JOC*Note*

Synthesis of 2,3-Substituted Thienylboronic Acids and Esters

Claus Christophersen,*[,†,‡] Mikael Begtrup,[‡] Søren Ebdrup,[§] Henning Petersen,[§] and Per Vedsø[§]

Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark, Department of Medicinal Chemistry, The Danish University for Pharmaceutical Sciences, Universitetsparken 2, DK-2200 Copenhagen N, Denmark, and Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark

clcp@novonordisk.com

Received June 27, 2003

Abstract: A noncryogenic protocol for the synthesis of 2-substituted 3-thienylboronic acids and esters as well as 3-substituted 2-thienylboronic acids and esters has been developed. Electrophiles were introduced regiospecifically in the 2-position of 2,3-dibromothiophene and in the 3-position of 2-bromo-3-iodothiophene by halogen−magnesium exchange followed by quenching with electrophiles. Palladium-catalyzed borylation of the 2,3-substituted halothiophenes with pinacolborane and P(*t*-Bu)$_3$ as ligand for Pd produced **9** and **10**. The borylation protocol was tolerated by a range of functional groups; however, strongly electron-withdrawing substituents decreased the stability of the thienylboronic acids and esters.

Polyfunctionalized thiophenes are of interest in research fields such as natural product synthesis,[1] drug design,[2] and material science.[3] Therefore, the ready availability of suitable precursors such as disubstituted thiophenes is of great importance. A number of methods have been developed for the synthesis of disubstituted thiophenes. In addition to ring-closure protocols,[4] electrophilic aromatic substitution,[5] proton−metal exchange,[6] halogen−metal exchange,[6a,7] and oxidative addition of metals to halothiophenes have been utilized.[7a,8] However, the ring-closure methods are generally not suitable for preparation of thiophenes possessing sensitive substituents, and thiophenes that can be synthesized by electrophilic aromatic substitution are limited due to the inherent activation of the 2- and 5-position and the directing effects of substituents already present. Synthesis of disubstituted thiophenes via proton−metal exchange is restricted to 2,5-disubstituted or 2,3-disubstituted thiophenes, and in the case of lithiation in the 3-position of 2-substituted thiophenes, low temperature and specific ortho-directing groups have to be applied.[6] Only a few disubstituted thiophenes have been synthesized via halogen−metal exchange or oxidative addition to dihalothiophenes, although regiospecific metalations have been reported.[6−8] Dihalothiophenes are commercially available or can be prepared in good yields.[9]

The versatility of organoboron compounds in metal-catalyzed coupling reactions has made arylboronic acids or aryl boronates attractive nucleophiles.[10] A number of substituted aryl boronates have been synthesized by metal-catalyzed borylations of substituted aryl halides or triflates with dialkoxyhydroboranes[11] or tetraalkoxydiboranes.[12] These borylation reactions are compatible with a wide range of functional groups, making these methodologies useful for the preparation of functionalized aryl boronates. However, only a few substituted thienyl boronates have been synthesized by Pd(0)-catalyzed

† Novo Nordisk A/S, Novo Allé.

‡ The Danish University for Pharmaceutical Sciences.

§ Novo Nordisk A/S, Novo Nordisk Park.

(1) (a) Bohlmann, F.; Zdero, C. In *The Chemistry of Heterocyclic Compounds: Thiophenes and Its Derivatives*; Gronowitz, S., Ed.; John Wiley & Sons: New York, 1985; Vol. 44, Part 1, pp 261−323. (b) Pelkey, E. T. *Prog. Heterocycl. Chem.* **1998**, *10*, 87−108.

(2) Press, J. B. In *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*; Gronowitz, S., Ed.; John Wiley & Sons: New York, 1991; Vol. 44, Part 4, pp 397−502. (b) Negwer Database on http://cwgen.chemweb.com/negwersearch.html. (c) *Index Nominum 2000, International Drug Directory*; Swiss Pharmaceutical Society, Ed.; Medpharm Scientific Publishers: Stuttgart, 2000.

(3) (a) Roncali, J. *Chem. Rev.* **1992**, *92*, 711−738. (b) Schopf, G.; Koβmehl, G. In *Advances in Polymer Science: Polythiophenes − Electrically Conductive Polymers*; Abel, A., Ed.; Springer-Verlag: Berlin, Heidelberg, New York, 1997; Vol. 129.

