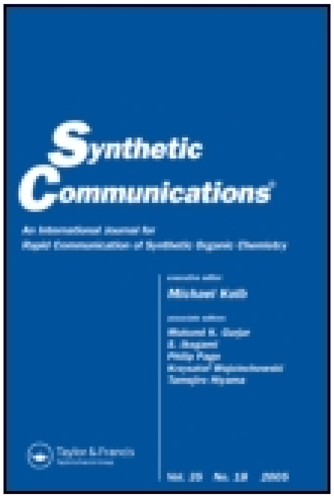
This article was downloaded by: [Heriot-Watt University]
On: 06 October 2014, At: 12:47
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 2-Bromo-2′-phenyl-5,5′-thiophene: Suzuki Reaction Versus Negishi Reaction

Nai-Xing Wang [a]

[a] Institute of Photographic Chemistry , Chinese Academy of Sciences , Beijing, P.R. China

Published online: 17 Aug 2006.

To cite this article: Nai-Xing Wang (2003) Synthesis of 2-Bromo-2′-phenyl-5,5′-thiophene: Suzuki Reaction Versus Negishi Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:12, 2119-2124, DOI: 10.1081/SCC-120021039

To link to this article: http://dx.doi.org/10.1081/SCC-120021039

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the “Content”) contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 12, pp. 2119–2124, 2003

Synthesis of 2-Bromo-2′-phenyl-5,5′-thiophene: Suzuki Reaction Versus Negishi Reaction

Nai-Xing Wang*

Institute of Photographic Chemistry, Chinese Academy
of Sciences, Beijing, P.R. China

ABSTRACT

2-Bromo-2′-phenyl-5,5′-thiophene was synthesized by cross- coupling reaction of phenylboric acid and 2,2′-dibromo-5,5′-bithiophene with a Suzuki reaction; we found the Suzuki reaction to give a higher yield when compared to the Negishi reaction.

INTRODUCTION

The cross-coupling reaction of organoboranes with a number of organic halides in presence of a catalytic amount of palladium complexes and bases was reported as a versatile and useful method for conjugated

---

*Correspondence: Nai-Xing Wang, Institute of Photographic Chemistry, Chinese Academy of Sciences, Beijing 100101, P.R. China; E-mail: naixingwang@hotmail.com.

DOI: 10.1081/SCC-120021039
0039-7911 (Print); 1532-2432 (Online)
www.dekker.com

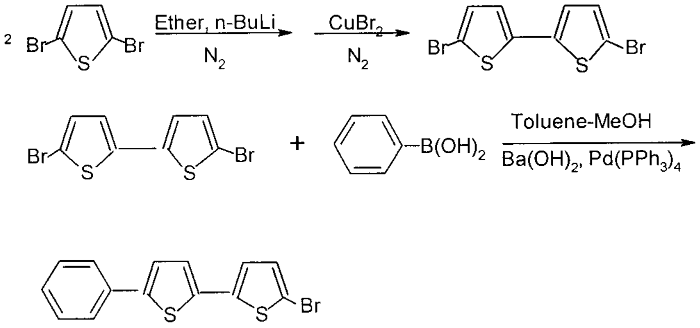
alkadiene, arylated alkenes, 1,4-alkadienes, allylic benzene, α,β-unsaturated carboxylic acid and 2,4-alkadienoates.[1–4]

The cross-coupling reaction of organoboron compounds, which involves the transmetallation to palladium(II) halides as a key step, was found to proceed smoothly when these were activated with suitable bases and technique for a wide range of selective carbon-carbon bond formation.[5–9] Many organometallic reagents undergo similar cross-coupling reactions, however, recently much attention has been focused on the use of organoboronic acids in laboratories and industry since they are convenient reagents, which are generally thermally stable and inert to water and oxygen, thus allowing their handling without special precautions.

RESULTS AND DISCUSSION

Using the cross-coupling of organoboranes with an organic halide in the presence of a catalytic amount of palladium complexes and bases, the conjugated coupled thiophene derivative 2-bromo-2-phenyl-5,5′-thiophene was synthesized. Our experiments found that the Suzuki reaction gave a higher yield when compared to the Negishi reaction.

