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Double Couplings of Dibromothiophenes using Boronic Acids and Boronates

Samantha Varello and Scott T. Handy*

Department of Chemistry, Middle Tennessee State University, Murfreesboro, TN 37129

Abstract

One-pot double couplings of dibromothiophenes have been investigated. Standard Suzuki couplings work well for 2,4-dibromothiophene, but are much more sensitive to steric effects in the case of 2,3-dibromothiophene. By using the recently reported potassium borates, though, good yields for both dibromothiophene isomers can be achieved.

Keywords

Suzuki couplings; regioselectivity; heteroaromatics; thiophenes; cross-coupling reactions; palladium catalysis

Introduction

Substituted thiophenes are highly important molecules present in a wide range of compounds of biological and materials interest.¹ Although many routes have been developed for the preparation of such compounds, the most widely employed method for the installation of carbon substituents is transition metal catalyzed cross coupling chemistry.² Such reactions have been used innumerable times and with great efficiency.

As part of a project aimed at improving the efficiency of cross-coupling chemistry for the preparation of multiply substituted heteroaromatics, we have been exploring the use of one-pot double Suzuki couplings.³ Prior work has focused more on azoles,⁴ but more recently has begun to examine thiophenes.⁵

The regioselectivity of couplings of dibromothiophenes is fairly well established.^{6,7} In particular, the work of de Lera, demonstrated that the initial site of coupling of 2,3-dibromothiophene in Stille, Suzuki, or Sonogashira couplings is always at C2 (Scheme 1).⁷ Generally good yields were achieved for many of these couplings. At the same time, little was done with regards to the possibility of conducting a second coupling at the remaining bromide. Indeed, there have been no prior reports of one-pot double couplings on 2,3- or 2,4-dibromothiophenes.⁸

Results

Initial efforts explored application of the conditions used successfully on 4,5-dibromothiophene-2-carboxaldehyde to a simple dibromothiophene such as 2,4-dibromothiophene. (Scheme 2) Interestingly, although some decoupled product was isolated,

the overall yield was quite modest. Further analysis of the crude reaction mixture demonstrated that much of the material balance was mono-coupled thiophenes.⁹ Further attempts noted that catalyst decomposition appeared to be rapid. This decomposition could be greatly reduced by degassing the reaction mixture prior to the addition of the palladium tetrakis. Further, reducing the temperature of the first coupling to 80 °C as well as cutting the reaction time to 3 hours also improved the yield of the decoupled product. In a brief survey of reaction conditions, a slight increase in yield was noted by employing DMF as the solvent and aqueous sodium carbonate as the base.¹⁰ The ratio of DMF to water was important, as highly aqueous conditions (>30% water by volume) resulted in poor conversion. Additionally, the use of 2-M sodium carbonate (as had been employed in many of our previous double couplings) resulted in poor reproducibility. The problem may be due to precipitation of the sodium carbonate upon addition to the DMF, which then appears to facilitate catalyst decomposition and precipitation as palladium black. Dilution to a 1-M sodium carbonate resolved this issue and proved generally satisfactory.

These reaction conditions proved quite satisfactory for a range of aryl boronic acids, including the sterically hindered o-methoxyphenyl boronic acid, as well as an alkenyl boronic acid. (Table 1) In general, overall yields are good, although the double coupling in which 2-thiophenyl boronic acid is used in the first coupling is unexpected low (entry 7), particularly in light of the much better result when this same boronic acid is used in the second coupling (entry 8).

Armed with these results, the same conditions were applied to 2,3-dibromothiophene. (Table 2) The reactions again afforded generally good results, although the yields were definitely lower than those for the corresponding couplings on 2,4-dibromothiophene. The reduced yields are not the result of a less efficient first coupling. By simply running the first coupling under these reaction conditions, the monocoupled products could be isolated in 80–95% yield. Thus, the problem appears to be the steric hindrance that results from the presence of the initially coupled group at C2. It is possible that employing a more active catalyst may be sufficient to overcome this problem, but this option has not yet been explored.

