, G.; Pockels, U.; Dröge, H. *Chem. Ber.* **1938**, *9*, 1903. (b) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109.
(11) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.
(12) Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054.

10.1021/jo052400g CCC: $33.50
Published on Web 02/24/2006

TABLE 1. In Situ Trapping of Para-Substituted Benzonitriles



entry	base	X	**2**	**3**	**4**	yield[b] (%)	purity[c] (%)
1	LTMP	OMe (**a**)	30	70		96	95
2	LTMP	CF_3 (**b**)	>99	<1		99	99
3	LTMP	F (**c**)	40	60		94	95
4	LTMP	Cl (**d**)	93	7		99	95
5	LTMP	Br (**e**)	90	10		98	99
6	LDA	OMe (**a**)	25	25	60		
7	LDA	CF_3 (**b**)	40		60		
8	LDA	F (**c**)	35	45	20		
9	LDA	Cl (**d**)	60	35	5		
10	LDA	Br (**e**)	70	25	5		

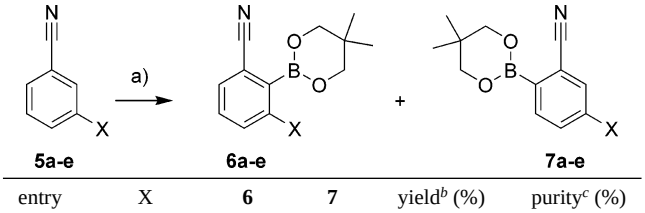
[a] See the Experimental Section for details. [b] Isolated yield of crude product on a 10 mmol scale. [c] Purity of crude pruduct with respect to **2a**−**e**/**3a**−**e**, as determined from NMR and GC−MS.

esters.[13] The nonnucleophillic nature of LTMP makes it possible to ortho-lithiate benzonitrile and ethyl benzoate, substrates not suited for classical DOM reactions. This procedure is easily scalable to produce multigrams of material.[14] Herein, we wish to report the extension of this methodology to the ortho-lithiation/in-situ borylation of ortho-, meta-, and para-substituted benzonitriles. We intentionally chose to include substrates that were expected to yield mixtures of regioisomers to test the scope of the reaction.

Submitting para-substituted benzonitriles **1a**−**e** to our standard condition for in situ trapping on a 10 mmol scale gave full conversion of the starting benzonitriles to yield mixtures of the two possible regioisomeric neopentylglycol arylboronic esters; see Table 1, entries 1−5. The borylation of 4-methoxybenzonitrile (**1a**) and 4-fluorobenzonitrile (**1c**) was unselective, giving 30:70 and 40:60 mixtures of the two possible isomers. In contrast, 4-trifluoromethylbenzonitrile (**1b**) yielded a single arylboronic ester (**2b**) in 99% isolated yield. Chloro- and bromo-substituted benzonitriles **1d** and **1e** yielded preparatively useful 93:7 and 90:10 mixtures of the corresponding arylboronic esters.[15]

Attempts to improve the selectivity in the in situ trapping with LTMP/B(O-*i*-Pr)$_3$ via the addition of TMEDA were unsuccessful.[16] LDA/B(O-*i*-Pr)$_3$ was tested, but as seen from Table 1, the selectivity remained largely unchanged (entries 7 and 8) or dropped (entries 6, 9, and 10). Furthermore, the *N*,*N*-diisopropylbenzamides **4a**−**e**, resulting from nucleophilic attack of LDA on the cyanogroups in **1a**−**e**, were produced as byproducts in 5−60% yield.[17]

TABLE 2. In Situ Trapping of Meta-Substituted Benzonitriles



entry	X	**6**	**7**	yield[b] (%)	purity[c] (%)
1	OMe (**a**)	>99	<1	96	>99
2	CF_3 (**b**)	<1	>99	98	>99
3	F (**c**)	>99	<1	96	95[d]
4	Cl (**d**)	>99	<1	*e*	*e*
5	Br (**e**)	>99	<1	96	95[f]

[a] See the Experimental Section for details. [b] Isolated yield of crude product on a 10 mmol scale. [c] Purity of crude product with respect to **6a**−**e**/**7a**−**e**, as determined from NMR and GC−MS. [d] Contains 5% diborylated product. [e] See text for details. [f] Contains 3% of **5e** and 2% of diborylated product.