The title compound was synthesized by Suzuki reaction (Sch. 1):



Scheme 1.

Synthesis of 2-bromo-2′-phenyl-5,5′-thiophene via palladium-catalyzed cross-coupling reactions (Suzuki reaction) related to an interesting mechanism, which might be described as three steps: 1) oxidative addition 2) transmetallation 3) reductive elimination sequence.

1. Oxidative addition:

$$
\begin{aligned}
&\mathrm{Ar\text{-}X} \;\text{————}\; [\mathrm{Ar^{+}\ X^{-}}\,]\\
&\mathrm{Pd(PPh_3)_4} \;\text{————}\; [\mathrm{Pd^{o}+PPh_3}]\\
&[\mathrm{Ar^{+}\ X^{-}}\,]+\mathrm{Pd^{0}} \;\text{————}\; [\mathrm{Ar^{-}\ Pd^{2+}\ X^{-}}\,]
\end{aligned}
$$

2. Transmetallation:

$$[\mathrm{Ar^{-}\ Pd^{2+}\ X^{-}}\,]+\mathrm{Ar'B(OH)_2} \;\text{————}\; \mathrm{Ar\text{-}Pd\text{-}Ar'}+\mathrm{X\text{-}B(OH)_2}$$

3. Reductive elimination:

$$\mathrm{Ar\text{-}Pd\text{-}Ar'} \;\text{————}\; \mathrm{Ar\text{-}Ar'}+\mathrm{Pd^{0}}$$

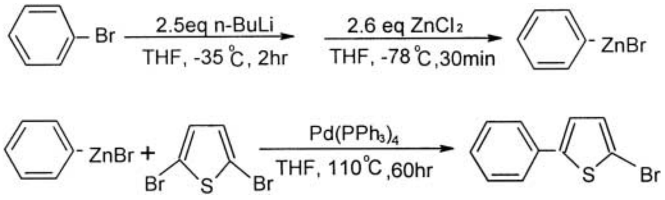
Oxidative addition of 1-alkenyl, 1-alkynyl, allyl, benzyl, and aryl halides to a palladium(0) complex affords a stable palladium(II) complex.[10–13] The reaction proceeds with complete retention of configuration for alkenyl halides and with inversion for allylic and benzylic halides.

Oxidative addition was the rate-determining step in the catalytic cycle. The reaction activity decreased with the order of $\mathrm{I} > \mathrm{Br} \gg \mathrm{Cl}$.[10–13] Aryl and 1-alkenyl halides were activated by the proximity effect of electron-withdrawing groups, which were more reactive to the oxidative addition than those with donating group, thus, chlorides were allowed for the cross-coupling reaction. A very wide range of palladium(0) catalysts or precursors were used for cross-coupling reaction, reagent $\mathrm{Pa(PPh_3)_4}$ was most commonly used.

The cross-coupling reaction was accelerated exceptionally by weak bases, the stronger bases such as potassium carbonate gave byproduct arising from further coupling of the product with aryl halides, here barium hydroxide was used as a base to achieve the selected cross coupling. Since the halogen ligand on organopalladium(II) in the oxidative addition mechanism, halide was readily displaced by alkoxy anion to provide Ar-Pd-OR complexes, which had been postulated as reaction intermediates[14–16] or isolated[17,18] from the reaction of organopalladium(II) halides with methoxide, therefore, methanol was used as a solvent here.

$$
\begin{aligned}
&[R^{-}\ \mathrm{Pd^{2+}\ X^{-}}]+\mathrm{MeO^{-}} \;\text{————}\; R\text{-}\mathrm{Pd\text{-}OMe}+\mathrm{X^{-}}\\
&R\text{-}\mathrm{Pd\text{-}OMe}+\mathrm{Ar\text{-}B(OH)_2} \;\text{————}\; R\text{-}\mathrm{Pd\text{-}Ar}+\mathrm{MeO\text{-}B(OH)_2}\\
&R\text{-}\mathrm{Pd\text{-}Ar} \;\text{————}\; R\text{-}\mathrm{Ar}+\mathrm{Pd^{0}}
\end{aligned}
$$

The formation of alkoxy palladium intermediate should be considered to be one of the crucial transmetallation processes in the base-palladium induced cross-coupling reactions.



