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2,5-Bis-(butyltelluro) thiophene as a convenient precursor for the synthesis of 2,5-bis-(acetylenic) thiophenes

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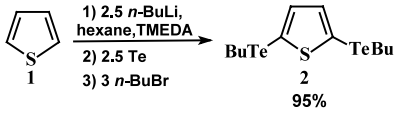
Abstract—Both symmetrically and unsymmetrically substituted 2,5-bis-(acetylenic) thiophene derivatives were obtained in good yields under mild conditions through palladium-catalyzed cross coupling reaction of 2,5-bis-(butyltelluro) thiophene **2** and terminal alkynes. The methodology represents a general and efficient protocol for carrying out the synthesis of thiophene derivatives with potential biological activities. © 2003 Elsevier Science Ltd. All rights reserved.

Palladium-catalyzed reactions play an important role in organic synthesis.[1] The cross coupling reaction of vinyl bromides, iodides, chlorides and triflates with monosubstituted acetylenes has been achieved using Pd(0) or Pd(II)/CuI catalysts and an amine as base.[2–6] The reaction has also been performed with bromoalkynes and vinyl boron,[7] copper,[8] zinc,[9] aluminum[10] or magnesium reagents[11] leading to a wide variety of compounds. Of the variety of reactions that fall in this category, the preparation of conjugated enyne, and enediyne systems as well as thiophene derivatives represent a great area of investigation.[12] These compounds are important synthetic intermediates, and they are present in numerous natural products.[13] In addition, several thiophene derivatives have been found to show nematocidal,[14] insecticidal,[15] antibacterial,[16] antifungal[17] and antiviral[18] activity.

The use of vinylic tellurides in the preparation of unsaturated systems has been previously described.[19] The reaction of vinylic tellurides with terminal alkynes occurs smoothly and leads to the corresponding enynes in good yields.[20] In connection with our previous work describing the synthesis of monosubstituted acetylenic thiophenes,[21] we decided to examine the possibility in extending the methodology for the synthesis of 2,5-bis-(acetylenic) thiophenes using 2,5-bis-(butyltelluro) thiophene, **2** as starting material. In this way, compound **2**, was obtained from the metalation of thiophene **1** with *n*-butyllithium[22] followed by treatment of the 2,5-dilithio-derivative with elemental tellurium. Subsequent addition of *n*-bromobutane gave **2** in good yield (Scheme 1). This compound is stable and can be chromatographed and stored in the dark at room temperature for several days.

Treatment of **2** with an excess of 1-alkynes in methanol using $PdCl_2$ as catalyst and triethylamine as base at room temperature gave the corresponding 2,5-bis-(acetylenic) thiophenes **3a–f** in good yields after purification (Table 1).

Since our initial research efforts were dedicated to developing a good catalytic system, we investigated the nature of the catalyst. A variety of palladium catalyst systems [$Pd(PPh_3)_4$, $PdCl_2/PPh_3$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $PdCl_2(PhCN)_2$] afforded little if any, of the desired coupling product. A rather different trend was noted when the reaction was performed in the presence of 3–10% mol of $PdCl_2$. Even better results were obtained when $PdCl_2$ (20 mol%) was used. Copper salts, such as CuI,[2,23] which is indispensable for Sonogashira's protocol, did not improve our results.



Scheme 1.

Keywords: tellurium; cross-coupling; palladium; thiophenes.
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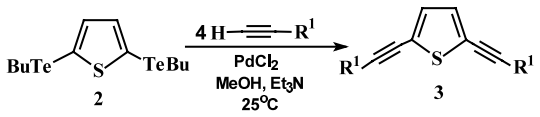
Table 1. $PdCl_2$-catalyzed cross-coupling of **2** and acetylenes