(4) Weissberger, A.; Taylor, E. C. In *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*; Gronowitz, S., Ed.; John Wiley & Sons: New York, 1985; Vol. 44, Part 1, pp 1−213.

(5) Weissberger, A.; Taylor, E. C. In *The Chemistry of Heterocyclic Compounds*: *Thiophene and Its Derivatives*; Gronowitz, S., Ed.; John Wiley & Sons: New York, 1986; Vol. 44, Part 2, pp 1−117.

(6) (a) Frejd, T. In *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*; Weissberger, A., Taylor, E. C., Eds.; John Wiley & Sons: New York, 1992; Vol. 44, Part 5, pp 257−754. (b) Carpenter, A. J.; Chadwick, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 173−181. (c) Chadwick, D. J.; Ennis, D. S. *Tetrahedron* **1991**, *47*, 9901−9914. (d) Grimaldi, T.; Romero, M.; Pujol, M. D. *Synlett* **2000**, 1788−1792.

(7) (a) Reinicke, M. G.; Pedaja, P. In *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*; Weissberger, A., Taylor, E. C., Eds.; John Wiley & Sons: New York, 1986; Vol. 44, Part 2, pp 159−522. (b) Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449−7453. (c) Abarbri, M.; Thibonnet, L.; Bérillon, F.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618−4638. (d) Iida, T.; Wada, T.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2001**, *42*, 4841−4844.

(8) (a) Steinkopf, W.; Schmitt, H. F.; Friedler, H. *Justus Liebigs. Ann. Chem.* **1937**, *527*, 237−261. (b) Lawesson, S.-O. *Arkiv Kemi* **1957**, *11*, 337−343. (c) Gronowitz, S.; Petterson, K. *J. Heterocycl. Chem.* **1976**, *13*, 1099−1100. (d) Lawesson, S.-O. *Arkiv Kemi* **1957**, *11*, 317−324. (e) Lawesson, S.-O. *Arkiv Kemi* **1957**, *11*, 325−336. (f) Kim, S.-H.; Rieke, R. D. *Tetrahedron Lett.* **1997**, *38*, 993−996. (g) Rieke, R. D.; Kim, S.-H.; Wu, X. *J. Org. Chem.* **1997**, *62*, 6921−6927.

(9) The three isomeric dibromothiophenes are commercially available. 2-Bromo-3-iodothiophene can be prepared according to ref 8c. 2-Bromo-4-iodothiophene can be prepared according to: Gronowitz, S.; Holm, B. *Acta Chem. Scand.* **1976**, *B30*, 505−511. 3-Bromo-2-chlorothiophene can be prepared according to: Gronowitz, S.; Holm, B. *Acta Chem. Scand.* **1976**, *B30*, 423−429. 4-Bromo-2-chlorothiophene can be prepared according to: Dettmeier, U.; Eichler, K.; Kühlein, K.; Leupold, E. I.; Litterer, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 468−469.

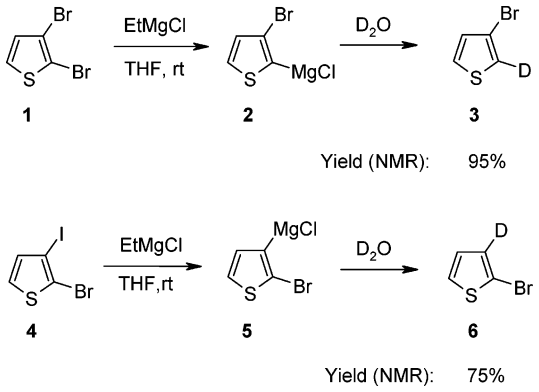
(10) For reviews: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (c) Suzuki, A. In *Metal-catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 49−97.

(11) (a) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458−6459. (b) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164−168. (c) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268−9271. (d) Song, Y.-L.; Morin, C. *Synlett* **2001**, 266−268. (e) Melaimi, M.; Mathey, F.; Le Floch, P. *J. Organomet. Chem.* **2001**, *640*, 197−199.