Because catalyst stability was proving to be such an issue, we were interested in finding an even more mild set of reaction conditions or a more robust catalyst. Recently, Miyuara and co-workers reported the Suzuki-type coupling using stable boronate salts such as **1**.¹¹ (Figure 1) Of great interest to us was their observation that these salts reacted under very mild conditions: no added base, palladium acetate as catalyst, and short, room temperature reactions. Gratifyingly, application of these same conditions to the double coupling of dibromothiophenes worked as well or better than the corresponding double Suzuki couplings using boronic acids.¹²

Using the boronate salts, the yields of double couplings were generally higher for both the 2,3- and 2,4-dibromothiophenes. Further, although the couplings of 2,3-dibromothiophenes still afforded slightly lower yields than those in the 2,4-dibromothiophene, the difference is quite modest. As a result, it appears that steric issues are less important.

Alkenyl boronate salts were also successful in these double couplings (entries 3 and 4). Quite encouragingly, so was an ortho-substituted boronate (entries 5 and 6). It should be noted that the efficient preparation of this particular boronate salt did require the use of the organolithium route (halogen-metal exchange on 2-bromoanisole, followed by reaction with trimethylborate and then treatment with 1,1,1-tris(hydroxymethyl)methane) as attempts at preparing this boronate from the corresponding boronic acid resulted in very low yields of the product. Fortunately, the organolithium route afforded a nearly quantitative yield of the desired boronate salt.

In conclusion, one-pot double couplings of dibromothiophenes are clearly readily achievable. The use of boronates as the coupling partners affords the products in good yield for either dibromothiophene isomer. In some preliminary studies, it appears that the same boronate reaction conditions are applicable to a range of heteroaromatics, including pyrroles, furans, and pyridines. This has not been the case in simple double Suzuki couplings, where it seems that each a different set of reaction conditions are required for good yields with each different heteroaromatic. Thus, the boronate couplings hold promise for the development of a more general set of reaction conditions for these double couplings. Studies to this end are underway and will be reported in due course.

Experimental Section

General Procedure for Double Suzuki Couplings

2,4-dibromothiophene (48.3 mg, 0.207 mmol) and p-fluorophenylboronic acid (31.8 mg, 0.228 mmol) were combined in a vial and dissolved in 4 mL of DMF. 600 μ L of 1-M sodium carbonate was added and the resultant solution was degassed by bubbling Ar through the solution for 10 minutes. Tetrakis(triphenylphosphine) palladium(0) (6.9 mg, 0.103 mmol) was added and the vial was sealed and shaken on an orbital shaker at 110 rpm at 80 °C for 3 hours. Tolyboronic acid (27.8 mg, 0.228 mmol) and 600 μ L of 1-M sodium carbonate were then added and the reaction was shaken at 110 rpm at 95 °C for an additional 16 hours. The final reaction mixture was cooled, diluted with water (15 mL), and extracted with ether (3 $\times$ 10 mL). The organic layer was dried with MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified on silica using 1:3 methylene chloride/hexanes as eluent.¹³

General Procedure for Double Boronate Couplings

2,4-dibromothiophene (80 mg, 0.33 mmol), p-fluorophenylboronate (87 mg, 0.34 mmol), and palladium acetate (2.2 mg, 0.015 mmol) were combined in a vial and dissolved in 1 mL of 4:1 (v/v) DMF/water. The vial was sealed and stirred at room temperature for 3 hours. The reaction rapidly became a dark brown. Tolyboronate (86 mg, 0.34 mmol) was then added and the reaction was stirred for an additional 16 hours. The final reaction mixture was diluted with water (4 mL) and extracted with ether (3 $\times$ 3 mL). The organic layer was dried with MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified on silica using 1:3 methylene chloride/hexanes as eluent.

4-(4'-fluorophenyl)-2-(4'-tolyl)thiophene

brown solid, mp = 26–28 ° C. IR (CDCl₃) 3100, 3000, 1500, 1240, 1160, 940, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.60-7.42 (m, 4H), 7.28-7.02 (m, 6H), 2.38 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 144.3, 138.1, 129.8, 128.4 (d, J = 8 Hz), 127.6 (d, J = 6 Hz), 127.3 (d, J = 195 Hz), 125.8, 125.7, 122.0, 121.5, 116.2 (d, J = 22 Hz), 110.6, 21.3. HRMS (EI) calcd for C₁₇H₁₃FS 268.3546, found 268.3544.