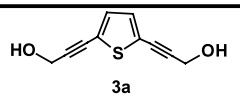
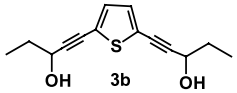
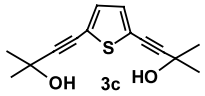
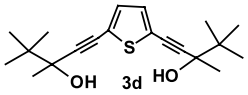
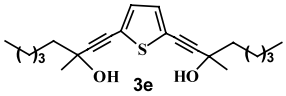
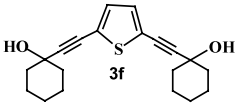
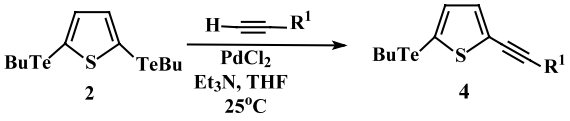
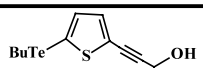
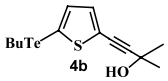
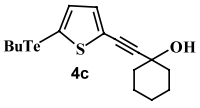
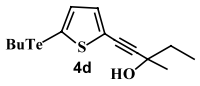
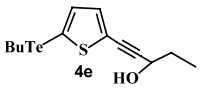
Entry	2,5-bis-acetylenic thiophene **3**	Time (h)	Yield (%)
1	 **3a**	4	89
2	 **3b**	5	83
3	 **3c**	4	85
4	 **3d**	6	80
5	 **3e**	5	79
6	 **3f**	8	75

Table 2. $PdCl_2$-catalyzed formation of 2-(butyltelluro)-5-(acetylenic) thiophenes **4**



Entry	2-(butyltelluro)-5-(acetylenic) thiophenes **4**	Time (h)	Yield (%)
1	 **4a**	5	86
2	 **4b**	4	85
3	 **4c**	5	79
4	 **4d**	6	83
5	 **4e**	6	72

An investigation on the influence of the base in the reaction suggested that Et_3N, was the reagent of choice.

The use of *n*-$PrNH_2$, Et_2NH, pyrrolidine, or piperidine proved to be less effective. Other solvents such as *N*,*N*-dimethylformamide, acetonitrile, tetrahydrofuran, or dichlorometane, proved to be ineffective for the cross coupling instead of MeOH as the solvent.

In this way, the optimum condition for the coupling was $PdCl_2$ (20 mol%), MeOH (5 mL), 2,5-bis-(butyltelluro) thiophene **2** (1 mmol), the appropriate 1-alkyne (4 mmol) and Et_3N (0.8 mL) at 25°C. By extending the coupling reaction to other alkynes, various 2,5-bis-(acetylenic) thiophenes **3** were obtained in good yields[24] (Table 1). The formation of the products were confirmed by the analysis of the ^1H and ^{13}C NMR spectra.

With the success in the development of cross-coupling system, we further investigated the synthesis of other derivatives. In this way, when the cross-coupling reaction of **2** (1 equiv.) was realized using one equivalent of 1-alkynes instead four equivalents and using THF instead of methanol, as described above, the 2-(butyltelluro)-5-(acetylenic) thiophenes **4a–e** were obtained in good yield after purification (Table 2).[25] ^1H NMR analysis of thiophene chemical shifts and coupling constants pattern for products **4a–e** unequivocally showed that the butyltelluro group had been maintained at the α position in the thiophene ring.

Finally, the possibility of generating 2,5-bis-(acetylenic) thiophenes with different acetylenic groups was also investigated. As illustrated in Table 3, the cross coupling reaction of **4** and terminal alkynes, under the same reaction conditions described above, led to the unsymmetrically substituted acetylenic thiophene derivatives **5** in excellent yields (Table 3).[26] Analysis of the ^1H and ^{13}C NMR spectra showed that compounds **5a–e** presented analytical and spectroscopic data in agreement with their assigned structures.

In summary, we have developed a general and efficient protocol for carrying out the synthesis of thiophene derivatives in high yield under mild conditions. Further investigations concerning the application of these methodologies in the total synthesis of thiophene derivatives with biological activity are currently underway and will be reported in due course.

Acknowledgements

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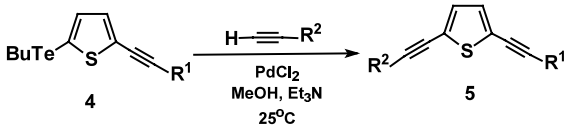
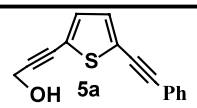
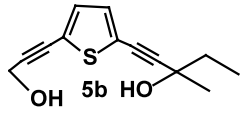
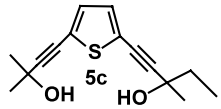
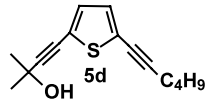
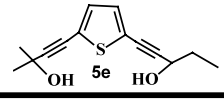
Table 3. $PdCl_2$-catalyzed formation of unsymmetrically substituted acetylenic thiophenes **5**