The lithiation of meta-substituted benzonitriles **5a**−**e** gave the arylboronic esters resulting from lithiation between the two substituents on the ring; see Table 2. The exception was **5b**, where lithiation occurred exclusively para to the CF_3 group, giving **7b** as the only detectable species in 98% isolated yield. This result is in good agreement with observations made by Schlosser, who showed that trifluoromethylbenzenes possessing a DMG in the 3-position are lithiated in the 4-position when bulky bases like LTMP are employed.[18]

Arylboronic ester **6d** proved impossible to isolate as a single entity: It readily hydrolyzed to give a mixture of the boronic acid and boronic acid anhydrides. Furthermore, **6d** deborylated to give the **5d** upon storage at rt. This was also the case for **6e**, which deborylated upon storage at rt. for several weeks.[19] Szumigala et al. reported the borylation of **5c** using LDA/B(O*i*Pr)$_3$ giving the arylboronic acid analogous to **6c** in 75% yield, but were unable to fully characterize this species as it was obtained as a complex mixture of the free acid and different anhydrides.[5b] Cyanoarylboronic ester **6c** was isolated and easily characterized as a single, stable entity with well-defined ^{1}H and ^{13}C NMR spectra.

The lithiation of ortho-substituted benzonitriles was generally more regioselective than the lithiation of para-substituted benzonitriles; see Table 3. Most noteworthy is the completely selective borylation of 2-methoxybenzonitrile (**8a**) in which **9a** is produced exclusively in excellent yield and purity. Compared with the borylation of **1a**, which gave a 30:70 mixture (Table 1, entry 1), this result is quite astounding. We speculate that the highly selective lithiation of **8a** is due to hindered rotation of the methoxygroup because of the adjacent cyanogroup, impeding coordination of the oxygen lone pair to LTMP.

2-Fluorobenzonitrile (**8c**) furnished a similar unselective mixture of regioisomers as was the case with **1c**. In the lithiation of 2-chlorobenzonitrile (**8d**) and 2-bromobenzonitrile (**8e**), the regioselectivity was improved to give only 5% and 2% of the other regioisomer.[15]

(13) (a) Kristensen, J. L.; Lysén, M.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435. (b) Hansen, H. M.; Lysén, M.; Begtrup, M.; Kristensen, J. L. *Tetrahedron* **2005**, *61*, 9955.

(14) Kristensen, J. L.; Lysén, M.; Vedsø, P.; Begtrup, M. *Org. Synth.* **2005**, *81*, 134.

(15) Isomerically pure **2d**, **2e**, **9d**, and **9e** can be obtained through recrystallization, but the purity of the crude products is sufficient to be used directly in most subsequent transformations. Isomerically pure samples of **2a**/**3a**, **2c**/**3c**, and **9c**/**10c** were not obtained.

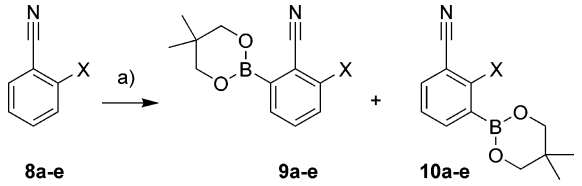
(16) (a) Fraser, R. R.; Mansour, T. S. *Tetrahedron Lett.* **1986**, *27*, 331. (b) For an exellent discussion on the use of TMEDA, see: Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 488.

(17) Recently, Chotana et al. obtained very similar product ratios in the synthesis of cyanoarylboronic esters via Ir-catalyzed coupling of **1a**−**c** with pinacolborane. The regioisomeric mixtures of pinacolarylboronic esters were isolated in 65−76% yield based on the borylating agent; see: Chotana, G. A.; Rak, M. A.; Smith, M. R. *J. Am. Chem.* Soc. **2005**, *127*, 10539.

(18) Schlosser, M. *Angew. Chem., Int. Ed.* **1998**, *110*, 1496.

(19) All other cyanoarylboronic esters reported herein are stable for several months at rt when stored without special precautions.

TABLE 3. In Situ Trapping of Ortho-Substituted Benzonitriles



entry	X	9	10	yield[b] (%)	purity[c] (%)
1	OMe (**a**)	>99	<1	96	>99
2	CF3 (**b**)	>99	<1	99	>99
3	F (**c**)	40	60	99	>99
4	Cl (**d**)	95	5	96	>99
5	Br (**e**)	98	2	97	>99

[a] See the Experimental Section for details. [b] Isolated yield of crude product on a 10 mmol scale. [c] Purity of crude pruduct respect to **9a**−**e**/**10a**−**e**, as determined from NMR and GC−MS.