2-(4'-fluorophenyl)-4-(4'-tolyl)thiophene

yellow solid, mp = 43–44 ° C. IR (CDCl₃) 3100, 3000, 1500, 1300, 1280, 1200, 900, 860, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.73-7.44 (m, 4H), 7.33-7.02 (m, 6H), 2.41 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 145.7, 138.4, 129.6 (d, J = 10 Hz), 128.5 (d, J = 210 Hz), 127.6 (d, J = 8 Hz), 125.7, 125.2, 122.0, 121.5, 116.2 (d, J = 25 Hz), 110.7, 110.5, 21.3. HRMS (EI) calcd for C₁₇H₁₃FS 268.3546, found 268.3545.

3-(4'-fluorophenyl)-2-(4'-tolyl)thiophene

pale yellow oil. IR (CDCl₃) 3100, 3000, 1550, 1500, 1200, 960, 880, 840, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.70-7.51 (m, 4H), 7.43-7.32 (m, 4H), 7.06 (d, J = 6.8 Hz, 2H), 2.37 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 138.7, 136.9, 131.7, 130.8, 130.0, 129.5, 129.3, 129.0 (d, J = 8 Hz), 127.3 (d, J = 8 Hz), 126.9 (d, J = 210 Hz), 124.8, 116.7 (d, J = 25 Hz), 21.4. HRMS (EI) calcd for C₁₇H₁₃FS 268.3546, found 268.3547.

2-(4'-fluorophenyl)-3-(4'-tolyl)thiophene

pale yellow oil. IR (CDCl₃) 3100, 3000, 1500, 1220, 1160, 940, 880, 860 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.70-7.51 (m, 4H), 7.39-7.32 (m, 3H), 7.14 (t, 2H), 7.06 (d, J = 3.8 Hz, 1H), 2.39 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 138.7, 136.9, 131.7 (d, J = 8 Hz), 130.8, 130.0, 129.5 (d, J = 200 Hz), 129.3, 129.0, 127.3, 126.9, 124.8 (d, J = 10 Hz), 115.8 (d, J = 22 Hz), 21.2. HRMS (EI) calcd for C₁₇H₁₃FS 268.3546, found 268.3543.

4-(2'-methoxyphenyl)-2-(phenyl)thiophene

pale yellow oil. IR (CDCl₃) 3100, 3000, 1500, 1250, 1140, 960, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.62-7.53 (m, 2H), 7.42-7.24 (m, 5H), 7.21 (t, J = 1 Hz, 1H), 7.18 (d, J = 1 Hz, 1H), 6.98 (d, J = 8 Hz, 2H), 3.94 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 131.1, 129.2, 129.1, 128.4, 128.2, 127.8, 127.1, 125.8, 125.7, 122.6, 122.0, 121.1, 120.6, 111.7, 55.6. HRMS (EI) calcd for C₁₇H₁₄OS 266.3636, found 266.3636.

2-(2'-methoxyphenyl)-4-(phenyl)thiophene

pale yellow oil. IR (CDCl₃) 3100, 3000, 1500, 1220, 1100, 960, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, J = 1 Hz, 1H), 7.69-7.61 (m, 3H), 7.43 (d, J = 1 Hz, 1H), 7.41-7.25 (m, 4H), 7.02 (d, J = 8 Hz, 2H), 3.92 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 136.1, 129.2, 129.1, 128.9, 128.7, 128.6, 127.8, 127.1, 126.4, 124.7, 123.6, 121.0, 120.6, 111.7, 55.2. HRMS (EI) calcd for C₁₇H₁₄OS 266.3636, found 266.3633.

3-(2'-methoxyphenyl)-2-(phenyl)thiophene

pale yellow oil. IR (CDCl₃) 3100, 3000, 1500, 1240, 1140, 960, 800 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.65 (d, J = 7 Hz, 2H), 7.45-7.26 (m, 5H), 7.05 (dd, J = 6, 1 Hz, 2H), 7.00 (t, J = 7 Hz, 2H), 3.84 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 132.1, 131.8, 130.6, 130.4, 129.2, 128.6, 128.2, 127.9, 125.5, 125.0, 120.0, 116.8, 116.4, 111.4, 55.7. HRMS (EI) calcd for C₁₇H₁₄OS 266.3636, found 266.3638.