Entry	2,5-bis-(acetylenic) Thiophene **5**	Time (h)	Yield (%)
1		6	68
2		8	65
3		6	71
4		7	73
5		5	78

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24. **General procedure for 2,5-bis-(acetylene) thiophenes 3** (Table 1): To a two-necked 25 mL round-bottomed flask under an argon atmosphere containing a suspension $PdCl_2$ (0.035 g, 20 mol%) in dry methanol (5 mL) was added **2** (0.450 g, 1 mmol). After stirring for 15 min at room temperature, the appropriate acetylene (4 mmol) and Et_3N (0.8 mL) were successively added. The reaction was stirred at room temperature for the time indicated in Table 1 and then filtered under vacuum. The filtrate was washed with brine and extracted with dichloromethane (3×25 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexane/ethyl acetate (20:80). Compound **3a**: yield 0.170 g (89%); ^1H NMR (200 MHz, DMSO-d_6): δ 7.02 (s, 2H), 4.50 (s, 4H), 1.76 (s, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 132.52, 123.21, 95.07, 76.20, 49.41; MS m/z (%): 191 (13), 173 (33), 155 (44), 136 (100), 82 (54); IR (KBr, film): ν 3500–3100 (O–H), 3058, 2963, 2837, 1221, 1532, 1447, 1239, 858 cm^{-1}.
25. **General procedure for 2-(telluro)-5-(alkynyl) thiophenes 4**: To a two-necked 25 mL round-bottomed flask under an argon atmosphere containing a suspension $PdCl_2$ (0.035 g, 20 mol%) in dry THF (5 mL) was added **2** (0.450 g, 1 mmol). After stirring for 15 min at room temperature, the appropriate acetylene (1 mmol) and Et_3N (0.8 mL) were

successively added. The reaction was stirred at room temperature for the time indicated in Table 2 and then filtered under vacuum. The filtrate was washed with brine and extracted with dichloromethane (3×25 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexane/ethyl acetate (80:20). Compound **4a**: yield 0.276 g (86%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.2 (d, 3.5 Hz, 1H), 6.99 (d, 3.5 Hz, 1H), 4.52 (s, 2H), 2.81 (t, 7.0 Hz, 2H), 2.04 (s, 1H), 1.75 (quint., 7.1 Hz, 2H), 1.32 (sext., 7.1 Hz, 2H), 0.89 (t, 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.88, 132.36, 130.73, 100.24, 92.91, 78.01, 51.64, 33.65, 24.77, 13.74, 11.72; MS m/z (%): 320 (12), 302 (30), 287 (20), 273 (20), 258 (11), 345 (33), 183 (100), 127 (80), 66 (98), 57 (60); IR (KBr, film): ν 3500–3100 (O–H), 3064, 2958, 2831, 1240, 1545, 1438, 1241, 867 cm^{-1}.

26. **General procedure for 2,5-bis-(alkynyl) thiophenes 5**: To a two-necked 25 mL round-bottomed flask under an argon atmosphere containing a suspension $PdCl_2$ (0.035 g, 20 mol%) in dry methanol (5 mL) was added **4** (1 mmol). After stirring for 15 min at room temperature, the appropriate acetylene (2 mmol) and Et_3N (0.8 mL) were successively added. The reaction was stirred at room temperature for the time indicated in Table 3 and then filtered under vacuum. The filtrate was washed with brine and extracted with dichloromethane (3×25 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexane/ethyl acetate (20:80). Compound **5a**: yield 0.161 g (68%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37–7.29 (m, 2H), 7.25–7.20 (m, 3H), 7.01 (d, 3.4 Hz, 1H), 6.94 (d, 3.4 Hz, 1H), 4.46 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.21, 132.78, 130.28, 128.76, 128.58, 124.33, 124.02, 123.31, 93.21, 89.03, 82.09, 77.29, 52.14; MS m/z (%): 237 (15), 219 (20), 206 (33), 182 (100), 102 (83), 77 (58); IR (KBr, film): ν 3500–3100 (O–H), 3059, 2965, 2839, 1247, 1552, 1427, 1239, 872 cm^{-1}.