Scheme 2.

To research on the synthesis of 2-bromo-2′-phenyl-5,5′-thiophene, we also set up the Negishi reaction by using *n*-butyl lithium and zinc chloride reagents. However, our experiments found that the Suzuki reaction gave a much more higher yield when compared to the Negishi reaction.

The title compound also could be synthesized by Negishi reaction (Sch. 2).

EXPERIMENTAL SECTION

Synthesis of 2,2′-Dibromo-5,5′-bithiophene

To a cooled (−78°C) solution of dry ether (20 mL), 2, 5-dibromothiophene (3.5 mmol, 0.4 mL) and *n*-BuLi (1.56 mL, 3.9 mmol, 1.1 eq) under N_2 were added. The mixture was stirred at −78°C for 2 h, dry $CuBr_2$ (2.69 g) then was added into the mixture under N_2 at −78°C, cooling bath was removed and the reaction mixture was stirred at r.t. overnight. The mixture was poured into 40 mL of ice water, extracted with $CHCl_3$ (50 mL × 3), the $CHCl_3$ layer was washed with 25 mL of 15% HCl, the organic layer was washed with $NaHCO_3$ (aq., 50 mL), then water (50 mL), and dried with anhydrous $MgSO_4$ for 30 min. Solvent was evaporated to get slightly gray solid 543.5 mg (yield 94%). TLC (hexane, $R_f = 0.45$). Recrystallization with hexane, plate crystal was got, melting point: 81°C. ^{1}H NMR ($CDCl_3$, TMS, 500 MH_z), δ 6.96 (d, $J = 3.6$, 2H), 6.85 (d, $J = 3.6$, 2H). ^{13}C NMR ($CDCl_3$, TMS, 500 MH_z), δ 112.047 (2C), 124.667 (2C), 131.168 (2C), 138.302 (2C). GC-MS (EI): 324 [M^+] (100%).

Synthesis of 2-Bromo-2′-phenyl-5,5′-thiophene by Suzuki Reaction

Phenylboric acid (225.8 mg, 1.8 mmol) and barium hydroxide octahydrate (583 mg, 1.8 mmol) were put into a reaction flask and vacuumed for 40 min, then N_2 was filled. $Pd(PPh_3)_4$ (48.16 mg, 0.0417 mmol) was dissolved in 10 mL toluene and methanol (1:1), bubbled with N_2, then it was transfer into the reaction flask under N_2. 2,2′-dibromo-5,5′-bithiophene (546 mg, 1.68 mmol) was vacuumed for 30 min, and filled with N_2, then it was dissolved in 15 mL chloroform (bubbled with N_2) and then was transferred into the reaction flask under N_2. The result reaction mixture was stirred at 100°C under N_2 for 48 h. The reaction mixture was allowed to add into 80 mL $CHCl_3$, washed with 15% HCl (aq.) (80 mL), then 80 mL $NaHCO_3$ solution (aq.), finally washed with water, dried with anhydrous $MgSO_4$, crude product (0.82 g) was got, separation by chromatograph on silica gel column, hexane and toluene (98:2) was used as eluent, pure compound 275.03 mg was obtained (yield 51%). TLC (hexane, $R_f = 0.314$). Recrystallization with hexane, melting point: 145°C. ^{1}H NMR ($CDCl_3$, TMS, 500 MH$_z$), δ 7.58 (m, 2H), 7.37 (m, 2H), 7.29 (m, 1H), 7.21 (d, $J = 3.61$Hz, 1H), 7.08 (d, $J = 3.61$, 1H), 6.98 (d, 1H, $J = 3.62$, 1H), 6.94 (d, $J = 3.62$, 1H). GC-MS (EI): 322 [M^+], 240 $[M\text{-}Br]^+$.