(12) (a) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392−402. (b) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 0, 7508−7510. (c) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447−3450. (d) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813−9816. (e) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390−391. (f) Fürstner, A.; Seidel, G. *Org. Lett.* **2002**, *4*, 541−543. (g) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649−5651.

10.1021/jo034919n CCC: $25.00
Published on Web 10/31/2003

SCHEME 1. Preparation of 2,3-Bromothienylmagnesium Chlorides from 2,3-Dihalothiophenes



borylation with tetraalkoxydiboranes,[12b,g] and to the best of our knowledge, no substituted thienyl boronates have been synthesized using cheaper dialkoxyhydroboranes.

We report herein a protocol for the synthesis of 2-substituted 3-thienylboronic acids and esters as well as 3-substituted 2-thienylboronic acids and esters from 2,3-dihalothiophenes using a combination of halogen−magnesium exchange followed by trapping with an electrophile and then by palladium-catalyzed borylation of 2-substituted 3-bromothiophenes or 3-substituted 2-bromothiophenes.

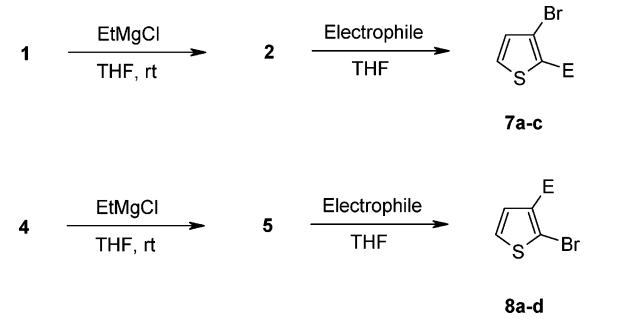
To have flexible protocols for the preparation of 2,3-disubstituted thiophenes, we investigated regiospecific metalation and functionalization of the 2-position followed by metalation and functionalization of the 3-position and vice versa.

Initially, a protocol for the preparation of 2,3-substituted bromothiophenes was investigated. Regiospecific preparations of 2,3-halothienylmagnesium halides from 2,3-dihalothiophenes have been demonstrated by using the entrainment method (Mg, ethyl bromide, or 1,2-dibromoethane)[8a−c] or by halogen−magnesium exchange (ethylmagnesium bromide).[8b] The entrainment method provides good yields but is less attractive since large excesses of magnesium and entrainers are prerequisites. Therefore, halogen−magnesium exchange was studied (Scheme 1) though only moderate yields have been reported with this protocol.[8b]

Treatment of 2,3-dibromothiophene (**1**) with ethylmagnesium chloride (1.1 equiv) in THF at room temperature gave 100% conversion of **1** with formation of 95% 3-bromo-2-thienylmagnesium chloride and 5% of 3-bromothiophene.[13] The amount of active Grignard reagent was established after quench with D_2O followed by NMR determination of the 2-deuterio-3-bromothiophene (**3**) formed. Using the same procedure, 2-bromo-3-iodothiophene (**4**) was consumed to an extent of 98% with formation of 75% of 2-bromo-3-thienylmagnesium chloride (**5**) trapped as the deutero compound **6**. The D_2O-trapped reaction mixture also contained 10% of 2-bromothiophene,[13] 6% of 2-deuterio-3-iodothiophene and 7% of 3-bromo-2-deuteriothiophene, indicating a slight lack of selectivity as well as positional instability of **5**. In an attempt to improve the selectivity of the halogen−metal exchange, the reaction was performed at −20 °C on 2-bromo-3-iodothiophene but resulted in only 30% conversion after 30 min of reaction and poor specificity for iodine−magnesium exchange at the 3-position.

(13) The protonation of the active Grignard species resulting in 2-bromothiophene and 3-bromothiophene may be a result of elimination of hydrogen bromide and hydrogen iodide from ethyl bromide and ethyl iodide by reaction with 2-bromo-3-thienylmagnesium chloride and 3-bromo-2-thienylmagnesium chloride, respectively.