2-Cyanoarylboronic esters are very efficiently employed in Suzuki couplings with aryl halides[13a] and carbamoyl chlorides.[20] They are also readily acylated,[21] aminated,[22] or converted to indenones and indanones.[23] Furthermore, cyanoarylboronic esters can be converted to the corresponding aryltetrazole boronic esters via treatment with $TMSN_3$.[24] To briefly demonstrate the synthetic utility of the arylboronic esters reported in this study, a two-step synthesis of a substituted phenanthridine was performed (see Scheme 1).

Coupling of crude **7b** with 1-bromo-4-chloro-2-fluorobenzene under standard Suzuki coupling conditions produced the corresponding biphenyl **11** in 67% unoptimized yield on a 5 mmol scale. This biphenyl was converted to the corresponding 6-substituted phenanthridine **12** in 74% isolated yield via addition of lithium morpholide to the cyano group followed by intramolecular displacement of the fluorine.[25]

(20) Lysén, M.; Kelleher, S.; Begtrup, M.; Kristensen, J. L. *J. Org. Chem.* **2005**, *70*, 5342.

(21) (a) Urawa, Y.; Ogura, K. *Tetrahedron Lett.* **2003**, *44*, 271. (b) Urawa, Y.; Nishiura, K.; Souda, S.; Ogura, K. *Synthesis* **2003**, 2882.

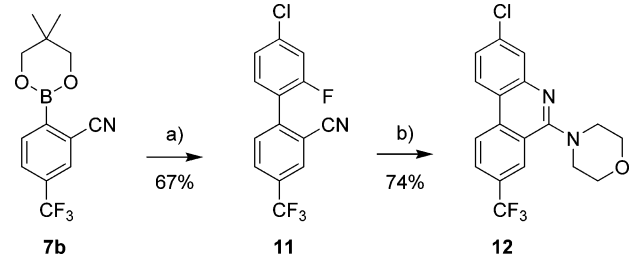
(22) Nishiura, K.; Urawa, Y.; Souda, S. *Adv. Synth. Catal.* **2004**, *346*, 1679.

(23) Miura, T.; Murakami, M. *Org Lett.* **2005**, *7*, 3339.

(24) Schlutz, M. J.; Coats, S. J.; Hlasta, D. J. *Org. Lett.* **2004**, *6*, 3265.

(25) Lysén, M.; Kristensen, J. L.; Vedsø P.; Begtrup, M. *Org. Lett.* **2002**, *4*, 257.

SCHEME 1. Application of 2-Cyanoarylboronic Esters in the Two-Step Synthesis of Phenanthridines[a]



In conclusion, we have demonstrated that the lithiation/in situ trapping protocol with LTMP/$B(O\text{-}i\text{-}Pr)_3$ is a very efficient procedure for the preparation of substituted 2-cyanoarylboronic esters.

Experimental Section

General Procedure for the Lithiation/In Situ Trapping on Substituted Benzonitriles: Synthesis of Cyanoarylboronic Esters. In a 100 mL dry Schlenk flask under N_2 was dissolved 2,2,6,6-tetramethylpiperidine (12 mmol) in dry THF (25 mL) and the mixture was cooled to −10 °C before *n*-buLi (12 mmol) was added over 2 min. The mixture was stirred for 10 min before cooling to −78 °C. At −78 °C, $B(O\text{-}i\text{-}Pr)_3$ (14 mmol) was added over 2 min and stirred for 5 min at −78 °C before the benzonitrile (10 mmol) dissolved in dry THF (10 mL) was added dropwise over 5 min. The reaction was left in the dry ice bath overnight, slowly reaching room temperature. The reaction was quenched with glacial acetic acid (14 mmol) followed by addition of 2,2-dimethyl-1,3-propanediol (15 mmol). The mixture was stirred for 1 h at room temperature and then transferred to a separating funnel with CH_2Cl_2 (75 mL) and washed with aqueous KH_2PO_4 (10 w/v %) (4 × 60 mL). The combined water phase was back-extracted once with CH_2Cl_2 (15 mL), the combined organic phase was dried over $MgSO_4$, and the solvents were evaporated to give the crude cyanoarylboronic ester.

Supporting Information Available: Full experimental details and charaterization of new compounds, including copies of ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052400G