Synthesis of 2-Bromo-2′-phenyl-5,5′-thiophene by Negishi Reaction

Bromobenzene (1.14 g, 7.26 mmol) was dissolved in 45 mL dry THF in a schlenk's vessel at −35°C, *n*-BuLi (2.5 eq., 1.16268 g) was added dropwise to the reaction vessel at −35°C, and the brightly yellow-green solution was stirred at −35°C for 2 h, the reaction mixture was cooled to −78°C for 15 min, $ZnCl_2$ (18.876 mmol, 19.30 mL, 0.978 M/ether) was added at −78°C for 3 min, then the stirring was continued at ambient temperature for 2 h, 2,2′-dibromo-5,5′-thiophene (3 eq. 21.78 mmol, 7.056 g) and $Pd(PPh_3)_4$ (251 mg) was dissolved in 30 mL of dry THF under nitrogen and then was added to reaction vessel at ambient temperature, stirring was continued at ambient temperature for 2 h in the dark, then the reaction mixture was stirred at 110°C for 60 h in the dark. The brown mixture was cooled to ambient temperature, 150 mL of water was added, extracted with $CHCl_3$ (3 × 100 mL) and washed with 100 mL of 15% hydrochloric acid, 150 mL of saturated $NaHCO_3$ solution and 100 mL of H_2O, organic phase was dried over anhydrous $MgSO_4$, the solvent was removed to give a brown solid, which was chromatographed (silica gel, hexane). Recrystallization with hexane, 636.2 mg product was obtained (yield 27.3%). melting point: 145°C. ^{1}H NMR ($CDCl_3$, TMS, 500 MH_z), δ 7.58 (m, 2H), 7.36 (m, 2H), 7.28 (m, 1H), 7.21 (d, $J = 3.61$Hz, 1H), 7.08 (d, $J = 3.61$, 1H), 6.98 (d, 1H, $J = 3.62$, 1H), 6.93 (d, $J = 3.62$, 1H). GC-MS (EI): 322 [M^+], 240 $[M\text{-}Br]^+$.

REFERENCES

1. Suzuki, A. Pure & Appl. Chem. **1985**, *57*, 1749.
2. Miyaura, N.; Suzuki, A. Chem. Rev. **1995**, *95*, 2457.
3. Suzuki, A. Pure & Appl. Chem. **1994**, *66*, 213.
4. Maddaford, S.P.; Keay, B.A. J. Org. Chem. **1994**, *59*, 6501.
5. Negishi, E. *Aspects of Mechanism and Organometallic Chemistry*; Brewster, J.H., Ed.; Plenum Press: New York, 1978; 285.
6. Suzuki, A. Acc. Chem. Res. **1982**, *15*, 178.
7. Miyaura, N.; Suzuki, A. J. Synth. Org. Chem. Jpn. **1988**, *46*, 848.
8. Miyaura, N.; Suzuki, A. J. Synth. Org. Chem. Jpn. **1993**, *51*, 1043.
9. Suzuki, A. Pure & Appl. Chem. **1991**, *63*, 419.
10. Tamao, K. *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, I., Pattenden, G., Eds.; Pergamon: New York, 1991; Vol. 3, 435.
11. Hegedus, L.S. *Organometallics in Organic Synthesis*; Schlosser Ed.; Wiley: New York, 1994, 383.
12. Aliprantis, A.O.; Canary, J.W. J. Am. Chem. Soc. **1994**, *116*, 6985.
13. Stille, J.K.; Lau, K.S.Y. Acc. Chem. Res. **1977**, *10*, 434.
14. Anderson, C.B.; Burreson, B.J.; Michalowski, T.J. J. Org. Chem. **1976**, *41*, 1990.
15. Blackburn, T.F.; Schwartz, J. J. Chem. Soc., Chem. Commun. **1977**, 157.
16. Zask, A.; Helquist, P. J. Org. Chem. **1978**, *43*, 1619.
17. Yoshida, T.; Okano, T.; Otsuka, S. J. Chem. Soc., Dalton Trans. **1976**, 993.
18. Grushin, V.V.; Alper, H. Organometallics **1993**, *12*, 1890.

Received in the USA September 16, 2002