2-(2'-methoxyphenyl)-3-(phenyl)thiophene

pale yellow oil. IR (CDCl₃) 3100, 3000, 1500, 1260, 1140, 920, 840 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.16 (m, 10H), 6.85 (d, J = 8 Hz, 1H), 3.90 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 132.8, 131.0, 129.4, 129.3, 128.5, 128.2, 128.1, 127.6, 126.5, 125.2, 120.1, 120.0, 112.3, 109.7, 55.2. HRMS (EI) calcd for C₁₇H₁₄OS 266.3636, found 266.3634.

4-(phenyl)-2-(trans-styrenyl)thiophene

white solid, mp = 44–46 °C. IR (CDCl₃) 3100, 3000, 1500, 1280, 980, 920, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.73-7.21 (m, 13H), 7.06 (d, J = 12 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 132.3, 129.4, 129.1, 128.9, 128.8, 128.4, 127.7, 127.3, 126.6, 126.5, 125.8, 125.8, 122.1, 110.8. HRMS (EI) calcd for C₁₈H₁₄S 262.3752, found 262.3755.

2-(phenyl)-4-(trans-styrenyl)thiophene

yellow solid, mp = 48–50 °C. IR (CDCl₃) 3100, 3000, 1500, 1260, 980, 940, 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.57 (d, J = 5 Hz, 2H), 7.40-7.30 (m, 11H), 7.26 (d, J = 12 Hz,

1H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.4, 133.3, 129.4, 129.2, 128.9, 128.8, 128.4, 127.7, 126.6, 126.5, 125.8, 125.7, 122.0, 110.6. HRMS (EI) calcd for $\text{C}_{18}\text{H}_{14}\text{S}$ 262.3752, found 262.3755.

3-(phenyl)-2-(trans-styrenyl)thiophene

yellow solid, mp = 87–90 ° C. IR (CDCl_3) 3100, 3000, 1500, 1240, 980, 900, 820 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.55–7.25 (m, 11 H), 7.08–6.93 (m, 2H), 6.68 (d, J = 12 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.4, 132.9, 131.3, 130.7, 130.1, 129.3, 129.2, 128.8, 128.4, 127.7, 126.6, 125.2, 123.8, 120.1. HRMS (EI) calcd for $\text{C}_{18}\text{H}_{14}\text{S}$ 262.3752, found 262.3754.

2-(phenyl)-3-(trans-styrenyl)thiophene

white solid, mp = 44–46 ° C. IR (CDCl_3) 3100, 3000, 1500, 1260, 980, 940, 840 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.68 (d, J = Hz, 1H), 7.60–7.25 (m, 10 H), 7.08–6.90 (m, 2H), 6.65 (d, J = 12 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.6, 132.9, 131.4, 130.9, 130.1, 129.4, 129.2, 128.9, 128.6, 127.7, 126.5, 125.1, 124.0, 120.1. HRMS (EI) calcd for $\text{C}_{18}\text{H}_{14}\text{S}$ 262.3752, found 262.3753.

4-(phenyl)-2-(2'-thiophenyl)thiophene

mp = 73–74 (lit 74–76)¹⁴. IR (CDCl_3) 3100, 3000, 1500, 1240, 1160, 940, 820 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.76–6.84 (m, 10H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.1, 139.1, 137.3, 133.9, 129.2, 127.9, 127.8, 126.3, 124.1, 123.4, 122.2, 119.2. HRMS (EI) calcd for $\text{C}_{14}\text{H}_{10}\text{S}_2$ 346.3972, found 346.3970.