TABLE 1. Synthesis of 2,3-Substituted Bromothiophenes from Bromothienylmagnesium Chlorides



entry	Grignard reagent	electrophile	−E	product	yield[a] (%)
1	**2**	$CNCO_2Et$	$-CO_2Et$	**7a**	81 (59)
2	**2**	*t*-BuNCO	−C(O)NH-*t*-Bu	**7b**	83 (76)
3	**2**	$(CH_3)_3SiCl$	$-Si(CH_3)_3$	**7c**	89 (81)
4	**5**	Ac_2O	−Ac	**8a**	82 (69)[b]
5	**5**	TsCN	−CN	**8b**	83 (64)[c]
6	**5**	DMF	−CHO	**8c**	87 (49)
7	**5**	$CNCO_2Et$	$-CO_2Et$	**8d**	71 (49)[d]

[a] Content of compound in the crude product based on ^{1}H NMR data. Yields in parentheses are isolated yields (not optimized) by crystallizations or distillations in gram-scale. [b] Contains about 3% of 2-acetyl-3-bromothiophene (ref 14). [c] Contains about 4% of 3-bromo-2-cyanothiophene (see ref 15). [d] Contains about 4% of **7a**.

The halogen−magnesium exchange procedure was used to synthesize a variety of 2-substituted 3-bromothiophenes and 3-substituted 2-bromothiophenes by quenching the bromothienylmagnesium chlorides (**2** or **5**) with various electrophiles (Table 1).

Formation of the 2,3-substituted bromothiophenes were usually good; however, in some cases isolation of the products (by distillation or crystallization) resulted in low isolated yields. Optimization of the purification procedures for each compound and a larger batch size will probably result in improved isolated yields.

Initially, compound **7a** (entry 1) was synthesized using ethyl chloroformate as the electrophile. This gave a maximum formation of product of 55% after 6 h at 33 °C. Workup by quenching with D_2O did not result in any deuterium incorporation, suggesting that all active Grignard reagent had been consumed. Performing the reaction at 4 °C for 4 days resulted in formation of 44% of **7a** with no active Grignard reagent left. By using the more reactive electrophile ethyl cyanoformate[16] the yield of **7a** increased to 81% after 30 min at ambient temperature.

(14) Muratake, H.; Hayakawa, A.; Natsume, M. *Chem. Pharm. Bull.* **2000**, *48*, 1558−1566.

(15) Crude 3-bromo-2-cyanothiophene was prepared from 3-bromo-2-thienylmagnesium chloride and *p*-toluenesulfonyl cyanide according to the procedure described in the Experimental Section. ^{1}H NMR data for this product: ^{1}H NMR ($CDCl_3$) δ 7.11 (d, J = 4.9 Hz, 1 H), 7.54 (d, J = 4.9 Hz, 1 H). These data are in accordance with the data observed for the byproduct in **8b**.

(16) Rho, T.; Abuh, Y. F. *Synth. Commun.* **1994**, *24*, 253−256.

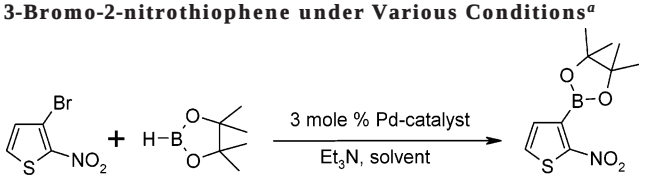
These results indicate that the active thienylmagnesium species decomposed in the reaction mixture in the course of few hours at ambient temperature. Therefore, utilization of reactive electrophiles seems to be crucial for good yields. Treatment of **2** with *tert*-butyl isocyanate or trimethylchlorosilane (entries 2 and 3) gave **7b** and **7c** in 76% and 81% isolated yields, respectively. **8a** was formed in 82% yield (entry 4) by addition of **5** to acetic anhydride.[17] The product was isolated by distillation in 69% yield, and it contained 3% of the isomeric 2-acetyl-3-bromothiophene.[14] Addition of **5** to *p*-toluenesulfonyl cyanide (entry 5) resulted in formation of 83% **8b**.[18] The product was isolated by distillation in 69% yield, and it contained 4% of the isomeric 3-bromo-2-cyanothiophene.[15] Compounds **8c** and **8d** (entries 6 and 7) were prepared from **5** and DMF and ethyl cyanoformate, respectively. Both compounds were isolated in 49% yields.