2-(phenyl)-4-(2'-thiophenyl)thiophene

white solid, mp = 70–72 ° C. IR (CDCl_3) 3100, 3000, 1500, 1240, 1160, 940, 820 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.68–7.64 (m, 2H), 7.53 (d, J = 1 Hz, 1H), 7.48–7.40 (m, 2H), 7.36–7.30 (m, 2H), 7.28–7.23 (m, 2H), 7.08 (dd, J = 5, 4 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.2, 139.1, 137.4, 133.9, 129.1, 127.9, 127.8, 126.0, 124.1, 123.3, 122.2, 119.1. HRMS (EI) calcd for $\text{C}_{14}\text{H}_{10}\text{S}_2$ 346.3972, found 346.3973.

3-(phenyl)-2-(2'-thiophenyl)thiophene

mp = 72–74 (lit 75–76)¹⁴. IR (CDCl_3) 3100, 3000, 1500, 1240, 1160, 940, 820 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.40–7.434 (m, 5H), 7.30–6.85 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.4, 129.8, 129.6, 128.0, 127.9, 126.3, 126.0, 125.7, 124.4, 124.0, 122.4, 118.6. HRMS (EI) calcd for $\text{C}_{14}\text{H}_{10}\text{S}_2$ 346.3972, found 346.3971.

2-(phenyl)-3-(2'-thiophenyl)thiophene

brown solid, mp = 68–69 ° C. IR (CDCl_3) 3100, 3000, 1500, 1240, 1160, 940, 820 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.65–7.47 (m, 2H), 7.38–7.19 (m, 7H), 7.08 (d, J = 5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.6, 129.8, 129.7, 128.0, 127.9, 126.3, 125.8, 125.7, 124.5, 123.9, 122.7, 118.7. HRMS (EI) calcd for $\text{C}_{14}\text{H}_{10}\text{S}_2$ 346.3972, found 346.3972.

Acknowledgments

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9. These monocoupled thiophene products were used to confirm the regioselectivity of the first coupling by hydrodehalogenation of the remaining bromide and then comparison with reported spectral data for the mono-arylated thiophenes.
10. Ethanol/toluene afforded poor conversions, while aqueous dioxane was almost as efficient as DMF. In terms of base, potassium carbonate and potassium phosphate afforded slightly lower (5–10%) yields.
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12. The boronate salts were prepared as described in reference 11 starting from the commercially available boronic acids with the exception of the ortho-methoxyphenyl boronate salt, which was prepared via the organolithium route also described in reference 11.
13. The use of methylene chloride/hexane mixtures for chromatography was important as attempts to use ethyl acetate/hexanes or ether/hexanes mixtures resulted in much lower isolated yields due to limited product solubility in these solvents.
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Figure 1.

Scheme 1.

Scheme 2.

Table 1

Double Suzuki Couplings of 2,4-Dibromothiophene

Entry	R	R'	Isolated Yield
1	p-Tolyl	p-Fluorophenyl	88
2	p-Fluorophenyl	p-Tolyl	80
3	Trans-styrenyl	Phenyl	67
4	Phenyl	Trans-styrenyl	64
5	o-MeOphenyl	Phenyl	54
6	Phenyl	o-MeOphenyl	42
7	2-thiophenyl	Phenyl	38
8	Phenyl	2-thiophenyl	75

Table 2

Double Suzuki Couplings of 2,3-Dibromothiophene

Entry	R	R'	Isolated Yield
1	p-Tolyl	p-Fluorophenyl	46
2	p-Fluorophenyl	p-Tolyl	40
3	Trans-styrenyl	Phenyl	12
4	Phenyl	Trans-styrenyl	18
5	o-MeOphenyl	Phenyl	21
6	Phenyl	o-MeOphenyl	15
7	2-thiophenyl	Phenyl	42
8	Phenyl	2-thiophenyl	38

Table 3

Double Boronate Couplings of Dibromothiophenes

Entry	R	R'	Isolated Yield (2,4 product)	Isolated Yield (2,3 product)
1	p-Tolyl	p-Fluorophenyl	95	85
2	p-Fluorophenyl	p-Tolyl	71	64
3	Trans-styrenyl	Phenyl	64	70
4	Phenyl	Trans-styrenyl	65	67
5	o-MeOphenyl	Phenyl	81	64
6	Phenyl	o-MeOphenyl	94	61
7	2-thiophenyl	Phenyl	77	62
8	Phenyl	2-thiophenyl	81	73