Having established the protocols for regiospecific preparation of 2,3-substituted bromothiophenes we investigated the borylation of these substrates. The borylation protocol developed by Murata et al.[11a,b] using palladium-catalyzed borylation between pinacolborane and aryl halides was preferred as a wide range of functional groups are compatible with this protocol and dialkoxyhydroboranes are cheaper than tetraalkoxydiboranes.

The borylation conditions developed by Murata et al.[11a,b] on 3-bromo-2-nitrothiophene (**7d**) (Table 2, entries 1 and 2) failed, as only debromination to 2-nitrothiophene was observed. This is in agreement with the results that electron-withdrawing substituents caused decreased borylation yields.[11a,b] We therefore decided to investigate the borylation of 3-bromo-2-nitrothiophene (**7d**) under different conditions (Table 2). In the choice of ligand we focused on testing more bulky and electron-rich ligands, as these have been successfully employed in Suzuki coupling[19] under mild conditions and in borylation of ortho-substituted aryl bromides.[11c]

Palladium dibenzylideneacetone in combination with tri-*o*-tolylphosphine (entry 3), 2-(di-*tert*-butylphosphino)-biphenyl (entry 4), or 2-(dicyclohexylphosphino)biphenyl (entry 5) also resulted in formation of 2-nitrothiophene as the major product, although high degrees of conversions were obtained. In contrast, palladium dibenzylideneacetone in combination with tri-*tert*-butylphosphine ($P(t\text{-}Bu)_3$) at 100 °C (entry 6) catalyzed the borylation reaction efficiently. The reaction temperature could be reduced to 40 °C (entry 7), and the carcinogenic dioxane could be substituted with THF (entry 8) to give complete conversion in 1 h and 95% of the boronic ester **9d**. At 25 °C, the reaction became sluggish and even after 23 h only 70% of **9d** was obtained (entry 9). Lower yields were also obtained when toluene was used as the solvent (entry 10). Applying the more user-friendly $Pd(P(t\text{-}Bu)_3)_2$ (air stable)[19b] (entry 11) also gave complete conversion in 1 h at 40 °C with formation of 94% of **9d**. If the borylation was conducted using palladium dibenzylideneacetone without a ligand (entry 12) only low conversion and no formation of product was observed, indicating that the tri-*tert*-butylphosphine ligand is crucial.

TABLE 2. Cross-Coupling of Pinacolborane and 3-Bromo-2-nitrothiophene under Various Conditions[a]



7d **9d**

entry	catalyst[b]	solvent	*T* (°C)	time (h)	conv[c] (%)	yield of **9d** (%)[d]
1	$PdCl_2(PPh_3)_2$	dioxane	100	17	42[e]	0
2	$PdCl_2$(dppf)	dioxane	80	17	10[e]	0
3	$Pd_2dba_3/P(o\text{-}Tol)_3$	dioxane	100	17	89[e]	0
4	$Pd_2dba_3/P(t\text{-}Bu)_2$(BiPh)	dioxane	100	17	88[e]	0
5	$Pd_2dba_3/P(Cy)_2$(BiPh)	dioxane	100	17	62[e]	0
6	$Pd_2dba_3/P(t\text{-}Bu)_3$	dioxane	100	1	100	96
7	$Pd_2dba_3/P(t\text{-}Bu)_3$	dioxane	40	1	100	92
8	$Pd_2dba_3/P(t\text{-}Bu)_3$	THF	40	1	100	95
9	$Pd_2dba_3/P(t\text{-}Bu)_3$	THF	25	23	85	70
10	$Pd_2dba_3/P(t\text{-}Bu)_3$	toluene	40	21	100	64
11	$Pd(P(t\text{-}Bu)_3)_2$	THF	40	1	100	94
12	Pd_2dba_3	THF	40	1	24[e]	0

[a] Reactions of 3-bromo-2-nitrothiophene **7d** (0.10 mmol) with pinacolborane (0.15 mmol) and triethylamine (0.30 mmol) were carried out in 2 mL of solvent using 3 mol % catalyst. The Pd/ligand ratio was 1:1 except otherwise noted. [b] Abbreviations are listed in ref 20. [c] HPLC conversions based on consumed **7d**. [d] Content of compound in the crude product based on ^{1}H NMR data. [e] Major product was 2-nitrothiophene.

In the borylation of ortho-substituted aryl bromides, Baudoin et al.[11c] found $P(Cy)_2$(BiPh)/$Pd(OAc)_2$ to be the catalyst of choice whereas $P(t\text{-}Bu)_3/Pd_2dba_3$ only gave the dehalogenated product. Compared to the results reported above this indicates that in the Pd-catalyzed borylation, the choice of ligand may be very dependent on the substrates employed.

On the basis of this optimization study the borylation of **7**,**8a**−**d** was performed in THF at 40 °C using $Pd(P(t\text{-}Bu)_3)_2$ as catalyst, triethylamine as base, and pinacolborane as borylating agent (Table 3).

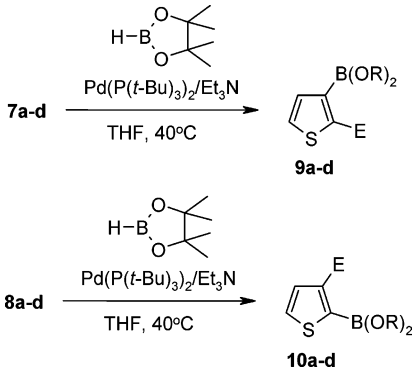
In general, this protocol provides the desired 2,3-substituted thienylboronic acids and esters in good to excellent yields. However, the electronic nature of the substituents significantly influences the stability of the products. The borylation products containing ethyl ester or acetyl substituents (entries 1, 5, and 8) were not isolated as the pinacolboronates as these deborylated during alkaline or strong acidic (pH 1−3) aqueous workup. Under slight acidic (pH 3−5) conditions the pinacolboronates were hydrolyzed to the corresponding boronic acids and **9a**, **10a**, and **10d** were isolated in fair to excellent yields. All attempts to isolate the boronic esters by sublimation from the reaction mixtures prior

(17) Initially 2-bromo-3-thienylmagnesium chloride was converted to the corresponding manganese species by transmetalation with Li_2MnCl_4: Normant, J. F.; Cahiez, G. In *Organomanganese Reagents in Modern Synthetic Methods*; Scheffold, R., Ed.; John Wiley & Sons: New York, 1983; Vol. 3, pp 173−216. However, 2-bromo-3-thienylmanganese chloride did not react with acetic anhydride, indicating a very low reactivity of this organometallic species.

(18) Bromo-3-thienylmagnesium chloride was converted to the corresponding organozinc species by transmetalation with $ZnCl_2$: Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P. *Tetrahedron* **1996**, *52*, 7201−7220. Subsequent reaction with *p*-toluenesulfonyl cyanide only formed 19% of **8b** after 17 h of reaction (^{1}H NMR).

(19) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (c) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. (d) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561.

TABLE 3. Synthesis of 2,3-Substituted Thienylboronic Acids and Esters

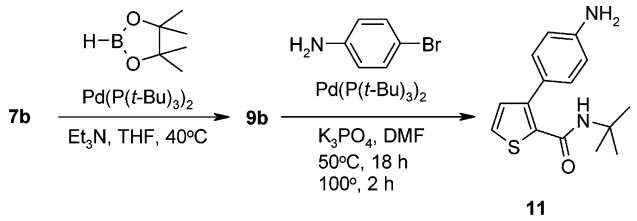


entry	−E	−B(OR)$_2$[a]	catalyst (mol %)	reaction time (h)	product	yield[b] (%)
1	−CO_2Et	boronic acid	0.5	2	**9a**	91 (88)
2	−C(O)NH-*t*-Bu	pinacol boronate	0.5	2	**9b**	86 (54)[c]
3	−$Si(CH_3)_3$	pinacol boronate	0.5	3	**9c**	81 (61)[d]
4	−NO_2	pinacol boronate	3.0	1	**9d**	92 (43)[c]
5	−Ac	boronic acid	0.5	1	**10a**	79 (23−56)
6	−CN	pinacol boronate	3.0	3	**10b**	45 (0)[e]
7	−CHO	pinacol boronate	1.0	3	**10c**	88 (49)
8	−CO_2Et	boronic acid	0.5	1	**10d**	87 (64)

[a] The products were isolated either as the pinacol boronates or as the boronic acids. [b] Content of compound in the crude product based on ^{1}H NMR data. Yields in parentheses are yields isolated by crystallizations in gram-scale except otherwise noted. [c] Isolated in milligram scale by sublimation. [d] Isolated by chromatography. [e] All attempts to isolate the product failed.

to hydrolysis were unsuccessful since significant amounts of pinacol co-sublimed with the products. Borylation of **7b**−**d** and **8c** (entries 2−4 and 7) resulted in pinacolboronates which were isolated by sublimation or chromatography. To complete the borylation reactions (at 40 °C) of **7d** (−NO_2) and **8b** (−CN), it was necessary to increase the amount of catalyst from 0.5−1 mol % to 3 mol %. The strongly electron-withdrawing substituents in the products **9d** and **10b** cause a significant decrease in their stability, and attempted aqueous workup resulted in complete deborylation. Compound **9d** was isolated in 43% yield (92% formed as analyzed by NMR) (entry 4) by sublimation from the crude reaction mixture, whereas all attempts to isolate **10b** (entry 6) failed due to deborylation.[21] On the contrary, **9c** possessing the slight electron-donating trimethylsilyl group (entry 3) was sufficiently stable to be isolated by silica gel chromatography (slightly acidic conditions).[22] In general, the present protocol provides access to 2,3-substituted thienylboronic acids and pinacol esters unless substituted with strongly electron-withdrawing substituents where poor stability renders the isolation difficult.

SCHEME 2. Borylation of 7b and Subsequent Suzuki Coupling of Crude 9b with *p*-Bromoaniline



Overall isolated yield: 59%

The crude 2,3-substituted thienylboronic acids and pinacol esters may be used in further coupling reactions as demonstrated in the Suzuki coupling of in situ generated crude **9b** with *p*-bromoaniline (Scheme 2).

In the process, **7b** was borylated by the optimized procedure, and then the reaction mixture was diluted with *tert*-butyl methyl ether and filtered. The solvent was removed under reduced pressure, and the crude mixture was used in the subsequent Suzuki coupling applying a slightly modified procedure than that described by Watanabe et al.[23] using Pd(P(*t*-Bu)$_3$)$_2$ as the catalyst.[19] The cross-coupling product **11** was isolated in an overall yield of 59%.

In conclusion, new gram-scale protocols for 2-substituted 3-thienylboronic acids and esters as well as 3-substituted 2-thienylboronic acids and esters have been developed. Metalation of the 2-position in 2,3-dibromothiophene or metalation of the 3-position in 2-bromo-3-iodothiophene by halogen−magnesium exchange followed by quenching with an electrophile provides access to a number of various 2-substituted 3-bromothiophenes or 3-substituted 2-bromothiophenes, respectively. The substituted bromothiophenes were borylated by palladium-catalysis to the corresponding 2-substituted 3-thienylboronic acids and esters or 3-substituted 2-thienylboronic acids and esters. Borylation and subsequent cross-coupling can advantageously be combined without isolation of the boronate. In this way, the problematic isolation of unstable thienyl boronates with strong electron-withdrawing substituents can be circumvented.

Acknowledgment. The Danish Academy of Technical Sciences has kindly supported this work financially.

Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra for all isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034919N

(20) PPh_3 = triphenylphosphine. dppf = 1,1′-bis(diphenylphosphino)-ferrocene. dba = dibenzylideneacetone. P(*o*-Tol)$_3$ = tri(*o*-tolyl)phosphine. P(*t*-Bu)$_2$(BiPh) = 2-(di-*tert*-butylphosphino)biphenyl. P(Cy)$_2$-(BiPh) = 2-(dicyclohexylphosphino)biphenyl. P(*t*-Bu)$_3$ = tri(*tert*-butyl)phosphine.

(21) The compound has been prepared, but not isolated: Blackaby, P. W.; Castro Pinero, J. L.; Chambers, M. S.; Goodacre, S. C.; Hallet, D. J.; Jones, P.; Lewis, R. T.; MacLeod, A. M.; Maxey, R. J.; Moore, K. W.; Street, L. J. Pat. Appl. WO 0276983, 2002.

(22) Herr, R. J.; Meckler, H.; Scuderi, F. *Org. Process Res. Dev.* **2000**, *4*, 43−45.

(23) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207−210.